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CLINICAL PROTOCOL CA2097FL

A Randomized, Multicenter, Double-blind, Placebo-controlled Phase 3 Study of Nivolumab Versus Placebo in Combination With Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy in Patients With High-risk, Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Primary Breast Cancer

(CheckMate 7FL: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 7FL)

Short Title:

Nivolumab or Placebo with Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy in ER+, HER2- Breast Cancer

Protocol Amendment 03

Incorporates Administrative Letters 06, 07, and 08

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	27-Jun-2022	Key changes in Protocol Amendment 03 include the following: • Details of study enrollment closure with provision for enrolled participants on treatment to continue in the study. • The primary endpoint of the trial was updated to focus solely on pathological complete response (pCR) in the intent-to-treat (ITT) population. Event-free survival (EFS) was moved from primary to exploratory endpoint and will be evaluated up to long-term follow-up at approximately 12 months (± 2 months) post-Surgery visit. pCR in the programmed death-ligand 1-positive (PD-L1+) population will be evaluated as a secondary endpoint. The study will remain blinded through the neoadjuvant treatment and surgery phases, and will transition to open label when participants enter into adjuvant treatment. • Removal of nivolumab placebo infusion at Adjuvant phase for participants in Arm B. • Removal of pharmacokinetic and immunogenicity samples collection at Adjuvant phase for participants in Arm B. • The study will follow participants until completion of safety follow-up Visits 1 and 2 and a single long-term follow-up visit at approximately 12 months (± 2 months) post-Surgery. Subsequent long-term follow-up visits have been removed. • The study objectives, endpoints, and statistical analysis have been updated and clarified.
Administrative Letter 08	01-Apr-2022	Updated BMS study contact information.
Administrative Letter 07	27-Jul-2021	Corrected an error found in the Exclusion Criteria 1b to ensure proper alignment throughout the protocol.
Administrative Letter 06	15-Jun-2021	Corrected protocol footer to reflect change from revised protocol to protocol amendment.
Protocol Amendment 02	21-May-2021	• Updated BMS study contact information. • Aligned dose modification criteria and IO management algorithms with CTCAE v5. • [redacted] • Incorporated additional revisions to improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, sample collection, and treatment administration. • Added surgical clips placement prior starting neoadjuvant treatment. • Incorporated Administrative Letters 03, 04 and 05.
Administrative Letter 05	22-Jan-2021	• Updated BMS medical monitor information.
Administrative Letter 04	02-Nov-2020	• Updated BMS medical monitor information.
Administrative Letter 03	20-Jul-2020	• Updated BMS study contact information. • Clarified cortisol result requirement and sample collection. • Clarified on bilateral breast imaging to align with Section 9.1.5.1.

Document	Date of Issue	Summary of Change
		• Corrected inconsistency on how to manage participants who may not proceed to definitive surgery between Sections 5.1.2.1 and 9.1.2. [redacted]
Revised Protocol 01	24-Mar-2020	• Clarified and/or update some of the study procedures to align with local practice. • Aligned with recent ASCO-CAP Guidelines for estrogen and progesterone testing in breast cancer. • Removed requirements related to RECIST v1.1. to allow for unidimensional methods for assessing response with a modification of RECIST criteria in the neoadjuvant setting. • Clarified menopausal status definitions, contraception requirements, and timing for prohibition of concurrent hormonal contraception. • Updated exclusion criteria related to HIV status to allow increased opportunity for potential enrollment. • Updated window for tumor sample to be ≤ 90 day prior to enrollment for FFPE block or ≤ 60 day for unstained slides from primary breast lesion submitted at baseline. • Allowed option for concomitant administration of adjuvant systemic treatment with nivolumab/nivolumab placebo plus endocrine therapy and radiotherapy for participant requiring radiotherapy. • Clarified eCOA capture methods and remove FACIT-GP5 COA assessments on Days 8,15, and 22. • Included assessment of PD-L1 expression by combined positive score (CPS) as an exploratory objective. • Clarified dose modification expectations for the different study treatments. • Clarified prohibited/restricted and permitted concomitant therapies including growth factors, LHRH agonists, and bisphosphonates. • Incorporated Administrative Letters 01 and 02.
Administrative Letter 02	26-Aug-2019	• Updated BMS Medical Monitor information. • Provided clarification on luteinizing hormone-releasing hormone agonists. • Corrected inconsistency regarding start of adjuvant treatment in participants not receiving radiotherapy.
Administrative Letter 01	25-Jul-2019	Removed France from the country specific requirement.
Original Protocol	01-Jul-2019	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

[redacted] On 07-Apr-2022, Bristol-Myers Squibb (BMS) informed sites and the steering committee of the decision to stop new enrollment to the CA2097FL study. The study committee was supportive of the decision. Participants who had signed study consent prior to this decision and were undergoing screening were permitted to be randomized to study treatment. The decision to stop new enrollment was not based on any safety signal or review of any efficacy data. There has been no change in the understanding of the safety profile of nivolumab in combination with paclitaxel, cyclophosphamide, epirubicin/doxorubicin, and endocrine therapy.

Key changes in Protocol Amendment 03 include the following:

- Details of study enrollment closure with provision for enrolled participants on treatment to continue in the study.
- The primary endpoint of the trial was updated to focus solely on pathological complete response (pCR) in the intent-to-treat (ITT) population. Event-free survival (EFS) was moved from primary to exploratory endpoint and will be evaluated up to long-term follow-up at 12 months (± 2 months) post-Surgery visit. pCR in the programmed death-ligand 1-positive (PD-L1+) population will be evaluated as a secondary endpoint. The study will remain blinded through the neoadjuvant treatment and surgery phases and will transition to open label when participants enter into adjuvant treatment.
- Removal of nivolumab placebo infusion at Adjuvant phase for participants in Arm B.
- Removal of pharmacokinetic and immunogenicity samples collection at Adjuvant phase for participants in Arm B.
- The study will follow participants until completion of safety follow-up visits 1 and 2 and a single long-term follow-up visit at approximately 12 months (± 2 months) post-surgery. Subsequent long-term follow-up visits have been removed.
- The study objectives, endpoints, and statistical analysis have been updated and clarified.

Additional revisions, including to the Protocol Synopsis, have been made to align the protocol amendment with respect to these changes.

Other clarifications and editorial updates were made throughout the protocol to improve clarity and readability and to keep consistency throughout the document.

Changes instituted in Protocol Amendment 03 should override any existing protocol requirements in the event of any apparent discrepancies.

This amendment also incorporates the changes from the approved Administrative Letters 06, 07, and 08, which are detailed in the Document History but not listed in the Summary of Key Changes below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA2097FL)	The screening procedures are not applicable as of Protocol Amendment 03 as the study has been closed to enrollment. This is clarified in footnote "a" as well.	Because the study is unlikely to complete enrollment in a reasonable timeframe and may no longer be able to achieve the scientific objectives of the trial, BMS decided to stop new enrollment to the CA2097FL study.
Table 2-2: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q2W Schedule Table 2-5: Follow-up Procedural Outline (CA2097FL)	[redacted]	For consistency within protocol.
Table 2-5: Follow-up Procedural Outline (CA2097FL) Section 5.1: Overall Design Section 5.1.3.2: Long-term Follow-up Visit [redacted]	In Protocol Amendment 03, Long-term Follow-up has been changed to a single visit at 12 months (± 2 months) post-Surgery. There will be no further follow-up beyond this visit.	Ten-year long-term follow-up visits are not required.
Table 2-4: On-treatment Adjuvant (Post-surgery) Procedural Outline (CA2097FL)	"Mammogram or breast MRI for participants with remaining breast tissue post-surgery" row was removed.	Mammogram or breast MRI assessment will not be performed before 1 year post-surgery.
Table 2-5: Follow-up Procedural Outline (CA2097FL)	In the row for Mammogram or breast MRI, the notes were updated to add that for participants that already performed a mammogram or breast MRI at 1-year post-surgery, a second examination is not required.	Further clarify mammogram or breast MRI at 1 year post-surgery.
Table 2-2: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q2W Schedule Table 2-3: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q3W Schedule	Changed the requirements of completion of Clinical Outcome Assessments. "COAs will be completed by the participants and **should** be completed before the participant sees the physician and any study related procedures are performed."	Completion of COAs is recommended before the participant sees the physician and any study-related procedures are performed.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-4: On-treatment Adjuvant (Post-surgery) Procedural Outline (CA2097FL)		
Section 3: Introduction Section 5.1.1: Screening Period Section 6: Study Population Table 7-1: Study Treatments for CA2097FL	Added statement regarding study enrollment closure as of 07-Apr-2022.	BMS decided to stop new enrollment to the CA2097FL study.
Section 3: Introduction	Modification of the primary endpoints to move EFS to an exploratory endpoint.	Ten-year long-term follow-up visits are not required for this study.
Section 3.1.1: Research Hypothesis	Added text that nivolumab added to anthracycline-taxane-based neoadjuvant will increase pCR.	Updated research hypothesis.
Section 3.1.2: Changes per Protocol Amendment 03	New section added. Background information for the changes in Protocol Amendment 03 has been provided.	This section is added to provide key changes and rationales.
Section 3.2.5: Background for Endocrine Adjuvant Therapy Section 3.3.5: Nivolumab and Endocrine Therapy Combination Safety Profile	Data (efficacy and safety) from MonarchE study with adjuvant abemaciclib has been added.	In Oct-2021, FDA approved abemaciclib in combination with ET as adjuvant therapy for high-risk HR+, HER2- early BC. Toxicity observed with concurrent administration of abemaciclib with pembrolizumab.
Section 3.3: Benefit/Risk Assessment	Benefit/risk of the trial are re-assessed with changes to endpoints and unblinding in Adjuvant phase.	Benefit/risk of the trial was reassessed as new adjuvant treatment landscape has evolved.
Section 4: Objectives and Endpoints Section 8.1.4: Post-study Treatment Follow-up	Multiple changes were made to the objectives and endpoints: • EFS has moved from a primary endpoint to an exploratory endpoint. • Pathological complete response in the PD-L1+ population has been moved to a secondary endpoint. • Secondary quality of life endpoints have been removed. • Reduced number of exploratory biomarker endpoints.	New enrollment to the study is stopped; therefore, the study objectives and endpoints were updated.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-4: On-treatment Adjuvant (Post-surgery) Procedural Outline (CA2097FL), footnote "c" Section 5.1: Overall Design Section 5.1.2.4: Adjuvant (Post-surgery) Phase Section 7.1.3: Adjuvant (Post-surgery) Phase	As of Protocol Amendment 03, treatment in the Adjuvant phase will be open label and no crossover is allowed on the protocol.	The study design transitioned to open label at Adjuvant phase per Protocol Amendment 03.
Section 5.1: Overall Design	The total duration of the study is 4 years, with the changes to long-term follow-up length.	The duration of study was recalculated from first randomized participant to the last study visit at 1 year after surgery.
Figure 5.1-1: Study Design Schema	Schema has been updated to reflect the changes in Protocol Amendment 03.	Treatment assignment was unblinded at Adjuvant phase. Long-term follow-up visits are changed to 1 long-term follow-up visit at 1 year post-surgery. Nivolumab placebo removed from Adjuvant phase.
Section 5.1.2.3: Radiotherapy	More detail has been provided regarding timing of when adjuvant systemic therapy may start.	To further clarify when adjuvant therapy can be started along with RT.
Section 5.1.2.1: Neoadjuvant (Pre-surgery) Phase Section 5.1.2.4: Adjuvant (Post-surgery) Phase Table 7.1-3: Selection and Timing of Dose - Adjuvant (Post-surgery) Phase Section 7.1.1: Nivolumab/Nivolumab Placebo Dosing Section 7.1.3: Adjuvant (Post-surgery) Phase	As of Protocol Amendment 03, participants randomized to Arm B will no longer receive nivolumab placebo infusion treatment in the Adjuvant phase.	To align with nivolumab placebo being removed from the Adjuvant phase.
Section 5.1.2.4: Adjuvant (post-surgery) Phase	Two clarifications were made: Description of no further nivolumab placebo infusion adjuvant treatment except endocrine treatment (ET) for Arm B participants was provided. Ovarian function suppression is allowed to be used with ET.	To align with nivolumab placebo being removed from the Adjuvant phase.
Section 5.2: Number of Participants	An updated number of participants screened and randomized has been provided.	New enrollment to the study was stopped on 07-Apr-2022.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.4.5: Rationale for Stratification Factors	Removed maximum number of participants who must have PD-L1 < 1% as the study has closed to enrollment.	As this cap of stratification factor is no longer applicable.
Section 6.1: Inclusion Criteria 2) a) i)	Deleted mention of "clinical" before the node.	The criteria is for pathological assessment of nodes.
Section 7.3: Blinding	Language has been added regarding the open label treatment/unblinding in the Adjuvant phase of the study.	Treatment assignment is transitioned to open label at Adjuvant phase.
Section 7.4.2.1: Dose Delay for Paclitaxel Therapy	Changed the number of neutrophils for febrile neutropenia from 1500 cells/mm^3 down to 1000 cells/mm^3 for > 1 week to dose delay.	To correct typographical error.
Section 7.7.1.1: Prohibited and/or Restricted Treatments for Nivolumab Section 7.7.1.2: Prohibited and/or Restricted Treatments for Chemotherapy and Endocrine Therapy	CDK4/6 inhibitors are listed as examples of anti-neoplastic therapy that cannot be administered concurrently with nivolumab.	Toxicity observed when abemaciclib is concurrently administered with pembrolizumab.
Section 8: Discontinuation Criteria Section 8.1: Discontinuation from Study Treatment	Start of subsequent cancer therapy and unblinding prior to Adjuvant phase are newly added discontinuation criteria.	Emergency unblinding through IRT system prior to Adjuvant phase disqualifies the participant to continue to stay on study treatment.
Table 2-4: On-treatment Adjuvant (Post-surgery) Procedural Outline (CA2097FL) Section 9.5: Pharmacokinetics and Immunogenicity Table 9.5-1: Pharmacokinetic and Anti-drug Antibody Sampling Schedule for All Participants (CA2097FL)	For participants randomized to Arm B, PK and immunogenicity samples are no longer required to be collected at Adjuvant phase.	Nivolumab placebo is removed from Adjuvant phase, so PK and immunogenicity samples will only be collected in Arm A.
Section 5.1: Overall Design Section 5.4.5: Rationale for Stratification Factors Section 5.4.5.1: PD-L1 Status Section 9.8.2.1: PD-L1 Expression	Provided additional details on determination of PD-L1 status.	To further clarify the methodologies used for determination of PD-L1 expression.
Section 9.8.3.4: Plasma for Circulating Tumor DNA	Updated wording provided for circulating tumor DNA (ctDNA) testing.	For further clarification.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1: Sample Size Determination Table 10.1-1: Power Assumptions	Sample size and power calculations have been updated based on changes to the primary endpoint and enrollment closure of the study. Timing for final analysis of pCR was added.	New enrollment to the study is stopped and the timing for final pCR analysis is provided.
Table 10.2-1: Population for Analyses	Clarified that the randomized population is the ITT population	For clarification of ITT population.
Section 10.3.1: Efficacy Analyses Section 10.3.2: Safety Analyses	The endpoints and statistical analysis methods were updated based on the changes to the objectives of the protocol.	To align study endpoints and statistical analysis across the protocol.
Section 10.3.5.1: Futility Analysis Based on pCR	Timing of futility analysis was noted in the protocol and details of interim analyses were removed.	To provide the timing and clarification for futility analysis.
Section 11: References	Reference list updated.	Added emergent data/literature about PD-L1.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Randomized, Multicenter, Double-blind, Placebo-controlled Phase 3 Study of Nivolumab Versus Placebo in Combination With Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy in Patients With High-risk, Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Primary Breast Cancer

Short Title:

Nivolumab or Placebo with Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy in ER+, HER2- Breast Cancer

Study Phase: 3

Rationale:

Neoadjuvant therapy is used increasingly in patients with primary breast cancer (BC) to improve the likelihood of local tumor control, assess the treatment sensitivity of the disease in vivo, and increase the potential for curable disease by targeting the micrometastatic disease burden. Robust individual patient-level data meta-analyses from well-conducted clinical trials suggest that achieving a pathological complete response (pCR) is positively associated with improvement in event-free survival (EFS) and overall survival (OS); these associations are more robust within populations with high-risk BC subtypes. Further, use of the neoadjuvant setting as a research platform permits rapid assessment of drug efficacy and may expedite clinical development of new agents in this setting. Agents that positively and substantially impact pCR rates may have a reasonable expectation of meaningful improvement in EFS.

Current neoadjuvant standard of care (SOC), consisting of anthracycline-taxane-based chemotherapy, is effective and tolerable among most patients with primary BC. Chemotherapy is effective in high-risk, primary estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) disease and pCR rates range from 7-16%, which are lower than those achieved in human epidermal growth factor receptor 2-positive (HER2+) and triple-negative breast cancer (TNBC) subtypes through chemotherapy with or without human epidermal growth factor receptor 2 (HER2) blockade, respectively (30-50%). In addition, SOC clinical management of patients with ER+ BC also includes endocrine therapy (ET) for up to a 10-year period. In the setting of a high-risk disease population receiving neoadjuvant chemotherapy, ET is administered in the adjuvant setting, with the 2 treatment modalities not being administered concomitantly.

Programmed cell death-1 (PD-1) pathway inhibition has demonstrated clinical activity across multiple tumor types, including BC. An accumulating body of preclinical and clinical data supports the combination of anti-PD-1 agents and chemotherapy to improve clinical outcomes in early and advanced settings across BC subtypes; such data culminated recently in the first approval of a programmed death-ligand 1 (PD-L1) inhibitor, atezolizumab, coupled with single-agent chemotherapy for patients with newly diagnosed, programmed death-ligand 1-positive (PD-L1+; assessed in the immune-cell component of the disease) metastatic TNBC. Preliminary clinical data from a Phase 2 adaptive-design neoadjuvant trial (I-SPY2) in participants with HER2- BC (ER+, HER2-, and TNBC cohorts) assessed an anti-PD-1 agent added to standard paclitaxel

chemotherapy and demonstrated clinically meaningful improvements in pCR relative to historical controls. These and other early clinical trials support currently ongoing Phase 3 neoadjuvant-adjuvant trials that are evaluating anti-PD-1 agents in the HER2- population.

On 07-Apr-2022, Bristol-Myers Squibb (BMS) informed sites and the steering committee to stop new enrollment into the CA2097FL study. The study steering committee was supportive of the decision. The decision to stop new enrollment was not based on any safety signal or review of any efficacy data. There has been no change in our understanding of the safety profile of nivolumab in combination with paclitaxel, cyclophosphamide, epirubicin/doxorubicin, and endocrine therapy.

The trial will continue with the participants currently enrolled and the primary endpoint will be amended to focus solely on pCR.

Study Population:

Newly diagnosed, treatment-naive, high-risk, ER+, HER2- BC.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare efficacy of nivolumab plus chemotherapy vs nivolumab placebo plus chemotherapy as neoadjuvant treatment in terms of the absence of residual tumor disease in participants with untreated, high-risk ER+, HER2- BC.	• pCR, defined as no invasive residual disease in breast and lymph nodes (ie, ypT0/is, ypN0) by a local pathologist (ITT population).
Key Secondary	
• To compare efficacy of nivolumab plus chemotherapy vs nivolumab placebo plus chemotherapy as neoadjuvant treatment in terms of the absence of residual tumor disease in participants with untreated, high-risk ER+, HER2- BC in the PD-L1+ subgroup.	• pCR, defined as no invasive residual disease in breast and lymph nodes (ie, ypT0/is, ypN0) by a local pathologist (PD-L1+ population).
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy in terms of RCB.	• RCB class (0, I, II, III) frequency, for RCB assessed by a local pathologist in ITT and PD-L1+ populations.
• To evaluate the safety and tolerability of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy.	• Incidence of AEs, drug-related AEs, AEs leading to discontinuation, and SAEs as defined by NCI CTCAE v5.0.

Objectives	Endpoints
	• Incidence of deaths.
Key Tertiary/Exploratory	
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy in terms of pCR by alternative definitions.	• pCR, defined as no invasive or in situ residual disease in breast and lymph nodes (ie, ypT0 ypN0) by a local pathologist in ITT and PD-L1+ populations. • pCR, defined as no invasive residual disease in the breast irrespective of in situ or nodal involvement (ypT0/is) by a local pathologist in ITT and PD-L1+ populations.
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy in terms of ORR by investigator.	• ORR, defined as investigator-assessed tumor response rate per radiologic-based assessment (RECIST v1.1) in the Neoadjuvant (pre-surgery) phase in ITT and PD-L1+ populations.
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy and adjuvant ET in terms of EFS, survival, DFS, and DMFS.	• EFS in ITT population • OS in ITT population. • DFS in ITT population. • DMFS in ITT population.
• To characterize the PK and IMG of nivolumab when administered in combination with neoadjuvant chemotherapy.	• Nivolumab PK and IMG parameters.
• To characterize the PK and IMG of nivolumab when administered in combination with adjuvant ET.	• Nivolumab PK and IMG parameters.
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy and adjuvant ET in subgroups based on PD-L1 expression by IHC 28-8 CPS.	• Clinical efficacy endpoints (eg, pCR, RCB, ORR) by PD-L1 expression using PD-L1 IHC 28-8 CPS.
[redacted]	
• To assess cancer-specific symptoms and QOL domains across treatment groups.	• Mean EORTC QLQ-C30 and QLQ-BR23 subscale scores and post-baseline score changes.
• To assess perceptions of the overall bothersomeness of symptomatic AEs.	• Mean FACIT GP5 item scores and post-baseline score changes.
• To evaluate perceived general health status and utility between treatment groups.	• Mean EQ-5D-5L VAS and utility index scores and post-baseline score changes.
[redacted]	

Objectives	Endpoints
[redacted]	

Abbreviations: AE, adverse event; BC, breast cancer; CPS, combined positive score; CTCAE, Common Terminology Criteria for Adverse Events; DFS, disease-free survival; DMFS, distant metastasis-free survival; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, 5-Level EQ-5D; ER+, estrogen receptor-positive; ET, endocrine therapy; FACIT GP5, Functional Assessment of Chronic Illness Treatment General Physical Item 5; HER2-, human epidermal growth factor receptor 2-negative; IgG, immunoglobulin G; IHC, immunohistochemistry assay; IMG, immunogenicity; ITT, intent to treat; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PD-L1+, programmed death-ligand 1-positive; PK, pharmacokinetic; QLQ-BR23, Quality of Life Questionnaire-Breast Cancer-specific Module; QLQ-C30, Quality of Life Questionnaire-Core 30; QOL, quality of life; RCB, residual cancer burden; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; VAS, visual analog scale; vs, versus.

Overall Design:

This is a randomized, double-blind, placebo-controlled, multicenter, global Phase 3 study. The study is designed to evaluate nivolumab vs nivolumab placebo in combination with neoadjuvant chemotherapy and adjuvant ET in newly diagnosed, treatment-naive participants with high-risk (defined as Grade 3 disease or Grade 2 disease with low ER expression of 1-10%) BC that is ER+ and HER2-. Participants must have histologically confirmed invasive ductal breast carcinoma meeting the characteristics of the Inclusion Criteria.

The study is divided into 3 periods: Screening Period, Treatment Period (Neoadjuvant, Surgery, and Adjuvant Phases), and Follow-up Period. Following the confirmation of eligibility, participants will be randomized to either Arm A or Arm B in a 1:1 ratio.

The Treatment Period will consist of the following phases:

- Neoadjuvant (Pre-surgery) Phase: maximum of 8 cycles
  - Paclitaxel (PTX) Cycles 1-4 (1 cycle = every 3 weeks [Q3W]): nivolumab or nivolumab placebo + weekly paclitaxel

  Followed by

  - Anthracycline-Cyclophosphamide (AC) Cycles 1-4 (1 cycle = every 2 weeks [Q2W] or Q3W [dosing frequency to be determined by the Investigator]): nivolumab or nivolumab placebo + AC
- Surgery
- Adjuvant (Post-surgery) Phase: maximum of 7 cycles
  - Adjuvant Cycles 1-7 (1 cycle = every 4 weeks [Q4W]): nivolumab + ET or ET alone (per Protocol Amendment 03)

Treatment will start with the Neoadjuvant (Pre-surgery) Phase, in which participants will be randomized to receive an intended 4 cycles of nivolumab or nivolumab placebo in combination with weekly paclitaxel, **followed by** an intended 4 cycles of nivolumab or nivolumab placebo in combination with anthracycline (doxorubicin or epirubicin) + cyclophosphamide. Following

completion of the Neoadjuvant (Pre-surgery) Phase of treatment, participants who remain operative candidates will undergo breast surgery (per local standards) within 4 weeks. In cases when surgery does not occur within 4 weeks, surgery is permitted at a later date. The investigator must document the reason for delay of surgery in the CRF and the medical record.

Participants will return to the site within 7-14 days following surgery to begin their Adjuvant (Post-surgery) Phase of treatment, consisting of a maximum of 7 cycles of nivolumab +ET or with Investigator's choice of ET alone (per Protocol Amendment 03). The post-surgery visit and the first cycle of adjuvant treatment may be combined if adjuvant treatment starts within 7-14 days after the breast cancer surgery.

As of Protocol Amendment 03, the Adjuvant phase of the study will be converted to open label, and participants will be unblinded when they reach the Adjuvant phase of the study. Participants already on adjuvant treatment or in follow-up when Protocol Amendment 03 is approved will also be unblinded. No crossover to adjuvant nivolumab will be allowed for participants enrolled in Arm B. Adjuvant systemic therapy should be started no later than 6 weeks following Surgery in participants not receiving radiotherapy (RT). In participants receiving RT, adjuvant systemic therapy may start at the same time as RT or no later than 1 to 2 weeks after completion of RT per local standards. Starting adjuvant systemic therapy for a few adjuvant cycles then stopping or pausing therapy to administer RT then restarting adjuvant systemic therapy for remaining adjuvant cycles will not be permitted.

Randomized participants in the study will be stratified by the following factors:

1) PD-L1 on immune cells (≥ 1% or < 1%);
2) Tumor grade (2 or 3);
3) Axillary nodal status (pathological review positive versus radiographic and/or pathologic review negative); and
4) AC dose-frequency chemotherapy regimen (Q2W or Q3W).

PD-L1 status, used for stratification, is determined by qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 on the proportion of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells (% IC) of any intensity.

Clinical outcomes assessments (COAs) will be assessed throughout the study at the timepoints defined in the Schedule of Activities.

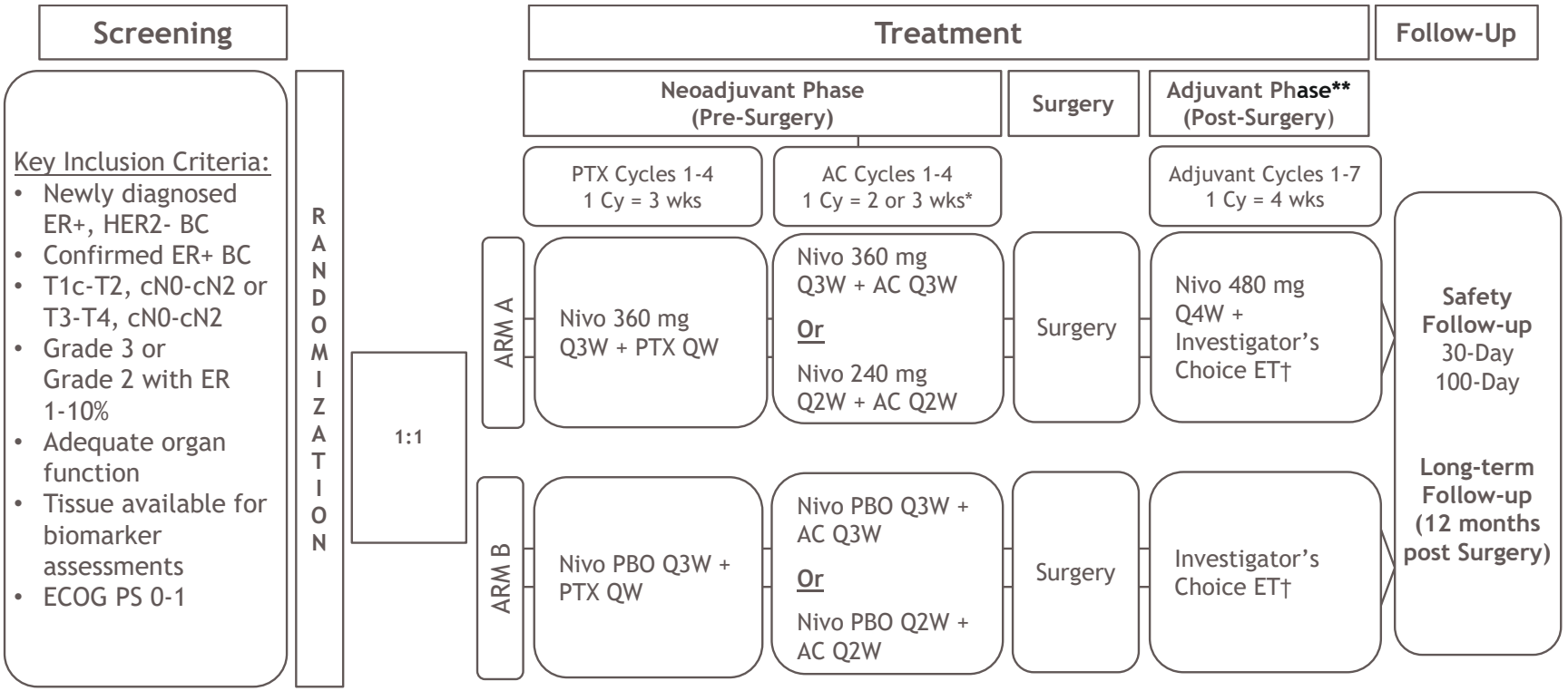
Participants who discontinue study treatment must continue to be followed in this study for collection of outcome and/or survival follow-up data, as required, until death or the conclusion of the study.

Safety Follow-up Visits will occur after the last Adjuvant (Post-surgery) Phase treatment. As of Protocol Amendment 03, the Long-term Follow-up visit will occur 12 months (± 2 months) following surgery. The Long-term Follow-up visit will be the final visit of the study. For participants in follow-up at the time of Protocol Amendment 03, the final study visit will happen at the time of the next previously scheduled study visit.

The total duration of the study is approximately 4 years from randomization of the first participant. The study may be terminated at any time by the Sponsor.

The study design schematic is presented in the figure below.

Study Design Schematic



Stratification Factors:
- PD-L1 IC (≥ 1% or <1%)
- Tumor Grade (3 or 2)
- Axillary Nodal Status (+ or -)
- AC (Q3W or Q2W)

*Investigator's choice anthracycline; dosing frequency of Q2W or Q3W for AC cycles determined by the Investigator.
†Available ET agents include tamoxifen, anastrozole, letrozole, and exemestane.
Abbreviations: AC = anthracycline + cyclophosphamide; BC = breast cancer; Cy = cycle; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = endocrine therapy; IC = immune cells; PBO = placebo; PTX = paclitaxel; Q2W = every 2 weeks; Q3W = every 3 weeks; QW = every week
**In Adjuvant phase, the study treatment will be open-label. Participants in Arm B will not receive Nivo PBO infusion

Number of Participants:

The study is closed to new enrollment on 07-Apr-2022. As of 16-May-2022, 831 participants are screened and 521 participants are randomized.

Treatment Arms and Duration:

The selection and timing of dose for each participant is provided in the tables below.

Selection and Timing of Dose - Neoadjuvant (Pre-surgery) Phase - PTX

Arm	Study Treatment	Dosage Level	Frequency of Administration	Start and Duration of Treatment	Route of Administration
A	Nivolumab	360 mg	Q3W	PTX Cycles 1-4	IV
	Paclitaxel	80 mg/m^2	QW	PTX Cycles 1-4	IV
B	Nivolumab Placebo	NA	Q3W	PTX Cycles 1-4	IV
	Paclitaxel	80 mg/m^2	QW	PTX Cycles 1-4	IV

Abbreviations: IV, intravenous; m^2, square meter; mg, milligram; NA, not applicable; PTX, paclitaxel; QW, every week; Q3W, every 3 weeks.

Selection and Timing of Dose - Neoadjuvant (Pre-surgery) Phase - AC

Arm	Study Treatment	Dosage Level	Frequency of Administration	Start and Duration of Treatment	Route of Administration
A	Nivolumab	360 mg	Q3W	AC Cycles 1-4	IV
		OR[a]			
		240 mg	Q2W		
	Doxorubicin[b]	60 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
	Epirubicin[b]	90 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
	Cyclophosphamide	600 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
B	Nivolumab Placebo	NA	Q3W or Q2W[a]	AC Cycles 1-4	IV
	Doxorubicin[b]	60 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
	Epirubicin[b]	90 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
	Cyclophosphamide	600 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV

Abbreviations: AC, anthracycline + cyclophosphamide; IV, intravenous; m^2, square meter; mg, milligram; NA, not applicable; Q2W, every 2 weeks; Q3W, every 3 weeks.

[a] Dosing frequency of Q2W or Q3W for AC cycles to be determined by the Investigator.

[b] Choice of anthracycline, either doxorubicin or epirubicin, to be determined by the Investigator.

[c] Prophylaxis with growth factors is required for the AC 2QW schedule .

Selection and Timing of Dose - Adjuvant (Post-surgery) Phase

Arm	Study Treatment	Dosage Level	Frequency of Administration	Start and Duration of Treatment	Route of Administration
A	Nivolumab	480 mg	Q4W	Cycles 1-7	IV
	Investigator's Choice ET	See Note[a]	See Note[a]	Cycles 1-7	See Note[a]
B	Investigator's Choice ET	See Note[a]	See Note[a]	Cycles 1-7	See Note[a]

Abbreviations: ET, endocrine therapy; IV, intravenous; mg, milligram; NA, not applicable; Q4W, every 4 weeks.

[a] May include tamoxifen, letrozole, anastrozole, or exemestane, to be administered per the respective package inserts.

All participants should begin study treatment within 3 days of randomization.

Study Treatment:

Study Drugs for CA2097FL

Medication	Potency	IP/Non-IP
Nivolumab Injection[a]	10 mg/mL; 100-mg fill volume and 10 mg/mL; 40-mg fill volume	IP
Paclitaxel Solution for Injection[b]	6 mg/mL; 100 mg fill volume	IP
Doxorubicin Hydrochloride Injection[b]	2 mg/mL; 200 mg fill volume	IP
Epirubicin Solution for Injection[b]	2 mg/mL; 200 mg fill volume	IP
Cyclophosphamide Injection[b]	1 g vial	IP
0.9% Sodium Chloride for Injection	NA	IP
5% Dextrose for Injection	NA	IP
Tamoxifen Tablets[b]	Various strengths	IP
Letrozole Tablets[b]	2.5 mg	IP
Anastrozole Tablets[b]	1 mg	IP
Exemestane Tablets[b]	25 mg	IP
Granulocyte colony-stimulating factor (G-CSF)[c]	Various strengths	Non-IP

Study Drugs for CA2097FL

Medication	Potency	IP/Non-IP
Granulocyte-macrophage colony-stimulating factor (GM-CSF)[c]	Various strengths	Non-IP

Abbreviations: g, gram; IP, investigational product; mg, milligram; mL, milliliter; NA, not applicable; 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 local standards.

[c] To be sourced locally by investigational sites. These products should be prepared/stored/administered in accordance with their package insert or SmPC or according to local standards.

Independent Data Monitoring Committee: Yes

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2097FL) - *Not Applicable per Protocol Amendment 03*

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 confirmed prior to randomization. See Section 6 (Study Population).
Medical History	X	All medical history relevant to the disease under study, including tobacco history and TNM staging.
Disease Biomarkers	X	Document hormonal receptors (ER, PgR) and HER2 status from local testing. Document results for mutation status (eg, *BRCA1/2, PALB2, PIK3CA*), if known. Document results, if known, of genomic test(s) for prognostic (eg, Oncotype, MammaPrint, Prosigna).
Documentation of Menopausal Status (Women only)	X	Document menopausal status. See Section 5.1.1 (Screening Period) for definitions.
Pretreatment Tumor Sample Submission	X	A recent archival primary breast tumor biopsy is required in the format of 1 FFPE tissue block (strongly preferred) containing 20 mm^3 of tissue, collected ≤ 90 days prior to enrollment or unstained tumor tissue sections (22 slides) prepared ≤ 60 days prior to enrollment from a tissue sample collected ≤ 90 days prior to enrollment. If a recent breast tumor specimen is not available, a fresh breast tumor biopsy collection is required. If < 22 slides are available, a minimum of 15 unstained slides must be submitted for a participant to be eligible. If < 15 unstained slides are available, the participant is not eligible. For participant with planned BCS, surgical clip(s) should be placed preferably prior to starting neoadjuvant treatment but no later than PTX C2D1. For participant with planned mastectomy, placement of surgical clip(s) is strongly recommended. Placement of surgical clip(s) marks the tumor bed to ensure its appropriate localization at the time of the surgery and to enable accurate sampling of the specimen by the pathologist. (Refer to pathology manual for additional details). Central laboratory results for PD-L1 status, ER status, and ER expression level must be available prior to randomization.

Table 2-1: Screening Procedural Outline (CA2097FL) - *Not Applicable per Protocol Amendment 03*

Procedure[a]	Screening Visit	Notes All windows are based on calendar days.
		For additional details, see [redacted] Laboratory Manual.
Safety Assessments		
PE, Measurements, Vital Signs, and ECOG PS	X	Complete PE (including review of systems), height, weight, temperature, BP, heart rate, RR, and ECOG PS (Appendix 5). Must be collected within 14 days prior to randomization.
ECG (12-lead)	X	Must be performed within 14 days prior to randomization.
ECHO (Preferred) or MUGA	X	Must be performed within 28 days prior to randomization. ECHO is the preferred method of assessment. The method used for the baseline assessment should be used consistently for additional assessments.
Assessment of Signs and Symptoms	X	Must be performed within 14 days prior to randomization.
Concomitant Medication Use	X	Must be collected within 28 days prior to randomization. Vaccine use within 30 days prior to randomization.
SAE Assessment	X	Must be collected from the time of consent. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent.
Laboratory Tests		
CBC with Differential, Chemistry, and Serology	X	Must be performed within 14 days prior to randomization. Serology must be completed within 28 days prior to randomization. See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests.
Cortisol[c]	X	Must be performed within 14 days prior to randomization.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of HCG) to be done at screening and repeated within 24 hours prior to the first dose of study therapy. An extension up to 72 hours prior to the start of study treatment is permissible in the situations where results cannot be obtained within the standard 24-hour window.
[redacted]	[redacted]	[redacted]

Table 2-1: Screening Procedural Outline (CA2097FL) - *Not Applicable per Protocol Amendment 03*

Procedure[a]	Screening Visit	Notes All windows are based on calendar days.
[redacted]	[redacted]	[redacted]
Efficacy Assessments		
Documentation of Planned Surgery	X	Record type of planned BC surgery (ie, BCS, mastectomy).
Clinical Breast Examination	X	Perform clinical breast examination by palpation of breast and axilla.
Bilateral Ultrasound or Mammogram of Breast and Axilla or Breast MRI	X	Perform bilateral ultrasound or mammogram of breast and axilla or breast MRI per local standards within 45 days prior to randomization. See Section 9.1.5 (Imaging Assessment for the Study). The method used for the baseline assessment should be used consistently for additional assessments during the neoadjuvant phase.
Other Imaging (eg, ultrasound, X-ray, CT, MRI, PET)	X	Permitted if clinically indicated and per local standards. 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 is available prior to the Screening Period.

Abbreviations: AE, adverse event; BC, breast cancer; BCS, breast-conserving surgery; BP, blood pressure; CBC, complete blood count; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; ER+, estrogen receptor-positive; FFPE, formalin-fixed paraffin-embedded; HCG, human chorionic gonadotropin; HER2-, human epidermal growth factor receptor 2-negative; IRT, interactive response technology; IU, international unit; L, liter; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition; PD-L1, programmed death-ligand 1; PE, physical examination; PET, positron emission tomography; PS, performance status; PTX, paclitaxel; RR, respiratory rate; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; TNM, tumor, node, metastasis; WOCBP, women of childbearing potential.

[a] Some of the assessments referred to in this section may not be captured as data on 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. As of 07-Apr-2022, this study is closed to new participant enrollment.

[redacted]

[c] Cortisol must be collected at AC C1D1 (predose) and prior to surgery. Result is not required prior to dosing.

Table 2-2: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q2W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 2 weeks)		
	D1	D8	D15		D1		
Safety Assessments							
Targeted PE, Measurements, Vital Signs, and ECOG PS	X				X		Weight, BP, heart rate, temperature, and ECOG PS (Appendix 5).
ECHO (Preferred) or MUGA						X	ECHO is the preferred method of assessment. The method used for the baseline assessment should be used consistently for additional assessments.
AEs Assessment (Including SAEs)	Continuously.						Record at each visit. All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.
Concomitant Medication Use	Continuously.						Record at each visit.
Laboratory Tests							
CBC with Differential and Chemistry	X				X		See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests.

Table 2-2: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q2W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 2 weeks)		
	D1	D8	D15		D1		
							Must be performed within 3 calendar days prior to dosing and results must be available prior to dosing for all timepoints, except PTX C1D1 which does not need to be repeated if baseline assessment performed within 7 days prior to first dose.
Cortisol					X	X	Cortisol must be collected at AC C1D1 (predose) and prior to surgery. Result is not required prior to dosing.
[redacted]						[redacted]	[redacted]
Pregnancy Test (WOCBP Only)	See Notes.						Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24 hours prior to D1 of each PTX cycle and prior to D1 of AC C1 and AC C3. An extension up to 72 hours prior to the start of study treatment is permissible in

Table 2-2: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q2W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 2 weeks)		
	D1	D8	D15		D1		
							situations where results cannot be obtained within the standard 24-hour window.
Efficacy Assessments							
Clinical Breast Examination				X		X	Perform clinical breast examination by palpation of breast and axilla after the last PTX cycle and prior to surgery.
Bilateral Ultrasound or Mammogram of Breast and Axilla or Breast MRI						X	Perform after completion of neoadjuvant treatment, or as clinically indicated. The method used for the baseline assessment should be used consistently for additional assessments during the neoadjuvant phase.
Other Imaging (eg, ultrasound, X-ray, CT, contrast-enhanced MRI, PET)	See Notes.						Permitted as clinically indicated and per local standards. See Section 9.1 (Efficacy Assessments) for further details.
Tumor Biopsy	See Notes.						Tumor biopsy collection is optional on PTX C2D1 (± 2 days) and required at the time of surgery. [redacted]
Clinical Outcomes Assessments							
EORTC QLQ-C30	X				X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study-related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.

