Official Title of Study:

A Phase 2, Randomized, Open-label Study of Relatlimab in Combination with Nivolumab in Participants with Advanced Hepatocellular Carcinoma who are Naive to IO Therapy but Progressed on Tyrosine Kinase Inhibitors (RELATIVITY-073)

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CLINICAL PROTOCOL CA224073

A Phase 2, Randomized, Open-label Study of Relatlimab in Combination with Nivolumab in Participants with Advanced Hepatocellular Carcinoma who are Naive to IO Therapy but Progressed on Tyrosine Kinase Inhibitors (RELATIVITY-073)

Short Title: Phase 2 study of relatlimab and nivolumab in IO-naive 2nd/3rd-line HCC

Protocol Amendment 04

[redacted] Medical Monitor
Bristol-Myers Squibb Company
Route de Perreux 1
2017 Boudry, Switzerland
Telephone (mobile): [redacted]
Email: [redacted]

[redacted]
Bristol-Myers Squibb Company
3401 Princeton Pike
Lawrenceville, NJ, USA
Telephone (mobile): [redacted]
Email: [redacted]

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

Bristol Myers Squibb Company
3401 Princeton Pike
Lawrenceville, NJ 08648

Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

6-5-1 Nishi-Shinjuku, Shinjuku-ku,
Tokyo, 163-1327, Japan

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	26-May-2022	[redacted] Additional updates, including personnel changes and changes to sections of the Synopsis, have been made to align the protocol with respect to these changes. This protocol amendment applies to all participants.
Administrative Letter 01	10-Mar-2022	The purpose of this administrative letter is to communicate the change of the Medical Monitor and Clinical Scientist.
Protocol Amendment 03	29-Jul-2021	[redacted] Additional updates, including to sections of the Synopsis, have been made to align the protocol with respect to these changes. This protocol amendment applies to all participants.
Protocol Amendment 02	15-Apr-2021	The primary reasons for these changes are to include participants with advanced immuno-oncology (IO) therapy-naive hepatocellular carcinoma (HCC) who have received one or two lines of tyrosine kinase inhibitor (TKI) therapies and have shown radiographic progression on or after the last line of TKI therapy; clarify expectations for sample collection, study assessments, and participant eligibility; [redacted].
Revised Protocol 01	28-Oct-2020	The primary reasons for these changes are to align dose modification criteria [redacted] with the current Common Terminology Criteria for Adverse Event (CTCAE) version (v5); add serologic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status; and incorporate additional updates to improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, sample collections, treatment administration, and country-specific requirements.
Original Protocol	29-May-2020	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04:

The primary rationale for Protocol Amendment 04 is to make overall study design changes and clarify several items throughout the protocol.

The original design of CA224-073 was a 3-arm study randomized 2:1:2 with the following treatment arms:

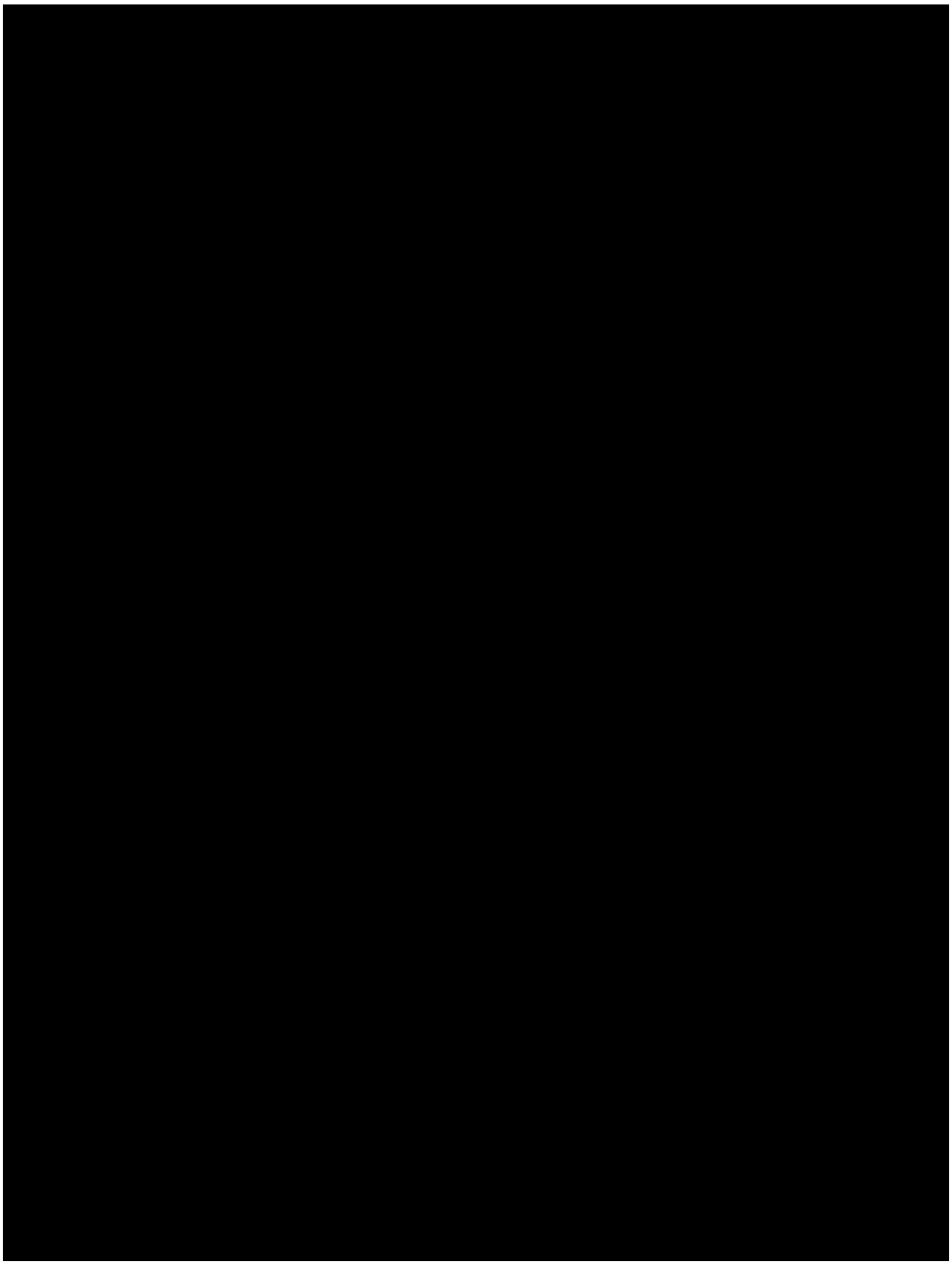
- Arm A: nivolumab 480 mg every 4 weeks (Q4W)
- Arm B: nivolumab 480 mg Q4W + relatlimab 480 mg Q4W
- Arm C: nivolumab 480 mg + relatlimab 960 mg Q4W

