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Clinical Protocol CA018001

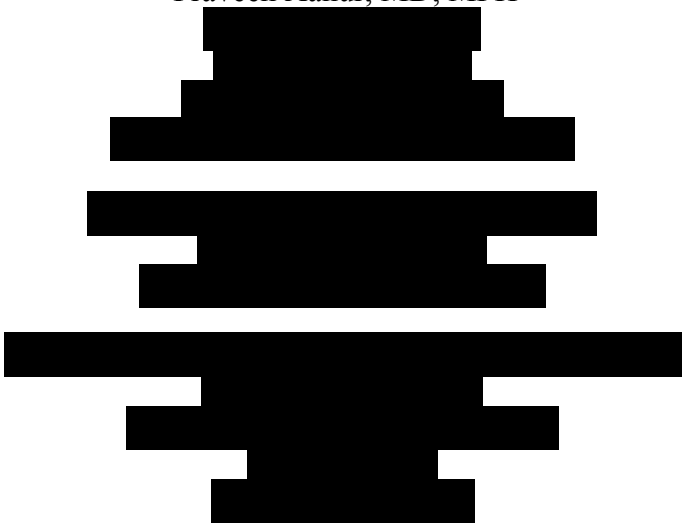
A Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Subjects with Advanced Non-small Cell Lung Cancer (FRACTION-Lung)

Revised Lung Master Protocol: 07

Incorporates Administrative Letter: 01

Study Director / Medical Monitor

Praveen Aanur, MD, MPH



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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 07	22-Apr-2019	Removed option to retreat after follow-up begins and removed Response/Survival Follow-up periods. Inclusion criteria 2) c) ii) and 2) c) iii) were deemed no longer applicable and inclusion criterion 2) c) iv) was added. Additional research retention was aligned throughout the protocol. [redacted] Appendix 04 (Revised Protocol Summary of Change History) was added. Language (Inclusion Criteria, WOCBP, Adverse Events, Pregnancy) was updated to align with the current BMS Protocol Model Document.
Administrative Letter 01	13-Nov-2019	Study Director/Medical Monitor was updated. Clarification was made that during screening of patients for Track 4, the results of the PD-L1 testing must be obtained by the site prior to randomization and communicated to the study team; study team will inform the site if randomization may occur.
Revised Protocol 06	12-Apr-2018	Removed stratification by PD-L1 expression in Track 4 and introduced the option of new randomization schedules in Sub-Protocols. Two-stage design may be used in Track 5, as opposed to a single-stage design, based on specific Sub-Protocols. Emphasis added to direct readers to Sub-Protocols for additional inclusion and exclusion criteria including the following: inclusion criteria 1c and 3. Emphasis added to direct readers to Sub-Protocols for additional statistical considerations. Inclusion criteria 2.c.i was modified to note that EGFR testing must be performed using tumor tissue. Urinalysis added to the screening and the baseline for retreatment/re-randomization procedural outlines. Added clarification that death resulting from disease progression within 100 days of discontinuation of dosing must be reported as an SAE within 24 hours. Minor formatting and typographical corrections.
Revised Protocol 05	16-Feb-2017	Incorporates Amendment 05
Amendment 05	16-Feb-2017	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. 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. Updated data from the literature regarding anti-PD-1 and other targeted therapies. 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). Added sample size determination for Tracks 4 and 5 and simplified sample size determination for Tracks 1, 2, and 3. Added assessment schedule for retreatment/re-randomization in place of existing footnote, for clarity. Additionally, minor clarifications and typographical errors have also been made throughout the document.
Revised Protocol 04	13-Oct-2016	Incorporates Amendment 04
Amendment 04	13-Oct-2016	Removed the Treatment Procedural Outline tables (previously Table 5.1-2 and Table 5.1-3) and added to Sub-Protocol A. Updated exclusion criteria to clarify all subjects with active CNS metastases are excluded. Clarified prohibition of concurrent neoplastic treatment. Corrected typographical errors and made minor clarifications also.

Document	Date of Issue	Summary of Change
Revised Protocol 03	21-Sep-2016	Incorporates Amendment 03
Amendment 03	21-Sep-2016	Updated to include Management Algorithms for Immuno-Oncology Agents (Appendix 3) that were not included in Revised Protocol 02.
Revised Protocol 02	27-Jul-2016	Incorporates Amendment 02
Amendment 02	27-Jul-2016	Updated to remove requirement for platinum based chemotherapy as one of the prior treatments for Tracks 1 and 2. Removed the option for less effective methods of birth control. The exclusion criteria for patients with CNS metastases was clarified. Section 3.5.1 was updated to remove the prohibition of receptor activator of nuclear kappa-B ligand inhibitors or bisphonates. The term "Pretreatment AEs" was changed to "Assessment of Baseline Signs and Symptoms". Figure 8.1.3-1 was updated to fix a typographical error in the Stage 2 number of subjects (changed 15 to 23). Corrected typographical errors and made minor clarifications also.
Revised Protocol 01	08-Apr-2016	Incorporates Amendment 01
Amendment 01	08-Apr-2016	Updated the statistical study design from a 2-stage design to a 4 stage design. Additionally, updates were made to the study design figures and tables to clarify retreatment and re-randomization options, including the procedures required for re-baselining prior to re-randomization and re-treatment. [redacted] Corrected typographical errors and made minor clarifications. also
Original Protocol	10-Feb-2016	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 07:

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	The text in the synopsis was updated.	[redacted]
Section 3.1.1 FRACTION-Lung Track 4 (Naïve) and 5 (Experienced) Design	Removal of option of retreatment for subjects with CR, PR, or SD who enter study follow up.	[redacted]
Section 3.1.1 FRACTION-Lung Track 4 (Naïve) and 5 (Experienced) Design, Figure 3.1.1-1 Track 4 and 5 Study Design	The option in the study schematic to "re-treat with current assigned study treatment, 1 time only (additional 6 cycles/24 weeks)" once the subject enters follow-up was removed. Note b was adjusted to remove reference to Response and Survival Follow-up periods. Note d was adjusted to remove retreatment options after progression once in follow-up.	[redacted]
Section 3.2 Study Phases	Updated the number of phases of the study from 4 to 3 and removed reference to response/survival follow-up and re-treatment.	[redacted]
Section 3.2.3.1 Safety Follow-up Section 3.6 Discontinuation of Subjects Following any Treatment with Study Drug Section 5.1 Flow Chart/Time and Events Schedule Section 5.3 Safety Assessments	Section was updated to remove reference to retreatment.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2.3.2 Response Follow-up Section 3.2.3.3 Survival Follow-up Section 3.2.3.4 Retreatment During Survival Follow-up	Sections were removed.	[redacted]
Section 3.4.1 Inclusion Criteria	The following 2 inclusion criteria were deemed no longer applicable: Inclusion Criterion 2) c) ii) If tested for ALK translocations, use of an approved test is strongly encouraged. Inclusion Criterion 2) c) iii) Subjects with unknown or indeterminate ALK status may be enrolled. These criteria were replaced with Criterion 2) c) iv) "**All subjects with nonsquamous histology must have been tested for ALK rearrangements. Use of an approved test is strongly encouraged**."	[redacted]
Section 3.4.1 Inclusion Criteria	Inclusion criteria 3 e) was modified to include fetal protection language as well as language clarifying that azoospermeric males are exempt from contraceptive requirements **unless the potential exists for fetal toxicity due to study drug being present in seminal fluid, even if the participant has undergone a successful vasectomy or if the partner is pregnant.**	[redacted]
Section 3.4.1 Inclusion Criteria	Addition of language: Investigators shall counsel WOCBP, and male subjects who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy **and when applicable, the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.**	[redacted]
Section 3.4.1 Inclusion Criteria	Additional details were added to the "Highly Effective Methods of Contraception." "Less than Highly Effective Methods of Contraception" were added. It was clarified that "**Male participants with female partners of childbearing potential are eligible to participate if they agree to inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.**"	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.4.3 Women of Child Bearing Potential	A detailed description of women who are NOT of childbearing potential was added and the definition of "menopause" was replaced with the definition of "a postmenopausal state."	[redacted]
Section 3.7 Post Study Drug Follow-up	Section was updated to remove reference to survival follow-up and indicate that subjects will be followed through **Safety** follow-up. Reference to retreatment was also removed.	[redacted]
Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1-2	Table title was updated to remove reference to retreatment. Procedure for "Subject Registration" was updated to remove reference to retreatment. Procedure note for "Physical Examination" was updated to remove reference to retreatment. Procedure note for "Mandatory Pretreatment Tumor Biopsy" was updated to remove reference to retreatment.	[redacted]
Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1-3	Column "Response/Survival Follow-up" was removed from the table. Procedure "Tumor Assessment" was shifted from Response/Survival Follow-up to Safety FU 3 (100 Days). Note b was removed.	[redacted]
Section 5.4 Efficacy Assessments	Section was updated to remove the performance of assessments "every 12 weeks during the response follow-up (subjects with CR, PR, or SD at study drug discontinuation)" and add the performance of assessments **at the end of the follow-up period**.	
Section 5.4.3 Exploratory Efficacy Assessments	Section was updated to change collection of OS data from "up to 5 years from subject's last dose" to **"the Safety Follow-up period."**	
Section 5.7 Outcomes Research Assessments	Section was updated to change collection of EQ-5D from the "Survival" Follow-Up phase to the "**Safety**" Follow-Up phase.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.10 Additional Research Collection	Additional research retention was updated from "mandatory" to "**encouraged**."	[redacted]
Section 6 Adverse Events	"Events Meeting the AE Definition" were added. "Events Not Meeting the AE Definition" were added. The brief causal relationship description was removed and replaced with "Assessment of Causality." In addition, prevention of reporting bias was removed and replaced with the following description: "**Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol**." Finally, language was added clarifying that if an event does not meet the definition of an AE, then it cannot be an SAE even if serious conditions are met.	[redacted]
Section 6.1 Serious Adverse Events	The following language was removed "Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs" and replaced with **"Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs."**	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.4 Pregnancy	Language was updated to indicate that continuation or reintroduction of study treatment in a pregnant subject must be discussed with the Medical Monitor. If pregnancy has ended and is confirmed, treatment may resume with proper approvals. Language was added to indicate that the female partner of a male participant must sign an informed consent form for pregnancy surveillance information to be collected. Fetal toxicity language was added: **In cases where a study drug can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (e.g. vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.**	[redacted]
Section 8.3.1 Primary Endpoints	Tumor assessments were updated to conclude at the completion of the safety follow-up period. Reference to retreatment therapy was removed.	[redacted]
Appendix 03	[redacted]	[redacted]
Appendix 04	Appendix 04 Revised Protocol Summary of Change History was added.	

SYNOPSIS

Clinical Protocol CA018001

Protocol Title: 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)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Specific IPs are listed in each FRACTION-Lung Sub-Protocol.

Specific dosing and treatment regimens for each FRACTION-Lung treatment combination and/or nivolumab monotherapy are outlined in each FRACTION-Lung Sub-Protocol.

Protocol-specified assessments are described in Table 5.1-1 (Screening Procedural Outline) and Table 5.1-3 (Follow-up Procedural Outline). Procedures for Re-Randomization are listed in Table 5.1-2 (Baseline for Re-randomization Procedural Outline). Treatment Phase procedures are described in each FRACTION-Lung Sub Protocol.

Follow Up visits at Days 30, 60, and 100 (+/- 7 days) should occur after the last dose of study drug or coinciding with the date of discontinuation 30 days, if date of discontinuation is greater than 30 days after the last dose, to monitor for AEs.

Approximately 1200+ subjects are expected to be treated over a 3 to 5 year period.

Study Phase: 2

Research Hypothesis: We hypothesize that combination of IO agents will demonstrate improved efficacy in subjects with recurrent NSCLC.

Objectives: The overall FRACTION-Lung study-wide objectives are presented in the following sections. Any changes to these objectives for specific treatments are specified in each FRACTION-Lung Sub-Protocol.

The primary objective is to assess the efficacy (objective response rate [ORR], duration of response [DOR], and progression-free survival rate [PFSR] at 24 weeks) of each FRACTION-Lung treatment combination in subjects with NSCLC.

The secondary objective is to investigate additional safety and tolerability of each FRACTION-Lung treatment combination in subjects with NSCLC.

Study Design: The FRACTION-Lung Master Protocol is a rolling, Phase 2, adaptive study that will evaluate the preliminary efficacy, safety, tolerability, PK, and pharmacodynamics of novel treatment combinations which will be described in FRACTION-Lung Sub-Protocols.