Table 2-2: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q2W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 2 weeks)		
	D1	D8	D15		D1		
EORTC QLQ-BR23	X				X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study-related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
EQ-5D-5L	X				X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study-related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
FACIT GP5	X				X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study-related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
Healthcare Resource Utilization							
Healthcare Resource Utilization	X				X	X	Must be completed by site staff and recorded on the eCRF. See Section 9.9 (Health Economics OR Medical Resource Utilization and Health Economics) for details.

Table 2-2: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q2W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 2 weeks)		
	D1	D8	D15		D1		
PK and IMG Assessments	See Notes.						See Table 9.5-1 for PK/IMG sample collection schedule.
[redacted]	[redacted]					[redacted]	[redacted]
Optional Tumor Tissue Sample Collection Upon Recurrence and/or Progression	At disease recurrence and/or progression (within 40 days).						If biopsy or surgical resection is performed at recurrence and/or progression, submit a tumor sample (1 FFPE block or 22 unstained slides) to the central laboratory. [redacted]
Study Treatment							
Randomization	X						
IRT Drug Assignment	X	X	X		X		
Administer Nivolumab or Nivolumab Placebo	X				X		Treatment must be administered within 3 calendar days after randomization.
Administer PTX	X	X	X				
Administer Anthracycline					X		Anthracycline may be doxorubicin or epirubicin. See Table 7.1-1 for dose regimens. G-CSF or GM-CSF prophylaxis per international guidelines is required for dose-dense administration of AC.
Administer Cyclophosphamide					X		G-CSF or GM-CSF prophylaxis per international guidelines is required for dose-dense administration of AC.

Table 2-2: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q2W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 2 weeks)		
	D1	D8	D15		D1		
Documentation of Actual Breast Surgery						X	Record the actual type of BC surgery (ie, BCS, mastectomy) on day of or within 7 days after surgery.
Surgery (SOC)						X	Surgery per local SOC should be performed within 4 weeks after the completion of the neoadjuvant treatment phase (ie, 6-7 weeks after last neoadjuvant dose depending on AC treatment schedule). In cases, when surgery does not occur within 4 weeks surgery is permitted at a later date. The investigator must document reason for delay of surgery in the eCRF and the medical record. Surgery may be either BCS or mastectomy as determined by the participant and surgeon as per local SOC. Appropriate PE, pathologic TNM staging (after resection) and laboratory assessments should be performed as per local SOC prior to surgery. [redacted] Refer to Pathology Manual for a detailed listing of surgical specimen details to be included on the participant pathology report and in the eCRF.

Abbreviations: AC, anthracycline + cyclophosphamide; AE, adverse event; BC, breast cancer; BCS, breast-conserving surgery; BP, blood pressure; C, cycle; CBC, complete blood count; COA, clinical outcomes assessment; CT, computed tomography; D, day; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC, European Organisation for the Research and Treatment of Cancer; EQ-5D-5L, 5-Level EQ-5D; FACIT GP5, Functional Assessment of Chronic Illness Therapy General Physical Item 5; G-CSF,= granulocyte-colony stimulating factor; GM-CSF, granulocyte-

macrophage colony-stimulating factor; HCG, human chorionic gonadotropin; IgG, immunoglobulin G; IMG, immunogenicity; IRT, interactive response technology; IU, international unit; L, liter; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition; PE, physical examination; PET, positron emission tomography; PK, pharmacokinetic; PS, performance status; PTX, paclitaxel; Q2W, every 2 weeks; QLQ-BR23, Quality of Life Questionnaire-Breast Cancer-specific Module; QLQ-C30, Quality of Life Questionnaire-Core 30; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2;SOC, standard of care; TNM, tumor, node, metastasis; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures schedule for that same timepoint should also be delayed to coincide with when that timepoint's dosing actually occurs, with the exception of the optional tissue sample collection.

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

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

[d] Between end of neoadjuvant treatment and before surgery.

[e] End of PTX is defined as 3 weeks after PTX C4D1 or sooner if participant discontinues prior to completion of the 4 PTX cycles.

Table 2-3: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q3W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 3 weeks)		
	D1	D8	D15		D1		
Safety Assessments							
Targeted PE, Measurements, Vital Signs, and ECOG PS	X				X		Weight, BP, heart rate, temperature, and ECOG PS (Appendix 5).
ECHO (Preferred) or MUGA						X	ECHO is the preferred method of assessment. The method used for the baseline assessment should be used consistently for additional assessments.
AEs Assessment (Including SAEs)	Continuously.						Record at each visit. All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.
Concomitant Medication Use	Continuously.						Record at each visit.

Table 2-3: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q3W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 3 weeks)		
	D1	D8	D15		D1		
Laboratory Tests							
CBC with Differential and Chemistry	X				X		See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests. Must be performed within 3 calendar days prior to dosing and results must be available prior to dosing for all timepoints, except PTX C1D1 which does not need to be repeated if baseline assessment performed within 7 days prior to first dose.
Cortisol					X	X	Cortisol must be collected at AC C1D1 (predose) and prior to surgery. Result is not required prior to dosing.
[redacted]						[redacted]	[redacted]

Table 2-3: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q3W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 3 weeks)		
	D1	D8	D15		D1		
Pregnancy Test (WOCBP Only)	X				X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24 hours prior to D1 of each cycle. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.
Efficacy Assessments							
Clinical Breast Examination				X		X	Perform clinical breast examination by palpation of breast and axilla after the last PTX cycle and prior to surgery.
Bilateral Ultrasound or Mammogram of Breast and Axilla or Breast MRI						X	Perform after completion of neoadjuvant treatment, or as clinically indicated. The method used for the baseline assessment should be used consistently for additional assessments.
Other Imaging (eg, ultrasound, X-ray, CT, contrast enhanced MRI, PET)	See Notes.						Permitted as clinically indicated and per local standards. See Section 9.1 (Efficacy Assessments) for further details.
Tumor Biopsy	See Notes.						Tumor biopsy collection is optional on PTX C2D1 (± 2 days) and required at the time of surgery. [redacted]

Table 2-3: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q3W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 3 weeks)		
	D1	D8	D15		D1		
Clinical Outcomes Assessments							
EORTC QLQ-C30	X				X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
EORTC QLQ-BR23	X				X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
EQ-5D-5L	X				X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
FACIT GP5	X				X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.

Table 2-3: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q3W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 3 weeks)		
	D1	D8	D15		D1		
Healthcare Resource Utilization							
Healthcare Resource Utilization	X				X	X	Must be completed by site staff and recorded on eCRF. See Section 9.9 (Health Economics OR Medical Resource Utilization and Health Economics) for details.
PK and IMG Assessments	See Notes.						See Table 9.5-1 for PK/IMG sample collection schedule.
[redacted]	[redacted]					[redacted]	[redacted]
Optional Tumor Tissue Sample Collection Upon Recurrence and/or Progression	At recurrence and/or disease progression (within 40 days).						If biopsy or surgical resection is performed at recurrence and/or progression, submit a tumor sample (1 FFPE block or 22 unstained slides) to the central laboratory. [redacted]
Study Treatment							
Randomization	X						
IRT Drug Assignment	X	X	X		X		
Administer Nivolumab or Nivolumab Placebo	X				X		Treatment must be administered within 3 calendar days after randomization.
Administer PTX	X	X	X				
Administer Anthracycline					X		Anthracycline may be doxorubicin or epirubicin. See Table 7.1-1 for dose regimens.
Administer Cyclophosphamide					X		

Table 2-3: On-treatment Neoadjuvant (Pre-surgery) Procedural Outline (CA2097FL) with PTX and AC Q3W Schedule

Procedure[a]	Neoadjuvant Treatment[b]					Pre-surgery[d]	Notes[c] All windows are based on calendar days.
	PTX Cycles 1-4 (1 cycle = 3 weeks)			End of PTX[e]	AC Cycles 1-4 (1 cycle = 3 weeks)		
	D1	D8	D15		D1		
Documentation of Actual Breast Surgery						X	Record the actual type of BC surgery (ie, BCS, mastectomy) on day of or within 7 days after surgery.
Surgery (SOC)						X	Surgery per local SOC should be performed within 4 weeks after the completion of the neoadjuvant treatment phase (ie, 6-7 weeks after last neoadjuvant dose depending on AC treatment schedule). In cases, when surgery does not occur within 4 weeks surgery is permitted at a later date. The investigator must document reason for delay of surgery in the eCRF and the medical record. Surgery may be either BCS or mastectomy as determined by the participant and surgeon as per local SOC. Appropriate PE, pathologic TNM staging,(after resection) and laboratory assessments should be performed as per local SOC prior to surgery. [redacted] Refer to Pathology Manual for a detailed listing of surgical specimen details to be included on the participant pathology report and in the eCRF.

Abbreviations: AC, anthracycline + cyclophosphamide; AE, adverse event; BC, breast cancer; BCS, breast-conserving surgery; BP, blood pressure; C, cycle; CBC, complete blood count; COA, clinical outcomes assessment; CT, computed tomography; D, day; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC, European Organisation for the Research and Treatment of Cancer; EQ-5D-5L, 5-Level EQ-5D;

FACIT GP5, Functional Assessment of Chronic Illness Therapy General Physical Item 5; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HCG, human chorionic gonadotropin; IgG, immunoglobulin G; IMG, immunogenicity; IRT, interactive response technology; IU, international unit; L, liter; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition; PE, physical examination; PET, positron emission tomography; PK, pharmacokinetic; PS, performance status; PTX, paclitaxel; Q3W, every 3 weeks; QLQ-BR23, Quality of Life Questionnaire-Breast Cancer-specific Module; QLQ-C30, Quality of Life Questionnaire-Core 30; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; SOC, standard of care; TNM, tumor node metastasis; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures schedule for that same timepoint should also be delayed to coincide with when that timepoint's dosing actually occurs, with the exception of the optional tissue sample collection.

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

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

[d] Between end of neoadjuvant treatment and before surgery.

[e] End of PTX is defined as 3 weeks after PTX C4D1 or sooner if participant discontinues prior to completion of the 4 PTX cycles.

Table 2-4: On-treatment Adjuvant (Post-surgery) Procedural Outline (CA2097FL)

Procedure[a]	Post-surgery Visit[b]	Adjuvant Treatment[c] Cycles 1-7 (1 cycle = 4 weeks)	End of Adjuvant[e]	Notes[d] All windows are based on calendar days.
	Post-surgery (within 7-14 days)	D1		
Safety Assessments				
Targeted PE, Measurements, Vital Signs, and ECOG PS	X	X		Weight, BP, heart rate, temperature, and ECOG PS (Appendix 5).
Documentation of Menopausal Status (Women only)	X			Document menopausal status in participants who were premenopausal at screening/baseline. See Section 5.1.2.4 [Adjuvant (Post-surgery) Phase] for definition.
ECHO (Preferred) or MUGA			X	Perform assessment upon completion of adjuvant treatment, or as clinically indicated. ECHO is the preferred method of assessment. The method used for the baseline assessment should be used consistently for additional assessments.
AEs Assessment (Including SAEs)	Continuously.			Record at each visit. Collect continuously throughout the Treatment Period and for a minimum of 100 days after last dose of study treatment. All AEs (SAE or non-serious AE) related to the protocol-specified definitive breast surgery should be collected continuously during the treatment period and for a minimum of 100 days after last dose of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section

Table 2-4: On-treatment Adjuvant (Post-surgery) Procedural Outline (CA2097FL)

Procedure[a]	Post-surgery Visit[b]	Adjuvant Treatment[c] Cycles 1-7 (1 cycle = 4 weeks)	End of Adjuvant[e]	Notes[d] All windows are based on calendar days.
	Post-surgery (within 7-14 days)	D1		
				8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.
Concomitant Medication Use	Continuously.			Record at each visit.
Radiotherapy	See Notes.			Post-operative RT is required if BCS is subsequent treatment. Post-operative RT is optional if mastectomy is subsequent treatment and should follow local practice.
Laboratory Tests				
CBC with Differential and Chemistry	X	X		See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests.
Estradiol	X			For pre-menopausal women ONLY.
Pregnancy Test (WOCBP only)		X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24 hours prior to D1 of each cycle. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.
Efficacy Assessments				
Clinical Breast Examination	See Notes.			Perform clinical breast examination by palpation of breast and axilla as clinically indicated and per local standards. See Section 9.1 (Efficacy Assessments) for further details.
Other Imaging (eg, ultrasound, X-ray, CT, contrast-enhanced MRI, PET)	See Notes.			Permitted if clinically indicated and per local standards. See Section 9.1 (Efficacy Assessments) for further details.

Table 2-4: On-treatment Adjuvant (Post-surgery) Procedural Outline (CA2097FL)

Procedure[a]	Post-surgery Visit[b]	Adjuvant Treatment[c] Cycles 1-7 (1 cycle = 4 weeks)	End of Adjuvant[e]	Notes[d] All windows are based on calendar days.
	Post-surgery (within 7-14 days)	D1		
Clinical Outcomes Assessments				
EORTC QLQ-C30	X	X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
EORTC QLQ-BR23	X	X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
EQ-5D-5L	X	X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
FACIT GP5	X	X	X	COAs will be completed by the participants and should be completed before the participant sees the physician and any study related procedures are performed. See Section 9.1.8 (Clinical Outcomes Assessments) for details.
Healthcare Resource Utilization				
Healthcare Resource Utilization	X	X	X	Must be completed by site staff and recorded on eCRF. See Section 9.9 (Health Economics OR Medical Resource Utilization and Health Economics) for details.
PK and IMG Assessments		See Notes.		As of Protocol Amendment 03, PK/IMG sample collection is only to be performed in participants in Arm

Table 2-4: On-treatment Adjuvant (Post-surgery) Procedural Outline (CA2097FL)

Procedure[a]	Post-surgery Visit[b]	Adjuvant Treatment[c] Cycles 1-7 (1 cycle = 4 weeks)	End of Adjuvant[e]	Notes[d] All windows are based on calendar days.
	Post-surgery (within 7-14 days)	D1		
(Arm A only)				A. See Table 9.5-1 for PK/IMG sample collection schedule.
[redacted]		[redacted]		[redacted]
Optional Tumor Tissue Sample Collection Upon Recurrence and/or Progression	At disease recurrence and/or progression (within 40 days).			If biopsy or surgical resection is performed at recurrence and/or progression, submit a tumor sample (1 FFPE block or 22 unstained slides) to the central laboratory. [redacted]
Study Treatment				
IRT Drug Assignment		X		
Administer Nivolumab (Arm A only)		X		Participants Not Receiving RT: Adjuvant systemic therapy should be started no later than 6 weeks following Surgery. Participants Receiving RT: Adjuvant systemic therapy may start at the same time as RT or no later than 1 week after completion of RT, per local standard. See Section 5.1.2.3 (Radiotherapy) for guidance.
Dispense Investigator's Choice ET and Provide/Review Patient Diary		See Notes.		To be administered PO. Dispense and review patient diary at each study visit.
[redacted]		[redacted]	[redacted]	[redacted]

Table 2-4: On-treatment Adjuvant (Post-surgery) Procedural Outline (CA2097FL)

Procedure[a]	Post-surgery Visit[b]	Adjuvant Treatment[c] Cycles 1-7 (1 cycle = 4 weeks)	End of Adjuvant[e]	Notes[d]
	Post-surgery (within 7-14 days)	D1		All windows are based on calendar days.
				[redacted]

Abbreviations: AE, adverse event; BCS, breast-conserving surgery; BP, blood pressure; C, cycle; CBC, complete blood count; COA, clinical outcomes assessment; CT, computed tomography; D, day; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC, European Organisation for the Research and Treatment of Cancer; EQ-5D-5L, 5-Level EQ-5D; ET, endocrine therapy; FACIT GP5, Functional Assessment of Chronic Illness Therapy General Physical Item 5; HCG, human chorionic gonadotropin; IgG, immunoglobulin G; IMG, immunogenicity; IRT, interactive response technology; IU, international unit; L, liter; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition; PE, physical examination; PET, positron emission tomography; PK, pharmacokinetic; PO, by mouth; PS, performance status; QLQ-BR23, Quality of Life Questionnaire-Breast Cancer-specific Module; QLQ-C30, Quality of Life Questionnaire-Core 30; RT, radiotherapy; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures schedule for that same timepoint should also be delayed to coincide with when that timepoint's dosing actually occurs.

[b] Post-surgery visit and first cycle of adjuvant treatment may be combined if adjuvant treatment starts within 7-14 days after the breast cancer surgery.

[c] On-treatment procedures may generally be performed within a ± 3-day window, unless otherwise specified (eg, breast ultrasound or mammogram or breast MRI, tumor biopsy). As of Protocol Amendment 03, all participants in the Adjuvant phase will be unblinded.

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

[e] End of adjuvant therapy is defined as 4 weeks after Adjuvant C7D1 or sooner if participant discontinues prior to completion of the 7 Cycles.

Table 2-5: Follow-up Procedural Outline (CA2097FL)

Procedure	30-Day Safety Follow-up Visit 1[a] (FU1) (± 7 days)	100-Day Safety Follow-up Visit 2[b] (FU2) (± 7 days)	Long-term Follow-up Visit[c] 12 months post-surgery (± 2 months)	Notes[d]
Safety Assessments				
Targeted PE, Measurements, Vital Signs, and ECOG PS	X	X		Weight, BP, heart rate, temperature, and ECOG PS (Appendix 5).
AE Assessment (Including SAEs)	X	X	See Notes.	Non-serious and serious AEs are collected continuously throughout the Treatment Period and for a minimum of 100 days after the last dose of study treatment. All AEs (SAE or non-serious AE) related to the protocol-specified definitive breast surgery should be collected continuously during the treatment period and for a minimum of 100 days after last dose of study treatment. Participants will be followed for treatment-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. SAEs to be collected after FU2, if the SAE is deemed to be related or residual toxicities are persisting. AEs of special interest to be collected at Long-term Follow-up visit. See Section 9.2.1 (Immune-mediated Adverse Events). Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.

Table 2-5: Follow-up Procedural Outline (CA2097FL)

Procedure	30-Day Safety Follow-up Visit 1[a] (FU1) (± 7 days)	100-Day Safety Follow-up Visit 2[b] (FU2) (± 7 days)	Long-term Follow-up Visit[c] 12 months post-surgery (± 2 months)	Notes[d]
Concomitant Medication				
Concomitant Medication (including endocrine therapy) Use	X	X	See Notes.	All concomitant medications are collected at FU1 and FU2. Record Investigator's choice ET taken after the last dose of adjuvant treatment at FU1, FU2, and the Long-term Follow-up visit.
Subsequent Cancer Treatment	X	X	X	Record at each visit any new surgery, RT, and systemic cancer therapy given for the disease under study.
Laboratory Tests				
CBC with Differential and Chemistry	X	X	X	See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests. Must be performed at FU1. If study drug-related toxicities persist, must be repeated at FU2 If a participant has an abnormal TSH value while 'on treatment', TSH testing (with reflexive fT3 and fT4 testing for abnormal values) will be performed at FU1, FU2, and 12 months (± 2 months) post-Surgery. If the abnormal lab value resolves and falls within normal limits, then testing may be discontinued earlier than the 12 months (± 2 months) post-Surgery.
[redacted]	[redacted]			[redacted]
Cortisol	X	X	X	If a participant has an abnormal value (1x ULN) while "on treatment", additional tests will be performed at FU1, FU2, and 12 months (± 2 months) post-Surgery.

Table 2-5: Follow-up Procedural Outline (CA2097FL)

Procedure	30-Day Safety Follow-up Visit 1[a] (FU1) (± 7 days)	100-Day Safety Follow-up Visit 2[b] (FU2) (± 7 days)	Long-term Follow-up Visit[c] 12 months post-surgery (± 2 months)	Notes[d]
				If the abnormal lab value then resolves and falls within normal limits, then testing may be discontinued earlier than 12 months (± 2 months) post-Surgery.
Pregnancy Test (WOCBP only)	X	X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) is required
Optional Tumor Tissue Sample Collection Upon Recurrence and/or Progression	At disease recurrence and/or progression (within 40 days).			If biopsy or surgical resection is performed at recurrence and/or progression, a tumor sample (1 FFPE block or 22 unstained slides) should be submitted to the central laboratory. [redacted]
[redacted]			[redacted]	[redacted]
Efficacy Assessments				
Mammogram or Breast MRI for Participants with Remaining Breast Tissue Post-surgery			X	Imaging is not recommended for participants who underwent bilateral mastectomy with or without breast reconstruction. For patients who underwent unilateral mastectomy, with or without reconstruction, and for patients with breast conserving surgery, imaging of the remaining breast must be done 12 months (± 2 months) post-Surgery according to imaging method used per local SOC. For participants that already performed a mammogram or breast MRI at 1-year post-Surgery, a second examination is not required.
Other Imaging (eg, ultrasound, X-ray, CT, contrast-enhanced MRI, PET)		See Notes.		Permitted as clinically indicated and per local standards. See Section 9.1 (Efficacy Assessments) for further details.
Clinical Breast Examination/Survival Status	X	X	X	To be collected at FU1, FU2, and Long-term Follow-up Visit.

Table 2-5: Follow-up Procedural Outline (CA2097FL)

Procedure	30-Day Safety Follow-up Visit 1[a] (FU1) (± 7 days)	100-Day Safety Follow-up Visit 2[b] (FU2) (± 7 days)	Long-term Follow-up Visit[c] 12 months post-surgery (± 2 months)	Notes[d]
Clinical Outcomes Assessments				
EORTC QLQ-C30	X	X		All Clinical Outcomes Assessments to be collected at FU1 and FU2.
EORTC QLQ-BR23	X	X		All Clinical Outcomes Assessments to be collected at FU1 and FU2.
EQ-5D-5L	X	X		All Clinical Outcomes Assessments to be collected at FU1 and FU2.
FACIT GP5	X	X		All Clinical Outcomes Assessments to be collected at FU1 and FU2.
Healthcare Resource Utilization				
Healthcare Resource Utilization	X	X		All Clinical Outcomes Assessments to be collected at FU1 and FU2.

Abbreviations: AE, adverse event; BP, blood pressure; CBC, complete blood count; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC, European Organisation for the Research and Treatment of Cancer; EQ-5D-5L, 5-Level EQ-5D; ET, endocrine therapy; FACIT GP5, Functional Assessment of Chronic Illness Therapy General Physical Item 5; FFPE, formalin-fixed paraffin-embedded; FU1, follow-up visit 1; FU2, follow-up visit 2; HCG, human chorionic gonadotropin; IgG, immunoglobulin G; IU, international unit; L, liter; MRI, magnetic resonance imaging; PE, physical examination; PET, positron emission tomography; PS, performance status; QLQ-BR23, Quality of Life Questionnaire-Breast Cancer-specific Module; QLQ-C30, Quality of Life Questionnaire-Core 30; RT, radiotherapy; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; SOC, standard of care; WOCBP, women of childbearing potential.

[a] FU1 should occur 30 days from the last dose (± 7 days) of study treatment (refer to Table 7-1 for a list of study treatments) or can be performed on the date of discontinuation if that date is great than 42 days from the last dose of study treatment. The safety follow-up visit should be conducted in person.

[b] Participants must be followed for at least 100 days after the last dose of study treatment. As such, FU2 occurs approximately 100 days (± 7 days) from last dose of study treatment. The safety follow-up visit should be conducted in person.

[c] As of Protocol Amendment 03, a single Long-term Follow-up Visit will be conducted at 12 months (± 2 months) post-Surgery. The Long-term Follow-up Visit should be conducted in person. FU2 and Long-term Follow-up Visit may be combined if the timing of the 2 visits overlap. For participants in follow-up at the time that Protocol Amendment 03 is approved, the final study visit will happen at the time of the next previously scheduled study visit under Protocol Amendment

02. Survival data must be collected on all randomized participants, unless a participant withdraws consent. The Sponsor may request that survival data be collected on all participants outside of the specified windows. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

[d] Some of the assessments referred to in this section may not be captured as data on 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

CA2097FL is a Phase 3, randomized, global study assessing the efficacy and safety of nivolumab or nivolumab placebo combined with standard neoadjuvant anthracycline-taxane-based chemotherapy, followed by nivolumab combined with endocrine therapy (ET) or ET alone (per Protocol Amendment 03) as adjuvant treatment, in participants with high-risk, estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) primary breast cancer (BC).

The study originally aimed to demonstrate that treatment with nivolumab combined with standard neoadjuvant anthracycline-taxane-based chemotherapy, followed by nivolumab combined with ET as adjuvant treatment, improves clinical efficacy in terms of pathological complete response rate (pCR) and/or event-free survival (EFS), when compared to standard-of-care (SOC) treatment alone. On 07-Apr-2022, new enrollment to the study was stopped. As of Protocol Amendment 03, pCR is the only primary endpoint and EFS has been changed to an exploratory endpoint.

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

3.1 Study Rationale

Neoadjuvant therapy is used increasingly in patients with primary BC to improve the likelihood of local tumor control, assess the treatment sensitivity of the disease in vivo, and increase the potential for curable disease by targeting the micrometastatic disease burden.[1] Robust individual patient-level data meta-analyses from well-conducted clinical trials suggest that achieving a pCR is positively associated with improvement in EFS and overall survival (OS); these associations are more robust within populations with high-risk BC subtypes.[2,3,4] Further, use of the neoadjuvant setting as a research platform permits rapid assessment of drug efficacy and may expedite clinical development of new agents in this setting. Agents that positively and substantially impact pCR rates may have a reasonable expectation of meaningful improvement in EFS.[5,6]

Current neoadjuvant SOC, consisting of anthracycline-taxane-based chemotherapy, is effective and tolerable among most patients with primary BC.[7,8,9] Chemotherapy is effective in high-risk, primary ER+, HER2- disease and pCR rates range from 7-16%, which are lower than those achieved in human epidermal growth factor receptor 2-positive (HER2+) and triple-negative breast cancer (TNBC) subtypes through chemotherapy with or without human epidermal growth factor receptor 2 (HER2) blockade, respectively (30-50%).[2] In addition, SOC clinical management of patients with ER+ BC also includes ET for up to a 10-year period. In the setting of a high-risk disease population receiving neoadjuvant chemotherapy, ET is administered in the adjuvant setting, with the 2 treatment modalities not being administered concomitantly.[8,9]

Programmed cell death-1 (PD-1) pathway inhibition has demonstrated clinical activity across multiple tumor types, including BC.[10,11,12,13,14,15,16] An accumulating body of preclinical[17] and clinical data[10,11,12,16] supports the combination of anti-PD-1 agents and chemotherapy to improve clinical outcomes in early and advanced settings across BC subtypes; such data culminated

recently in the first approval of a programmed death-ligand 1 (PD-L1) inhibitor, atezolizumab, coupled with single-agent chemotherapy for patients with newly diagnosed, programmed death-ligand 1-positive (PD-L1+; assessed in the immune-cell component of the disease) metastatic TNBC.[11] Preliminary clinical data from a Phase 2 adaptive-design neoadjuvant trial (I-SPY2) in participants with HER2- BC (ER+, HER2-, and TNBC cohorts) assessed an anti-PD-1 agent added to standard paclitaxel chemotherapy and demonstrated clinically meaningful improvements in pCR relative to historical controls.[12] These and other early clinical trials support currently ongoing Phase 3 neoadjuvant-adjuvant trials that are evaluating anti-PD-1 agents in the HER2- population.[18,19,20]

3.1.1 Research Hypothesis

The original research hypothesis was that the combination of nivolumab with anthracycline-taxane-based neoadjuvant chemotherapy followed by nivolumab with Investigator's choice adjuvant ET will increase pCR rate and/or prolong EFS in participants with newly diagnosed, high-risk, treatment-naive ER+, HER2- BC. As of Protocol Amendment 03, the new research hypothesis is that the addition of nivolumab to anthracycline-taxane-based neoadjuvant chemotherapy will increase the pCR rate.

3.1.2 Changes per Protocol Amendment 03

[redacted] On 07-Apr-2022, Bristol-Myers Squibb (BMS) informed sites and the steering committee of the decision to stop new enrollment into the CA2097FL study. The study steering committee was supportive of the decision. As of 07-Apr-2022, the following measures were put into effect:

- Enrollment of new participants is closed.
- Participants who had signed study consent prior to this decision and who were undergoing screening were permitted to be randomized to study treatment.
- Participants who are on treatment or in survival follow-up continued on the trial per protocol until Protocol Amendment 03 is approved by the relevant Health Authorities and Ethics Committees/Institutional Review Boards at the site.

Key changes in Protocol Amendment 03 include the following:

- Details of closure of study enrollment with provision for participants currently on treatment to continue in the study as per the current protocol.

- The primary endpoint of the trial will be focusing solely on pCR in the intent-to-treat (ITT) population. EFS will be evaluated as an exploratory endpoint. pCR in the programmed death-ligand 1-positive (PD-L1+) population will be evaluated as a secondary endpoint.
- The study will remain blinded through the Neoadjuvant treatment and Surgery phases and will transition to open label when participants enter into the Adjuvant treatment phase.
- Removal of nivolumab placebo infusions during the Adjuvant phase for participants in Arm B.
- Removal of PK and immunogenicity samples collection during the Adjuvant phase for participants in Arm B.
- The study will follow up participants until completion of safety follow-up phase and long-term follow-up 12 months (± 2 months) after surgery visit. The subsequent long-term follow-up visits are cancelled. For participants in follow-up at the time that Protocol Amendment 03 is approved, the final study visit will happen at the time of the next previously scheduled study visit.
- The study objectives, endpoints, and statistical analysis have been updated and clarified (refer to Table 4-1 for detail).

The changes instituted in Protocol Amendment 03 should override any existing protocol requirements in the event of any apparent discrepancies.

3.2 Background

3.2.1 ER+, HER2- Breast Cancer

ER+, HER2- disease is the most common BC subtype, occurring in ~70% of cases. BC ranks second as a cause of cancer-death in women after lung cancer.[21,22,23,24] An estimated 42,170 BC deaths (41,760 women) are expected in 2020 in the United States (US).

In clinical practice, BC tumors are classified by the expression status of estrogen receptor (ER), progesterone receptor (PgR), and HER2. The BC subtypes, identified on the basis of these receptors, have been reported to bear distinct gene expression profiles,[25,26] as well as different clinical behaviors, prognoses, and treatment vulnerabilities. Seventy percent of invasive BCs in women > 45 years of age express ER and/or PgR, but not HER2, and are termed hormone receptor-positive (HR+), HER2-.[22] Seminal studies performed with gene expression profiling (GEP) analysis of primary BC samples indicated that the tumors in the HR+, HER2- group are significantly enriched with cases showing high expression of genes related to the 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. Luminal A comprises 50-60% of all BC, showing higher dependence on ER signaling, slower proliferation rate, and an overall more indolent clinical course. Luminal B comprises 15-20% of all BC, showing lower dependence on ER signaling, higher proliferation rate, and overall, a more aggressive clinical course and worse prognosis compared with their Luminal A counterparts.[23] Patients with Luminal B disease are more likely to benefit from chemotherapy compared with the Luminal A subtype.[7]

ER+, HER2- BC is emerging as a continuing challenge to balance outcomes with treatment options. This BC subtype is generally associated with lower recurrence rates than other BC subtypes within the first 5 years after diagnosis and is associated with a good prognosis when diagnosed early and appropriately treated. However, despite the availability of both chemotherapy and ET options, the risk of recurrence persists over time in participants with ER+, HER2- BC, arguing for additional treatment strategies for an unmet need in this population.[24]

3.2.2 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 immunosurveillance 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 immunosurveillance and escape effective innate and adaptive immune responses.[27,28,29] 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).[30] 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).[31] 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.[32] 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 various 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 (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and programmed death-ligand 2 (PD-L2; 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 indicated 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 enhanced the anti-tumor immune response and resulted in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[33]

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab is provided in the current IB.[34]

3.2.3 Clinical Experience with Nivolumab

The overall clinical safety experience with nivolumab, as either monotherapy or in combination with other therapeutics, including cytotoxic chemotherapy, is based on experience in approximately 17,700 participants with different tumor types.[34] 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 (cHL), 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.[34]

In 39 participants with heavily pretreated, metastatic TNBC, nivolumab alone or in combination with ipilimumab were tolerable without additional safety signals detected in the CheckMate 32 study (unpublished data). In 66 participants with newly diagnosed or pretreated metastatic TNBC, nivolumab with or without various induction therapies, including different classes of low-dose cytotoxic chemotherapy (radiation therapy, cyclophosphamide, cisplatin, or doxorubicin) demonstrated objective response rates (ORRs) ranging from 17% without induction therapy to 35% with doxorubicin induction therapy (TONIC trial).[35] A number of clinical trials of nivolumab alone or in combination with other treatment modalities focused on participants with BC are currently ongoing.[36,37,38]

Details on the clinical safety and pharmacokinetic (PK) profile of nivolumab, including results from other clinical studies, are summarized in the nivolumab IB.[34]

3.2.4 Neoadjuvant Chemotherapy

Neoadjuvant (ie, preoperative) therapy is used increasingly in patients with primary BC to improve the likelihood of local tumor control, assess the treatment sensitivity of the disease in vivo, and increase the potential for curable disease by targeting earlier the micrometastatic disease burden.[1]

Neoadjuvant chemotherapy also enables anatomic down staging of the tumor and involved lymph nodes and may allow more conservative surgery of the breast and axilla. Furthermore, neoadjuvant chemotherapy facilitates research in identifying radiological, histological, and molecular predictors for response. Lastly, the neoadjuvant approach expedites the evaluation of new treatment strategies by using early surrogate endpoints, such as pCR.

The use of neoadjuvant therapy for BC has been studied in several large randomized trials that have compared neoadjuvant chemotherapy with standard adjuvant treatment.[39,40,41,42] The randomized studies evaluating neoadjuvant therapy, as well as meta-analyses of these studies, have shown that neoadjuvant therapy can improve breast conservation rates, decreasing the number of women needing to undergo mastectomy.[43,44] A meta-analysis of 9 randomized studies comparing adjuvant with neoadjuvant systemic therapy for BC showed no difference in rates of death, disease progression, or distant disease recurrence based upon the timing of the systemic therapy.[45] The aforementioned studies culminated in the neoadjuvant therapy being recommended in international guidelines for patients with high-risk/high-grade ER+, HER2- primary BC.

Neoadjuvant chemotherapy has been shown to be effective in primary BC. Robust meta-analyses of individual patient-level data from well-conducted clinical trials suggest that achieving a pCR is positively associated with improvement in EFS and OS; in particular, the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis evaluated 11,955 individuals with primary BC treated with neoadjuvant chemotherapy as part of clinical trials.[2] The results of this meta-analysis confirmed an association of pCR with favorable long-term outcomes in high-risk populations (ie, HER2+, high-grade HR+, and TNBC subtypes), although the magnitude of pCR improvement predictive of the long-term survival benefits could not be determined.[2,3,4] Further, use of the neoadjuvant platform permits rapid assessment of drug efficacy and may expedite clinical development of new agents in this setting. Agents that positively and substantially impact pCR rate may have a reasonable expectation of meaningful improvement in EFS.[5,6] This was exemplified in Sep-2013, when Food and Drug Administration (FDA) granted accelerated approval of pertuzumab, an anti-HER2 monoclonal antibody, as part of a complete treatment regimen for patients with HER2+, locally advanced, inflammatory, or early-stage BC in the neoadjuvant setting.

A number of established chemotherapy regimens have activity in the neoadjuvant setting, including the following:

- Dose-dense (Q2W) Adriamycin® (doxorubicin) or epirubicin + cyclophosphamide (ddAC), followed by paclitaxel weekly
- AC every 3 weeks (Q3W) followed by paclitaxel weekly (QW)
- AC followed by docetaxel Q3W
- AC Q3W
- Docetaxel + AC
- ddAC
- Cyclophosphamide + methotrexate + fluorouracil
- Epirubicin + cyclophosphamide
- Docetaxel + cyclophosphamide

According to the National Cancer Care Network (NCCN) Guidelines for BC,[8] regimens recommended in the adjuvant setting may also be used in the neoadjuvant setting. In both settings,

the underlying aim remains the same: eradication or control of undiscovered distant micrometastases. Preferred regimens include anthracycline- and taxane-based regimens in patients with high-risk, ER+, HER2- BC.

3.2.5 Background for Adjuvant Endocrine Therapy

The prognosis of patients with primary BC has vastly improved since the first adjuvant chemo-endocrine therapy trials in the 1970s. This treatment modality was designed originally to address the problem of distant disease relapse due to micrometastases, which, once clinically established, are the ultimate cause of death for the majority of patients with relapsed BC. Incremental improvements in outcomes were achieved through systematic therapeutic escalation, including the use of treatment regimens of longer duration, the integration of novel agents, or the inclusion of a higher number of agents, albeit at the cost of greater toxicity.[46]

Adjuvant ET, corresponding to systemic treatment blocking of ER signaling, is the cornerstone of systemic treatment of individuals with primary ER+, HER2- BC.[47] To date, numerous trials have established the survival benefit of adjuvant ET.[44,46,47] Extended treatment of 5-10 years with tamoxifen or an aromatase inhibitor (AI) with or without ovarian suppression is now recommended for most patients, based on results from several landmark trials;[48,49,50,51] these trials demonstrated a 15-20% relative reduction in the risk of recurrence, which translates to a 2-4% absolute improvement in disease-free survival (DFS) for average-risk participants included in these trials.[52] Further, among premenopausal women with early BC, the addition of ovarian suppression to tamoxifen resulted in significantly higher 8-year rates of DFS and OS than tamoxifen alone (83.2% vs 78.9%). The use of exemestane plus ovarian suppression resulted in even higher rates of DFS (85.9%).[52,53,54]

Since the adoption of adjuvant ET with tamoxifen and AIs (anastrozole, letrozole, and exemestane), current efforts now focus on how best to identify patients at risk for recurrence despite optimal adjuvant ET and how best to manage them. Current recommendations suggest that patients with ER+, HER2- primary BC who are at a higher risk of relapse occurrence (ie, higher grade, low levels of ER expression) receive treatment with chemotherapy followed by ET.

Recent data from the MonarchE study demonstrated benefit in terms of invasive disease‑free survival (iDFS) with the addition of adjuvant abemaciclib (an inhibitor of cyclin-dependent kinases 4 and 6 [CDK4/6i]) to endocrine treatment for high-risk HR-positive breast cancer patients. Abemaciclib plus ET demonstrated superior iDFS versus ET alone ($p = 0.01$; hazard ratio, 0.75; 95% CI, 0.60 to 0.93), with 2-year iDFS rates of 92.2% versus 88.7%, respectively. This led to the US FDA approval on 12-Oct-2021, of abemaciclib in combination with ET (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥ 20% as determined by an FDA-approved test.[55]

3.3 Benefit/Risk Assessment

Based on preclinical and clinical data, treatment of nivolumab in combination with anthracycline-taxane-based chemotherapy or in combination with 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 (see Section 5.4 [Scientific Rationale for Study Design]).

Participants in this study will be carefully monitored for key toxicities. Risks will be further minimized by adherence to inclusion and 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 9.2.1 [Immune-mediated Adverse Events], 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.

An Independent Data Monitoring Committee (IDMC; see Section 5.1.4.1 [Independent Data Monitoring Committee]) will be constituted and will monitor safety and efficacy as outlined in the protocol. A Study Steering Committee (SSC; see Section 5.1.4.2 [Study Steering Committee]) will be established, comprising of Investigators and Sponsor 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 respective IBs, Patient Information Leaflets, Package Inserts,[56,57,58,59,60,61,62,63,64] Development Safety Update Reports, or Summaries of Product Characteristics (SmPCs).[65,66,67,68,69,70,71,72,73]

Due to the need to develop improved therapies to improve pCR rates and/or prolong EFS or OS in ER+, HER2- BC, and on the basis of the clinical and nonclinical data in support of the current study, the benefit-risk profile of nivolumab in combination with anthracycline-taxane-based chemotherapy or in combination with ET in newly diagnosed, treatment-naive, high-risk ER+, HER2- primary BC is favorable for proceeding with the proposed randomized Phase 3 clinical trial.

Starting in Oct-2021, abemaciclib has been approved as an adjuvant treatment in several countries and it is expected that some participants may want to receive adjuvant abemaciclib if/when it is available. As of Protocol Amendment 03, participants will be unblinded to treatment assignment in the Adjuvant phase to enable treatment decision making. The primary endpoint has been amended to focus solely on pCR after neoadjuvant treatment, and EFS has been changed to an exploratory endpoint.

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 (MTD) reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few

related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-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.

