Official Title of Study:

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

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STATISTICAL ANALYSIS PLAN

RANDOMIZED, NON-COMPARATIVE NEOADJUVANT PHASE II STUDY IN PATIENTS WITH ER+/HER2- BREAST CANCER >= 2 CM WITH SAFETY RUN-IN, ASSESSING NIVOLUMAB + PALBOCICLIB + ANASTROZOLE

PROTOCOL CA2097A8

VERSION # 1.0

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1 BACKGROUND AND RATIONALE

CA2097A8 is an open-label, randomized, non-comparative Phase 2 study assessing nivolumab, plus abemaciclib (per original protocol) or palbociclib, and anastrozole as either concurrent or phased neoadjuvant treatment for men and postmenopausal women with primary breast cancer (BC) ≥ 2 cm that are estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2-negative (HER2-) with safety run-in. As of Revised Protocol 03, abemaciclib related cohorts will no longer be investigated in this trial.

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

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

PD-1 pathway inhibition has demonstrated clinical activity across multiple tumor types, including BC. An accumulating body of evidence supports PD-1/CDK4/6 blockade potential synergy, as it has become more apparent that CDK4/6 inhibitors modulate the tumor immune microenvironment (ie, increases expression of PD-L1, enhances antigen presentation and secretion of cytokines from both tumor and CD8+ T cells, and suppresses proliferation of immunosuppressive regulatory T cells [Tregs]). Preliminary clinical data in support of synergistic activity of the combination of pembrolizumab and abemaciclib has been demonstrated in a Phase 1b study on heavily pretreated participants with metastatic hormone receptor-positive (HR+), HER2- BC. Clinical data on combinations of other CDK4/6 inhibitors with PD-(L)1 blocking agents are being generated in multiple clinical trials spanning from the neoadjuvant to metastatic setting (ClinicalTrials.gov: NCT03573648, NCT02778685, NCT03294694). Additional treatment benefit (improved anti-

tumor efficacy and complete tumor regression) was observed in a syngeneic mouse tumor model by priming the anti-cancer immune response with abemaciclib in a phased administration of abemaciclib and an anti-PD-L1 therapy. Therefore, an additional phased therapy arm has been added for each CDK4/6 inhibitor to explore possible treatment benefit in patients.

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

Research Hypothesis:

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

Schedule of Analyses:

An analysis will be conducted when enrollment to the safety run-in phase is completed and all patients have completed at least one cycle of study treatment (1 cycle = 4 weeks) and have been followed up for an additional 4 weeks or discontinued from the study prior to that in order to support the dose selection for the randomized phase.

Final analysis will be conducted when all participants in the Randomized Phase are treated and evaluated in terms of RCB and pCR and completed the study, including the follow up phase, or discontinued from the study prior to that.

2 STUDY DESCRIPTION

2.1 Study Design

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

[redacted]

[redacted]

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

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

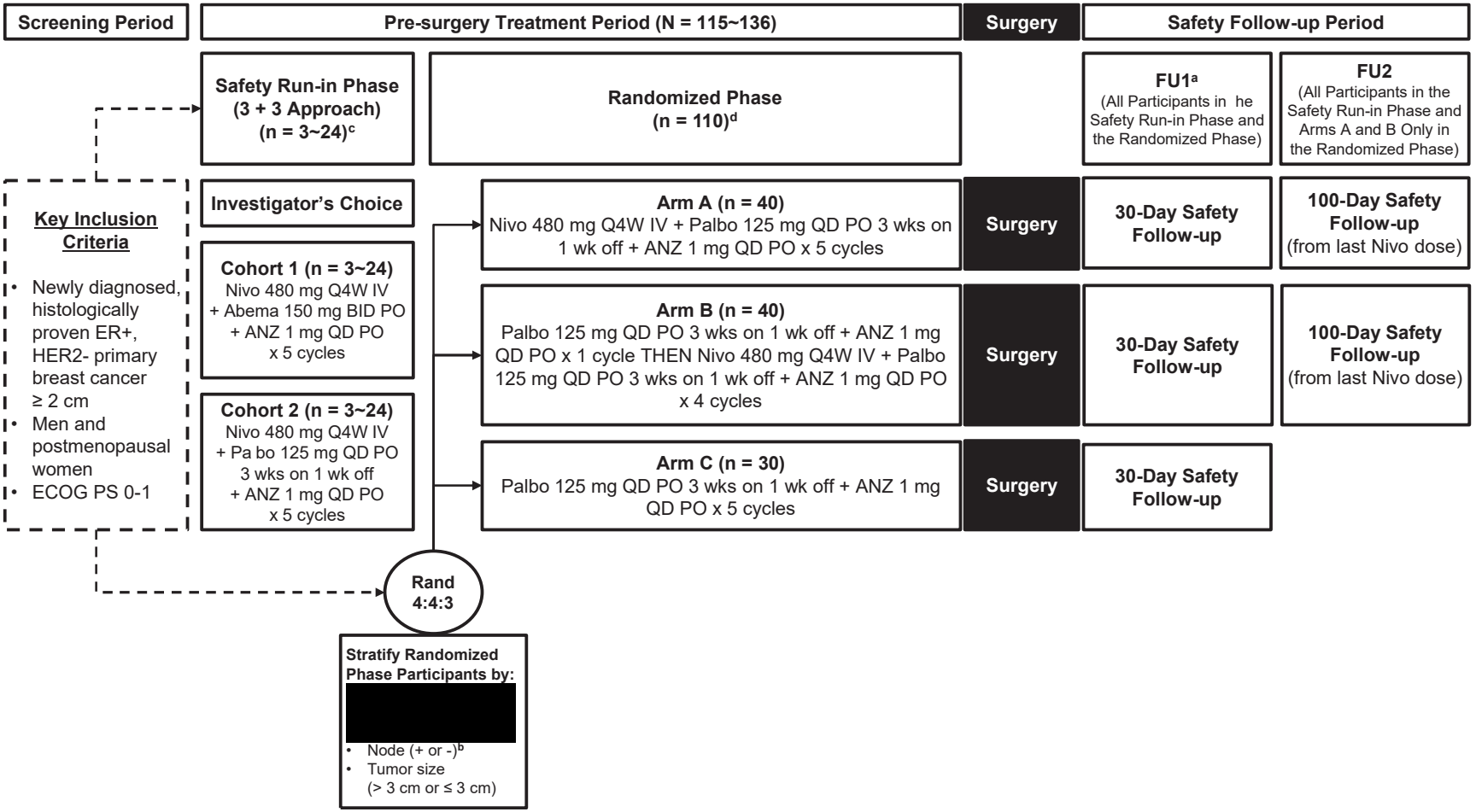
The study will start with a Safety Run-in Phase for the combination of nivolumab, with abemaciclib or palbociclib, plus anastrozole and will begin the Randomized Phase after the regimen is determined to be safe. Participant assignment will be carefully managed by the study team with the Investigator in the Safety Run-in Phase to ensure equal distribution of participants in both cohorts (abemaciclib or palbociclib). The abemaciclib cohort (cohort 1) was closed after two participants were dosed per Revised Protocol 03. No further investigation of abemaciclib related arms is planned in the Randomized Phase. Participants in the Safety Run-in Phase will move to the Safety Follow-up Period upon completion of the neoadjuvant treatment or upon discontinuation. Potential needs for additional enrollment or for dose de-escalation will be discussed with Investigators and BMS during the Safety Run-in Phase. Once a safe dose for each regimen has been determined by BMS in collaboration with Investigators, the Randomized Phase of the study will begin.

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

For both the Safety Run-in Phase and Randomized Phase, participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks). Participants with progressive disease prior to completion of the 5-cycle study treatment must discontinue all study drugs and proceed to the Safety Follow-up Period. Participants who permanently discontinue the study drugs for any reason are considered to have completed the On-treatment Pre-surgery (neoadjuvant) Period, and hence reach end of treatment (EOT). After Cycle 5 or EOT, participants must continue to receive anastrozole (as concomitant medication and not as study treatment) until subsequent SOC breast surgery. Following the completion of neoadjuvant treatment, all participants who remain operative

candidates will undergo definitive surgery for BC within 4 weeks of the last neoadjuvant treatment administration. If anastrozole can no longer be administered after EOT, participants will go to breast surgery right away. Pre-surgical lymph node biopsy is not allowed. Information on the type of the surgery will be collected and recorded in the electronic case report form (eCRF). Surgical specimens will be collected for the analyses outlined in the protocol. Depending on treatment assignment, up to 2 safety follow-up visits will be conducted in person. The first safety follow-up visit (FU1) will be completed for all participants within 30 days (± 7 days) from the last study treatment (oral or intravenous [IV], whichever occurs later). The second safety follow-up visit (FU2) will occur approximately within 100 days (± 7 days) from the last dose of nivolumab and will be required for participants in the Safety Run-in Phase and participants randomized to Arms A and B in the Randomized Phase. Further planned treatment of participants in the adjuvant setting (i.e., radiotherapy, endocrine treatment, chemotherapy or any other treatment modality) will be at the discretion of the treating physician, following local clinical guidelines, and collected in the appropriate eCRF. The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Design Schematic



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

a FU1 begins at the end of study treatment.

b Cytologically positive vs radiologically or cytologically negative.