[redacted] 24 participants were randomized in Arm C.

[redacted]

[redacted]

[redacted]



SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Changed Medical Monitor from [redacted], to [redacted], Clinical Scientist from [redacted] to [redacted], and their associated contact information.	To report important personnel changes.
[redacted]		
Table 2-1: Screening Procedural Outline (CA224073)	Removed the following text from notes corresponding to the "Pre-screening for Tumor Tissue Sample" row: "All other procedures may be performed within 14 days if pre-screening ICF is used."	To avoid confusion regarding procedures that can be done with pre-screening informed consent form (ICF).
	Modified the language from "Most" to "All" inclusion/exclusion criteria in notes corresponding to the Inclusion/Exclusion Criteria row.	For clarity.
	[redacted]	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added the following text to notes corresponding to the row Physical Examination: "Full physical examination including height, weight, and BMI. Any findings during the PE will be recorded as medical history in the participant's medical records and on the appropriate CRF."	Clarified requirements for physical examination.
	Oxygen saturation was added to vital sign assessments.	Clarified requirements for vital sign assessments.
	Added the following text to notes corresponding to the row 12-lead ECG: "ECGs must be collected and assessed using the site's own ECG machine."	To maintain consistency with the text stated in future visits.
	Replaced "24 hours" with "1 day" in the notes corresponding to the row, Pregnancy Test (WOCBP only).	To update window to 1 day instead of 24 hours and maintain consistency among sections.
Section 5.1.1: Screening Period	Added the following text: If the subject is awaiting central laboratory results, then the participant does not have to reconsent until day 42 (additional +14 days beyond screening window). Other screening procedures should be conducted within the windows specified in Table 2-1.	For clarity.
Table 2-2: On-Treatment Assessments (CA224073)	• Clarified on-treatment monitoring requirements between Arm A and B. • [redacted] • [redacted] • Added: Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response.	To clarify that the enhanced monitoring requirements are specific to Arm B. [redacted] To clarify confirmatory imaging requirements.
	[redacted]	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Replaced "24 hours" with "1 day" in the notes corresponding to the row, Pregnancy Test (WOCBP only). • Added the following text to notes corresponding to the row Body Imaging: " disease progression (unless treatment beyond progression) or treatment discontinuation (including treatment beyond progression), whichever occurs later."	To maintain consistency among sections. To clarify imaging requirements and maintain consistency across protocol.
Table 2-3: Follow-up Procedural Outline (CA224073)	Added the following text to notes corresponding to the row Targeted Physical Examination: "Any findings during the PE will be evaluated for AEs and reported as such."	To emphasize adverse event (AE) reporting requirements during follow-up.
	Added the following text to notes corresponding to the row Body Imaging: "Participants with SD, PR, or CR at the time of the EOT visit or at the time of study treatment discontinuation will continue to have radiologic and clinical tumor assessments every 8 weeks (± 7 days) after discontinuation of study treatment/EOT visit, until the start of subsequent therapy, disease progression (unless treatment beyond progression), or withdrawal of study consent." Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response."	To clarify and maintain consistency across protocol-regarding imaging requirements.
Section 5.1.3: Follow-up Period Section 7.7.1 Prohibited and/or Restricted Treatments Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information Section 9.2.2: Methods of Detecting AEs and SAEs	Updated duration of clinical safety follow-up from 100 days to 135 days.	Safety follow-up period extension to cover 5 half-lives of relatlimab.
Section 3.2.3: Relatlimab Combined with Nivolumab Clinical Activity	Updated the section with results from Study CA224047, a global, double-blind, randomized, Phase 2/3 study comparing a fixed-dose combination (FDC) formulation of nivolumab 480 mg + relatlimab 160 mg FDC Q4W to nivolumab 480 mg Q4W in participants with previously untreated advanced melanoma.	To provide background information on recent Phase 3 trial results in melanoma with nivolumab + relatlimab.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04