The initial Sub-Protocol for FRACTION-Lung (nivolumab [BMS-936558] in combination with dasatinib [BMS-354825], nivolumab in combination with BMS-986016 (anti-LAG-3 mAb) and, and nivolumab in combination with ipilimumab) will be described in the FRACTION-Lung Sub-Protocol A.

The FRACTION-Lung study has been designed for Recurrent NSCLC subjects.

Subjects will be enrolled into 1 of 2 tracks based on their previous exposure to PD-1/PD-L1 treatment (experienced or naïve).

Subjects will be enrolled in 1 of 2 tracks. Subjects who have not had prior anti-PD-1/PD-L1 therapy will be assigned to Track 4. Subjects who have had prior anti-PD-1/PD-L1 therapy will be assigned to Track 5.

Treatment Phase is defined in cycles each of 4 weeks duration.

Tumor assessments will be conducted every 8 weeks (±1 week).

Details about track treatment are available in the protocol, Section 3.1.1.

Study Population:

In addition to the study-wide inclusion criteria noted in the FRACTION-Lung Sub-Protocols, which must be met for study participation, the following criteria are also required for participation.

1) Target Population
   a) Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.
   b) Subjects must have histologic or cytologic confirmation of NSCLC (per the seventh International Association for the Study of Lung Cancer [IASLC]) with squamous or nonsquamous histology that is advanced (metastatic and/or unresectable)
   c) Subjects with known EGFR mutations or ALK rearrangements must have received EGFR or ALK inhibitors, respectively, prior to study entry.
   d) Track-specific eligibility criteria
      i) Track 4: Anti-PD-1/PD-L1 treatment-naïve subjects
         (1) Subjects must be naïve to PD-1/PD-L1 therapy.
      ii) Track 5: Anti-PD-1/PD-L1 treatment-experienced subjects
         (1) Subjects must have had progressive or recurrent disease during or after anti-PD-1 or anti-PD-L1 therapy and, in the opinion of the investigator, must be unlikely to benefit from nivolumab monotherapy.
         (2) Subjects who have had prior treatment with 1 of the agents (or any other IO agent that is directed against the same target) in any combination regimen in a Sub-Protocol are eligible for treatment on Track 5.
         (3) Subjects who have had prior combination treatment with the same IO agents (or IO agents that are directed against the same target) as 1 of the combination regimens in a FRACTION-Lung Sub-Protocol are eligible for treatment on Track 5 but must be randomized to another IO combination regimen (as outlined in Section 3.4 Inclusion Criteria of each FRACTION-Lung Sub-Protocol).
      iii) Tracks 4 and 5
         (1) Subjects may have had up to 1 prior cytotoxic chemotherapy for advanced phase NSCLC.
            (a) Subjects enrolled in FRACTION-lung prior to implementation of Amendment 5 who are re-enrolling in Track 5 may have received 1 or more prior chemotherapies for progressive or recurrent disease.
            (b) Maintenance therapy does not count as an additional line of treatment.
         (2) Subjects should have been offered a platinum-based chemotherapy for NSCLC.
            (a) The platinum-based chemotherapy may have been in the adjuvant, neoadjuvant, or recurrent setting.

In addition to the study-wide exclusion criteria noted in the FRACTION-Lung Sub-Protocols, which must be met for participation, the following criteria are also required for participation.

1) Target Population
   a) Subjects must not have known EGFR mutations that are sensitive to available targeted inhibitor therapy.
   b) Subjects must not have known ALK translocations that are sensitive to available targeted inhibitor therapy.
   c) Subjects must not have active CNS metastases.

Study Drug: Includes both investigational [medicinal] products (IP/IMP) and non-investigational [medicinal] products (Non-IP/Non-IMP). Specific IPs are listed in each FRACTION-Lung Sub-Protocol.

Study Assessments:

AEs will be assessed continuously during the study and for 100 days after the last study drug treatment. AEs will be evaluated according to the NCI CTCAE Version 4.03 and should be followed per requirements in Sections 6.1.1 and 6.2.1 of the FRACTION-Lung Master Protocol. Subjects should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.

Changes in tumor measurements and tumor responses will be assessed by the investigator using RECIST v1.1 criteria, and the time point of tumor assessments will be reported on the CRF based on the investigator's assessment using RECIST v1.1 criteria.

Tumor assessments will be submitted to a third party radiology vendor on an ongoing basis; subject management is not dependent on third party review of tumor assessments.

[redacted]

The effects of lung cancer and its treatment on health status and quality of life will be assessed using the EQ-5D-3L and FLSI-12. Subjects will be asked to complete the EQ-5D and FLSI-12 during on-study clinic visits and the EQ-5D at designated visits during the Safety Follow-up Phase.

Statistical Considerations:

Sample Size: Tracks 1 through 4 include a Multi-Stage adaptive design with 12-70 subjects/treatment arm, and use the Simon and Fleming statistical plan that gives early strong evidence of efficacy or futility that may be used to terminate an arm. In Track 5, a single stage design with 35 subjects/treatment arm is used.

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.

Endpoints: The primary objective of preliminary efficacy will be measured by ORR, DOR, and PFSR at 24 weeks based on RECIST v1.1 criteria. Tumor response will be based on tumor assessments at screening, every 8 weeks from the first dose until investigator assessed initial disease progression (per RECIST v1.1) 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 safety follow-up, or until subjects withdraw from the study.

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

AEs and laboratory values will be graded according to the current version of the NCI CTCAE 4.0.3.

Analyses: The following analyses will be performed: demographics and baseline characteristics, efficacy analyses, safety analyses, [redacted], outcomes research analyses, other analyses, and interim analyses.

TABLE OF CONTENTS

[redacted]

1.3 Research Hypotheses

We hypothesize that combination of IO agents will demonstrate improved efficacy in subjects with recurrent NSCLC.

1.4 Objectives for FRACTION-Lung

The overall FRACTION-Lung study-wide objectives are presented in the following sections. Any changes to these objectives for specific treatments are specified in each FRACTION-Lung Sub-Protocol.

1.4.1 Primary Objective

- To assess the efficacy (ORR, duration of response [DOR], and progression-free survival rate [PFSR] at 24 weeks) of each FRACTION-Lung treatment combination in subjects with NSCLC

1.4.2 Secondary Objective

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

[redacted]

1.5 Overall Risk/Benefit Assessment

An overall risk/benefit assessment for each novel FRACTION-Lung treatment combination will be provided in each FRACTION-Lung Sub-Protocol.

1.5.1 Safety Monitoring on Study Therapy

Frequent safety assessments will be carried out by the Sponsor/BMS Medical Monitor (or designee) and investigators throughout the study to determine whether dose modification, additional safety measures, or termination of the combination arm, is required at any time. In addition, adverse events (AEs) and serious adverse events (SAEs) will be reviewed regularly by the BMS Medical Monitor (or designee) and the Pharmacovigilance group to look for trends and potential safety signals. Treatment of AEs will follow institutional guidelines and recommended management algorithms, as listed in the Investigator Brochures (IBs) and prescribing information, as applicable, for each combination agent, and provided as appendices to this protocol. Specific algorithms for the management of immune-related AEs are provided in Appendix 3 and are applicable to immune-related AEs for all FRACTION-Lung treatment combinations.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations (CFR), Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects, and any updates.

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

2.3 Informed Consent

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

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

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

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form(s) and any other information to be provided to the subjects, prior to the beginning of the study and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed informed consent form and, in the US, the subjects' signed Health Insurance Portability and Accountability Act Authorization.

The consent form(s) must also include a statement that BMS and regulatory authorities have direct access to subject records.

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

For the FRACTION Program, subjects should receive consent forms that include relevant information for all treatments to which they are eligible for enrollment; subjects will not receive consent forms that include data relevant to agents within the FRACTION Program that are not within the Sub-Protocol for which they are screened. Informed consents to Sub-Protocols which are closed, terminated early or in any way no longer in effect will not be provided to new subjects as an eligible treatment consent. Subjects in any follow-up phase for a Sub-Protocol which is closed or terminated will receive pertinent updated safety and risk information if it becomes known. Subjects in any follow-up phase may receive revised informed consent via mail and follow-up phone call by the investigator site.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

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. The details pertaining to the specific treatment regimens are provided in each FRACTION-Lung Sub-Protocol.

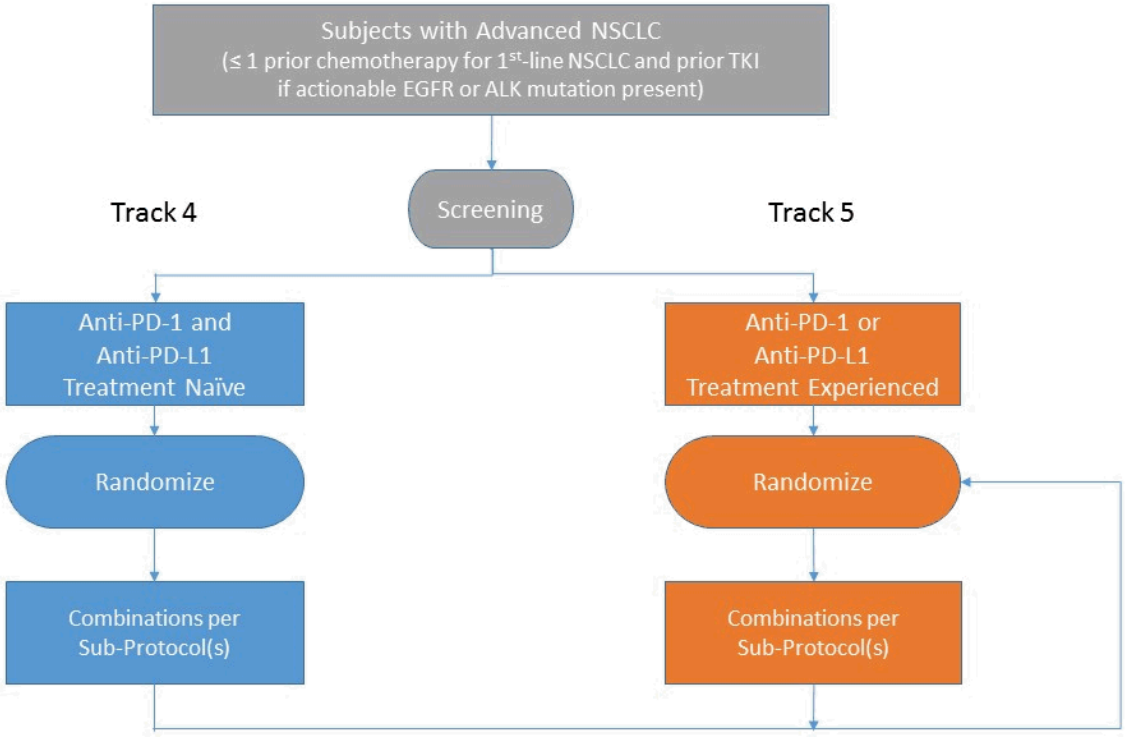
A study design update occurred with the implementation of Amendment 5 due to the change in the standard of care for NSCLC. Data for a PD-1 inhibitor demonstrated a significant improvement in ORR, PFS, and overall survival compared to platinum-based chemotherapy in previously untreated metastatic NSCLC expressing ≥ 50% PD-L1 on tumor cells.[28] In addition, nivolumab did not demonstrate a difference in PFS or overall survival compared to platinum-based doublet chemotherapy in first line metastatic NSCLC among patients with PD-L1 positive tumor (> 5%).[29] Also, pembrolizumab combined with platinum doublet chemotherapy in patients with advanced, chemotherapy-naïve NSCLC demonstrated a significantly improved response rate compared to chemotherapy alone.[30] For this reason, the nivolumab monotherapy treatment in Tracks 1 and 2 was removed, including the nivolumab run-in phase. This change eliminated differences between Track 1 and 2 and resulted in the establishment of a new Track of PD-1/PD-L1-naïve subjects (Track 4). Track 3 was modified in order to test immuno-oncology combinations in an earlier setting in subjects with a more intact immune system. This group of PD-1/PD-L1 experienced subjects was re-established as Track 5. Safety, efficacy, PK, and pharmacodynamic data from subjects enrolled in Tracks 1, 2, and 3 will be analyzed separately from subjects in Tracks 4 and 5.

