Official Title of Study:

A Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Subjects with Advanced Non-small Cell Lung Cancer (FRACTION-Lung)

NCT Number: NCT02750514

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 2, FAST REAL-TIME ASSESSMENT OF COMBINATION THERAPIES IN IMMUNO-ONCOLOGY STUDY IN SUBJECTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (REACTION-LUNG)

PROTOCOL(S) CA018001

VERSION # 3.0

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[redacted]

The FRACTION Program will consist of several FRACTION studies, each in a specific tumor

[redacted]

Research Hypothesis:

It is anticipated that combination of IO agents will demonstrate improved efficacy in subjects with recurrent NSCLC.

Schedule of Analyses:

Safety data from this study will be monitored by an independent Safety Monitoring Board (SMB). Details are specified in the SMB charter.

Interim analysis for individual treatment arm under each track per design (Single stage, Simon 2-stage or multi-stage) may be performed when appropriate number of subjects are treated and followed. These interim analyses will be performed independent of each other. Additional interim analyses on safety and efficacy may be performed at various times prior to study completion in order to facilitate program decisions and to support scientific publications or presentations. Potential interim analyses of efficacy for each combination arm under each track are listed in Table 1-1. No formal inferences requiring any adjustment to statistical significance level will be performed. Additional survival analysis may be performed beyond analysis for the final CSR and presented in a CSR addendum.

Table 1-1: Potential Interim Analyses of Efficacy

Track	Interim Analyses
Track 3 Anti-PD-1/PD-L1 Treatment-experienced Subjects	End of Simon Stage 1
Track 4 Anti-PD-1/PD-L1 Treatment-naïve Subjects	End of Simon Stage 1

Due to early termination of Track 1, 2 and 3 per Master Protocol amendment 5 and the limited number of subjects treated under Track 1 and 2 per treatment arm, interim analyses for these two tracks will focus on safety. Track 5 used single stage design, only interim analyses for safety may be performed.

2 STUDY DESCRIPTION

2.1 Study Design

This is a rolling, Phase 2, adaptive study that will evaluate the preliminary efficacy, safety, tolerability, PK, and pharmacodynamics of novel FRACTION-Lung treatment combinations in subjects with advanced NSCLC.

A study design update occurred with the implementation of Amendment 5 due to the change in the standard of care for NSCLC. Prior to implementation of Amendment 5, subjects are enrolled in 1

of 3 tracks depending on prior treatment and PD-L1 status (Tracks 1, 2, or 3) (see Section 2.1.1). Post implementation of Amemdment 5, subjects will be enrolled in 1 of 2 tracks depending on prior treament (Track 4 and 5) (see Section 2.1.2).

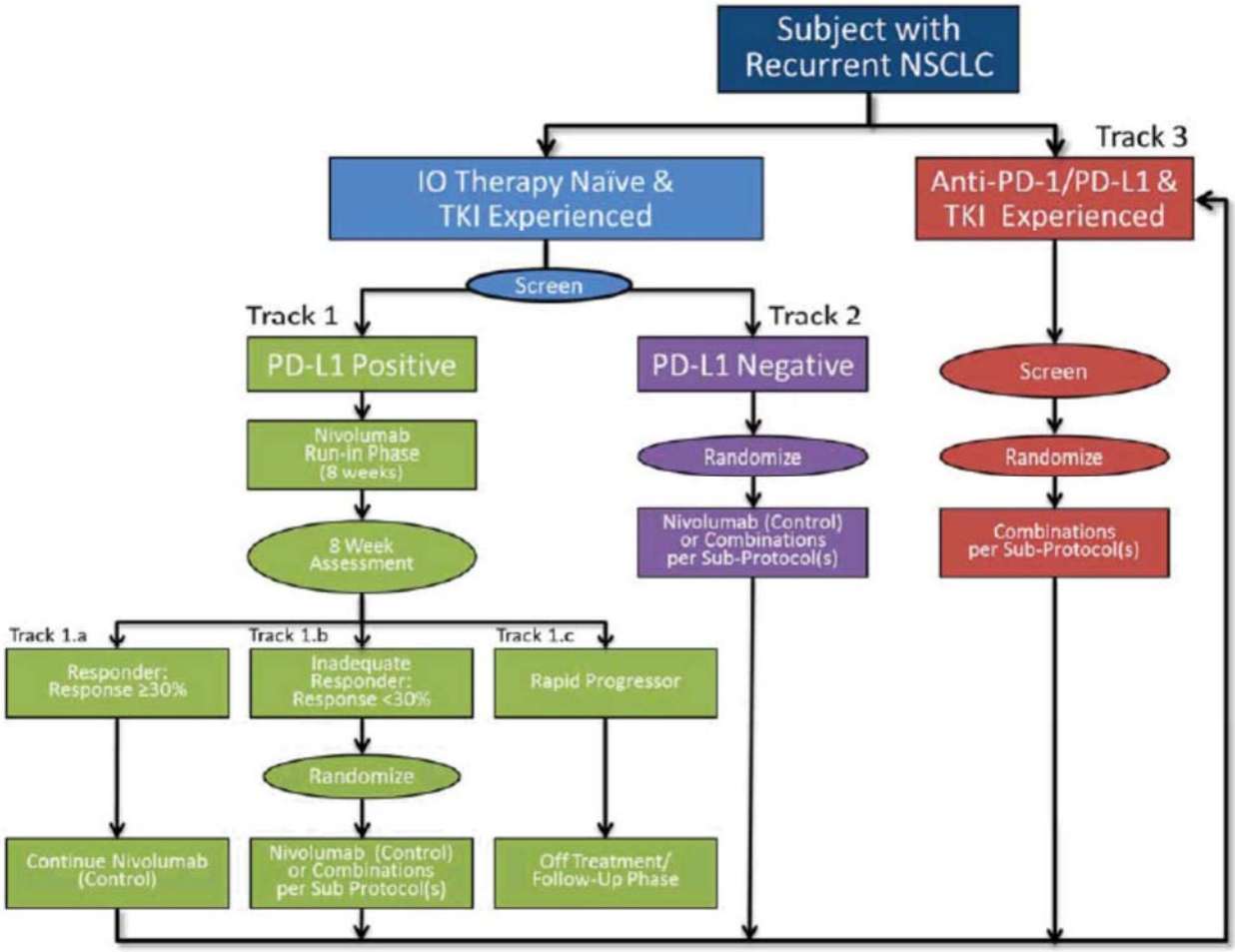
2.1.1 Original Design (up to and includes Master Protocol Amendment 4)

Anti-PD-1/PD-L1 naive subjects are assigned into Track 1 and 2. Track 1 is for subjects whose tumor expresses programmed death-ligand 1 (PD-L1), and Track 2 is for subjects whose tumor does not express PD-L1 (as outlined in Figure 2.1.1-1). Subjects who have had prior anti-PD-1/PD-L1 therapy and have been offered platinum-based chemotherapy (and received prior TKI if their tumor contained an EGFR mutation or ALK rearrangement) are assigned to Track 3 as outlined in Figure 2.1.1-1.

Subjects in Track 1 have a nivolumab Run-in phase with nivolumab administrated every 2 weeks for four treatments. Following the nivolumab Run-in phase, these subjects enter Track 1.a or 1.b and begin the Treatment phase, or Track 1.c and begin follow-up. The Treatment phase is defined in cycles each of 4 weeks duration. Subjects on Track 1.a receive treatment cycles for a maximum of 2 years. Subjects on Track 1.b receive 6 cycles each of 4 weeks duration (a total 24 weeks). Subjects on Track 2 and 3 do not have a nivolumab Run-in phase and begin on the Treatment phase defined as 6 cycles each of 4 weeks duration (a total of 24 weeks). Tumor assessments are conducted every 8 weeks (±1 week).

For Track 1 only, subjects with inadequate response to the therapy are randomized after the nivolumab Run-in phase; responders continue nivolumab and rapid progressors are off treatment and enter follow-up Phase.

Figure 2.1.1-1: FRACTION-Lung Original (Tracks 1-3) Study Design



Note* Subjects will be considered PD-1/PD-L1-experienced if they have previously received at least 1 cycle of therapy with a PD-1/PD-L1 inhibitor.

Abbreviations: Response = Response by RECIST v 1.1 criteria

Subjects in Figure 2.1.1-1: Tracks 1-3 are treated until completion of the Treatment phase, progression, toxicity, or protocol-specified discontinuation. Except for Track 1.a and 1.c, the decision to continue treatment beyond investigator-assessed progression is possible (for 6 additional cycles only) and should be discussed with the BMS Medical Monitor (or designee) and documented in the study records. A subject with progressive disease (PD) has several treatment options including continued treatment (for additional 6 cycles only) and/or entry into Track 3, assuming that he/she continues to fulfill all entry criteria at each new randomization point and is not considered a "rapid progressor."

In Track 1.b or 2, a 4-stage design is used to evaluate the possibility of expanding the combination arms and the nivolumab monotherapy arm and the possibility of terminating a combination arm early. In Track 3, a Simon 2-stage (optimal) design is used to evaluate the possibility of terminating an arm early. The number of subjects planned for enrollment may vary by track and is described

in Section 5. Subjects who continue to fulfill entry criteria may move from Tracks 1 or 2 into Track 3, as described in Sections 2.1.1.1.1and 2.1.1.2.

2.1.1.1 FRACTION-Lung Track 1 Design - Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-positive Subjects

A detailed study schematic for Track 1 is presented in Figure 2.1.1.1-1.

Subjects who are naïve to IO therapy and have a positive PD-L1 tumor status (defined by ≥ 1% of the membranous tumor staining for PD-L1) are enrolled into Track 1 and receive nivolumab monotherapy every 2 weeks for 4 treatments in the nivolumab Run-in phase. Based on results from the first tumor assessment (i.e, after the first 8 weeks of therapy), subjects are categorized as follows with treatment as designated:

- Responder (subjects with tumor response of ≥ 30% [i.e., at least 30% reduction in target lesion burden] continue nivolumab monotherapy as the contemporaneous control therapy in Track 1.a.
- Inadequate responder (subject with tumor response of < 30% [i.e., less than 30% reduction in target lesion burden] are randomized into Track 1.b.
- Rapid progressor (subjects deemed by either the treating physician or BMS medical Monitor (or designee) to have no reasonable possibility of response to further immunotherapy, such as a subject whose lesions have increased in size by > 50%) are off treatment (Track 1.c) and enter study follow-up.

FRACTION-Lung Track 1.a Design

Responders to treatment on Track 1 nivolumab Run-in phase at the first tumor assessment (i.e., at 8 weeks) enter Track 1.a and continue nivolumab monotherapy for a total of 2 years. Subjects are not allowed nivolumab monotherapy treatment beyond 2 years.

- **Subjects with CR, PR, or SD** at the completion of the treatment phase in Track 1.a (after receiving nivolumab monotherapy for a total of 2 years) enter study follow-up.
- **Subjects with PD** during the Track 1.a treatment phase have the option to:
- Enter study follow-up or
- Enter Track 3, if eligible and a treatment combination is available, and be randomized to combination treatment.
- **Subjects with rapid progression** (as defined above) are taken off study treatment and enter study follow up.

FRACTION-Lung Track 1.b Design

Inadequate responders to study treatment on Track 1 nivolumab Run-in phase at the first tumor assessment (i.e., at 8 weeks) have the option to be randomized into Track 1.b to nivolumab

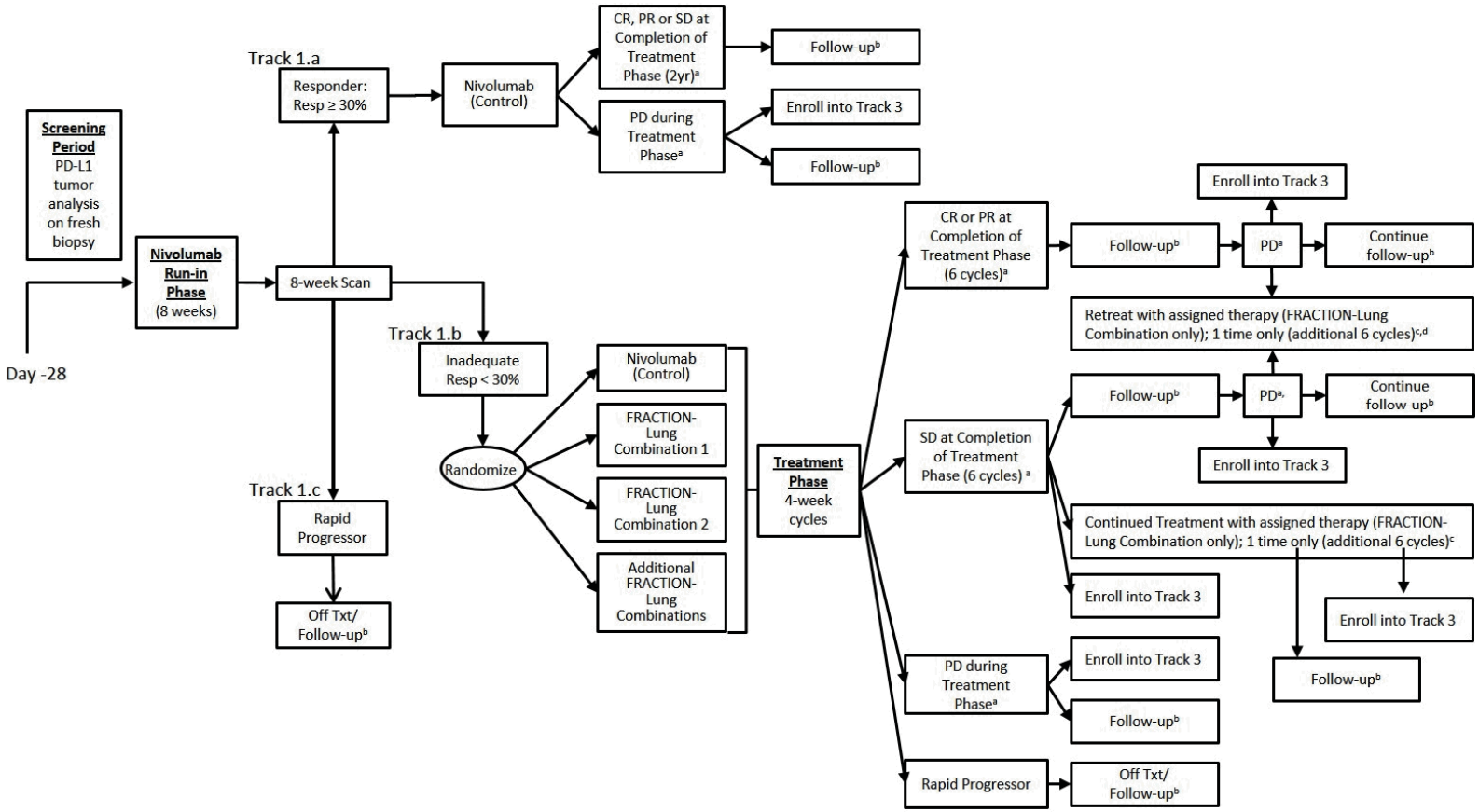
monotherapy or to one of the novel FRACTION-Lung combinations. These subjects receive their assigned treatment in Track 1.b until completion of the treatment phase.