See Sections 6.2, 6.4.1, and 7.4.1 for specific severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) risk mitigation recommendations.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.[34]

3.3.2 Anthracycline-Taxane-Based Chemotherapy Safety Profile

Overall, the safety profiles of anthracycline-taxane-based chemotherapy are manageable and generally consistent across completed and ongoing trials.[74]

Extensive details on the safety profiles of doxorubicin, epirubicin, cyclophosphamide, and paclitaxel are available in the respective Patient Information Leaflets, Package Inserts,[57,58,59,60] or SmPCs.[66,67,68,69]

3.3.3 Endocrine Therapy Safety Profile

Overall, the safety profiles of tamoxifen and the AIs used in this study are manageable and generally consistent across completed and ongoing trials.[52,53,54]

Extensive details on the safety profiles of tamoxifen and the AIs (anastrozole, letrozole, and exemestane) are available in the respective Patient Information Leaflets, Package Inserts,[61,62,63,64] or SmPCs.[70,71,72,73,75,76]

3.3.4 Nivolumab and Anthracycline-Taxane-Based Chemotherapy Combination Safety Profile

The safety profile of nivolumab is well characterized and manageable when administered alone or in combination with chemotherapy, targeted agents, as well as additional immuno-oncology (IO) products across many tumor types. In particular, several clinical trials have assessed neoadjuvant chemotherapy plus checkpoint inhibition combination approaches for participants with primary BC. Relevant safety data from such studies are given below.

In a Phase 2 adaptive-design neoadjuvant trial (I-SPY2), 69 participants with primary HER2- (ER+ and TNBC) BC were randomized to pembrolizumab, a PD-1 inhibitor, given as 200 mg Q3W plus weekly paclitaxel, followed by anthracycline + cyclophosphamide (AC; every 2 weeks [Q2W] or Q3W) without pembrolizumab. A total of 46 participants underwent surgery as of Nov-2016. In the TNBC cohort (n = 29), pembrolizumab increased the raw and estimated pCR rates by > 50% and 40%, respectively. In the ER+, HER2- cohort (n = 40), the raw and estimated pCR rates increased by 13% and 21%, respectively. Five participants had immune-related Grade 3 AEs, including hypophysitis (n = 1) and adrenal insufficiency (n = 4). Of these, 4 participants presented

with the AE after completing the AC treatment (149-179 days after pembrolizumab was initiated); 1 participant presented prior to the AC treatment (37 days after pembrolizumab was initiated). Seven participants had Grade 1 to 2 thyroid abnormalities reported. Overall, the safety profile of pembrolizumab was consistent with that observed in previously reported studies across tumors. However, adrenal insufficiency was observed at a higher rate than previously reported in advanced cancer. Resolution of symptoms of adrenal insufficiency with use of replacement therapy was reported.[12]

In the Phase 1b KEYNOTE-173 study, pembrolizumab was combined with neoadjuvant treatment consisting of weekly nab-paclitaxel (with or without carboplatin area under the curve [AUC]6 Q3W), followed by 4 cycles of AC Q3W in 20 participants with TNBC. In the nab-paclitaxel cohort, the pCR rate in breast and nodes (ypT0/Tis ypN0) was 60% (n = 10) and 90% (n = 10) in participants receiving carboplatin plus nab-paclitaxel. Dose-limiting toxicities (DLTs) of myelosuppression occurred in 7 participants and were unrelated to pembrolizumab. Grade 3/4 treatment-related AEs occurred in 8 participants in the nab-paclitaxel cohort and in 10 participants in the nab-paclitaxel-carboplatin cohort, of which, none were fatal. Three participants discontinued for a treatment-related AE (alanine aminotransferase [ALT] elevations with pembrolizumab, n = 2; deep vein thrombosis with chemotherapy, n = 1). No DLT was attributed to pembrolizumab.[10] In a recent update in 60 participants evaluating 6 treatment cohorts assessing either nab-paclitaxel or paclitaxel with or without carboplatin,[77] 22 (36.7%) participants had a DLT. Most DLTs were Grade 3 or 4, with neutropenia the most commonly reported (n = 9). One DLT was Grade 5 (septic shock), occurring in a nab-paclitaxel-carboplatin arm. Grade ≥ 3 treatment-related AEs were reported in 54 (90%) participants. Grade 3/4 treatment-related AEs were neutropenia (73%), febrile neutropenia (22%), anemia (20%), and thrombocytopenia (8%). Eighteen participants (30%) had immune-mediated AEs (IMAEs; Grade 2 hypothyroidism, n = 4; Grade 1 hyperthyroidism, n = 3; Grade 3 colitis, n = 2; and Grade 3 rash, n = 2). Eleven participants discontinued pembrolizumab due to treatment-related AEs. As expected, toxicity was higher in the carboplatin groups.

The combination of neoadjuvant chemotherapy with PD-L1 inhibition has been assessed in GeparNuevo, a randomized, Phase 2 neoadjuvant study; a total of 174 participants with primary TNBC were randomized to receive neoadjuvant nab-paclitaxel, followed by epirubicin/cyclophosphamide chemotherapy with or without durvalumab, a PD-L1 inhibitor. A numerically higher, but statistically non-significant increase in pCR (44.2% vs 53.4%, odds ratio [OR] 1.53; p = 0.182) was reported. The addition of durvalumab to neoadjuvant chemotherapy was well tolerated. All received growth factor support during epirubicin/cyclophosphamide treatment. Grade 3/4 hematologic AEs were similar in the 2 groups and included anemia (2.2% vs 2.4%), neutropenia (37.1% vs 41.5%), thrombocytopenia (1.1% vs 2.4%), and febrile neutropenia (4.3% vs 2.4%) in the durvalumab and control arms, respectively. Immune-related AEs were higher in the durvalumab arm and included hypothyroidism (6.5% vs 2.4%) and hyperthyroidism (7.6% vs 0%), in the durvalumab and control arms, respectively.[16]

In the Phase 3, randomized (2:1), placebo-controlled, KEYNOTE 522 study, pembrolizumab (200 mg Q3W) was combined with paclitaxel (80 mg/m^2 QW) and carboplatin (AUC 5 Q3W or AUC 1.5 QW) followed by anthracycline (doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2)-cyclophosphamide (600 mg/m^2) neoadjuvant chemotherapy (8 cycles) and adjuvant pembrolizumab (200 mg Q3W for 9 cycles) in patients with untreated, primary TNBC.[78] The addition of pembrolizumab to platinum-containing neoadjuvant chemotherapy resulted in a statistically significant and clinically meaningful absolute increase in pCR (ypT0/Tis ypN0) of 13.6 percentage points (64.8% vs 51.2%, p = 0.00055). A consistent benefit also was observed with pCR defined as ypT0 ypN0 and ypT0/Tis. The benefit of pembrolizumab was independent of PD-L1 status using the combined positive score (CPS) method of assessment. Preliminary, early data suggest there was a favorable trend for EFS in the pembrolizumab arm (HR = 0.63 [95% CI, 0.43-0.93]). Safety was consistent with the known profiles of each regimen albeit with only 9% of the total number of targeted EFS events. Dose-intensity, characterized by the mean number of doses administered and mean treatment duration, was similar across the treatment groups. Across neoadjuvant and adjuvant phases, Grade 3 or higher treatment-related AE rates were 78.0% in the pembrolizumab-chemotherapy group and 73.0% in the chemotherapy alone group, and the incidence of death was 0.4% vs 0.3%, respectively.[78]

The above studies suggest that the combination of anti-PD-(L)1 and SOC neoadjuvant multi-regimen chemotherapy is feasible in patients with primary BC. Thus, the ***potential benefit of combination therapy appears to outweigh the known risks of these agents and warrants clinical investigation.***

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of the study treatments may be found in the respective IBs, Patient Information Leaflets, Package Inserts,[56,57,58,59,60] Development Safety Update Report, or SmPCs.[65,66,67,68,69]

3.3.5 Nivolumab and Endocrine Therapy Combination Safety Profile

The safety profile of nivolumab is well characterized and manageable when administered alone or in combination with chemotherapy, targeted agents, as well as additional IO products. Similarly, extensive clinical trials have established the efficacy and safety of ET in participants with BC. The agents used for standard ET have extensive, established safety databases in this setting. No data are available evaluating the combination of nivolumab and ET (eg, tamoxifen, AIs).

One of the initial BC studies assessing checkpoint inhibitors was a Phase 1 study of tremelimumab, an anti-CTLA-4 antibody, combined with exemestane, in 26 women with heavily pretreated ER+ metastatic BC.[79] Most treatment-related AEs were mild to moderate (Grade 1 or 2) in nature. The most common events included diarrhea (46%), pruritus (42%), constipation (23%), and fatigue (23%). DLTs were transient serum transaminase elevations (n = 1) and diarrhea (n = 4). The MTD of tremelimumab with exemestane was 6 mg/kg every 90 days, which was lower than in other tremelimumab trials. Among 13 participants treated at the MTD, none developed Grade 3 or Grade 4 treatment-related diarrhea. No PK interaction was observed between tremelimumab and exemestane. At the time of the trial, algorithm-based management of immune-related

diarrhea/colitis was not yet available nor implemented in the trial; however, it cannot be ruled out that diarrhea may have been exacerbated by the combination. With regard to anti-tumor activity, no objective responses were noted; however 11 of the 26 participants experienced stable disease, including 4 participants who previously progressed on exemestane. Evidence of T-cell activation was reported in the periphery, as measured by ICOS expression. Treatment was associated with T-cell activation, as revealed by an increase in ICOS-expressing T cells in blood and a marked increase in the ratio of ICOS-positive T cells to FoxP3-positive regulatory T cells (Tregs).[79,80] Several ongoing studies are evaluating different endocrine agents in combination with checkpoint inhibitors.[81,82]

Recent data from the MonarchE study demonstrated benefit in terms of iDFS with the addition of adjuvant abemaciclib to ET for high-risk HR-positive breast cancer. However, the combination of pembrolizumab (anti-PD-1) with abemaciclib (CDK4/6 inhibitor) was demonstrated to be not feasible because of dose-limiting toxicities. Concurrent administration of abemaciclib to pembrolizumab caused an increased incidence of pneumonitis/interstitial lung disease and increased rates of Grade 3-4 liver enzyme elevations.[83,84,85] The incidence was above that which would be expected with either agent alone. Three treatment-related deaths associated with pneumonitis occurred.[84,85] Increased toxicity rates were also observed in CheckMate-7A8 testing the combination of nivolumab plus palbociclib, the same class of drug (CDK4/6i) as abemaciclib.[86] Based on the findings, it does not appear that anti-PD-1 and CDK4/6 inhibitors can be safely combined due to increased risk of hepatic and lung toxicities.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of the study treatments may be found in the respective IBs,[34] Patient Information Leaflets, Package Inserts,[56,61,62,63,64] Development Safety Update Report, or SmPCs.[65,70,71,72,73]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare efficacy of nivolumab plus chemotherapy vs nivolumab placebo plus chemotherapy as neoadjuvant treatment in terms of the absence of residual tumor disease in participants with untreated, high-risk ER+, HER2- BC.	• pCR, defined as no invasive residual disease in breast and lymph nodes (ie, ypT0/is, ypN0) by a local pathologist (ITT population).
Key Secondary	
• To compare efficacy of nivolumab plus chemotherapy vs nivolumab placebo plus chemotherapy as neoadjuvant treatment in terms of the absence of residual tumor disease in participants with untreated, high-risk ER+, HER2-BC in the PD-L1+ subgroup.	• pCR, defined as no invasive residual disease in breast and lymph nodes (ie, ypT0/is, ypN0) by a local pathologist (PD-L1+ population).
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy in terms of RCB.	• RCB class (0, I, II, III) frequency, for RCB assessed by a local pathologist in ITT and PD-L1+ populations.
• To evaluate the safety and tolerability of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy.	• Incidence of AEs, drug-related AEs, AEs leading to discontinuation, and SAEs as defined by NCI CTCAE v5.0. • Incidence of deaths.
Key Tertiary/Exploratory	
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy in terms of pCR by alternative definitions.	• pCR, defined as no invasive or in situ residual disease in breast and lymph nodes (ie, ypT0 ypN0) by a local pathologist in ITT and PD-L1+ populations. • pCR, defined as no invasive residual disease in the breast irrespective of in situ or nodal involvement (ypT0/is) by a local pathologist in ITT and PD-L1+ populations.
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy in terms of ORR by investigator.	• ORR, defined as investigator-assessed tumor response rate per radiologic-based assessment (RECIST v1.1) in the Neoadjuvant (Pre-surgery) Phase in ITT and PD-L1+ populations.
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy and adjuvant ET in terms of EFS, survival, DFS, and DMFS.	• EFS in ITT population • OS in ITT population. • DFS in ITT population. • DMFS in ITT population.
• To characterize the PK and IMG of nivolumab when administered in combination with neoadjuvant chemotherapy.	• Nivolumab PK and IMG parameters.
• To characterize the PK and IMG of nivolumab when administered in combination with adjuvant ET.	• Nivolumab PK and IMG parameters.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To assess the efficacy of nivolumab and nivolumab placebo in combination with neoadjuvant chemotherapy and adjuvant ET in subgroups based on PD-L1 expression by IHC 28-8 CPS.	• Clinical efficacy endpoints (eg, pCR, RCB, ORR) by PD-L1 expression using PD-L1 IHC 28-8 CPS.
[redacted]	
• To assess cancer-specific symptoms and QOL domains across treatment groups.	• Mean EORTC QLQ-C30 and QLQ-BR23 subscale scores and post-baseline score changes.
• To assess perceptions of the overall bothersomeness of symptomatic AEs.	• Mean FACIT GP5 item scores and post-baseline score changes.
• To evaluate perceived general health status and utility between treatment groups.	• Mean EQ-5D-5L VAS and utility index scores and post-baseline score changes.
[redacted]	

Abbreviations: AE, adverse event; BC, breast cancer; CPS, combined positive score; CTCAE, Common Terminology Criteria for Adverse Events; DFS, disease-free survival; DMFS, distant metastasis-free survival; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, 5-Level EQ-5D; ER+, estrogen receptor-positive; ET, endocrine therapy; FACIT GP5, Functional Assessment of Chronic Illness Treatment General Physical Item 5; HER2-, human epidermal growth factor receptor 2; IgG, immunoglobulin G; IHC, immunohistochemistry assay; IMG, immunogenicity; ITT, intent to treat; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PD-L1+, programmed death-ligand 1-positive; PK, pharmacokinetic; QLQ-BR23, Quality of Life Questionnaire-Breast Cancer-specific Module; QLQ-C30, Quality of Life Questionnaire-Core 30; QOL, quality of life; RCB, residual cancer burden; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; VAS, visual analog scale; vs, versus.

5 STUDY DESIGN

5.1 Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter, global Phase 3 study. The study is designed to evaluate nivolumab vs nivolumab placebo in combination with neoadjuvant chemotherapy and adjuvant ET in newly diagnosed, treatment-naive participants with high-risk ER+, HER2- BC. High-risk disease is defined as a participant having either Grade 3 disease or having Grade 2 disease with low ER expression of 1-10%. Participants must have histologically confirmed invasive ductal breast carcinoma meeting the characteristics described in Section 6.1 (Inclusion Criteria).

The study is divided into 3 periods: Screening Period, Treatment Period (Neoadjuvant [Pre-surgery] Phase, Surgery, and Adjuvant [Post-surgery] Phase), and Follow-up Period. Following the confirmation of eligibility, participants will be randomized to either Arm A or Arm B in a 1:1 ratio.

The Treatment Period will consist of the following phases:

- Neoadjuvant (Pre-surgery) Phase: maximum of 8 cycles
  - Paclitaxel (PTX) Cycles 1-4 (1 cycle = Q3W): nivolumab or nivolumab placebo + weekly paclitaxel

    Followed by
  - Anthracycline-Cyclophosphamide (AC) Cycles 1-4 (1 cycle = every 2 weeks [Q2W] or 1 cycle = Q3W [dosing frequency to be determined by the Investigator]): nivolumab or nivolumab placebo + AC cycles 1-4 (1 cycle = Q2W or 1 cycle = Q3W).
- Surgery
- Adjuvant (Post-surgery) Phase: maximum of 7 cycles
  - Adjuvant Cycles 1-7 (1 cycle = every 4 weeks [Q4W]): nivolumab + ET or ET alone (per Protocol Amendment 03)

Treatment will start with the Neoadjuvant (Pre-surgery) Phase, in which participants will be randomized to receive an intended 4 cycles of nivolumab or nivolumab placebo in combination with weekly paclitaxel, **followed by** an intended 4 cycles of nivolumab or nivolumab placebo in combination with anthracycline (doxorubicin or epirubicin) + cyclophosphamide. Following completion of the Neoadjuvant (Pre-surgery) Phase of treatment, participants who remain operative candidates will undergo surgery of the breast and axilla (per local standards) within 4 weeks. In cases when surgery does not occur within 4 weeks, surgery is permitted at a later date. The investigator must document the reason for delay of surgery in the CRF and the medical record.

Participants will return to the site within 7-14 days following surgery to begin their Adjuvant (Post-surgery) Phase of treatment, consisting of a maximum of 7 cycles of nivolumab with Investigator's choice of ET or ET alone (per Protocol Amendment 03). The post-surgery visit and the first cycle of adjuvant treatment may be combined if adjuvant treatment starts within 7-14 days after the breast cancer surgery.

As of Protocol Amendment 03, the Adjuvant phase will be converted to open label, and participants will be unblinded when they reach the Adjuvant phase of the study. Participants already on adjuvant treatment or in follow-up when Protocol Amendment 03 is approved will also be unblinded. No crossover to adjuvant nivolumab will be allowed for participants enrolled in Arm B. Adjuvant systemic therapy should be started no later than 6 weeks following Surgery in participants not receiving radiotherapy (RT). In participants receiving RT, adjuvant systemic therapy may start at the same time as RT or no later than 1 to 2 weeks after completion of RT per local standards. Starting adjuvant systemic therapy for a few adjuvant cycles then stopping or pausing therapy to administer RT then restarting adjuvant systemic therapy for remaining adjuvant cycles will not be permitted.

Randomized participants in the study will be stratified by the following factors:

1) PD-L1 on immune cells (≥ 1% or < 1%);
2) Tumor grade (2 or 3);
3) Axillary nodal status (pathological review positive versus radiographic and/or pathologic review negative) and
4) AC dose-frequency chemotherapy regimen (Q2W or Q3W).

PD-L1 status, used for stratification, is determined by qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 on the proportion of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells (% IC) of any intensity.

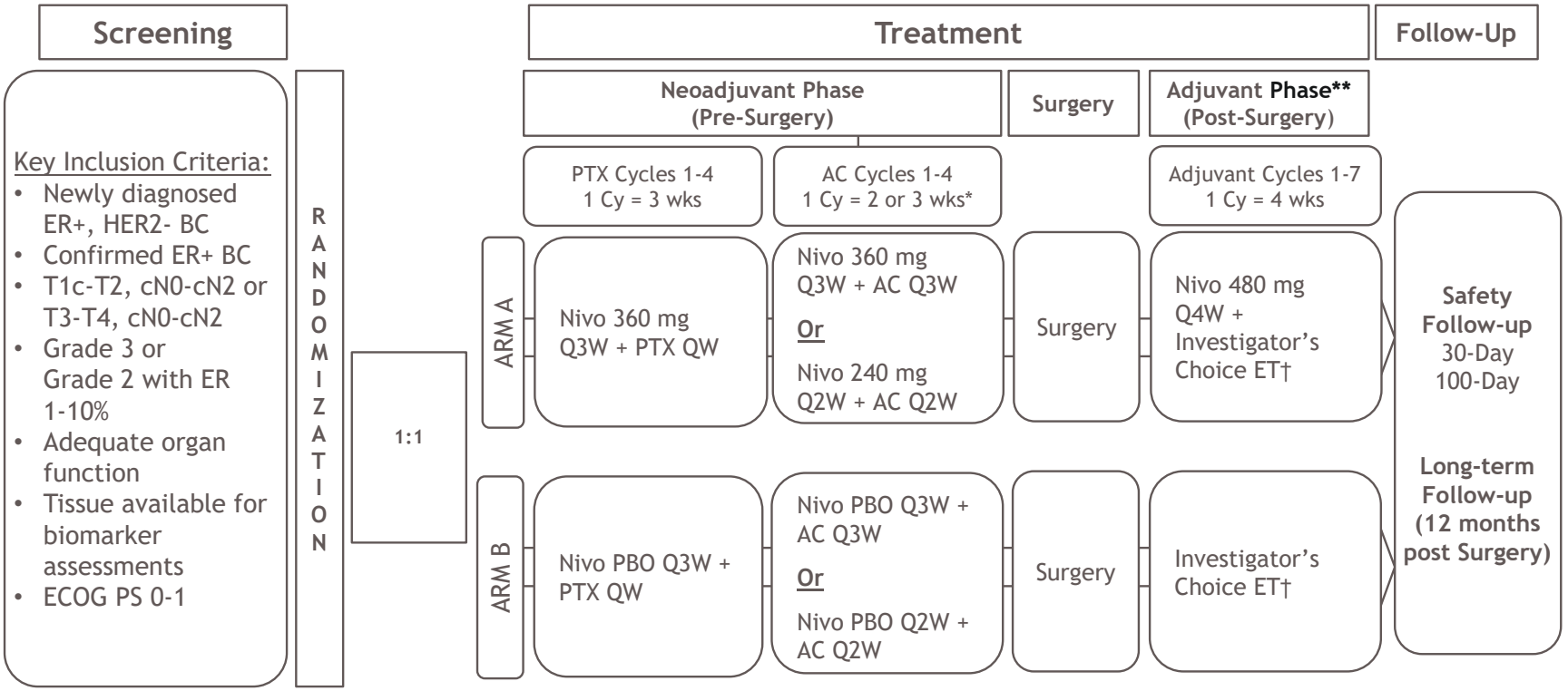
Clinical outcomes assessments (COAs) will be assessed throughout the study at the timepoints defined in the Schedule of Activities (Section 2).

Safety Follow-up Visits will occur per Table 2-5, after the last Adjuvant (Post-surgery) Phase treatment. As of Protocol Amendment 03, the Long-term Follow-up visit will occur 12 months (± 2 months) following surgery per Table 2-5. The Long-term Follow-up visit will be the final visit of the study. For participants in follow-up at the time of Protocol Amendment 03, the final study visit will happen at the time of the next previously scheduled study visit under Protocol Amendment 02 (see Table 2-5).

The total duration of the study is approximately 4 years from randomization of the first participant. The study may be terminated at any time by the Sponsor. See Section 5.1.3 (Follow-up Period) and Section 8.1 (Discontinuation from Study Treatment) for additional details.

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

Figure 5.1-1: Study Design Schematic



*Investigator's choice anthracycline; dosing frequency of Q2W or Q3W for AC cycles determined by the Investigator.
†Available ET agents include tamoxifen, anastrozole, letrozole, and exemestane.
Abbreviations: AC = anthracycline + cyclophosphamide; BC = breast cancer; Cy = cycle; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = endocrine therapy; IC = immune cells; PBO = placebo; PTX = paclitaxel; Q2W = every 2 weeks; Q3W = every 3 weeks; QW = every week
**In Adjuvant phase, the study treatment will be open-label. Participants in Arm B will not receive Nivo PBO infusion

5.1.1 Screening Period

As of 07-Apr-2022, new participant enrollment to this study is closed.

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 enrolled into Interactive Response Technology (IRT) and then be evaluated for eligibility. The screening assessments are shown in Table 2-1.

Documentation of the participant's menopausal status at screening/baseline is required for women only, following the definitions provided below:

- Premenopausal status is defined as < 12 months since last menstrual period and no prior bilateral ovariectomy and not receiving estrogen replacement, or biochemical evidence of premenopausal status, according to local standards.
- Post-menopausal status is defined as ≥ 12 consecutive months since last menstrual period in a woman over age 45 years (with no identified cause other than menopause), prior bilateral oophorectomy, age < 55 years and amenorrheic for 12 or more consecutive months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) > 40 mIU/mL and estradiol in the post-menopausal range.[8]

Participants must provide a pretreatment (baseline) primary tumor tissue sample meeting eligibility requirements as described in Section 6.1 (Inclusion Criteria). The tumor biopsy will be submitted to the central laboratory with a pathology report for determining PD-L1 and ER status as well as ER expression level. [redacted]. Participants should not have received any local or systemic anticancer therapy before or after the date that the submitted tumor tissue was obtained.

Prior to randomization, PD-L1, ER status and ER expression level percentage, disease grade, axillary nodal status, and AC frequency must be available in IRT. Participants with a PD-L1, ER, or HER2 status of unknown/not evaluable are not eligible (see Section 6.1 [Inclusion Criteria]). Treatment should begin within 3 calendar days following randomization.

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). If re-enrolled, the participant must be re-consented.

5.1.2 Treatment Period

Schedules of on-treatment visits and assessments for the Neoadjuvant (Pre-surgery) Phase and Adjuvant (Post-surgery) Phase are provided in Table 2-2, Table 2-3, and Table 2-4.

5.1.2.1 Neoadjuvant (Pre-surgery) Phase

Following confirmation of eligibility, participants will be randomized to receive nivolumab or nivolumab placebo administered in combination with weekly paclitaxel chemotherapy for maximum 4 cycles (Paclitaxel Cycles 1-4; 1 cycle = 3 weeks). This will be followed by nivolumab

or nivolumab placebo in combination with anthracycline (doxorubicin or epirubicin) + cyclophosphamide chemotherapy for a maximum of 4 additional cycles (AC Cycles 1-4; 1 cycle = 2 weeks or 3 weeks); the dose frequency will be selected by the treating physician prior to randomization and entered in IRT. Participants will be informed of their scheduled surgery prior to the completion of the Neoadjuvant (Pre-surgery) Phase.

Dose reduction will not be allowed for nivolumab. Some participants may not receive all 8 cycles of planned neoadjuvant therapy (eg, toxicity, refusal to receive further therapy). However, participants should receive as much of the planned neoadjuvant therapy as possible. Such treatment decisions will be at the discretion of the Investigator and participant.

Additional guidance is given below regarding potential study conduct scenarios that may occur for some participants during the course of the Neoadjuvant Phase:

- If a participant discontinues nivolumab or nivolumab placebo study treatment during the Neoadjuvant Phase and continues with chemotherapy study treatment, the participant may continue on-study, to receive surgery, and transition to the Adjuvant phase to receive endocrine therapy and nivolumab or ET study treatment alone (per Protocol Amendment 03), unless consent is withdrawn and/or medical conditions necessitate the participant to discontinue study treatment. See Section 7 (Treatment) for additional details.
- If a participant discontinues paclitaxel during the Neoadjuvant Phase, the participant may continue on-study to receive neoadjuvant AC and nivolumab or nivolumab placebo study treatment or may transition to the Adjuvant Phase, after Surgery, to receive endocrine therapy and nivolumab or ET study treatment alone (per Protocol Amendment 03) at an earlier timepoint, unless consent is withdrawn and/or medical conditions necessitate the participant to discontinue the study treatment. See Section 7 (Treatment) for additional details.
- If a participant discontinues the AC treatment during the Neoadjuvant Phase, nivolumab or nivolumab placebo must also be discontinued and the participant may continue on study to receive Surgery and transition to the Adjuvant Phase to receive endocrine therapy and nivolumab or ET study treatment alone (per Protocol Amendment 03), unless consent is withdrawn and/or medical conditions necessitate the participant to discontinue study treatment.
- If chemotherapy is delayed, nivolumab or nivolumab placebo is also delayed. Nivolumab or nivolumab placebo can resume within 3 days of the scheduled chemotherapy dose if chemotherapy re-treatment criteria are met.

If participant has worsening of disease or disease progression during the Neoadjuvant Phase that precludes definitive surgery or results in metastatic disease the event is recorded as an EFS event, and the participant continues in the follow-up period. See Section 5.1.3 (Follow-up Period).

Participants who discontinue study treatment must continue to be followed in this study for collection of outcome and/or survival follow-up data, as required and in line with Section 5 (Study Design), until death, withdrawal of consent, or the conclusion of the study.

5.1.2.2 Surgery

Following the completion of the neoadjuvant treatment phase (completion of paclitaxel cycles 1-4, 1 cycle = 3 weeks and AC cycles 1-4, 1 cycle = Q2W or Q3W), all participants who remain

operative candidates will undergo surgery of the breast and axilla (per local standards) within 4 weeks of the completion of the neoadjuvant treatment phase (ie, 6-7 weeks after last neoadjuvant dose depending on AC treatment schedule).

In cases when surgery does not occur within 4 weeks of the completion of the neoadjuvant treatment phase, surgery is permitted at a later date. The investigator must document the reason for the delay of surgery in the eCRF and the medical record.

For participants who undergo BCS, the margins of the resected surgical specimen must be histologically free of invasive tumor as well as ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed at the discretion of the treating physician to obtain clear margins. If tumor is still present at the resected margin after potential subsequent re-excision(s), the participant must undergo total mastectomy to be eligible for the Adjuvant (Post-surgery) Phase. Participants with margins positive for lobular carcinoma in situ (LCIS) are eligible for the Adjuvant Phase without additional resection.

For participants who undergo mastectomy (and/or nipple- or skin-sparing mastectomy), margins must be free of gross residual tumor. It is recommended that participants should have a negative microscopic margin in accordance with local pathology protocol. Participants with a microscopic positive deep margin are eligible for the Adjuvant Phase. Information on the type of surgery performed and reason why different from the planned surgery at baseline will be collected and recorded in the eCRF and in the patient medical record.

Surgery specimens will be collected for histological examination of pCR, as well as other pathology parameters and endpoint analyses, as outlined in Section 4 (Objectives and Endpoints). For additional details, please refer to the Pathology Manual.

5.1.2.3 Radiotherapy

Post-operative RT is required if breast-conserving surgery (BCS) is performed, per international guidelines and/or local standards. In the event of mastectomy, administration of adjuvant RT should follow local clinical practice.

In participants receiving RT, adjuvant systemic therapy (nivolumab + endocrine therapy [ET] or ET alone [per Protocol Amendment 03]) may start:

1) Any time from the post-surgery visit or
2) At the same time as RT or
3) During RT or
4) Within 1 to 2 weeks of completion of RT per local standards.

Note: Starting adjuvant systemic therapy, then stopping or pausing to administer RT, and then restarting adjuvant systemic therapy for remaining adjuvant cycles will not be permitted.

In participants not receiving RT, adjuvant systemic therapy should be started no later than 6 weeks following surgery.

In cases of BCS, breast RT after complete local excision is mandatory. Breast RT may be contraindicated in participants with significant comorbidity (for example, scleroderma and systemic lupus erythematosus). Reasons for not delivering breast RT after complete local excision of the primary breast cancer should be discussed with the Medical Monitor (or designee) and documented in the eCRF.

Recommendations for post-surgical RT are described in Appendix 7 (Radiotherapy Guidelines).

5.1.2.4 Adjuvant (Post-surgery) Phase

Participants will return to the clinic within 7-14 days following Surgery for a post-surgical visit. The post-surgery visit and the first cycle of adjuvant treatment may be combined if adjuvant treatment starts within 7-14 days after the breast cancer surgery.

Documentation of the participant's menopausal status at the post-surgical visit for participants who were premenopausal at baseline is required, following the definition provided below:

- Premenopausal status is defined as < 12 months since last menstrual period and no prior bilateral ovariectomy and not receiving estrogen replacement, or biochemical evidence of premenopausal status, according to local standards.[8]

As of Protocol Amendment 03, treatment in the Adjuvant phase will be open label; participants will be treated according to their unblinded randomized treatment assignment. No crossover is allowed per protocol.

Adjuvant (Post-surgery) Phase of treatment will begin with the administration of nivolumab in combination with Investigator's choice ET (Arm A) or Investigator's choice ET only (Arm B) for a maximum of 7 cycles (Cycles 1 to 7; 1 cycle = 4 weeks), except in the event of disease recurrence or progression, withdrawal of consent, death, unacceptable toxicity, or symptomatic deterioration. Participants who discontinue study treatment for reasons other than death or withdrawal of consent will proceed to the Follow-Up Period of the study.

Besides the ET (Arm B) and ET in combination with nivolumab (Arm A), no further adjuvant treatment (chemotherapy, iCDK4/6 inhibitor, or any drug administered with the intent of treating the cancer) is allowed in the Adjuvant Phase, irrespective of the pCR outcome of the surgery.

The selected ET may be rotated, changed, or switched to another ET (ie, from tamoxifen to an AI, from an AI to tamoxifen, from AI to another AI) during the study at the discretion of the Investigator. Ovarian function suppression (chemical or surgical) is allowed to be used with ET. The respective change should be clearly recorded in the source documents.

5.1.3 Follow-up Period

5.1.3.1 Safety Follow-up Visits

There will be 2 in-person safety follow-up visits. Follow-up visit 1 (FU1) will occur 30 days (± 7 days) from the last dose of the study treatment. Follow-up visit 2 (FU2) will occur approximately 100 days (± 7 days) from the last dose of study treatment. Study treatments are defined in Table 7-1.

5.1.3.2 Long-term Follow-up Visit

As of Protocol Amendment 03, there will be a single Long-term Follow-up Visit at 12 months post-surgery (± 2 months). For participants in follow-up at the time that Protocol Amendment 03 is approved, the final study visit will happen at the time of the next previously scheduled study visit and should consist of the study procedures outlined in the Long-term Follow-up Visit (see Table 2-5). If a participant requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the Investigator. If the participant withdraws from study, the study staff may use a public information source (eg, county records) to obtain information about survival status only.

5.1.4 External Committees

5.1.4.1 Independent Data Monitoring Committee

An IDMC will provide oversight of safety and efficacy considerations in protocol CA2097FL and provide advice to the Sponsor regarding actions the committee deems necessary for the continued protection of participants enrolled in the study. The IDMC will be charged with assessing such actions in light of an acceptable benefit-risk profile.

The IDMC will act in an advisory capacity to the Sponsor, monitor participant safety, and evaluate the available efficacy data for the study. The oncology therapeutic area of the Sponsor has primary responsibility and decision-making authority for the design and conduct of the study, as well as any protocol-related aspects.

The IDMC will hold regular meetings to evaluate the ongoing benefit-risk of the trial, including data internal and external to the trial. The IDMC will meet to review all available data (safety and efficacy) at each meeting, to be held approximately every 6 months, or more frequently, as needed. At the conclusion of each IDMC meeting, the committee will provide the Sponsor with a recommendation to continue, modify, or terminate the study protocol based upon their review. Ultimately, decisions regarding the study protocol will be made by the Sponsor in conjunction with feedback from the Investigators and IDMC.

When required, adjudicated events will be submitted to the IDMC and Health Authorities for review on a specified timeframe, in accordance with the adjudication documentation.

Additional details concerning IDMC oversight are provided in the IDMC charter.

5.1.4.2 Study Steering Committee

A SSC, consisting of Investigators and personnel members representing the Sponsor of the study, will be established to obtain scientific guidance and advice for 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

As of 07-Apr-2022, enrollment for new participants was closed. As of 16-May-2022, the number of participants screened was 831 and the number of participants randomized was 521.

5.3 End of Study Definition

The start of the trial is defined as the first participant screened. The end of the trial is defined as the last participant's last study visit. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Choice of Patient Population

Participants with newly diagnosed, treatment-naive, high-risk, histologically proven ER+, HER2- primary BC, who are eligible for neoadjuvant chemotherapy, will be included in this study population. Despite the availability of cytotoxic chemotherapy, as well as ET in this setting, relapses occur for a not insignificant proportion of patients with high-risk ER+, HER2- BC. Furthermore, due to the lower pCR typically achieved compared with other BC subtypes, there remains an unmet medical need in this patient population.

ER+, HER2- disease is the most common BC subtype occurring in ~70% of BC cases and most BC deaths occur in ER+ patients.[22,23,24] ER+ cancer is emerging as a continuing challenge to balance outcomes with treatment options. This BC subtype is generally associated with lower recurrence rates than other BC subtypes within the first 5 years after diagnosis and is associated with a good prognosis when diagnosed early and appropriately treated. However, despite the availability of both chemotherapy and ET options, the risk of recurrence persists over time within this patient population, arguing for additional treatment strategies for an unmet need in this population.[24]

The ER+, HER2- population is a heterogeneous BC subtype. There is a subgroup of patients with high-risk clinicopathologic features and a poorer prognosis that is characteristic of the so-called Luminal B molecular subtype, which was identified by GEP analysis studies.[87,88] ER+, HER2- tumors that are high-grade have higher measures of proliferation and lower levels of ER and PgR expression tend to be less sensitive to ET and more likely to benefit from chemotherapy, compared to their counterparts falling under the so-called Luminal A subtype,[7] but patients still recur despite treatment. The current study will assess the combination of nivolumab and anthracycline-taxane-based chemotherapy and nivolumab combined with SOC ET in this patient population.

Patients with newly diagnosed, non-metastatic, high-risk ER+, HER2- BC represent an important unmet need. Their risk of disease relapse is high, especially in those who do not obtain a pCR after their neoadjuvant chemotherapy. In contrast, those who do achieve pCR have a better prognosis concerning disease relapse. There are preclinical as well as emerging clinical data available to suggest the potential of PD-1 inhibition to improve clinical outcomes in early BC.

5.4.2 Rationale for Choice of Endpoints

Neoadjuvant therapy is increasingly used in patients with early BC to improve the likelihood of local tumor control, assess the treatment sensitivity of the disease in vivo, and increase the potential for curable disease by targeting the micrometastatic disease burden.[1] Robust individual

patient-level data meta-analyses from well-conducted clinical trials suggest that achieving a pCR is positively associated with improvement in EFS and OS; these associations are more robust within populations with high-risk BC subtypes.[2,3,4] Further, use of the neoadjuvant platform permits rapid assessment of drug efficacy and may expedite clinical development of new agents in this setting. Agents that positively and substantially impact pCR rate may have a reasonable expectation of meaningful improvement in EFS.[5,6]

5.4.3 Rationale for Chemotherapy Plus PD-1 Inhibition

Immunotherapy in combination with chemotherapy has been shown to improve response and OS, when compared to these agents used individually, in BC and other tumor types in the metastatic setting. It is hypothesized that chemotherapy may modify the immune response to tumors by influencing multiple mechanisms, including inducing immunogenic cell death, stimulating release of tumor antigens and/or depleting immuno-suppressive Tregs.

Current SOC, consisting of anthracycline-taxane-based chemotherapy administered in the neoadjuvant setting, is effective and tolerable among most patients with early BC.[7,8,9] Chemotherapy is effective in high-risk, primary ER+, HER2- disease and pCR rates range from 7-16%, which are lower than those achieved in other BC subtypes (30-50%).[2]

PD-1 pathway inhibition has demonstrated clinical activity across multiple tumor types, including BC.[10,11,12,13,14,15,16] There is strong rationale for combining checkpoint blockade with chemotherapy in patients with newly diagnosed ER+, HER2- BC. An accumulating body of preclinical[17] and clinical data[10,11,12,16] supports the combination of anti-PD-1 agents and chemotherapy to improve clinical outcomes in early and advanced settings across BC subtypes; such data culminated recently in the first approval of a PD-L1 inhibitor coupled with single-agent chemotherapy for patients with newly diagnosed, PD-L1+ (assessed in the immune-cell component of the disease) metastatic TNBC.[11]

Increasing understanding of the immunobiology of BC indicates that PD-1 inhibition could exert potent antitumor activity across all BC subtypes, including cases with ER+, HER2- disease. A recently reported study employed single-cell proteomics-based analysis, based on a panel of 73 antibodies, tailored to interrogate the different (immune-)phenotypes of BC.[89] A total number of 144 tumor samples were analyzed, exceeding a total of 26 million single cells phenotypically characterized. High frequencies of PD-L1+ tumor-associated macrophages and exhausted T cells were found in high-grade ER+ and ER- tumors, thus indicating that PD-1 inhibition may be a viable therapeutic strategy to reactivate the exhausted immune system. Furthermore, lymphocytic infiltration of ER+, HER2- BC tumors has been reported frequently, with a positive correlation with lower ER expression and/or high grade.[90,91]

Preliminary clinical data from a Phase 2 adaptive design neoadjuvant trial (I-SP) in participants with HER2- BC (ER+, HER2-, and TNBC cohorts) assessed an anti-PD-1 agent added to standard paclitaxel chemotherapy, and demonstrated clinically meaningful improvements in pCR rates relative to historical controls.[12] An absolute increase in the estimated pCR of 21% was observed

(34% with pembrolizumab 200 mg Q3W plus standard therapy compared to 13% with standard therapy alone) in participants with HR+, HER2- BC. The safety profile of pembrolizumab was consistent with that observed in previously reported studies across tumors.[12] Similar results in the TNBC subtype from Phase 2 trials, indicating increased pCR rates (~60-80%) with either pembrolizumab or durvalumab plus taxane and anthracycline-based neoadjuvant chemotherapy with or without carboplatin in participants with TNBC, suggest potential clinical activity with tolerable safety, while maintaining a full dose of chemotherapy.[10,16]

Data are available for nivolumab in participants with BC. Nivolumab was evaluated after a short induction with 1 of 3 low-dose chemotherapy treatments, irradiation, or no induction, in 50 participants with metastatic TNBC in a Phase 2 trial. After a 2-week induction period, participants received nivolumab 3 mg/kg Q2W until progression. With a median 4-month follow-up, the ORR was 22%, with 2 complete responses (4%) and 9 partial responses (18%). Median duration of response was 10.9 months. These findings suggest that administering nivolumab after priming the tumor microenvironment (TME) with either low-dose chemotherapy or irradiation is feasible and may render the TME more sensitive to anti-PD-1 agents, which may help to improve clinical response rates.[35]

Nivolumab was evaluated in 39 participants with metastatic TNBC in the CheckMate 32 (CA209032) study, which demonstrated a favorable safety profile for nivolumab monotherapy and nivolumab in combination with ipilimumab. The safety profile of nivolumab is well characterized from a large safety database at different doses and schedules, as monotherapy or in combination. Consistent with the mechanism of action of nivolumab, the most frequently reported drug-related AEs observed in clinical trials are those associated with activation of the immune system. The most common types of IMAEs include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis, and rash.

A number of ongoing studies are evaluating different chemotherapeutic agents in combination with checkpoint inhibitors in patients with BC.

5.4.4 Rationale for Endocrine Therapy Plus PD-1 Inhibition

The safety profile of nivolumab is well characterized and manageable when administered alone or in combination with chemotherapy, targeted agents, as well as additional IO products. No data are available evaluating the combination of nivolumab and ET (eg, tamoxifen, AIs).