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

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

2.2 Treatment Assignment

CA2097A8 is an open-label, randomized trial. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by calling the IRT to obtain a participant number. Every participant that signs the informed consent form must be assigned a participant number in IRT.

Safety Run-in Phase

Participants will receive either abemaciclib in combination with nivolumab plus anastrozole (Cohort 1) or palbociclib in combination with nivolumab plus anastrozole (Cohort 2). Participant assignment will be carefully managed by the study team with the Investigator in the Safety Run-in Phase to ensure equal distribution of participants in both cohorts (abemaciclib or palbociclib). As per Revised Protocol 03, Cohort 1 (abemaciclib + nivolumab + anastrozole) was closed permantely. For cohort 2, 3 DLT-evaluable participants will be treated with the below starting doses:

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

If any DLT evaluable participants experiences DLT during DLT period, a lower dose of Palbociclib will be tested using a 3 + 3 schema. If no participants (0 of 3 DLT-evaluable participants) experience a DLT during the DLT period (4 weeks), the Randomized Phase will be initiated at this dose level. If 1 evaluable participant (1 of 3 DLT-evaluable participants) experiences DLT, then the cohort will be expanded to 6 DLT-evaluable participants. If no more DLTs are observed (1 of 6 DLT-evaluable participants), then the Randomized Phase will be initiated at the dose level tested. If 1 or more additional evaluable participants (2 of 6 DLT-evaluable participants) experiences DLT during the DLT period, a lower dose will be tested using the same 3 + 3 schema.

The recommended abemaciclib dose modifications for adverse reactions are provided in Table 2.2-1. Discontinue abemaciclib for participants unable to tolerate 50 mg BID.

Table 2.2-1: Abemaciclib Dose Modifications for Adverse Reactions

Dose Level	Abemaciclib Dose Combination with an Aromatase Inhibitor
Recommended starting dose	150 mg BID
First dose reduction	100 mg BID
Second dose reduction	50 mg BID
Third dose reduction	NA

Abbreviations: BID = twice daily; NA = not applicable.

The dose modifications permitted for palbociclib in combination with anastrozole are based on the dose level changes outlined in Table 2.2-2.

Table 2.2-2: Dose Levels for Palbociclib

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

Abbreviations: mg = milligram; QD = once daily.

Randomized Phase

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be ready to be randomized through IRT in a 4:4:3 ratio to treatment Arm A, B or C, respectively.

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

The randomization will be stratified by the following factors:

[redacted]

- Evaluation of lymph nodes (cytologically positive vs radiologically or cytologically negative)
- Tumor size (> 3 cm or ≤ 3 cm)

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

2.3 Blinding and Unblinding

This is an open-label study. Blinding procedures between participants and investigators are not applicable.

2.4 Protocol Amendments

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

3 OBJECTIVES

3.1 Primary

Safety Run-in Phase: Number of participants with occurrence of DLT.

Randomized Phase: To assess RCB 0-I rate by central assessment of palbociclib plus anastrozole with or without nivolumab in all participants with untreated primary BC ≥ 2 cm (ER+, HER2-).

3.2 Secondary

- To assess the safety and tolerability of palbociclib plus anastrozole with or without nivolumab.
- To assess pCR rate by local assessment of palbociclib plus anastrozole with or without nivolumab in participants with untreated primary BC ≥ 2 cm (ER+, HER2-)
- To assess ORR (clinical and radiological [ultrasound (preferred) or mammography]) by Investigator assessment and BCS rate of palbociclib plus anastrozole with or without nivolumab in participants with untreated primary BC ≥ 2 cm (ER+, HER2-)

[redacted]

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

4.1.1 Dose-limiting Toxicity

Dose-limiting Toxicity (DLT) is defined as treatment-emergent adverse event (TEAE, graded according to the NCI CTCAE v5.0) that occurs during the first 4 weeks after treatment start and that meets specific criteria. [redacted]

4.1.2 Residual Cancer Burden

Residual Cancer Burden (RCB) is a continuous index combining pathological measurements of primary tumor (size and cellularity) and nodal metastases (number and size) defined by a point system at surgery (refer to Appendix 7 of protocol [RCB Methods]). RCB is assessed by central assessment at the time of definitive surgery. RCB 0-I rate is defined as number of randomized subjects who achieve a RCB 0 or RCB I divided by the number of all randomized subjects.

4.2 Secondary Endpoints

4.2.1 Pathological Complete Response, Primary Definition

Pathological Complete Response (pCR) is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0/Tis ypN0 in the current AJCC staging system). Pathological complete response is assessed by the local pathologist at the time of definitive surgery. The pCR rate is defined as number of randomized subjects who achieve a pCR divided by the number of all randomized subjects.

4.2.2 Objective Response Rate

Objective Response Rate (ORR) is defined as the number of randomized subjects who achieve a best response of complete response (CR) or partial response (PR) based on investigator assessments (using RECIST v1.1 criteria, by clinical or radiological) divided by the number of all randomized subjects. Best Overall Response (BOR) is defined as the best response, as determined by the investigator (using RECIST v1.1 criteria, by clinical or radiological), recorded between the

date of randomization and the date of objectively documented progression per RECIST v1.1 criteria, the date of surgery, or date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy before surgery, all available pre-surgery response designations will contribute to the BOR determination. Confirmation of response is not required due to the limited number of planned tumor measurement before surgery.