Section Number & Title	Description of Change	Brief Rationale
[redacted]		
Section 1: Synopsis Section 5.1: Overall Design Figure 5.1-1: Study Design Schematic for CA224073 [redacted]	Updated sample size to total approximately 250 participants, with 226 in Arm A and B, and 24 in Arm C.	[redacted]
Section 5.2: Number of Participants	Updated sample size to total approximately 250 participants, with 226 in Arm A and B and 24 in Arm C.	To clarify total sample size plan.
Section 6.1: Inclusion Criteria	[redacted] • Excluded participants with prior chemotherapy in inclusion criterion 2) b) iii). • Added to inclusion criterion 3) b) i): "No contraception is required for male participants."	[redacted] To clarify that only patients with prior tyrosine kinase inhibitor (TKI) treatment, not chemotherapy, are eligible to enroll. For clarity.
Section 6.1: Inclusion Criteria Section 6.4.1: Retesting During Screening Period	Removed language allowing participant re-randomization from inclusion criterion 1) c. The term "pre-treatment failure" was changed to "screen failure" for further clarification.	To prevent re-randomization to the trial which would impact the intent-to-treat population; this does not change language allowing re-enrollment of pre-treatment/screen failures.
Section 1 Synopsis Section 6.2: Exclusion Criteria	Added "pregnant or" to the existing exclusion criterion 2) a).	To make it consistent with Section 6.1 Inclusion Criterion 3) a) x) of the protocol.
Section 7.1.3: Palliative Therapy	Clarified palliative therapy language.	To better define circumstances when

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
		palliative therapy is permitted.
Section 7.3: Blinding	Clarified blinding language regarding open-label design.	To clarify that study has been treated as open label per design.
Section 7.7.1: Prohibited and/or Restricted Treatments	Clarified that "systemic" chemotherapy is prohibited while on study treatment.	To clarify that locally administered chemotherapy that is not directed at hepatocellular carcinoma may be permissible.
Section 8.1.3: Criteria to Resume Treatment	Clarified the criterion, as shown below, to resume [redacted] treatment in participants [redacted].	To fix an inconsistency in this protocol regarding requirements for re-initiation of treatment [redacted].
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Clarified the requirement to report deaths occurring within the follow-up period as SAEs.	To continue to report deaths within the follow-up period as SAEs regardless of initiation of new anti-neoplastic treatment.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.8.4: Additional Research Collection	Clarified that additional research collection and analysis will not occur [redacted] as per Protocol Amendment 04.	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.3.3: Other Analyses	[redacted] Language describing the plan to conduct [redacted] analyses using data obtained from the study was added.	Language added [redacted]
[redacted]		
Appendix 2: Study Governance Considerations	Added 2 new sections: BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy, and Data Security.	Added to align with BMS commitment to diversity in clinical trials and to comply with European Union Clinical Trials Regulation requirement.
[redacted]		
Section 11 References	3 new literature references.	Minor, therefore, have not been summarized.
All	Changed references to protocol amendment 03 to be in the past tense.	To clarify statements referencing protocol amendment 03 have already been implemented or are no longer relevant.
	Minor formatting and typographical corrections.	Minor, therefore, have not been summarized.

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1 SYNOPSIS

Protocol Title: A Phase 2, Randomized, Open-label Study of Relatlimab in Combination with Nivolumab in Participants with Advanced Hepatocellular Carcinoma who are Naive to IO Therapy but Progressed on Tyrosine Kinase Inhibitors (RELATIVITY-073)

Short Title: Phase 2 study of relatlimab and nivolumab in IO-naive 2nd/3rd-line HCC

Study Phase: 2a

Rationale:

Hepatocellular carcinoma (HCC) results in approximately 800,000 deaths globally per year. HCC has unique geographic, sex, and age distributions that are likely determined by specific etiologic factors. The preferred therapy for localized HCC is surgical resection, but the majority of patients are not eligible because of tumor extent or underlying liver dysfunction. For patients with disease that is not surgically resectable, liver transplantation is the only other potentially curative option. For patients with liver-limited disease who are not eligible for resection or liver transplantation, treatment options are locoregional therapies. Upon progression on locoregional therapy, systemic therapy is an option if performance status and underlying liver function are adequate. Currently, the standard of care for patients in first-line (1L) advanced/metastatic HCC are small molecule tyrosine kinase inhibitors (TKIs; eg, sorafenib and lenvatinib); however, with the data from the IMbrave 150 study, anti-programmed death-ligand 1 (PD-L1) and vascular endothelial growth factor (VEGF) inhibitor (atezolizumab and bevacizumab) combination therapy has reshaped the current landscape and also the subsequent therapies.