- **Subjects with CR or PR** at the end of the Track 1.b Treatment phase enter study follow-up.
- **Subjects with SD** at the end of the Track 1.b Treatment phase have the option to:
- Enter study follow-up,
- Receive continued treatment (at the discretion of the investigator) for a further 6 cycles (12 cycles total treatment) with their Track 1.b randomized combination treatment or nivolumab monotherapy, or
- Enter Track 3, if eligible and if a new treatment combination is available, and be randomized to a new combination.
- **Subjects with SD who opt to continue treatment** upon completion of a total of 12 cycles of treatment have the option to:
- Enter study follow-up
- Enter Track 3, if eligible and if a new treatment combination is available, and be randomized to a new combination.
- **Subjects with PD** during the Track 1.b Treatment phase have the option to:
- Enter study follow-up or
- Enter Track 3 if eligible and if a new treatment combination is available, and be randomized to a new combination.
- **Subjects with rapid progression** (as defined above) are taken off study treatment and enter study follow-up.
- Subjects who elect to **re-treat** with their Track 1.b randomized combination treatment are allowed to do so one time only. Upon completion of the Track 1.b retreatment, these subjects have the option to
- a) Enter study follow-up or
- b) Enter Track 3 and be randomized to a new combination
- **Subjects with CR, PR or SD <u>who enter study follow-up and subsequently progress</u>** within 12 months of their last study dose have the option to be considered for retreatment with the same treatment pending a discussion of this option with the investigator and BMS Medical Monitor (or designee). Subjects who fail retreatment, or are deemed by the investigator not to be appropriate for retreatment, have the option to:
- Enter study follow-up or
- Enter Track 3, if eligible and if a new treatment combination is available, and be randomized to a new combination.

FRACTION-Lung Track 1.c Design

Subjects with rapid progression (as defined above) should be discontinued from study treatment and enter study follow-up.

Figure 2.1.1.1-1: Track 1 Design Schematic - Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-positive Subjects



Note: This diagram presents the protocol-mandated treatment flow for Track 1. Alternatives must be discussed with the BMS Medical Monitor (or designee).

[a] Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) as defined by RECIST v1.1

[b] Safety follow-up phase, followed by Response/Survival Follow-up phase.

[c] Each individual subject may receive multiple therapies, including initial treatment, treatment beyond investigator-assessed progression, continued treatment (for an additional 6 cycles only), retreatment after progression (for an additional 6 cycles only), and/or entry into Track 3, assuming the subject continues to fulfill all eligibility criteria at each new randomization point.

[d] For subjects with PD, retreatment with the assigned therapy (for an additional 6 cycles only) pending discussion with the BMS Medical Monitor (or designee).

Abbreviations: Resp = response; Txt = treatment.

2.1.1.2 FRACTION-Lung Track 2 Design - Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-negative Subjects

A detailed study schematic for Track 2 is presented in Figure 2.1.1.2-11

Subjects who are naïve to IO therapy and have a negative PD-L1 tumor status (defined by < 1% of the membranous tumor staining for PD-L1) are enrolled into Track 2 and randomized to nivolumab monotherapy or to 1 of the FRACTION-Lung combination treatments. These subjects receive their assigned treatment in Track 2 until completion of the Treatment phase.

- **Subjects with CR or PR** at the end of the Track 2 Treatment phase enter study follow-up.
- **Subjects with SD** at the end of the Track 2 Treatment phase have the option to:
- Enter study follow-up,
- Receive continued treatment (at the discretion of the investigator) for a further 6 cycles (12 cycles total treatment) with their Track 2 randomized combination treatment or nivolumab monotherapy, or
- Enter Track 3 if eligible and if a new treatment combination is available, and be randomized to a new combination.
- **Subjects with SD who opt to continue treatment** upon completion of a total of 12 cycles of treatment have the option to:
- Enter study follow-up or
- Enter Track 3, if eligible and if a new treatment combination is available, and be randomized to a new combination.
- **Subjects with PD** during the Track 2 Treatment phase have the option to:
- Enter study follow-up or
- Enter Track 3, if eligible and if a new treatment combination is available, and be randomized to a new combination.
- **Subjects with rapid progression** (as defined above) are taken off study treatment and enter study follow-up.

Subjects with CR, PR or SD who enter study follow-up and subsequently progress within 12 months of their last study dose have the option to be considered for retreatment with the same treatment pending a discussion of this option with the investigator and BMS Medical Monitor (or designee). Subjects who fail retreatment, or are deemed by the investigator not to be appropriate for retreatment, have the option to:

a) Enter Study follow-up or

b) Enter Track 3, if eligible and if a new treatment combination is available, and be randomized to a new combination.

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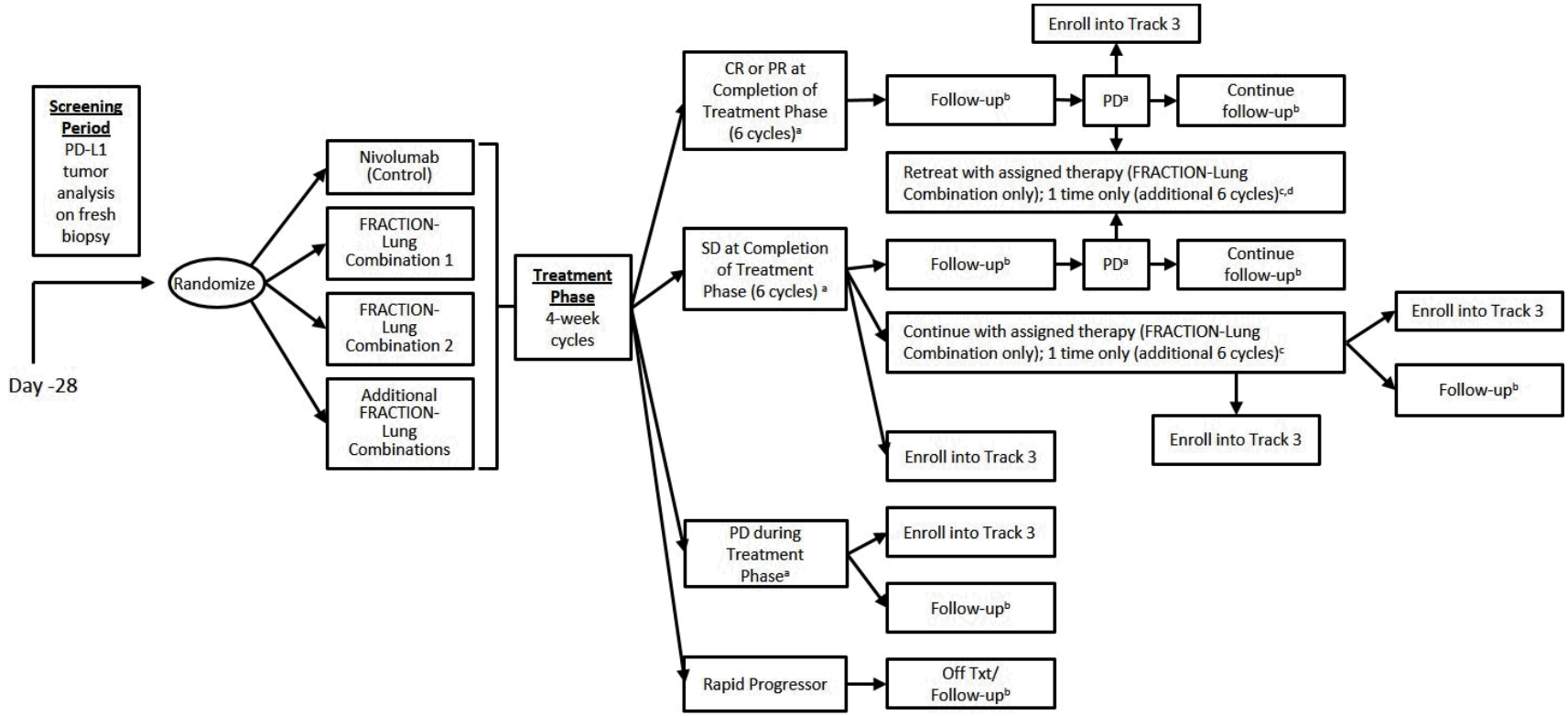
Figure 2.1.1.2-1: Track 2 Design Schematic - Anti-PD-1/PD-L1 Treatment-Naive, PD-L1-negative Subjects



Note: This diagram presents the protocol-mandated treatment flow for Track 2. Alternatives must be discussed with the BMS Medical Monitor (or designee).

a Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) as defined by RECIST v1.1

b Safety follow-up phase, followed by response/survival follow-up phase.

c Each individual subject may receive multiple therapies including initial treatment, treatment beyond investigator-assessed progression, continued treatment (for an additional 6 cycles only), retreatment after progression (for an additional 6 cycles only), and/or entry into Track 3, assuming that the subject continues to fulfill all eligibility criteria at each new randomization point

d For subjects with PD, retreatment with the assigned therapy (for an additional 6 cycles only) pending discussion with the BMS Medical Monitor (or designee).

Abbreviations: Txt = treatment.

2.1.1.3 FRACTION-Lung Track 3 Design - Anti-PD-1/PD-L1 Treatment-experienced Subjects

A detailed study schematic for Track 3 is presented in Figure 2.1.1.3-11.

Subjects who have received anti-PD-1/PD-L1 therapy are enrolled into Track 3 and randomized to one of the FRACTION-Lung treatment combinations (nivolumab monotherapy is not a treatment option under Track 3).

In addition, subjects who were treated in Track 1 or Track 2 and continue fulfill all entry criteria can be enrolled in Track 3 and randomized to a new combination other than that previously received, if applicable. These subjects receive their assigned treatment in Track 3 until completion of the treatment phase.

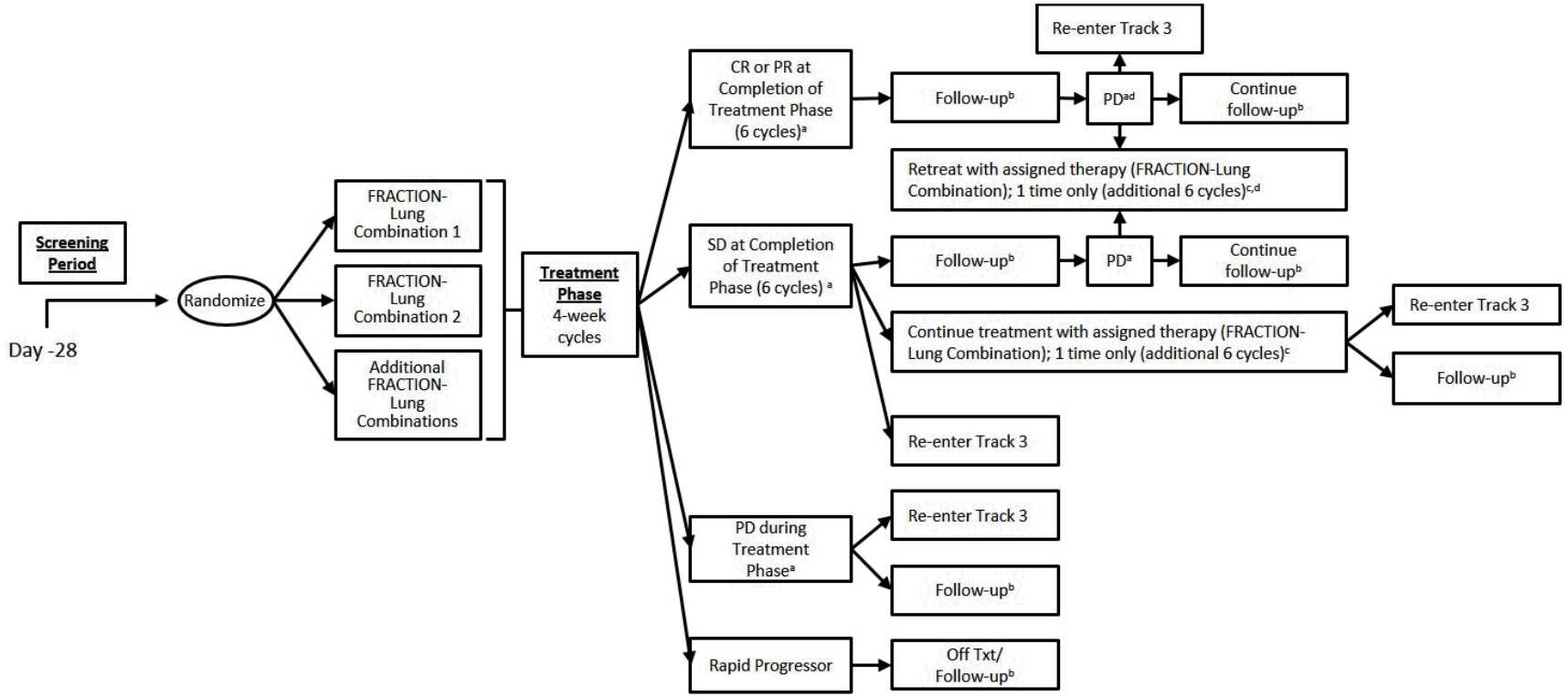
- **Subjects with CR or PR** at the end of the Track 3 Treatment phase enter study follow-up.
- **Subjects with SD** at the end of the Track 3 Treatment phase have the option to:
- Enter study follow-up,
- Receive continued treatment (at the discretion of the investigator) for a further 6 cycles (total of 12 cycles of treatment) with their Track 3 randomized treatment, or
- Re-enter Track 3, if eligible and if a new combination is available, and be randomized to a new combination
- **Subjects with SD who opt to continue treatment** upon completion of a total of 12 cycles of treatment have the option to:
- Enter study follow-up or
- Re-enter Track 3, if eligible and if a new treatment combination is available, and be randomized to a new combination.
- **Subjects with PD** during the Track 3 Treatment phase have the option to:
- Enter study follow-up or
- Re-enter Track 3, if eligible and if a new treatment combination is available, and be randomized to a new combination.
- **Subjects with rapid progression** (as defined above) are taken off study treatment and enter study follow-up.

Subjects with CR, PR or SD <u>who enter study follow-up and subsequently progress</u> within 12 months of their last study dose have the option to be considered for retreatment with the same treatment pending a discussion of this option with the investigator and BMS Medical Monitor (or designee). Subjects who fail retreatment, or are deemed by the investigator not to be appropriate for re-induction, have the option to:

a) Enter Study follow-up or

- Re-enter Track 3, if eligible and if a new treatment combination is available, and be randomized to a new combination.

Figure 2.1.1.3-1: Track 3 Design Schematic - Anti-PD-1/PD-L1 Treatment-experienced Subjects



a Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) as defined by RECIST v1.1

b Safety follow-up phase, followed by response/survival follow-up phase.

c Each individual subject may receive multiple therapies, including initial treatment, treatment beyond investigator-assessed progression, continued treatment (for an additional 6 cycles only), retreatment after progression (for an additional 6 cycles only), and/or re-entry into Track 3, assuming that the subject continues to fulfill all eligibility criteria at each new randomization point.

Note: subjects will be randomized to a combination other than the previously received Track 3 (and/or Track 1 or Track 2) combination treatment, if applicable.

d For subjects with PD, retreatment with the assigned therapy (for an additional 6 cycles only) pending discussion with the BMS Medical Monitor (or designee).