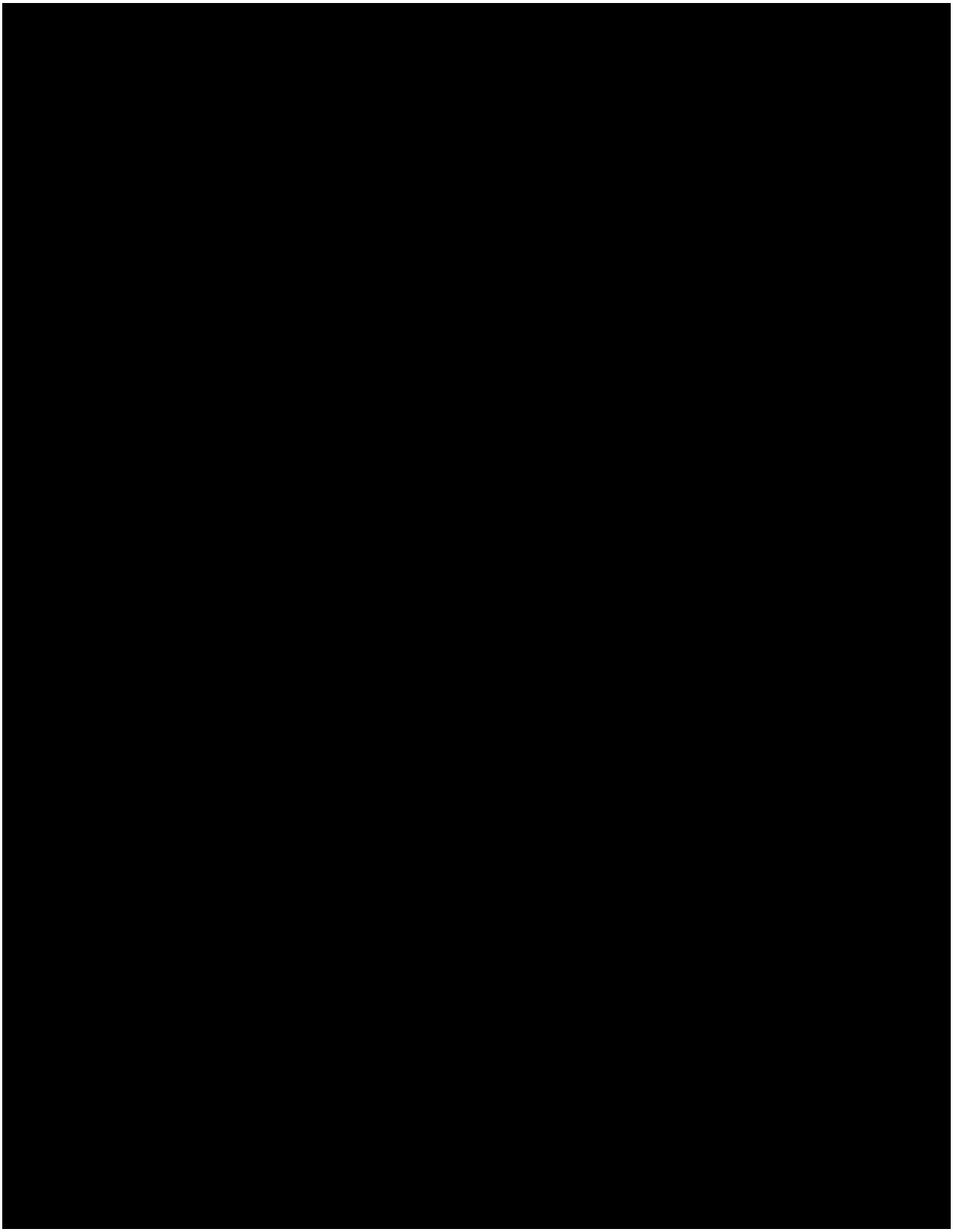
4.2.3 Breast-conserving Surgery Rate

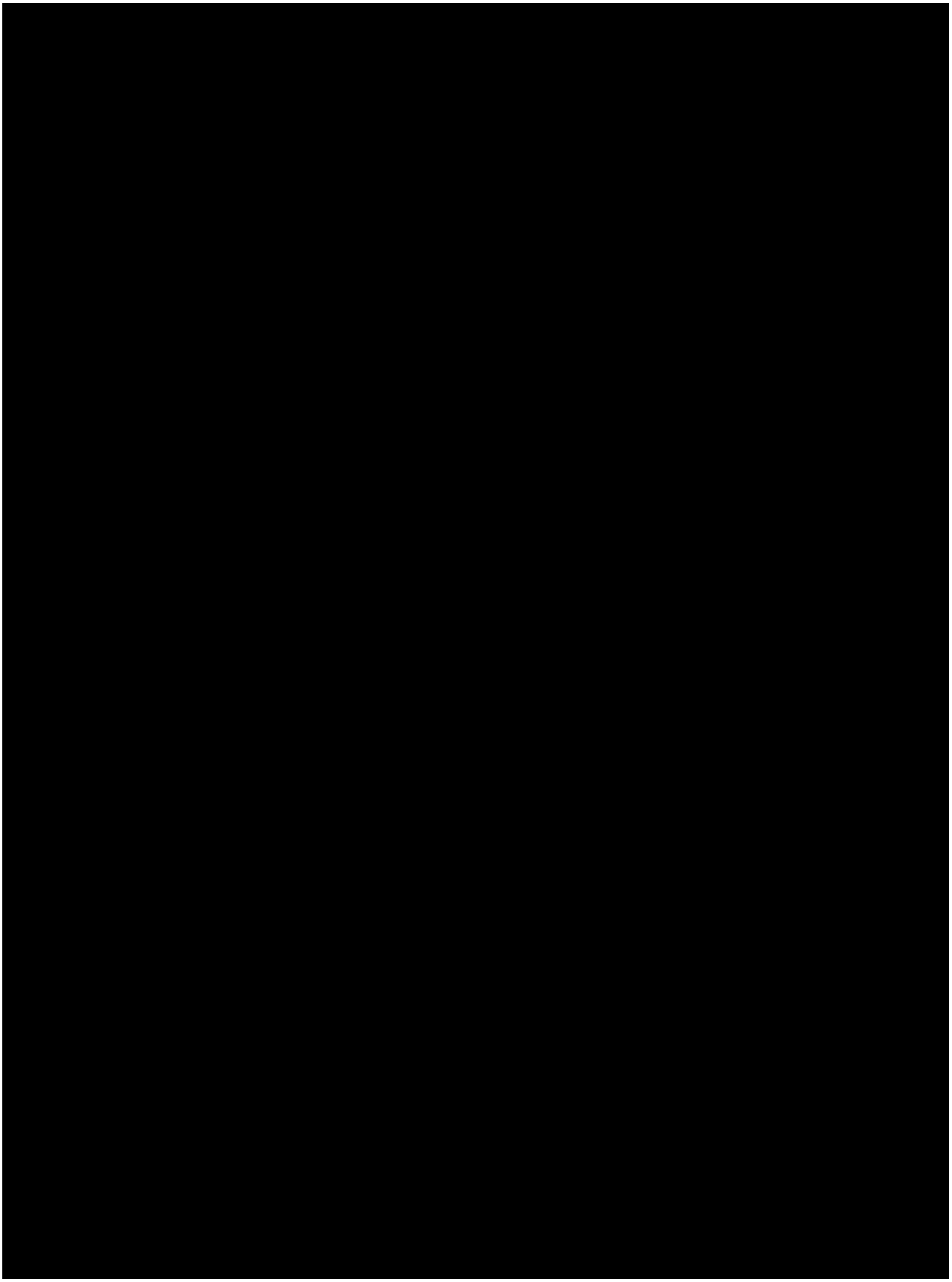
Breast-conserving Surgery (BCS) rate is defined as the number of randomized subjects who undergo BCS after completing the study treatments divided by the number of all randomized subjects.

4.2.4 Safety and Tolerability

Other safety endpoints will include the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, immune-related adverse events and specific laboratory abnormalities (worst grade) in each treatment group. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. See details in the IO Core SAP[1].

[redacted]



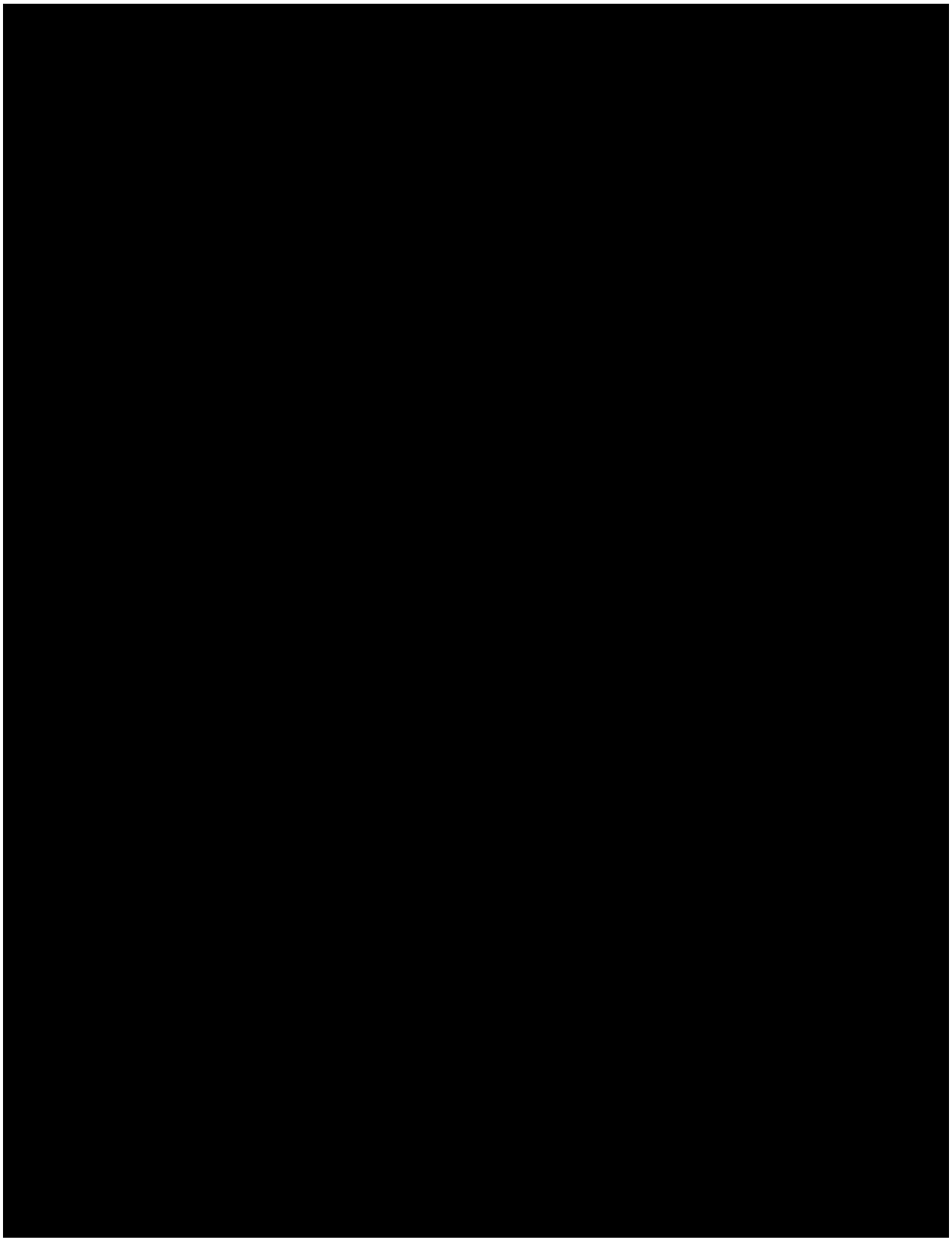


[redacted]

5 SAMPLE SIZE AND POWER

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

[redacted]



[redacted]

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

- Baseline period:
  - Baseline evaluations or pre-treatment events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment. Evaluations (laboratory tests, pulse oximetry, vital signs[redacted]) on the same date and time of the first dose of study treatment will be considered as baseline evaluations. Events (AEs) on the same date and time of the first dose of study treatment will not be considered as pre-treatment events.
  - In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:
    - Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment;
    - Baseline evaluations (laboratory tests, pulse oximetry, vital signs[redacted]) will be defined as evaluations with a date (and time if collected) on or prior to the date of first dose of study treatment.
  - If there are multiple valid observations in the baseline period, then the latest non missing observation will be used as the baseline in the analyses. If multiple observations exist on the latest collection date (and time if collected), the record with the latest data entry date and time will be used. If multiple observations exist on the latest collection date (and time if collected) and data entry date and time, then the first observation is used as baseline, unless otherwise specified.