Individually targeting immune checkpoint receptors, such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death-1 (PD-1), has been clinically successful across multiple tumor types, including HCC. It is possible, however, that combination therapies could potentially lead to greater depth of response and overall survival (OS), as has been noted with anti-PD-1 and anti-CTLA-4 combination therapy in advanced melanoma patients. Targeting additional checkpoints, such as lymphocyte activation gene 3 (LAG-3), is considered a promising, novel approach. Dual blockade of LAG-3 and PD-1 has potential to improve efficacy in comparison with blocking PD-1 alone, without adding significant toxicity. [redacted] There is also evidence that fibrinogen-like protein 1 (FGL-1), a liver-secreted protein, is a major LAG-3 functional ligand independent from major histocompatibility complex (MHC) Class II. FGL-1 inhibits antigen-specific T-cell activation, and ablation of FGL-1 in mice promotes T-cell immunity. Blockade of the FGL-1:LAG-3 interaction by monoclonal antibodies stimulates tumor immunity and is therapeutic against established mouse tumors in a receptor-ligand, inter-dependent manner. FGL-1 is highly produced by human cancer cells, and elevated FGL-1 in the plasma of cancer patients is associated with a poor prognosis and resistance to anti-PD-1/B7-H1 therapy. [redacted]

Nivolumab is currently in development and has been registered in a variety of tumors. Development of nivolumab for HCC was initiated in 2012 with CA209040, which is a Phase 1/2 clinical trial evaluating the safety and efficacy of nivolumab in advanced HCC. Data from the dose-escalation and expansion cohorts of this study led initially to the accelerated approval of nivolumab for the second-line (2L) therapy of advanced HCC patients who progressed on or were intolerant to sorafenib in many, but not all (eg, not approved in Japan), countries. As of the most recent analysis, with 27 months of follow-up, with 154 participants treated with nivolumab 3 mg/kg every 2 weeks (Q2W), the objective response rate (ORR) was 14%, the median progression-free survival (mPFS) was 2.83 months, and the median OS (mOS) was 15.6 months.

Most recently, the doublet combination of nivolumab and ipilimumab received accelerated approval in the United States in the same setting in HCC. This approval was based on data from the 28-month follow-up, demonstrating an ORR of 33% among the 49 participants treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 doses, followed by nivolumab 240 mg Q2W.

After the approval of atezolizumab and bevacizumab combination in 1L HCC, the treatment recommendations shifted to indicate that previously approved 1L TKI therapies are now recommended after atezolizumab and bevacizumab therapies, and agents that were recommended after failure of 1L TKI therapies are now recommended in subsequent settings, according to the most recent guidelines. Although, for patients who are not eligible or cannot get access to atezolizumab and bevacizumab regimen, the recommendations remain the same. Recommendations for 2L therapy differ depending on which regimen was administered 1L.

[redacted]

This Phase 2 study will evaluate the safety and efficacy of relatlimab in combination with nivolumab in 2L/third-line (3L) IO-naive HCC. Efficacy will be evaluated in the all-comer patient population for 480 mg relatlimab in combination with 480 mg nivolumab compared to nivolumab 480 mg monotherapy. [redacted] Approximately 226 participants will be randomized into Arm A and Arm B.

Study Population:

Adult (≥ 18 years) male and female participants with histologically confirmed HCC of any etiology (hepatitis C virus [HCV]-HCC, hepatitis B virus [HBV]-HCC, or non-viral related-HCC) who have never been exposed to prior IO therapy but progressed on TKI therapy in the advanced/metastatic setting.

- **Key inclusion criteria:**
  - Male and female participants must be ≥ 18 years at the time of informed consent.

- Participants with histologic confirmed advanced/metastatic 2L or 3L HCC.
- [redacted]
- Participants who have experienced progression that was demonstrated radiographically on or after one or two prior TKI therapies without prior exposure to IO agents.
- Child-Pugh score of 5 or 6 points (ie, Child-Pugh A).
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

- **Key Exclusion Criteria:**
  - Women who are pregnant or breastfeeding.
  - Untreated symptomatic central nervous system metastases or leptomeningeal metastases.
  - Participants with uncontrolled or significant cardiovascular disease.
  - Participants with clinically significant ascites defined by any prior (within 1 year) or current clinically significant ascites as measured by physical examination and that requires active paracentesis for control.
  - Participants with evidence of portal hypertension with bleeding esophageal or gastric varices within the past 6 months prior to randomization.
  - Episodes of hepatic encephalopathy (≥ Grade 2) within 12 months prior to randomization.
  - Prior organ allograft or allogeneic bone marrow transplantation.
  - Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
  - Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
  - Participants with active co-infection with:
    - Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV deoxyribonucleic acid (DNA) and HCV ribonucleic acid (RNA), OR
    - Hepatitis D infection in participants with HBV.
  - Participants with symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
    - Additionally, in the case of prior SARS-CoV-2 infection, acute symptoms must have resolved and, in consultation with Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.
  - Prior treatment with relatlimab or any other LAG-3 targeted agents.
  - Prior exposure to IO therapies such as, but not limited to, an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody, oncolytic viruses, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

Table 1-1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To evaluate the efficacy of relatlimab in combination with nivolumab relative to nivolumab monotherapy in IO therapy-naive participants after prior treatment with TKI therapy	• ORR assessed by BICR using RECIST v1.1
Key Secondary	
• To investigate safety and tolerability of relatlimab in combination with nivolumab in participants with advanced HCC	• Incidence of AEs, SAEs, and AEs leading to discontinuation, deaths, and clinical laboratory test abnormalities
• To further evaluate the preliminary efficacy of relatlimab in combination with nivolumab	• DCR, DOR, and PFS assessed by BICR per RECIST v1.1 • ORR, DCR, DOR, and PFS assessed by Investigator per RECIST v1.1 • OS

Abbreviations: AE = adverse event; BICR = Blinded Independent Central Review; DCR = disease control rate; DOR = duration of response; HCC = hepatocellular carcinoma; IO = immuno-oncology; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TKI = tyrosine kinase inhibitor.