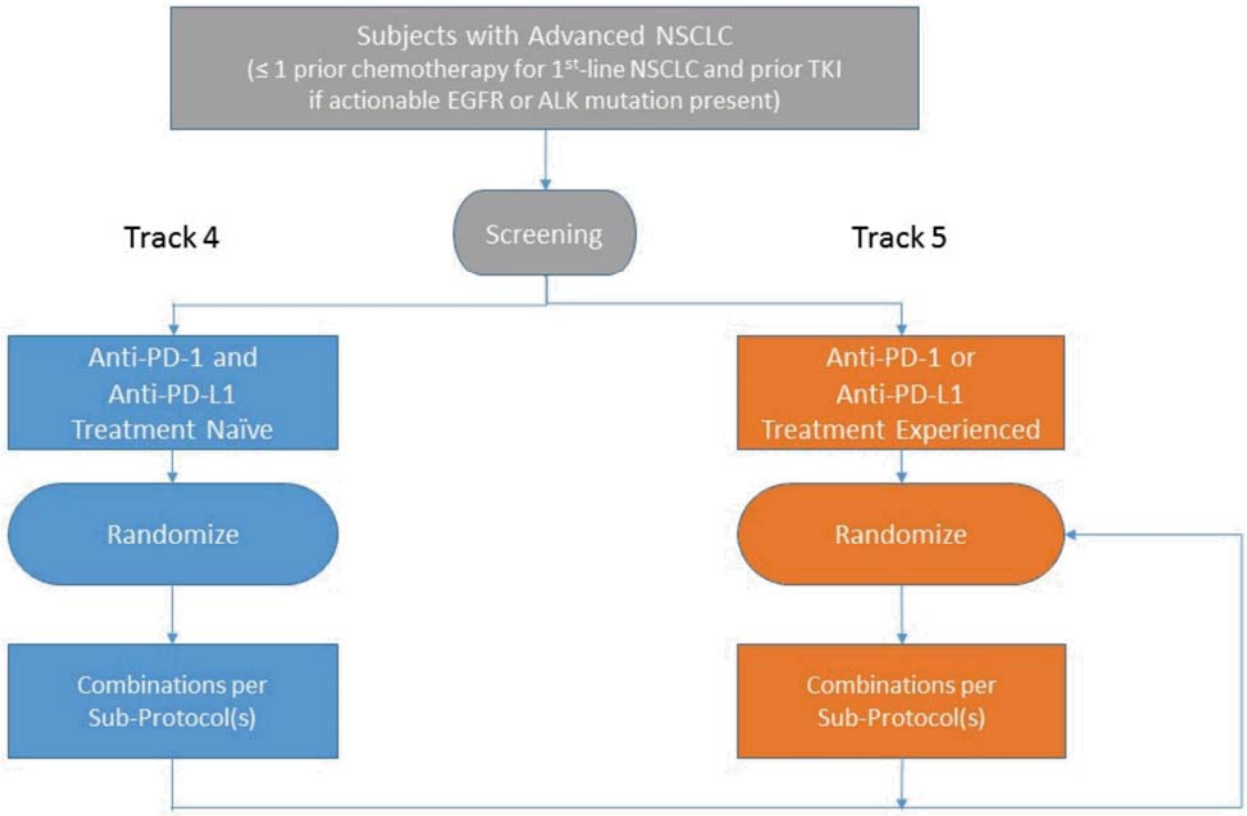
- Abbreviations: Txt = treatment.

2.1.2 Current Design (Master Protocol Amendment 5)

Subjects will be enrolled in 1 of 2 tracks following treatment for advanced NSCLC with ≤ 1 prior chemotherapy regimen and prior TKI (for subjects with a known EGFR or ALK rearrangement).

Subjects who are naïve to anti-PD-1 and anti-PD-L1 therapy will be enrolled into Track 4. Subjects who have received prior anti-PD-1 or anti-PD-L1 treatment will be enrolled in Track 5, as outlined in Figure 2.1.2-11.

Figure 2.1.2-1: Fraction-Lung Current (Track 4 and 5) Study Design



Note: Subjects will be considered PD-1/PD-L1-experienced if they have previously received at least 1 dose of a PD-1/PD-L1 inhibitor

Analysis in Track 4 will be stratified by PD-L1 expression (< 1%, ≥ 1% and < 50%, and ≥ 50%)

Subjects in Tracks 1, 2, or 3 who experience PD during the treatment phase and continue to fulfill all entry criteria may be re-enrolled in Track 5 and re-randomized to a new combination other than that previously received, if applicable.

Subjects in Tracks 4 and 5 will be treated until completion of the treatment phase, progression, toxicity, or protocol-specified discontinuation. The decision to continue treatment beyond the investigator-assessed progression is possible (for up to completion of that treatment phase) and should be discussed with BMS medical monitor (or designee) and documented in the study records. Subjects receiving treatment on Tracks 1, 2 or 3 prior to implementation of Amendment 5 will continue to receive treatment on their assigned track until completion, progression, toxicity, or protocol-specified discontinuation. Subjects in Tracks 1, 2 or 3 who experience PD during the

treatment phase and continue to fulfill all entry criteria may be re-enrolled in Track 5 and re-randomized to a new combination other than that previously received, if applicable.

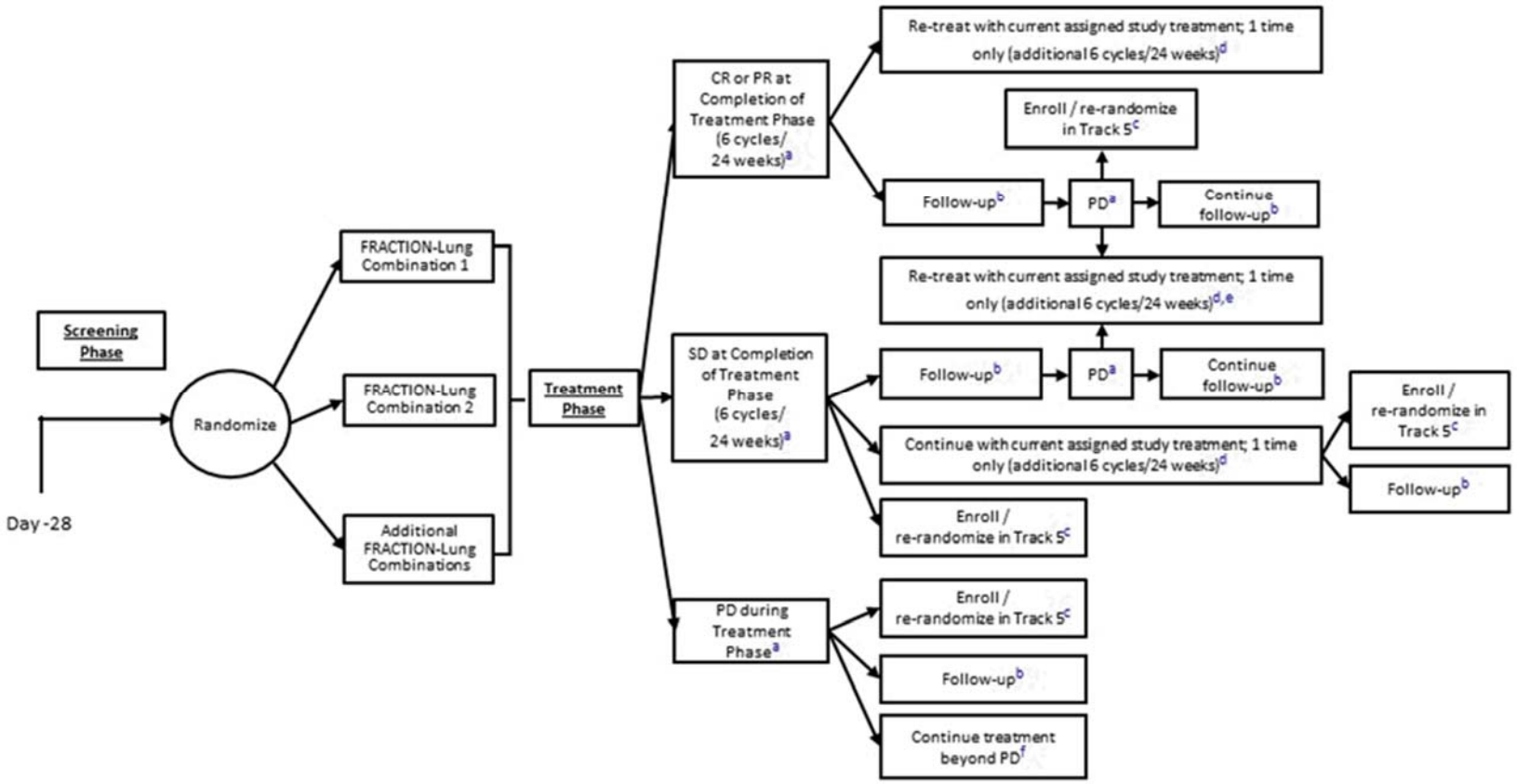
2.1.2.1 Fraction Lung Track 4 (Naive) and 5 (Experienced) Design

A detailed study schematic for both Tracks 4 and 5 is presented in Figure 2.1.2.1-1.

Subjects with CR or PR at the end of the Track 4 or 5 Treatment Phase will have the option to:

- Enter study follow-up or
- Receive continued study treatment (at the discretion of the investigator) for a further six 4-week cycles (a further approximately 24 weeks; approximately 48 weeks of total study treatment) with their Track 4 or 5 randomized combination treatments.
- **Subjects with SD** at the end of the Track 4 or 5 Treatment Phase will have the option to:
- Enter study follow-up,
- Receive continued study treatment (at the discretion of the investigator) for a further six 4-week cycles (a further approximately 24 weeks; approximately 48 weeks of total study treatment) with their Track 4 or 5 randomized combination treatments, or
- Enter (or re-enter) Track 5, if eligible and if a new treatment combination is available, and be randomized to a new combination.
- **Subjects with SD who opt to continue study treatment** upon completion of a total of twelve 4-week cycles (approximately 48 weeks of study treatment)will have the option to:
- Enter study follow-up or
- Enter (or re-enter) Track 5, if eligible and if a new treatment combination is available, and be randomized to a new combination
- **Subjects with PD** during the Track 4 or 5 Treatment Phase will have the option to:
- Enter study follow-up or
- Enter (or re-enter) Track 5, if eligible and if a new treatment combination is available, and be randomized to a new combination, or
- Continue study treatment beyond progression, for up to completion of that Treatment Phase.
- **Subjects with CR, PR or SD <u>who enter study follow-up and subsequently have PD within 12 months of their last study dose</u>** will have the option to be considered for re-treatment with the same treatment pending a discussion of this option with the investigator and BMS Medical Monitor (or designee). Subjects who fail retreatment, or are deemed by the investigator not to be appropriate for retreatment, will have the option to:
- Enter study follow-up or
- Enter (or re-enter) Track 5, if eligible and if a new combination is available, and be randomized to a new combination.

Figure 2.1.2.1-1: Track 4 and 5 Study Design Schematic:



Note: This diagram presents the protocol-mandated treatment flow for Tracks 4 and 5. Alternatives must be discussed with the BMS Medical Monitor (or designee).

[a] Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) as defined by RECIST v1.1. Subjects who the investigator believes may still benefit from further therapy may, after consultation with the Sponsor/BMS Medical Monitor (or designee), continue with their assigned study treatment, 1 time only (for an additional six 4-week cycles [approximately 24 weeks] only).

[b] Safety Follow-up Phase, followed by Response/Survival Follow-up Phase.

[c] If subjects are eligible and if a new study treatment combination is available, they can enroll/re-randomize to a new combination.

[d] Each individual subject may receive multiple therapies, including initial treatment, treatment beyond investigator-assessed progression (for up to completion of that Treatment Phase), continued treatment (for an additional six 4-week cycles [approximately 24 weeks] only), retreatment after progression (for an additional six 4-week cycles [approximately 24 weeks] only), and/or entry into Track 5, assuming that the subject continues to fulfill all eligibility criteria at each new randomization point.

[e] For subjects with PD within follow-up, retreatment with the assigned therapy (for an additional six 4-week cycles [approximately 24 weeks] only) is pending discussion with the BMS Medical Monitor (or designee).

[f] Subjects with PD during treatment may continue treatment beyond progression if criteria are met.

2.2 Treatment Assignment

Randomization schedules will be generated and maintained by IRT vendor. At the conclusion of the trial, BMS will receive copies of all generated schedules form the vendor. Because of the nature of the study design, limited early access to the randomization information will be granted to the study team to facilitate early analyses for internal decision making (early termination of treatment arm, etc.).

Each subject who is randomized will be assigned a unique randomization number. This is not the primary identifier for the subject, but used for the randomization schedule. A subject being re-randomized will be assigned a different randomization number but will retain the same patient identification number. Randomization numbers will be assigned using a Central Randomization System in the order in which subjects qualify for treatment, not in the order of study enrollment. If, within a given track, treatment arms from more than one sub-protocol within the Master Protocol are simultaneously open to enrollment, then a new subject could be assigned to any of the open arms.

Pre-specified treatment arm caps will be utilized to control the accrual for each combination arm under different tracks. In the event that one or more subjects go off-study without being evaluable for response (i.e., with no on-study tumor measurements and no evidence of clinical progression or death due to disease progression), the enrollment cap for that arm may be correspondingly raised if needed to ensure that a sufficient number evaluable subjects are available for decision making. If the decision is made to close any arm for safety concerns, the cap for that arm will be reduced to the current number of subjects already randomized. Accrual will be stopped immediately.

Specific instructions for randomization into the Central Randomization System will be provided in a separate manual.

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

All available Master Protocol amendments are shown in Table 2.4-1

Table 2.4-1: Master Protocol Amendment

Protocol Amendment	Date	Purpose
Amendment 1	08-Apr-2016	1) Updated the study design from a 2-stage design to a 4-stage design with corresponding updates to study design figures [redacted] 3) corrected typographical errors and made minor clarifications

Table 2.4-1: Master Protocol Amendment

Protocol Amendment	Date	Purpose
Amendment 2	27-Jul-2016	1) Remove requirement for platinum based chemotherapy as one of the prior treatments for tracks 1 and 2. 2) Remove the option for less effective methods of birth control. 3) Clarify the exclusion criteria for patients with CNS metastases. 4) Update Section 3.5.1 to remove the prohibition of receptor activator of nuclear kappa-B ligand inhibitors or bisphonates. 5) Change the term "Pretreatment AEs" to "Assessment of Baseline Signs and Symptoms". 6) Update Figure 8.1.3-1 to fix a typographical error in the Stage 2 number of subjects (change 15 to 23)
Amendment 3	21-Sep-2016	[redacted]
Amendment 4	13-Oct-2016	1) Remove the Treatment Procedural tables (previously Table 5.1-2 and Table 5.1-3) 2) Update exclusion criteria to clarify all subjects with active CNS metastases are excluded. 3) Clarify prohibition of concurrent neoplastic treatment.
Amendment 05	16-Feb-2017	1) Removed the FRACTION-Lung nivolumab monotherapy treatment arm, including nivolumab monotherapy run-in, consolidated 3 tracks into 2 tracks (PD-1/PD-L1 treatment naïve and experienced), and simplified the study design accordingly. 2) Clarified study assessments for pulse oximetry. Removed patient-reported outcome assessment of quality of life at screening, as this is also being performed at baseline. 3) Updated data from the literature regarding anti-PD-1 and other targeted therapies. 4) Updated eligibility criteria to clarify the population for Track 4 (ie, PD-1/PD-L1 treatment naïve with up to 1 prior therapy for progressive or recurrent disease). 4) Added sample size determination for Tracks 4 and 5 and simplified sample size determination for Tracks 1, 2, and 3. 5) Added assessment schedule for retreatment/re-randomization in place of existing footnote, for clarity.

Table 2.4-1: Master Protocol Amendment

Protocol Amendment	Date	Purpose
		6) Minor clarifications and typographical errors have also been made throughout the document.

Sub Protocol A (originally named Sub Protocol 1) was provided at initiation of the study with detailed treatment information for nivolumab monotherapy, nivolumab in combination with dasatinib therapy, nivolumab in combination with BMS-986016 therapy, and nivolumab in combination with ipilimumab. Sub Protocol B was provided after Master Protocol Amendment 5 with detailed treatment information for nivolumab in combination with BMS-986205 (IDO inhibitor) therapy.