    [redacted]

    - Refer to the study-specific protocol for potential additional baseline evaluations definition such as baseline tumor evaluation, etc.
- Post baseline period:
  - On-treatment AEs will be defined as AEs with an onset date and time on or after the date and time of the first dose of study treatment (or with an onset date on or after the day of

first dose of study treatment if time is not collected or is missing). For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.

– On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment.

•

6.2 Treatment Regimens

Treatment group in Safety Run-in Phase (Align with IRT Data Specification):

Cohort 1 Dose Level 1: Nivo 480mg Q4W + Abema 150mg BID + Anast 1mg QD

Cohort 2 Dose Level 1: Nivo 480mg Q4W + Palbo 125mg QD + Anast 1mg QD

Cohort 2 Dose Level 2: Nivo 480mg Q4W + Palbo 100mg QD + Anast 1mg QD

Cohort 2 Dose Level 3: Nivo 480mg Q4W + Palbo 75mg QD + Anast 1mg QD

Cohort 2 Dose Level 4: Nivo 480mg Q4W + Anast 1mg QD

Treatment group in Randomized Phase (Align with IRT Data Specification):

A: Nivo + Palbo + Anast for 5 cycles

B: Palbo + Anast for 1 cycle + Nivo 4 cycles

C: Palbo + Anast for 5 cycles

Treatment group "as randomized" corresponds to the treatment group assigned by the Interactive Response Technology (IRT) system.

The treatment group "as treated" will be same as the treatment group "as randomized" by IRT unless a subject received the incorrect study treatment for the entire period of treatment, in which case the subject's treatment group "as treated" will be defined as the incorrect study treatment.

Unless otherwise specified, the safety analysis will be based on the treatment group "as treated".

Unless otherwise specified, the efficacy analysis will be based on the treatment group "as randomized".

6.3 Populations for Analyses

Populations for purposes of analysis are defined in Table 6.3-1 below.

Table 6.3-1: Populations for Analyses

Population	Description
All Enrolled	All participants who signed an ICF and were registered into the IRT.
All Randomized	All participants who were randomized to any treatment arm in the study. Participants are grouped within the All Randomized population by the treatment to which they were randomized. This is the primary analysis set for demography, protocol deviations, baseline characteristics, and primary efficacy analyses.
All Treated	All randomized participants who receive at least 1 dose of study drug. Participants are grouped within the All Treated population according to the treatment they actually received. This is the analysis set for all safety analyses and study drug administration.
All Treated from Safety Run-in Phase	All enrolled participants who received at least 1 dose of study drug in the Safety Run-in Phase. Participants are grouped within the All Treated from Safety Run-in Phase population according to the treatment and dose level they actually received. This is part of the analysis set for all safety analysis and study drug administration.
All DLT-Evaluable	All participants treated in Safety Run-in Phase who have discontinued due to a DLT or who have received 1 dose of nivolumab and 75% of accumulative doses of abemaciclib or palbocicllib of the cycle, and have completed the 4-week DLT period.
All RCB Evaluable	All Treated participants who have an RCB of 0, I, II, or III from both the Safety Run-in Phase and Randomized Phase. [redacted]

[redacted]

7 STATISTICAL ANALYSES

7.1 General Methods

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

Time-to-event variables (e.g. time-to resolution) will be analyzed using the Kaplan-Meier technique. When specified, the median will be reported along with 95% CI using Brookmeyer and Crowley method[2] (using log-log transformation for constructing the confidence intervals[3]).

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

7.1.1 Adverse Events, Serious Adverse Events, Multiple events, and Immune-Mediated Adverse Events

Drug-related AEs are those events with relationship to study drug "Related", as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.

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

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

Adverse events that led to dose interruption of the drug will be coded with action "Drug was interrupted".

Adverse events that led to dose omission of the drug will be coded with action "Dose was omitted".

Adverse events leading to dose reduction are AEs with action taken regarding study drug(s) = "Dose was reduced".

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

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

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

Analyses that take into account the multiple occurrences of a given adverse event will be conducted (see Section 7.6.11). To prepare these analyses, the CRF data will be processed according to standard BMS algorithms[4] in order to collapse adverse event records into unique records based on the preferred term. These data will be presented as the rate per 100 person-years of exposure. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total exposure time. The person-year exposure will be computed as the sum over the subjects' exposure expressed in years where the exposure time is defined as

- Patients treated in Arm C of randomized phase: (Date of last dose of study treatment - date of first dose of study treatment + 31 days)/365.25, for subject who are off study treatment and were followed for at least 30 days after last dose of study treatment.

- Patients treated in Safety run-in phase and Arm A, B of randomized phase: (Date of last dose of study treatment - date of first dose of study treatment + 101 days)/365.25, for subject who are off study treatment and were followed for at least 100 days after last dose of nivolumab.
- (Last known alive date - date of first dose of study treatment +1)/365.25, for subjects who are still on-treatment or who are off study treatment and were followed less than 30 days in Arm C (or 100 days in Arm A or B) after last dose of study treatment.

7.1.1.1 Select Adverse Events (EU/ROW Submissions)

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories, etc.). AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. Categories of select AEs may include subcategories (e.g. adrenal disorders, diabetes, pituitary disorders, and thyroid disorders are subcategories of the endocrine event category).

The list of MedDRA preferred terms used to identify select adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock will be provided by categories/subcategories.

In addition to the frequency and worst severity of select AEs, time-to onset, time-to resolution, and time-to resolution where immune modulating medication was initiated will be analyzed for each specific category/subcategory of drug-related select AEs when applicable.

Further details on the definitions time-to onset and time-to resolution are described in APPENDIX 1.

7.1.1.2 Other Events of Special Interest

Other events of special interest (OEOSI) consist of a list of preferred terms grouped by specific category (e.g. Myositis Event, Myocarditis Event, Demyelination Event, Guillain-Barre Syndrome, Pancreatitis Event, Uveitis Event, Encephalitis Event, Myasthenic Syndrome, Rhabdomyolysis Event, Graft Versus Host Disease). The list of MedDRA preferred terms used to identify OEOSI is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.1.3 Immune-Mediated Adverse Events (US Submission)

In order to further characterize AEs of special clinical interest, analysis of immune-mediated AEs (IMAE) will be conducted. IMAEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator that meet the definition summarized below:

- those occurring within 100 days of the last dose,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism,

diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).

- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component.

The list of MedDRA preferred terms used to identify IMAEs is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.2 Laboratory Tests

Clinical laboratory parameters (hematology, serum chemistry and electrolytes) will be evaluated.

Laboratory tests will be graded using the NCI Common Terminology Criteria, and the most recent version of the criteria at the time of the database lock will be used.

Clinical laboratory data will be first analyzed using International System of Units (SI).

Analyses will be repeated using US conventional units if needed.

In the laboratory summary tables, unless otherwise specified, subjects will be counted only once for each lab parameter according to their worst on treatment CTC grade (worst being the highest CTC grade). The laboratory tables and listings will be sorted by laboratory category, laboratory subcategory and laboratory test code sequence number.

[redacted]

7.2 Study Conduct

Unless otherwise specified, the study conduct data will be presented by cohort and all treated subjects (for safety run-in phase), or by treatment arm and all randomized subjects (for randomized phase).

7.2.1 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized by treatment group and overall in all treated subjects (for safety run-in phase) and in all randomized subjects (for randomized phase). Non-programmable relevant eligibility and on-study protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-study protocol deviations will be reported through [redacted] listings.

Eligibility:

- Subjects without measurable disease at baseline as per investigator, or with measurable baseline primary tumor of < 2 cm in largest diameter
- Subjects with unknown or negative ER
- Subjects with unknown or positive HER2

- Subjects received any treatment, including radiotherapy, chemotherapy, and/or targeted therapy, administered for the currently diagnosed BC prior to enrollment.
- Subjects with baseline ECOG performance status > 1
- Subjects with misclassified stratification factor levels (IVRS vs clinical database; for randomized phase only)

On-study:

- Subjects receiving any concurrent anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) outside of the protocol-specified neoadjuvant therapy while on study.
- Subjects whose "as treated" arm different than their as randomized arm (subjects who received the wrong treatment for the entire neoadjuvant treatment period, excluding the never treated)

7.2.2 Accrual

Enrollment by country and site, and enrollment by month will be summarized and listed for all enrolled subjects.

A by-subject listing of batch numbers for all treated subjects will be provided.

7.3 Study Population

Analyses in this section will be tabulated for all randomized subjects in randomized phase by treatment group as randomized; and for all treated subjects in Safety Run-in phase by cohort group, unless otherwise specified.

7.3.1 Subject Disposition

The total number of subjects enrolled (randomized or not randomized for randomized phase; treated or not treated for safety run-in phase) will be presented along with the reason for not being randomized/treated. This analysis will be performed on all enrolled subjects population only.

Number of subjects randomized but not treated along with the reason for not being treated will be tabulated by treatment group as randomized in randomized phase.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group as treated. Reason for discontinuation will be derived from subject status CRF page. Number of subjects who did not receive surgery along with corresponding reason will be tabulated by treatment group as treated. Reason for not receiving surgery will be derived from subject status CRF page. This analysis will be performed only on all treated subjects population.