Overall Design:

This Phase 2 study will evaluate the safety and efficacy of relatlimab in combination with nivolumab in participants with 2L or 3L IO-naive HCC.

As of 19-July-2021, participants are being randomized 1:1 to receive:

- **Arm A:** Nivolumab 480 mg Q4W
- **Arm B:** Nivolumab 480 mg Q4W+ Relatlimab **480** mg Q4W

- [redacted]

Arm C: Nivolumab 480 mg Q4W+ Relatlimab **960** mg Q4W

[redacted] 24 participants were randomized to Arm C.

[redacted]

For Protocol Amendment 03, all participants in Arm B and Arm C were re-consented. All new participants at the time had signed the updated informed consent for Protocol Amendment 03.

This is an open-label, randomized Phase 2 study in adult (≥ 18 years) male and female participants with advanced, Child-Pugh A, IO-naive HCC who have experienced progression that was demonstrated radiographically on or after one or two prior TKI therapies in the advanced/metastatic setting. Participants must not be amenable for management with surgery or locoregional therapy or have progressed after surgery or locoregional therapy.

Stratification will occur by region (Asia [excluding Japan] vs Rest of the World [including Japan]) and macrovascular invasion and/or extrahepatic spread (MVI/EHS; present or absent). For the purposes of randomization, LAG-3 will also be treated as a stratification factor.

MVI is defined as:

- Hepatic vein tumor thrombus, OR
- Inferior vena cava tumor thrombus, OR

- Portal vein tumor thrombus; Vp3/Vp4 (presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe or first-order branches of the portal vein) participants are also eligible.

EHS is defined as presence of metastatic disease in lymph nodes or distant sites outside the liver.

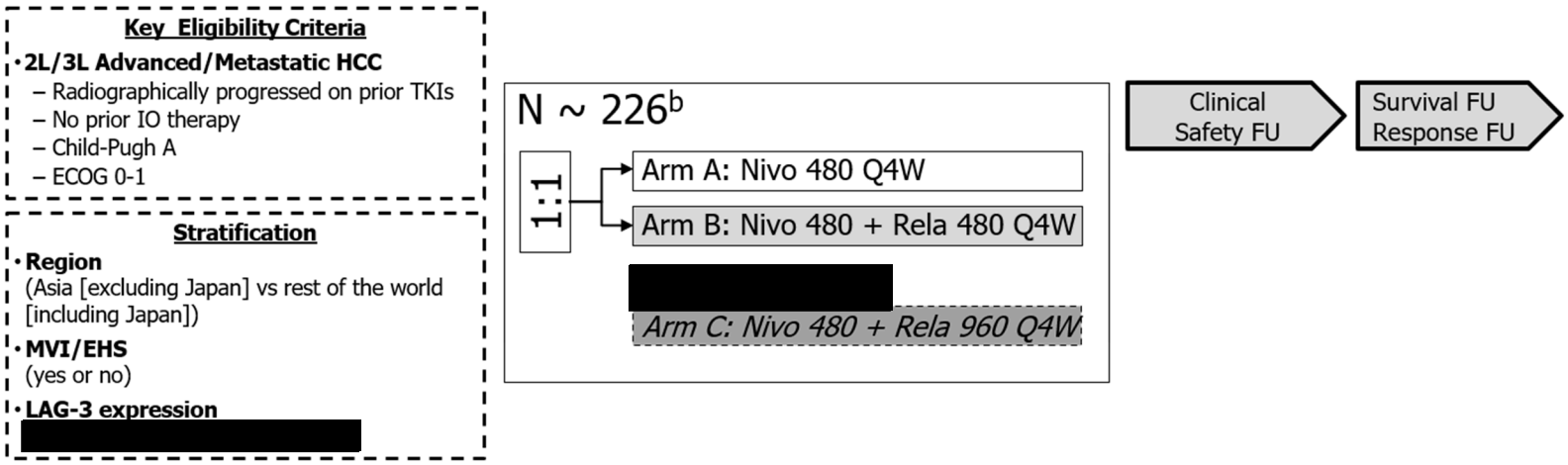
All participants will be treated until disease progression or unacceptable toxicity. Treatment beyond initial Investigator-assessed RECIST v1.1-defined progression is permitted if the participant has Investigator-assessed clinical benefit and is tolerating study treatment.

Individual participants with confirmed complete response (CR) will be given the option to discontinue study therapy on a case-by-case basis after specific consultation and agreement between the Investigator and BMS Medical Monitor in settings where benefit/risk justifies discontinuation of study therapy.

[redacted] Approximately 226 participants will be randomized into Arm A and Arm B.

A study design schematic for CA224073 is provided in Figure 1-1.

Figure 1-1: Study Design Schematic for CA224073



Abbreviations: [redacted] 2L = second line; 3L = third line; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; FU = follow-up; HCC = hepatocellular carcinoma; IO = immuno-oncology; LAG-3 = lymphocyte activation gene 3; MVI = macrovascular invasion; N = number; Nivo = nivolumab; Q4W = every 4 weeks; Rela = relatlimab; TKI = tyrosine kinase inhibitor.