Prior to implementation of Amendment 5, subjects were enrolled in 1 of 3 tracks depending on prior treatment and PD-L1 status (Tracks 1, 2, or 3). Following implementation of Amendment 5, subjects will be enrolled in 1 of 2 tracks following treatment for advanced NSCLC with ≤ 1 prior chemotherapy regimen and prior tyrosine kinase inhibitor (for subjects with a known epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK] rearrangement). Subjects who are anti-PD-1 and anti-PD-L1 treatment naïve will be eligible for Track 4. Subjects who have had prior experience with anti-PD-1 or anti-PD-L1 treatment will be assigned to Track 5, as outlined in Figure 3.1-1 and described in Section 3.1.1. Treatment duration may extend to up to approximately six 4-week cycles (24 weeks) for both Tracks 4 and 5.

Subjects in Tracks 4 and 5 will be treated until completion of the Treatment Phase (as outlined below), progression, toxicity, or protocol-specified discontinuation (see Section 4.5.2 and each FRACTION-Lung Sub-Protocol). 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 the BMS Medical Monitor (or designee) and documented in the study records (see Section 4.5.3). In addition, a subject with progressive disease (PD) will have several treatment options including continued treatment (for additional six 4-week cycles [approximately 24 weeks] only) and/or entry into Track 5, assuming that he/she continues to fulfill all eligibility criteria at each new randomization point (see Section 3.1.1). 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.

A 2-stage design will be used as a guide to evaluate the possibility of terminating an arm early in Track 4, and a single-stage design will be used in Track 5 (see Section 8.1; a 2-stage design may be used, also see Section 8.1 in specific Sub-Protocols). In Track 4, 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 subjects planned for enrollment may vary by track and is described in Section 8.1. Subjects who continue to fulfill eligibility criteria may move from Track 4 into Track 5 or re-enter Track 5, as described in Section 3.1.1.

Figure 3.1-1: FRACTION-Lung 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.

Note: 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.

3.1.1 FRACTION-Lung Track 4 (Naïve) and 5 (Experienced) Design

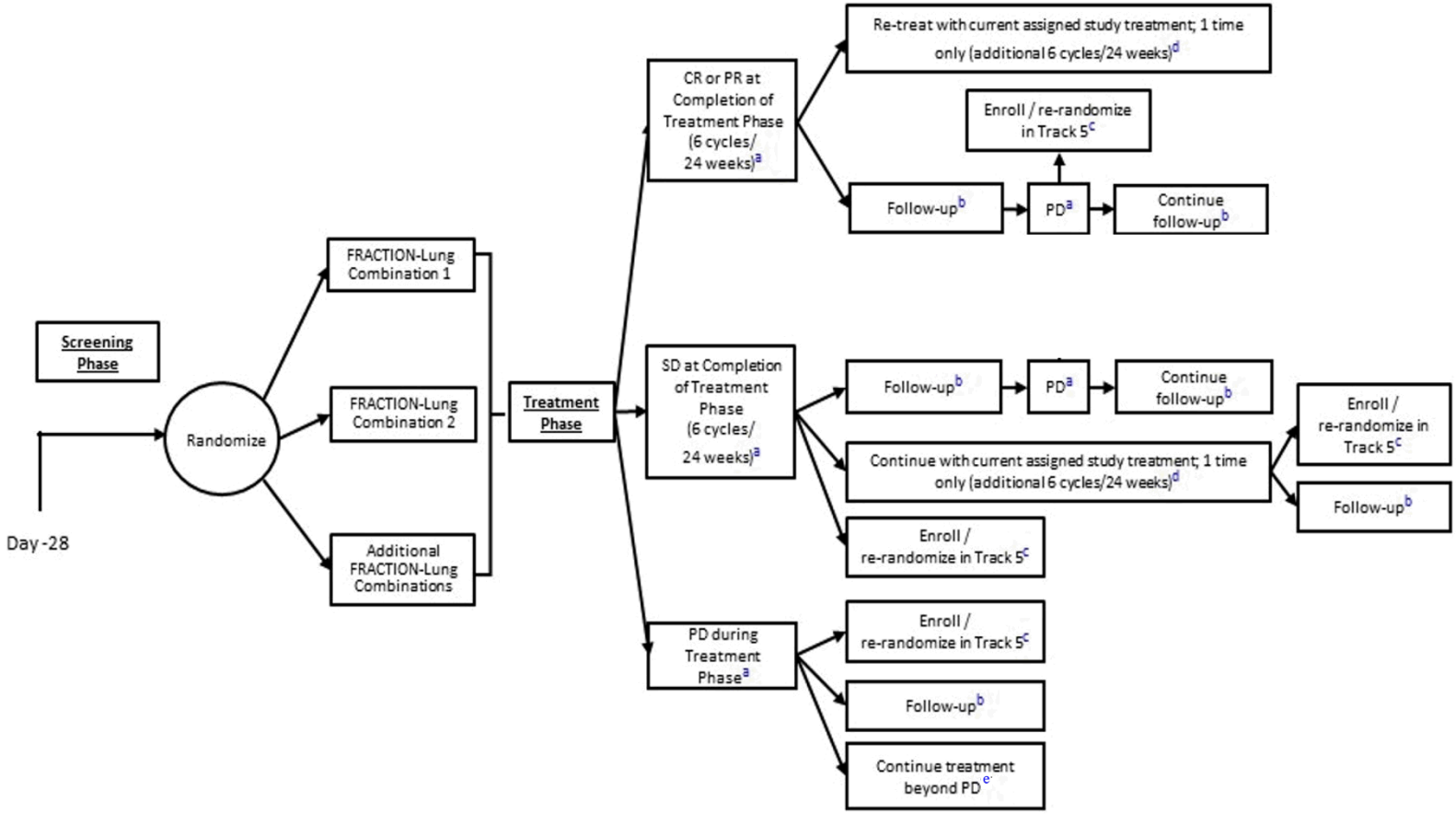
A detailed study schematic for both Tracks 4 and 5 is presented in Figure 3.1.1-1.

Subjects who are naïve to anti-PD-1 and anti-PD-L1 therapy will be enrolled into Track 4 and randomized to 1 of the FRACTION-Lung combination treatments. These subjects will receive their assigned treatment in Track 4 until completion of the Treatment Phase.

Subjects who have received prior anti-PD-1 or anti-PD-L1 treatment will be enrolled in Track 5 and randomized to 1 of the FRACTION-Lung combination treatments. In addition, subjects who experience PD during the Treatment Phase in Tracks 4 or 5 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. These subjects will receive their assigned study treatment in Track 5 until completion of the Treatment Phase. The number of subjects who enroll in Tracks 4 or 5 is described in Section 8.1.

- **Subjects with CR or PR** at the end of the Track 4 or 5 Treatment Phase will have the option to:
    a) Enter study follow-up or
    b) 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:
    a) Enter study follow-up,
    b) 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
    c) 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:
    a) Enter study follow-up or
    b) 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:
    a) Enter study follow-up or
    b) Enter (or re-enter) Track 5, if eligible and if a new treatment combination is available, and be randomized to a new combination, or
    c) Continue study treatment beyond progression, if criteria in Section 4.5.3 are met, for up to completion of that Treatment Phase.

Figure 3.1.1-1: 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.

[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), and/or entry into Track 5, assuming that the subject continues to fulfill all eligibility criteria at each new randomization point (see Section 3.1.1 for details).

[e] Subjects with PD during treatment may continue treatment beyond progression if criteria in Section 4.5.3 are met.

3.2 Study Phases

Subjects will complete up to 3 phases of the study: screening, treatment, and safety follow-up within each track (not considering re-randomization), as described below:

3.2.1 Screening

Prior to screening for the protocol, investigative sites are required to determine if a subject is anti-PD-1/PD-L1 treatment-naïve or not through their Institutional database, subject medical history, or Institutional pre-screening process. Once determined, treatment experience is considered source data for this FRACTION-Lung study, and the subject must be provided with the FRACTION-Lung study IRB-approved written consent. The subject is then considered to have entered screening. The treatment status must be entered into the enrollment management system and subjects will be required to submit a tumor biopsy to score for PD-L1 status by a BMS approved and validated vendor in the Screening Phase; local laboratory results will not be accepted. Subjects must submit tumor biopsy material before randomization. Subjects may not 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.

The Screening Phase for each track will last for up to 28 days. The Screening Phase, also called enrollment, begins by establishing the subject's initial eligibility and signing of the consent form. Subjects will be enrolled using Interactive Response Technology (IRT).

If a subject surpasses the 28-day window during the Screening Phase due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting time for a study-related laboratory value), the subject must be re-consented, but does not need to be assigned a new subject identification number. In this situation, the fewest repeat procedures from the initial screening to qualify the subject, while maintaining safety and eligibility under the discretion of the BMS Medical Monitor (or designee) and investigator, may be done to reduce any undue burden of procedure in this subject population.

Enrollment into all arms in each track will be competitive.

3.2.2 Treatment

The details of the treatment phase duration are provided in Section 3.1. Further details of the treatment administration are in each FRACTION-Lung Sub-Protocol. Study assessments are to be collected as outlined in the On-treatment Procedural Outline(s) specific to each FRACTION-Lung Sub-Protocol.

For subjects on any track, assessment of response will be every 2 cycles (8 weeks ± 1 week) to be completed before the first dose in the next cycle. Assessments of PR and CR must be confirmed no less than 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using RECIST v1.1 criteria for solid tumors (see Appendix 2).

Treatment beyond progression may be allowed in select subjects with initial PD, as defined using RECIST v1.1 criteria, after discussion and agreement with the BMS Medical Monitor (or designee) that the benefit/risk assessment favors continued administration of study therapy (eg, subjects are

continuing to experience clinical benefit, as assessed by the investigator, tolerating treatment, and meeting other criteria specified in Section 4.5.3).

Subjects will generally be allowed to continue study therapy until the first occurrence of either: 1) completion of the maximum number of cycles, 2) PD, 3) clinical deterioration suggesting that no further benefit from treatment is likely, 4) intolerable toxicity, or 5) the subject meets criteria for discontinuation of study therapy, as outlined in protocol Section 4.5.2. Individual subjects with confirmed CR will be given the option to discontinue study therapy prior to completion of the maximum number of cycles on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor (or designee) in settings where the benefit/risk ratio justifies discontinuation of study therapy.

All subjects will be treated as per Section 3.1, unless criteria for study drug discontinuation are met earlier (Section 4.5.2). Upon completion of the Treatment Phase, all subjects will enter the Safety Follow-up Phase (Section 3.2.3 and Table 5.1-3).

3.2.3 Follow-up

3.2.3.1 Safety Follow-up

Upon completion of the Treatment Phase and once the decision is made to discontinue the subject from treatment, all subjects will complete the EOT visit and enter the Safety Follow-up Phase.

For subjects that complete all scheduled cycles of therapy, EOT visit will be the same as the last scheduled and completed on-treatment visit and the start of Week 1 safety follow-up visit. For subjects that do not complete all scheduled cycles of therapy, EOT visit will be the most recent on-treatment visit (with all available safety and response data; does not need to be repeated) and will be considered the start of Week 1 safety follow-up visit.

After the EOT visit, all subjects will be evaluated for any new AEs for at least 100 days after the last dose of study drug, as specified in each FRACTION-Lung Sub-Protocol. Follow-up visits should occur at Days 30, 60, and 100 (± 7 days) after the last dose of study drug or coinciding with the date of discontinuation (± 7 days), if date of discontinuation is greater than 30 days after the last dose, to monitor for AEs. All subjects will be required to complete the 3 clinical safety follow-up visits, regardless of whether they start a new anti-cancer therapy, except for those subjects who withdraw consent for study participation or those subjects who are re-randomized.

3.3 Post-study Access to Therapy

At the end of the study, BMS will not continue to provide BMS-supplied study drug to subjects/investigator unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.4 Study Population

For entry into the FRACTION-Lung Master Protocol, the following criteria MUST be met prior to dosing on Day 1. For entry into a treatment in a Sub-Protocol, additional treatment-specific criteria, if applicable, must also be met.

No exceptions will be granted.

In addition to the inclusion and exclusion guidelines noted below, please refer to the individual Sub-Protocols for additional requirements. As with the inclusion and exclusion criteria of the FRACTION-Lung Master Protocol, the inclusion and exclusion criteria of the FRACTION-Lung Sub-Protocols are also required to be followed.

3.4.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subjects must be able to give self-consent and then sign and date an IRB/IEC-approved written informed consent in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not considered part of normal patient care.