A by-subject listing for all treated subjects will be provided showing the subjects off treatment date, whether the subject continue in the treatment period/study along with the reason for going off treatment period/study, and whether subject received surgery along with the reason for not receiving surgery. A by-subject listing for all enrolled subjects will also be provided, showing whether the subject was randomized/treated along with the reason for not being randomized/treated.

7.3.2 Demographics and Other Baseline Disease Characteristics

The following demographic and baseline disease characteristics will be summarized and listed by treatment group as randomized (in randomized phase) or treatment group as treated (in safety run-in phase):

- Age (continuous)
- Age categorization (< 65, ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85, ≥ 75, ≥ 65)
- Sex (Male vs. Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific, Asian Indian, Chinese, Japanese, Malay, Asian Other, Other)
- Ethnicity (Hispanic/Latino and Not Hispanic/Latino)
- Country by geographic region
- ECOG performance status (0, 1, >1)
- Tumor size (> 3 cm or ≤ 3 cm) (randomized phase only)
- Evaluation of lymph nodes (cytologically positive vs radiologically or cytologically negative) (randomized phase only)
- [redacted]

Summary table (cross-tabulation) by treatment group for stratification factor (except for region) will be provided to show any discrepancies between what was reported through IRT vs. other data sources at baseline. This summary will be performed based on all randomized subjects (randomized phase only).

A listing of randomization scheme presenting randomized treatment group and as treated treatment group will be provided for all randomized subjects (randomized phase only).

A by-subject listing of FSH level and/or Estradiol level for female participants with age ≤ 55 will be provided to confirm menopause at screening.

7.3.3 Medical History

A by-subject listing of general medical history for all randomized subjects in the randomized phase and for all treated subjects in the Safety Run-in phase will be provided.

7.3.4 Prior Therapy Agents

- Prior cancer therapy will be summarized by treatment group and overall.
- Prior systemic cancer therapy will be summarized by treatment group and overall and listed by subject.
- Prior radiotherapy and prior surgery related to other cancer will be listed by subject.

7.3.5 Physical Examinations

Subjects with abnormal baseline physical examination will be listed by subject.

7.3.6 Baseline Physical Measurements

Baseline physical measurements will be listed by subject.

7.4 Extent of Exposure

Listings will include all available exposure data. Analyses will be performed by treatment group "as treated" in all treated subjects, unless otherwise specified.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by treatment group (groups are also differentiated by phase: Safety Run-in Phase, Randomized Phase):

- Time from randomization to first dose of study therapy (0 to 3 days, > 3 to 7, >7 to 14, >14 to 21, >21 to 28, >28), for randomized phase only.
- The following parameters will be summarized (descriptive statistics) by study therapy and treatment group:
- Number of doses received (nivolumab, anastrozole, palbociclib and abemaciclib [for participants in cohort 1])
- Cumulative dose
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%
- Average daily dose

Duration of study therapy will be summarized (descriptive statistics) by treatment group.

A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose changes) will be also provided.

Table 7.4.1-1: Administration of study therapy: definition of parameters, IV therapy

	Nivolumab
Dosing schedule per protocol	**480 mg every 4 weeks**
Dose	Dose (mg) is defined as Total Dose administered (mg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative dose	Cum dose (mg is sum of the doses (mg) administered to a subject during the treatment period.
Relative dose intensity (%)	[Cum dose (mg)/((Last dose date - Start dose date + 28) x 480 / 28)] x 100
Duration of study therapy	Last dose date - Start dose date +1

Table 7.4.1-2: Administration of study therapy: definition of parameters, PO therapies in Randomized Phase

	Anastrozole	**Abemaciclib**	**Palbociclib**
Dosing schedule per protocol	1 mg QD	150[a] mg BID	125[b] mg QD × 3 weeks on and 1 week off

Table 7.4.1-2: Administration of study therapy: definition of parameters, PO therapies in Randomized Phase

	Anastrozole	Abemaciclib	Palbociclib
Dose	Dose (mg) is defined as Total Dose administered (mg). Dose administered in mg at each dosing date and weight are collected on the CRF.	Dose (mg) is defined as Total Dose administered (mg). Dose administered in mg at each dosing date and weight are collected on the CRF.	Dose (mg) is defined as Total Dose administered (mg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative dose	Cum dose (mg) is sum of the doses (mg) administered to a subject during the treatment period.	Cum dose (mg) is sum of the doses (mg) administered to a subject during the treatment period.	Cum dose (mg) is sum of the doses (mg) administered to a subject during the treatment period.
Average daily dose (actual)	Cumulative dose in mg / duration of treatment in days	Cumulative dose in mg / duration of treatment in days	Cumulative dose in mg / duration of treatment in days
Average daily dose (planned)	1 mg	300[c] mg	93.75[d] mg (125 mg × 21 days / 28 days)
Relative dose intensity (%)	(Actual average daily dose / planned average daily dose) × 100	(Actual average daily dose / planned average daily dose) × 100	(Actual average daily dose / planned average daily dose) × 100
Duration of treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1	Last dose date - Start dose date +8

[a] Scheduled dose of abemaciclib could be 150 mg, 100 mg or 50 mg BID depending on the dose cohort in safety run-in phase and the recommended phase 2 dose (RP2D) identified from safety run-in phase which is applied in randomized phase.

[b] Scheduled dose of palbociclib could be 125 mg, 100 mg or 75 mg QD × 3 weeks on (1 week off) depending on the dose cohort in safety run-in phase and RP2D in randomized phase.

[c] Planned average daily dose of abemaciclib could be 300 mg, 200 mg or 100 mg depending on the dose cohort in safety run-in phase and RP2D in randomized phase.

[d] Planned average daily dose of palbociclib could be 93.75 mg, 75 mg or 56.25 mg depending on the dose cohort in safety run-in phase and RP2D in randomized phase.

7.4.2 Modifications of Study Therapy

Participants are to start nivolumab within 3 calendar days of randomization. Participants will receive nivolumab at a dose of 480 mg as a 30-minute IV infusion for a maximum of 5 cycles (maximum 4 cycles for Arm B). Doses of nivolumab may be interrupted, omitted, or discontinued, depending on how well the participant tolerates the treatment. There will be no dose escalations or reductions of nivolumab allowed. For Q4W dosing cycles, participants may be dosed within a ± 3-day window. If a participant cannot receive nivolumab within a ± 3-day window, nivolumab must be omitted (skipped) for that cycle. If nivolumab is omitted, the other study medications may continue. If a participant discontinues nivolumab, the entire study treatment (CDK4/6 inhibitor

and anastrozole) must be discontinued. When nivolumab is scheduled to be administered on the same day with palbociclib plus anastrozole, nivolumab dosing should be started > 1 hour after palbociclib plus anastrozole ingestion. If nivolumab cannot be given within 3 days of palbociclib plus anastrozole administration for a given cycle, nivolumab must be omitted for that cycle. Participants who require a dose omission for nivolumab should be re-evaluated and resume treatment at the next cycle when re-treatment criteria are met.

Palbociclib can be interrupted, reduced, or discontinued both within a cycle and between cycles.

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

Dose escalations (within subject) are not permitted for any study drugs.

Reason for dose modification will be retrieved from CRF dosing pages.

- The following parameters will be summarized by treatment group:
- Number of subjects with at least one dose modification (interrupted nivolumab dose, omitted nivolumab dose, interrupted palbociclib dose, reduced palbociclib dose).
- Number of nivolumab and/or palbociclib dose modifications per subject.
- Reason of nivolumab and/or palbociclib dose modification.

7.4.2.1 Infusion Interruptions and Rate Changes

Each nivolumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

- The following parameters will be summarized by treatment group:
- Number of subjects with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per subject.
- Number of subjects with at least one IV infusion rate reduction, the reason for reduction and the number of infusions with IV rate reduction per subject.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of nivolumab in Arm A, B and Safety Run-in cohorts; on or after the first day of study therapy and within 30 days following the last dose of study treatment in Arm C), will be coded using the UMC WHO Drug Global Dictionary. Anastrozole administered after completion of 5 cycles of neoadjuvant treatment (or EOT) up to subsequent breast surgery must be collected as concomitant medication.

The following summary table will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term)

A by-subject listing(s) will accompany the table(s).

7.4.3.1 Immune modulating medication

Immune modulating concomitant medications are medications entered on an immune modulating medication form or available from the most current pre-defined list of immune modulating medications. The list of anatomic class, therapeutic class and generic name used for the selection at the time of the database lock will be provided.

The percentage of subjects who received immune modulating concomitant medication for

- management of adverse event
- premedication
- other use
- any use
- management of drug-related select adverse event (any grade, grade 3-5) by select AE category/ subcategory (EU/ROW Submissions)
- management of IMAEs (any grade, grade 3-5) by IMAE category (US Submission)

will be reported separately for each treatment group (percentages of treated subjects by medication class and generic term).

For each category/subcategory of drug-related select AEs (any grade, grade 3-5) and IMAEs (any grade, grade 3-5), the following will be reported for each treatment group:

- The total immune modulating medication treatment duration (excluding overlaps), duration of high dose of corticosteroid, initial dose of corticosteroid, and tapering duration (summary statistics)

Duration represents the total duration the subject received the concomitant medication of interest. If the subject took the medication periodically, then DURATION in the summation of all use. Initial dose represents the dose of the concomitant medication of interest received at the start of the event. In the case multiple medications started on the same date, the highest equivalent dose is chosen and converted to mg/kg by dividing by the subject's recent weight.