[redacted]

[b] Total patients planned is approximately 250 with an additional 24 patients randomized to Arm C [redacted].

Number of Participants:

Approximately 250 participants will be randomized (226 to Arm A and B, and 24 in Arm C).

It is estimated that approximately 357 enrolled participants will be needed to achieve these 250 randomized.

Treatment Arms and Duration:

Information on the treatment groups and duration is provided in Table 1-2.

Table 1-2: Treatments Administered

Study Arm	Study Treatment	Dose Level	Frequency of Administration and Duration of Treatment	Route of Administration	Approximate Infusion Time, minutes
Arm A	Nivolumab	480 mg	Q4W Until progression, unacceptable toxicity, or withdrawal of consent	IV	30
Arm B	Nivolumab/ Relatlimab[a]	480 mg/ 480 mg	Q4W Until progression, unacceptable toxicity, or withdrawal of consent	IV	60
Arm C	Nivolumab/ Relatlimab[a]	480 mg/ 960 mg	Q4W Until progression, unacceptable toxicity, or withdrawal of consent	IV	60[b]

[redacted]

Abbreviations: IV = intravenous; mg = milligram; Q4W = every 4 weeks.

[a] Nivolumab and relatlimab are co-administered.

[b] Infusions will occur over approximately 60 minutes for participants weighing equal to or greater than 45 kg, and for participants weighing less than 45 kg, infusions will occur over approximately 90 minutes.

Study Treatment:

Information on the study treatments is provided in Table 1-3.

Table 1-3: Study Treatment for CA224073

Medication	Potency	IP/Non-IP
Relatlimab[a] Injection (10 mg/mL)	10 mg/mL	IP
Nivolumab[a] Injection (10 mg/mL)	10 mg/mL	IP

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

[a] Relatlimab is sometimes referred to as BMS-986016; Nivolumab is sometimes referred to as BMS-936558.

Data Monitoring Committee: No.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA224073)

Procedure	Screening Visit -28 Days	Day -14 to Day -1 Visits	Notes[a] (All windows are based on calendar days.)
Pre-screening for Tumor Tissue Samples	X		[redacted] The participant may proceed to additional screening procedures after signing the main study ICF.
Eligibility Assessments			
Pre-screening or Main Informed Consent	X		Prior to any screening procedures. Study allows for re-enrollment of a participant that has discontinued the study as a screen failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT. For Protocol Amendment 03, all current participants in Arm B and Arm C were re-consented. All new participants had signed the updated informed consent for Protocol Amendment 03.
Contact IRT	X		For participant number assignment at time main or pre-screening informed consent is obtained.
Inclusion/Exclusion Criteria	X		All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization, including LAG-3 expression status (see Section 6).
Medical History	X		All medical history relevant to HCC, including disease characteristics (including stratification factors, Barcelona Clinic Liver Cancer stage [see Appendix 10]), concomitant medications, prior cancer therapy, and alcohol history.
Prior Systemic Therapies	X		Includes prior cancer treatment regimens and medications administered within 4 weeks of study dose administration.
Child-Pugh Score	X		Child-Pugh A score is required (see Appendix 5 and Section 6.1 for inclusion criteria).

Table 2-1: Screening Procedural Outline (CA224073)

Procedure	Screening Visit -28 Days	Day -14 to Day -1 Visits	Notes[a] (All windows are based on calendar days.)
Required Tumor Tissue Samples	X		An FFPE tumor tissue block (preferred) or a minimum of 20 freshly cut unstained slides* of tumor tissue obtained from core biopsy, incisional biopsy, excisional biopsy, or surgical specimen prior to enrollment is required. [redacted] Fine needle aspirates or other cytology samples and biopsies of bone lesions that do not have a soft tissue component are not acceptable. Note the following for the required tumor sample: • Samples should be collected within 3 months of enrollment. Biopsy can be taken any time during or after TKI treatment, with no intervening systemic anti-cancer treatment between time of acquisition and randomization. • If a tumor sample (as described above) is not available, then a fresh pre-treatment biopsy may be obtained. This fresh biopsy should be excisional, incisional, or core needle. • If the first 2 options are not feasible, then, in rare instances, an archival tissue sample may be submitted if approval from BMS (Medical Monitor or Clinical Scientist) is obtained. Tumor sample must be sent to the central laboratory. [redacted] Other screening procedures should be conducted within the windows specified. **If despite best efforts, a minimum of 20 slides are not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with BMS Medical Monitor or Clinical Scientist.* [redacted]
[redacted]			
Safety Assessments			
Physical Examination		X	Full physical examination, including height, weight, and BMI. Any findings during the PE will be recorded as medical history in the participant's medical records and on the appropriate CRF.