All available Sub Protocol A amendments are shown in Table 2.4-2

Table 2.4-2: Sub Protocol A Amendment

Sub Protocol A amendment	Date	Purpose
Amendment 1	08-Apr-2016	1) Added cardiac troponin and additional ECG monitoring for the nivolumab and BMS-986016 combination. Additional language with regards to cardiac troponin monitoring and management of changes has been included. 2) Added Hepatitis B core antibody test to the procedural outline. 3) Minor clarifications and typographical errors have also been made throughout the document.
Amendment 2	13-Oct-2016	1) Added a new Fraction-Lung combination treatment (nivolumab in combination with ipilimumab) throughout the Sub-Protocol. 2) Moved Table 5.1-1 and 5.51-1 into Sub-Protocol from Fraction-lung Master Protocol and combined Table 5.1-2 with full Treatment Procedural outline table (previously included in the Fraction-Lung Master Protocol) Sub-Protocol A. 3) Added text regarding additional hepatitis B serology tests in Table 5.1-2, clarifying that these are for subjects in the nivolumab and dasatinib Fraction-Lung combination only. 4) Updated Sub-Protocol identification from Sub-Protocol 01" to Sub-Protocol A". 5) Updated content to be consistent with the current guidance for the Fraction-Lung combination treatments.
Amendment 3	16-Feb-2017	1) Removed the FRACTION-Lung nivolumab monotherapy treatment arm, including nivolumab

Table 2.4-2: Sub Protocol A Amendment

Sub Protocol A amendment	Date	Purpose
		monotherapy run-in, and simplified the study design accordingly. 2) Clarified study assessments for vital signs and pulse oximetry. 3) Updated information regarding nivolumab experience and approvals and nivolumab in combination with dasatinib were added. 4) Dosing descriptions were consolidated, and the timing of dasatinib administration relative to nivolumab infusion was updated. 5) The eligibility criteria regarding pleural or pericardial effusion were clarified, as were the PK and immunogenicity assessments and analyses. 6) Minor clarifications and typographical errors have also been made throughout the document.

2.5 Safety Monitoring Board

A safety monitoring board (SMB) was established to provide safety monitoring and to provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the study. The SMB meets at least twice per year concurrent with BMS internal continuous safety assessment. If needed, additional ad-hoc SMB meetings may be convened. Safety related data summary and listings (by study track and treatment arm as appropriate) are provided to the SMB to facilitate safety monitoring. The SMB acts in an advisory capacity to BMS and monitors subject safety throughout the study. Additional details are provided in the SMB Charter.

2.6 Independent Review Committee (IRC)

An IRC is established. The IRC may review all available tumor assessment scans to determine response (RECIST v1.1 criteria). IRC-determined response and progression may be used in the analyses of objective response rate [ORR], progression free survival rate [PFSR] and duration of response [DOR].

3 OBJECTIVES

3.1 Primary

- To assess the efficacy (ORR, DOR, and PFSR at 24 weeks) of each FRACTION-Lung treatment combination in subjects with NSCLC

3.2 Secondary

- To investigate additional safety and tolerability of each FRACTION-Lung treatment combination in subjects with NSCLC

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint

The primary objective of preliminary efficacy will be measured by ORR, DOR, and PFSR at 24 weeks based on RECIST Version 1.1 criteria. Tumor response will be based on tumor assessments at screening, every 8 weeks from first dose until investigator assessed initial disease progression (per RECIST 1.1) or confirmed disease progression (defined as an additional 10% or greater increase in tumor burden volume from the time of initial progression [including all target lesions and new measurable lesions]), at the completion of follow-up or every 12 weeks from completion of follow-up until 2 years after last dose of study drug, or until subjects withdraw from the study.

4.1.1 Objective Response Rate (ORR)

ORR is defined as the total number of subjects whose best overall response (BOR) is either a complete response (CR) or partial response (PR) divided by the total number of treated subjects. BOR for a subject will be assessed by investigator per RECIST1.1.

BOR is the best response designation over the round of treatment (with corresponding follow-up) as a whole, recorded between the dates of the first dose until the last tumor assessment prior to subsequent anticancer therapy (see Table 4.1.1-1). For subjects who received retreatment of their initial therapy or are re-randomized to new combination therapy, the retreatment therapy and re-randomized therapy will be considered as subsequent anticancer therapy. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed at least 4 weeks after the criteria for response are first met. For those subjects who have surgical resection of target/non-target/new lesion, only pre-surgical tumor assessments will be considered in the determination of BOR.

Table 4.1.1-1: Tumor Assessments for BOR Consideration

Track	Baseline Tumor Assessment	On-treatment Tumor Assessments to be Considered
Track 1	Latest tumor assessment prior to first dose of nivolumab	From first dose date of nivolumab, up to last tumor assessment prior to subsequent anticancer therapy [a] (including tumor assessments done in nivolumab run-in)
Track 2/3/4/5	Latest tumor assessment prior to randomization	From first dose date of randomized treatment, up to last tumor assessment prior to subsequent anticancer therapy [a]

[a] Retreatment with the same therapy after the initial treatment period and re-randomized treatment are considered subsequent anticancer therapy

Note: For Track 1 subjects received combination therapy, a set of exploratory efficacy endpoints may be used for exploratory efficacy analysis. For such set of efficacy endpoints, latest tumor assessment prior to randomization (end of Nivolumab run-in) will be used as baseline; all tumor assessment post randomization (and prior to subsequent therapy) will be used as on-treatment tumor assessments.

ORR and BOR of Retreatment (considering all tumor assessments from first dose date of retreatment, up to last tumor assessment prior to subsequent anticancer therapy) may be assessed as exploratory endpoints for exploratory analyses.

4.1.2 Duration of Response (DOR)

DOR, computed for all treated subjects with a BOR of CR or PR, is defined as the time between the date of first response and the date of first documented disease progression as determined by RECIST 1.1 or death due to any cause (death occurring after retreatment or randomization to new combination treatment will not be considered), whichever occurs first. (DOR = disease progression date/death date -first response date + 1)

Subjects who started subsequent anticancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment on or prior to initiation of the subsequent anticancer therapy. Subjects who drop out study without documented progression will be censored at the last evaluable tumor assessment. For subjects received retreatment or randomized to new combination treatment, the retreatment therapy and newly randomized therapy will be considered as subsequent anticancer therapy. Progression censor derivation details are presented in Table 4.1.3-1.

DOR of Retreatment may be assessed as exploratory endpoints for exploratory analyses.

4.1.3 Progression Free Survival Rate (PFSR) at 24 Weeks

The PFSR at 24 weeks is defined as the proportion of treated subjects remaining progression free and surviving at 24 weeks since the first dosing date. The proportion will be calculated by the Kaplan-Meier estimate which takes into account censored data.

PFS for a subject is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause (death occurring after retreatment or randomization to new combination treatment will not be considered), whichever occurs first. (PFS = disease progression date/death date - first dose date +1). For subjects treated under Track 1

combination therapy, first dosing date of nivolumab monotherapy will be used. (Subjects with RECIST 1.1 progression prior to receiving combination therapy will be excluded from the primary analysis)

Subjects who died without a reported prior progression will be considered to have progressed on the date of their death. Subjects who remained alive and have not progressed will be censored on the last evaluable tumor assessment date. Subjects who started subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessment on or prior to initiation of the subsequent anticancer therapy. Subjects who did not have any post-baseline tumor assessment and did not die will be censored on the date of first dose of study medication. For subjects who received retreatment with their initial treatment or were re-randomized to another treatment, the retreatment therapy and re-randomized therapy will be considered as subsequent anticancer therapy. (See Table 4.1.3-1)

Table 4.1.3-1: Censoring Scheme for Progression (for DOR and PFS Derivation)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	First dosing date [a]	Censored
No post-baseline tumor assessments and no death [b]	First dosing date [a]	Censored
Documented progression [c]	Date of first documented progression per RECIST 1.1	Progressed
No progression [c] and no death [b]	Date of last evaluable tumor assessment on or prior to subsequent anti-cancer therapy	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without progression reported prior or on the same day	Date of last evaluable tumor assessment on or prior to the date of initiation of subsequent therapy	Censored
Death [b] without progression	Date of death	Progressed

[a] First dosing date for Track 1.a, 1.c, 2, 3, 4, and 5; first nivolumab run-in dose date for Track 1.b

[b] Death occurring after retreatment or randomization to new combination treatment or other subsequent therapy will not be considered.

[c] Progression occurring after subsequent therapy (including retreatment and randomized to new combination treatment) will not be considered.

[redacted]

4.2 Secondary Endpoints

The assessment of safety will be based on the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, and deaths. In addition clinical laboratory test abnormalities will be examined.

AEs and laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) version 4.0.3.

[redacted]

[redacted]

[redacted]

a 5-point scale ranging from 0 (not at all) to 4 (very much). In addition to a total score based on

[redacted]

5 SAMPLE SIZE AND POWER

Sample sizes are guided by Simon 2-stage, single-stage or multi-stage designs as described in Table 5-1. Because of the different patient populations and existing standard of care options under each track, different criteria apply to determine the number of patients for each stage and the strength of the efficacy signal required to the next stage.

For sample size calculation and for simplicity of description, decision criteria for stopping or progressing to the next stage are based on the number of objective responses observed. However, since BOR does not necessarily capture the full extent of clinical benefit, and since response can be delayed or of short duration, the Sponsor will also review other aspects of clinical benefit which may better predict OS benefit, such as DOR and PFSR, as well as the relative performance of different combination arms, before making a final determination.

Additional subjects may be enrolled to account for subjects who may drop out of the study without being evaluable for response. For example, assuming a 25% dropout rate, up to 5 additional subjects per arm could be enrolled into Track 2 Stage 1 to achieve 20 “evaluable “ subjects (with any over-enrollment counting towards Stage 2), while in Stage 2, an additional 4 subjects over the

planned 15 could be enrolled to achieve 35 total evaluable subjects. Similarly in Track 3 Stage 1, up to 15 subjects may initially be enrolled to achieve 12 evaluable subjects.

Although the sample size calculations are based on efficacy considerations, safety will also be continuously assessed, and will be taken into account in the decision to continue or terminate an arm. Thirty-five subjects per arm in Stage 1 and 2 combined will result in 83% probability of detecting an AE that has a true rate of 5%.

Table 5-1: Multi-Stage or Single-stage Design

Track	Stage 1	Stage 1 Responders		Stage 2	Stage 2 Responders			Stage 3	Stage 3 Responders		Stage 4	Stage 4 Responders	
	n	Futility Stop	Go to Stage 2	n	Futility Stop	Go to Stage 3	Efficacy Stop	n	Futility Stop	Go to Stage 4	n	Futility Stop	Efficacy Stop
1.b	20	≤ 3	≥ 4	15	≤ 6	≥ 7	≥ 11	15	≤ 11	≥ 12	20	≤ 13	≥ 14
2	20	≤ 2	≥ 3	15	≤ 4	≥ 5	≥ 9	15	≤ 8	≥ 9	20	≤ 9	≥ 10
3	12	≤ 1	≥ 2	23	≤ 5		≥ 6						
4 (PD-L1 exp. < 1%)	19	≤ 3	≥ 4	17	≤ 10		≥ 11						
4 (PD-L1 exp. ≥ 1% & < 50%)	28	≤ 11	≥ 12	13	≤ 20		≥ 21						
4 (PD-L1 exp. ≥ 50%)	16	≤ 11	≥ 12	9	≤ 20		≥ 21						
5	35												

Note: n values presented in this table are per treatment arm.
Abbreviations: exp = expression.

With regards to sample size, subjects who are re-randomized to a different treatment will be counted once for each randomization; subjects who are re-treated within the same arm will only be counted once.

With the implementation of Amendment 5, enrollment in Tracks 1, 2, and 3 will cease. Sample size descriptions provided in Section 5.2 are, therefore, applicable only until implementation of Amendment 5.

5.1 Sample Sizes for Tracks 4 and 5

With the implementation of Amendment 5, subjects will be enrolled in Tracks 4 and 5. The sample size for Track 4 is guided by a 2-stage design and for Track 5 is guided by a single-stage design. Track 4 subjects will be stratified into 3 groups according to their PD-L1 expression level as assessed by the baseline tumor biopsy. Section 5.1.1 describes the sample size determination for all three strata in Track 4, while Section 5.1.2 describes the sample size determination for Track 5.

5.1.1 Track 4 - Anti-PD-1/PD-L1 Treatment-naïve Subjects

Track 4 subjects will be enrolled into 1 of 3 strata based on their PD-L1 expression level as assessed by the baseline tumor biopsy. Subjects may in some cases be randomized before the results of their PD-L1 expression testing are known. As a result, there may be a small number of subjects (estimated no more than 10% to 15%) who are randomized but are subsequently found to be unevaluable for PD-L1 expression. Such unevaluable subjects may continue their randomized treatment but will not be counted towards the sample size for any of the three strata. Data for such subjects will be reported as if coming from a fourth stratum. In the situation that one or two of the strata has reached or is approaching full enrollment, the Sponsor may choose to require the results of PD-L1 testing to be available before randomizing additional subjects, to reduce the risk of over-enrollment.

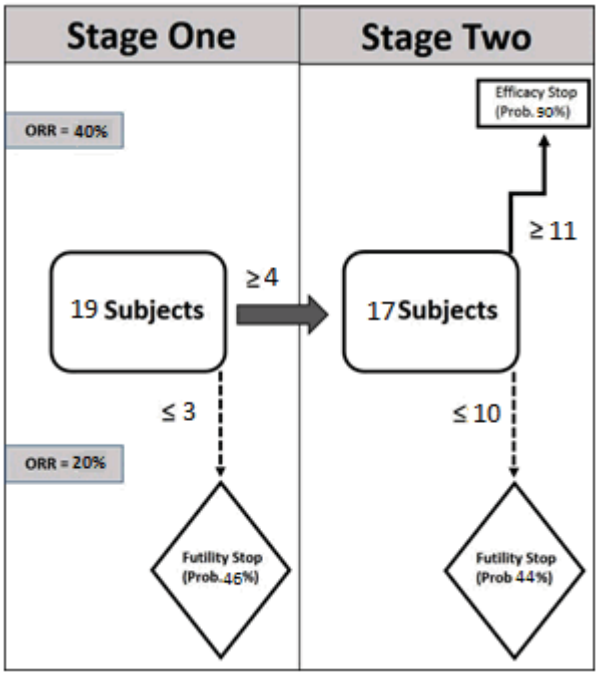
Enrollment will be continued during initial efficacy evaluation (ie, with the indicated number of subjects at Stage 1) to allow additional subjects to enroll to account for unexpected trial impact, such as response non-evaluable subjects due to early drop-out, design parameter change (eg, historical rate update), etc. The number of responses given here is used as a guide for sample size calculation and for simplicity of description. Before making a decision to terminate or continue an arm, BMS will also review the totality of all available data, which includes: other aspects of efficacy that may help predict OS benefit, such as DOR and PFSR; clinical safety information; and biomarker data, as well as the relative performance of other treatment arms on a continuing basis.

Track 4 - Anti-PD-1/PD-L1 Treatment-naïve subjects with PD-L1 expression less than 1%

As shown in Table 5-1, a minimum of 19 subjects in each study treatment combination arm will be treated in Stage 1 for an initial evaluation of efficacy. If the number of responses observed in Stage 1 is ≤ 3/19, the study treatment combination arm would likely not be considered efficacious. In Stage 2, an additional 17 subjects will be treated. More than 10 responses observed at the end of Stage 2 would suggest the efficacy target has been met. The totality of efficacy data and response profile for each combination will be considered when making decisions to terminate or continue an arm. The operating characteristics of the Simon 2-stage design to be used as a guide are provided in Figure 5.1.1-1. With the stopping boundaries as shown in Table 5-1, if the combination has an ORR no better than the historical control ([redacted]) at 20%, then there is a 90% overall chance of declaring futility, with a 46%

chance of stopping at Stage 1; there is a 10% false positive rate. If the combination has an ORR equal to the target of 40%, then there is a 90% chance of declaring efficacy after Stage 2, whereas if the ORR is equal to 35%, 30%, and 25%, there will be, respectively, 76%, 52%, and 27% chance of declaring efficacy.