These analyses, except the ones related to IMAEs will be conducted using the 30-day safety window. The analyses related to IMAEs will be conducted using the 100-day safety window.

7.4.3.2 Subsequent Cancer Therapy

Number and percentage of subjects receiving subsequent cancer therapies will be summarized for all treated subjects (in safety run-in period) and all randomized subjects (in randomized phase). Categories include:

- Subsequent systemic therapy
- Subsequent surgery for treatment of tumors
- Subsequent radiotherapy for treatment of tumors

A by-subject listing of subsequent therapies will also be produced.

7.5 Efficacy

Analyses in this section will be tabulated for all randomized subjects by treatment group as randomized, unless otherwise specified.

CIs for all efficacy endpoints will be at the two-sided 95% level and two-sided 90% level. Point estimates and confidence bounds for efficacy variables will be rounded to the second decimal place.

- A by-subject listing of efficacy results will be presented including treatment group, planned and actual surgery type, RCB, pCR, ORR, death date, etc.

7.5.1 Analysis of Residual Cancer Burden (RCB)

The primary objective of the Randomized phase of the study is to estimate the RCB 0-I rate per central assessment in the treatment groups among all randomized subjects.

The number and percentage of subjects in each category of RCB per central assessment (0, I, II, III) will be presented, by treatment group. Estimates of RCB 0-I rate along with its exact two-sided 95% and two-sided 90% CI by Clopper and Pearson[5] will be presented, by treatment group.

- A by-subject listing of RCB will be presented including treatment group, RCB, randomization date, surgery date [redacted].

7.5.2 Analysis of Pathological Complete Response (pCR)

One of the secondary objectives of the study is to estimate the pCR rate per local assessment in the treatment groups among all randomized subjects.

The number and percentage of subjects in each category of pathological response per local assessment (pCR, non-pCR) will be presented, by treatment group. Estimates of pCR rate along with its exact two-sided 95% CI by Clopper and Pearson[5] will be presented, by treatment group.

- A by-subject listing of pCR will be presented including treatment group, pCR, randomization date, surgery date [redacted].

7.5.3 Analysis of Breast-Conserving Surgery (BCS) Rate

One of the secondary objectives of the study is to estimate the BCS rate in the treatment groups among all randomized subjects.

The number and percentage of subjects in each category of planned surgery (breast-conserving, mastectomy) and actual surgery (breast-conserving, mastectomy) will be presented, by treatment group. BCS rate is defined as the number of participants who actually undergo BCS after completing the study treatment divided by the number of all randomized participants in each treatment group. Estimates of BCS rate along with its exact two-sided 95% CI by Clopper and Pearson[5] will be presented, by treatment group.

- A by-subject listing of planned and actual surgery will be presented including treatment group, randomization date, planned surgery type, actual surgery type, surgery date [redacted].

7.5.4 Analysis of Objective Response Rate (ORR)

One of the secondary objectives of the study is to estimate the ORR per investigator radiographic assessment in the treatment groups among all randomized subjects.

The number and percentage of subjects in each category of BOR per investigator assessment (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or not evaluable [NE]) will be presented, by treatment group. Estimates of response rate, along with its exact two-sided 95% and two-sided 90% CI by Clopper and Pearson[5] will be presented, by treatment group.

- A by-subject listing of best overall response will be presented including treatment group, best overall response and dates of CR/PR/progression.
- A by-subject, by-visit, by-lesion listing of tumor assessment will be presented.

Similar analyses will be repeated based on the investigator clinical assessment of ORR. A by-subject listing of per time point tumor response per clinical assessment will be presented.

[redacted]

[redacted]

7.6 Safety

Analyses in this section will be tabulated for all treated subjects by treatment group as treated, unless otherwise specified.

7.6.1 Dose Limiting Toxicities (Safety Run-In Phase)

Dose limiting toxicities will be summarized by cohort and dose level. A corresponding by-subject listing will be provided for all treated subjects.

7.6.2 Deaths

Deaths will be summarized by treatment group:

- All deaths, reasons for death.
- Deaths within 30 days of last dose received, reasons for death.
- Deaths within 100 days of last dose received, reasons for death.

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

7.6.3 Serious Adverse Events

Serious adverse events will be summarized by treatment group:

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

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

7.6.4 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized by treatment group:

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

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

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

7.6.5 Adverse Events Leading to Dose Modification

AEs leading to dose delay/reduction will be summarized by treatment group:

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

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

A by-subject AEs leading to dose delay/reduction listing will be provided.

7.6.6 Adverse Events

Adverse events will be summarized by treatment group.

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

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

The following analyses will be conducted using the 30 days safety window and repeated using the 100 days safety window:

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

A by-subject AE listing will be provided. A by-subject listing of any AE requiring immune modulating medications will also be provided.

7.6.7 Select Adverse Events (EU/ROW Submissions)

Unless otherwise specified, analyses will be performed by select AE category. Analyses will also be repeated by subcategory of endocrine events.

7.6.7.1 Incidence of Select AE

Select AEs will be summarized by treatment group for each category/subcategory.

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

- Overall summaries of any select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any drug-related select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of any select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Summary of frequency of unique select AEs by Category.

A by-subject select AE listing will be provided.

7.6.7.2 Time-to Onset of Select AE

Time-to onset of drug-related select AEs (any grade, grade 3-5) will be summarized for each category/subcategory by treatment group.

Time-to onset analyses are restricted to treated subjects who experienced at least one drug-related select AE in the category/subcategory. The analyses will be conducted using the 30-day safety window.

Additional details regarding the time-to onset definition are described in time-to onset definition subsection of APPENDIX 1.

7.6.7.3 Time-to Resolution of Select AE

Time-to resolution of the following specific events will be summarized separately for each category/subcategory.

- Time-to resolution of drug-related select AE (any grade, grade 3-5) by treatment group.
- Time-to resolution of drug-related select AE (any grade, grade 3-5) where immune modulating medication was initiated, by treatment group.

Time-to resolution analyses are restricted to treated subjects who experienced the specific events. Time-to resolution where immune modulating medication was initiated analyses are restricted to treated subjects who experienced the specific events and who received immune modulating medication during the longest select AE.

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

The following summary statistics will be reported: percentage of subjects with resolution of the longest select AE, median time-to resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.

See time-to resolution definition subsection of APPENDIX 1 for additional details.

7.6.8 Immune-Mediated Adverse Events (US Submission)

IMAEs will be summarized by treatment group for each immune-mediated category / PT using the 100-day safety window:

- Overall summary of non-endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT.
- Overall summary of endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT.
- Overall summary of non-endocrine IMAEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT.
- Overall summary of endocrine IMAEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT.
- Overall summary of non-endocrine IMAEs leading to dose delay or reduction by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT
- Overall summary of endocrine IMAEs leading to dose delay or reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT.
- Summaries of time-to onset and time-to resolution of non-endocrine IMAEs where immune modulating medication was initiated presented by Category.
- Summaries of time-to onset and time-to resolution of endocrine IMAEs presented by Category.

A by-subject listing of IMAEs will be provided. By-subject listings of time-to resolution for longest IMAEs cluster (any grade and grade 3-5 in separate summaries) will also be provided. For new studies which collect investigator assessment of potential IMAE data, a by-subject listing of AEs considered as immune-mediated events per investigator but not qualified for IMAEs definition will also be provided.

In addition, for all nivolumab treated subjects who experienced at least one IMAE, the following data presentation will be provided:

- Summary of subjects who were re-challenged with nivolumab by IMAE category, with extended follow-up.
- Summary of subjects who were re-challenged with nivolumab by IMAE category, with extended follow-up.

For these, re-challenge is considered to have occurred when last nivolumab infusion was administered after the onset of an IMAE.

7.6.9 Other Events of Special Interest

OEOSI will be summarized by treatment group for each category.

The following analyses will be conducted using the 100-day safety window:

- Overall summary of OEOSI by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT

- Overall summary of drug-related OEOSI by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT

A by-subject listing of OEOSI will be provided.

7.6.10 Adverse Events of pneumonitis and lung disease

The following adverse events will be summarized by treatment group:

- Interstitial Lung Disease
- Pneumonitis
- Immune-Mediated Pneumonitis

The following analyses will be conducted using the 100-day safety window:

- Overall summary by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT

A by-subject listing will be provided.

7.6.11 Multiple Events

The following summary tables will be provided:

- A table showing the total number and rate (exposure adjusted) of occurrences for all AEs.
- A table showing the total number and rate (exposure adjusted) of occurrences for AEs occurring in at least 5% of subjects in any treatment group.

A listing displaying the unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e. same PT) have been collapsed will be provided. No formal comparisons will be made between treatment groups.

7.6.12 Laboratory Parameters

In the laboratory summary tables, unless otherwise specified, subjects will be counted only once for each lab parameter according to their worst on treatment CTC grade (worst being the highest CTC grade). The laboratory tables and listings will be sorted by laboratory category, laboratory subcategory and laboratory test code sequence number.