Table 2-1: Screening Procedural Outline (CA224073)

Procedure	Screening Visit -28 Days	Day -14 to Day -1 Visits	Notes[a] (All windows are based on calendar days.)
Physical Measurements		X	Includes height and weight.
Performance Status		X	ECOG performance status (see Appendix 6).
Vital Signs		X	Including BP, heart rate, oxygen saturation by pulse oximetry, and temperature. BP and heart rate should be measured after the participant has been seated quietly for at least 5 minutes.
Assessment of Signs and Symptoms		X	Within 14 days of randomization.
Concomitant Medication Use	X		Concomitant medication use within 28 days of randomization and vaccine use within 30 days prior to randomization.
2D-Echocardiogram	X		LVEF assessment with documented LVEF ≥ 50% by either TTE (preferred test) or MUGA scan within 6 months from first study drug administration. If more than 1 scan is performed, the most recent scan is applicable.
12-lead ECG		X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes. ECGs must be collected and assessed using the site's own ECG machine.
Chest Radiograph	X		Posterior-anterior and lateral (either side) chest x-ray to establish baseline.
Serious Adverse Events Assessment	X		SAEs collected from time of consent (pre-screening and/or main ICF). All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent. See Section 9.2. AEs are graded per CTCAE v5, except as described for hepatic and endocrinopathies [redacted].
Laboratory Tests		X	Local laboratory testing, including testing for symptomatic SARS-CoV-2 infection. Hematology, serum chemistry, and urinalysis, as outlined in Section 9.4.4.
Urinalysis		X	See Section 9.4.4.
Thyroid Function Tests		X	See Section 9.4.4.
Serology	X		Hep B surface antigen, Hep B surface antibody, Hep B core antibody, Hep B DNA viral load (PCR), Hep C RNA viral load (PCR), Hep C antibody, and Hep D antibody (if chronic HBV infection). See Section 9.4.4.

Table 2-1: Screening Procedural Outline (CA224073)

Procedure	Screening Visit -28 Days	Day -14 to Day -1 Visits	Notes[a] (All windows are based on calendar days.)
			HIV (when required by local regulations [see Appendix 7]), must be done at local laboratory within 28 days prior to randomization. See Section 9.4.4.
Coagulation Profile	X		Including PT/INR and aPTT. If screening laboratory test samples are drawn within 4 days of first treatment, then these laboratory samples will also qualify as Day 1 (predose) laboratory samples. See Section 9.4.4.
Disease Assessment: Serum Alpha-fetoprotein	X		See Section 9.4.4.
[redacted]			
Pregnancy Test (WOCBP only)	X		Local laboratory testing Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within 1 day prior to first dose of study treatment. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.
Follicle-stimulating Hormone	X		If needed to document post-menopausal status, as defined in Section 9.4.4. Females under the age of 55 years must have a serum FSH level > 40 mIU/mL to confirm menopause.
Efficacy Assessments			
Body Imaging: Baseline Tumor Assessments	X		Contrast-enhanced CT of the chest, CT or MRI of abdomen and pelvis (including required tri-phasic CT or MRI of the liver), and all other known and/or suspected sites of disease should be performed within 28 days prior to randomization. See Section 9.1.1 for further details.
Brain Imaging	X		MRI of the brain with and without contrast is required for participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain within 28 days of randomization. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 for further details.

Table 2-1: Screening Procedural Outline (CA224073)

Procedure	Screening Visit -28 Days	Day -14 to Day -1 Visits	
Notes[a] (All windows are based on calendar days.)			
Other Imaging: Bone Scan	X		See Section 9.1.1; as clinically indicated per local standards.

Abbreviations: 2D = 2-dimensional; AE = adverse event; BMS = Bristol Myers Squibb; BP = blood pressure; [redacted] CRF = case report form; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCG = human chorionic gonadotropin; Hep = hepatitis; HIV = human immune deficiency virus; ICF = informed consent form; IgG = immunoglobulin G; [redacted] INR = international normalized ratio; IRT = Interactive Response Technology; IU = international unit; L = liter; LAG-3 = lymphocyte activation gene 3; LVEF = left ventricular ejection fraction; mL = milliliter; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PCR = polymerase chain reaction; PT = prothrombin time; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TKI = tyrosine kinase inhibitor; TTE = transthoracic echocardiogram; WOCBP = women of child bearing potential.

[a] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Table 2-2: On-Treatment Assessments (CA224073)

Procedure[a]	Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment (EOT)[b]	Notes[c] (All windows are based on calendar days.)
	D1	D15 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)		
Eligibility Assessments						
Inclusion/Exclusion Criteria	X					**Cycle 1 Day 1 only:** All inclusion/exclusion criteria should be confirmed prior to first dose.
Safety Assessments						
Targeted Physical Examination	X	X	X	X	X	To be performed only as clinically indicated prior to dosing, using local oncology/hepatology physical examination guidelines when new symptoms or laboratory abnormalities occur.
Child-Pugh Score	X		X		X	See Appendix 5.
Vital Signs	X	X	X	X	X	Including BP, heart rate, and temperature prior to dosing. BP and heart rate should be measured after the participant has been seated quietly for at least 5 minutes.
Oxygen Saturation	X		X		X	Prior to dosing; collect at rest via pulse oximetry. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O2 levels will not be used in isolation to document or diagnose pulmonary toxicity.
Physical Measurements and Performance Status	X		X		X	Weight and ECOG (see Appendix 6), prior to dosing.
Adverse Event and Serious Adverse Event Assessments	Continuously					All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. See Section 9.2. AEs are graded per CTCAE v5, except as described for hepatic and endocrinopathies [redacted].
Concomitant Medication Use	Continuously					