However, checkpoint inhibition via a different immune pathway (CTLA-4) has been reported in combination with endocrine therapy in patients with breast cancer.[79] In cancer patients, CTLA-4 appears to regulate immune responses early in T-cell activation, whereas PD-1 inhibits the effector phase of T-cell activity in the tumor microenvironment. Based on current understanding, checkpoint inhibitors all act to attenuate T-cell activity, and it is thought that anti-CTLA-4 (eg, ipilimumab and tremelimumab) and anti-PD-1 (eg, nivolumab) primarily act at different stages of the cancer immunity cycle.[92,93]

One of the initial BC studies assessing checkpoint inhibitors was a Phase 1 study of tremelimumab, an anti-CTLA-4 antibody, combined with exemestane in 26 women with heavily pretreated ER+

metastatic BC.[79] No objective responses were noted; however 11 of 26 participants experienced stable disease, including 4 participants who previously progressed on exemestane. Evidence of T-cell activation was reported in the periphery, as measured by ICOS expression. Treatment was associated with T-cell activation, as revealed by an increase in ICOS-expressing T cells in blood and a marked increase in the ratio of ICOS-positive T cells to FoxP3-positive Tregs.[79,80] Most treatment-related AEs were mild to moderate (Grade 1 or 2) in nature. The most common events included diarrhea (46%), pruritus (42%), constipation (23%), and fatigue (23%).

Rationale for combining immunotherapy with ET comes from several sources. In a pooled assessment of stromal TIL concentrations in participants with BC treated in 6 randomized trials of neoadjuvant chemotherapy, pCR had a strong positive correlation with TIL concentrations in all BC subtypes. Of note, there was a negative survival effect with higher TIL concentration in participants with ER+, HER2- BC, unlike the positive survival effect observed with TNBC and HER2+ BC subtypes. In the ER+, HER2- BC cohort, tumor-infiltrating lymphocytes (TILs) were not prognostic for DFS and low TIL concentrations were associated with improved survival. Therefore, the effect of TILs on OS had the opposite effect for ER+, HER2- BC tumors, as compared with TNBC and HER2+ BC subtypes. The negative effect of higher TILs on survival in participants with ER+, HER2- tumors was most pronounced in the large group of participants not achieving a pCR and was stronger for OS than for DFS.[90,94]

The negative impact of higher TILs may be explained by increasing resistance to ET in ER+, HER2- BC. Poor response to AI treatment has been associated with increased immune activity, TILs, and immune-related genes.[95,96] Pretreatment expression of an inflammatory signature correlated with antiproliferative response to anastrozole in 112 postmenopausal women receiving 2-week treatment. Higher expression of immune-related genes, such as signaling lymphocytic activation molecule family member 8 (SLAMF8) and tumor necrosis factor (TNF), as well as lymphocytic infiltration were associated with poorer response ($p < 0.001$) to neoadjuvant anastrozole.[95] Similar findings suggest that the presence of immune-related genes were highly predictive of poor antiproliferative response to AIs.[96] These data suggest that patients with evidence of high immune-related gene expression and/or lymphocytic infiltration may be candidates for immune-modulators in combination with ET.

These findings suggest a rationale for further evaluation of checkpoint inhibitors, such as nivolumab, in combination with ET.

See Section 3.3.5 (Nivolumab and Endocrine Therapy Combination Safety Profile) for additional details.

Several ongoing studies are evaluating different ET agents in combination with checkpoint inhibitors.[81,82]

5.4.5 Rationale for Stratification Factors

Randomized participants in the study will be stratified by the following factors:

1) PD-L1 on immune cells (≥ 1% or < 1%);

2) Tumor grade (2 or 3, with maximum number of participants with tumor grade 2 BC not exceeding 20% of the ITT population);
3) Axillary nodal status (pathologic review positive versus radiographic and/or pathologic review negative, with maximum number of participants with node-negative BC not exceeding 20% of the ITT population); and
4) AC dose-frequency chemotherapy regimen (Q3W or Q2W).

PD-L1 status, used for stratification, is determined by qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 on the proportion of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells (% IC) of any intensity.

5.4.5.1 PD-L1 Status

PD-L1 expression has previously been evaluated as a potential predictive marker for treatment outcome in patients receiving anti-PD-L1 therapy for advanced TNBC. In a Phase 1 study evaluating 116 participants with metastatic TNBC who were treated with atezolizumab, those with PD-L1 expression in ≥ 1% of tumor-infiltrating immune cells had higher ORRs and longer OS (12% [11 of 91] and 10.1 [95% CI, 7.0-13.8] months, respectively) than those with PD-L1 expression in < 1% of tumor-infiltrating immune cells (0% [0 of 21] and 6.0 [95% CI, 2.6-12.6] months, respectively), while no major differences in ORR were seen between participants with PD-L1 expression on ≥ 1% of tumor cells (12% [95% CI, 2.5%-31.2%]) and those with PD-L1 expression on < 1% of tumor cells (9.2% [95%CI, 4.1%-17.3%]).[13] Similar findings in a Phase 1b study of avelumab in heavily pretreated participants with metastatic BC (TNBC and ER+, HER2- cohorts) demonstrated a trend toward a higher ORR in participants with PD-L1+ vs PD-L1-negative (PD-L1-) tumors associated immune cells in the overall population (16.7% vs 1.6%) and in the TNBC cohort (22.2% vs 2.6%).[15] In participants with untreated metastatic TNBC, atezolizumab and nab-paclitaxel combination therapy reduced the risk of disease worsening or death by 20% in all participants and 38% in the subgroup expressing PD-L1, as reported from the IMpassion 130 study.[11] In the IMpassion 130 study, PD-L1 positivity was defined as expression on tumor-infiltrating immune cells in ≥ 1% of the tumor area.

Similar findings suggesting PD-L1 positivity on immune cells is associated with response was reported in the Phase 2 KATE2 study in 200 participants with previously treated advanced HER2+ BC. This placebo-controlled study evaluated trastuzumab emtansine (T-DM1) plus atezolizumab vs T-DM1. The primary endpoint of progression-free survival (PFS) in the ITT population was not met; however, in participants expressing PD-L1 ≥ 1% on immune cells, PFS was 8.5 months with T-DM1 plus atezolizumab vs 4.1 months with T-DM1 alone. Response rates were 54% vs 33%, respectively. Similarly, in participants with high levels of TILs, the median PFS was higher with atezolizumab (8.5 vs 5.3 months, respectively). In the PD-L1- group, atezolizumab added no benefit, nor did it add benefit for participants with higher HER2 expression (immunohistochemistry [IHC] 3+ vs 1+ or 2+).[97]

In a Phase 1b study, pembrolizumab and abemaciclib demonstrated a confirmed ORR of 28.6% in heavily pretreated participants with metastatic HR+, HER2- BC, without association to PD-L1

positivity.[98] In this case, PD-L1 positivity was defined as the CPS of PD-L1 expression on both tumor and immune cells, relative to the total tumor cells, of ≥ 1%.

More recent data in the neoadjuvant breast cancer setting have suggested that PD-L1 expression may be prognostic and not predictive of treatment benefit from anti-PD-L1.[99,100,101]

To evaluate PD-L1 status on efficacy analyses, PD-L1 expression on tumor-infiltrating immune cells of ≥ 1% based on PD-L1 SP142 was selected as a stratification factor for this study and used for secondary endpoint analysis. In addition, for exploratory analysis PD-L1 expression determined by PD-L1 IHC 28-8 CPS will also be explored to assess its potential impact on efficacy.

5.4.5.2 Tumor Grade

Pathologic characteristics of the tumor are recognized as having prognostic significance.[102] Tumor grade is a known prognostic factor in patients with early BC.[103]

Multiple grading systems are available, with the most widely accepted being the Scarff-Bloom-Richardson (SBR) classification.[102] Mitotic index, differentiation, and pleomorphism are scored from 1 to 3 and the scores from each category are totaled. Tumors with scores from 3 to 5 are well differentiated (Grade 1), while scores from 6 to 7 are moderately differentiated (Grade 2), and scores from 8 to 9 are poorly differentiated (Grade 3).

Robust studies and meta-analyses have reported a correlation between histologic grade and EFS and/or DFS, such that higher grade or low ER expression portends a poorer long-term survival.[2,104]

In a large meta-analysis in early BC, the pCR rate was positively associated with EFS (HR, 0.49 [95% CI, 0.33-0.71]) and OS (HR, 0·43 [95% CI, 0.23-0.71]) in the ER+/HER2- population. The association between pCR and long-term outcome was stronger in patients with higher-grade tumors than in those with lower-grade tumors.[2] Similarly, pCR rates appear higher in patients having lower ER expression compared with those having higher ER expression after neoadjuvant chemotherapy.[105] Patients with low ER expression appear to behave similarly to ER-negative (ER-) disease, and this may translate to improved longer-term outcome[106,107] in those having a pCR. Thus, tumor grade was selected as a stratification factor for this study.

5.4.5.3 Axillary Nodal Status

A significant prognostic factor for patients with primary BC is the presence or absence of axillary lymph node involvement. There is a direct relationship between the number of involved axillary nodes and the risk for distant recurrence. Nodal groups were characterized based on the National Surgical Adjuvant Breast and Bowel Project (NSABP) data: negative nodes (0 nodes), 1-3 positive nodes, 4-9 positive nodes, and 10 or more positive nodes. The 5-year survival for patients with node-negative disease is 82.8% compared with 73% for 1-3 positive nodes, 45.7% for 4-12 positive nodes, and 28.4% for ≥ 13 positive nodes.[108]

A recent retrospective review with long-term follow-up demonstrated an increased risk of recurrence and BC-related death in women who had occult or micrometastatic tumor deposits in

their axillary lymph nodes.[109] Similar results were observed in the International Breast Cancer Study Group Trial V of 1,275 node-negative women randomly assigned to a single cycle of perioperative cyclophosphamide, methotrexate, and 5-flourouracil (CMF) vs no chemotherapy.[110] These micrometastases, detected by either method, were associated with a higher risk of recurrence.

Axillary nodal status (confirmed pathologically) is the most consistent prognostic factor used in therapy decision making and was selected as a stratification factor for enrollment in this study.

5.4.5.4 Anthracycline-Cyclophosphamide Dose Frequency

Increasing the dose intensity of adjuvant chemotherapy by shortening the interval between treatment cycles, or by giving individual drugs sequentially rather than giving the same drugs concurrently, moderately reduces the 10-year risk of recurrence and death from BC without increasing mortality from other causes.[111]

An individual patient-level meta-analysis of trials comparing 2-weekly vs standard 3-weekly schedules, and of trials comparing sequential vs concurrent administration of anthracycline and taxane chemotherapy was conducted by the Oxford group. Individual patient data were provided for 26 of 33 relevant trials identified, comprising 37,298 (93%) of 40,070 women randomized. Most women were aged younger than 70 years and had node-positive disease.

Combined data showed fewer BC recurrences with dose-intense than with standard-schedule chemotherapy (10-year recurrence risk, 28.0% vs 31.4%; relative risk 0.86 [95% CI, 0.82-0.89]; $p < 0.0001$). Ten-year BC mortality was similarly reduced (18.9% vs 21.3%; relative risk, 0.87 [95% CI, 0.83-0.92]; $p < 0.0001$), as was all-cause mortality (22.1% vs 24.8%; relative risk, 0.87 [95% CI, 0.83-0.91]; $p < 0.0001$). Death without recurrence was, if anything, lower with dose-intense than with standard-schedule chemotherapy (10-year risk, 4.1% vs 4.6%; relative risk, 0.88 [95% CI, 0.78-0.99]; $p = 0.034$). Recurrence reductions were similar in the 7 trials ($n = 10,004$) that compared 2-weekly chemotherapy with the same chemotherapy given 3-weekly (10-year risk, 24.0% vs 28.3%; relative risk, 0.83 [95% CI, 0.76-0.91]; $p < 0{\cdot}0001$), in the 6 trials ($n = 11,028$) of sequential vs concurrent anthracycline plus taxane chemotherapy (28.1% vs 31.3%; relative risk, 0.87 [95% CI, 0.80-0.94]; $p = 0.0006$), and in the 6 trials ($n = 6532$) testing both shorter intervals and sequential administration (30.4% vs 35.0%; relative risk, 0.82 [95% CI, 0.74-0.90]; $p < 0.0001$). The proportional reductions in recurrence with dose-intense chemotherapy were similar and highly significant ($p < 0.0001$) in ER+ and ER- disease and did not differ significantly by other patient or tumor characteristics.[111]

To evaluate AC dose intensity on efficacy analyses, AC frequency was selected as a stratification factor for this study.

5.5 Justification for Dose

5.5.1 Justification for Dose of Nivolumab

5.5.1.1 Nivolumab 240-mg Every-2-Week Dosing Regimen

Nivolumab 240 mg Q2W infused over 30 minutes is approved by FDA and European Medicines Agency (EMA) for all nivolumab approved indications as monotherapy.[56,65] Nivolumab 240 mg Q2W infused over approximately 30 minutes will be examined in combination with neoadjuvant chemotherapy in this study.

5.5.1.2 Nivolumab 360-mg Every-3-Week Dosing Regimen

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, and urothelial carcinoma, using body weight-normalized dosing (mg/kg), and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab is currently approved for the treatment of various tumors, including melanoma, NSCLC, RCC, cHL, SCCHN, and urothelial carcinoma, using a regimen of either nivolumab 240 mg Q2W, nivolumab 3 mg/kg Q2W, or nivolumab 480 mg Q4W.

Nivolumab has been shown to be safe and well tolerated up to a dose level of nivolumab 10 mg/kg Q2W. Population PK (PPK) analyses have shown that the PK of nivolumab is linear, with proportional exposures over a dose range of 0.1 to 10 mg/kg; no differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including nivolumab 360 mg Q3W. The simulated steady-state average concentration (Cavgss) following administration of nivolumab 360 mg Q3W are expected to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to participants weighing 80 kg, the approximate median weight of participants with NSCLC, melanoma, and RCC used in the PPK analyses. Given that the Cavgss estimates for nivolumab 360 mg Q3W are predicted to be similar to those for nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W, the efficacy is predicted to be similar for these regimens. It should be noted that the maximum-observed concentrations at steady state following nivolumab 360 mg Q3W are predicted to be less than those following the administration of nivolumab 10 mg/kg Q2W, providing sufficient safety margins. Further details on nivolumab 360 mg Q3W dosing can be found in the IB.[34]

Finally, nivolumab 360 mg Q3W is currently being investigated in combination with a number of other agents, including platinum-doublet chemotherapy dosing, with no new or increased safety events observed to date. By using nivolumab 360 mg Q3W in this study, it allows for aligning doses of nivolumab at the same dosing frequency of the experimental agent.

Nivolumab 360 mg Q3W infused over approximately 30 minutes will be examined in combination with neoadjuvant chemotherapy in this study.

5.5.1.3 Nivolumab 480-mg Every-4-Week Dosing Regimen

Nivolumab 480 mg Q4W infused over 30 minutes was approved by FDA in Mar-2018 for the majority of indications approved for nivolumab. The EMA has also approved inclusion of this dosing schedule in the label for nivolumab for the treatment of patients with advanced melanoma and previously treated RCC.

Nivolumab 480 mg Q4W infused over approximately 30 minutes will be examined in combination with Investigator's choice of ET in this study.

5.5.2 Justification for Dose of Chemotherapy Agents

Chemotherapy regimens used in the neoadjuvant setting are the same as those used in the adjuvant setting. An anthracycline-cyclophosphamide-taxane-containing regimen is the most widely recommended chemotherapy regimen in the neoadjuvant setting for patients with ER+, HER2- BC in national and international guidelines.[7,8,9] The doses of the individual chemotherapy agents in this study are consistent with the national and international guidelines.

The choice among various anthracycline-taxane-based regimens is often a matter of toxicity and duration. Within sequential regimens, weekly paclitaxel (80 mg/m^2) was shown to have improved DFS and OS compared with 3-weekly paclitaxel.[112,113] In addition, more frequent administration of the AC component (ie, dose-dense approach) was shown to be more effective in minimizing residual tumor burden than dose-escalation.[114] In a meta-analysis of 10 randomized controlled trials, dose-dense chemotherapy improved OS by 16% [hazard ratio (HR), 0.84 [95% CI, 0.72-0.98]; p = 0.03] and DFS by 17% (HR, 0.83 [95% CI, 0.73-0.94]; p = 0.005).[115] The superiority of dose-dense chemotherapy, in terms of improved long-term clinical outcome for patients with primary BC, has been recently demonstrated by an individual patient-level data meta-analysis, pooling data from more than 37,000 individual patients. Importantly, the proportional reductions in recurrence with dose-intense chemotherapy were similar and highly significant (p < 0.0001) in both ER+ and ER- disease and did not differ significantly by other patient or tumor characteristics.[47]

Nivolumab 360 mg Q3W infused over approximately 30 minutes will be examined in combination with paclitaxel 80 mg/m^2 QW for a maximum 4 cycles (1 cycle = 3 weeks), followed by either:

- Nivolumab 360 mg Q3W infused over approximately 30 minutes in combination with either doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 Q3W for a maximum of 4 cycles (1 cycle = 3 weeks); or
- Nivolumab 240 mg Q2W infused over approximately 30 minutes in combination with either doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 Q2W for a maximum of 4 cycles (1 cycle = 2 weeks).

5.5.3 Justification for Dose of Endocrine Therapy

Adjuvant ET is the cornerstone of treatment for patients with primary ER+, HER2- BC. Use of tamoxifen and/or an AI (anastrozole, letrozole, or exemestane) are recommended agents for patients with ER+, HER2- BC in national and international guidelines.[7,8,9,52] The doses of the individual ET agents in this study are consistent with the national and international guidelines. Investigator's choice of ET is permitted from the following options:

- Tamoxifen 20 mg per os (by mouth; PO) quaque die (once daily; QD)
- Anastrozole 1 mg PO QD
- Letrozole 2.5 mg PO QD
- Exemestane 25 mg PO QD

Investigator's choice of the above ET options will be examined in combination with nivolumab 480 mg Q4W in this study.

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met. As of 07-Apr-2022, new participant enrollment to this study is closed.

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 schedules, 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 documentation of the following characteristics:

i) Localized invasive breast ductal carcinoma, confirmed by the local pathologist, that includes the following combined primary tumor and node (N) categories:

(1) T1c (tumor size = 2 cm)-T2 (tumor size > 2 cm), N1-N2

OR

(2) T3-T4, N0-N2

Note: Axillary lymph node status must be assessed by fine needle biopsy or core biopsy. 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 is available prior to the screening period. Participants with tumors classified as T1c-T2 without nodal involvement are not eligible.

ii) In the case of a multifocal tumor (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 all subsequent tumor evaluations.

(1) 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.

iii) Documentation of T1c-T2 (tumor size ≥ 2 cm), clinical node stage (cN)1-cN2 or T3-T4, cN0-cN2.

(1) 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.

iv) ***Not applicable per Revised Protocol 01***-Participants must have measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (refer to Appendix 8), as determined by local radiology review.

v) Participants must have measurable disease based on modified Respond Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (refer to Appendix 8), as determined by local radiology review.

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

i) ER+ BC and with or without PgR expression (determined on the most recently analyzed tissue sample, tested locally, and confirmed by the central laboratory), as defined in the relevant American Society of Clinical Oncology [ASCO]-College of American Pathologists [CAP] Guidelines).[116]

ii) HER2- BC tested in the local laboratory, defined as a negative in situ hybridization test or an immunohistochemistry (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, is required from the local laboratory.[117]

iii) Participant must have either:
(1) Grade 3 BC of ductal histology

or

(2) Grade 2 BC of ductal histology having an ER expression level percentage between 1-10%, (tested locally and confirmed by central laboratory) according to the most recent ASCO-CAP Guidelines.[117]

c) Participants must be deemed eligible for neoadjuvant chemotherapy.

d) Participants must be deemed eligible for surgery.

e) Participants must have an Eastern Cooperative Oncology Group (ECOG) scale performance status of 0 or 1 (refer to Appendix 5).

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

g) Participants must agree to provide primary breast tumor tissue at baseline (collected ≤ 90 days prior to enrollment if FFPE block is submitted or prepared ≤ 60 days prior to

enrollment from a tissue sample collected ≤ 90 days prior to enrollment) and at Surgery. The tumor tissue must be in the format of either one FFPE tissue block (containing 20 mm^3 of tissue) or unstained tumor tissue sections (22 slides) from the primary breast tumor lesion.

Note: At least 15 slides must be submitted for a participant to be eligible. If < 15 slides are available, the participant is not eligible. If a recent tumor specimen is not available, a fresh tumor biopsy collection is required. [redacted]

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). If re-enrolled, the participant must be re-consented and inclusion/exclusion criteria reassessed.

i) Randomized participants: PD-L1 status, ER status, and ER expression level percentage from the central laboratory must be provided to IRT prior to randomization. Participants with PD-L1, ER, or HER2 unknown/not evaluable status are not eligible.

3) Age and Reproductive Status

a) Males and females, aged at least 18 years or age of majority.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study treatment. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

c) ***Not applicable per Revised Protocol 01*** **-** Female participants must agree to use effective contraception during the Treatment Period and for at least 12 months for participants who receive cyclophosphamide, or 6 months for participants who do not receive cyclophosphamide, after the last dose of study treatment with nivolumab or nivolumab placebo, whichever is longer.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) and for 12 months for participants who receive cyclophosphamide, or 6 months for participants who do not receive cyclophosphamide, after the last dose of study treatment with nivolumab or nivolumab placebo, whichever is longer.

e) Males 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 neoadjuvant (pre-surgery) treatment phase and 12 months after the last dose of cyclophosphamide OR 6 months after the last dose of paclitaxel, whichever is the last dose.

f) ***Not applicable per Revised Protocol 01*** **-** Male participants must agree to use contraception during the Treatment Period and for at least 6 months after the last dose of study treatment(s).

g) Azoospermic males are exempt from contraceptive requirements, unless the potential exists for fetal toxicity due to study drug being present in seminal fluid, even if the participant has undergone a successful vasectomy or if the partner is pregnant. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements and must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy and, when applicable, the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant. Investigators shall advise on the use of highly effective methods of contraception (refer to Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Women who are breastfeeding.
b) Participants who are pregnant or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 12 months for participants who receive cyclophosphamide, or 6 months for participants who do not receive cyclophosphamide, after the last dose of study treatment.
c) The following BC characteristics:
   i) History of ipsilateral invasive BC, regardless of treatment, ipsilateral ductal carcinoma in situ treated with radiation, or contralateral invasive BC, at any time.
   ii) Definitive clinical or radiologic evidence of metastatic disease.
   iii) ***Not applicable per Revised Protocol 01*** **-** Inoperable BC.
   iv) Multicentric BC (the presence of > 1 tumor in different quadrants of the breast).
   v) Bilateral invasive BC.
   vi) Any of the following clinical lymph node staging based on radiological and/or clinical assessment: cN3, cN3a, cN3b, or cN3c.
   vii) History of DCIS, unless a complete remission was achieved at least 2 years prior to study start and no additional therapy is required or anticipated to be required during the study.
   viii) History of pleomorphic lobular carcinoma in situ (LCIS), except for participants surgically managed > 5 years prior to diagnosis of the current BC.
   ix) Evidence of ER- BC, regardless of PgR status.
   x) Undergone excisional biopsy of the primary tumor and/or axillary lymph nodes or has undergone sentinel lymph node biopsy prior to study treatment.
d) Participants with > Grade 1 peripheral neuropathy.
e) Participants with an active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
f) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

g) ***Not Applicable per Protocol Amendment 02 -*** Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS) defining opportunistic infection within the last year, or a current CD4 count of <350 cells/µL. Participants enrolled with known HIV need monitoring of CD4 counts and viral load during the study and antiretroviral therapy administered as clinically indicated.
Note: Testing for HIV must be performed at sites where mandated locally (refer to Appendix 9).

h) ***Not Applicable per Protocol Amendment 02 -*** 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.

i) Participants with serious or uncontrolled medical disorders.
   i) Additionally, in the case of prior SARS-CoV-2 infection within 4 weeks prior to screening, participant may be enrolled if acute symptoms have resolved and based on Investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment (see Section 6.4.1).

j) 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 gastrointestinal (GI) function.

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

l) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participants has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or noninvasive or in situ cancer that have undergone definitive treatment at any time are also eligible, except for ipsilateral ductal carcinoma in situ treated with radiation.

m) Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the 12 months or a current CD4 count < 350 cells/µL, participants with HIV are eligible if:
   i) They have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization, as clinically indicated.
   ii) They continue on ART as clinically indicated while on study treatment.
   iii) CD4 counts and viral load are monitored per standard of care by a local health care provider while on study treatment.

   NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally (refer to Appendix 9).

2) Prior/Concomitant Therapy

a) 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.

b) Any treatment, local or systemic, including prior chemotherapy, ET, targeted therapy, and/or radiation therapy for the currently diagnosed BC prior to enrollment.

c) Concurrent use of hormone replacement therapy, hormonal contraception, or any other estrogen-containing medication, including vaginal estrogens. Participant is eligible if the therapy is discontinued prior to randomization (refer to Appendix 4).

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

e) Surgical excisional biopsy of primary tumor.

f) Participants for whom upfront ET alone is judged clinically appropriate as optimal neoadjuvant therapy.

g) ***Not applicable per Protocol Amendment 02*** - Treatment with botanical preparations (eg, herbal supplements, traditional Chinese medicines) to treat the disease under study within 2 weeks prior to start of study treatment. See Section 7.7.1 (Prohibited and/or Restricted Treatments for Nivolumab) for prohibited therapies.

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

i) Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1.1 (Prohibited and/or Restricted Treatments for Nivolumab) for prohibited therapies.

j) Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in Bristol-Myers Squibb (BMS) clinical trials until the protocol-specific washout period is achieved. COVID-19 vaccines that are NOT live may be administered during the study, including during IP treatment and after the last administration of investigational product (IP). If a study participant has received a live COVID-19 vaccine prior to screening, enrollment should be delayed until the impact of the vaccine is stabilized as per the asset level standard, unless a delay would compromise patient health, as determined by discussion between the Investigator and the Medical Monitor. No data are available on the response to COVID-19 vaccines. The efficacy and safety of vaccination in subjects who are receiving IP are unknown.

3) Physical and Laboratory Test Findings

a) White blood cells < 2,000/μL.

b) Neutrophils < 1500/μL.

c) Platelets < 100×10^3/μL.

d) Hemoglobin < 9.0 g/dL.

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

f) Aspartate aminotransferase (AST)/ALT: > 3.0 × ULN.

g) Total bilirubin > 1.5 × ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 × ULN).

h) Not applicable per Revised Protocol 01 - Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus (eg, hepatitis B surface antigen [HBsAg, Australia antigen] positive, or hepatitis C antibody [anti-HCV] positive [except if HCV-ribonucleic acid (RNA) negative]).

i) Has significant cardiovascular disease, such as:
   i) LVEF < 50% at baseline as assessed by ECHO (preferred) or MUGA scan;
   ii) Class III or Class IV myocardial disease as described by the New York Heart Association (refer to Appendix 10);
   iii) Recent history (within 6 months prior to enrollment) of myocardial infarction; or
   iv) Symptomatic arrhythmia at the time of randomization.

j) Evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis.

k) ***Not Applicable per Protocol Amendment 02 -*** Serologic evidence of chronic HBV infection with an HBV viral load above the limit of quantification. Patients with chronic HBV infection must be on concurrent viral suppressive therapy.

l) ***Not Applicable per Protocol Amendment 02 -*** Serologic evidence of current HCV infection with an HCV viral load above the limit of quantification.

m) Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV-RNA). Note: participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.

n) Any positive test result for hepatitis B virus (HBV) indicating presence of virus (eg, Hepatitis B surface antigen [HBsAg, Australian antigen] positive).

4) Allergies and Adverse Drug Reaction

a) History of allergy or severe hypersensitivity (≥ Grade 3) 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 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

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but 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

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 will be permitted (in addition to any parameters that require a confirmatory value).

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

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

Testing for asymptomatic COVID-19 (eg, by reverse transcription polymerase chain reaction [RT-PCR] or viral antigen) is not required. However, some participants may develop suspected or confirmed symptomatic COVID-19 or be discovered to have asymptomatic COVID-19 during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result.
- At least 24 hours have passed since last fever without the use of fever-reducing medications.
- Acute symptoms (eg, cough, shortness of breath) have resolved.
- In the opinion of the Investigator and in consultation with the Medical Monitor or Study Director, there are no COVID-19-related sequelae (eg, cardiovascular) that may place the participant at a higher risk of receiving investigational treatment.
- Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local, or regional guidelines.

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:

- Nivolumab (BMS-936558)
- Nivolumab placebo
- Chemotherapy
  - Paclitaxel
  - Anthracycline
    - Doxorubicin
    - Epirubicin
  - Cyclophosphamide
- Growth Factors
  - Granulocyte colony-stimulating factor
  - Granulocyte-macrophage colony-stimulating factor
- Endocrine Therapy
  - Anastrozole
  - Exemestane
  - Letrozole
  - Tamoxifen

An IP, also known as an IMP in some regions, is defined as 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.

Consider, if possible, avoiding overlap of administration of vaccine and protocol therapy (eg, at least 2 days, preferably 7 days, apart).

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.

Solutions used as diluent or placebo (ie, 0.9% sodium chloride injection, 5% dextrose injection) should also be sourced by investigative sites, if available and permitted by local regulations.

Table 7-1: Study Treatments for CA2097FL

Product Description/ Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open Label[a]	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Injection[b]	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.
Paclitaxel Solution for Injection[c]	6 mg/mL; 100-mg fill volume	IP	Open Label	Vials	Refer to the label or container and/or Pharmacy Manual .
Doxorubicin Hydrochloride Injection[c]	2 mg/mL; 200-mg fill volume	IP	Open Label	Vials	Refer to the label or container and/or Pharmacy Manual.
Epirubicin Solution for Injection[c]	2 mg/mL; 200-mg fill volume	IP	Open Label	Vials	Refer to the label or container and/or Pharmacy Manual.
Cyclophosphamide Injection[c]	1-g vial	IP	Open Label	Vials	Refer to the label or container and/or Pharmacy Manual.
0.9% Sodium Chloride for Injection	NA	IP	Open Label	Various (local commercial product)	Refer to the label or container and/or Pharmacy Manual.
5% Dextrose for Injection	NA	IP	Open Label	Various (local commercial product)	Per active IP.
Tamoxifen Tablets[c]	Various strengths	IP	Open Label	Various packing configurations	Refer to the label or container and/or Pharmacy Manual.
Letrozole Tablets[c]	2.5 mg	IP	Open Label	Various packing configurations	Refer to the label or container and/or Pharmacy Manual.
Anastrozole Tablets[c]	1 mg	IP	Open Label	Various packing configurations	Refer to the label or container and/or Pharmacy Manual.
Exemestane Tablets[c]	25 mg	IP	Open Label	Various packing configurations	Refer to the label or container and/or Pharmacy Manual.
Granulocyte colony-stimulating factor (G-CSF)[d]	Various strengths	Non-IP	Open Label	Various (local commercial product)	Refer to the label

Table 7-1: Study Treatments for CA2097FL

Product Description/ Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open Label[a]	Packaging/ Appearance	Storage Conditions (per label)
Granulocyte-macrophage colony-stimulating factor (GM-CSF)[d]	Various strengths	Non-IP	Open Label	Various (local commercial product)	Refer to the label

Abbreviations: g, gram; IMP, investigational medicinal product. IP, investigational product; mg, milligram; mL, milliliter; NA, not applicable; SmPC, summary of product characteristics.

[a] The term "open label" refers to the medication as it is upon receipt at the pharmacy. The trial will be conducted in a double-blinded fashion. As of Protocol Amendment 03, participants will be unblinded in the Adjuvant phase.

[b] May be labeled as either "BMS-936558-01" or "Nivolumab."

[c] 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 local standards.

[d] To be sourced locally by investigational sites. These products should be prepared/stored/administered in accordance with their package insert or SmPC or according to local standards.

7.1 Treatments Administered

The selection and timing of dose for each participant is provided in Table 7.1-1, Table 7.1-2, and Table 7.1-3.

Table 7.1-1: Selection and Timing of Dose - Neoadjuvant (Pre-surgery) Phase - PTX

Arm	Study Treatment	Dosage Level	Frequency of Administration	Start and Duration of Treatment	Route of Administration
A	Nivolumab	360 mg	Q3W	PTX Cycles 1-4	IV
	Paclitaxel	80 mg/m^2	QW	PTX Cycles 1-4	IV
B	Nivolumab Placebo	NA	Q3W	PTX Cycles 1-4	IV
	Paclitaxel	80 mg/m^2	QW	PTX Cycles 1-4	IV

Abbreviations: IV, intravenous; m^2, square meter; mg, milligram; NA, not applicable; PTX, paclitaxel; QW, every week; Q3W, every 3 weeks.

Table 7.1-2: Selection and Timing of Dose - Neoadjuvant (Pre-surgery) Phase - AC

Arm	Study Treatment	Dosage Level	Frequency of Administration	Start and Duration of Treatment	Route of Administration
A	Nivolumab	360 mg	Q3W	AC Cycles 1-4	IV
		OR[a]			
		240 mg	Q2W		
	Doxorubicin[b]	60 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
	Epirubicin[b]	90 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
	Cyclophosphamide	600 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
B	Nivolumab Placebo	NA	Q3W or Q2W[a]	AC Cycles 1-4	IV
	Doxorubicin[b]	60 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
	Epirubicin[b]	90 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV
	Cyclophosphamide	600 mg/m^2	Q3W or Q2W[a,c]	AC Cycles 1-4	IV

Abbreviations: AC, anthracycline + cyclophosphamide; IV, intravenous; m^2, square meter; mg, milligram; NA, not applicable; Q2W, every 2 weeks; Q3W, every 3 weeks.

[a] Dosing frequency of Q2W or Q3W for AC cycles to be determined by the Investigator.

[b] Choice of anthracycline, either doxorubicin or epirubicin, to be determined by the Investigator.

[c] Prophylaxis with growth factors is required for the AC 2QW schedule.

Table 7.1-3: Selection and Timing of Dose - Adjuvant (Post-surgery) Phase

Arm	Study Treatment	Dosage Level	Frequency of Administration	Start and Duration of Treatment	Route of Administration
A	Nivolumab	480 mg	Q4W	Cycles 1-7	IV
	Investigator's Choice ET	See Note[a]	See Note[a]	Cycles 1-7	See Note[a]
B	Investigator's Choice ET	See Note[a]	See Note[a]	Cycles 1-7	See Note[a]

Abbreviations: ET, endocrine therapy; IV, intravenous; mg, milligram; NA, not applicable; Q4W, every 4 weeks.

[a] May include tamoxifen, letrozole, anastrozole, or exemestane, to be administered per the respective package inserts.

All participants should begin study treatment within 3 days of randomization.

7.1.1 Nivolumab/Nivolumab Placebo Dosing

The study design requires a total of 8 cycles of neoadjuvant treatment with nivolumab or nivolumab placebo in combination with anthracycline-taxane-based chemotherapy, followed by 7 cycles of adjuvant treatment with nivolumab + Investigator's choice of ET or Investigator's choice of ET alone (per Protocol Amendment 03).

There will be no dose escalations or reductions of nivolumab or nivolumab placebo allowed. If at a particular cycle, nivolumab or nivolumab placebo cannot be administered within a ± 3-day window from the scheduled chemotherapy dose, nivolumab or nivolumab placebo administration must be omitted for that cycle.

- Participants may be dosed no less than 12 days from the previous dose during Q2W cycles.
- Participants may be dosed no less than 18 days from the previous dose during Q3W cycles.
- Participants may be dosed no less than 25 days from the previous dose during Q4W cycles.

Premedications are not recommended for the first dose of nivolumab or nivolumab placebo. Premedication with corticosteroids should be avoided. However, if considered clinically necessary, premedication with corticosteroids can be used in accordance with the local treatment guidelines.

Participants should be carefully monitored for infusion reactions during nivolumab or nivolumab placebo administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.1.3 (Treatment of Nivolumab Infusion Reaction).

Doses of nivolumab or nivolumab placebo may be interrupted, delayed, omitted, or discontinued, depending on how well the participant tolerates the treatment. For additional information, please see Sections 7.4.1 (Dose Modifications for Nivolumab), Section 7.4.1.2 (Criteria to Resume Treatment with Nivolumab) and Section 8.1.1 (Nivolumab Dose Discontinuation). Instructions for dilution and infusion of nivolumab or nivolumab placebo injection may be provided in the clinical protocol, pharmacy manual, 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 Neoadjuvant (Pre-surgery) Phase

During the Neoadjuvant (Pre-surgery) Phase, when given in combination with chemotherapy, nivolumab or nivolumab placebo is to be given first. Nivolumab or nivolumab placebo must be given on the same day as the assigned chemotherapy. Nivolumab or nivolumab placebo infusion must be promptly followed by a saline flush to clear the line per local standards. Separate infusion bags and filters should be used when administering nivolumab or nivolumab placebo and assigned chemotherapy as per local standards. Do not co-administer other drugs through the same intravenous line. Chemotherapy starts after the infusion line has been flushed, filters changed, and the participant has been observed for approximately 30 minutes, to ensure no infusion reaction has occurred.

Participants should receive neoadjuvant nivolumab or nivolumab placebo at a dose of 360 mg infusion given over approximately 30 minutes on Day 1 of each treatment cycle (Q3W), for a maximum of 8 cycles, until disease worsening or disease progression, unacceptable toxicity, withdrawal of consent, neoadjuvant treatment is completed, death, the study ends, or Q4W dosing begins, whichever occurs first. If needed, flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride or 5% dextrose in water to ensure that the complete dose is administered over approximately 30 minutes).

In cases where a dose-dense regimen of AC is administered Q2W, nivolumab or nivolumab placebo will also be administered on a Q2W schedule. Participants should receive nivolumab or nivolumab placebo at a dose of 240 mg infusion given over approximately 30 minutes on Day 1 of each treatment cycle, until disease worsening or disease progression, unacceptable toxicity, withdrawal of consent, neoadjuvant treatment is completed, death, the study ends, or Q4W dosing begins, whichever occurs first.

7.1.3 Adjuvant (Post-surgery) Phase

As of Protocol Amendment 03, treatment in the Adjuvant phase will be open label. Participants who are randomized to Arm B will not receive adjuvant nivolumab placebo infusions, only Investigator's choice of ET (per Protocol Amendment 03).

Participants will follow previous randomization and will receive nivolumab with Investigator's choice of ET or Investigator's choice of ET alone (per Protocol Amendment 03) as adjuvant treatment.

During the Adjuvant (Post-surgery) Phase of treatment, when nivolumab is scheduled to be administered on the same day with Investigator's choice of ET, nivolumab dosing should be started > 1 hour after the ET (ie, tamoxifen or AI) administration.

Participants should receive adjuvant nivolumab at a dose of 480 mg infusion given over approximately 30 minutes on Day 1 of each treatment cycle (Q4W) (± 3 days), for a maximum of 7 cycles, until disease recurrence or progression, unacceptable toxicity, withdrawal of consent, adjuvant treatment is completed, death, or the study ends, whichever occurs first.

7.1.4 Chemotherapy Dosing

7.1.4.1 Paclitaxel

Participants will receive paclitaxel at a dose of 80 mg/m^2 over a minimum of 60 minutes as an intravenous (IV) infusion or per institutional policy on Day 1, Day 8, and Day 15 of each 3-week treatment cycle. Paclitaxel will be administered for PTX Cycles 1-4 until disease worsening or disease progression, unacceptable toxicity, withdrawal of consent, PTX Cycles 1-4 are completed, death, or the study ends, whichever occurs first.

Dosing calculations should be based on the body surface area calculation. The dose should remain the same if the participant's weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram or per institutional standards. All participants should be carefully monitored for infusion reactions during the paclitaxel administration.

Participants should be treated in a facility with the necessary medical-resuscitation equipment and medications on hand to manage serious acute infusion reactions.

Paclitaxel premedication with corticosteroids should be avoided, if clinically justifiable. However, if considered clinically necessary or in accordance with the local treatment guidelines, premedication with corticosteroids can be used. Corticosteroids can be administered after the observation period of approximately 30 minutes following nivolumab.

Doses of paclitaxel may be interrupted, delayed, reduced, or discontinued, depending on how well the participant tolerates the treatment. For additional information, please see Section 7.4.2.1 (Dose Delay for Paclitaxel Therapy), Section 7.4.2.2 (Dose Reductions for Paclitaxel Chemotherapy), Section 7.4.2.3 (Criteria to Resume Treatment with Paclitaxel Chemotherapy), and Section 8.1.2 (Chemotherapy Dose Discontinuation). Participants may be dosed no less than 6 days from the previous dose of paclitaxel.

Every effort should be made to administer a total of 4 cycles of paclitaxel chemotherapy in combination with nivolumab or nivolumab placebo.

7.1.4.2 Anthracycline and Cyclophosphamide

The first dose of AC should be administered at the completion of 4 cycles (PTX Cycles 4D1 + 3 weeks) of paclitaxel, unless the participant meets criteria for a treatment delay.

Participants will receive doxorubicin at a dose of 60 mg/m^2 as an IV bolus over 3-5 minutes or as an infusion over approximately 15-30 minutes, or per institutional-standard IV infusion, followed by cyclophosphamide as an IV infusion at a dose of 600 mg/m^2 over approximately 60 minutes, or per institutional-standard IV infusion, on Day 1 of each cycle.

If per SOC, epirubicin 90 mg/m^2 can be administered in place of doxorubicin. Epirubicin may be given as an IV bolus over 3-5 minutes or as an infusion over approximately 15-30 minutes, or per institutional-standard IV infusion followed by cyclophosphamide as an IV infusion at a dose of 600 mg/m^2 over approximately 60 minutes, or per institutional-standard IV infusion, on Day 1 of each cycle.

AC will be administered for AC Cycles 1-4 until disease worsening or disease progression, unacceptable toxicity, withdrawal of consent, AC Cycles 1-4 are completed, death, or the study ends, whichever occurs first.