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

c) Subjects must provide consent for mandatory tumor biopsy samples (ie, pretreatment, on treatment, and at progression; see Section 5.6.2.1). Requirements for collection of biomarkers, including tumor biopsy samples, may differ based on the sub-protocol. Please refer to the specific sub-protocol for specific requirements.

2) Target Population

a) Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 (see Appendix 1).

b) Subjects must have histologic or cytologic confirmation of NSCLC (per the seventh International Association for the Study of Lung Cancer [IASLC][31]) with squamous or nonsquamous histology that is advanced (metastatic and/or unresectable)

i) Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 4 weeks prior to enrollment.

ii) Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 4 weeks prior to enrollment.

c) Subjects with known EGFR mutations or ALK rearrangements must have received EGFR or ALK inhibitors, respectively, prior to study entry.

i) All subjects with nonsquamous histology must have been tested for EGFR mutation status; use of an approved test is strongly encouraged. (Note: EGFR testing may only be performed on tumor tissue. Blood EGFR testing may not be used.) Subjects with nonsquamous histology and unknown or indeterminate EGFR status are excluded.

ii) ***Not applicable per Revised Protocol 07:*** If tested for ALK translocations, use of an approved test is strongly encouraged.

iii) ***Not applicable per Revised Protocol 07:*** Subjects with unknown or indeterminate ALK status may be enrolled.

iv) All subjects with nonsquamous histology must have been tested for ALK rearrangements. Use of an approved test is strongly encouraged.

d) Track-specific eligibility criteria

i) Track 4: Anti-PD-1/PD-L1 treatment-naïve subjects

(1) Subjects must be naïve to PD-1/PD-L1 therapy.

ii) Track 5: Anti-PD-1/PD-L1 treatment-experienced subjects

(1) Subjects must have had progressive or recurrent disease during or after anti-PD-1 or anti-PD-L1 therapy and, in the opinion of the investigator, must be unlikely to benefit from nivolumab monotherapy.

(2) Subjects who have had prior treatment with 1 of the agents (or any other IO agent that is directed against the same target) in any combination regimen in a Sub-Protocol are eligible for treatment on Track 5.

(3) Subjects who have had prior combination treatment with the same IO agents (or IO agents that are directed against the same target) as 1 of the combination regimens in a FRACTION-Lung Sub-Protocol are eligible for treatment on Track 5 but must be randomized to another IO combination regimen (as outlined in Section 3.4 Inclusion Criteria of each FRACTION-Lung Sub-Protocol).

iii) Tracks 4 and 5

(1) Subjects may have had up to 1 prior cytotoxic chemotherapy for advanced phase NSCLC.

(a) Subjects enrolled in FRACTION-lung prior to implementation of Amendment 5 who are re-enrolling in Track 5 may have received 1 or more prior chemotherapies for progressive or recurrent disease.

(b) Maintenance therapy does not count as an additional line of treatment.

(2) Subjects should have been offered a platinum-based chemotherapy for NSCLC.

(a) The platinum-based chemotherapy may have been in the adjuvant, neoadjuvant, or recurrent setting.

e) Subjects must have a life expectancy of at least 3 months following their most recent chemotherapy or immunotherapy for entry onto all tracks.

i) Subjects who wish to be re-randomized to a new combination treatment on Track 5 following progression on a prior treatment in Track 4 must have a life expectancy of at least 3 months following the last study treatment.

f) Subjects receiving prior palliative radiotherapy to a non-central nervous system (CNS) lesion must have completed that therapy at least 2 weeks prior to the first dose of study drug.

i) Subjects with symptomatic tumor lesions at baseline who may require palliative radiotherapy within 4 weeks of the first dose of study drug are strongly encouraged to receive palliative radiotherapy prior to enrollment.

g) Subjects must have at least 1 lesion with measurable disease as defined by RECIST v1.1 criteria for solid tumors response assessment (see Appendix 2).

   i) Subjects with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll, provided the lesion(s) have demonstrated clear progression and can be measured accurately.

h) Subjects with toxicity from any prior anti-cancer therapy must have their toxicity returned to Grade ≤ 1 (NCI Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03) or baseline before administration of study drug.

   i) Subjects Grade ≥ 2 with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long-lasting sequela, such as neuropathy after a platinum-based therapy, are eligible.

   ii) Grade >1 alopecia or fatigue is permitted.

i) Subjects must allow a pretreatment tumor biopsy, an on-treatment tumor biopsy, and a tumor biopsy at EOT/progression of disease (at acceptable clinical risk as judged by the investigator) for each treatment regimen. After signing the informed consent, subjects will be required to submit a fresh tumor biopsy with sufficient tissue for immunohistochemical staining to determine PD-L1 status. PD-L1 status will be performed by a BMS-approved and validated vendor using an approved assay. Local laboratory results for PD-L1 tumor status will not be accepted.

   i) Subjects who do not have accessible or suitable lesions are not eligible.

      (1) Biopsies may be collected from subjects with a single measureable lesion, as long as it is not an excisional biopsy. See details in Section 5.6.2.1.

   ii) Subjects whose pretreatment biopsy is known prior to randomization to yield inadequate tissue quantity or quality will not be ineligible for treatment on Tracks 4 or 5; however, re-biopsy is permitted.

   iii) Study personnel must ensure that the archival tissue block or slides samples, if available, are located and shipped to the central laboratory within 6 weeks of signing the written informed consent.

   iv) The solid tumor tissue specimen must be a core-needle biopsy, excisional or incisional biopsy. Fine-needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

   v) The biopsy at progression of disease after treatment on any track may function as the pretreatment biopsy for subsequent treatment on Track 5.

j) Subjects with solid tumor histologies must have adequate organ function, as defined by the following:

   i) White blood cells ≥ 2,000/μL (stable and discontinued growth factor more than 4 weeks of the first study drug administration)

ii) Neutrophils ≥ 1,500/μL (stable off any growth factor within 4 weeks of the first study drug administration)

iii) Platelets ≥ 100×10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of the first study drug administration)

iv) Hemoglobin ≥ 9.0 g/dL (transfusion to achieve this level is not permitted within 2 weeks of the first study drug administration)

v) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3× institutional upper limit of normal (ULN)

vi) Total bilirubin ≤ 1.5× institutional ULN (except for subjects with Gilbert's syndrome who must have normal direct bilirubin)

vii) Serum creatinine ≤ 1.5× institutional ULN or creatinine clearance (CrCl) ≥ 50 mL/min (measured using the Cockcroft-Gault formula below):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

k) Subjects must be able to comply with restrictions and prohibited activities/treatments listed in Section 3.5.1.

l) Subject re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pretreatment failure (eg, subject has not been treated). If re-enrolled, the subject must be re-consented.

3) Age and Reproductive Status

In addition to the reproductive guidelines noted below, please refer to the individual Sub-Protocols for additional requirements regarding reproductive guidelines. As with the inclusion and exclusion criteria of the FRACTION-Lung Master Protocol, the criteria of the FRACTION-Lung Sub-Protocols are also required to be followed.

a) Subjects must be males and females ≥ 18 years of age at the time of informed consent.

b) Subjects who are women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study drug.

c) Subjects who are women must not be breastfeeding.

d) Subjects who are WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives (T-HALF) of study drug plus 30 days (duration of ovulatory cycle).

i) Subjects who are WOCBP who are continuously not heterosexually active are exempted from contraceptive requirements but still must undergo pregnancy testing as described in this section.

e) Subjects who are males and who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection for the duration of treatment with study drug(s) plus 5 half-lives (T-HALF) of study drug(s) plus 90 days (duration of sperm turnover). In addition, male subjects must be willing to refrain from sperm donation during this time.

   i) Subjects who are azoospermic males are exempted from contraceptive requirements unless the potential exists for fetal toxicity due to study drug being present in seminal fluid, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

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

At a minimum, all non-exempt subjects must agree to use 1 highly effective method of contraception:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP are expected to use one of the highly effective methods of contraception listed below. Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

Contraceptive methods are as follows:

1) Progestogen only hormonal contraception associated with inhibition of ovulation (oral and injectable).
2) Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited): oral (birth control pills), intravaginal (vaginal birth control suppositories, rings, creams, gels), transdermal.
3) Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
4) Nonhormonal IUDs such as ParaGard®
5) Bilateral tubal occlusion

6) Vasectomized partner
   - Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
7) Intrauterine hormone-releasing system (IUS) (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
8) Sexual abstinence
   - Complete sexual abstinence is defined as the complete avoidance of heterosexual intercourse.
   - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
   - It is not necessary to use any other method of contraception when complete abstinence is elected.
   - Subjects who choose complete abstinence must continue to have pregnancy tests as specified in Section 6.4.
   - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
   - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

LESS THAN HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Less than highly effective methods of contraception have a failure rate of > 1% per year when used consistently and correctly.

1) Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
2) Diaphragm with spermicide
3) Cervical cap with spermicide
4) Vaginal Sponge with spermicide
5) Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2) Withdrawal (coitus interruptus)
3) Spermicide only
4) Lactation amenorrhea method (LAM)

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

3.4.2 Exclusion Criteria

1) Target Population

a) Subjects must not have known EGFR mutations that are sensitive to available targeted inhibitor therapy, as per Section 3.4.1.

b) Subjects must not have known ALK translocations that are sensitive to available targeted inhibitor therapy, as per Section 3.4.1.

c) Subjects must not have active CNS metastases.

i) Subjects with treated CNS metastases are eligible if they have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to the first dose of study drug. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to the first dose of study drug.

ii) Subjects with small, untreated, asymptomatic CNS metastases without associated edema, shift, or requirement for steroids are eligible after discussion with the BMS Medical Monitor (or designee).

iii) The CNS must not be the only site of metastatic disease.

iv) Subjects must not have leptomeningeal disease or carcinomatous meningitis.

2) Medical History and Concurrent Diseases

a) Subjects must not have had previous malignancies (except nonmelanoma skin cancers and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.

b) Subjects must not have other active malignancy requiring concurrent intervention.

c) Subjects must not have received a prior organ allograft.

d) Subjects must not have received any anti-cancer therapy (eg, chemotherapy, radiotherapy, biologics, immunotherapies, or hormonal treatment), including investigational drugs, within 4 weeks prior to the first dose of study drug administration.

i) Subjects who have received non-cytotoxic anti-cancer therapies (eg, prior use of targeted therapy or hormonal therapy) and who completed treatment at least 4 weeks or 5 half-lives (whichever is shorter) prior to the first dose of study drug are eligible to enroll. However, if 5 half-lives is shorter than 4 weeks, agreement with the BMS Medical Monitor (or designee) is mandatory.

e) Subjects must not have active, known, or suspected autoimmune disease.

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

f) Subjects must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration.

   i) Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

g) Subjects must not have a history of life-threatening toxicity related to prior IO treatment.

   i) Subjects with toxicities that are unlikely to recur with standard countermeasures (eg, hormone replacement after adrenal crisis) are eligible.

h) Subjects must not have interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

i) Subjects must not have uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

   i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months

   ii) Uncontrolled angina within the past 3 months

   iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

   iv) Corrected QT interval with Fridericia's formula interval > 480 msec

   v) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV, myocarditis, pericarditis, or significant pericardial effusion)

j) Subjects who require daily supplemental oxygen therapy are excluded.

k) Subjects must not have a history of any acute or chronic hepatitis, as evidenced by a positive test for hepatitis B surface antigen (HBsAg) or a positive test for qualitative hepatitis C viral load (by polymerase chain reaction)

   i) Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by polymerase chain reaction are eligible.

   ii) Subjects with a history of resolved hepatitis A virus infection are eligible.

l) Subjects must not have evidence of active infection requiring antibacterial, antifungal, or antiviral therapy ≤ 7 days prior to initiation of study drug therapy.

m) Subjects must not have a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.

   i) Testing for HIV must be performed at sites mandated by local requirements.

n) Subjects must not have known or suspected active tuberculosis.

o) Subject must not have had any major surgery within 4 weeks of study drug administration and must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study drug.

p) Subjects must not have received nononcology vaccines containing live virus for prevention of infectious diseases within 12 weeks prior to the first dose of study drug.

i) The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on study without restriction.

q) Subjects must not have received packed red blood cell or platelet transfusion within 2 weeks prior to the first dose of study drug.

r) Subjects must not have a known or underlying medical condition that, in the opinion of the investigator or Sponsor, could make the administration of study drug hazardous to the subjects or could adversely affect the ability of the subject to comply with or tolerate the study.

3) Allergies and Adverse Drug Reaction

a) Subjects must not have a history of allergy to nivolumab.

b) Subjects must not have a history of any significant drug allergy (such as anaphylaxis or hepatotoxicity) to prior anti-cancer immune-modulating therapies (eg, checkpoint inhibitors and T-cell co-stimulatory antibodies).