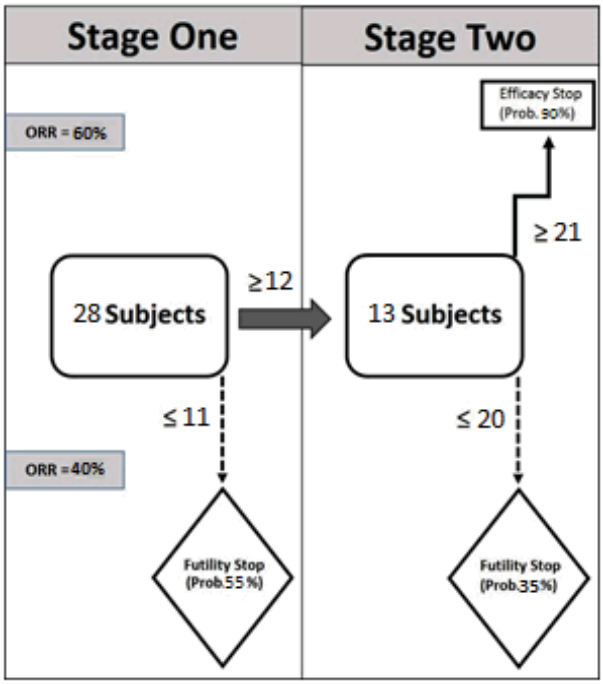
Figure 5.1.1-1: Operating Characteristics of Simon 2-Stage Design for Track 4 Subjects with PD-L1 Expression < 1% (Power = 90%, Alpha = 10%)



Track 4 - Anti-PD-1/PD-L1 Treatment-naïve Subjects with PD-L1 Expression ≥ 1% and < 50%

As shown in Table 5-1, a minimum of 28 subjects in each study treatment combination arm will be treated in Stage 1 for an initial evaluation of efficacy. If the number of responses observed in Stage 1 is ≤ 11/28, the study treatment combination arm would likely not be considered efficacious. In Stage 2, an additional 13 subjects will be treated. More than 20 responses observed at the end of Stage 2 would indicate the efficacy target has been met. The totality of efficacy data and response profile for each combination will be considered when making decisions to terminate or continue an arm. The operating characteristics of the Simon 2-stage design, used as a guide, are provided in Figure 5.1.1-2. With the stopping boundaries as shown in Table 5-1, if the combination has an ORR no better than the historical control ([redacted]) at 40%, then there is a 90% overall chance of declaring futility, with a 55% chance of stopping at Stage 1; there is a 10% false positive rate. If the combination has an ORR equal to the target of 60%, then there is a 90% chance of declaring efficacy after Stage 2, whereas if the ORR is equal to 55%, 50%, and 45%, there will be, respectively, 74%, 50%, and 27% chance of declaring efficacy.

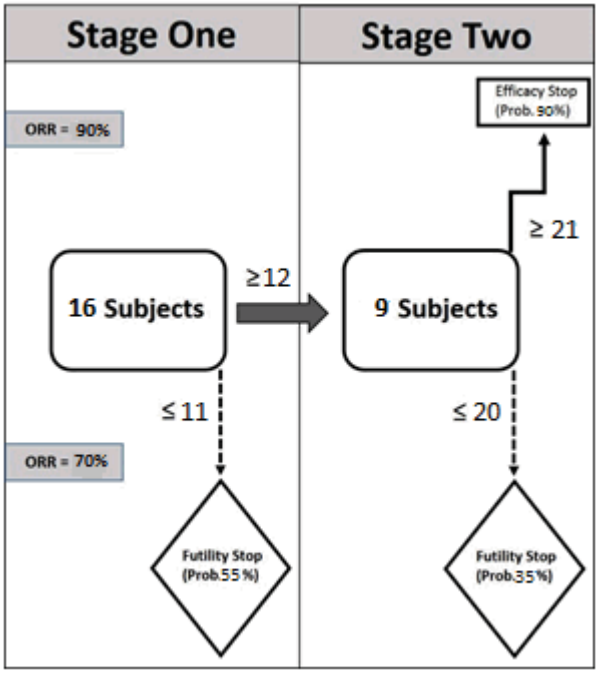
Figure 5.1.1-2: Operating Characteristics of Simon 2-Stage Design for Track 4 Subjects with PD-L1 Expression Between 1% and < 50% (Power = 90%, Alpha = 10%)



Track 4 - Anti-PD-1/PD-L1 Treatment-naïve Subjects with PD-L1 Expression ≥ 50%

As shown in Table 5-1, a minimum of 16 subjects in each study treatment combination arm will be treated in Stage 1 for an initial evaluation of efficacy. If the number of responses observed in Stage 1 is ≤ 11/16, the study treatment combination arm would likely not be considered efficacious. In Stage 2, an additional 9 subjects will be treated. More than 20 responses observed at the end of Stage 2 would indicate the efficacy target has been met. The totality of efficacy data and response profile for each combination will be considered when making decisions to terminate or continue an arm. The operating characteristics of the Simon 2-stage design, used as a guide, are provided in Figure 5.1.1-3. With the stopping boundaries as shown in Table 5-1, if the combination has an ORR no better than the historical control ([redacted]) at 70%, then there is a 90% overall chance of declaring futility, with a 55% chance of stopping at Stage 1; there is a 10% false positive rate. If the combination has an ORR equal to the target of 90%, then there is a 90% chance of declaring efficacy after Stage 2, whereas if the ORR is equal to 85%, 80%, and 75%, there will be, respectively, 68%, 42%, and 21% chance of declaring efficacy.

Figure 5.1.1-3: Operating Characteristics of Simon 2-Stage Design for Track 4 Subjects with PD-L1 Expression ≥ 50% (Power = 90%, Alpha = 10%)



5.1.2 Track 5 - Anti-PD-1/PD-L1 Treatment-experienced Subjects

It is not known whether PD-L1 expression levels affect response rates for combination therapy in anti-PD-1/PD-L1 experienced patients. Therefore, Track 5 participants will not be stratified on their PD-L1 expression levels; however, subset analyses may be performed. The sample size of 35 participants for Track 5 is based on a 1-sided alpha of 0.1 for testing the null hypothesis that the ORR is equal to the null rate of 10%, and a power of 90% against the alternative hypothesis that the ORR is equal to the target rate of 30% (Table 5.1.2-1). Unlike in Track 4, participants whose PDL-1 status is unevaluable will count towards the sample size in Track 5.

Table 5.1.2-1: Single-stage Design for Track 5

PD-L1 Stratum	Null ORR	Target ORR	Type 1 Error	Power	Sample size
All	0.1	0.3	0.1	0.9	35

Efficacy will be continuously monitored in all participants who are evaluable for response using the measurements described in Section 4.1. In Track 5, 8/35 responses would result in CIs for ORR which are strictly higher than 10%. If at any point it appears very unlikely that this track will meet its efficacy target, the Sponsor will consider closing that arm to further enrollment. Both subjects previously treated in Tracks 4 and 5 (re-randomized subjects) and new subjects who meet eligibility criteria are permitted to enter Track 5. Some slots in Track 5 will be reserved for re-randomized subjects to ensure that both types of subjects are enrolled in Track 5.

5.2 Sample Sizes for Tracks 1, 2 and 3

With the implementation of Amendment 5, enrollment in Tracks 1, 2, and 3 will cease. Sample size descriptions provided in Sections5.2.1 through 5.2.3 are, therefore, applicable only until implementation of Amendment 5. The sample sizes for Tracks 1b and 2 are guided by a 4-stage design, whereas the sample size for Track 3 is guided by a Simon 2-stage design.

5.2.1 Track 1.a and 1.c - Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-positive Subjects

Week 8 Responders and Rapid Progressors

The number of subjects entering Track 1.a is not pre-specified but is determined by patient response to 8 weeks of nivolumab monotherapy. It is estimated that approximately 15% of subjects who enter Track 1 would enter Track 1.a. Similarly the number of subjects who enter Track 1.c and discontinued from treatment after Week 8 due to fast progression cannot be pre-specified. It is estimated that approximately 10% of subjects who enter Track 1 would enter Track 1.c. The remaining 75% of subjects who enter Track 1 would enter Track 1.b.

5.2.2 Track 1.b - Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-positive Subjects and Track 2 - Anti-PD-1/PD-L1 Treatment - naïve, PD-L1 -negative Subjects

For each combination arm under Tracks 1.b and 2, a four-stage approach will be used (nested Simon/Fleming). Initially 20 subjects per combination arm will be treated in Stage 1, and preliminary efficacy will be assessed when those subjects are evaluable. If futility is demonstrated at that point, the corresponding arm will be terminated; otherwise an additional 15 Stage 2 subjects will be enrolled. At the end of Stage 2, the arm can be stopped for futility, continue to Stage 3, or be stopped for efficacy. Stage 3 will enroll 15 additional subjects, and when those subjects are evaluable for efficacy, the arm may be stopped for futility or proceed to Stage 4. Stage 4 will enroll 20 subjects. The total potential enrollment for all 4 Stages is 70 subjects per combination per Track. More details including the Track-specific criteria for stopping or continuing, are given in Section 5.2.2.1 and 5.2.2.2. The nivolumab monotherapy arm will enroll the same number of subjects as its largest corresponding combination arm.

Historical ORRs from nivolumab Phase 3 clinical studies are used for the initial sample size assessment and sizes for the multi-stage approach are based on Simon/Fleming-like single-arm efficacy and futility boundaries. However the ORR from the nivolumab monotherapy control arm will also be considered in the final decision making process. Sample sizes may be re-adjusted using the observed ORR in the nivolumab monotherapy arms if those differ substantially from historical rates, and so the final sample size may deviate from the original assessment.

5.2.2.1 Track 1.b - Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-positive Subjects

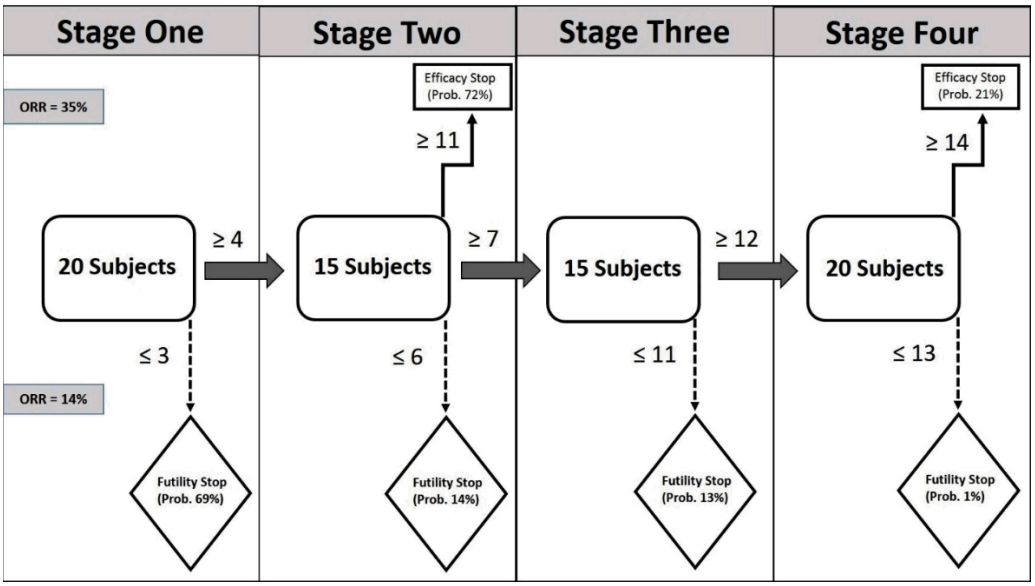
Week 8 Inadequate Responders

As shown in Table 5-1, a minimum of 20 subjects per combination arm will be treated in Stage 1 for an initial evaluation of efficacy. If the number of responses observed in Stage 1 is ≤ 3/20, the combination arm would be terminated for futility, otherwise enrollment to Stage 2 will continue,

and an additional 15 subjects will be treated. If the total number of responses at the end of Stage 2 is ≤ 6/35, the arm will be terminated for futility; if there are ≥ 11/35 responses the arm will be terminated for efficacy; while if the total number of response is ≥ 7/25 but ≤ 10/35, Stage 3 will be initiated. Stage 3 will enroll 15 subjects, and if the total number of response is then ≤ 11/50, then the arm will stop for futility; otherwise Stage 4 will be initiated and enroll 20 additional subjects.

The operating characteristics of this design are provided in Figure 5.2.2.1-1. The stopping criteria specific to Track 1.b were selected via simulation to 1) control the probability of stopping for futility if the true ORR is 14%; and 2) maximize the probability of stopping for efficacy if the true ORR is 35%. With the stopping boundaries as shown in Figure 5.2.2.1-1, if the combination has an ORR no better than the historical control at 14%, then there is a 97% overall chances of stopping for futility, with a 69% chance of stopping at Stage 1; there is a 3% false positive rate. If the combination has an ORR equal to the target of 35%, then it has a 93% chance of stopping for efficacy overall (power), with a 72% chance of declaring efficacy at Stage 2; whereas if the true ORR is 20%, 25% or 30%, the power would be 25%, 55%, or 80% respectively.

Figure 5.2.2.1-1: Operating Characteristics of Track 1b 4-Stage Design (Power = 93%, Alpha = 3%)



If at least 11 responses are observed at the end of Stage 2, then the lower limit of the 95% confidence interval (CI) for ORR will be higher than the historical ORR of 14%. The CI is calculated using the Clopper-Pearson method.

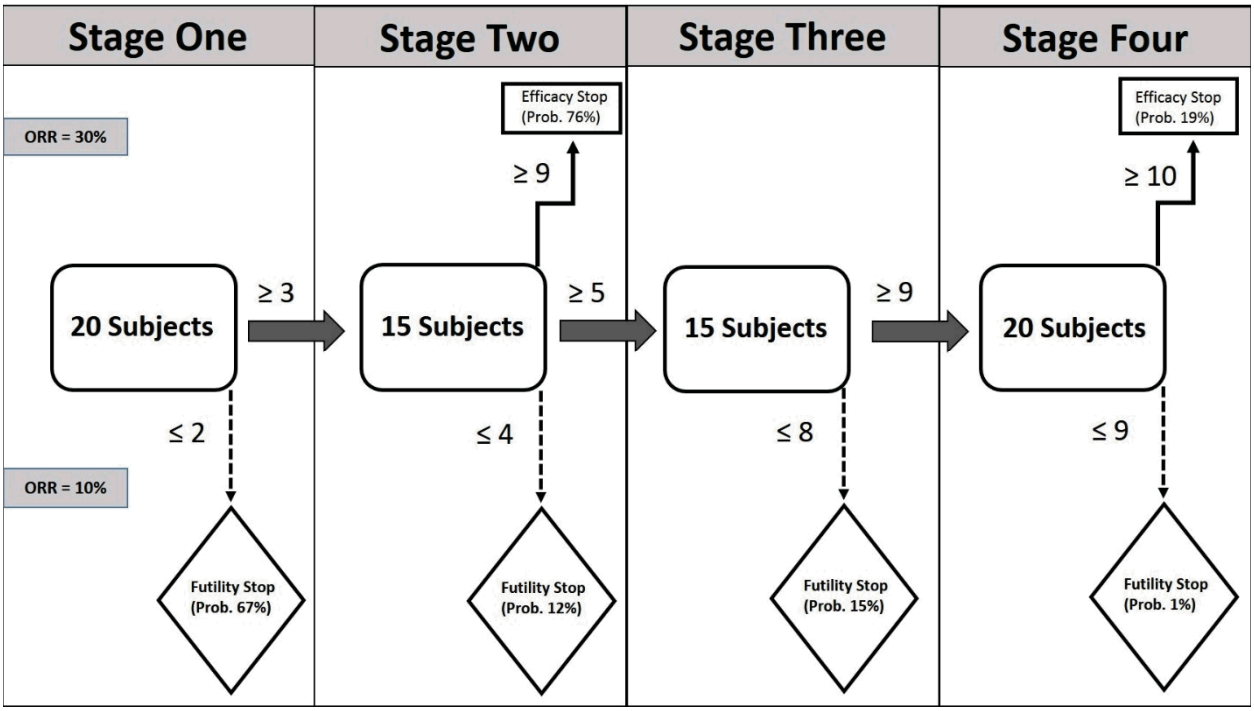
5.2.2.2 Track 2 - Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-negative Subjects

As shown in Table 5-1, a minimum of 20 subjects in each combination arm will be treated in Stage 1 for an initial evaluation of efficacy. If the number of responses observed in Stage 1 is ≤ 2/20, the combination arm would be terminated for futility, otherwise enrollment to Stage 2 will continue, and an additional 15 subjects will be treated. If the total number of responses at the end of Stage 2 is ≤ 4/35, the arm will be terminated for futility; if there are ≥ 9/35 responses the arm will be

terminated for efficacy; while if the total number of responses is ≥ 5/35 but < 9/35, Stage 3 will be initiated. Stage 3 will enroll 15 subjects, and if the total number of response is then ≤ 8/50, the arm will stop for futility; otherwise Stage 4 will be initiated and enroll 20 additional subjects.