Participants may receive the AC treatment on a Q3W or Q2W schedule. See Section 7.1 (Treatments Administered) for more details regarding nivolumab or nivolumab placebo dosing with AC treatment schedules.

Dosing calculations should be based on the body surface area calculation. The dose should remain the same if the participant's weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram or per institutional standards.

AC premedication with corticosteroids should be avoided. However, if considered clinically necessary, or in accordance with the local treatment guidelines, premedication with corticosteroids can be used.

Doses of anthracycline or cyclophosphamide may be interrupted, delayed, reduced, or discontinued, depending on how well the participants tolerates the treatment. For additional information, please see Section 7.4.2.4 (Dose Delay for Anthracycline and Cyclophosphamide Chemotherapy), Section 7.4.2.5 (Dose Reductions for Anthracycline-Cyclophosphamide Chemotherapy), Section 7.4.2.6 (Criteria to Resume Treatment with for Anthracycline-Cyclophosphamide Chemotherapy), and Section 8.1.2 (Chemotherapy Dose Discontinuation).

Every effort should be made to administer a total of 4 cycles of AC chemotherapy in combination with nivolumab or nivolumab placebo.

7.1.5 Endocrine Therapy Dosing

Following definitive surgery, the Investigator can decide which ET (tamoxifen, anastrozole, letrozole, or exemestane) will be administered to a particular participant. The decision must be recorded in the source documents. The selected ET may be rotated, changed, or switched to another ET during the study. The respective change should be clearly recorded in the source documents. ET may be given for a maximum of 10 years, per local standards. ET will be documented as study treatment up to the last dose of adjuvant treatment and documented as concomitant medication

after the last dose of adjuvant treatment. Participants will be required to complete a drug diary to assess compliance during the Adjuvant (Post-surgery) Phase.

No dose reductions are permitted for the ET (ie, tamoxifen, anastrozole, letrozole, or exemestane). ET may be interrupted, delayed, or discontinued, depending on how well the participant tolerates treatment. For additional information, please see Section 7.4.3 (Dose Modifications for Investigator's Choice Endocrine Therapy) and Section 8.1.3 (Endocrine Therapy Dose Discontinuation).

More detailed information about administration, known and expected benefits and risks, and reasonably anticipated AEs of the study treatments may be found in the respective Patient Information Leaflets, Package Inserts,[61,62,63,64] Development Safety Update Reports, or SmPCs.[70,71,72,73]

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. An IRT will be employed to manage participant randomization. The Investigator or designee will register the participant for enrollment by following the enrollment procedures established by the Sponsor.

The following information is required for enrollment:

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

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be ready to be randomized through the IRT. The following information is required for participant randomization:

- Participant number
- Year of birth
- Gender at birth (female or male)
- ER status/expression levels tumor type
- PD-L1 on immune cells (≥ 1% or < 1%)
- Tumor grade (2 or 3)
- Axillary nodal status (pathological review positive versus radiographic and/or pathologic review negative)
- AC dose-frequency regimen (Q3W or Q2W)

The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

This is a randomized, double-blinded study. Access to treatment codes will be restricted from all participants and site and Sponsor personnel prior to each interim and final database lock, with exceptions as specified below.

Each investigative site must assign an unblinded pharmacist or designee, and an unblinded site monitor will be assigned by the Sponsor to provide oversight of drug supply and other unblinded study documentation.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant, in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the Investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the Investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor (or designee), but the Investigator always has the ultimate authority for the decision to unblind. The Principal Investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is through the IRT. Refer to the IRT manual for details.

In the case of an emergency, the Investigator(s) has unrestricted access to randomization information via the IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. Following the unblinding, the Investigator shall notify the Medical Monitor and/or Study Director (or designee). After emergency unblinding through the IRT, participant will be discontinued from study treatment and move to safety follow-up phase.

In cases of accidental unblinding, contact the Medical Monitor (or designee) and ensure that every attempt is made to preserve the blind.

Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor (or designee). Non-emergency unblinding will be requested by the Principal Investigator or appointed designee upon approval by the Medical Monitor. The latter will start internal process (outside of IRT system) to unblind the participants' treatment. The unblinded participant continues to receive the randomized study treatment.

With Protocol Amendment 03, treatment assignment remains blinded through the Neoadjuvant and Surgical phases. When participants enter the Adjuvant phase, treatment assignment will be open label to both the Sponsor and the study sites. For participants entering the Adjuvant phase or already in the Adjuvant or Follow-up phases at the time Protocol Amendment 03 is approved,

treatment assignment will be provided. Treatment assignment will only be provided after the pathological response information is entered in the CRF.

Designated staff of BMS Research & Development (R&D) may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of PK samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS R&D (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples from control group participants.

The pharmacist at the site and/or designee will be unblinded to the randomized treatment assignments in order to prepare blinded study treatment from bulk supplies, as needed. This (these) individual(s) will be unblinded to study drug identification but will not be involved in any other aspect of study conduct.

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.

Recommendations for dose reduction, delay, interruption, or discontinuation of individual study drugs in the management of study drug-related adverse reactions are summarized below. For additional information, please refer to individual drug labels. 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 electronic case report form (eCRF).

7.4.1 Dose Modifications for Nivolumab

Participants who require a dose delay for nivolumab or nivolumab placebo should be re-evaluated and resume treatment at the next cycle or within ± 3 days from scheduled chemotherapy dose when retreatment criteria are met. AE criteria for delaying, resuming, and discontinuing of study treatment is provided in Table 7.4.1-1.

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

Drug-related AE per CTCAE v5.0	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria[a]
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1
	Grade 3 or 4	Permanently discontinue	
Hepatic			
AST, ALT, or T.bili Increased	AST or ALT >3x and ≤5x ULN or T.Bili >1.5x and ≤3x ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline after discussion with the Medical Monitor.
	AST or ALT >5x ULN or T.Bili >3x ULN, regardless of baseline value	Permanently discontinue	
	Concurrent AST or ALT >3x ULN and T.Bili >2x ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement,

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

Drug-related AE per CTCAE v5.0	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria[a]
			participant may not require discontinuation of study drug
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value, or is adequately controlled with glucose-controlling agents
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug
Hypophysitis/ Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area

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

Drug-related AE per CTCAE v5.0	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria[a]
	SJS, TEN or DRESS	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to ≤ 10% body surface area
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Neurological			
GBS	Any Grade	Permanently discontinue	
MG	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if encephalitis is not drug-related, then dosing may resume when AE resolves
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if myelitis is not drug-related, then dosing may resume when AE resolves
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	
Cardiovascular			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated	Permanently discontinue	
Cardiac Troponin I or Troponin T Increased	Asymptomatic	Delay dose	All troponin elevations (including asymptomatic elevations) will require a dose delay in order for the participant to undergo a cardiac evaluation (via prompt

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

Drug-related AE per CTCAE v5.0	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria[a]
			cardiology consult) and a confirmatory repeat within 24 hours. If troponin elevation is not confirmed within 24 hours in an asymptomatic participant, the dose delay may not be needed provided that the cardiac evaluation is completed, and a cardiologist has made the recommendation to proceed with treatment. Otherwise, if troponin elevation is confirmed, dosing may resume when AE resolves to baseline
Other Clinical AEs			
Pancreatitis: Amylase or Lipase Increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay Dosing may resume when participant becomes asymptomatic
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If participant requires oral steroids for uveitis, then permanently discontinue study drug
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-related AE (**not listed above**)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	

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

Drug-related AE per CTCAE v5.0	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria[a]
Other Laboratory Abnormalities			
Other Drug-related Laboratory Abnormality (**not listed above**)	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Infusion Reactions **(manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)**			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	See Section 7.4.1.3 (Treatment of Nivolumab Infusion Reaction)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DRESS, drug reaction with eosinophilia and systemic symptoms; GBS, Guillain-Barre Syndrome; MG, Myasthenia Gravis; SJS, Stevens-Johnson syndrome; T.bili, total bilirubin; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.

[a] All actions taken, clarifications, exceptions, and resume criteria apply to nivolumab.

7.4.1.1 Dose Delay Criteria for Nivolumab

Nivolumab administration should be delayed for the following:

- For participants receiving nivolumab, dose delay criteria apply for all drug-related AEs (regardless of) whether the event is attributed to nivolumab. Delay administration of nivolumab if any of the delay criteria in Table 7.4.1-1 are met. Delay nivolumab dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
- Study treatment must also be delayed for SARS-CoV-2 infections, either confirmed or suspected.
- For participants who require delay of nivolumab reevaluate weekly, or more frequently if clinically indicated, and resume nivolumab dosing when the retreatment criteria are met (see Table 7.4.1-1). Continue tumor assessment per protocol, even if dosing is delayed.

The other study treatments may still be administered.

7.4.1.2 Criteria to Resume Treatment with Nivolumab

- Participants may resume treatment with study treatment following Table 7.4.1-1.
- Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after all of the following:
- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen); and
- Resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications); and
- Evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment; **and**
- Consultation with the Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.

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.

7.4.1.3 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, arthralgia, 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 (or designee) and reported as an SAE, if it meets the criteria. Infusion reactions should be graded according to

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 guidelines.

Treatment recommendations are provided below based on CTCAE v5.0 and may be modified based on local treatment standards and guidelines, as appropriate:

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

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg, at least 30 minutes before subsequent nivolumab/nivolumab placebo 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 approximately 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor the 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/nivolumab placebo 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 the participant until recovery of the symptoms.

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

7.4.2 Dose Modifications for Chemotherapy

Recommendations for dose reduction, delay, interruption, or discontinuation of individual study drugs in the management of study drug-related adverse reactions are summarized below.

Participants who require a dose delay for chemotherapy should be re-evaluated and resume treatment at the next cycle, when retreatment criteria are met.

For participants who meet criteria to delay chemotherapy (paclitaxel, doxorubicin or epirubicin, or cyclophosphamide), the corresponding drug will be delayed and nivolumab or nivolumab placebo will also be delayed in an effort to maintain synchronization of the combination regimen.

Efforts to maintain dose intensity and the intended treatment schedule are recommended.

7.4.2.1 Dose Delay for Paclitaxel Therapy

It is permissible, in cases of a dose held due to AEs, to omit the dose in the cycle in order to re-synchronize the participant with the next cycle visit.

Chemotherapy delay should not exceed 6 weeks. In the event that treatment with chemotherapy needs to be delayed beyond 6 weeks due to toxicity, a participant may continue on study to receive neoadjuvant AC study treatment at an earlier timepoint, or may transition to the Adjuvant (Post-surgery) Phase at an earlier timepoint. Such treatment decisions will be at the discretion of the Investigator and participant, and upon consultation with the Medical Monitor (or designee).

Paclitaxel should be delayed for the following:

- Presence of febrile neutropenia or neutropenia < 1000 cells/mm^3 for > 1 week, despite the use of growth factors.
- Platelets < 100,000/mm^3.
- Any Grade ≥ 2 neuropathy (sensory or motor).
- Any Grade ≥ 2 non-skin, chemotherapy-related AE, except for alopecia, fatigue, or laboratory abnormalities.
- Any Grade 3 skin chemotherapy-related AE.
- Any Grade 3 chemotherapy-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia does not require a dose delay.
  - Delay if total bilirubin > 1 × ULN or if AST and/or ALT > 1.5 × ULN occurs concomitant with alkaline phosphatase (ALP) > 2.5 × ULN.
- Any AE, laboratory abnormality, or inter-current illness which, in the judgment of the Investigator, warrants omitting the dose of study medication.

Subsequent dose reductions may be required, per Section 7.4.2.2 (Dose Reductions for Paclitaxel Chemotherapy). Granulocyte colony-stimulating factor (G-CSF; ie, filgrastim or pegfilgrastim) or human granulocyte-macrophage colony-stimulating factor (GM-CSF) treatment is permitted for participants receiving chemotherapy and is required during the AC portion of chemotherapy if given as Q2W dose-dense regimen.[9,118] Such primary prophylaxis should be administered per the ASCO, European Organisation for the Research and Treatment of Cancer (EORTC) or European Society for Medical Oncology (ESMO) guidelines, or per local standard practice for all participants receiving ddAC chemotherapy. Participants may receive growth factors (including G[M]-CSF and erythropoietin) at the discretion of the Investigator, in accordance with institutional and/or current ASCO guidelines for secondary prophylaxis.

A dose given more than 3 days after the intended dose date will be considered a dose delay. Longer delays may be allowed following discussion with the Medical Monitor (or designee).

7.4.2.2 Dose Reductions for Paclitaxel Chemotherapy

The full dose of paclitaxel is 80 mg/m^2. This dose may be reduced by 1 dose level to 65 mg/m^2 and subsequently by 1 more dose level to 52 mg/m^2. In the case of any toxicity requiring more than 2 dose reductions, paclitaxel must be discontinued, unless the participant is benefitting from therapy.

Any participant experiencing the following toxicities described below (see Table 7.4.2.2-1) may have the paclitaxel dose reduced by 1 dose level for all subsequent cycles.

Table 7.4.2.2-1: Dose Modifications for Paclitaxel Chemotherapy

Toxicity	Paclitaxel Dose
Neutrophils ≥ 1000/mm^3 and platelets ≥ 100,000/mm^3	Maintain dose
Neutrophils 500-999/mm^3 and platelets ≥ 100,000/mm^3	Hold therapy until ANC ≥ 1000/mm^{3}and resume at same dose/ may use prophylactic G-CSF or GM-CSF
Grade 4 neutropenia lasting ≥ 7 days	Prophylactic G-CSF or GM-CSF and/or decrease 1 dose level
Febrile neutropenia (≥ 38.5°C) associated with ANC < 1000/mm^3	Prophylactic G-CSF or GM-CSF and/or decrease 1 dose level
Platelets < 100,000/mm^3	Decrease 1 dose level
Neuropathy (sensory or motor), Grade 2 lasting ≥ 7 days OR Grade 3 lasting < 7 days	Decrease 1 dose level
Grade 3 neuropathy (sensory or motor) lasting ≥ 7 days OR Grade 4 neuropathy (sensory or motor)	Discontinue paclitaxel
≥ Grade 3 stomatitis, vomiting, diarrhea	Decrease 1 dose level
Other Grade ≥ 3 non-hematologic toxicities[a]	Decrease 1 dose level or discontinue therapy as medically indicated

Abbreviations: ANC, absolute neutrophil count; C, Celsius; G-CSF, granulocyte colony-stimulating factor; GM-CSF, human granulocyte-macrophage colony-stimulating factor; mm^3, cubic millimeters.

[a] Despite adequate/maximal medical intervention and/or prophylaxis. Except Grade 3 transient fatigue or joint or muscle pain, for which no dose modifications are required.

A maximum of 2 dose reductions per chemotherapy are permitted, unless otherwise noted; if additional reductions are required, that particular study drug must be discontinued. Once a dose has been decreased, it should remain reduced for all subsequent dosing unless the dose is further reduced. No dose escalations will be allowed.

7.4.2.3 Criteria to Resume Treatment with Paclitaxel Chemotherapy

Participants may resume treatment with paclitaxel when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, 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.
- Participants with decreased neutrophil counts, or with elevations in total bilirubin, AST, or ALT must meet criteria for resuming treatment, according to the boxed warning contained within the paclitaxel prescribing information.
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.2 [Chemotherapy Dose Discontinuation]) should have treatment permanently discontinued.

Participants that meet retreatment criteria for the chemotherapy, but have not yet met retreatment criteria for nivolumab or nivolumab placebo, are to receive the chemotherapy alone and delay nivolumab or nivolumab placebo (Section 7.4.1.1 Dose Delay Criteria for Nivolumab).

7.4.2.4 Dose Delay for Anthracycline and Cyclophosphamide Chemotherapy

Chemotherapy delay should not exceed 6 weeks. In the event that treatment with chemotherapy needs to be delayed beyond 6 weeks due to toxicity, a participant may transition to the Adjuvant (Post-surgery) Phase at an earlier timepoint. Such treatment decisions will be at the discretion of the Investigator and participant, and upon consultation with the Medical Monitor (or designee).

Participants may only receive a cycle of anthracycline (doxorubicin or epirubicin) and cyclophosphamide if absolute neutrophil count (ANC) is ≥ $1000/mm^3$, platelets are ≥ $100{,}000/mm^3$, and treatment-related non-hematologic toxicity has resolved to baseline or Grade 1 (except for Grade 2 alopecia, myalgia, arthralgia, and fatigue, for which resolution is not required). Once the dose at the start of a new treatment cycle has been reduced, no re-escalation is permitted.

7.4.2.5 Dose Reductions for Anthracycline-Cyclophosphamide Chemotherapy

The full dose of doxorubicin is 60 mg/m^2 and that of cyclophosphamide is 600 mg/m^2. Doses of anthracycline and cyclophosphamide may be reduced jointly or stopped, depending on the toxicity (Table 7.4.2.5-1). Growth factors, such as G-CSF or GM-CSF, may be used at the discretion of the Investigators, in accordance with institutional and/or current ASCO guidelines; per such guidelines, G-CSF or GM-CSF support is considered SOC for patients undergoing ddAC chemotherapy, as primary prophylaxis. However, recurrence of neutropenia despite adequate growth factor support would allow dose reduction in addition to growth factor support.

A maximum of 2 AC dose reductions are permitted; if additional reductions are required, that particular study drug must be discontinued. Once a dose has been decreased, it should remain reduced for all subsequent dosing, unless the dose is further reduced. No dose escalations will be allowed.

Participants will receive a maximum of 4 cycles of AC chemotherapy.

Table 7.4.2.5-1: Dose Levels of AC Chemotherapy

Dose Level	Doxorubicin/Cyclophosphamide	Epirubicin/Cyclophosphamide
1 (full dose)	60/600 mg/m^2	90/600 mg/m^2
-1	45/450 mg/m^2	75/450 mg/m^2
-2	33/330 mg/m^2	56/330 mg/m^2

Abbreviations: m^2, squared meter; mg, milligram.

Participants experiencing toxicities described in Table 7.4.2.5-2 during the previous cycle may receive colony-stimulating growth factors and/or have the AC doses reduced by approximately 20% of the previous dose or discontinue AC, depending on the toxicity.

Table 7.4.2.5-2: Dose Modifications for AC Chemotherapy

Toxicity	AC
Grade 4 neutropenia lasting ≥ 7 days	Prophylactic G-CSF or GM-CSF and/or decrease 1 dose level
Febrile neutropenia (≥ 38,3°C) associated with ANC < 1000/mm^3	Prophylactic G-CSF or GM-CSF and/or decrease 1 dose level
Infection with neutropenia ANC < 1000/mm^3	Prophylactic G-CSF or GM-CSF and/or decrease 1 dose level
Failure of platelets to recover to ≥ 100,000/mm^3 at next scheduled retreatment	Decrease 1 dose level
Platelets < 50, 000/mm^3 with significant bleeding or requiring blood transfusion	Decrease 1 dose level

Table 7.4.2.5-2: Dose Modifications for AC Chemotherapy

Toxicity	AC
Platelets < 25, 000/mm^3	Decrease 1 dose level
≥ Grade 3 stomatitis, vomiting, diarrhea	Decrease 1 dose level
≥ Grade 3 cardiovascular toxicity (eg, arrhythmias, CHF or Grade ≥ 3 LVEF)	Discontinue AC and manage the cardiac condition
Other Grade ≥ 3 non-hematologic toxicities[a]	The treating physician may adjust dose or discontinue therapy as medically indicated

Abbreviations: °C, degrees Celsius; AC, anthracycline and cyclophosphamide; ANC, absolute neutrophil count; CHF, congestive heart failure; G-CSF, granulocyte colony-stimulating factor; GM-CSF, human granulocyte-macrophage colony-stimulating factor; LVEF, left ventricular ejection fraction; mm^3, cubic millimeters.

[a] Despite adequate/maximal medical intervention and/or prophylaxis, except Grade 3 transient fatigue or joint or muscle pain, for which no dose modifications are required.

If 1 of the study drugs is delayed due to drug-related toxicities during a treatment cycle, the other study drugs in the regimen may be administered at the discretion of the Investigator; when dosing is resumed, dose reduction should only be applied to the study drug that was withheld.

7.4.2.6 Criteria to Resume Treatment with Anthracycline-Cyclophosphamide Chemotherapy

Participants may resume treatment with study treatment when the drug-related AE(s) resolve as follows:

- Participants may resume treatment with an anthracycline when the ANC returns to ≥ 1000/mm^3, the platelet count returns to ≥ 100,000/mm^3, and all other drug-related toxicities have returned to baseline or Grade ≤ 1 (or Grade ≤ 2 for alopecia and fatigue).
  - If a participant fails to meet criteria for reinitiating treatment, then treatment should be delayed, and the participant should be re-evaluated weekly or more frequently, as clinically indicated.
- Participants may resume treatment with cyclophosphamide when the ANC returns to ≥ 1500/mm^3, the platelet count returns to ≥ 50,000/mm^3, severe infections have improved to ≤ Grade 1, and all other drug-related toxicities have returned to baseline or Grade ≤ 1 (or Grade ≤ 2 for alopecia and fatigue).
  - If a participant fails to meet criteria for reinitiating treatment, then the treatment should be delayed and the participant should be re-evaluated weekly or more frequently, as clinically indicated.
  - Participants that meet retreatment criteria for the chemotherapy, but have not yet met retreatment criteria for nivolumab or nivolumab placebo, are to receive the chemotherapy alone and delay nivolumab or nivolumab placebo until the subsequent chemotherapy treatment.

7.4.3 Dose Modifications for Investigator's Choice Endocrine Therapy

No dose reductions are permitted for the ET (ie, tamoxifen, anastrozole, letrozole, or exemestane). Dose delay or interruption may be considered.

Participants who require a dose delay or interruption for ET should be re-evaluated and resume treatment when retreatment criteria are met.

For participants who meet criteria to delay ET (ie, tamoxifen, anastrozole, letrozole, or exemestane), the corresponding drug will be delayed but nivolumab may be continued as scheduled.

Efforts to maintain the intended treatment schedule are recommended.

7.4.3.1 Dose Delay for Investigator's Choice Endocrine Therapy

Dose delay or interruption for a period of up to 3 consecutive weeks for ET-related AEs are permitted at the discretion of the Investigator.

All possible efforts should be made to maintain the participant on ET during study treatment, through the use of dose delay, interruption (ie, drug holiday), or rotation to another ET agent.

7.4.3.2 Criteria to Resume Treatment with Investigator's Choice Endocrine Therapy

More detailed information regarding resuming treatment following AEs resulting in dose delay or interruption of the individual ET agents may be found in the respective Patient Information Leaflets, Package Inserts,[61,62,63,64] and SmPCs.[70,71,72,73]

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.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability, as well as the ET dosing diary, participant's medical records and eCRF. Study drug will be administered in the clinic by trained personnel. Drug accountability should be reviewed by the site study staff at each visit. 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 Period and Follow-up Period in the appropriate section of the eCRF at each visit.

All medications (prescription and over-the-counter [OTC]), vitamin and mineral supplements, and/or herbs taken by the participant, from the Screening Period through the 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.

ET therapy taken after completion of the Adjuvant (Post-surgery) Phase, will be collected as concomitant medication.

Prior anti-cancer treatments will be recorded during the Screening Period and documented on the appropriate eCRF. Any subsequent anti-cancer therapy will be recorded until end of study or death, in the appropriate section of the eCRF.

7.7.1 Prohibited and/or Restricted Treatments

7.7.1.1 Prohibited and/or Restricted Treatments for Nivolumab

The following medications are prohibited during study treatment (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]) within 30 days prior to first dose, during treatment and until 100 days after the last dose.
- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.2 [Exclusion Criteria]).
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, CDK4/6 inhibitors, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of BC) not already specified in the protocol.
- Treatment with complementary medications (eg, herbal supplements, traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.

7.7.1.2 Prohibited and/or Restricted Treatments for Chemotherapy and Endocrine Therapy

The following medications not already specified in the protocol are prohibited and/or restricted during the study treatment. Medications taken within 4 weeks prior to study drug administration must be recorded on the eCRF.

- **Anticancer agents:** No additional investigational or commercial anticancer agents (ie, chemotherapy, CDK4/6 inhibitors, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, radiation therapy in the neoadjuvant setting, or standard or investigational agents for treatment of BC) other than those specified in the protocol will be permitted during the study treatment. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted during the study treatment. Use of megestrol acetate as an appetite stimulant is not permitted.
- **Investigational agents:** Exposure to any investigational drug or placebo within 4 weeks of prior study drug administration or during the study treatment.
- **Hormonal agents:** Concurrent use of an oral, injectable, or implantable hormonal contraceptive agent.
- **OTC Agents:** No concomitant medications (prescription, OTC, or herbal) are to be administered during the study treatment, unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the eCRF.
- **Other prohibited and/or restricted treatments:**
  - Co-administration of letrozole, anastrozole, or exemestane with other anti-estrogens or estrogens should be avoided.
  - Co-administration of tamoxifen with potent cytochrome p-450 (CYP)2D6 inhibitors (eg, paroxetine, fluoxetine, quinidine, cinacalcet, bupropion) should be avoided.
  - Co-administration of paclitaxel with known inducers of either CYP2C8 or CYP3A4 (eg, rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended.
  - Stop cimetidine during treatment with epirubicin.
  - Neither doxorubicin nor epirubicin should be administered with other cardiotoxic agents or other cardioactive compounds (eg, calcium channel blockers), unless the participant's cardiac function is closely monitored.
  - Cyclophosphamide is inactive, but is metabolised in the liver, mainly by CYP2A6, 2B6, 2C9, 2C19 and 3A4, into two active metabolites. Planned co-administration or sequential administration of other substances or treatments with cyclophosphamide that could increase the likelihood or severity of toxic effects (by means of pharmacodynamic or pharmacokinetic interactions) requires careful individual assessment of the expected benefit and the risks (eg, CYP2B6 inducers such as rifampicin, efavirenz and nevirapine; CYP2C9 inducers such as carbamazepine, and rifampicin, and CYP3A4 inhibitors such as ketoconazole, clarithromycin, itraconazole, ritonavir, nelfinavir, and saquinavir).
  - Vaccination with a live vaccine should be avoided in participants receiving doxorubicin or epirubicin.

Additional information regarding prohibited and/or restricted medications may be found in the respective Patient Information Leaflets, Package Inserts,[56,57,58,59,60] Development Safety Update Report, or SmPCs.[65,66,67,68,69]

7.7.2 Other Restrictions and Precautions

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

Additional information about the known restrictions, precautions, and/or contraindications of study treatments may be found in the respective IBs, Patient Information Leaflets, Package Inserts,[56,57,58,59,60] Development Safety Update Report, or SmPCs.[65,66,67,68,69]

7.7.2.1 Imaging Restriction and Precautions

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

Gentle hydration before and after IV contrast should follow local 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.

7.7.3 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less-than-3-weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Participants receiving the dose-dense administration of AC must receive G-CSF or GM-CSF prophylaxis per international guidelines. In addition, men and premenopausal women may receive concurrent luteinizing hormone-releasing hormone (LHRH) agonist using an approved dose or as per local standard for these agents. Participants may receive a bisphosphonate using an approved dose or as per local standard for these agents.[119,120]

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:

- The study is terminated due to safety concerns.
- The development of nivolumab is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives.
- 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 or from the study are given below. Participants are expected to complete 8 cycles of neoadjuvant therapy, undergo definitive surgery, and complete 7 cycles of adjuvant therapy, except in the event of disease progression that precludes definitive surgery, local or distant recurrence, second primary malignancy, death, unacceptable toxicity, symptomatic deterioration, Investigator's decision to discontinue treatment, start of subsequent cancer treatment, the participant's decision to discontinue treatment or withdraw consent, the participant being lost to follow-up, or if the Sponsor terminates 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 the participant to provide this information (see Section 8.2 [Discontinuation from the Study]).
- 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.)
- In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Medical Monitor (or designee) of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if

necessary for participant safety). See Section 9.2.6 (Pregnancy). For additional details on country specific requirements, refer to Appendix 9.

- Occurrence of an EFS event. See Section 9.1.2 (Definition of Event-free Survival) for details.
- Disease progression. See Section 9.1.2 (Definition of Event-free Survival) for details.
- See Section 8.1.1 for Nivolumab Discontinuation criteria.
- Start of subsequent cancer treatment, including abemaciclib, during the Adjuvant phase.
- Emergency unblinding prior to the Adjuvant phase.

All participants who discontinue study treatment should comply with protocol-specified procedures, as outlined in Section 2 (Schedule of Activities) and Section 7 (Treatment). The only exception to this requirement is when a participant withdraws consent for all study procedures (see Section 8.2 [Discontinuation from the Study]), 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

Nivolumab treatment should be permanently discontinued if meets criteria for discontinuation in Table 7.4.1-1.

- Any event that leads to delay in dosing lasting > 8 weeks with the Q3W schedule or > 6 weeks with the Q2W schedule in the Neoadjuvant (Pre-surgery) Phase, or > 10 weeks with the Q4W schedule in the Adjuvant (Post-surgery) Phase, from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 8 weeks with the Q3W schedule, > 6 weeks with the Q2W schedule, or > 10 weeks with the Q4W schedule from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee).
    - Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks with the Q3W schedule, > 6 weeks with the Q2W schedule, or > 10 weeks with the Q4W schedule, the Medical Monitor (or designee) must be consulted.
    - Tumor assessments should continue per protocol, even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks, or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

- The underlying reason(s) for any instance of study treatment discontinuation should be documented in the eCRF.

8.1.2 Chemotherapy Dose Discontinuation

If unacceptable toxicities related to paclitaxel occur, as determined by Investigator judgment and in accordance with the prescribing information, paclitaxel may be discontinued, but other study treatments may be continued. For example, a participant may continue on study to receive neoadjuvant AC study treatment at an earlier timepoint, or may transition to the Adjuvant (Post-surgery) Phase at an earlier timepoint. Such treatment decisions will be at the discretion of the Investigator and participant, and upon consultation with the Sponsor's Medical Monitor (or designee).

If unacceptable toxicities related to doxorubicin or epirubicin and/or cyclophosphamide occur, as determined by Investigator judgment and in accordance with the prescribing information, doxorubicin or epirubicin and/or cyclophosphamide may be discontinued, but other study treatments may be continued. For example, a participant may transition to the Adjuvant (Post-surgery) Phase at an earlier timepoint. Such treatment decisions will be at the discretion of the Investigator and participant, and upon consultation with the Sponsor's Medical Monitor (or designee).

The underlying reason(s) for any instance of study treatment discontinuation should be documented in the eCRF.

8.1.3 Endocrine Therapy Dose Discontinuation

If unacceptable toxicities related to the Investigator's choice of ET occur, as determined by Investigator judgment and in accordance with the prescribing information, the Investigator's choice of ET may be discontinued, but the other study treatments may be continued.

The underlying reason(s) for any instance of study treatment discontinuation should be documented in the eCRF.

8.1.4 Post-study Treatment Study Follow-up

In this study, pCR is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data, as required and in line with Section 5 (Study Design) and Section 8.1 (Discontinuation from Study Treatment), until death or the conclusion of the study.

8.2 Discontinuation from the Study

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

- Participants should notify the Investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate 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 the 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 third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The Investigator will maintain a

screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of a participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes, provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).

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

If a participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations), the participant should be immediately evaluated to rule out cardiac or pulmonary toxicity.

Some of the assessments referred to in this section may not be captured as data on 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 Pathological Assessment of Effect

9.1.1.1 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).

Tumor and lymph node collection from definitive surgical resection is mandatory on the day of surgery. Tumor sample acquisition guidelines and submission process will be outlined in the study Laboratory Manual. Additional details are provided in the Pathology Manual.

9.1.1.2 Residual Cancer Burden Determination

Residual cancer burden (RCB) is estimated from routine pathologic sections of the primary breast tumor site and the regional lymph nodes after the completion of neoadjuvant therapy.[121] Six variables are included in a calculation formula.

Local 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 include the following:

- 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.
- The overall cancer cellularity (percentage of area).
- The proportion of in situ disease (percentage of area).
- The number of positive lymph nodes.
- 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 the Pathology Manual.

9.1.2 Definition of Event-free Survival

EFS is defined as the time from randomization to disease progression that precludes definitive surgery, results in a local or distant recurrence, results in a second primary malignancy, or results in death due to any cause.

The diagnosis of a BC recurrence or second primary tumor should be confirmed histologically whenever clinically feasible. In cases where confirmation is not feasible, efforts should be made to obtain an autopsy report.

With respect to timing of an EFS event, the earliest date of diagnosis of recurrent disease should be used and recorded. This date should be based on objective clinical, radiological, histological, or cytological evidence. The recurrence of disease should correspond to the date of the first diagnosis of lesion (ie, an objective finding), and not to the date of occurrence of the first symptom (eg, a participant presenting with shortness of breath is found to have possible lesions in the lungs on thorax CT scan of uncertain significance). If a subsequent CT scan confirms disease progression, the date of the first diagnostic CT scan should be taken as the date of recurrence, and not the date of presentation with shortness of breath. The date of disease relapse is the time of first appearance of a suspicious lesion (in a radiological procedure in this example), later proven to be a definitive recurrence or metastasis.

Details on EFS events are provided below:

- Worsening of disease that precludes surgery (as determined by the Investigator).
- If surgery is possible but not performed for other reasons (eg, participant refuses, worsening of medical condition), then the participant may continue on study treatment and will be considered to have an EFS event if and when there is defined progression or biopsy confirmed local recurrence.
- If surgery is attempted but gross resection is abandoned, due to unresectable tumor or worsening of disease, then that will be considered an EFS event.
- If surgery is completed with no or only microscopic residual disease (positive margins, not visible on imaging), then the participant will continue on study and will be considered to have an EFS event if and when radiographically visible recurrence occurs.
- If surgery is completed after the development of distant disease (visible on imaging) or in-transit disease, it will be considered as an EFS event.
- Local recurrence
  - Local relapse: Defined as the area bound by the midline of the sternum, extending superiorly to the clavicle and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or extending across the midline will be considered as evidence of local recurrence. Provide histologic or cytological confirmation if clinically feasible.
  - Regional relapse: Defined as evidence of tumor in the axillary scar, ipsilateral nodal areas (axillary, internal mammary, supraclavicular), extra-nodal soft tissue of the ipsilateral axilla, as well as skin or soft tissues within the regional area. Provide histologic, cytological, or radiologic confirmation if clinically feasible.
  - Contralateral BC: Defined as invasive tumor in the contralateral breast.
- Distant recurrence
  - Distant relapse: Defined as evidence of tumor beyond the local-regional level, as previously defined. This includes the following: lymph nodes not included in the areas defined above (ie, contralateral supraclavicular, contralateral axilla, paratracheal); skin not included in the areas defined above; liver; lung; bone; central nervous system; other sites not defined above. Provide histologic or cytological confirmation if clinically feasible.
- Development of a second non-breast primary cancer
  - Defined as any other histopathologically proven invasive cancer. Excluded are non-melanoma skin cancer, in situ carcinoma of the cervix, in situ carcinoma of the breast (LCIS/DCIS), and ipsilateral invasive primary BC with the same histologic features of the first tumor. Provide histologic or cytological confirmation if clinically feasible.
- Death due to any cause.

9.1.3 Definition of Disease-free Survival

DFS is defined as the time after surgery to disease progression that results in a local or distant recurrence, results in a second primary malignancy, or results in death due to any cause. Details on DFS events are provided below:

- Local recurrence

  - Local relapse: Defined as the area bound by the midline of the sternum, extending superiorly to the clavicle and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or extending across the midline will be considered as evidence of local recurrence. Provide histologic or cytological confirmation if clinically feasible.
  - Regional relapse: Defined as evidence of tumor in the axillary scar, ipsilateral nodal areas (axillary, internal mammary, supraclavicular), extra-nodal soft tissue of the ipsilateral axilla, as well as skin or soft tissues within the regional area. Provide histologic, cytological, or radiologic confirmation if clinically feasible.
  - Contralateral BC: Defined as invasive tumor in the contralateral breast.
- Distant recurrence
  - Distant relapse: Defined as evidence of tumor beyond the local-regional level, as previously defined. This includes the following: lymph nodes not included in the areas defined above (ie, contralateral supraclavicular, contralateral axilla, paratracheal); skin not included in the areas defined above; liver; lung; bone; central nervous system; other sites not defined above. Provide histologic or cytological confirmation if clinically feasible.
- Development of a second non-breast primary cancer
  - Defined as any other histopathologically proven invasive cancer. Excluded are non-melanoma skin cancer, in situ carcinoma of the cervix, in situ carcinoma of the breast (LCIS/DCIS), and ipsilateral invasive primary BC with the same histologic features of the first tumor.
- Death due to any cause.

9.1.4 Definition of Distant Metastasis-free Survival

Distant metastasis-free survival (DMFS) is defined as the time from randomization to disease progression that results in a distant recurrence. Details on DMFS events are provided below:

- Distant recurrence
  - Distant relapse: Defined as evidence of tumor beyond the local-regional level as previously defined. This includes the following: lymph nodes not included in the areas defined above (ie, contralateral supraclavicular, contralateral axilla, paratracheal); skin not included in the areas defined above; liver; lung; bone; central nervous system; other sites not defined above. Provide histologic or cytological confirmation if clinically feasible.

9.1.5 Imaging Assessment for the Study

Screening and on-study images should be acquired as outlined in Section 2 (Schedule of Activities).

Radiological response for progression or local or distant recurrence will be assessed by the Investigator.

Images will also be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study until the EFS event is documented. Prior to

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

Tumor assessments at other timepoints may be performed if clinically indicated, and should be submitted to the central imaging vendor as soon as possible. X-rays that clearly demonstrate interval progression of disease (eg, most commonly as unequivocal lesions that are unmistakably new) should be submitted to the central imaging vendor; otherwise, radiographs do not need to be submitted centrally. Any additional imaging that may demonstrate tumor response or disease recurrence or disease progression (including scans performed at unscheduled timepoints and/or at an outside institution) should be submitted to the central imaging vendor.

Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints. Tumor assessments for all participants should continue per protocol, even if dosing is delayed or discontinued. Tumor measurements should be made by the same Investigator or radiologist for each assessment, whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the modified RECIST v1.1 criteria (refer to Appendix 8).

9.1.5.1 Objective Response Rate

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

For the purposes of this study, tumor response assessments will be performed by bilateral ultrasound or mammogram of breast and axilla or breast MRI. 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.

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.

9.1.6 Clinical Response by Physical Examination

Clinical response by physical examination (PE; palpation) will be assessed throughout study visits as outlined in Section 2 (Schedule of Activities).

Target lesions should be followed clinically and their clinical size recorded at baseline. Measurements are required at the completion of the PTX neoadjuvant cycles and at the completion of the Neoadjuvant Phase prior to Surgery. In situ carcinoma does not represent a non-target lesion and should not be recorded or followed.

9.1.7 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 surgery (mastectomy or BCS) at the time of diagnosis or baseline and the actual surgery the participants undergo after completion of the study treatment will be captured on

the eCRF, to assess BCS rate with neoadjuvant chemotherapy with or without nivolumab in participants with untreated high-risk ER+, HER2- primary BC.

9.1.8 Clinical Outcomes Assessments

The evaluation of COAs is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting. Additionally, generic health-related quality of life (HRQOL) measures provide data needed for calculating utility values to inform health economic models.

Participants will be asked to complete the EORTC Quality of Life Questionnaire–Core 30 (QLQ-C30), EORTC Quality of Life Questionnaire-Breast Cancer-specific Module (QLQ-BR23), 5-level EQ-5D (EQ-5D-5L) questionnaires and selected items Functional Assessment of Chronic Illness Therapy General Physical Item 5 (FACIT GP5) as indicated in Section 2 (Schedule of Activities). The questionnaires will be provided in the participant's preferred language, if available, and may be administered using electronic devices or a web-based platform. At sites, where the electronic device is not available at study start or where the language is not yet available in the device, paper administration of questionnaires will be permitted. When the electronic device and/or language becomes available at those sites, paper administration of the questionnaires will no longer be allowed. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternative administration methods may be required after consultation with Sponsor or the Sponsor's representative.

The questionnaires should be administered during the Neoadjuvant (Pre-surgery) Phase, at the pre-surgery visit, at the post-surgery visit, during the Adjuvant (Post-surgery) Phase, and at the end of adjuvant therapy at the start of any visit before the participant sees the physician and before any study-related procedures are performed (with the exception of procedures completed 72 hours prior to a visit). Section 2 (Schedule of Activities) provides information regarding the timing of COAs.

9.1.8.1 EORTC QLQ-C30

The EORTC QLQ-C30 will be used to assess the effects of disease symptoms on functioning and well-being. The EORTC QLQ-C30[122] is the most commonly used QOL instrument in oncology trials. The instrument's 30 items are divided among 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/QOL scale. With the exception of 2 items included in the global health/QOL scale, for which responses range from 1 (very poor) to 7 (excellent), item responses range from 1 (not at all) to 4 (very much). Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric, such that higher values indicate better functioning or QOL or a higher level of symptoms. A score difference of 10 will be used as an estimate of a clinically meaningful difference for the subscales of the EORTC QLQ-C30.[123]

9.1.8.2 EORTC QLQ-BR23

The EORTC QLQ-BR23[124] will be used to assess symptoms and QOL domains specific to a BC patient population. It is a valid and reliable measure of concerns and symptoms specific to BC and its treatment. The questionnaire's 23 items are divided among multi-item scales measuring systemic therapy side effects (7 items), bodily image (4 items), breast symptoms (4 items), arm symptoms (3 items), and sexual functioning (2 items), as well as single-item measures of sexual enjoyment, future perspective, and bother due to hair loss. The questionnaire's items use a 4-point response scale ranging from 1 (Not at all) to 4 (Very much). Similar to the EORTC QLQ-C30, raw scores for the EORTC QLQ-BR23 are transformed to a 0-100 metric, such that higher values indicate better functioning or QOL or a higher level of symptoms. A score difference of 10 will be used as an estimate of a clinically meaningful difference for the subscales of the EORTC QLQ-BR23.