4) Other Exclusion Criteria

a) Subjects must not be prisoners or be involuntarily incarcerated.

b) Subjects must not be compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

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

3.4.3 Women of Childbearing Potential

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

Women in the following categories are not considered WOCBP

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

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

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

Females treated with hormone replacement therapy are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of hormone replacement therapy used. The durations of the washout periods below are suggested guidelines, and the investigators should use their judgement in checking serum FSH levels:

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

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

[redacted]

[redacted]

[redacted]

3.6 Discontinuation of Subjects Following any Treatment with Study Drug

Subjects MUST discontinue IP (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment and/or participation in the study
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Pregnancy
- Documented disease progression as defined by RECIST v1.1 (see Appendix 2), unless the subject meets criteria for treatment beyond progression (Section 4.5.3), or the subject continues treatment by entering another track (Section 3.1)

- Clinical deterioration while receiving active study therapy that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Discretion of the investigator
- Inability to comply with the protocol requirements
- Protocol-defined reasons for discontinuation (see Section 4.5.2)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor (or designee) of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please notify the BMS Medical Monitor (or designee) within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor (or designee) must occur.

All subjects who discontinue IP should comply with protocol-specified follow-up procedures, as outlined in Table 5.1-3. The only exception to this requirement is when a subject withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

3.7 Post Study Drug Follow-up

In this study, OS is an exploratory endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or safety follow-up data, as required and in line with Table 5.1-3, until death, withdrawal of consent, conclusion of the study, or to be randomized to a new treatment regimen in Track 5 if applicable.

3.7.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only, as appropriately directed in accordance with local law.

3.7.2 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, texts, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both IP and noninvestigational product. Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications) will be considered study drug. A table describing the study drugs and dosage information is provided in each Sub-Protocol.

For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the package insert, Summary of Product Characteristics (SmPC), or similar documentation.

4.1 Investigational Product

An IP, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

Specific IPs are listed in each FRACTION-Lung Sub-Protocol.

4.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

Specific noninvestigational products, as applicable, are listed in each FRACTION-Lung Sub-Protocol.

4.3 Storage and Dispensing

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

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

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

Infusion-related supplies (eg, intravenous bags, in-line filters, 0.9% NaCl solution) will not be supplied by the Sponsor and should be purchased locally if permitted by local regulations.

Please refer to each Sub-Protocol, the current version of the IBs, and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.

For noninvestigational product, if marketed product is utilized, it should be stored in accordance with the package insert, SmPC, or similar.

4.4 Method of Assigning Subject Identification

This is an open-label study. All subjects must be assigned a patient identification number upon providing a signed IRB/IEC-approved written informed consent. During the screening visit, the investigative site will utilize the IRT for enrollment and receive a 5-digit patient identification number designated by BMS that will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned sequential patient identification numbers starting with 00001 (eg, 00001, 00002, 00003...00010). The patient identification number will ultimately comprise the site number and patient identification number. For example, the first subject screened (eg, enrolled) at Site Number 1 will have a subject identification number of 0001-00001. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth
- IO Therapy and PD-1/PD-L1 Therapy Treatment Experience (Section 3.2.1)

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

- Subject number
- Date of birth

Randomization subject schedules will be generated and maintained by the IRT vendor. At the conclusion of the trials, BMS will receive copies of all generated subject schedules from 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. The primary identifier will be patient identification number described above, for use on the case report form and source documents. 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. New randomization schedules may be added for specific Sub-Protocols (randomization ratios will be specified in corresponding Sub-Protocols). Subjects will be equally allocated to all existing randomization schedules within a given track. If the randomization ratio is not specified in the Sub-Protocol, subjects will be equally assigned to any of the open arms.

Pre-specified treatment arm caps (as described in Section 8.1) 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 (ie, 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 of 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.

4.5 Selection and Timing of Dose for Each Subject

Specific dosing and treatment regimens for each FRACTION-Lung treatment combination are outlined in each FRACTION-Lung Sub-Protocol.

4.5.1 Dose Reductions and Delays and Criteria to Resume Dosing

Tumor assessments for all subjects should continue as per protocol **even if dosing is delayed**.

Guidelines for dose reductions and delays due to toxicity and for resuming treatment for each FRACTION-Lung combination therapy are provided in each FRACTION-Lung Sub-Protocol.

4.5.2 Permanent Treatment Discontinuation

Criteria for permanent discontinuation for each FRACTION-Lung combination therapy are provided in each FRACTION-Lung Sub-Protocol.

4.5.3 Treatment Beyond Disease Progression

Accumulating evidence indicates that a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[32]

Subjects will be permitted to continue on treatment beyond initial RECIST v1.1-defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Subject continues to meet relevant eligibility criteria, as determined by the BMS Medical Monitor (or designee) in discussion with the investigator
- Stable performance status
- Subject is tolerating study treatment
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)

The decision to continue treatment beyond initial investigator-assessed progression should be discussed with the BMS Medical Monitor (or designee) and documented in the study records. A follow-up scan should be performed at the next scheduled imaging evaluation 8 weeks later (but no less than 4 weeks) to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the study and continue to receive monitoring according to the Time and Events Schedule Table 5.1-1, Table 5.1-2, and the On-treatment Procedural Outline(s) specific to each FRACTION-Lung Sub-Protocol).

For subjects who continue study therapy beyond initial RECIST v1.1-defined PD, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD assessment. This includes an increase in all target lesions and/or the development of new measurable lesions. Study therapy should be discontinued in any subject for whom these criteria are met and should be documented. New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered nonmeasureable at the time of initial progression may become measureable and, therefore, included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions that become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

[redacted]

4.5.5 *Treatment of Drug-related Infusion Reactions*

Treatment of drug-related infusion reactions for each FRACTION-Lung treatment combination therapy is provided in each FRACTION-Lung Sub-Protocol.

4.6 Combination Treatment Arm Discontinuation Criteria

In the event that 20% or more of study subjects in a novel FRACTION-Lung combination arm of a given track, at any given time, meet any of the toxicity criteria for permanent discontinuation (as described in Section 4.5.2), then consideration will be given to discontinue that FRACTION-Lung combination arm in that track. This will include early side effects seen with IO agents and longer term effects such as endocrinopathies. This action will be taken in consultation with the Safety Monitoring Board (SMB) and will consider other pertinent facts in coming to a decision, including toxicity profile of that combination seen outside FRACTION-Lung and subject benefit as measured by anti-tumor response.

Discontinuation of a combination arm in a given track for any reason WILL NOT lead to discontinuation for that combination in all tracks. Safety of all open-label combination arms in other tracks that contain the same agent (or agents) will be assessed by SMB and the Sponsor. In the event of serious, unexpected, or life-threatening emergent toxicities, relevant combination arms may then be modified to maintain the safety of subjects. Decisions on such steps and the re-initiation of any combination arms that had been stopped would be made by SMB in consultation with the Sponsor and relevant authorities (eg, IRB/IEC).

4.7 Blinding/Unblinding

Not applicable.

4.8 Treatment Compliance

Study drug will be administered in the clinical facility by trained medical personnel. Treatment compliance will be monitored by drug accountability, as well as by recording administration of each study drug in subjects' medical records and CRF.

4.9 Destruction of Study Drug

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

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor (or designee), unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's Standard Operating Procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the BMS Study Monitor (or designee) to review throughout the clinical trial period.
- If conditions for destruction cannot be met, the responsible BMS Study Monitor (or designee) will make arrangements for return of study drug.
- It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures and provided that appropriate records of disposal are kept.

4.10 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible study monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1 (Screening Procedural Outline), Table 5.1-2 (Baseline for Re-randomization Procedural Outline), and Table 5.1-3 (Follow-up Procedural Outline). Additional screening or follow-up requirements that are specific for individual study treatments are provided in each FRACTION-Lung Sub-Protocol. The On-treatment Procedural Outline(s) for each study treatment are included in each FRACTION-Lung Sub-Protocol.

Table 5.1-1: Screening Procedural Outline

Procedure	Screening Visit[a]	Notes
Informed Consent	X	Obtain patient identification number via IRT after signing of the written informed consent.
Utilize IRT	X	To obtain patient identification number
Inclusion/Exclusion Criteria	X	
Medical History	X	Includes risk factors (eg, smoking history, alcohol consumption, pleural effusion and pneumonitis)
Collect Data on Prior Anti-PD-1/PD-L1 Therapy Exposure	X	Prior to screening for the protocol, investigative sites are required to determine subject exposure to anti-PD-1/PD-L1 therapy. Those data will be collected as part of the Screening Phase.
Physical Examination	X	
Oxygen Saturation	X	Record at rest via pulse oximetry to establish baseline. If subject has oxygen saturation ≤ 90%, consult BMS Medical Monitor (or designee) prior to enrollment.
Vital Signs	X	Temperature, blood pressure, heart rate, and respiratory rate
Height and Weight	X	
ECOG Performance Status	X	
Pretreatment Medications	X	Medications taken within 14 days prior to treatment
Assessment of Baseline Signs and Symptoms	X	Within 14 days prior to first dose.
Serious Adverse Events	X	All SAEs must be collected from the date of the subject's written consent until 100 days post-discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.
Chest X-ray	X	
12-Lead ECG	X	ECGs should be recorded after the subject has been supine for at least 5 minutes. Record QTcF
Pregnancy Serum or Urine Test	X	Serum or urine, within 72 hours prior to first dose of assigned treatment

Table 5.1-1: Screening Procedural Outline

Procedure	Screening Visit[a]	Notes
Serum Chemistry and Urinalysis	X	Within 14 days prior to first dose of assigned treatment (see Section 5.3.2)
Hematology	X	Complete blood count with differential and platelets, within 14 days prior to first dose of assigned treatment
Thyroid Function Panel	X	TSH, within 14 days prior to first dose of assigned treatment; if TSH is abnormal, then obtain free T3 and free T4.
Virology Tests	X	HBsAg or hepatitis C viral load, HIV (if required by local law), within 14 days prior to first dose of assigned treatment
Mandatory Pretreatment Tumor Biopsy	X	Biopsy must be performed during the Screening Phase in all subjects prior to first dose of assigned treatment. Sample(s) may be retained for additional research. Results of the PD-L1 testing must be communicated to the Sponsor Team prior to randomization to determine if randomization may proceed.
Archival Tumor Block	X	An archival, formalin-fixed, paraffin-embedded tumor tissue block, or slides samples, is to be provided by all subjects, if available.
Disease assessments	X	Assessment should include the chest/abdomen/pelvis at a minimum, and should include other anatomic regions as indicated based on the subject's tumor type and/or disease history.

[a] Within 28 days of first dose of assigned treatment

Abbreviations: T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Table 5.1-2: Baseline for Re-randomization Procedural Outline (Following Implementation of Amendment 5)

Procedure	Days -1 to -28[a]	Notes
Utilize IRT	X	
Subject Registration for Re-randomization	X	Ensure subject continues to meet eligibility for study treatment.
Physical Examination	X	If the re-randomization baseline physical examination is performed within 24 hours prior to dosing on Day 1, then a single examination may count as both the re-randomization baseline and predose evaluation.
Oxygen Saturation	X	Record at rest via pulse oximetry to establish baseline. If subject has oxygen saturation ≤ 90%, consult BMS Medical Monitor (or designee) prior to enrollment.
Vital Signs	X	Temperature, blood pressure, and heart rate
Weight	X	
ECOG Performance Status	X	
[redacted]	[redacted]	[redacted]
Assessment of Baseline Signs and Symptoms	X	If re-baseline or re-randomization occurs > 100 days after the last dose, signs and symptoms that occur up to 14 days prior to the next dose of study treatment should be recorded.
Serious Adverse Events	X	All SAEs must be collected from the date of the subject's written consent until 100 days post-discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.
Chest X-ray	X	
12-Lead ECG	X	ECGs should be recorded after the subject has been supine for at least 5 minutes. Record QTcF.
Pregnancy Serum or Urine Test	X	Serum or urine, within 72 hours prior to first dose of assigned treatment
Serum Chemistry and Urinalysis	X	See Section 5.3.2
Hematology	X	Includes complete blood count with differential including platelets
Thyroid Function Panel	X	Includes T3, T4, and TSH; if TSH is abnormal, then obtain free T3 and free T4

Table 5.1-2: Baseline for Re-randomization Procedural Outline (Following Implementation of Amendment 5)

Procedure	Days -1 to -28[a]	Notes
Virology Tests	X	Virology must be collected if > 6 months has passed since the previous assessment. Perform testing for HBsAg, hepatitis C antibody (if hepatitis C antibody is positive, reflex to hepatitis C RNA), or hepatitis C RNA. (Note: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.)
Mandatory Pretreatment Tumor Biopsy	X	Biopsy must be performed in all subjects within 28 (± 2 days) prior to first dose of assigned retreatment. If a biopsy is performed for another reason within that window, re-biopsy for purposes of re-randomization baseline is not necessary. Sample(s) may be retained for additional research.
Disease assessments	X	Assessment should include the chest/abdomen/pelvis at a minimum, and should include other anatomic regions as indicated based on the subject's tumor type and/or disease history.