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test. Laboratory tests (in addition to the tests specified below) with CTC criteria collected in the specific studies may also be included in the summaries.

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

The analyses will be conducted using the 30-day.

7.6.12.1 Hematology

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: hemoglobin (HB), hematocrit, total leukocyte count (including differential), platelets, white blood counts (WBC), absolute neutrophils count (ANC) and lymphocyte count (LYMPH).

A by-subject listing of these laboratory parameters will be provided.

7.6.12.2 Serum Chemistry

The following will be summarized by treatment group as worst CTC grade on-treatment per subject: ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, creatinine, blood urea nitrogen (BUN) or serum urea, lipase and amylase.

A by-subject listing of these laboratory parameters will be provided.

7.6.12.3 Electrolytes

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: sodium (high and low), potassium (high and low), chloride (high and low), calcium (high and low), phosphorus (high and low), and Glucose Serum (fasting hyperglycemia and hypoglycemia regardless of fasting status).

A by-subject listing of these laboratory parameters will be provided.

7.6.12.4 Additional Analyses

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

Abnormal Hepatic Function Test

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

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

A by-subject listing of these specific abnormalities will be provided.

Abnormal Thyroid Function Test

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

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

- with FT3/FT4 missing within 2-week window after the abnormal TSH test.

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

A by-subject listing of these specific abnormalities will be provided.

7.6.13 Vital Signs and Pulse Oximetry

Vital signs and pulse oximetry (i.e. % oxygen saturation) collected on the CRF will be provided in separate listings.

7.6.14 Physical Measurements

Physical measurements will be listed by subject.

7.6.15 Electrocardiograms (ECG) /ECHO or MUGA

A by-subject listing of ECG abnormalities and the corresponding grading information will be provided.

Normal ranges for ECG parameters

- HR: 60 to 100 beats per minute
- PR interval: 120-200 milliseconds
- QRS complex: 80-100 milliseconds
- QT interval: 390-450 milliseconds in men; 390-460 milliseconds in women
- QTcB and QTcF: <= 430 milliseconds in men; <= 450 milliseconds in women

7.6.16 Non-Protocol Medical Procedures

Non-protocol medical procedures will be listed by subject.

[redacted]

[redacted]

7.6.18 Pregnancy

Not applicable. This study allows only for women not of childbearing potential.

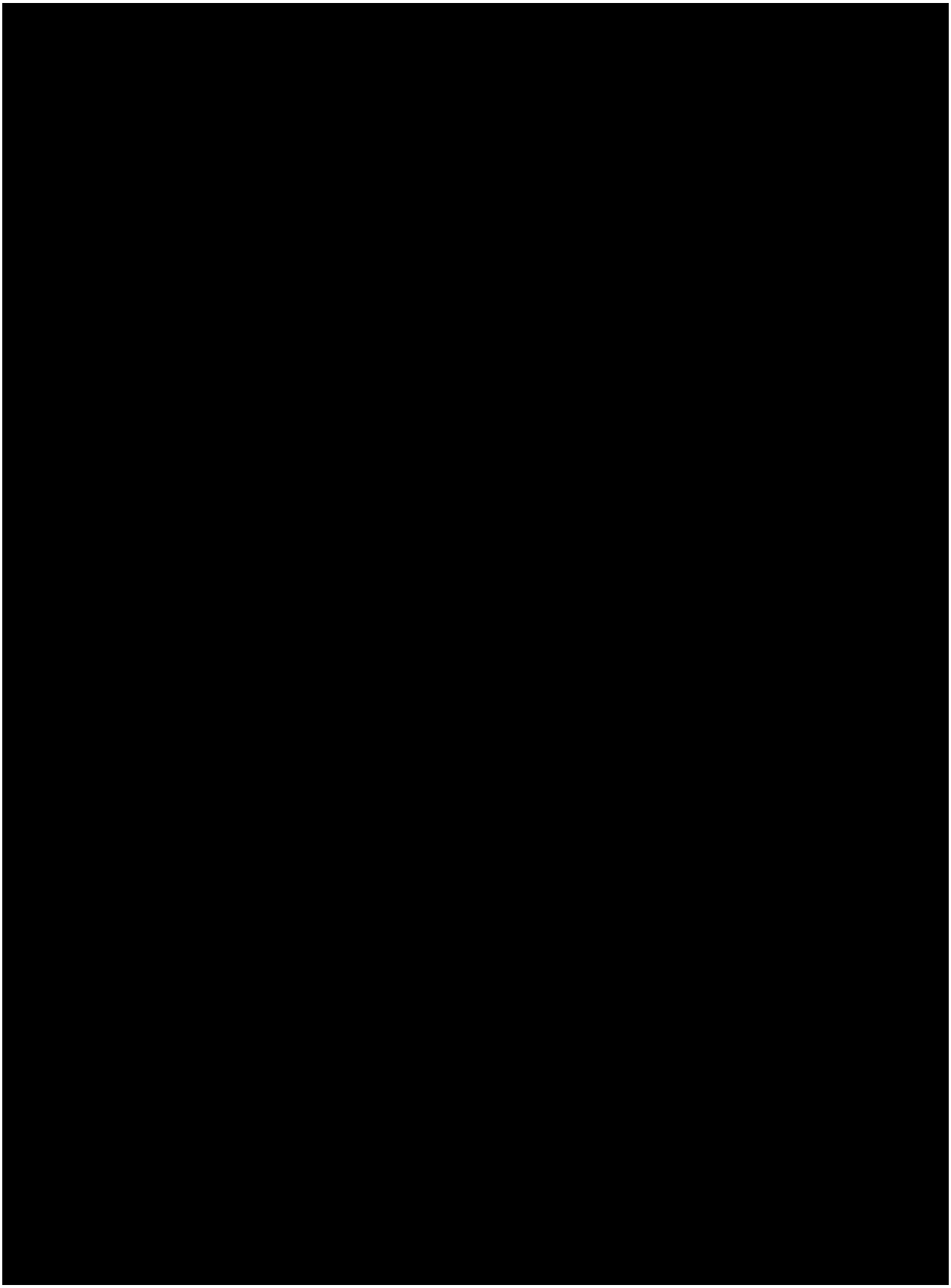
7.6.19 Adverse Events by Subgroup (Randomized Phase only)

Overall summary of any AEs and drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT and for each treatment group for the following subgroups:

- Sex (Male vs. Female)
- Race
- Age (< 65 vs. 65 - < 75 vs. 75 - < 85 vs. ≥ 85 vs. ≥ 75 vs. ≥ 65)
- Region (US/Canada, Europe, Rest of the World)

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

[redacted]



[redacted]

[redacted]

[redacted]

7.10 Analyses at the time of the decision for the dose level to be evaluated in the randomized phase.

At the time of the analysis for the selection of the dose to be evaluated in the randomized phase of the study (see paragraph Schedule of Analyses in Section 1 for the timing of the analysis), the following analyses will be produced using all available data from the safety run-in phase:

- Summary and listing of the relevant protocol deviations during the safety run-in phase
- Summaries and listings of subject disposition for each study period of the safety run-in phase
- Summaries of demographic and baseline disease characteristics
- Listing of medical history
- Summaries and listings of prior therapy agents
- Listing of physical examinations
- Summaries and listings of administration of study therapy
- Summaries of modifications of study therapy
- Summary and listing of concomitant medications
- Summary and listing of dose-limiting toxicities
- Summary and listing of deaths
- Summaries of SAEs, drug-related SAEs, AEs leading to discontinuation, drug-related AEs leading to discontinuation, AEs leading to dose delay/reduction, drug-related AEs leading to dose delay/reduction, AEs, drug-related AEs, any select AEs, any non-endocrine and endocrine IMAEs where immune modulating medication was initiated, OEOSI, AEs of Interstitial Lung

Disease (ILD), pneumonitis and immune-mediated pneumonitis. All these summaries will be presented by worst CTC grade (any grade, grade 3-4, grade 5) using the 30 days safety window.

- Listing of AEs
- Summary and listing of marked laboratory abnormalities in both US and SI units using the 30 days safety window.

At the time of this analysis, the safety run-in phase will not be completed. A clinical study report may not be prepared at this point. For the analyses for the clinical study report, the full set of analyses for the safety run-in phase, as described in this statistical analysis plan, will be produced when all patients in the safety run in phase either completed the study duration or discontinued from it.

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

- For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[6]
- For missing and partial adverse event resolution dates, imputation will be performed as follows (these conventions may change):
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day. If the imputed date is after the death date or the last known alive date, then the latest known alive date or death date is considered as the resolution date.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- Missing and partial non-study medication domain dates will be imputed using the derivation algorithm described in 4.1.3 of BMS Non-Study Medication Domain Requirements Specification[7].
- Missing and partial radiotherapy and surgery dates will be imputed using algorithm described in APPENDIX 2.
- For death dates, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.
  - If the month or the year is missing, the death date will be imputed as the last known alive date.
  - If the date is completely missing but the reason for death is present, the death date will be imputed as the last known date alive.
- For date of progression after start of study therapy, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. In case of the date of death is present and complete, the imputed progression

date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

  - If the day and month are missing or a date is completely missing, it will be considered as missing.