9.1.8.3 FACIT GP5

A single item drawn from the FACIT measurement system, item GP5, will be administered to assess the overall extent of perceived bother due to symptomatic AEs. Evidence exists for the validity of this item and its usefulness as an overall summary measure of burden due to symptomatic treatment toxicities.[125]

9.1.8.4 EQ-5D-5L

Participants' reports of general health status will be assessed using the 5-level EQ-5D (EQ-5D-5L) questionnaire. The EQ-5D-5L has 2 components: a descriptive system and a visual analogue scale (VAS). The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension describes 5 levels of problems, including "no," "slight," "moderate," "severe," and "extreme" or "unable to." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Thus, the numbers 11111 and 55555 represent the best health state and the worst health state, respectively, described by the EQ-5D-5L. Altogether, the instrument describes 5^5 = 3,125 health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L to generate a utility index measuring the value to society of his or her current health. In addition, the EQ-5D-5L a VAS allows respondents to rate their own current health on a 101-point scale ranging from 0 = "worst imaginable" to 100 = "best imaginable." In oncology applications, post-baseline score changes 7 for the VAS are considered to be clinically meaningful.

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 Immune-mediated Adverse Events

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

9.2.2 Time Period and Frequency for Collecting AE and SAE Information

All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

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

All AEs of special interest (SAE or nonserious AE) as described in Section 9.2.1 (Immune-mediated Adverse Events) must be collected throughout the Long-term Follow-up (until the end of the study).

All AEs (SAE or non-serious AE) related to the protocol-specified definitive breast cancer surgery should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

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 CRF 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 the updated information being available.

All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.

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.

9.2.3 Method of Detecting AEs and SAEs

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

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

9.2.4 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 9.2.1 [Immune-mediated Adverse Events]) and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, or the participant is lost to follow-up (as defined in Section 8.3 [Lost to Follow-up]) or for suspected cases, until SARS-CoV-2 infection is ruled out.

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

9.2.5 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 suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and will be reported to the appropriate regulatory authorities and Investigators, following local and global guidelines and requirements.

9.2.6 Pregnancy

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

If the Investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment or re-initiation of study treatment, a discussion between the Investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/Sponsor/IRB/IEC, as applicable.

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

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

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 the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form. For additional details on country specific requirements, refer to Appendix 9.

9.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious 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).

9.2.8 Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI (p-DILI) event. All occurrences of p-DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2.5 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.

9.2.9 Other Safety Considerations

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

9.2.10 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.

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 an 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 Record of Study Medication eCRF.

There is no available information concerning overdose with nivolumab. Depending on the symptoms and/or signs leading to the suspicion of overdose, supportive medical management should be provided. There is no specific antidote.

More detailed information regarding overdose for the study treatments may be found in the respective IBs, Patient Information Leaflets, Package Inserts,[56,57,58,59,60] Development Safety Update Report, or SmPCs.[65,66,67,68,69]

9.4 Safety

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

9.4.1 Physical Examinations

Physical examinations are to be performed as outlined in the Schedule of Activities (refer to Section 2) and as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or SAE page.

9.4.2 Vital Signs

See the Schedule of Activities (Section 2).

9.4.3 Electrocardiograms and ECHO or MUGA

See the 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 must be available within 3 calendar days prior to dosing.

- A list of the clinical laboratory analyses to be tested is provided in Table 9.4.4-1. Please see Section 2 (Schedule of Activities) for additional information on timing of assessments.

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 Blood Urea Nitrogen (BUN) or serum urea Fasting glucose Albumin - screening only	Sodium Potassium Chloride Calcium Phosphorus TSH with reflexive fT3 and fT4 at screening, TSH, with reflexive fT3 and fT4 if TSH abnormal on treatment
Serology	
Hepatitis B/C (HBV sAG, HCV antibody or HCV RNA) - screening only	
HIV testing where locally mandated. Refer to Appendix 9.	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG)	
FSH screening - only required to confirm menopause in women < age 55	
Cortisol	
Estradiol	

Abbreviations: CBC, complete blood count; FSH, follicle stimulating hormone; HBV sAG, hepatitis B surface antigen; HCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IU, international unit; L, liter; RNA, ribonucleic acid; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

9.4.5 Imaging Safety Assessment

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

9.5 Pharmacokinetics and Immunogenicity

Samples for PK and immunogenicity assessments will be collected for study participants in both the Neoadjuvant (Pre-surgery) Phase and the Adjuvant (Post-surgery) Phase at prespecified timepoints, as described in Table 9.5-1. All timepoints are relative to the start of nivolumab or nivolumab placebo administration. All timepoints during the Treatment Period are intended to

align with days on which nivolumab or nivolumab placebo is administered. If it is known that a nivolumab dose is going to be delayed/omitted, then the predose sample should be collected just prior to the next scheduled dose. However, if a predose sample is collected but the dose is subsequently delayed/omitted, an additional predose sample should not be collected. During the Adjuvant phase, when the treatment assignment is unblinded, PK and immunogenicity samples should no longer be collected in the placebo cohort for participants randomized to Arm B. Further details of sample collection, processing, and shipment will be provided in the Laboratory Procedures Manual. In addition, bioanalytics staff will be unblinded to the randomized treatment assignment in order to permit PK/IMG assays on samples from investigational arm only.

Serum PK samples will be analyzed for nivolumab concentrations by a validated ligand binding immunoassay method, and immunogenicity serum samples will be analyzed for anti-nivolumab antibodies by a validated immunoassay method. Immunogenicity serum samples may also be analyzed for nivolumab-neutralizing antibodies by a validated cell-based method. In addition, selected serum samples may be analyzed by an exploratory method that measures nivolumab, or detects anti-nivolumab antibodies for technology exploration purposes; exploratory results will not be reported. The corresponding serum samples designated for either PK, immunogenicity, or biomarker assessments may also be used for any of those analyses, if required (eg, insufficient sample volume to complete testing or to follow up on a suspected immunogenicity-related AE).

Table 9.5-1: Pharmacokinetic and Anti-drug Antibody Sampling Schedule for All Participants (CA2097FL)

Study Day of Sample Collection	Event	Time (Relative To Nivolumab/Placebo Dose) Hour:Min	Nivolumab PK Sample	Nivolumab IMG Sample
Neoadjuvant (Pre-surgery) PTX Treatment (Cycles 1-4, 1 cycle = 3 weeks)				
C1D1	Predose[a]	0:00	X	X
	EOI[b]	0:30	X	
C2D1	Predose[a]	0:00	X	X
C3D1	Predose[a]	0:00	X	X
Neoadjuvant (Pre-surgery) AC Treatment (Cycles 1-4, 1 cycle = 2 or 3 weeks)				
C1D1	Predose[a]	0:00	X	X
C2D1	Predose[a]	0:00	X	X
C3D1	Predose[a]	0:00	X	X
Adjuvant (Post-surgery)Treatment (Cycles 1-7, 1 cycle = 4 weeks) [c]				
C1D1	Predose[a]	0:00	X	X
	EOI[b]	0:30	X	
C2D1	Predose[a]	0:00	X	X
C3D1	Predose[a]	0:00	X	X
C7D1	Predose[a]	0:00	X	X

Abbreviations: AC, anthracycline + cyclophosphamide; C, cycle; D, day; EOI, end of infusion; IMG, immunogenicity; IV, intravenous; PK, pharmacokinetic; PTX, paclitaxel.

[a] All predose samples for nivolumab must be taken prior to the start of nivolumab infusion (within approximately 30 minutes prior to infusion).

[b] Since the EOI-PK sample is drawn with the intent of accurately estimating the maximum concentration of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after the EOI. If a flush is administered to clear the IV lines of the drug and to ensure the delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered.

[c] When the treatment assignment is unblinded, and the participant is assigned to Arm B, PK and IMG samples should no longer be collected.

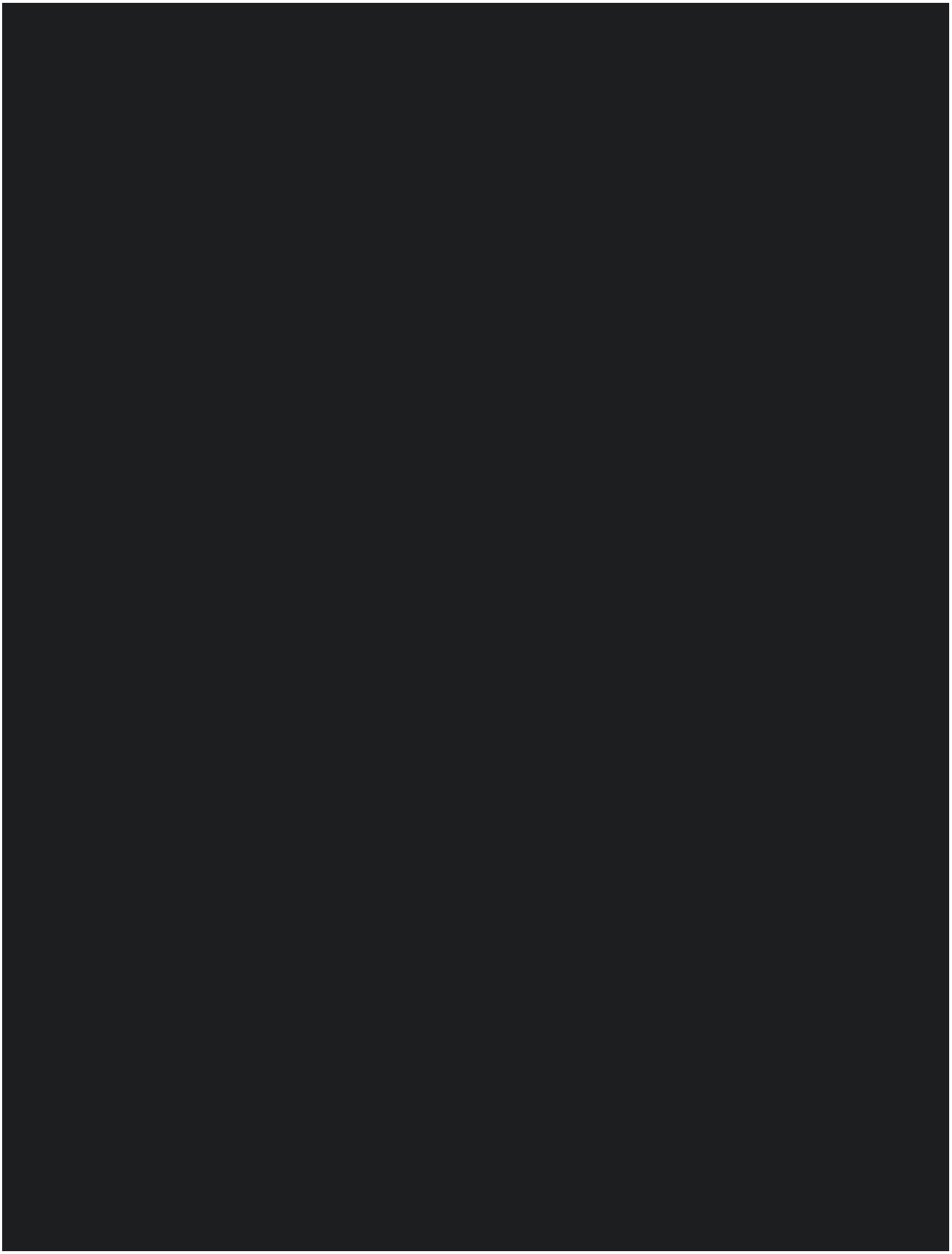
[redacted]

9.8 Biomarkers

[redacted]

[redacted]

[redacted]



[redacted]

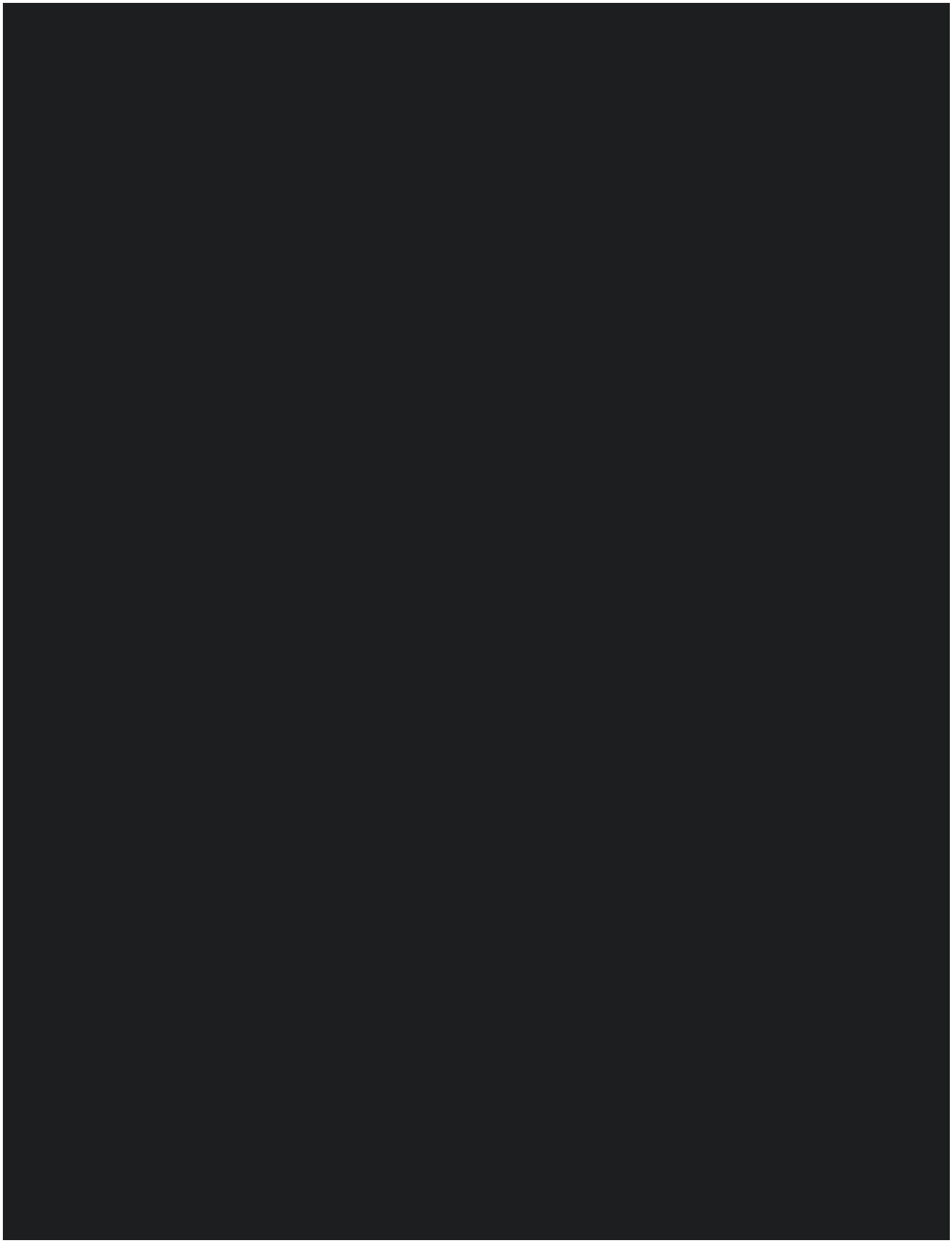
9.8.2 Tumor-based Biomarkers

9.8.2.1 PD-L1 Expression

The PD-L1 status in the study is primarily determined by an analytically validated qualitative IHC assay, PD-L1 SP142, using rabbit monoclonal anti-PD-L1 clone SP142 on the proportion of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells (% IC) of any intensity. The PD-L1 status must be confirmed from a designated central laboratory prior to randomization. Participants with PD-L1 expression (% IC) higher than the defined cutoff (eg, 1%) will be considered as the PD-L1+ population. Several secondary and exploratory endpoints of the study will be conducted in the PD-L1+ population. Participants with a PD-L1 status of unknown/not evaluable are not eligible.

In addition, PD-L1 expression determined by another quantitative IHC assay, PD-L1 28-8, using Combined Positive Score (CPS) will also be explored, in which the PD-L1 status in all PD-L1 staining cells including tumor cells, lymphocytes, and macrophages would be reported.

[redacted]



9.8.4 Additional Research Collection

This protocol will include residual sample storage for additional research (AR). Any remaining tissue collected for this study will be used for AR. Residual blood (or blood derivatives, such as serum, plasma, plasma ctDNA, PBMCs, and extracted RNA/DNA), tumor tissue (archival or fresh biopsy and extracted RNA/DNA) from tumor biopsy, and stool collections (Table 9.8.4-1) will also be retained for AR purposes.

For All US sites:

AR is required for all study participants, except where prohibited by IRBs/IECs, or academic/institutional requirements. Where 1 or more of these exceptions occurs, participation in the AR should be encouraged but will not be a condition of overall study participation.

- If the IRB/IEC and site agree to the mandatory AR retention and/or collection, then the study participant must agree to the mandatory AR as a requirement for inclusion in the study.

- If optional participation is permitted and approved, then the study participants may opt out of the additional AR and/or collection.

For non-US Sites

AR is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, IECs, or institutional requirements.

This collection for AR is intended to expand the translational R&D capability at BMS, and will support as-yet-undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, response to treatment, etc.

Sample Collection and Storage

All requests for access to samples or data for AR will be vetted through a diverse committee of the study Sponsor's senior leaders in R&D (or designee) to ensure that the research supports appropriate and well-defined scientific research activities.

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

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

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

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

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

[redacted]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Healthcare resource utilization (HCRU) data will be collected for all randomized participants using an internal measure developed for use in previous trials. The questionnaire records information about medical care encounters, including hospital admissions and their duration, outpatient visits, diagnostic tests and procedures, concomitant medications, and reasons for encounters.

HCRU data associated with medical encounters will be collected on the eCRF by the Investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient).
- Duration of hospitalization (total days length of stay, including duration by wards [eg, intensive care unit]).
- Number and character of diagnostic and therapeutic tests and procedures.
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The primary objective of this study is to compare the pCR rates between treatment groups in all randomized participants. The pCR rates will be compared at the 0.05 alpha level.

As of 16-May-2022, a total of 521 participants were randomized in a 1:1 ratio to Arm A and Arm B. See Table 10.1-1 for a summary of the power assumptions.

Given a 2-sided alpha of 0.05, 521 participants will provide approximately 87% power to detect a 10% pCR difference between Arm A and Arm B, assuming a pCR of 22% and 12% for all randomized participants in Arm A and Arm B, respectively.

The final analysis for pCR will be conducted at approximately 37 months from the first participant's randomization date.

Power calculation of pCR analysis was estimated using EAST 6.4.1.

Table 10.1-1: Power Assumptions

Population	ITT
Sample Size	521
Accrual Duration, months	29
Endpoint	pCR
Hypothesized Rates Control vs Experimental, %	12 vs 22
Alpha 2-sided	0.05
Power, %	87
Timing of pCR Final Analysis (from randomization of first participant), months	37

Abbreviations: ITT, intent to treat; pCR, pathological complete response; vs, versus.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined in Table 10.2-1.

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 (ITT Population)	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 efficacy analyses.
All Treated	All enrolled participants who received 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 Randomized PD-L1+	All participants with PD-L1 expression on immune cells ≥ 1% who were randomized to any treatment arm in the study. Participants are grouped within the all randomized PD-L1+ population by the treatment to which they were randomized.
All Treated PD-L1+	All enrolled participants with PD-L1 expression on immune cells ≥ 1% who receive at least 1 dose of study drug. Participants are grouped within the all treated PD-L1+ population according to the treatment they actually received.
PK	All treated participants with available serum concentration data for nivolumab.
Immunogenicity	All treated participants with baseline and at least 1 pre-infusion immunogenicity assessment.
[redacted]	

Abbreviations: ICF, informed consent form; IRT, interactive response technology; PD-L1, programmed death-ligand 1; PK, pharmacokinetic.

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, secondary, and key exploratory endpoints.

A description of the participant population will be included in a statistical output report, including subgroups of age, gender, race, and other baseline characteristics.

10.3.1 Efficacy Analyses

Statistical analyses for efficacy are shown in Table 10.3.1-1. Primary efficacy endpoint will be explored in the ITT population.[100,126,127]

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
Primary	
• pCR, defined as no invasive residual disease in breast and lymph nodes (eg, ypT0/is, ypN0) by a local pathologist (ITT population).	• pCR rates and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each treatment arm in the all randomized participants (ITT). Participants who do not undertake surgery will be counted as non-pCR and will be included in the denominator. • The pCR rates in all randomized participants will be compared using a 2-sided stratified CMH test with alpha = 0.05. Associated odds ratios with 2-sided 95% CIs will be calculated.
Secondary	
• pCR, defined as no invasive residual disease in breast and lymph nodes (eg, ypT0/is, ypN0) by a local pathologist (PD-L1+ population).	• Rates and exact 95% CI will be calculated using the same method as the primary analysis.
• RCB class (0, I, II, III) frequency, for RCB assessed by a local pathologist in ITT and PD-L1+ populations.	• Rates and exact 95% CI will be calculated using the same method as the primary analysis.
Exploratory	
• pCR, defined as no invasive or in situ residual disease in breast and lymph nodes (ie, ypT0 ypN0) by a local pathologist in ITT and PD-L1+ populations. • pCR, defined as no invasive residual disease in the breast irrespective of in situ or nodal involvement (ypT0/is) by a local pathologist in ITT and PD-L1+ populations. • ORR, defined as investigator-assessed tumor response rate per radiologic-based assessment (RECIST v1.1) in the Neoadjuvant (pre-surgery) phase in ITT and PD-L1+ populations.	• Response rates and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each treatment arm in the all randomized (ITT) participants and all randomized PD-L1+ participants.
• EFS in ITT population. • OS in ITT population. • DFS in ITT population. • DMFS in ITT population.	• The EFS, OS, DFS, and DMFS curves for each randomized arm will be estimated using the KM product-limit method. A 2-sided 95% CI for median survival time in each randomized arm will be computed via the log-log transformation. • EFS, OS, DFS, and DMFS rates at 1 year will be estimated and associated 2-sided 95% CIs will be calculated. These estimates will be derived from the KM estimates, and corresponding CIs will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survival function.

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
• Clinical efficacy endpoints (eg, pCR, RCB, ORR) by PD-L1 expression using PD-L1 IHC 28-8 CPS.	• Rates and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for a specific population.
[redacted]	

Abbreviations: BCS, breast-conserving surgery; CI, confidence interval; CPS, combined positive score; DFS, disease-free survival; DMFS, distant metastasis-free survival; EFS, event-free survival; ER+, estrogen receptor positive; IHC, immunohistochemistry assay; ITT, intent to treat; KM, Kaplan-Meier; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PD-L1+, programmed death-ligand 1-positive; RCB, residual cancer burden; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

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
Secondary	
• Incidence of AEs, drug-related AEs, AEs leading to discontinuation, and SAEs as defined by NCI CTCAE v5.0. • Incidence of deaths.	AEs will be graded according to NCI CTCAE v5.0. Frequency distribution of treated participants with AEs will use 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.

Abbreviations: AE, adverse event; CTC, common toxicity criteria; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; PT, preferred term; SAE, serious adverse event.

10.3.3 Clinical Outcomes Assessments

Change from baseline in the EORTC QLQ-C30 Global Health Status and Physical Functioning subscale are secondary endpoints. Summary statistics and 95% CIs at each assessment point for both these PRO secondary endpoints will be provided for each treatment arm (as randomized) in the treatment period. All remaining subscales of the EORTC QLQ-C30 and all other PROs are exploratory endpoints. Summary statistics for other COA measures at each assessment point will be provided for each treatment arm (as randomized) in the Treatment Period.

10.3.3.1 EORTC QLQ-C30 and EORTC QLQ-BR23

Change from baseline scores in EORTC QLQ-C30 global health/QOL and physical functioning subscale scores will be assessed. Change in baseline scores in all other EORTC QLQ-C30 domains and individual items and QLQ-BR23 subscales will be assessed. These analyses will use all available data from randomized participants.

Additional analyses for all other domains of the EORTC QLQ-C30 and EORTC QLQ-BR23 will be described in the SAP.

10.3.3.2 EQ-5D-5L

The EQ-5D will be described in the following 3 ways:

1) Participant's overall health state on a visual analog scale (EQ-VAS) at each assessment timepoint will be summarized using descriptive statistics, as randomized.
2) Proportion of participants reporting problems for the 5 EQ-5D dimensions at each assessment timepoint will be summarized by level of problem, as randomized for all randomized participants.
3) Percentages will be based on number of participants assessed at assessment timepoint.

A by-participant listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number), and EQ-5D VAS will be provided.

10.3.3.3 FACIT GP5

FACIT GP5 responses will be analysed using mean and post-mean baseline changes for each treatment group at each assessment timepoint. Additional analyses will include the proportion of participants who endorse each response category at each timepoint.

10.3.4 Other Analyses

PK, [redacted] analyses will be described in the SAP, which will be finalized before database lock. The PPK analysis [redacted] will be presented separately from the main clinical study report.

10.3.4.1 Pharmacokinetic Analyses

The nivolumab concentration vs time data obtained in this study may be combined with data from other studies in the clinical development program to develop a PPK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab to determine measures of individual exposure. Model-determined exposures may be used for exposure-response analyses of selected efficacy and safety endpoints, if the data permit. The PPK and exposure-response analyses will be presented separately from the main clinical study report, if conducted.

10.3.4.2 Immunogenicity Analyses

Immunogenicity will be reported for positive status of anti-drug antibodies (ADAs) for nivolumab and ADA-negative status, relative to baseline. In addition, presence of neutralizing antibody may be reported, if applicable. Effect of immunogenicity on safety, efficacy, and PK may be explored.

[redacted]

10.3.5 Interim Analyses

The SAP will further describe the planned interim analysis.

10.3.5.1 Futility Analysis Based on pCR

An interim futility analysis of pCR will be conducted when approximately 260 ITT participants are randomized and have the opportunity to be evaluated for pCR (approximately 29 months from the first participant randomization date). At the time of the analysis, IDMC will evaluate whether the following futility stopping criterion is met and notify the Sponsor. The futility analysis is non-binding and the decision of whether to continue the trial will be made by the study team based on the analysis results. The study will remain blinded at the futility analysis.

Consider stopping the trial when both ΔpCR in PD-L1+ participants ≤ 4% and ΔpCR in ITT participants ≤ 2%, where ΔpCR = estimated pCR in Arm A - estimated pCR in Arm B.

11 REFERENCES

1 Steenbruggen TG, van Ramshorst MS, Kok M, et al. Neoadjuvant Therapy for Breast Cancer: Established Concepts and Emerging Strategies. Drugs 2017;77(12):1313-36.

2 Cortazar P, Zhang L, Untch M, et al. Pathological Complete Response and Long-term Clinical Benefit in Breast Cancer: The CTNeoBC Pooled Analysis. Lancet 2014;384(9938):164-72.

3 von Minckwitz G, Untch M, Blohmer JU, et al. Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2012;30(15):1796-804.

4 Spring LM, Fell G, Arfe A, et al. Abstract GS2-03: Pathological Complete Response After Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Mortality, Stratified by Breast Cancer Subtypes and Adjuvant Chemotherapy Usage: Individual Patient-level Meta-analyses of Over 27,000 Patients. Cancer Research 2019;79(4 Supplement): GS2-03.

5 Prowell TM, Beaver JA, Pazdur R. Residual Disease after Neoadjuvant Therapy - Developing Drugs for High-risk Early Breast Cancer. The New England Journal of Medicine 2019; 380(7):612-5.

6 Guidance for Industry: Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). 2014. Available from: URL: https://www.fda.gov/media/83507/download. Accessed June 19, 2019.

7 Coates AS, Winer EP, Goldhirsch A, et al. Tailoring Therapies--Improving the Management of Early Breast Cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Annals of Oncology: Official Journal of the European Society for Medical Oncology 2015;26(8):1533-46.

8 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1.2019.

9 Cardoso F, Kyriakides S, Ohno S, et al. Early Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Annals of Oncology: Official Journal of the European Society for Medical Oncology 2019;301194-1220.

10 Schmid P, Park YH, Muñoz-Couselo E, et al. Pembrolizumab (Pembro) + Chemotherapy (Chemo) as Neoadjuvant Treatment for Triple Negative Breast Cancer (TNBC): Preliminary Results from KEYNOTE-173. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2017;35(suppl_15):556-6.

11 Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-paclitaxel in Advanced Triple-negative Breast Cancer. The New England Journal of Medicine 2018;379;2108-21.

[12] Nanda R, Liu MC, Yau C, et al. Pembrolizumab Plus Standard Neoadjuvant Therapy for High-risk Breast Cancer (BC): results from I-SPY2. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2017;35(suppl_15):506.

[13] Emens LA, Cruz C, Eder JP, et al. Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients with Metastatic Triple-negative Breast Cancer: A Phase 1 Study. JAMA Oncology 2019;5(1):74-82.

[14] Rugo HS, Delord JP, Im SA, et al. Safety and Antitumor Activity of Pembrolizumab in Patients With Estrogen Receptor-positive/Human Epidermal Growth Factor Receptor 2-negative Advanced Breast Cancer. Clinical Cancer Research 2018;24(12):2804-11.

[15] Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, An Anti-PD-L1 Antibody, in Patients with Locally Advanced or Metastatic Breast Cancer: A Phase 1b JAVELIN Solid Tumor Study. Breast Cancer Research and Treatment 2018;167(3):671-86.

[16] Loibl S, Untch M, Burchardi N, et al Randomized Phase II Neoadjuvant Study (GeparNuevo) to Investigate the Addition of Durvalumab to a Taxane-anthracycline Containing Chemotherapy in Triple Negative Breast Cancer (TNBC). Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2018;36(15_suppl):104.

[17] Emens LA, Middleton G. The Interplay of Immunotherapy and Chemotherapy: Harnessing Potential Synergies. Cancer Immunology Research 2015;3(5):436-43.

[18] ClinicalTrials.gov. Study of Pembrolizumab (MK-3475) Versus Placebo in Combination With Neoadjuvant Chemotherapy & Adjuvant Endocrine Therapy in the Treatment of Early-stage Estrogen Receptor-positive, Human Epidermal Growth Factor Receptor 2-negative (ER+/HER2-) Breast Cancer (MK-3475-756/KEYNOTE-756). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT03725059. Accessed April 30, 2019.

[19] ClinicalTrials.gov. Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs Placebo Plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy in Participants With Triple Negative Breast Cancer (TNBC) (MK-3475-522/KEYNOTE-522). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT03036488. Accessed April 30, 2019.

[20] ClinicalTrials.gov. Clinical Trial of Neoadjuvant Chemotherapy With Atezolizumab or Placebo in Patients With Triple-Negative Breast Cancer Followed After Surgery by Atezolizumab or Placebo. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT03281954. Accessed April 30, 2019.

[21] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2019. CA: A Cancer Journal for Clinicians 2019;69(1):7-34.

[22] Huang H, Groth J, Sossey-Alaoui K, et al. Aberrant Expression of Novel and Previously Described Cell Membrane Markers in Human Breast Cancer Cell Lines and Tumors. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 2005;11(12):4357-64.

[23] Yersal O, Barutca S. Biological Subtypes of Breast Cancer: Prognostic and Therapeutic Implications. World Journal of Clinical Oncology 2014;5(3):412-24.

[24] Pennisi A, Kieber-Emmons T, Makhoul I, Hutchins L. Relevance of Pathological Complete Response After Neoadjuvant Therapy for Breast Cancer. Breast Cancer: Basic and Clinical Research 2016;10:103-6.

[25] Sotiriou C, Pusztai L. Gene-expression Signatures in Breast Cancer. The New England Journal of Medicine 2009;360(8):790-800.

[26] Perou CM, Sorlie T, Eisen MB, et al. Molecular Portraits of Human Breast Tumours. Nature 2000;406(6797):747-52.

[27] Pardoll D. Does the Immune System See Tumors as Foreign or Self? Annual Review of Immunology 2003;21:807-39.

[28] Zitvogel L, Tesniere A, Kroemer G. Cancer Despite Immunosurveillance: Immunoselection and Immunosubversion. Nature Reviews Immunology 2006; 6(10):715-27.

[29] Dunn GP, Bruce AT, Ikeda H, et al. Cancer Immunoediting: From Immunosurveillance to Tumor Escape. Nature Immunology 2002;3(11):991-8.

[30] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 Family Revisited. Annual Review of Immunology 2005;23:515-48.

[31] Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation. The Journal of Experimental Medicine 2000;192(7):1027-34.

[32] Sharpe AH, Wherry EJ, Ahmed R, et al. The Function of Programmed Cell Death 1 and its Ligands in Regulating Autoimmunity and Infection. Nature Immunology. 2007;8(3):239-45.

[33] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-related Response Criteria. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 2009;15(23):7412-20.

[34] Nivolumab (BMS-936558) Investigator Brochure Version 17. Bristol-Myers Squibb Company, 2018. Document Control Number 930038243.

[35] Kok M, Voorwerk L, Horlings H, et al. Adaptive Phase II Randomized Trial of Nivolumab After Induction Treatment in Triple Negative Breast Cancer (TONIC Trial): Final Response Data Stage I and First Translational Data. Journal of Clinical Oncology 2018;36(15_suppl):1012.

[36] ClinicalTrials.gov. Carboplatin +/- Nivolumab in Metastatic Triple Negative Breast Cancer. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT03414684. Accessed April 30, 2019.

[37] ClinicalTrials.gov. NIMBUS: Nivolumab Plus Ipilimumab in Metastatic Hypermutated HER2-negative Breast Cancer. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT03789110. Accessed April 30, 2019.

[38] ClinicalTrials.gov. A Phase II Study of Nivolumab in Combination With Cabozantinib for Metastatic Triple-negative Breast Cancer. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT03316586. Accessed April 30, 2019.

[39] Mauriac L. Smith I. Aromatase Inhibitors in Early Breast Cancer Treatment. Seminars in Oncology 2003;30(4 Suppl 14):46-57.

[40] Scholl SM, Fourquet A, Asselain B, et al. Neoadjuvant Versus Adjuvant Chemotherapy in Premenopausal Patients With Tumours Considered Too Large for Breast Conserving Surgery: Preliminary Results of a Randomised Trial: S6. European Journal of Cancer 1994;30A(5):645-52.

[41] Fisher CS, Ma CX, Gillanders WE, et al Neoadjuvant Chemotherapy is Associated With Improved Survival Compared With Adjuvant Chemotherapy in Patients With Triple-negative Breast Cancer Only After Complete Pathologic Response. Annals of Surgical Oncology 2012;19(1):253-8.

[42] Wolff AC, Davidson NE. Early Operable Breast Cancer. Current Treatment Options in Oncology 2000;1(3):210-20.

[43] Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant Chemotherapy for Operable Breast Cancer. The British Journal of Surgery 2007;94(10):1189-200.

[44] Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2019;37(5):423-38.

[45] Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-analysis. Journal of the National Cancer Institute 2005;97(3):188-94.

[46] Ponde NF, Zardavas D, Piccart M. Progress in Adjuvant Systemic Therapy for Breast Cancer. Nature Reviews Clinical Oncology 2019; 16(1):27-44.

[47] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of Chemotherapy and Hormonal Therapy for Early Breast Cancer on Recurrence and 15-year survival: An Overview of the Randomised Trials. Lancet 2005;365(9472):1687-717.

[48] Goss PE, Ingle JN, Pritchard KI, et al. Extending Aromatase-inhibitor Adjuvant Therapy to 10 Years. The New England Journal of Medicine 2016;375:209-19.

[49] Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al. Extended Adjuvant Aromatase Inhibition After Sequential Endocrine Therapy (DATA): A Randomised, Phase 3 Trial. The Lancet Oncology 2017;18(11):1502-11.

[50] Mamounas EP, Lembersky B, Jeong JH, et al. NSABP B-42: A Clinical Trial to Determine the Efficacy of Five Years of Letrozole Compared With Placebo in Patients Completing Five Years of Hormonal Therapy Consisting of an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI in Prolonging Disease-free Survival in Postmenopausal Women With Hormone Receptor–positive Breast Cancer. Cancer Research 2017;77(4 Suppl):Abstract S1-05.

[51] Gnant M, Steger G, Greil R, et al. Abstract GS3-01: A Prospective Randomized Multi-center Phase-III Trial of Additional 2 Versus Additional 5 Years of Anastrozole After Initial 5 Years of Adjuvant Endocrine Therapy - Results From 3,484 Postmenopausal Women in the ABCSG-16 Trial. Cancer Research 2018;78(4 Suppl):Abstract GS3-01.

[52] Pagani O, Regan MM, Walley BA, et al. Adjuvant Exemestane With Ovarian Suppression in Premenopausal Breast Cancer. The New England Journal of Medicine 2014;371(2):107-18.

[53] Francis PA, Regan MM, Fleming GF, et al. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. The New England Journal of Medicine 2015;372(5):436-46.

[54] Francis PA, Pagani O, Fleming GF, et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. The New England Journal of Medicine 2018;379(2):122-137.

[55] Johnston SD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2−, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol 2020;38:3987-98.

[56] Nivolumab (Opdivo) US Prescribing Information. Bristol-Myers Squibb Company; Revised January 2018.

[57] Paclitaxel Injection (Taxol) Package Insert. Bristol-Myers Squibb Company; Revised April 2011. Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf. Accessed April 30, 2019.

[58] Doxorubicin Hydrochloride for Injection, USP Package Insert. Pfizer; Revised May 2010. Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050467s070lbl.pdf. Accessed April 29, 2018.

[59] Epirubicin Hydrochloride Injection (Ellence) Package Insert. Pfizer; Revised December 2014. Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050778s021lbl.pdf. Accessed April 29, 2019.

[60] Cyclophosphamide Injection Package Insert. Baxter Healthcare Corporation; Revised May 2013. Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf. Accessed April 2019, 2019.

[61] Tamoxifen Citrate (Nolvadex) Tablets Package Insert. AstraZeneca Pharmaceuticals, LP; Revised August 2004. Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/17970s053lbl.pdf. Accessed April 29, 2019.

[62] Letrozole (Femara) Tablets Package Insert. Novartis Pharmaceuticals Corporation; Revised January 2014. Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020726s027lbl.pdf. Accessed April 29, 2019.

[63] Anastrozole (Arimidex) Tablets Package Insert. AstraZeneca Pharmaceuticals, LP; Revised October 2010. Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020541s026lbl.pdf. Accessed April 29, 2019.

[64] Exemestane (Aromasin) Tablets Package Insert. Pfizer; Revised October 2005. Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020753s006lbl.pdf. Accessed April 29, 2019.

[65] Medicines.org.uk. OPDIVO 10 mg/mL Concentrate for Solution for Infusion - Summary of Product Characteristics - (eMC). Bristol-Myers Squibb Pharmaceuticals, Ltd; Updated April 2019. Available from: URL: https://www.medicines.org.uk/emc/medicine/30476. Accessed April 26, 2019.

[66] Medicines.org.uk. Paclitaxel 6 mg/mL Concentrate for Solution for Infusion - Summary of Product Characteristics - (eMC). Hospira UK, Ltd; Updated December 2016). Available from: URL: https://www.medicines.org.uk/emc/product/3891/smpc. Accessed April 26, 2019.

[67] Medicines.org.uk. Doxorubicin Hydrochloride 2 mg/mL Solution for Infusion - Summary of Product Characteristics - (eMC). medac GmbH; Updated August 2018. Available from: URL: https://www.medicines.org.uk/emc/product/4613/smpc. Accessed April 26, 2019.

[68] Medicines.org.uk. Epirubicin Hydrochloride 2 mg/mL Solution for Injection - Summary of Product Characteristics - (eMC). medac GmbH; Updated October 2016. Available from: URL: https://www.medicines.org.uk/emc/product/6361/smpc. Accessed April 26, 2019.

[69] Medicines.org.uk. Cyclophosphamide 500 mg Powder for Solution for Injection or Infusion - Summary of Product Characteristics - (eMC). Sandoz, Ltd; Updated June 2017. Available from: URL: https://www.medicines.org.uk/emc/product/3526/smpc. Accessed April 26, 2019.

[70] Medicines.org.uk. Tamoxifen 20-mg Film-Coated Tablets - Summary of Product Characteristics - (eMC). Wockhardt UK, Ltd; Updated August 2018. Available from: URL: https://www.medicines.org.uk/emc/product/2248/smpc. Accessed April 26, 2019.

[71] Medicines.org.uk. Letrozole 2.5-mg Film-Coated Tablets - Summary of Product Characteristics - (eMC). Cipla EU, Ltd; Updated March 2019. Available from: URL: https://www.medicines.org.uk/emc/product/9957/smpc. Accessed April 26, 2019.

[72] Medicines.org.uk. Anastrozole 1-mg Film-Coated Tablets - Summary of Product Characteristics - (eMC). Consilient Health, Ltd; Updated January 2016. Available from: URL: https://www.medicines.org.uk/emc/product/2960/smpc. Accessed April 26, 2019.

[73] Medicines.org.uk. Exemestane 25-mg Film-Coated Tablets - Summary of Product Characteristics - (eMC). Accord Healthcare, Ltd; Updated September 2018. Available from: URL: https://www.medicines.org.uk/emc/product/6069/smpc. Accessed April 26, 2019.

[74] Zaheed M, Wilcken N, Wilson ML, et al. Sequencing of Anthracyclines and Taxanes in Neoadjuvant and Adjuvant Therapy for Early Breast Cancer. The Cochrane Database of Systematic Reviews 2019; Feb 18;2:CD012873. doi: 10.1002/14651858.CD012873.pub2.

[75] Medicines.org.uk. Leuprorelin acetate Depot 3.75 mg Powder and Solvent for Prolonged-release Suspension for Injection - Summary of Product Characteristics - (eMC). Advanz Pharma; Revised April 2017. Available from URL: https://www.medicines.org.uk/emc/product/5085/smpc. Accessed May 10, 2019.