[a] Within 28 days of first dose of assigned treatment

Abbreviations: ECG = electrocardiogram; QTcF = QT correction using Fridericia's formula; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Table 5.1-3: Follow-up Procedural Outline

	Safety Follow-up			
Procedure	**FU 1 30 Days[a] (± 7 Days)**	**FU 2 60 Days (± 7 Days)**	**FU 3 100 Days (± 7 Days)**	**Notes**
SAFETY ASSESSMENTS				
Physical Examination	X	X	X	
ECOG Performance Status	X			
Vital Signs and Weight	X	X	X	Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
Oxygen Saturation	X	As clinically indicated		Collected at rest via pulse oximetry
Laboratory Tests	X		X	To include serum chemistry and hematology
Monitor for Serious Adverse Events	X	X	X	All SAEs must be collected from the date of the subject's written consent until 100 days post-discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time
Review of Concomitant Medications	X	X	X	
SAMPLE COLLECTION				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5.1-3: Follow-up Procedural Outline

	Safety Follow-up			
Procedure	**FU 1 30 Days[a] (± 7 Days)**	**FU 2 60 Days (± 7 Days)**	**FU 3 100 Days (± 7 Days)**	**Notes**
EFFICACY ASSESSMENTS				
Tumor Assessment	X		X	Assessed by RECIST v1.1 criteria (see Appendix 2) Subjects with a history of brain metastasis should have a MRI or CT of the brain if clinically indicated. Subjects with a history of bone metastasis should have a bone scan if clinically indicated. Subjects who have progressive disease will not require further assessments of response.
Collection of Survival Status and Subsequent Therapy Information	X	X	X	May be performed by phone contact or office visit
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] FU visits at Days 30, 60, and 100 (± 7 days) should occur after the last dose of study drug or coinciding with the date of discontinuation ± 7 days, if date of discontinuation is greater than 30 days after the last dose, to monitor for AEs.

Abbreviations: FU = follow-up.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (eg, relevant clinical laboratory tests and urinalysis). The site will have a well-calibrated scale for recording body weight, a 12-lead electrocardiogram (ECG) machine, and calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked advanced cardiac life support cart will be immediately available on the premises. The site will have urine collection containers, a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-70°C or below), as well as containers and dry ice for shipment and storage of blood and urine samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. The site will source marketed products from a single commercial lot.

BMS will provide a BMS-approved protocol (and any amendments or administrative letters, if required) and IBs for all IPs. CRFs (electronic or hard copy) will be provided by BMS. The central laboratory will provide labels and tubes for the collection of blood samples for PK/biomarker and genotyping analyses. Additionally, the IRT manual and pharmacy manual will be provided.

5.3 Safety Assessments

AEs will be assessed continuously during the study and for 100 days after the last study drug treatment. AEs will be evaluated according to the NCI CTCAE Version 4.03 and should be followed per requirements in Sections 6.1.1 and 6.2.1. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance. Subjects should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.

Protocol-specified assessments are described in Table 5.1-1 (Screening Procedural Outline), Table 5.1-2 (Baseline for Re-randomization Procedural Outline), Table 5.1-3 (Follow-up Procedural Outline), and the On-treatment Procedural Outline(s) specific to each FRACTION-Lung Sub-Protocol.

5.3.1 Imaging Assessment for the Study

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

5.3.2 Laboratory Test Assessments

A local laboratory will perform the analyses and will provide reference ranges for these tests. The clinical laboratory assessments are indicated in Table 5.3.2-1.

Table 5.3.2-1: Laboratory Test Assessments

Hematology	
CBC with differential and platelets	Hemoglobin
Total leukocyte count, including differential	Hematocrit
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST)	Total protein
Alanine aminotransferase (ALT)	Albumin
Total bilirubin	Sodium
Direct bilirubin (only if total bilirubin is elevated)	Potassium
Alkaline phosphatase	Chloride
Lactate dehydrogenase (LDH)	Carbon dioxide or bicarbonate
Creatinine	Calcium
Blood urea nitrogen (BUN) or urea	Phosphorus
Uric acid (screening only)	Magnesium
Glucose	Creatine kinase
Amylase	CrCl (screening only)
Lipase	C-reactive protein
Gamma-glutamyl transferase (only when alkaline phosphatase is abnormal)	
Urinalysis	
Protein	Leukocyte esterase
Glucose	Specific gravity
Blood	pH
Microscopic examination of the sediment if blood, protein, or leukocyte esterase are positive on the dipstick	
Serology	
Serum for hepatitis C antibody or hepatitis C RNA (if hepatitis C antibody is positive, reflex to hepatitis C RNA), HBsAg, and HIV-1 and HIV-2 antibodies (Testing for HIV-1 and HIV-2 antibodies must be performed at the sites mandated by local requirements.)	
Other Analyses	
Pregnancy test (WOCBP only)	
TSH with reflex to free T3 and free T4, as applicable	
FSH, if needed to document postmenopausal status, as defined in Section 3.4.3	

Abbreviations: CBC = complete blood count; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism, as agreed upon between the

investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3).

5.4 Efficacy Assessments

Disease assessment with contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen, and pelvis are to be performed for tumor assessments. CT scans should be acquired with 5-mm slices with no intervening gap (contiguous). Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of 5 mm with no gap (contiguous). Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points. Assessments will be performed at baseline and every 8 weeks (± 1 week) during the Treatment Phase until disease progression per RECIST v1.1 criteria (see Appendix 2) or confirmed disease progression for subjects treated beyond 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]), discontinuation of treatment, or withdrawal from study. Assessments will also be performed 30 days after discontinuation of study drug (ie, safety follow-up Visit 1; all subjects) and at the end of the follow-up period. Tumor assessments at other time points may be performed if the investigator is concerned about tumor progression. Assessments of PR and CR must be confirmed no less than 4 weeks following initial assessment. Assessment of tumor response will be reported by the investigator for appropriate populations of subjects, as defined by RECIST v1.1 criteria (see Appendix 2) for subjects with solid tumors. Same modality/scanner should be used for all assessments.

Changes in tumor measurements and tumor responses will be assessed by the investigator using RECIST v1.1 criteria.[33] Investigators will also report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the CRF based on the investigator's assessment using RECIST v1.1 criteria. (See Appendix 2 for specifics of RECIST v1.1 criteria to be utilized in this study.)

Tumor assessments will be submitted to a third party radiology vendor on an ongoing basis; subject management is not dependent on third party review of tumor assessments.

5.4.1 Primary Efficacy Assessments

The efficacy assessments will include the ORR (eg, PR plus CR), DOR, and PFSR at 24 weeks based on assessment of tumor response using RECIST v1.1 criteria.

5.4.2 Secondary Efficacy Assessments

Not applicable.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.8 Other Assessments

Not applicable.

5.9 Results of Central Assessments

Central assessments are not planned for this study; however, copies of all scans will be stored for possible future central analysis, if determined to be necessary by BMS. At the Sponsor's discretion, scans may be collected centrally to be reviewed by independent radiologists.

5.10 Additional Research Collection

All residual blood and tissue samples will be retained by the BMS Biorepository for additional research purposes. No additional sampling is required. Additional research retention is encouraged for all subjects, except where prohibited by local laws and regulations. Details of sample collection and processing will be provided to the site in the procedure manual.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

Events <u>Meeting</u> the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator),

should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Assessment of Causality

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

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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see Note below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent 1 of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint; if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anti-cancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Certain SAEs will be collected as clinical events and not as SAEs, this will include the expected clinical outcomes of disease progression, disease metastasis. If death results from disease progression, and within 100 days of discontinuation of dosing or subject's last scheduled visit, this SAE should also be reported within 24 hours.

Sections 5.6.1 and 5.6.2 in the Investigator Brochures (IBs) represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the Screening Phase and within 100 days of discontinuation of dosing. The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the electronic CRF. The paper SAE Report/Pregnancy Surveillance Forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture, electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

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

If only limited information is initially available, follow-up reports are required. (**Note:** Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as a serious adverse event.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment, as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

All nonserious adverse events (not only those deemed treatment-related) are to be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the IP, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during 100 days or at least

5 half-lives (if longer) after study drug administration, the investigator must immediately notify the BMS Medical Monitor (or designee) of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with the SAE reporting procedures described in Section 6.1.1.

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated.

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

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

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

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (p-DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential DILI is defined as the following:

- Aminotransferase (ALT or AST) elevation > 3× institutional ULN
  AND
- Total bilirubin > 2× institutional ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
  AND
- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic, or cancer metastases.

The key responsibilities for investigators during p-DILI assessment include the following: (i) early detection, medical evaluation (including the exclusion of other potential causes), and rapid laboratory confirmation of liver-related abnormalities and (ii) BMS notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, BMS is responsible for the following: (iii) timely evaluation and triaging of p-DILI cases, (iv) expedited reporting of p-DILI cases, and (v) expanded review of p-DILI cases, including a detailed assessment of all available clinical information, investigations, and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a subject meets p-DILI criteria. They are expected to promptly notify BMS of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a Hepatic Laboratory Panel (ALT, AST, total bilirubin, and alkaline phosphatase). Any subject with an abnormal Hepatic Laboratory Panel that meets p-DILI criteria is a candidate for study drug discontinuation. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to BMS as an SAE within 24 hours of confirmation.

An extensive clinical history, examination, and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, nonexhaustively and by way of example only, infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases (such as hepatocellular carcinoma), autoimmune diseases (such as primary biliary cirrhosis), and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill, and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the subject's age, gender, clinical history, and signs and symptoms.

6.7 Other Safety Considerations

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

7 SAFETY MONITORING BOARD AND OTHER EXTERNAL COMMITTEES

Two independent committees may be utilized: a Safety Monitoring Board (SMB) and an Independent Review Committee (IRC).

The SMB will be 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 will meet 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 listing (by study track and treatment arm as appropriate) will be provided to SMB to facilitate safety monitoring. The SMB will act in an advisory capacity to BMS and will monitor subject safety throughout the study. Additional details are provided in the SMB Charter.

The IRC may be established if needed. The IRC may review all available tumor assessment scans to determine response (RECIST v1.1 criteria). IRC-determined response may be used in the analyses of ORR, PFSR, and DOR.

8 STATISTICAL CONSIDERATIONS

Additional or Sub-Protocol-specific statistical considerations may be provided in Sub-Protocols. Please refer to the specific Sub-Protocol for guidance.

8.1 Sample Size Determination

Sample sizes are guided by Simon 2-stage, single-stage or multi-stage designs as described in the subsequent sections and in Table 8.1-1. 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 proceed 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. For example, 35 subjects per arm will result in 83% probability of detecting an AE that has a true rate of 5%.

Table 8.1-1: Multi-stage or Single-stage Design

Track	Stage 1 n	Stage 1 Responders		Stage 2 n	Stage 2 Responders			Stage 3 n	Stage 3 Responders		Stage 4 n	Stage 4 Responders	
		Futility Stop	Go to Stage 2		Futility Stop	Go to Stage 3	Efficacy Stop		Futility Stop	Go to Stage 4		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 regard 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.

8.1.1 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 8.1.1.1 describes the sample size determination for all three strata in Track 4, while Section 8.1.1.2 describes the sample size determination for Track 5.

8.1.1.1 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.