The operating characteristics of this design are provided in Figure 5.2.2.2-1. The stopping criteria specific to Track 2 were selected via simulation to 1) control the probability of stopping for futility if the true ORR is 10%; and 2) maximize the probability of stopping for efficacy if the true ORR is 30%. With the stopping boundaries as shown in Figure 5.2.2.2-1, if the combination has an ORR no better than the historical control at 10%, then there is a 96% overall chance of stopping for futility, with a 67% chance of stopping at Stage 1; there is a 4% false positive rate. If the combination has an ORR of 30%, then there is a 95% chance of stopping for efficacy overall (power), with a 76% chance of stopping for efficacy at Stage 2; whereas if the true ORR is 15%, 20%, or 25%, the power would be 28%, 62%, or 85%, respectively.

Figure 5.2.2.2-1: Operating Characteristics of Track 2 4-Stage Design (Power = 95%, Alpha = 4.4%)



If at least 9 responses are observed at the end of Stage 2, then the lower limit of the 95% CI for ORR will be higher than the historical ORR of 10%. The CI is calculated using the Clopper-Pearson method.

5.2.3 Track 3 - Anti-PD-1/PD-L1 Treatment-experienced Subjects

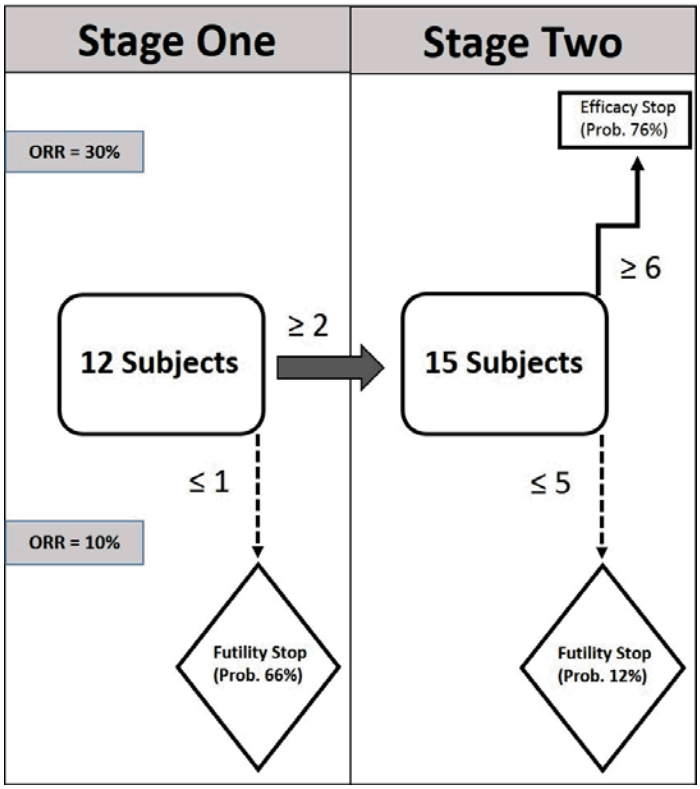
For each combination arm under Track 3, the Simon 2-stage (optimal) design will be used.

Initially, 12 subjects per combination arm will be treated in Stage 1 and preliminary efficacy will be assessed when those subjects are evaluable. If 1 or fewer responses is observed in Stage 1, the

arm will be terminated for futility; otherwise, Stage 2 will be initiated and enroll an additional 23 subjects, for a total of 35 subjects per combination arm.

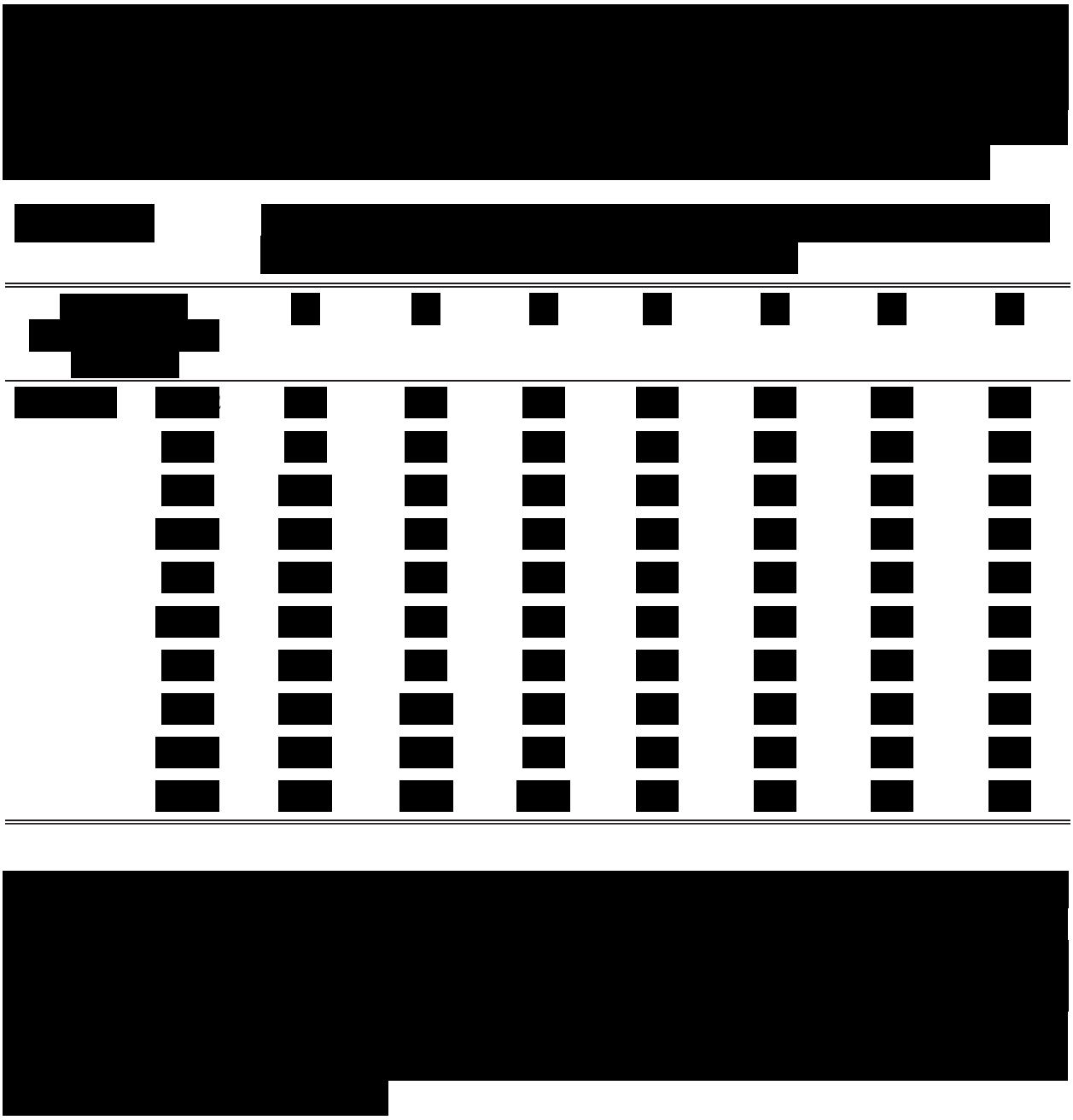
The operating characteristics of this Simon 2-stage (optimal) design are provided in Figure 5.2.3-1. With the stopping boundaries as shown in Table 5-1, if the combination has an ORR no better than 10%, then there is a 90% overall chance of stopping for futility, with a 66% chance of stopping at Stage 1; there is a 10% false positive rate. If the combination has an ORR equal to the target of 30%, then it has a 90% chance of stopping for efficacy after stage 2.

Figure 5.2.3-1: Operating Characteristics of Track 3 2-Stage Design (Power = 90%, Alpha = 10%)



Both subjects previously treated in any track (re-randomized subjects) and new subjects who meet eligibility criteria are permitted to enter Track 3. Some slots in Track 3 will be reserved for re-randomized subjects to ensure that both types of subjects are enrolled in Track 3. At the initiation of the study, recruitment of re-randomized subjects will be limited to 7 subjects per Track 3 combination arm in Stage 1 (with 25% drop out rate considered). In Stage 2, recruitment of additional re-randomized subjects will be limited to 13 subjects out of the 29 additional subjects (with 25% drop out rate considered). The limited number of re-randomized subjects may be re-adjusted depending on the enrollment rates, the rate of progression in Tracks 1 to 3, and the number of currently open arms in Track 3.

[redacted]



6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Study Periods for Treatment Arms Under Tracks 2, 3, 4 and 5

Under Tracks 2, 3, 4 and 5, each treatment assignment will go through two study periods: baseline period and post baseline period.

6.1.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment (and within 28 days of first dose date).

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 and vital signs) will be defined as evaluations with a date *on or* prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline. If same database entry date (and time if collected) or database entry date not available, the assessment with the latest modification date will be considered as baseline.

6.1.1.2 Post Baseline Period

Post baseline period is further characterized into Treatment, and Retreatment Periods.

Treatment Period

Treatment Period starts with the first dose date-time of study treatment and includes continued treatment [additional 24 week treatment] as agreed between investigator and BMS medical monitor.

- On-treatment AEs will be defined as AEs with an onset date-time on or after the date-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 treatment (off treatment date available), AEs will be counted as on-treatment if event occurred within 100 days of the last dose of study medication and prior to first dose of retreatment or randomized new combination treatment (if exist). For subjects who are still on study treatment (off treatment date not available), all available post baseline AEs will be counted as on-treatment.
- 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 treatment (off treatment date available), evaluations will be counted as on-treatment if evaluation is taken within 100 days of the last dose of study medication and on or prior to first dose of retreatment or randomized new combination treatment (if exist). For subjects who are still on study treatment (off treatment date not available), all available post baseline evaluations will be considered as on-treatment.

Primary analysis of safety endpoints will be based on the treatment period. AEs and other evaluations reported during the retreatment period will be listed and summarized separately (if exist).

Optional Retreatment Period

Optional Retreatment Period starts with the first dose date-time of retreatment.

- On-retreatment AEs, will be defined as AEs with an onset date-time on or after the date-time of the first dose of retreatment (or with an onset date on or after the day of first dose retreatment if time is not collected or is missing). For subjects who are off treatment in the retreatment period (off treatment date available), AEs will be counted as on retreatment if event occurred within 100 days of the last dose of retreatment and prior to first dose of randomized new combination treatment (if exist). For subjects who are still on retreatment of study medication (off treatment date not available), all available AEs with onset date-time on or after the date-time of first dose of retreatment will be counted as on-retreatment.
- On-retreatment 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 retreatment. For subjects who are off treatment in the retreatment period (off treatment date available), evaluations will be counted as on-retreatment if evaluation is taken within 100 days of the last dose of retreatment and on or prior to first dose of re-randomized treatment (if exist). For subjects who are still on retreatment (off treatment date not available), all available evaluations taken after the day of first dose of retreatment will be considered as on-retreatment.

6.1.2 Study Periods for Treatment Arms under Track 1

Under Track 1, each subject may go through three study periods: Baseline Period, Run-in Period and Post Run-in Period.

6.1.2.1 Baseline Period

Same definition and derivation rule as stated in Section 6.1.1.1 will be applied.

6.1.2.2 Run-in Period

Run-in period starts with the first dose date-time of nivolumab and end by the first dose date-time of study medication after Week 8 tumor assessment.

- Run-in Period AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of nivolumab (or with an onset date on or after the day of first dose of initial study treatment if time is not collected or is missing). For subjects who are off treatment during the Run-in Period (off treatment date available), AEs will be counted for Run-in Period if event occurred within 100 days of the last dose of nivolumab prior to week 8 tumor assessment. For subjects who enter into the Post Run-in Period, all post baseline AEs will be counted for Run-in Period if event occurred prior to first dose date-time of study medication post week 8 tumor assessment.

- Run-in Period 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 treatment during Run-in Period, evaluations will be counted for Run-in Period if evaluation is taken within 100 days of the last dose of study medication prior to week 8 tumor assessment. For subjects who entered into Post Run-in Period, all post baseline evaluations taken on or prior to first dose data-time of study medication post week 8 tumor assessment will be included in Run-in period.

6.1.2.3 Post Run-in Period

Post Run-in Period starts with the first dose date-time of study medication post week 8 tumor assessment scan (for subjects treated in Track 1.b, this is the first dose of study medication after randomization).

Post Run-in period can be further characterized into Treatment, and Retreatment Periods. Same definition and derivation rule as stated in section 6.1.1.2 will be applied.

6.1.2.4 Additional Period information

Analysis period to be used for Track 1 are listed below and summarized in Table 6.1.2.4-1

Track 1 Nivolumab monotherapy

Including subjects treated with nivolumab monotherapy only under track 1.a, 1.b, 1.c or still in nivolumab run-in. Run-in and post Run-in period will be combined as Post Baseline period. The same definition and derivation rule as stated in section 6.1.1.2 will be applied. First dose date-time of nivolumab will be used. Overall two periods: Baseline Period, and Post Baseline Period.

Track 1 combination therapy

Including subjects treated with nivolumab run-in, followed by combination therapy. Post Run-in Period is further characterized into Treatment, and Retreatment Periods. Same definition and derivation rule as stated in section 6.1.1.2 will be applied. Run-in and post Run-in period will be combined as Post Baseline period. Overall two periods: Baseline Period, and Post Baseline Period.

Table 6.1.2.4-1: Analysis Period Information for Track 1

Track	Period Used for Analysis	Period Defined in Section 6.1
Track 1 nivolumab monotherapy	Baseline Period	Baseline Period
	Post Baseline Period	Run-in Period + Post Run-in Period
Track1 Combination therapy	Baseline Period	Baseline Period
	Post Baseline Period	Run-in Period + Post Run-in Period

6.2 Treatment Regimens

Treatments included in Sub-Protocol A:

Trt N: Nivolumab 240 mg Q2W IV

Trt ND: Nivolumab 240 mg Q2W IV + Dasatinib 100 mg QD Oral

Trt NB: Nivolumab 240 mg Q2W IV + BMS-986016 20 mg Q2W IV

Trt NI: Nivolumab 240 mg Q2W IV + Ipilimumab 1 mg/kg Q6W IV

Treatments included in Sub-Protocol B:

Trt NO: Nivolumab 480 mg Q4W IV + BMS-986205 (IDO) 100mg QD Oral

Additional treatment regimens will be added per future Sub-Protocol.