[76] Medicines.org.uk. Zoladex 3.6 mg Implant - Summary of Product Characteristics - (eMC). AstraZeneca, Ltd; Revised January 2017. Available from URL: https://www.medicines.org.uk/emc/product/1543/smpc. Accessed May 10, 2019.

[77] Schmid P, Park YH, Muñoz-Couselo E, et al. Abstract PD5-01: KEYNOTE-173: Phase 1b Multicohort Study of Pembrolizumab (Pembro) in Combination with Chemotherapy as Neoadjuvant Treatment for Triple-negative Breast Cancer (TNBC). Cancer Research 2019;79(4 Suppl):Abstract PD5-01.

[78] Schmid P, Cortés J, Dent R, et al. KEYNOTE-522: Phase 3 Study of Pembrolizumab (pembro) + Chemotherapy (chemo) vs Placebo (pbo) + Chemo as Neoadjuvant Treatment, Followed by Pembro vs Pbo as Adjuvant Treatment for Early Triple-negative Breast Cancer (TNBC). Ann Oncol 2019;30 (suppl 5): LBA8.

[79] Vonderheide RH, LoRusso PM, Khalil M, et al. Tremelimumab in Combination with Exemestane in Patients with Advanced Breast Cancer and Treatment-associated Modulation of Inducible Costimulator Expression on Patient T cells. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 2010;16(13):3485-94.

[80] McArthur HL, Page DB. Immunotherapy for the Treatment of Breast Cancer: Checkpoint Blockade, Cancer Vaccines, and Future Directions in Combination Immunotherapy. Clinical Advances in Hematology & Oncology 2016;14(11):922-33.

[81] ClinicalTrials.gov. Pembrolizumab and Doxorubicin Hydrochloride or Anti-Estrogen Therapy in Treating Patients With Triple-Negative or Hormone Receptor-positive Metastatic Breast Cancer. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02648477. Accessed April 30, 2019.

[82] Santa-Maria CA, Wang C, Cimino-Mathews A, et al. Abstract OT3-02-03: IMMUNe mOdulation in Early Stage Estrogen Receptor Positive Breast Cancer Treated with neoADjuvant Avelumab, Palbociclib, and Tamoxifen: The ImmunoADAPT study (NCT03573648). Cancer Research 2019;79(4 Suppl):Abstract OT3-02-03.

[83] Rugo HS, Kabos P, Beck JT, et al. A phase Ib study of abemaciclib in combination with pembrolizumab for patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer (MBC) (NCT02779751): Interim results. J Clin Oncol 2020;38:1051.

[84] Rugo H, Beck JT, Jerusalem G, et al. Abstract CT108: A phase 1b study of abemaciclib in combination with pembrolizumab for patients (pts) with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (mBC) (NCT02779751): Preliminary results. Cancer Res 2020;80:CT108.

[85] Pujol JL, Vansteenkiste J, Rodriguez L, et al. Abemaciclib in combination with pembrolizumab for stage IV KRAS-mutant or squamous NSCLC: a phase 1b study. JTO Clin Res Rep 2021;2:100234.

[86] Jerusalem G, Prat A, Salgado R, et al. Neoadjuvant nivolumab + palbociclib + anastrozole for estrogen receptor positive/human epidermal growth factor receptor 2-negative primary breast cancer: CheckMate-7A8. Oral Presentation ESMO Breast Cancer, 2022.

[87] Sorlie T, Perou CM, Tibshirani R, et al. Gene Expression Patterns of Breast Carcinomas Distinguish Tumor Subclasses with Clinical Implications. Proceedings of the National Academy of Sciences of the United States of America 2001;98(19):10869-74.

[88] Dai X, Li T, Bai Z, et al. Breast Cancer Intrinsic Subtype Classification, Clinical Use and Future Trends. American Journal of Cancer Research 2015;5(10):2929-43.

[89] Wagner J, Rapsomaniki MA, Chevrier S, et al. A Single-cell Atlas of the Tumor and Immune Exosystem of Human Breast Cancer. Cell 2019;177(5):1330-45.

[90] Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating Lymphocytes and Prognosis in Different Subtypes of Breast Cancer: A Pooled Analysis of 3771 Patients Treated With Neoadjuvant Therapy. The Lancet Oncology 2018;19(1):40-50.

[91] Sobral-Leite M, Van de Vijver K, Michaut M, et al. Assessment of PD-L1 Expression Across Breast Cancer Molecular Subtypes, in Relation to Mutation Rate, BRCA1-like Status, Tumor-infiltrating Immune Cells and Survival. OncoImmunology 2018;7(12):e1509820.

[92] Reck M, Borghaei H, O'Byrne KJ. Nivolumab Plus Ipilimumab in Non-small-cell Lung Cancer. Future Oncology 2019. doi: 10.2217/fon-2019-0031.

[93] Wei SC, Duffy CR, Allison JP. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discovery 2018;8(9):1069-86.

[94] Tsang JY, Hui SW, Ni YB, et al. Lymphocytic Infiltrate is Associated With Favorable Biomarkers Profile in HER2-overexpressing Breast Cancers and Adverse Biomarker Profile in ER-positive Breast Cancers. Breast Cancer Research and Treatment 2014;143(1):1-9.

[95] Dunbier AK, Ghazoui Z, Anderson H, et al. Molecular Profiling of Aromatase Inhibitor-treated Postmenopausal Breast Tumors Identifies Immune-related Correlates of Resistance. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 2013;19(10):2275-86.

[96] Gao Q, Patani N, Dunbier AK, et al. Effect of Aromatase Inhibition on Functional Gene Modules in Estrogen Receptor–positive Breast Cancer and Their Relationship with Antiproliferative Response. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 2014;20(9):2485-94.

[97] Emens LA, Esteva F, Beresford M, et al. Abstract PD3-01: Results From KATE2, A Randomized Phase 2 Study of Atezolizumab (Atezo)+Trastuzumab Emtansine (T-DM1) Vs Placebo (Pbo)+T-DM1 in Previously Treated HER2+ Advanced Breast Cancer (BC). Cancer Research 2019;79(4 Suppl):Abstract PD3-01.

[98] Tolaney SM, Kabos P, Dickler MN, et al. Updated Efficacy, Safety, & PD-L1 Status of Patients with HR+, HER2- Metastatic Breast Cancer Administered Abemaciclib Plus Pembrolizumab. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2018;36(15_suppl):1059.

[99] Pusztai L, Yau C, Wolf DM, et al. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: Results from the adaptively randomized I-SPY2 trial. Cancer Cell 2021;39:989-98.e5.

[100] Schmid P, Cortes J, Pusztai L, et al, for the KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020;382:810-21.

[101] Harbeck N, Zhang H, Barrios CH, et al. IMpassion031: results from a phase III study of neoadjuvant (neoadj) atezolizumab + chemotherapy in early triple-negative breast cancer (TNBC). Ann Oncol. 2020b;31(suppl. 4):LBA11.

[102] Bloom HJ, Richardson WW. Histological Grading and Prognosis in Breast Cancer: A Study of 1409 Cases of Which 359 Have Been Followed for 15 Years. British Journal of Cancer 1957;11(3):359–77.

[103] Cianfrocca M, Goldstein LJ. Prognostic and Predictive Factors in Early-stage Breast Cancer. Oncologist 2014;9(6):606‑16.

[104] Le Doussal V, Tubiana-Hulin M, Friedman S, et al. Prognostic Value of Histologic Grade Nuclear Components of Scarff-Bloom-Richardson (SBR). An Improved Score Modification Based on a Multivariate Analysis of 1262 Invasive Ductal Breast Carcinomas. Cancer 1989;64(9):1914–1921.

[105] Landmann A, Farrugia DJ, Diego E, et al. Low Estrogen Receptor (ER) Positive Breast Cancer and Neoadjuvant Systemic Therapy (NAT): Is Response Similar to ER+ or to ER- Disease? Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2016;34(15_suppl):580.

[106] Gloyeske NC, Dabbs DJ,Bhargava R. Low ER+ Breast Cancer: Is This A Distinct Group? American Journal of Clinical Pathology 2014;141(5);697-701.

[107] Prabhu JS, Korlimarla A, Desai K, et al. A Majority of Low (1-10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors. Journal of Cancer 2014;5(2):156-65.

[108] Fisher B, Bauer M, Wickerham DL, et al. Relation of the Number of Positive Axillary Nodes to the Prognosis of Patients with Primary Breast Cancer. An NSABP Update. Cancer 1983;52(9):1551–7.

[109] Tan LK, Giri D, Panageas K, et al. Abstract 37a: Occult/Micrometastases in Axillary Lymph Nodes of Breast Cancer Patients are Significant: A Retrospective Study with Long Term Follow-up. Proc Am Soc Clin Oncol 2002;21:146.

[110] Cote RJ, Peterson HF, Chaiwun B, et al. Role of Immunohistochemical Detection of Lymph-node Metastases in Management of Breast Cancer. International Breast Cancer Study Group. Lancet 1999;354(9182):896–900.

[111] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the Dose Intensity of Chemotherapy by More Frequent Administration or Sequential Scheduling: A Patient-level Meta-analysis of 37 298 Women With Early Breast Cancer in 26 Randomised Trials. Lancet 2019;393(10179):1440-52.

[112] Sparano JA, Zhao F, Martino S, et al. Long-term Follow-up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2015;33(21):2353-60.

[113] Sparano JA, Wang M, Martino S, et al. Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer. The New England Journal of Medicine 2008;358(16):1663-71.

[114] Norton L. Theoretical Concepts and the Emerging Role of Taxanes in Adjuvant Therapy. The Oncologist 2001;6 Suppl 3:30-5.

[115] Bonilla L, Ben-Aharon I, Vidal L, et al. Dose-dense Chemotherapy in Nonmetastatic Breast Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Journal of the National Cancer Institute. 2010;102(24):1845-54.

[116] Hammond ME, Hayes DF, Wolff AC, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer. Journal of Oncology Practice 2010; 6(4):195-7.

[117] Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2018; 36(20):2105-2122.

[118] National Comprehensive Cancer Network Clinical Practice Guidelines. Hematopoietic Growth Factors Version 2.2020.

[119] Leuprolide acetate for depot suspension (Lupron Depot) Package Insert. Abbott Laboratories. June 2014. Available from URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020517s036_019732s041lbl.pdf. Accessed May 10, 2019.

[120] Goserelin acetate impant (Zoladex) Package insert. AbbVie Inc. June 2014. Available from URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020517s036_019732s041lbl.pdf. Accessed May 10, 2019.

[121] Symmans WF. Pathologic Response Following Neoadjuvant Chemotherapy As An Outcome For Clinical and Translational Research. UT M.D. Anderson Cancer Center. 2011. Available from: URL: http://knowledgehub.uscap.org/site~/99th/pdf/companion11h02.pdf. Accessed April 29, 2019.

[122] Aaronson, NK, Ahmedzai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A Quality-of-life Instrument for Use in International Clinical Trials in Oncology. Journal of the National Cancer Institute 1993;85(5):365-76.

[123] Osoba D, Rodrigues G, Myles J, et al. Interpreting the Significance of Changes in Health-related Quality-of-life Scores. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 1998;16(1):139-44.

[124] Sprangers MA, Groenvold M, Arraras JI, et al. The European Organisation for Research and Treatment of Cancer Breast Cancer-specific Quality-of-life Questionnaire Module: First Results from a Three-country Field Study. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 1996;14(10):2756-68.

[125] Pearman TP, Beaumont JL, Mroczek D, et al. Validity and Usefulness of a Single-item Measure of Patient-reported Bother from Side Effects of Cancer Therapy. Cancer 2018;124(5):991-7.

[126] Schmid P, Kockx M, Kim SB, et al. Dynamic changes of PD-L1 and T-cell activation in ECLIPSE: A phase II study investigating preoperative immune combination strategies in untreated, operable ER+ primary breast cancer. SABCS, Dec 8-11, 2020.

[127] Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet 2020;396:1090-100.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
°C	degrees Celsius
µL	microliter
%CA	proportion of cancer
%CIS	proportion of in situ component
AC	anthracycline + cyclophosphamide
ADA	anti-drug antibody
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
AR	additional research
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
ASCO-CAP	American Society of Clinical Oncology- College of American Pathologists
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the curve
BC	breast cancer
Bcl-xL	B-cell lymphoma-extra large
BCS	breast-conserving surgery
BICR	blinded independent central review
BID	bis in die, twice daily
BMS	Bristol-Myers Squibb
BP	blood pressure
BRCA1/2	breast cancer gene 1/2

Term	Definition
BTLA	B- and T-lymphocyte attenuator
BUN	blood urea nitrogen
C	cycle
Cavgss	steady state average concentration
CBC	complete blood count
CD28	cluster of differentiation 28
CFR	Code of Federal Regulations
CHF	congestive heart failure
cHL	classical Hodgkin lymphoma
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CISH	chromogenic in situ hybridization
Cm	centimeter
CMF	cyclophosphamide, methotrexate, and 5-flourouracil
CMH	Cochran Mantel Haenszel
CMV	cytomegalovirus
COA	clinical outcomes assessment
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTAg	clinical trial agreement
CTC	common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA

Term	Definition
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
CYP	cytochrome p-450
D	day
DCIS	ductal carcinoma in situ
DD	dose-dense
ddAC	dose-dense anthracycline + cyclophosphamid
DFS	disease-free survival
DILI	drug-induced liver injury
dL	deciliter
DLT	dose-limiting toxicity
DMFS	distant metastasis-free survival
DNA	deoxyribonucleic acid
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
EC	epirubicin and cyclophosphamide
EC	ethics committee
EC50	half-maximal effective concentration
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMR	electronic medical record
EOI	end of infusion
EORTC	European Organisation for the Research and Treatment of Cancer

Term	Definition
EOT	end of treatment
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ER	estrogen receptor
ER-	estrogen receptor-negative
ER+	estrogen receptor-positive
ESMO	European Society for Medical Oncology
ET	endocrine therapy
etc	et cetera
EU	Europe
FACIT GP5	Functional Assessment of Chronic Illness Treatment General Physical Item 5
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
FU	follow-up
FU1	follow-up visit 1
FU2	follow-up visit 2
g	gram
GBS	Guillian Barre Syndrome
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GEP	gene expression profiling
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin

Term	Definition
HCRU	healthcare resource utilization
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
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HR+	hormone receptor-positive
HRQOL	health-related quality of life
IB	Investigator's Brochure
IC	immune cells
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICOS	inducible T cell co-stimulator
IDMC	Independent Data Monitoring Committee
ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
IMAE	immune-mediated adverse event
IMG	immunogenicity
IMP	investigational medicinal product
IND	Investigational New Drug
IO	immuno-oncologic
IP	investigational product

Term	Definition
IRB	Institutional Review Board
IRT	interactive response technology
ISH	in situ hybridzation
ITT	intent to treat
IU	international unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
kg	kilogram
KM	Kaplan-Meier
L	liter
LAM	lactation amenorrhea method
LCIS	lobular carcinoma in situ
LD	longest diameter
LDH	lactate dehydrogenase
LHRH	luteinizing hormone-releasing hormone
LN	lymph node
m^2	meters squared
mm^3	cubic millimeters
M	distant metastasis
MD	medical doctor
MDSC	myeloid-derived suppressor cells
MG	Myasthenia Gravis
mg	milligram
min	minute
miRNA	micro ribonucleic acid
mL	milliliter
MLR	mixed lymphocyte reaction
mm^3	cubic millimeters
MMR	measles, mumps, rubella

Term	Definition
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
N	number of subjects or observations
NA	not applicable
NCCN	National Cancer Care Network
NCI	National Cancer Institute
Nivo	nivolumab
NE	not evaluable; inevaluable
nM	nanomolar
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OR	odds ratio
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PALB2	partner and localizer of BRCA2
PBMC	peripheral blood mononuclear cells
Pbo	placebo
pCR	pathological complete response
PD	progressive disease
PD-1	programmed cell death-1
p-DILI	potential drug-induced liver injury
PD-L1	programmed death-ligand 1
PD-L1+	programmed death-ligand 1-positive
PD-L1-	programmed death-ligand 1-negative
PD-L2	programmed death-ligand 2
PE	physical examination
PET	positron emission tomography

Term	Definition
PFS	progression-free survival
PgR	progesterone receptor
PIK3CA	phosphatidylinositol 3-kinase catalytic alpha polypeptide
PK	pharmacokinetic
PO	per os (by mouth route of administration)
PPK	population pharmacokinetics
PR	partial response
PRO-CTCAE	Patient-Reported Outcome-Common Terminology Criteria for Adverse Events
PS	performance status
PT	preferred term
PTX	paclitaxel
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QD, qd	quaque die, once daily
QLQ-BR23	Quality of Life Questionnaire-Breast Cancer-specific Module
QLQ-C30	Quality of Life Questionnaire-Core 30
QOL	quality of life
QW	every week
R&D	research and development
Rand	randomized
RCB	residual cancer burden
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RT	radiotherapy
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan

Term	Definition
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SISH	silver in situ hybridization
SJS	Steven Johnson Syndrome
SLAMF8	signaling lymphocytic activation molecule family member 8
SmPC	summary of product characteristics
SOC	standard of care
SOP	standard operating procedures
SSC	study steering committee
SUSAR	suspected, unexpected serious adverse reaction
T	tumor
T.bili	total bilirubin
TCR	T-cell receptor
T-DM1	trastuzumab emtansine
TEN	toxic epidermal necrolysis
TIL	tumor-infiltrating lymphocyte
TMB	tumor mutational burden
TME	tumor microenvironment
TNBC	triple-negative breast cancer
TNF	tumor necrosis factor
TNM	tumor node metastasis
Tregs	regulatory T cells
TSH	thyroid-stimulating hormone
UK	United Kingdom
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VAS	visual analog scale
vs	versus

Term	Definition
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

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 Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

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

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, also by the local Health Authority, must be sent to Bristol-Myers Squibb (BMS).

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant or his/her legally acceptable representative and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant or his/her legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant or his/her legally acceptable representative to inquire about the details of the study.
- Obtain an ICF signed and personally dated by participant or his/her legally acceptable representative and by the person who conducted the informed consent discussion.
- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

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

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

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

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

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.

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

SOURCE DOCUMENTS

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

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

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in the Source document location map (or equivalent) and Site Process Source Document.

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

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

reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the Sponsor or designee.

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

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

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

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

MONITORING

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE START AND CLOSURE

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

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

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

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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

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

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

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

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

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

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify “intentional overdose” as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.

Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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

Any component of a study endpoint that is considered related to study therapy should be reported as an 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 and/or product information for marketed products in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: [redacted]

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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

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

End of Relevant Systemic Exposure

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 12 months after the end of study treatment, for participants who receive cyclophosphamide, or for 6 months for participants who do not receive cyclophosphamide, after the last dose of study treatment with nivolumab or nivolumab placebo, whichever is longer.

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

In the CA209-7FL study, use of hormonal methods of contraception is prohibited in WOCBP.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b]

- Intrauterine device (IUD)[c]
- Intrauterine hormone-releasing system (IUS) (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b,c]
- Bilateral tubal occlusion

- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

NOTES:

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

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)

Unacceptable Methods of Contraception*
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus) • Spermicide only • LAM

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

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

Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

- Male who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection for the duration of neoadjuvant (pre-surgery) treatment phase, and 12 months after the last dose of cyclophosphamide OR 6 months after last dose of paclitaxel, whichever is the last dose.
- 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 12 months after the last dose of cyclophosphamide OR 6 months after the last dose of paclitaxel, whichever is the last dose.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.6 and Appendix 3.

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 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.

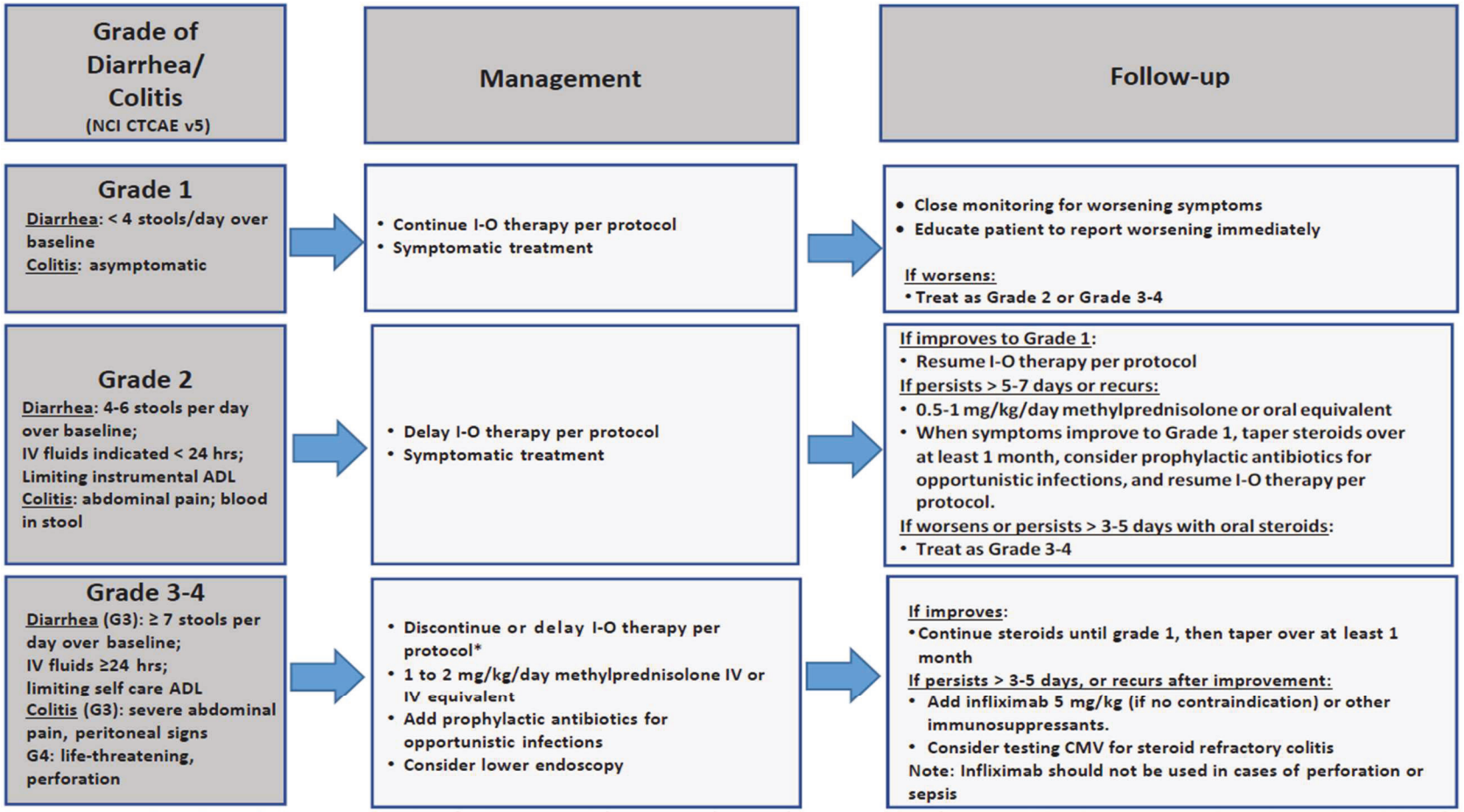
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



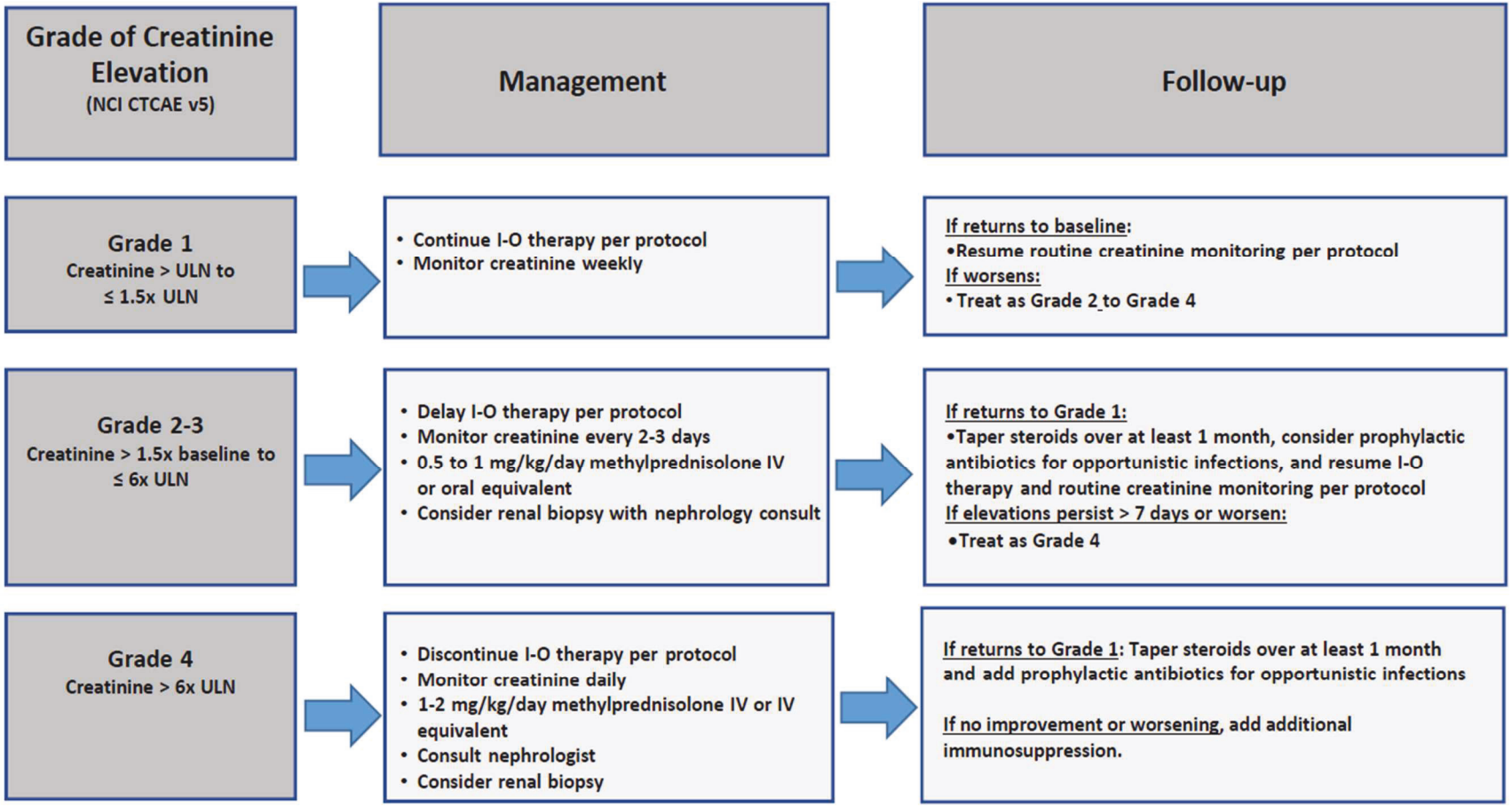
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

28-Sep-2020

Renal Adverse Event Management Algorithm

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

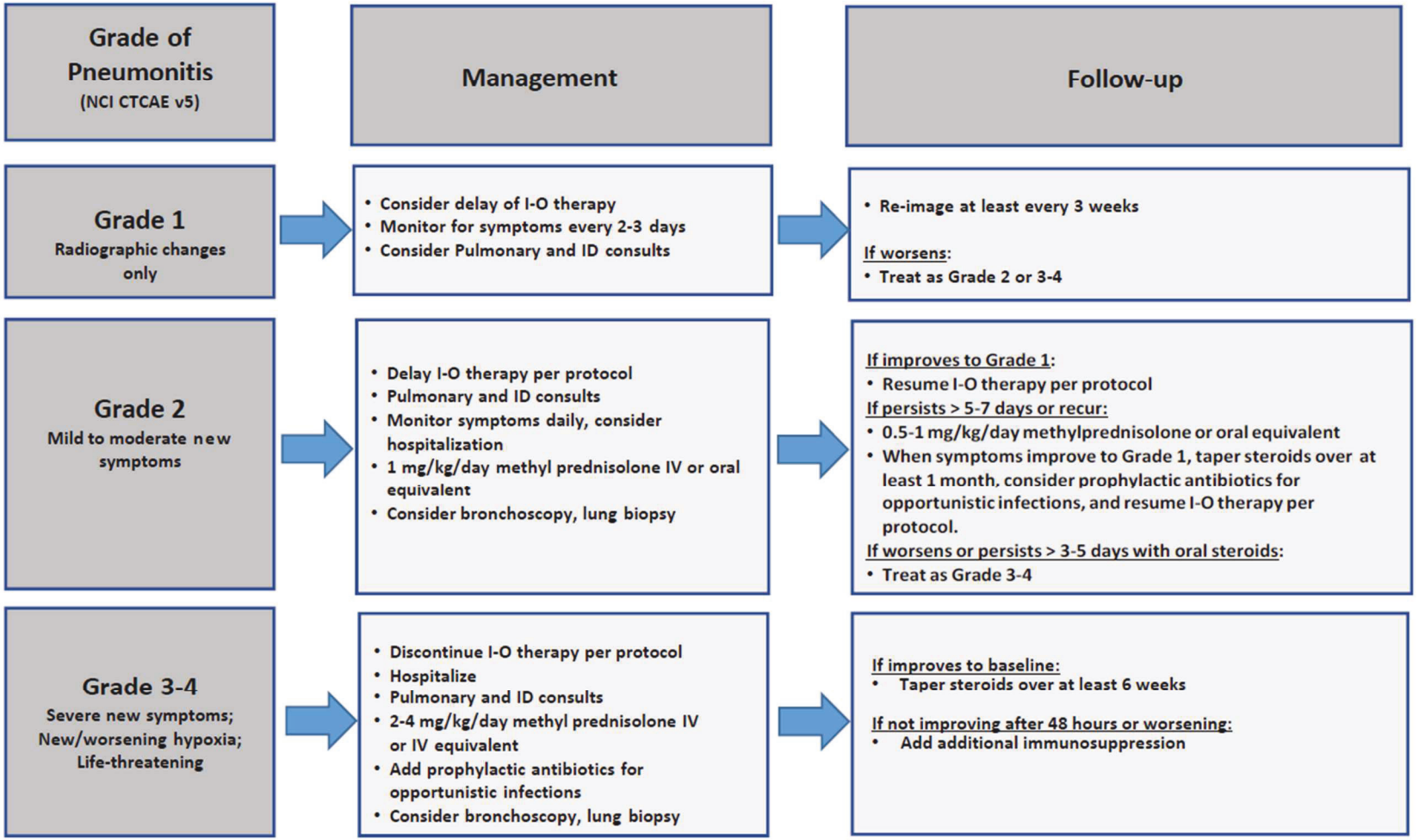


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.

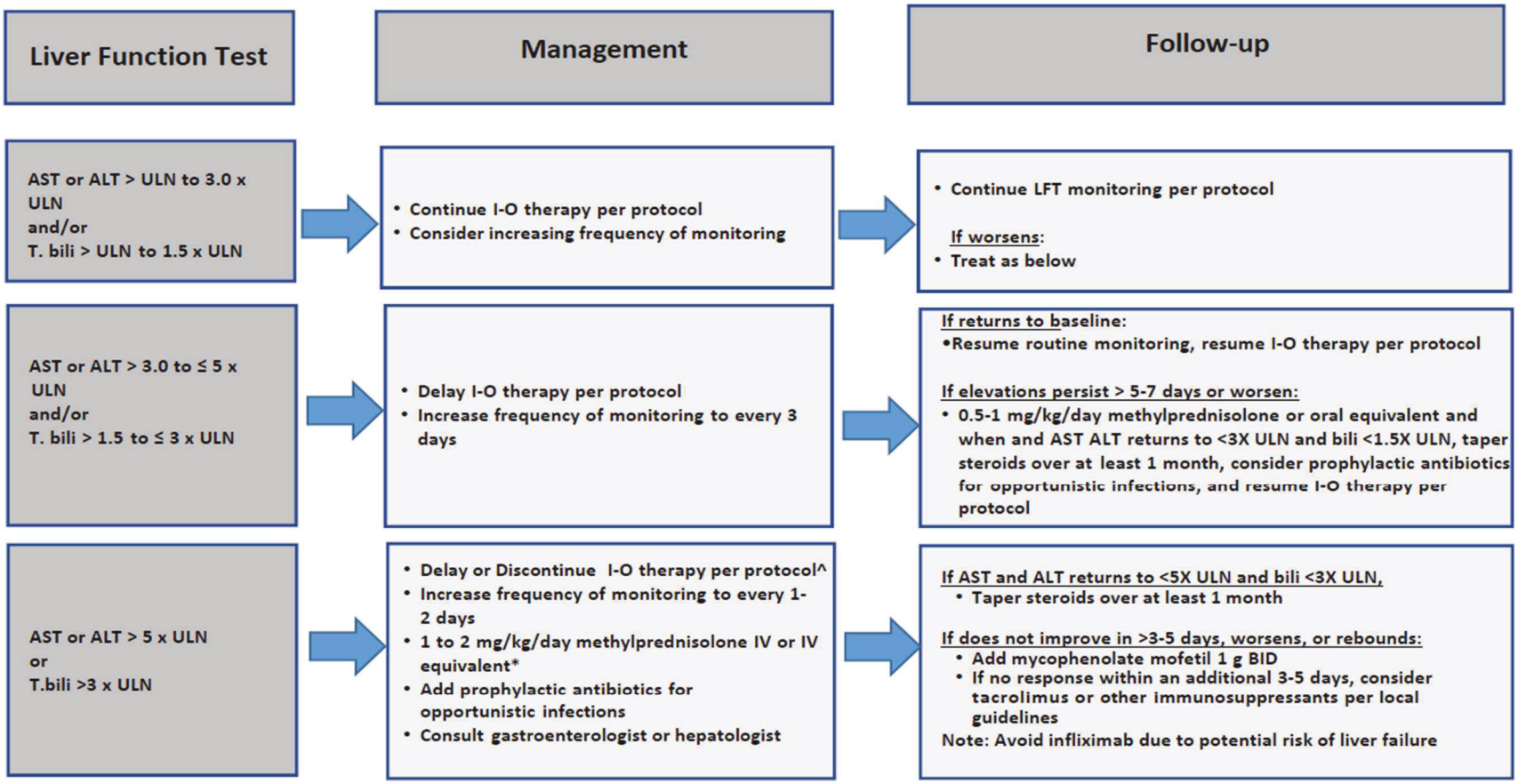


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

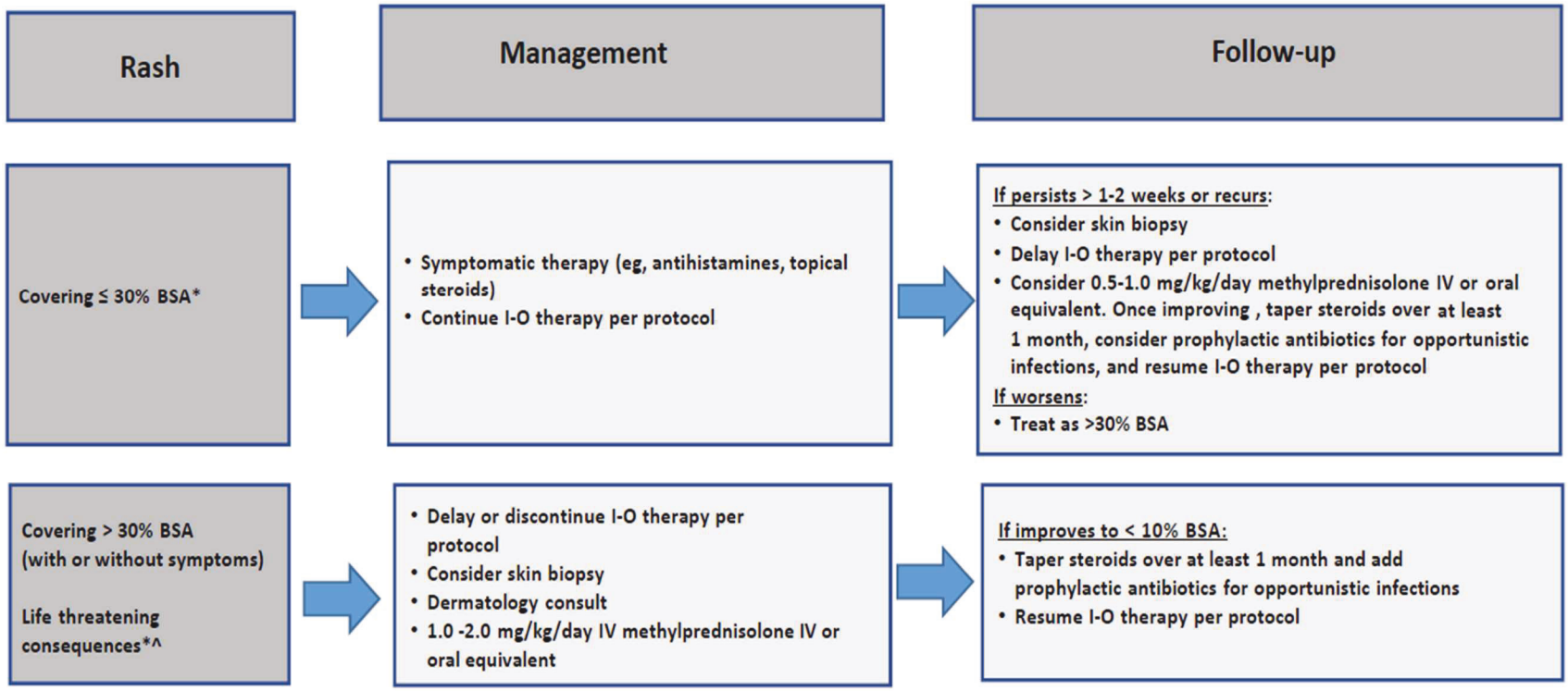
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: o include fT4 at subsequent cycles as clinically indicated; o consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

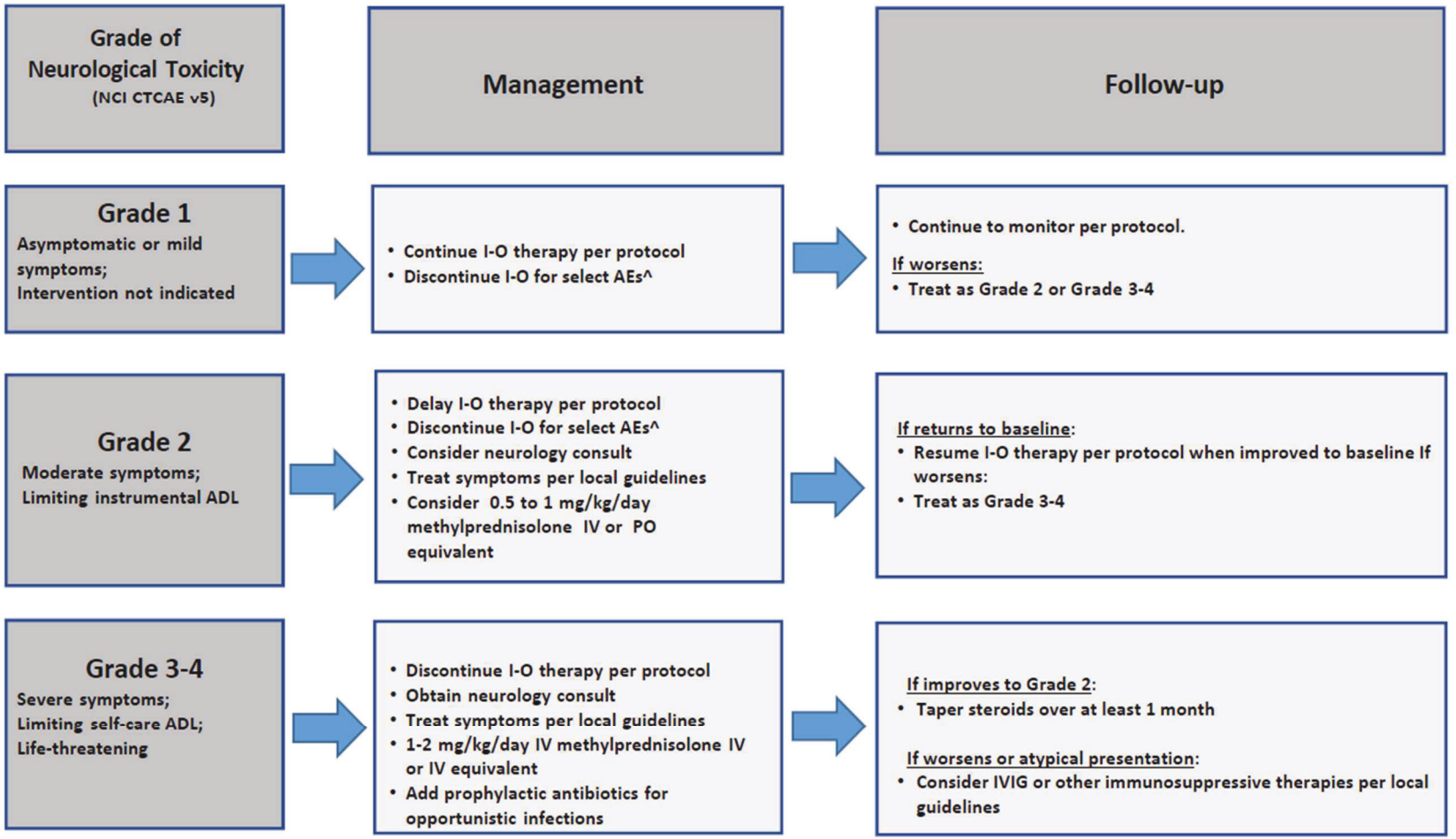
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

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



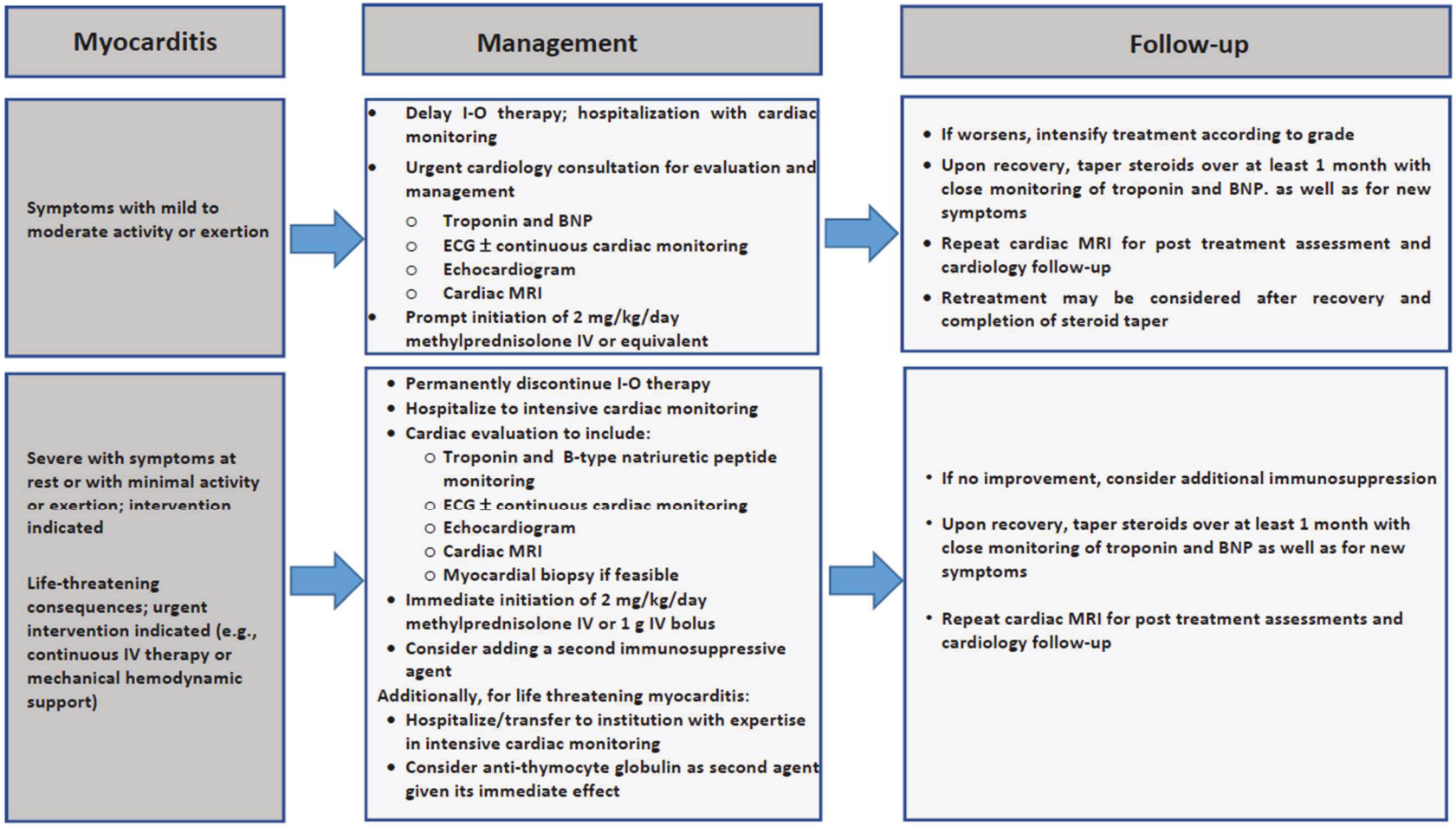
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

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



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

28-Sep-2020

APPENDIX 7 RADIOTHERAPY GUIDELINES

1 RADIOTHERAPY POST-BREAST CONSERVING THERAPY

Breast radiotherapy (RT) after complete local excision is mandatory.