- For date of progression to prior therapies, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- For other partial/missing dates, the following conventions were used:
  - If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
  - If both the day and the month are missing, "July 1" will be used to replace the missing information.
  - If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years:

1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time-to onset, time-to resolution) will be calculated as follows:

Duration = (Last date - first date + 1)

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

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

APPENDIX 1 TIME-TO ONSET AND TIME-TO RESOLUTION DEFINITION AND CONVENTIONS FOR SELECT ADVERSE EVENTS, IMMUNE-MEDIATED ADVERSE EVENTS AND EVENTS OF SPECIAL INTEREST

Time-to onset definition

Time-to onset of AE (any grade) for a specific category is defined as the time between the day of the first dose of study treatment and the onset date of the earliest AE (of any grade) in this category.

The time-to onset of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to onset of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous AEs within a specific category or subcategory will be collapsed into what will be termed "clustered" AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered AE from 1st to 12th January. Table 8-1 is summarizing key derivation steps for each type of clustered AEs.

Time-to resolution of AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered AEs experienced by the subject in this category per adverse event criteria category. Events which worsened into grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AE is considered as unresolved, the resolution date will be censored to the last known alive date. Improvement to the grade at baseline implies that all different events in the clustered adverse event should at least have improved to the corresponding (i.e. with same preferred term) baseline grade. This measure is defined only for subjects who experienced at least one AE in the specific category.

The time-to resolution of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to resolution of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

The time-to resolution of AE (any grade or grade 3-5, drug-related or all) where immune modulating medication was initiated is defined similarly. For data presentation not restricted to IMAE, the additional condition that the subject started an immune modulating medication during the longest AE resolution period will be applied.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Table 8-1: Derivation of clustered AE

Type of clustered AE	Derivation
Any grade	Collapse any on-treatment AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AE from the same category
Grade 3-5	Collapse any on-treatment AE from the same category. Resolution will be based on the onset date of the earliest grade 3-5 records (if no grade 3-5 record, clustered AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AE from the same category Resolution will be based on the onset date of the earliest grade 3-5 record (if no Grade 3-5 record, clustered AE is excluded)

The algorithm for collapsing adverse event records is using the following conventions:

For each subject and specified category, the corresponding adverse event records will be collapsed when:

4) Multiple adverse event records have the same onset date.
5) The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
6) The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

APPENDIX 2 MISSING AND PARTIAL RADIOTHERAPY AND SURGERY DATES IMPUTATION ALGORITHMS

Procedures – Imputation Rules.

If reported procedure start date is a full valid date, then set start date equal to the date part of procedure start date.

In case of partial date use imputation rules described below:

- If only day is missing, then
  - If month and year of procedure match month and year of first dose date, then impute as date of first dose.
  - If month and year of procedure don't match month and year of first dose date, then impute as first day of that month and year.
- If both day and month are missing, then impute as maximum between 01JAN of the year and date of the first dose.
- If date is completely missing or invalid, then leave missing.

Note: Imputation is not applicable to data where start date is not collected (for example "PRIOR RADIOTHERAPY" CRF). Set start date to missing in this case.

If reported end date is a full valid date, then set end date equal to the date part of the reported end date.

In case of partial date use imputation rules described below:

- If reported end date is partial, then set end date equal to the last possible reported end date based on the partial entered reported end date.
- If reported end date is missing, continuing, unknown or invalid then set end date equal to the most recent database extraction date.

If end date was imputed, then compare end date to the death date or last known alive date if subject is not dead. If posterior, then end date should be imputed to death date (or last known alive date if subject not dead).

Note: Imputation of partial dates only applies to data entered on "RADIOTHERAPY" CRF page. For other CRF pages in case of partial dates set end date to missing.

Surgeries – Imputation Rules.

If reported surgery date is a full valid date, then set start date equal to the date part of surgery date.

In case of partial date, use one of the two imputation rules described below:

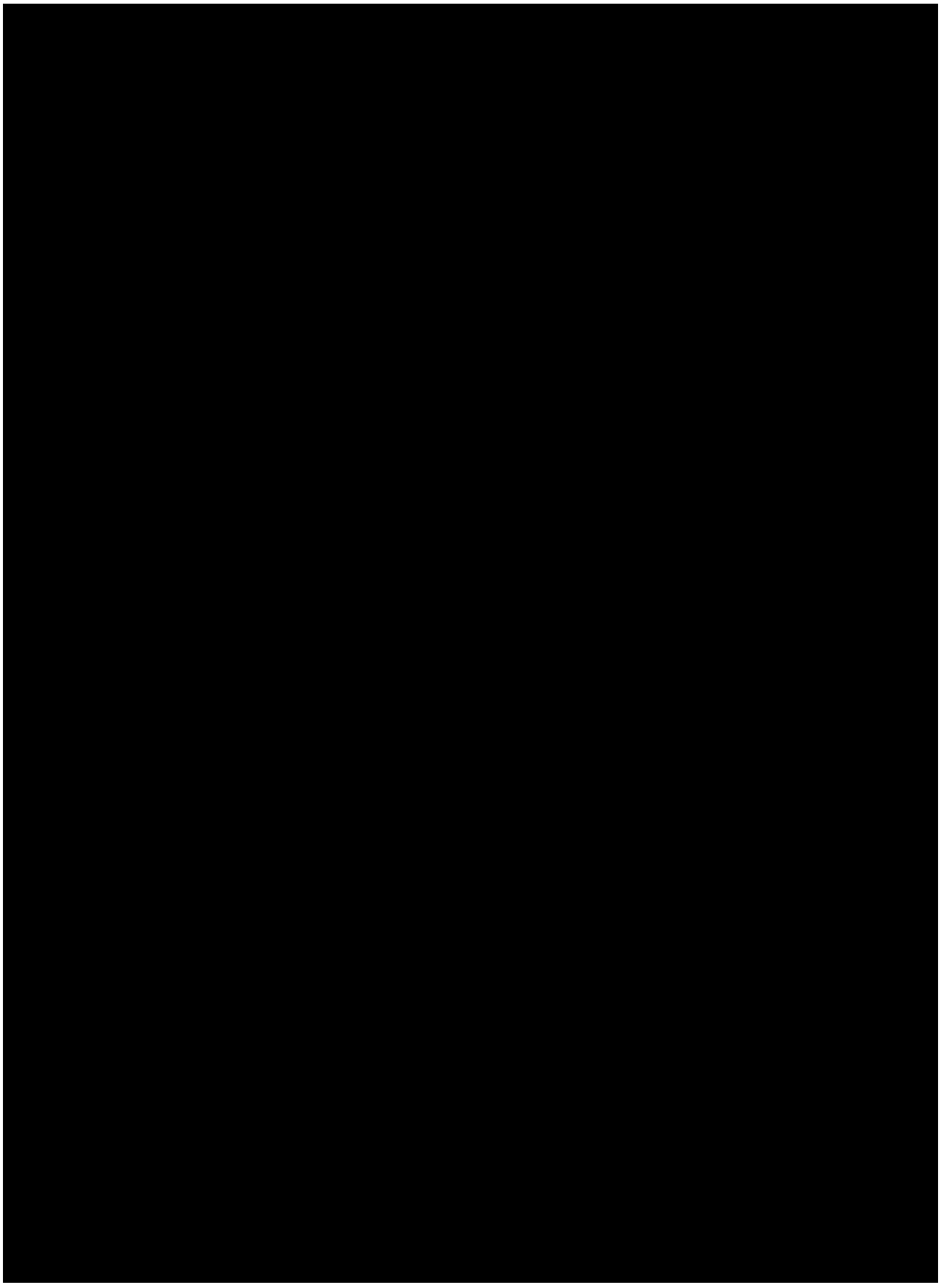
A. For data collected on "PRIOR SURGERY RELATED TO CANCER" CRF page:

- If only day is missing, then impute as the first day of the month;
- If both day and month are missing, then then impute as 01JAN of the year;
- If date is completely missing or invalid, then leave missing.

B. For data collected on other CRF pages (deemed to be on-treatment/subsequent surgeries):

- If only day is missing, then
  - If month and year of surgery match month and year of first dose date, then impute the missing date as the date of first dose;
  - If month and year of surgery don't match month and year of first dose date, then impute as first day of that month and year;
- If both day and month are missing, then impute as maximum between 01JAN of the year and date of the first dose;
- If date is completely missing or invalid, then leave missing.

[redacted]



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9 DOCUMENT HISTORY

Table 9-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Original Issue

10 REFERENCES

1 IO Core Statistical Analysis Plan for Multiple Indications

2 Brookmeyer R. and Crowley J. A confidence interval for the median survival time. Biometrics 38:29-41, 1982

3 Klein, J. P. and Moeschberger, M. L. (1997), Survival Analysis: Techniques for Censored and Truncated Data, New York: Springer-Verlag

4 Global Biometric Sciences, SAS Analysis Dataset Specification, Unique Adverse Events. Version 2.0, April 22, 2015

5 Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". *Biometrika* **26**: 404–413.

6 Adverse Event Domain Requirements Specification Bristol Myers Squibb Co. PRI. Version 2.3.0 April 23, 2018

7 Non-Study Medication Domain Requirements Specification Bristol Myers Squibb Co. PRI. Version 2.10.0 April 23, 2018