The treatment group "as randomized" will be retrieved from the IRT system, if applicable. The treatment group "as treated" will be the same as the arm as randomized by IRT, if applicable. However, if a subject received the incorrect drug for the entire period of treatment, the subject's treatment group will be defined as the incorrect drug the subject actually received.

6.3 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form
- All Randomized Subjects: All subjects who were randomized to any treatment arm in the study.
- All Treated Subjects: All subjects who received at least one dose of any study medication
- Pharmacokinetic Subjects: All subjects who received at least one dose of investigational product component and have corresponding evaluable plasma or serum concentration data
- Immunogenicity Subjects: All subjects who received at least one dose of investigational product component and have corresponding evaluable immunogenicity assessment (i.e., baseline and at least one post baseline assessment)
- Biomarker Subjects: All treated subjects with available biomarker data
- PD-L1+ Subjects: All treated subjects with positive PD-L1 tumor status at baseline (defined by ≥ 1% of the membranous tumor staining for PD-L1)
- PD-L1- Subjects: All treated subjects with negative PD-L1 tumor status at baseline (defined by < 1% of the membranous tumor staining for PD-L1)
- PD-L1 Unknown Subjects: All treated subjects with unknown PD-L1 tumor status at baseline
- PD-L1 + H Subjects: All treated subjects with high PD-L1 expression at baseline (defined by ≥ 50% of the membranous tumor staining for PD-L1)
- PD-L1 + L Subjects: All treated subjects with low PD-L1 expression at baseline (defined by ≥ 1% and < 50% of the membranous tumor staining for PD-L1)
- Retreatment Subjects: Subjects who received retreat of original treatment
- Re-Randomized Subjects: Subjects who were randomized and received new combination treatment under Track 3 or 5
- Outcome Research Subjects: All subjects who received at least one dose of investigational product component and have corresponding evaluable assessment (i.e., baseline and at least one subsequent assessment while on treatment)
-

7 STATISTICAL ANALYSES

All analyses will be performed in SAS using version 9.2 or higher. Some figures will be generated using S-Plus.

7.1 General Methods

Continuous variables will be summarized using descriptive statistics, ie, medians, minimums, maximums, means and standard deviations. Categorical variables will be summarized by frequencies and percentages. Percentages will be rounded and may not always add up to 100. If a missing category is not being presented in the data display, only those subjects with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distributions (i.e., progression free survival, overall survival) will be estimated using Kaplan Meier techniques. When appropriate, the median along with 95% confidence interval (CI) will be estimated based on Brookmeyer and Crowley methodology[4] (using log-log transformation for constructing the confidence intervals). Rates at fixed time points (e.g., PFSR at 24 weeks) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% CIs[5]. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[6].

7.2 Study Conduct

7.2.1 Study Information

- **Listing**:

- Batch number

7.2.2 Accrual

The following will be presented on the All Enrolled Subjects.

Summary:

- Number (%) of subjects accrued by country and investigational site: include country, site number, number of subjects enrolled, and number of subjects treated by Track
- Number (%) of subjects accrued per month: include number of subjects enrolled, and number of subjects treated by Track

Listing:

- Subjects accrued by country and investigational site

7.2.3 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and a listing will be provided.

Eligibility:

- Subjects without measurable disease at baseline
- Subjects with misclassified PD-L1 status for Tracks 1 and 2
- Subjects with prior anti-PD-1/PD-L1 treatment for Tracks 1, 2 and 4
- Subjects without prior anti-PD-1/PD-L1 treatment for Tracks 3 and 5

On-study:

- Subjects treated differently than randomized (subjects who received the wrong treatment for the entire treatment period, excluding the never treated)

7.3 Study Population

7.3.1 Subject Disposition

Summary:

The number (%) of subjects of the following will be summarized on All Enrolled Subjects.

- Subjects assigned to Tracks 1, 2, 3, 4, and 5
- Screen failure Subjects with reason

•

The number (%) of subjects of the following will be summarized on the All Treated Subjects.

- Subjects discontinued treatment with reason
- Subjects entered into follow up
- Subjects entered into Track 3 or 5 (re-randomized subjects)
- Subjects off study
- Subjects received re-treatment

Listing:

- Screen Failure Subjects with reason
- Treated subjects with off treatment reason (by Track and treatment)

7.3.2 Demographics and Other Baseline Characteristics

Summary:

Descriptive statistics will be summarized the following baseline characteristics for all treated subjects by treatment, and track.

- Age (in years) ; Age category (<65, ≥65); Gender; Race; Ethnicity
- Height; Weight; ECOG PS
- Disease characteristics such as histology, stage and disease status
- Mutation status (EGFR, ALK, K-RAS, etc.)
- Prior therapy (surgery, radiotherapy, systemic therapy--setting, number of regimen prior to this study (including subsequent therapy received during follow-up of treatment prior to re-randomized treatment if exist), number of regimens within this study, etc.)
- Baseline PD-L1 status
- Smoking status

Listing:

- All relevant data, generally variables listed above by treatment and track.
- Subject General medical history will be listed by treatment and track
- Subject abnormal baseline physical exam results will be listed by treatment and track

7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed. Analyses in this section will be performed on the All Treated Subjects "as treated". Extent of Exposure will be assessed separately for treatment and retreatment.

7.4.1 Study Therapy

Summary:

Descriptive statistics will be provided by study medication, treatment (treatment and retreatment) and track for the following.

- Number of doses, if appropriate
- Duration of therapy (days) = last dose date - first dose date + XX
- Cumulative dose (unit)= the sum of all actual doses that a subject received
- Dose intensity (unit) = cumulative dose/duration of therapy
- Relative dose intensity (%) = (dose intensity / planned dose)*100
  - Categories: <50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

Exposure parameter derivation for each treatment are show in Table 7.4.1-1, Table 7.4.1-2, Table 7.4.1-3, Table 7.4.1-4 and Table 7.4.1-5. More Tables will be added with new treatments added into the study through sub-protocol.

Table 7.4.1-1: Study Therapy Parameter Definitions - Nivolumab Monotherapy

	Nivolumab
Dosing Schedule per Protocol	240 mg every 2 weeks
Cumulative Dose	Cum Dose (mg) is the 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 + 14) × (240/14)]} × 100
Duration of Therapy	Last dose date - Start dose date +14

Note: Last dose date, Start dose date, Cumulative dose will be chosen/derived for corresponding treatment periods (treatment, retreatment).

Table 7.4.1-2: Study Therapy Parameter Definitions - Nivolumab + Dasatinib

	Nivolumab	**Dasatinib**
Dosing Schedule per Protocol	240 mg every 2 weeks	100 mg QD
Cumulative Dose	Cum Dose (mg) is the sum of the doses (mg) administered to a subject during the treatment period.	

Table 7.4.1-2: Study Therapy Parameter Definitions - Nivolumab + Dasatinib

	Nivolumab	Dasatinib
Relative Dose Intensity (%)	{Cum dose (mg)/[(Last dose date - Start dose date + 14) × (240/14)]} × 100	{Cum dose (mg)/[(Last dose date - Start dose date + 1) × (100)]} × 100
Duration of Therapy	Last dose date - Start dose date *+14*	Last dose date - Start dose date +1

Note: Last dose date, Start dose date, Cumulative dose will be chosen/derived for corresponding treatment periods (treatment, retreatment).

Table 7.4.1-3: Study Therapy Parameter Definitions - Nivolumab + BMS-986016

	Nivolumab	BMS-986016
Dosing Schedule per Protocol	240 mg every 2 weeks	20 mg every 2 weeks
Cumulative Dose	Cum Dose (mg) is the 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 + 14) × (240/14)]} × 100	{Cum dose (mg)/[(Last dose date - Start dose date + 14) × (20/14)]} × 100
Duration of Therapy	Last dose date - Start dose date +14	Last dose date - Start dose date +14

Note: Last dose date, Start dose date, Cumulative dose will be chosen/derived for corresponding treatment periods (treatment, retreatment).

Table 7.4.1-4: Study Therapy Parameter Definitions - Nivolumab + Ipilimumab

	Nivolumab	Ipilimumab
Dosing Schedule per Protocol	240 mg every 2 weeks	1 mg/kg every 6 weeks
Cumulative Dose	Cum Dose (mg) is the sum of the doses (mg) administered to a subject during the treatment period.	Cum Dose (mg/kg) is the sum of the total doses delivered (mg)/weight (kg) to a subject during the treatment period.
Relative Dose Intensity (%)	{Cum dose (mg)/[(Last dose date - Start dose date + 14) × (240/14)]} × 100	{Cum dose (mg/kg)/[(Last dose date - Start dose date + 42) × (1/42)]} × 100
Duration of Therapy	Last dose date - Start dose date +14	Last dose date - Start dose date +42

Note: Last dose date, Start dose date, Cumulative dose will be chosen/derived for corresponding treatment periods (treatment, retreatment).

Table 7.4.1-5: Study Therapy Parameter Definitions - Nivolumab + BMS-986205

	Nivolumab	BMS-986205
Dosing Schedule per Protocol	480 mg every 4 weeks	100 mg QD
Cumulative Dose	Cum Dose (mg) is the sum of the doses (mg) administered to a subject during the treatment period.	

Table 7.4.1-5: Study Therapy Parameter Definitions - Nivolumab + BMS-986205

	Nivolumab	BMS-986205
Relative Dose Intensity (%)	{Cum dose (mg)/[(Last dose date - Start dose date + 28) × (480/28)]} × 100	{Cum dose (mg)/[(Last dose date - Start dose date + 1) × (100)]} × 100
Duration of Therapy	Last dose date - Start dose date +28	Last dose date - Start dose date +1

Note: Last dose date, Start dose date, Cumulative dose will be chosen/derived for corresponding treatment periods (treatment, retreatment).

Listing:

- Drug administration of study medication
- Duration of therapy, cumulative dose, and relative dose intensity, etc.

Figure:

- Kaplan-Meier curve of Duration of treatment by treatment/retreatment under each track. Median duration of treatment and associated 95% CI will be provided.

7.4.2 Modification of Study Therapy

Summary:

The following will be provided by treatment and Track.

- Number (%) of subjects with dose delay with the reason, number of dose delayed per subject, Number (%) of subjects with omission with the reason
- Number (%) of subjects with dose reduction with reason, number (%) of subjects with a dose reduction to dose level -1 and dose level -2 (dasatinib and BMS-986205 specific)
- Infusion related modification (nivolumab, BMS-986016 and ipilimumab specific)
  - Number (%) of subjects with at least one infusion interruption along with the reason
  - Number of infusion interruptions per subject
  - Number (%) of subjects with at least one IV infusion rate reduction along with the reason
-

Listing:

- All relevant information on dose modification listed above
-

[redacted]

7.5 Efficacy

The primary efficacy analyses will be performed on All Treated Subjects. All analysis listed below will be performed for treatment period. Some of the analysis may be performed for retreatment period if deemed appropriate. Treatment under each track for different population will be analyzed independently. Treatment across tracks may be combined for exploratory analysis if appropriate. Subjects re-randomized into Track 3 or 5 will be combined with subjects originally randomized into Track 3 or 5 for primary efficacy analyses. Sub-group analysis of re-randomized subjects in Track 3 or 5 may be performed. After implementation of Master Protocol Amendment 5, enrollment to Track 1, 2, and 3 were ceased. Due to design change, the following treatment groups may be pooled together for efficacy analysis: Treatment under Track 2 (PD-L1 -) may be pooled with Track 4 PD-L1- treatment group.

Specific efficacy analyses to be performed for each track are shown in Table 7.5-1

Table 7.5-1: Analyses Planned for Each Track

Track	Situation	ORR	TTR	DOR	PFSR	OS
Track 1, 2, 3 and 5	End of stage 1, 2, or end of study	X	X	X	X	X
	Early termination at stage 1 or early termination of track/treatment					
Track 4	End of stage 1 and 2	X	X	X	X	X
	Early termination at stage 1				X	X

The following outputs related to ORR, [redacted], DOR, PFS and [redacted] will be produced accordingly.

Summary:

The following will be summarized by treatment under each Track or across Tracks. Summary will also be done by PD-L1 status under Track 4.

- ORR with corresponding 2-sided 95% CI along with each category of BOR

- DOR with median (95% CI) and range (min, max). The number of subjects still in response at the time of database lock will be indicated. This summary includes responders (BOR of CR or PR) only
- [redacted]
- PFSR at specified timepoints (Week 24)
- [redacted]
- [redacted]

Figure:

- Percent change from baseline in target lesions (aka spider plot)
- Maximum reduction in baseline target lesions (aka waterfall plot)
- K-M plot of DOR for responders only
- Swimmer plot of [redacted], DOR, and [redacted] for responders only
- K-M plot of PFS
- [redacted]

Listing:

The following will be listed by treatment under each Track.

- Tumor lesion measurements
- Tumor evaluation at each visit
- Subject level efficacy for all treated subjects- tumor best overall response (BOR), maximum response in tumor burden, PFS
- Duration of response for responders - BOR, [redacted], response duration, [redacted]
- [redacted]

[redacted]

[redacted]

7.5.2 Additional Analyses for Track 1.b and 2

Due to early termination of Track 1 and 2 through Master Protocol amendment 5, the analysis specified in this section for Track 1.b and 2 will not be performed as originally planned.

A descriptive odds ratio and estimate of the difference in ORRs, along with corresponding two-sided 95% CIs will be provided to evaluate difference between the 2 randomized arms (combination arm and nivolumab arm) at the end of each stage by Track.

A descriptive hazard ratio and corresponding two-sided 95% CIs of PFS and OS will be estimated in a Cox proportional hazard model using treatment as a single covariate to evaluate difference between the two arms at the end of each stage by Track.

Subset analyses of efficacy using the factors specified in Section 7.5.1 may be explored. The odds ratio of ORR and corresponding 95% CI may be presented for each subgroup in a forest plot. Forest plots of PFS and OS hazard ratios (along with 95% CI) may be produced for each level of the subgroups.

[redacted]

7.6 Safety

Analysis of safety will be based on All Treated Subjects, if not otherwise specified, and presented by treatment ("as treated") under each Track or combined across Tracks.

Adverse events (AEs) will be coded according to the most current version of MedDRA and be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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 =”Drug was discontinued”.

Listing of adverse events will include all enrolled subjects as SAEs and deaths are collected pretreatment. Summaries of adverse events will include all on-treatment adverse events as defined in Section 6.1. Adverse events occurring after treatment or retreatment will be summarized separately.

When reporting adverse events by CTC grade, summary tables will be provided based on the event with worst CTC grade. In the AE summary tables, unless otherwise specified, subjects will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the ‘Total subject’ row at their worst CTC grade, regardless of SOC or PT. The AE tables will list the SOCs (ordered by descending frequency) and PTs (ordered by descending frequency within each SOC) for each treatment group.

Analyses that take into account the multiple occurrences of a given adverse event will be conducted (see Section 7.6.9). To prepare these analyses, the CRF data will be processed according to standard BMS algorithms[7] in order to collapse adverse event records into unique records based on the preferred term. This 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. When specified the 95% CI of the rate per 100 person-year of exposure will be derived using normal approximation and variance estimation proposed in Cook and Lawless[8].

The analysis of laboratory results will be based on All Treated Subjects. Laboratory results will be categorized according to NCI CTCAE (version 4.03) grade. Summaries of laboratory results include baseline and on-treatment results as defined in Section 6.1. Clinical laboratory data will be first analyzed using US conventional units. Analyses will be repeated using International System of Units (SI).

7.6.1 Deaths

- **Summary**:

All deaths during the study will be summarized for cause of deaths by treatment under each Track or combined across Track. Death will be summarized under the most recent study treatment and track prior to death.

In addition, death within 100 days of last dose of treatment or last dose of re-treatment will be summarized for cause of deaths.