Breast RT may be contraindicated in participants with significant comorbidity (eg, scleroderma and systemic lupus erythematosus). Reasons for not delivering breast RT after complete local excision of the primary breast cancer should be documented in the eCRF.

1.1 Target Volume

Whole breast including the primary tumor bed.

Primary tumor bed boost in conjunction with whole breast RT may be used per local policy, declared by the center prior to local activation.

Partial breast RT may be used per local policy, declared by the center prior to local activation.

Regional nodal RT: Refer to Item 3 below.

1.2 Dose Fractionation

Whole breast - recommended schedules:

1) 50 Gy in 25 fractions, 5 fractions per week, or
2) 42.5 Gy in 16 fractions, 5 fractions per week, or
3) 40 Gy in 15 fractions, 5 fractions per week.

Other schedules may be used per local policy, declared by the center prior to local activation.

Primary tumor bed boost in conjunction with whole breast RT: Per local policy, declared by the center prior to local activation.

Partial breast RT: Per local policy declared by the center prior to local activation.

1.3 Treatment Planning

Computer tomography (CT)-based treatment planning is strongly recommended for whole breast RT and tumor bed boost.

CT-based treatment planning is mandatory for partial breast irradiation delivered using external-beam RT.

2 RADIOTHERAPY POST-MASTECTOMY

Breast RT after mastectomy is mandatory under the following conditions:

1) 4 or more positive axillary nodes or,
2) Pathologic T4 disease, or
3) 'Non-resectable' microscopic positive deep margin.

Breast RT after mastectomy is optional under the following conditions:

1) 1-3 positive axillary nodes, or
2) Higher-risk node-negative disease (eg, T3 primary in the presence of high histologic grade and/or lymphovascular invasion).

2.1 Target Volume

Whole breast including the primary tumor bed.

Primary tumor bed boost in conjunction with whole breast RT may be used per local policy, declared by the center prior to local activation.

Regional nodal RT: Refer to Item 3 below.

2.2 Dose Fractionation

Whole breast: Recommended schedule is 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used per local policy, declared by the center prior to local activation.

Primary tumor bed boost in conjunction with chest wall RT: Per local policy, declared by the center prior to local activation.

2.3 Treatment Planning

CT-based treatment planning is strongly recommended for chest wall RT.

3 REGIONAL NODAL RT

Regional nodal RT is **recommended** under the following conditions:

1) Any breast surgery, 4 or more positive axillary nodes.

Regional nodal radiotherapy is **optional** under the following conditions:

1) Any breast surgery, 0-3 positive axillary nodes, pathological T4 (pT4) disease.

3.1 Target Volume

If required:

- Supraclavicular fossa if there are 4 or more positive axillary nodes;
- Internal mammary nodes if tumor involvement is biopsy confirmed.

If optional:

- Supraclavicular fossa if there are 0-3 positive axillary nodes;
- Axilla as per local policy declared by the center prior to local activation (eg, known or high risk of residual axillary disease post surgery);
- Internal mammary nodes if there is a high risk of tumor involvement, per local policy, declared by the center prior to local activation.

3.2 Dose Fractionation

Recommended schedule: 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used per local policy, declared by the center prior to local activation. Hypofractionated schedules are not recommended.

3.3 Treatment Planning

CT-based treatment planning is strongly recommended for supraclavicular fossa and/or axillary RT.

CT-based treatment planning is mandatory for internal mammary nodal RT.

APPENDIX 8 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS FOR NEOADJUVANT BREAST CANCER

HIGH LEVEL SUMMARY OF THE MODIFICATIONS

- Up to two lesions in the breast may be identified as target lesions.
- Lymph nodes are not to be designated as target or non-target lesions.
- Target and Non-Target lesions can be selected from mammography, ultrasound, or MRI.
- Removal of fluid (ascites, pleural and pericardial effusions) from response assessment as non-target or new lesion due to potential unconfirmed etiology and volume changes resulting from interventional procedures unrelated to treatment response (thoracentesis).
- Best Overall Response of CR or PR does not require confirmation. SD must meet minimum time on study requirement as defined in protocol.

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) guideline[1] with BMS modifications for neoadjuvant breast cancer.

At baseline, breast tumor lesions will be categorized as measurable or non-measurable as follows:

1.1 Measurable

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded).

- Measurable lesions may be measured by mammography, ultrasound, or MRI.

1.2 Non-measurable

All other breast lesions are considered non-measurable, including small lesions.

1.3 Baseline Documentation Of 'Target' And 'Non-target' Lesions

Up to two lesions in the breast may be identified as target lesions. Per this protocol, first target lesion must be at least 20 mm and, if selected, second target lesion must be at least 10 mm.

Lymph nodes are not to be designated as target or non-target lesions at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) but in addition should be those that lend themselves to reproducible repeated measurements. A sum of the longest diameters for all target lesions will be calculated and reported as the baseline sum diameters. 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 breast lesions 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.

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions.
- **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. Appearance of one or more new lesions is also considered progression.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Target Lesions That Become 'Too Small to Measure'

While on study, all lesions 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 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 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. The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.2 Lesions That Split or Coalesce on Treatment

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

2.2 Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s).
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

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

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

2.2.1.1 When the Patient also has Measurable Disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the Patient has Only Non-measurable Disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: 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.

2.2.2 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.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment in the Neoadjuvant (Pre-surgery) Phase.

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. Assessments of partial response and complete response do not require confirmation.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response

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

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, inevaluable.

Table 2.3.2-2: Time Point Response

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

Abbreviations: CR, complete response; PD, progressive disease; NE, inevaluable; SD, stable disease.

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response does not require confirmation. 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.

2.3.4 Confirmation Scans

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 REQUIREMENTS/DIFFERENCES

Country	Section Number & Title	Original Language	Country-specific Language or Differences
Argentina, Czech Republic, Germany, Romania, and Any Other Countries Where Exclusion of HIV Positive Participants is Locally Mandated	2: Schedule of Activities, Table 2-1: Screening Assessments - Laboratory Tests		Add "HIV" to the list of laboratory tests.
Argentina, Czech Republic, Germany, and Any Other Countries Where Exclusion of HIV Positive Participants is Locally Mandated	6.2: Exclusion Criteria, Exclusion Criterion 1) g)	Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).	Positive test for HIV.
Czech Republic	8.1: Discontinuation from Study Treatment	In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Medical Monitor (or designee) of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). See Section 9.2.6 (Pregnancy).	In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Medical Monitor (or designee) of this event. In all cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). See Section 9.2.6 (Pregnancy).
Czech Republic	9.2.6: Pregnancy	If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study	If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study

Country	Section Number & Title	Original Language	Country-specific Language or Differences
		exposure, including during at least 5 half-lives after product administration, the Investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3. If the Investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment or re-initiation of study treatment, a discussion between the Investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/Sponsor/IRB/IEC, as applicable. Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In cases where a study drug can be present in seminal fluid, at exposures sufficient to	exposure, including during at least 5 half-lives after product administration, the Investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3. Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. 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 the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be

Country	Section Number & Title	Original Language	Country-specific Language or Differences
		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 the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.	collected on the Pregnancy Surveillance Form.
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Country	Section Number & Title	Original Language	Country-specific Language or Differences
		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Country	Section Number & Title	Original Language	Country-specific Language or Differences
		[redacted]	

APPENDIX 10 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 11 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol Amendment 02, 21-May-2021

The primary reasons for these changes are to align with current clinical practice, [redacted] provide clarification for study conduct, and ensure that the protocol is consistent with program level guidance, internal BMS policies and operating procedures. Additional revisions including to sections of the Synopsis have been made to align the protocol with respect to these changes.

The key updates include the following:

- Updated BMS study contact information.
- Aligned dose modification criteria and IO management algorithms with CTCAE v5.
- [redacted]
- Incorporated additional revisions to improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, sample collection, and treatment administration.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
2: Schedule of Activities Table 2-1 (Screening Procedural Outline) • PE, Measurements, Vital Signs, and ECOG PS • Table 2-1 Pregnancy Test (WOCBP only) Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W) Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) Table 2-4 (On-treatment Adjuvant Procedural Outline) Table 2-5 (Follow-up Procedural Outline) • Targeted PE, Measurements, Vital Signs, and ECOG PS 9.4.1: Physical Examination	Removed external ocular examination. Serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of HCG) to be done at screening and repeated within 24 hours prior to the first dose of study therapy. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.	Updated safety assessment, removed external ocular examination to align with updated Nivolumab guidance. Physical examination are to be performed if there are any new or worsening clinically significant changes since the last exam report changes on appropriate non-serious or SAE page.
2: Schedule of Activities Table 2-1 (Screening Procedural Outline) Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W)	Correction: Bilateral Breast and Axilla Ultrasound, Mammogram or Breast MRI.	Clarification: either Bilateral Ultrasound or Mammogram of Breast and Axilla or Breast MRI should be done.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3 (On-Treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) • Bilateral Ultrasound or Mammogram of Breast and Axilla or Breast MRI		
2: Schedule of Activities Table 2-1 (Screening Procedural Outline) • Pretreatment Tumor Sample Submission	Added: For participant with planned BCS, surgical clip(s) should be placed prior to starting neoadjuvant treatment but no later than PTX C2D1. For participant with planned mastectomy, placement of surgical clip(s) is strongly recommended. Placement of surgical clip(s) marks the tumor bed to ensure its appropriate localization at the time of the surgery and to enable accurate sampling of the specimen by the pathologist. (Refer to pathology manual for additional details).	Placement of clip(s) will facilitate localization of the tumor bed at time of the breast cancer surgery.
2: Schedule of Activities Table 2-1 (Screening Procedural Outline) • ECG	Updated ECG must be performed within 14 days prior to randomization.	Updated ECG safety assessment timelines to schedule of activities.
2: Schedule of Activities Table 2-1 (Screening Procedural Outline) Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W) Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) Table 2-4 (On-treatment Adjuvant Procedural Outline) • Pregnancy Test (WOCBP only) 6.1: Inclusion Criteria	Updated schedule of activities and inclusion criterion 3) b) to add an extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.	Updated pregnancy language to align with the current nivolumab program standard.
2: Schedule of Activities Table 2-1 (Screening Procedural Outline) • SAE Assessment • [redacted]	[redacted]	• Serum and AE/SAE collection in the context of SARS-CoV-2 was added in the event that coronavirus disease 2019 (COVID-19) sequelae may increase toxicity or impact interpretation of study events/results.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W) Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) Table 2-4 (On-treatment Adjuvant Procedural Outline) Table 2-5 (Follow-up Procedural Outline) • AEs Assessment (Including SAEs) • [redacted] 3.3.1: Nivolumab Safety Profile 4-1: Objectives and Endpoints 6.2: Exclusion Criteria 6.4.1: Retesting During Screening 7.4.1.1: Dose Delay Criteria for Nivolumab 7.4.1.2: Criteria to Resume Treatment with Nivolumab 9.2.2: Time Period and Frequency for Collecting AE and SAE Information 9.2.4: Follow up of AEs and SAEs [redacted] 9.8.3.6: Other Assessments	[redacted]	[redacted]

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
2: Schedule of Activities Table 2-1 (Screening Procedural Outline) Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W) Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) • Bilateral Ultrasound or Mammogram of Breast Axilla or Breast MRI Table 2-4 (On-treatment Adjuvant Procedural Outline) Table 2-5 (Follow-up Procedural Outline) • Mammogram or Breast MRI for Participants with Remaining Breast Tissue Post-surgery	The following modifications were made: • Added 'bilateral' to procedure. • Regarding breast reconstruction, clarified if the other breast remains, this needs to be imaged on an annual basis.	• Clarified the need to perform bilateral breast imaging and align with the requirement described for objective response rate assessment in Section 9.1.5.1 Objective Response Rate. • Clarified post-surgery breast imaging requirements.
2: Schedule of Activities Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W) Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) • Cortisol-Notes	Changed to: Cortisol must be collected at AC C1D1 (predose) and prior to surgery. Result is not required prior to dosing.	Clarified that the cortisol result is not required prior to the first dose of anthracycline and cyclophosphamide, but the cortisol testing sample must be collected prior to the first dose.
2: Schedule of Activities Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W) Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) • Surgery (SOC)	Clarified pathologic TNM staging is performed after tumor resection. Clarified surgery timelines.	Clarified that TNM staging is done on the breast surgical sample after surgery.
2: Schedule of Activities Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W)	Added footnote to define end of PTX as 3 weeks after PTX C4D1 or	Clarified timing of the End of PTX visit which is expected 3 weeks after PTX Cycle 4 D1 or sooner if

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) • End of PTX visit	sooner if participant discontinues prior to completion of the 4 cycles.	participant discontinues prior to completion of the 4 PTX cycles.
2: Schedule of Activities Table 2-4 On-treatment Adjuvant Procedural Outline [redacted]	Added a footnote to clarify the end of adjuvant therapy time point.	Clarified the end of adjuvant therapy time point to be 4 weeks after Adjuvant Cycle 7 Day 1, or sooner if the participant discontinues the adjuvant phase sooner.
Figure 5.1-1 Study design Schematic	Added T1c-T2, cN1-cN2 or T3-T4, cN0-cN2 as key inclusion criterion.	Clarified key TNM staging eligibility criterion.
5.1: Overall Design 5.4.5: Rationale for Stratification Factors	Clarified the need to confirm suspicious positive lymph node pathologically prior randomization.	Suspicious positive axillary lymph node after clinical/radiographic assessment must be confirmed pathologically prior randomization.
5.1.2.1: Neoadjuvant (Pre-surgery) Phase 5.1.2.2: Surgery 5.2: Number of Participants	Deleted 3rd paragraph: For participants to proceed to the Adjuvant (Post-surgery) Phase of the study, definitive surgery must occur and be recorded in the source document as such. If definitive surgery does not occur, the participant will move to the Follow-up Period. Clarified timeline for surgery. Updated that it is anticipated that approximately 1,870 participants will be screened to treat 1,200 eligible participants with nivolumab (Arm A; n = 600) or nivolumab placebo (Arm B; n = 600) in combination with neoadjuvant chemotherapy and adjuvant ET.	Corrected an inconsistency between Section 5.1.2.1 Neoadjuvant (Pre-surgery) Phase and Section 9.1.2 Definition of event-free survival on how to manage participants who may not proceed to definitive surgery. Those participants may continue in the study treatment phase (adjuvant phase). Clarified timeline for surgery. Updated number of participants.
6.1: Inclusion Criteria	The following modifications were made: • Inclusion criterion 2) a) i) Localized invasive breast ductal carcinoma, confirmed by the local pathologist, that includes the following combined primary tumor and clinical node (cN) categories with subcriteria detailed below. • Inclusion criterion 2) d) removed must agree to undergo	These changes were made for the following reasons: • Clarified nodal status pathological assessment. • Clarified inclusive tumor size with nodal status. • Updated inclusion criteria 2) d) with the protocol. • Updated contraceptive requirements for male participants

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	surgery after the completion of neoadjuvant therapy. • Updated male contraception criteria 3) e) and f). • Inclusion criterion 2) a) v) added to the protocol as: Participants must have measurable disease based on modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Refer to Appendix 8), as determined by local radiology review.	based on current safety information. • Protocol has ORR as a secondary endpoint, which requires imaging evaluation of tumor size changes after systemic treatment.
6.2: Exclusion Criteria	The following modifications were made: • Replaced criterion 1) g) with new criterion 1) m) related to human immunodeficiency virus. • Replaced criterion 1) h) with new criterion 1) l) related to concurrent or prior malignancy. • Replaced criterion 2) g) with new criterion 2) i) related to complementary medications. • Added new criterion 3) m) related to hepatitis C. • Added new criterion 3) n) related to hepatitis B. • Removed criteria 3) k) and l) related to chronic HBV and HCV infection, respectively.	These changes were made to include new clinical approaches for eligibility related to viral infections, and concurrent or prior malignancies, prior anticancer therapy AEs, supportive care, and eligibility criteria for participants in interventional trials.
Table 7.1-2 Selection and Timing of Dose - Neoadjuvant (Pre-surgery) Phase - AC	Updated footnote ‘c’ by clarifying prophylaxis medication with growth factors required for AC 2QW schedule.	Clarified the administration of prophylaxis growth factor.
7.1.2: Neoadjuvant (Pre-surgery) Phase	The following modifications were made: • Added ‘approximately’ in front of 30 minutes and ‘flush language’ for clarity. • Chemotherapy starts after the infusion line has been flushed, filter changes, and the participant has been observed for 30 minutes, to ensure no infusion reaction has occurred.	Clarified treatment administration window and flush language.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.1.4.1: Paclitaxel	Added that corticosteroids can be administered after the observation period of 30 minutes following nivolumab.	Clarified timings of the administration of premedication with corticosteroids before paclitaxel.
7.1.4.2: Anthracycline and Cyclophosphamide	Clarified the first dose of AC should be administered at the completion of 4 cycles (PTX C4D1 + 3 weeks) of paclitaxel, unless the participant meets criteria for a treatment delay.	Clarified initiation of the AC cycles in Section 7.1.4.2. Anthracycline and Cyclophosphamide. The first dose of AC should be administered at the completion of 4 cycles (3 weeks cycle) of paclitaxel, unless the participants meet criteria for treatment delay.
7.2:Method of Treatment Assignment: Axillary nodal status (pathological review positive versus radiographic and/or pathologic review negative) 7.4.1: Dosage Modification for Nivolumab 7.4.1.3: Treatment of Nivolumab Infusion Reaction 8.1.1: Nivolumab Dose Discontinuation	The following modifications were made: Added axillary nodal status clarification. • Added Table 7.4.1-1 for AE criteria for delaying, resuming, and discontinuation of nivolumab. • Clarified treatment recommendations are based on CTCAE v5. • Updated Section 8.1.1 to refer reader to Table 7.4.1-1 for nivolumab dose discontinuation criteria.	Reorganized dose delay, resume, and discontinuation criteria for improved readability and to align with CTCAE v5.
7.7.1.1: Prohibited and/or Restricted Treatments for Nivolumab	Updated language related to herbal supplements and traditional Chinese medicines for supportive care.	Aligned section with new exclusion criteria 2) i) in Section 6.2.
8.1: Discontinuation from Study Treatment 9.2.6: Pregnancy [redacted]	Referred the reader to Appendix 9 for additional details on country-specific requirements. [redacted]	Added reference to appendix based on health authority feedback. Clarification of end adjuvant therapy.
9.1.5: Imaging Assessment for the Study	Clarified text with imaging timelines.	Clarified image collection timelines.
9.2.6: Pregnancy	Added follow-up information must be reported on the Pregnancy Surveillance Form.	Clarified reporting requirements.
9.4.4: Clinical Safety Laboratory Assessments	Clarified TSH testing, TSH with reflexive fT3 and fT4 at screening,	Clarified TSH testing requirements.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	TSH, with reflexive fT3 and fT4 if TSH abnormal on treatment.	
Table 9.5-1 (Pharmacokinetic and Anti-drug Antibody Sampling Schedule for All Participants)	Updated footnote b in Table 9.5-1, instructions for end of infusion samples.	Changes were made to clarify timing and expectations for PK sample collection and provide additional flexibility for end-of-infusion samples.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Updated the text regarding male participant contraception.	Aligned methods of contraception with updates made to male contraceptive requirements in Section 6.1.
Appendix 6: Management Algorithms	Updated management algorithms.	Updated algorithms.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

Overall Rationale for the Revised Protocol 01, 24-Mar-2020

The primary reasons for these changes are to align with current clinical practice, align with recent updated international guidelines for assessing hormone receptor status in breast cancer, enhance exploratory objectives, enhance capture of relevant biomarkers at baseline, provide clarifications for study conduct, reduce participant burden, and 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.

The key updates include the following:

- Updated tumor assessment criteria to reflect modified RECIST v1.1 criteria relevant for the neoadjuvant setting.
- Updated the histologic Grade 2 low ER expression subgroup to be defined as Grade 2 with an ER expression level 1-10% to align with recently updated ASCO-CAP guidance on hormone receptor testing in breast cancer.
- Allow flexibility for use of breast MRI as an alternate method of tumor assessment during study conduct if it is the local standard instead of breast ultrasound and mammogram.
- Updated window for primary breast lesion tumor sample to be ≤ 90 days prior to enrollment for FFPE blocks or ≤ 60 days for cut unstained slides submitted at baseline.

- Removed requirement for mammography at the post-surgery visit.
- Allowed flexibility to accommodate sequential or concomitant administration of adjuvant systemic endocrine therapy and adjuvant radiotherapy per local standards.
- Included exploratory objectives related to efficacy assessments and PD-L1 expression using a combined positive score (CPS) algorithm.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
2: Schedule of Activities Table 2-1 (Screening Procedural Outline)	The following modifications were made to Table 2-1 (screening procedural outline): • Added disease biomarkers. • Clarified menopausal status is for women only. • Removed body surface area. • Added cortisol. • Increased imaging window to 45 days prior to randomization.	Tables were modified to add clarity on expectation and timing of assessments and to reduce participant burden.
2: Schedule of Activities Table 2-1 (Screening Procedural Outline) Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W) Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) Table 2-4 (On-treatment Adjuvant Procedural Outline) Table 2-5 (Follow-up Procedural Outline)	Added option for breast MRI.	Allowed flexibility for use of this method instead of breast ultrasound and mammogram to be used for tumor assessment per local standards.
2: Schedule of Activities Table 2-1 (Screening Procedural Outline) [redacted]	Updated window for primary breast lesion tumor sample to be ≤ 90 days prior to enrollment for FFPE blocks or ≤ 60 days for cut unstained slides submitted at baseline.	Aligned with similar trials and increased flexibility without compromising sample quality.
2: Schedule of Activities Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W)	The following modifications were made: • Added a column for end of PTX assessments. • Clarified pre-surgery window.	Tables were modified to add clarity on expectation and timing of assessments and to reduce participant burden.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W)	• Removed FACIT-GP5 on Days 8 and 15. • Added pathologic TNM staging at surgery.	
2: Schedule of Activities Table 2-4 (On-treatment Adjuvant Procedural Outline)	The following modifications were made to Table 2-4 (on-treatment adjuvant procedural outline): • Added a column for end of adjuvant assessments. • Clarified menopausal status is for women only. • Removed FACIT-GP5 collection on Days 8, 15, and 22. • Removed requirement for mammogram at the post-surgery visit. • Allowed for either annual mammogram or breast MRI for annual follow-up.	Table was modified to add clarity on expectation and timing of assessments and to reduce participant burden.
Table 2-4 (On Treatment Adjuvant Procedural Outline) Table 2-5 (Follow-up Procedural Outline) 9.2.2: Time Period and Frequency for collecting AE and SAE information	Added the need to collect AEs/SAEs related to breast surgery until 100 days after last dose of study treatment.	Added as part of the safety analysis.
2: Schedule of Activities Table 2-5 (Follow-up Procedural Outline)	The following modifications were made to Table 2-5 (follow-up procedural outline): • Clarified concomitant medication use includes endocrine therapy. • Added cortisol.	Table was modified to add clarity on expectation and timing of assessments.
Table 2-5 (Follow-up Procedural Outline) 5.1.3.1: Safety Follow-up Visits 5.1.3.2: Long-term Follow-up Visits	Updated the window for safety follow-up 2 to be approximately 100 days from last dose of study treatment instead of nivolumab and added a window for long-term follow-up visits ± 28 days.	Aligned requirement with similar trials.
3.2.4: Neoadjuvant Chemotherapy	Changed dose-dense anthracyclines from ‘twice weekly’ to ‘Q2W.’	Clarified dose frequency of dose-dense anthracyclines.
3.3.3: Endocrine Therapy Safety Profile	Removed luteinizing hormone releasing hormone (LHRH) agonists.	LHRH are not considered investigational product but may be used as concomitant medication.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.5.3: Justification for Dose of Endocrine Therapy 7: Treatment Table 7-1 (Study Treatments) Table 7.1-3 (Selection and Timing of Dose - Adjuvant Phase)		
3.3.4: Nivolumab and Anthracycline-Taxane-Based Chemotherapy Combination Safety Profile	Included summary of the KEYNOTE-522 study results.	Provided additional information regarding IO agents in the neoadjuvant and adjuvant setting in patients with early stage TNBC.
Table 4-1 (Objectives and Endpoints) 5.4.5.1: PD-L1 Status	Included exploratory objectives related to assessments of efficacy using a combined positive score (CPS) algorithm.	Updated to reflect new knowledge in the breast cancer field for potential use of CPS as a biomarker of response with checkpoint inhibitors.
5.1: Overall Design Figure 5.1-1 (Study Design Schematic) 6.1: Inclusion Criteria	Updated the histologic Grade 2 low ER expression subgroup to be defined as Grade 2 with an ER expression level 1-10%.	Aligned with recent ASCO-CAP Guidelines for estrogen and progesterone testing in breast cancer (Allison et al., *J Clin Oncol* January 2020).
5.1.1: Screening Period	The following changes were made: • Updated sequence of events to enroll a participant in IRT. • Updated post-menopausal status definition. • Removed specific details surrounding a pretreatment tumor tissue sample and referred the reader to Section 6.1 (inclusion criteria) for details. • Added ER status and ER expression level to central laboratory readout.	These changes were made for the following reasons: • Corrected inconsistency. • Aligned with post-menopausal definition in Appendix 4. • Reduced redundancy in text. • Clarified inclusion of ER testing at central laboratory.
5.1.2.1: Neoadjuvant (Pre-surgery) Phase	The following changes were made: • Updated patients to participants. • Clarified expectation with study conduct if participant discontinues chemotherapy or if chemotherapy is delayed.	These changes were made to correct inconsistency and to clarify study conduct requirement.
5.1.2.1: Neoadjuvant (Pre-surgery) Phase 7.1.2: Neoadjuvant (Pre-surgery) Phase	Updated disease recurrence to worsening of disease.	Clarified terminology.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.1.4.1: Paclitaxel 7.1.4.2: Anthracyclines and Cyclophosphamide		
5.1: Overall Design Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W) Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W) 5.1.2.2: Surgery	Clarified timing for surgery and expectation if not performed within the requested window or if actual surgery performed is different from the planned surgery at baseline. Added reference to the pathology manual.	Allowed for flexibility for countries with national health system standards greater than the optimal window.
5.1: Overall Design 5.1.2.3: Radiotherapy 5.1.2.4: Adjuvant (Post-surgery) Phase	Allowed adjuvant treatment with nivolumab/nivolumab placebo plus endocrine therapy to start at same time of radiotherapy for participant requiring radiotherapy.	Allowed increased flexibility to accommodate sequential or concomitant administration of adjuvant endocrine therapy and radiotherapy per local standards of care.
5.1.2.3: Radiotherapy	Removed the international guidelines for administration of breast RT in this section as recommendations are described in Appendix 7 (Radiotherapy Guidelines). Increased window for initiation of adjuvant systemic therapy from 1 week to 1-2 weeks after completion of RT in participants receiving sequential RT and adjuvant systemic therapy.	Removed redundancy. This change was made to reduce patient burden and to allow flexibility to accommodate local standards of care.
5.1: Overall Design 5.1.2.4: Adjuvant (Post-surgery) Phase	The following changes were made: • Option to group the post-surgery visit and the first cycle of adjuvant treatment if adjuvant treatment is started within 7-14 days after surgery. • Increased the window to begin adjuvant systemic therapy from '3' to '4-6' weeks following surgery.	These changes were made to reduce patient burden and to allow flexibility and consistency with local standards of care.
5.5.3: Justification for Dose of Endocrine Therapy	Updated anastrozole use from 'BID' to 'QD.'	Updated incorrect information in the frequency of anastrozole administration per package insert, SmPC.
5.1.3.2: Long-term Follow-up Visits	Included a window around each assessment of ±28 days.	Reduced participant burden.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.4.5: Rationale for Stratification Factors	Included description of the maximum number of participants allotted for each strata.	Added to increase awareness.
5.5.1.1: Nivolumab 240-mg every-2-week Dosing Regimen 5.5.1.2: Nivolumab 360-mg Every-3-Week Dosing Regimen 5.5.1.3: Nivolumab 480-mg every-4-week Dosing Regimen 5.5.1: Justification for Dose of Chemotherapy Agents 5.5.2: Justification for Dose of Chemotherapy Agents 7.1.3: Adjuvant (Post-surgery) Phase 7.4.1.3: Treatment of Nivolumab Infusion Reaction	Added window for nivolumab administration.	Allowed flexibility in study drug administration.
6.1: Inclusion Criteria	The following modifications were made: • Updated criterion 2) a) iii) removing the word 'operable.' • Removed the criterion 2) a) iv) requiring measurable disease per RECIST v1.1. • Removed female participant effective contraception criterion 3) c). • Extended window for male contraception criterion 3) e). • Removed male contraception criterion 3) f).	This change was made for the following reasons: • Removed redundancy with inclusion criterion 2) d). • RECIST 1.1 is not used in our study and the criterion for measurable disease criterion is already included in inclusion criterion 2) a). • Inclusion criterion 3) c) was duplicating inclusion criterion 3) d). • Aligned with Appendix 4. • Inclusion criterion 3) f) was duplicating inclusion criterion 3) e).
6.2: Exclusion Criteria	The following modifications were made: • Removed criterion 1) c) iii). • Updated criterion 1) d) excluding participant with > Grade 1 peripheral neuropathy. • Updated criterion 1) f) to increase immunosuppressive medication use window. • Clarified criterion 1) h) excluding participant with known HIV/AIDS within last	These changes were made for the following reasons: • Removed redundancy with inclusion criterion 2) d). • Included a window for exclusion in case of HIV/AIDS infection. • Corrected typographical error. • Aligned with Appendix 4 and consistent with standard practice in this setting. • Updated criteria to align with the nivolumab program standards.

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Section Number & Title	**Description of Change**	**Brief Rationale**
	year or a current CD4 count < 350 cells/μL. • Clarified criterion 2) c) excluding concurrent use of hormone replacement therapy or any other estrogen-containing medication. • Updated criterion 2) g) to clarify use of botanical preparations. • Added criteria 3) k) and 3) l) to clarify exclusion related to HCV and HBV infection.	
7: Treatment Table 7.1 (Study Treatments)	Added growth factors (G-CSF and GM-CSF) as Non-IMP.	Growth factors are required as premedication prior administration of anthracyclines at a dose dense schedule (Q2W).
7.1.1: Nivolumab/Nivolumab Placebo Dosing 7.1.4.1: Paclitaxel 7.1.4.2: Anthracycline and Cyclophosphamide	Updated guidance regarding corticosteroid premedication.	Clarified use of corticosteroid premedication.
7.1.2: Neoadjuvant (Pre-surgery) Phase)	Provided additional details for study treatment administration.	Clarified study treatment administration procedures.
7.1.4.2: Anthracycline and Cyclophosphamide	Added window for anthracycline and cyclophosphamide administration and clarified when administration will end.	Allowed flexibility in study drug administration and clarify timing.
7.1.5: Endocrine Therapy Dosing	Removed mention of LHRH agonists.	LHRH agonists removed as IMP. LHRH agonist permitted as concomitant medication.
7.4.1: Dose Modifications for Nivolumab	Clarified nivolumab/nivolumab placebo may be given within ±3 days from a scheduled chemotherapy dose in the event of chemotherapy delay.	Clarified study treatment administration procedures.
7.4.1.1: Dose Delay Criteria for Nivolumab	The following changes were made: • Added criterion to delay nivolumab or nivolumab placebo for Grade 3 drug-related diarrhea or colitis. • Clarified that other study treatment may continue to be administered.	Aligned with the nivolumab Investigator Brochure and clarified study treatment recommendations.

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7.4.2: Dose Modifications for Chemotherapy	The following changes were made: • Clarified that the dose modifications are recommendations for investigators. • Clarified expectations with regards nivolumab or nivolumab placebo in cases there is a delay of chemotherapy administration.	Clarified study treatment recommendations.
7.4.2.1: Dose Delay for Paclitaxel Therapy	Removed second sentence.	Redundant with clarification made in Section 7.4.2.
7.4.2.2: Dose Reductions for Paclitaxel Chemotherapy	Removed last paragraph.	Redundant with clarification made in Section 7.4.2.
7.4.2.4: Dose Delay for Anthracycline and Cyclophosphamide Chemotherapy	The following changes were made: • Removed first sentence. • Updated criterion to resume treatment with anthracycline-cyclophosphamide chemotherapy for ANC count from ≥ 1500 mm^3 to ≥ 1000 mm^3.	Aligned with clinical practice and remove redundancy.
7.4.2.6: Criteria to Resume Treatment with Anthracycline-cyclophosphamide Chemotherapy	Updated unit of measure for ANC count from uL to mm^3.	Aligned with criterion for ANC unit of measure.
7.4.3: Dose Modifications for Investigator's Choice Endocrine Therapy	Clarified that nivolumab or nivolumab placebo may be continued as scheduled in case of delay in endocrine therapy administration.	Clarified study treatment administration procedures.
7.5.1: Retained Samples for Bioavailability/Bioequivalence/ Biocomparability	Removed section.	Not applicable for registrational studies.
7.7.1.1: Prohibited and/or restricted Treatments for Nivolumab 7.7.1.2: Prohibited and/or Restricted Treatments for Chemotherapy and Endocrine Therapy	Updated period of prohibition/restriction of concurrent treatment.	Medications are no longer prohibited after participant completed study treatment.
7.7.1.2: Prohibited and/or Restricted Treatments for	The following changes were made:	Clarified the treatments which can be taken after completion of the study treatment (ie, during the follow-up

Summary of key changes for Revised Protocol 01		
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Chemotherapy and Endocrine Therapy	• Clarified use of hormonal agents is prohibited during study treatment. • Added restriction for cyclophosphamide. • Added restriction for live vaccine if doxorubicin is received.	phase) and to add restrictions to answer health authority requests.
7.7.3: Permitted Therapy	The following modifications were made: • Clarified that participants receiving anthracycline dose dense regimen must receive G-CSF or GM-CSF. • Allowed use of bisphosphonates. • Allowed use of LHRH agonists.	Aligned with local standard practice, prescribing information, and/or SmPCs.
8.1: Discontinuation from Study Treatment	Added occurrence of an EFS event to the criterion.	Clarified the need to discontinue study treatment in case of an EFS events as described in Section 9.1.2.
9: Study Assessments and Procedures	Added the need to evaluate participant to rule out cardiac toxicity in case of cardiac signs/events.	Aligned with nivolumab program standards.
9.1.5: Imaging Assessment for the Study	The following changes were made: • Added requirements to submit additional images demonstrating disease recurrence to vendor. • Clarified expectations with tumor measurement assessments which must be made using a modified RECIST v1.1 for neaoadjuvant breast setting.	Clarified expectations and procedures for tumor measurement assessments aligning with standard practice.
9.1.5.1: Objective Response Rate	Removed the need to perform imaging assessment as the end of paclitaxel treatment.	Clarified expectation with regards to assessment of radiographic tumor response in this setting.
9.1.6: Clinical Response by Physical Examination	Added when target lesions should be measured.	Clarified expectation with regards to assessment of clinical response by physical examination in this setting.
9.1.8: Clinical Outcomes Assessments	Changed section title and clarified that paper questionnaires are permitted when electronic devices are not available at study start.	This change was made to allow flexibility in case of operational challenge with the electronic device used to complete the questionnaires.

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9.2.10: Management Algorithms for Nivolumab	Updated the list of IMAEs adding myocarditis event.	Updated per nivolumab Investigator Brochure.
9.3: Overdose	Updated text with additional information referring reader to additional sources of information.	Provided additional details and clarification of available information for study treatments.
2: Schedule of Activities Table 2-1 (Screening Procedural Outline), footnote b Table 2-2 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q2W), footnote e Table 2-3 (On-treatment Neoadjuvant Procedural Outline with PTX and AC Q3W), footnote e Table 2-4 (On-treatment Adjuvant Procedural Outline), footnote e 9.4.1: Physical Examination	Clarified ocular examination included in target physical examination.	Ocular examination is included with the regular physical examination. If there are any abnormalities, participant can be referred to an ophthalmologist.
9.4.4: Clinical Safety Laboratory Assessments	Moved cortisol and estradiol to Other Analyses.	Incorrect categorization.
Table 9.5-1 (Pharmacokinetic and Anti-drug Antibody Sampling Schedule for All Participants)	Updated footnote a) to clarify window for PK collection to be preferably within 30 minutes prior to the infusion.	This change was made to allow flexibility in sample collection prior to the infusion.
[redacted]	[redacted]	[redacted]
10.1: Sample Size Determination	Corrected typographical error to clarify that PD-L1 negative participants will be capped to be within 40% of the total number of randomized participants.	Clarified which PD-L1 status will be capped within the randomized participants.
Appendix 4: Women of Childbearing Potential	Updated text to include contraception guidance to address all study treatments.	Improved consistency between protocol text and Appendix 4.

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Definitions and Methods of Contraception	Restated the use of hormonal methods of contraception were not permitted in the study.	
Appendix 6: Nivolumab Management Algorithm	Updated the nivolumab management algorithms and includes neurological and myocarditis AEs.	Aligned with latest nivolumab Investigator Brochure.
Appendix 8: Response Evaluation Criteria in Solid Tumors Guidelines (version 1.1) with BMS Modifications	Updated Appendix 8 to include modifications applicable for neoadjuvant breast studies.	Aligned with standard practice.
Appendix 9: Staging Criteria	Removed Appendix 9 and subsequent appendices were renumbered thereafter.	TNM status is being used for eligibility, not staging criteria which is specific to TNBC.
Appendix 12: Detailed Pathology Methods for Using Residual Cancer Burden	Removed Appendix 12 and subsequent appendices were renumbered thereafter.	Removed as information is included in the Pathology Manual.
Appendix 9: Country-specific Requirements/Differences	Appendix was renumbered. Revised presentation format of country–specific information to be more clear and concise. Removed France and Italy from the list of countries where HIV testing at baseline and exclusion of HIV-positive participants is locally mandated. Added or updated country-specific language revisions for the protocol for the following countries: • Czech Republic • Denmark	Renumbering required due to revision of Appendices. France and Italy no longer require HIV testing at baseline nor exclusion of HIV-positive participants at baseline per health authority feedback. Provide specific country-specific protocol language requirements based on local health authority standards or specific health authority feedback.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.