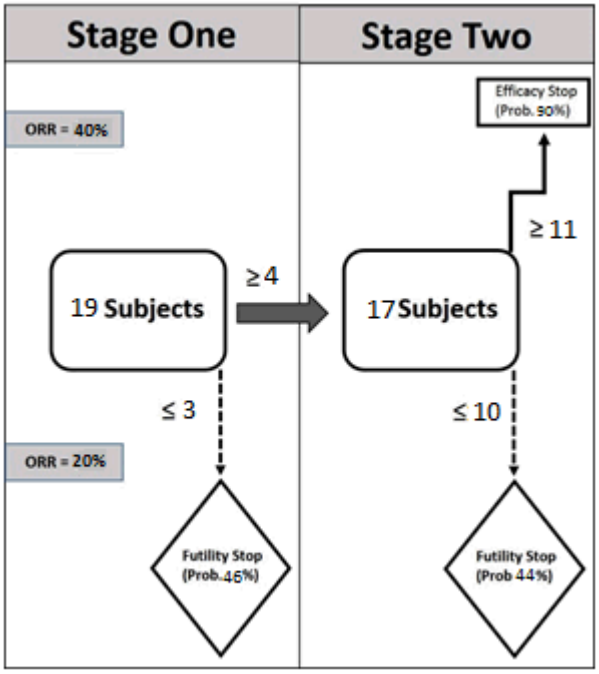
Enrollment will be continued during initial efficacy evaluation (ie, with the indicated number of subjects at Stage 1) to allow additional subjects to enroll to account for unexpected trial impact, such as response non-evaluable subjects due to early drop-out, design parameter change (eg, historical 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 8.1-1, 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 $\leq$ 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 8.1.1.1-1. With the stopping boundaries as shown in Table 8.1-1, if the combination has an ORR no better than the historical control (from nivolumab and ipilimumab combination data in Study CA209012) 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.

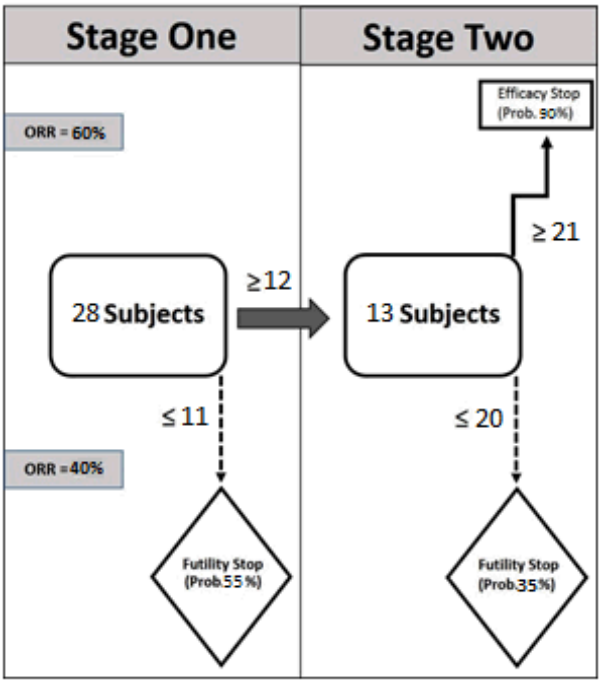
Figure 8.1.1.1-1: Operating Characteristics of Simon 2-Stage Design for Track 4 Subjects with PD-L1 Expression < 1% (Power = 90%, Alpha = 10%)



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

As shown in Table 8.1-1, 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 8.1.1.1-2. With the stopping boundaries as shown in Table 8.1-1, if the combination has an ORR no better than the historical control (from nivolumab and ipilimumab combination data in Study CA209012) 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.

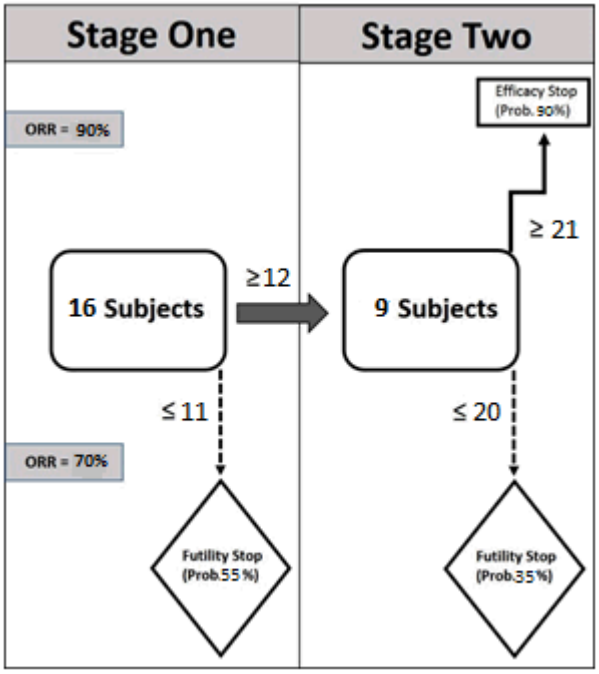
Figure 8.1.1.1-2: Operating Characteristics of Simon 2-Stage Design for Track 4 Subjects with PD-L1 Expression Between 1% and < 50% (Power = 90%, Alpha = 10%)



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

As shown in Table 8.1-1, 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 8.1.1.1-3. With the stopping boundaries as shown in Table 8.1-1, if the combination has an ORR no better than the historical control (from nivolumab and ipilimumab combination data in Study CA209012) 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 8.1.1.1-3: Operating Characteristics of Simon 2-Stage Design for Track 4 Subjects with PD-L1 Expression ≥ 50% (Power = 90%, Alpha = 10%)



8.1.1.2 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 8.1.1.2-1). Unlike in Track 4, participants whose PDL-1 status is unevaluable will count towards the sample size in Track 5.

Table 8.1.1.2-1: 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 8.3.1. 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.

8.1.2 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 Sections 8.1.2.1 through 8.1.2.3 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.

8.1.2.1 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 are 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. The actual percentage (number) of subjects entering Track 1.a and 1.c at the end of the Nivolumab Run-in Phase may be included in future Sub-Protocols based on experience from existing/on-going Sub-Protocol(s).

8.1.2.2 Track 1.b - Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-positive Subjects and Track 2 - Anti-PD1/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 below

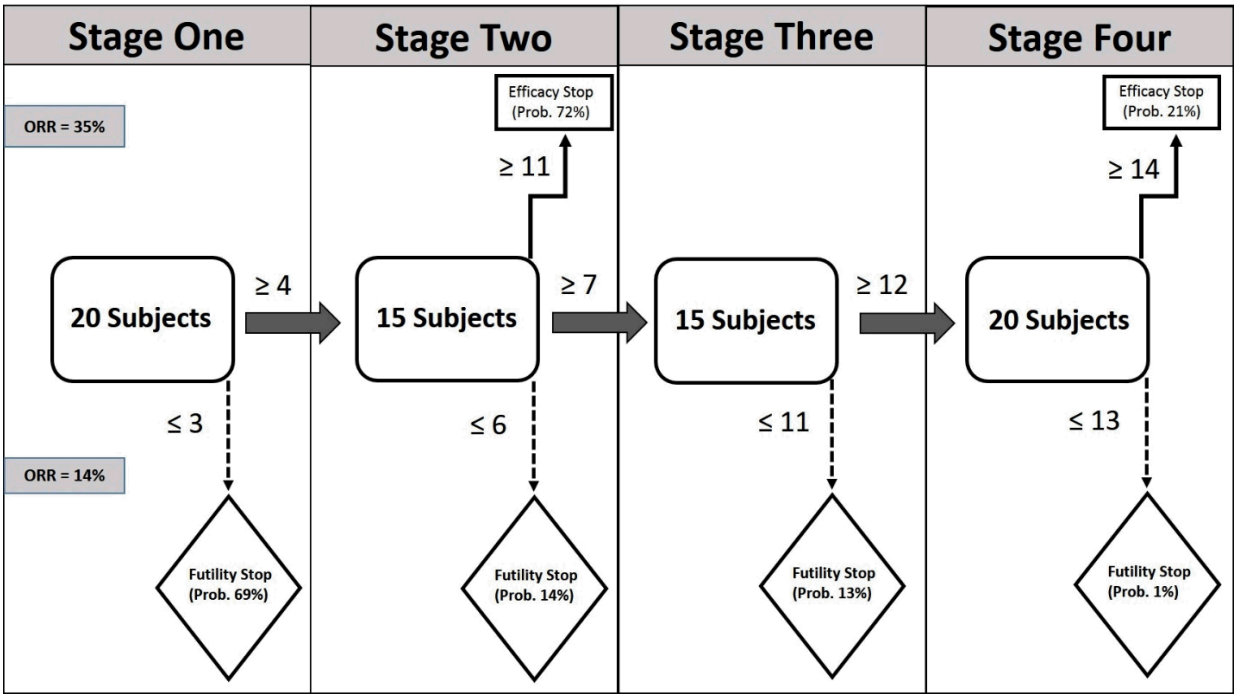
Track 1.b - Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-positive Subjects

Week 8 Inadequate Responders

The operating characteristics, futility stops, and efficacy boundaries of this design are provided in Figure 8.1.2.2-1. The stopping criteria specific to Track 1.b were selected via simulation to 1) control the probability of stopping for efficacy if the true ORR is 14% [redacted]; and 2) maximize the probability of stopping for efficacy if the true ORR is 35%. With the stopping boundaries as shown in Table 8.1-1, if the combination has an ORR no better than the historical control at 14%, then there is a 97% overall chance 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. If at least

11 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 14%. The CI is calculated using the Clopper-Pearson method.

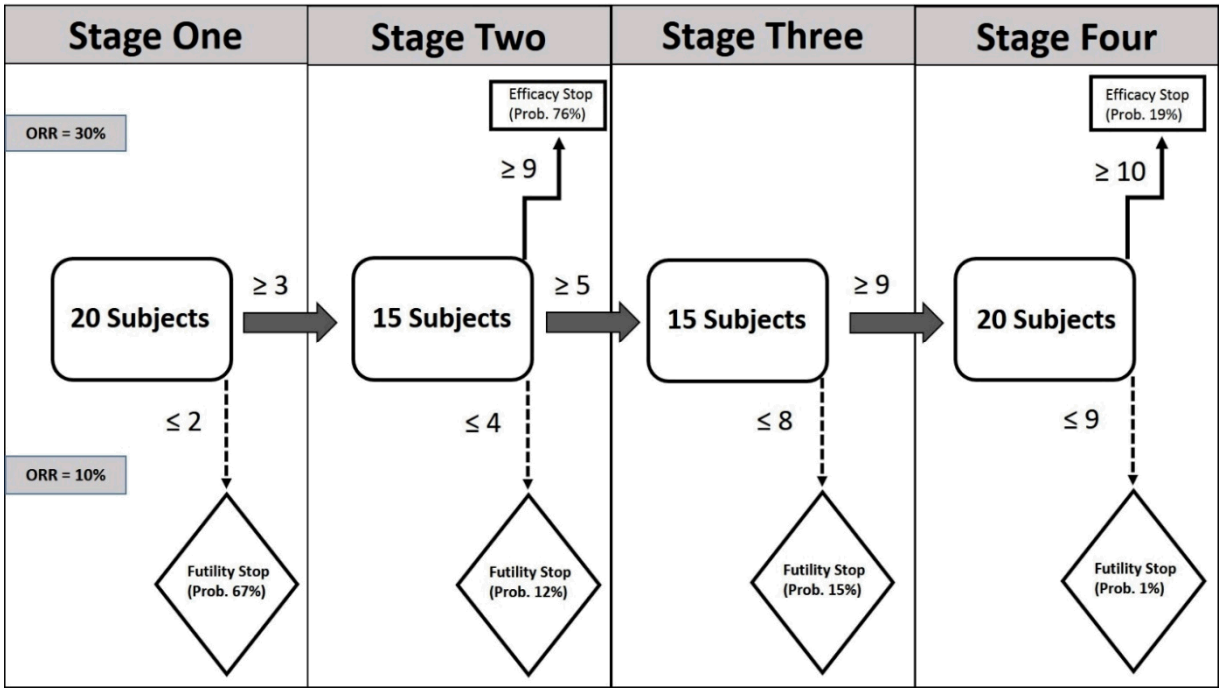
Figure 8.1.2.2-1: Operating Characteristics of Track 1b 4-Stage Design (Power =93%, Alpha = 3%)



Track 2 - IO Treatment-naïve, PD-L1-negative Subjects

The operating characteristics, futility stops, and efficacy boundaries of this design are provided in Figure 8.1.2.2-2. The stopping criteria specific to Track 2 were selected via simulation to 1) control the probability of stopping for efficacy 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 Table 8.1-1, if the combination has an ORR no better than the historical control at 10% ([redacted], 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. 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% (from nivolumab monotherapy data in Study CA209017). The CI is calculated using the Clopper-Pearson method.