- **Listing**:

All recorded deaths for All Enrolled subjects will be listed by treatment under each Track. Death will be listed under the most recent study treatment and track prior to death. Death date, cause of

death, study treatments (start/stop date) (including all prior and current study treatments), days since last dose, and days since first dose of study drug will be included in the listing.

7.6.2 Serious Adverse Events

Serious adverse events will be summarized by treatment under each Track or combined across Tracks.

- **Summary**:
- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT
- • Overall summary of drug-related SAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT
- **Listing**:

By-subject SAE listing will be provided for the All Enrolled Subjects.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

Adverse events leading to study drug discontinuation will be summarized by treatment under each Track or combined across Tracks.

Summary:

- Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT

Listing:

- By-subject AEs leading to discontinuation listing will be provided.

7.6.4 Adverse Event Leading to Dose Reduction (Dasatinib and BMS-986205 specific)

- Adverse events leading to dasatinib or BMS-986205 dose reduction will be summarized for nivolumab + dasatinib or nivolumab + BMS-986205 treatment under each Track or combined across Tracks.

Summary:

- Overall summary of AEs leading to dose reduction by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT

Listing:

- By-subject AEs leading to dose reduction listing will be provided.

7.6.5 Adverse Event Leading to Dose Delay

- Adverse events leading to dose delay will be summarized by treatment under each Track or combined across Tracks.

Summary:

- Overall summary of AEs leading to dose delay by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT

Listing:

- By-subject AEs leading to dose delay listing will be provided.
-

7.6.6 Overall Adverse Events

- Adverse events will be summarized by treatment under each Track or combined across Tracks.

Summary:

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT
- Overall summary of drug-related AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT
- Overall summary of any AEs that required immune modulating medication by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT
- **Listing**:
  - All recorded Adverse Events will be listed.
  - By-subject listing of AEs requiring immune modulating concomitant medication will be provided.

7.6.7 Select Adverse Event

Unless otherwise specified, analyses will be performed by select AE category. Some analyses may also be repeated by subcategory of endocrine events (Table 10.1-1)

7.6.7.1 Incidence of Select AE

Selected AE will be summarized by treatment group under each Track or combined across Tracks for each category/subcategory:

Summary:

- Overall summary of any select AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any drug-related select AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any serious select AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any drug-related serious select AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any select AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any drug-related select AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT

Listing:

- By subject select AEs listing will be provided.

7.6.7.2 Time to Onset of Select AE

Time to onset of the following specific events will be graphically displayed for each category/subcategory of select AE using the Kaplan-Meier technique:

- Time to onset of any grade select AE by treatment under each Track or across Tracks
- Time to onset of grade 3-5 select AE by treatment under each Track or across Tracks
- Time to onset of any grade drug-related select AE by treatment under each Track or across Tracks
- Time to onset of grade 3-5 drug-related select AE by treatment under each Track or across Tracks

Rates (derived from the graph) by landmark time points will be tabulated for these specific events and for each treatment under each Track or across Tracks.

Additional details regarding the time to onset definition and censoring rules are described in Section 10.1.1.

[redacted]

7.6.8 Immune Mediated Adverse Events (IMAE)

Immune Mediated Adverse Events consist of a list of preferred terms grouped by specific category (see Table 10.2-1) 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 IMAEs. The IMAEs and the categories are defined by the Sponsor and the list that is the most current at the time of analysis will be used. Changes may be made to this list with each

new version of MedDRA prior to database lock. Categories of IMAEs may include subcategories (e.g. adrenal disorders, diabetes, pituitary disorders, and thyroid disorders are subcategories of the endocrine event category).

Unless otherwise specified, analyses will be performed by IMAE category. Some analyses may also be repeated by subcategory of endocrine events.

7.6.8.1 Incidence of IMAE

IMAE will be summarized by treatment under each Track and across Tracks.

Summary:

- Overall summary of any IMAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any drug-related IMAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any serious IMAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any drug-related serious IMAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any IMAEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- Overall summary of any drug-related IMAEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by Category or subcategory/PT
- **Listing**:

By subject IMAE listing will be provided.

7.6.8.2 Time to Onset of IMAE

Time to onset of the following specific events will be graphically displayed for each category/subcategory of IMAE using the Kaplan-Meier technique:

- Time to onset of any grade IMAE by treatment under each Track or across Tracks

Additional details regarding the time to onset definition and censoring rules are described in time to onset definition subsection of Section 10.1.1

[redacted]

[redacted]

7.6.9 Multiple Events

Summary:

Analysis may be performed by treatment and retreatment separately. The following summary tables will be provided:

- Total number and rate (exposure adjusted, ie, patient-year event rate) of occurrences for all AEs
- For Select and/or IMAE AEs:
  - The number of subjects experiencing an AE once or multiple times by treatment arm under each track or across tracks

Listing:

- Unique instances of all AEs, ie, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (ie, same PT) have been collapsed.

7.6.10 Clinical Laboratory Evaluations

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test.

The following laboratory tests will be included for the analysis:

- Hematology: hemoglobin (HB), platelets, white blood counts (WBC), absolute neutrophils count (ANC) and lymphocyte count (LYMPH).
- Serum chemistry: ALT, AST, alkaline phosphatase (ALP), total bilirubin and creatinine
- Electrolytes: sodium (high and low), potassium (high and low), calcium (high and low), magnesium (high and low).

Summary:

The number (%) of subjects with the following will be summarized by treatment under each Track or combined across Track, using the worst CTC grade on-treatment (as defined in section 6.1) per subject.

- Post-baseline grade
- Grade change from baseline
- Descriptive statistics of laboratory test result and their changes from baseline by treatment and study day

Listing:

- A by-subject listing of these laboratory parameters will be provided. Laboratory abnormality criteria and laboratory results outside of normal range will be listed.

7.6.10.1 Abnormal Hepatic Test

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations (as defined in Section 6.1) will be summarized by treatment under each Track or combined across Track:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 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

Figure:

- Scatter plot of Total bilirubin peak vs AST peak
- Scatter plot of Total bilirubin peak vs ALT peak

On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

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

7.6.10.2 Abnormal Thyroid Test

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations (as defined in Section 6.1) will be summarized by treatment under each Track or combined across Track:

- TSH value > ULN and
  - With baseline TSH value ≤ ULN
  - At least one T3/T4 test value < LLN
- Low TSH < LLN and
  - With baseline TSH value ≥ LLN
  - At least one T3/T4 test value > ULN
- **Listing**:

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

7.6.11 Vital Signs and Other Safety Evaluation

Listing:

- Vital signs
- pulse oximetry (i.e. % oxygen saturation)
- ECG measures
  - Individual QTcF, PR, QRS or ΔQTcF values will be listed.
- ECG abnormalities
- Diagnostic procedures

- Medical treatment procedures

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8 CONVENTIONS

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

AE onset date following Adverse Event Domain Requirements Specification[9]

AE resolution/end date (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 day and month are missing or a date is completely missing, it will be considered as missing

Non-study medication date following Non-Study Medication Domain Requirements Specification[10]

Death date

- 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 date alive and the maximum will be considered as the death date.
- If month or the year is missing, the death date will be imputed as the last known date alive. If the date is completely missing but the reason for death is present (as in death module of CRF) the death date will be imputed as the last known date alive.

Disease progression date

- 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
- 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.

Other partial date, the following conventions may be 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., duration response, time to response, etc) will be calculated as follows:

Duration = (Last date - first date +1)

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in final Clinical Study Report(s) (per data availability). Multiple Clinical Study Reports may be produced depending on the maturity of different treatment arm under each Track. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 OTHER INFORMATION

10.1 Select Adverse Events Definition And Conventions

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories) and by subcategory (e.g. thyroid disorders, diabetes, pituitary, adrenal disorders subcategories). These categories and subcategories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Also changes may be made to this list with each new version of MedDRA.

For information, the select adverse events defined at the time of finalization of the first version of the document are listed in Table 10.1-1 using MedDRA version 18. The final list used for the clinical study report will be included in an Appendix of the CSR.

Table 10.1-1: Select Adverse Event

Category	Subcategory	Preferred Terms
Endocrine Adverse Event	ADRENAL DISORDER	ADRENAL INSUFFICIENCY
		ADRENAL SUPPRESSION
		BLOOD CORTICOTROPHIN DECREASED
		BLOOD CORTICOTROPHIN INCREASED
		HYPOTHAIAMIC PITUITARY ADRENAL AXIS SUPPRESSION
		SECONDARY ADRENOCORTICAL INSUFFICIENCY
	DIABETES	DIABETES MELLITUS
		DIABETIC KETOACIDOSIS
		LATENT AUTOIMMUNE DIABETES IN ADULTS
	PITUITARY DISORDER	HYPOPHYSITIS
	THYROID DISORDER	AUTOIMMUNE THYROIDITIS
		BLOOD THYROID STIMULATING HORMONE DECREASED

Table 10.1-1: Select Adverse Event

Category	Subcategory	Preferred Terms
		BLOOD THYROID STIMULATING HORMONE INCREASED
		HYPERTHYROIDISM
		HYPOTHYROIDISM
		THYROID FUNCTION TEST ABNORMAL
		THYROIDITIS
		THYROIDITIS ACUTE
		THYROXINE DECREASED
		THYROXINE FREE DECREASED
		THYROXINE FREE INCREASED
		THYROXINE INCREASED
		TRI-IODOTHYRONINE INCREASED
Hypersensitivity/Infusion Reactions		ANAPHYLACTIC REACTION
		ANAPHYLACTIC SHOCK
		BRONCHOSPASM
		HYPERSENSITIVITY
		INFUSION RELATED REACTION
Gastrointestinal Adverse Events		COLITIS
		COLITIS ULCERATIVE
		DIARRHOEA
		ENTERITIS
		ENTEROCOLITIS
		FREQUENT BOWEL MOVEMENTS
		GASTROINTESTINAL PERFORATION
Hepatic Adverse Event		ACUTE HEPATIC FAILURE
		ALANINE AMINOTRANSFERASE INCREASED
		ASPARTATE AMINOTRANSFERASE INCREASED
		AUTOIMMUNE HEPATITIS
		BILIRUBIN CONJUGATED INCREASED
		BLOOD ALKALINE PHOSPHATASE INCREASED
		BLOOD BILIRUBIN INCREASED
		DRUG-INDUCED LIVER INJURY
		GAMMA-GLUTAMYLTRANSFERASE INCREASED

Table 10.1-1: Select Adverse Event

Category	Subcategory	Preferred Terms
		HEPATIC ENZYME INCREASED
		HEPATIC FAILURE
		HEPATITIS
		HEPATITIC ACUTE
		HEPATOTOXICITY
		HYPERBILIRUBINAEMIA
		LIVER DISORDER
		LIVER FUNCTION TEST ABNORMAL
		LIVER INJURY
		TRANSAMINASES INCREASED
Pulmonary Adverse Events		ACUTE RESPIRATORY DISTRESS SYNDROME
		ACUTE RESPIRATORY FAILURE
		INTERSTITIAL LUNG DISEASE
		LUNG INFILTRATION
		PNEUMONITIS
Renal Adverse Events		BLOOD CREATININE INCREASED
		BLOOD UREA INCREASED
		CREATININE RENAL CLEARANCE DECREASED
		HYPERCREATININAEMIA
		NEPHRITIS
		NEPHRITIS ALLERGIC
		NEPHRITIS AUTOIMMUNE
		RENAL FAILURE
		RENAL FAILURE ACUTE
		RENAL TUBULAR NECROSIS
		TUBULOINTERSTITIAL NEPHRITIS
		URINE OUTPUT DECREASED
Skin Adverse Events		BLISTER
		DERMATITIS
		DERMATITIS EXFOLIATIVE
		DRUG ERUPTION
		ECZEMA
		ERYTHEMA

Table 10.1-1: Select Adverse Event

Category	Subcategory	Preferred Terms
		ERYTHEMA MULTIFORME
		EXFOLIATIVE RASH
		PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME
		PHOTOSENSITIVITY REACTION
		PRURITUS
		PRURITUS ALLERGIC
		PRURITUS GENERALISED
		PSORIASIS
		RASH
		RASH ERYTHEMATOUS
		RASH GENERALISED
		RASH MACULAR
		RASH MACULO-PAPULAR
		RASH PAPULAR
		RASH PRURITIC
		SKIN EXFOLIATION
		SKIN HYPOPIGMENTATION
		SKIN IRRITATION
		STEVERNS-JOHNSON SYNDROME
		TOXIC EPIDERMAL NECROLYSIS
		URTICARIA
		VITILIGO

Source: MedDRA version 18

10.1.1 Time to Onset Definition

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

If the subject did not experience a select AE (of any grade) in the category, time-to onset will be censored at the maximum follow-up time of all subjects in their respective treatment group (i.e. for subjects without an event, follow-up time is defined from first dosing date up to last dosing date +100 days or first dose date of retreatment/re-randomized treatment, whichever is earliest, if subjects are off treatment and followed for at least 100 days or started retreatment/re-randomized

treatment) , otherwise it is defined up to the last known alive date). The resulting Kaplan-Meier plot will represent the cumulative rate of the select AE (any grade) in the category over time.

Time-to onset of select AE (grade 3-5) for a specific category is defined similarly but restricted to grade 3-5 select AEs.

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

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

[redacted]

[redacted]

10.2 Immune Mediated Adverse Events Definition and Conventions

The Immune Mediated Adverse Events (IMAE) consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories). These categories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Also changes may be made to this list with each new version of MedDRA.

For information, the IMAE defined at the time of finalization of the first version of the document are listed in Table 10.2-1 using MedDRA version 18. The final list used for the clinical study report will be included in an Appendix of the CSR.

Table 10.2-1: Immune-Mediated Adverse Event Definition

Category	Preferred Terms
ADRENAL INSUFFICIENCY	ADRENAL INSUFFICIENCY
DIABETES MELLITUS	DIABETES MELLITUS
	DIABETIC KETOACIDOSIS
DIARRHEA/COLITIS	COLITIS
	DIARRHOEA
	ENTEROCOLITIS
HEPATITIS	ALANINE AMINOTRANSFERASE INCREASED

Table 10.2-1: Immune-Mediated Adverse Event Definition

Category	Preferred Terms
	ASPARTATE AMINOTRANSFERASE INCREASED
	AUTOIMMUNE HEPATITIS
	BLOOD ALKALINE PHOSPHATASE INCREASED
	BLOOD BILIRUBIN INCREASED
	HEPATITIS
	HEPATITIS ACUTE
	HEPATOTOXICITY
	HYPERBILIRUBINAEMIA
HYPERSENSITIVITY	HYPERSENSITIVITY
	INFUSION RELATED REACTION
HYPERTHYROIDISM	HYPERTHYROIDISM
HYPOTHYROIDISM/THYROIDITIS	AUTOIMMUNE THYROIDITIS
	HYPOTHYROIDISM
	THYROIDITIS
	THYROIDITIS ACUTE
NEPHRITIS AND RENAL DYSFUNCTION	BLOOD CREATININE INCREASED
	NEPHRITIS
	NEPHRITIS ALLERGIC
	RENAL FAILURE
	RENAL FAILURE ACUTE
	TYBULOINTERSTITIAL NEPHRITIS
PNEUMONITIS	INTERSTITIAL LUNG DISEASE
	PNEUMONITIS
RASH	RASH
	RASH MACULO-PAPULAR
THYROIDITIS	AUTOIMMUNE THYROIDITIS
	THYROIDITIS
	THYROIDITIS ACUTE

11 DOCUMENT HISTORY

Table 11-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Initial version -Mar-2016

Table 11-1: Document History

Version Number	Author(s)	Description
2.0	[redacted]	Incorporate Master Protocol amendment 2,3 and 4, incorporate Sub Protocol A amendment 1 and 2 (with addition of nivolumab + ipilimumab combination arm)
3.0	[redacted]	Incorporate Master Protocol amendment 5 and incorporate Sub Protocol B

[redacted]