Figure 8.1.2.2-2: Operating Characteristics of Track 2 4-Stage Design (Power =95%, Alpha = 4.4%)

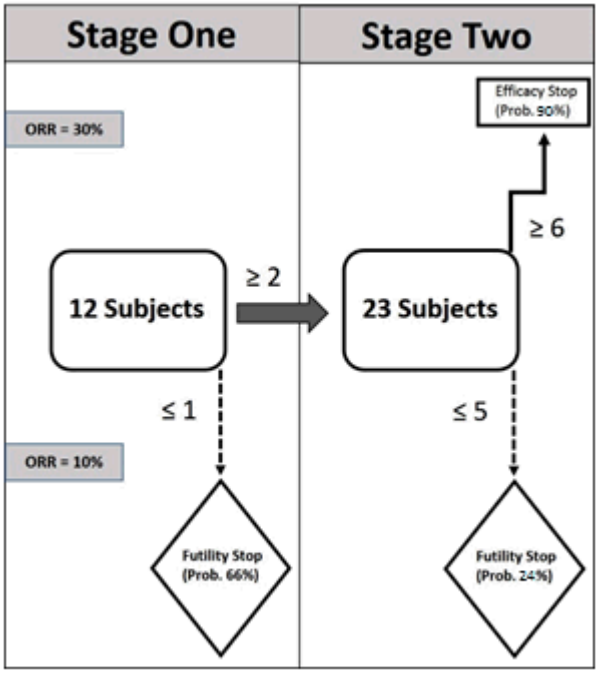


8.1.2.3 Track 3 - Anti-PD-1/PD-L1 Treatment-experienced Subjects

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 8.1.2.3-1. With the stopping boundaries as shown in Table 8.1-1, 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 8.1.2.3-1: Operating Characteristics of Track 3 Simon 2-Stage Design (Power = 90%, Alpha = 10%)



Both subjects previously treated in Tracks 1 and 2 (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% dropout 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% dropout 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]

[redacted] [redacted]

[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

8.2 Populations for Analyses

- All enrolled subjects include all subjects who signed the written informed consent and were registered into the IRT.
- All randomized subjects include all subjects who were randomized to any treatment arm of any track in this study.
- All treated subjects include all subjects who received at least 1 dose of study drug.
- [redacted]

8.3 Endpoints

8.3.1 Primary Endpoints

The primary objective of preliminary efficacy will be measured by ORR, DOR, and PFSR at 24 weeks based on RECIST v1.1 criteria. Tumor response will be based on tumor assessments at screening, every 8 weeks from the first dose until investigator assessed initial disease progression (per RECIST v1.1) 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 safety follow-up, or until subjects withdraw from the study.

- Best overall response (BOR) is defined as 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 therapy (re-randomized therapy will be considered as subsequent therapy). CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. For those subjects who have surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR.
- ORR is defined as the proportion of all treated subjects whose BOR is either a CR or a PR.
- 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 disease progression or death (death occurring after re-treatment or re-randomization will not be included), whichever occurs first.
- PFSR at 24 weeks is defined as the proportion of treated subjects remaining progression free and surviving at 24 weeks. The proportion will be calculated by the Kaplan-Meier estimate, which takes into account censored data.

8.3.2 Secondary Endpoints

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

AEs and laboratory values will be graded according to the current version of the NCI CTCAE 4.0.3.

[redacted]

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated by treatment arm under each track for different subject populations. Summary statistics for age, body weight, and height will be tabulated by treatment arm under each track for different subject populations.

8.4.2 Efficacy Analyses

Treatments under each track for different populations will be analyzed independently. There is no intention to combine the same treatment across tracks for efficacy analyses.

Efficacy from re-treatment will be assessed and analyzed separately from the initial treatment.

Subjects re-randomized into Track 3 or 5 will be combined with subjects originally randomized into Track 3 or 5 for efficacy analysis.

In general, the following efficacy analyses will be performed. Listings of tumor measurements will be provided by subject and study day in each treatment arm under each track for different subject populations. Individual subject's BOR will be listed. ORR and corresponding 2-sided 95% exact CI will be provided. Median DOR and corresponding 2-sided 95% CI will be reported. PFSR at 24 weeks will be estimated. The corresponding 95% CI will be derived. [redacted]

Time-to-event endpoints (DOR, PFS, PFSR, [redacted]) will be analyzed using Kaplan-Meier method, and the corresponding CI will be derived based on Greenwood formula. Exact CI for ORR will be calculated by Clopper-Pearson method.

Specific analyses to be performed for each track are shown in Table 8.4.2-1.

Table 8.4.2-1: Analyses Planned for Each Track

Track		ORR	DOR	PFSR	[redacted]
Track 1.a		X	X	X	
Track 1.c					
Tracks 1.b and 2	End of Stages 1, 2, 3, and 4	X	X	X	
	Early Termination at Stage 1			X	
Tracks 3 and 4	End of Simon Stage 2	X	X	X	
	Early Termination at Simon Stage 1			X	
Track 5		X	X	X	

8.4.3 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment under each track for different populations and will be coded according to the most current version of MedDRA. Vital signs and clinical laboratory test results will be listed and summarized by treatment under each track for different populations. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

Subjects receiving the same treatment in different tracks may be combined for safety analyses.

[redacted]

[redacted]

8.4.8 Other Analyses

Not applicable.

8.5 Interim Analyses

Data from individual treatment under each track of this study may emerge at different times; timely decision (including early termination) for each individual treatment under different tracks is needed. Database lock and analysis for certain FRACTION-Lung combination arms will be performed when all subjects in these combination arms (under each track) have completed treatment and with sufficient follow-up. Potential interim analyses for each combination arm under each track are listed in Table 8.5-1. These interim analyses will be performed independent of each other.

Table 8.5-1: Potential Interim Analyses

Track	Interim Analyses
Track 1.b Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-positive Subjects Who Are Inadequate Responders by Week 8	End of Stage 1, end of Stage 2, end of Stage 3
Track 2 Anti-PD-1/PD-L1 Treatment-naïve, PD-L1-negative Subjects	End of Stage 1, end of Stage 2, end of Stage 3
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

The SMB will have access to interim reports of safety and will provide advice to the Sponsor regarding arm termination due to safety concerns.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study, if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

9.1.2 Monitoring

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

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

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

9.1.2.1 Source Documentation

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

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

9.1.3 Investigational Site Training

BMS representatives will provide quality investigational staff training prior to study initiation. Training topics will include, but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study and BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label identification number or batch number
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Nonstudy disposition (eg, lost, wasted)
- Amount destroyed at study site

- Retained samples for bioavailability/bioequivalence, if applicable
- Dates and initials of person responsible for IP dispensing/accountability, as per the Delegation of Authority Form

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

9.2.3 Case Report Forms

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

For sites using the electronic data capture tool, electronic CRFs will be prepared for all data collection fields, except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE Report Form and Pregnancy Surveillance Form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature are completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

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

9.3 Clinical Study Report and Publications

A Signatory investigator must be selected to sign the clinical study report. Multiple clinical study reports for the FRACTION-Lung program may be generated to allow timely reporting of results for each completed FRACTION Sub-Protocol or results from a discontinued FRACTION-Lung treatment.

For this protocol, the Signatory investigator will be selected, as appropriate, based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS publication requirements, as set forth in the approved Clinical Trial Agreement. All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but (at any event) not less than 30 days before submission or presentation, unless otherwise set forth in the Clinical Trial Agreement. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for the purpose of filing a patent application.

10 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
ALK	anaplastic lymphoma kinase
BOR	best overall response
CR	complete response
DILI	drug-induced liver injury
DOR	duration of response
EGFR	epidermal growth factor receptor
EOT	end of treatment
EQ-5D-3L	EuroQol 5-Dimension 3-Level Questionnaire
FLSI-12	Functional Assessment of Cancer Therapy - Lung Symptom Index-12
FRACTION	Fast Real-time Assessment of Combination Therapy in Immuno-ONcology (program)
FRACTION-Lung	the current study (CA018001) for which this document serves as the Master Protocol
FRACTION-Lung Master Protocol	the current protocol, to which future FRACTION-Lung Sub-Protocols will be appended
FRACTION-Lung Sub-Protocol(s)	document(s) that will introduce additional novel FRACTION-Lung combination(s) and/or contemporaneous control treatments and will be appended to this FRACTION-Lung Master Protocol
FU	follow-up
GITR	glucocorticoid-induced tumor necrosis factor receptor-related gene
HRQoL	health-related quality of life
IFNγ	interferon gamma
IP	investigational product
IRC	independent review committee
IRT	Interactive Response Technology
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
SD	stable disease
SMB	Safety Monitoring Board
TKI	tyrosine kinase inhibitor
VAS	visual analog scale

12 APPENDICES

APPENDIX 1 ECOG PERFORMANCE STATUS

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD-ECOG-WHO	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	1	Symptoms, but fully ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death non imminent	30	4	Unable to get out of bed
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

[redacted]

APPENDIX 2 RECIST V1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

1.1 Measurable lesions

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

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥15 mm in ***short*** axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions.
- Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that in not measurable by reproducible imaging techniques.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

1.3.2 Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.4 Specifications by methods of measurements

1.4.1 Measurement of lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of the treatment.

1.4.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

1.4.2.1 CT/MRI scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.4.2.3 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.4.2.5 Endoscopy, laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

1.4.2.6 Tumor markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target lesions

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

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements.***

A ***sum of the diameters*** (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the ***baseline sum diameters.*** If lymph nodes are to be included in the sum, then as noted below, only the ***short*** axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

2.1.1 Lymph nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as **'present', 'absent', or in rare cases 'unequivocal progression'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of target lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a **30% decrease in the sum of diameters of target lesions,** taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.1.1 Special notes on the assessment of target lesions

3.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

3.1.1.2 Target lesions that become 'too small to measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be

assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

3.1.1.3 Target lesions that split or coalesce on treatment

- When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

3.2.1 Special notes on assessment of non-target lesions

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

3.2.1.1 When the subject also has measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

3.2.1.2 When the subject has only non-measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on

the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'.

- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. *If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.*

3.3.1 FDG-PET evaluation

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

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

4 RESPONSE CRITERIA

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For subjects who have **measurable disease** at baseline Table 1 provides a summary of the overall response status calculation at each time point.

Table 1. Time point response: subjects with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE =not evaluable.

4.1.1 Missing assessments and not evaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can

be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

4.1.2 Confirmation scans

- **Verification of Response**: Confirmation of PR and CR is required within 4 weeks to ensure responses identified are not the result of measurement error. To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.
- **Verification of Progression**: Not required.

4.2 Best overall response: All timepoints

The *best overall response* is determined once all the data for the subject is known. It is the best response recorded from the start of the study treatment until objectively documented progression per RECIST1.1 or the date of subsequent anticancer therapy taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all time points with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 2. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (not less than 4 weeks).

Table 2. Best overall response when confirmation of CR and PR *IS* required.

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2. Best overall response when confirmation of CR and PR *IS* required.		
Overall response	**Overall response**	**BEST overall response**
First time point	**Subsequent time point**	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.3 Duration of response

4.3.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 4 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 06, 12-Apr-2018

The FRACTION-Lung Master Protocol was revised with edits based on the addition of the FRACTION-Lung Sub-Protocol C.

Summary of key changes of Revised Protocol 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1: Study Design and Duration; Section 4.4	Removed stratification by PD-L1 expression in Track 4 and introduced the option of new randomization schedules in Sub-Protocols.	
Section 3.1: Study Design and Duration	Two-stage design may be used in Track 5, as opposed to a single-stage design, based on specific Sub-Protocols.	
Section 3.4: Study Population	Emphasis added to direct readers to Sub-Protocols for additional inclusion and exclusion criteria including the following: inclusion criteria 1c and 3.	
Section 8: Statistical Considerations	Emphasis added to direct readers to Sub-Protocols for additional statistical considerations.	
Section 3.4: Study Population	Inclusion criteria 2.c.i was modified to note that EGFR testing must be performed using tumor tissue.	
Table 5.1-1: Screening Procedural Outline; Table 5.1-2: Baseline for Retreatment/Re-randomization Procedural Outline	Urinalysis added to the screening and the baseline for retreatment/re-randomization procedural outlines.	
Section 6.1.1: Serious Adverse Event Collection and Reporting	Added clarification that death resulting from disease progression within 100 days of discontinuation of dosing must be reported as an SAE within 24 hours.	
All	Minor formatting and typographical corrections.