Table 2-2: On-Treatment Assessments (CA224073)

Procedure[a]	Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment (EOT)[b]	Notes[c] (All windows are based on calendar days.)
	D1	D15 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)		
Laboratory Tests [redacted]	X	X	X	X	X	Locally performed: **Within 3 calendar days prior to dosing**, including hematology, serum chemistry, urinalysis, thyroid function tests, [redacted] and coagulation profile, as outlined in Section 9.4.4. [redacted]
Thyroid Function Tests	X		X		X	See Section 9.4.4.
[redacted]						

Table 2-2: On-Treatment Assessments (CA224073)

Procedure[a]	Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment (EOT)[b]	Notes[c] (All windows are based on calendar days.)
	D1	D15 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)		
[redacted]						
Coagulation Profile	X	X	X	X	X	Including PT/INR and aPTT. See Section 9.4.4.
Disease Assessment: Serum Alpha-fetoprotein	X		X		X	See Section 9.4.4.
12-lead ECG	X	X	X			12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes. ECGs must be collected and assessed predose on Day 1 of each cycle using the site's own ECG machine; done on Day 1 only starting with Cycle 2.
2D Echocardiogram	See notes.					For all participants: performed locally as clinically indicated.
Chest Radiograph	See notes.					As clinically indicated.
Pregnancy Test (WOCBP only)	X		X			Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) within 1 day prior to administration of first dose of study treatment and then every 4 weeks (± 7 days), regardless of dosing schedule. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.
[redacted]						
Efficacy Assessments						
Body Imaging	See notes.					Contrast-enhanced CT of the chest, CT or MRI of abdomen and pelvis (including required tri-phasic CT or MRI of the liver), and all other known and/or suspected sites of disease should occur

Table 2-2: On-Treatment Assessments (CA224073)

Procedure[a]	Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment (EOT)[b]	Notes[c] (All windows are based on calendar days.)
	D1	D15 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)		
						every 8 weeks starting from randomization (± 7 days). Imaging should continue as per schedule until disease progression (unless treatment beyond progression) or treatment discontinuation (including treatment beyond progression), whichever occurs later. Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. See Section 9.1.1 for further details.
Brain Imaging	See notes.					Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks from randomization), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
Other Imaging: Bone Scan	See notes.					See Section 9.1.1; as clinically indicated per local standards.
[redacted]						
[redacted]						
[redacted]						

Table 2-2: On-Treatment Assessments (CA224073)

Procedure[a]	Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment (EOT)[b]	Notes[c] (All windows are based on calendar days.)
	D1	D15 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)		
[redacted]						
Additional Research Sampling	See notes.					See Section 9.8.4.
[redacted]						
[redacted]						

Table 2-2: On-Treatment Assessments (CA224073)

Procedure[a]	Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment (EOT)[b]	Notes[c] (All windows are based on calendar days.)
	D1	D15 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)		
[redacted]						
Study Treatment						
Contact IRT to Randomize the Participant	X					Only once eligibility is confirmed and treatment can be started. Only at Cycle 1.
Administer Study Treatment	X		X			See Section 7.1 for treatment administration details. Treatment should begin within 3 days of randomization/contacting IRT. Washout period between end of TKI treatment and start of dosing is 10 days for sorafenib, 6 days for lenvatinib, 6 days for regorafenib, and 21 days for cabozatinib. [1, 2, 3, 4] The washout period for any other TKI therapies can be discussed with the Medical Monitor. Treatment will continue until disease progression, unacceptable toxicity, or study ends.

Abbreviations: 2D = 2-dimensional; AE = adverse event; [redacted] aPTT = activated partial thromboplastin time; [redacted] BP = blood pressure; [redacted] CR = complete response; CRF = case report form; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; [redacted] D = day; [redacted] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; [redacted] HCG = human chorionic gonadotropin; [redacted] INR = International Normalized

Ratio; IRT = Interactive Response Technology; IU = international unit; L = liter; [redacted] MRI = magnetic resonance imaging; O2 = oxygen; [redacted] PR = partial response; PT = prothrombin time; SAE = serious adverse event; [redacted] SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted] TKI = tyrosine kinase inhibitor; WOCBP = women of child bearing potential.

[a] If a dose is delayed, then the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs, except for body imaging and pregnancy testing, which need to be performed as scheduled.

[b] EOT is defined as the last on-treatment visit or where a decision is made to discontinue the participant from treatment.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[redacted]

Table 2-3: Follow-up Procedural Outline (CA224073)

Procedure	Safety Follow-up Visit 1 and 2[a]	Survival Follow-up visits[b]	Notes[c]
Safety Assessments			
Targeted Physical Examination	X		Targeted physical examination to be performed only as clinically indicated. Any findings during the PE will be evaluated for AEs and reported as such.
Vital Signs	X		Weight, BP, heart rate, and temperature.
Assessment of Signs and Symptoms	X		
Adverse Event and Serious Adverse Event Assessments	X	See notes.	All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 135 days following discontinuation of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.
Review of Concomitant Medications	X		See Section 7.7.
Performance Status	X		ECOG performance status Score (see Appendix 6).
Laboratory Tests	X (see notes)		For Follow-up Visit 1, onsite/local including hematology, serum chemistry, and urinalysis, as outlined in Section 9.4.4. Repeat at Follow-up Visit 2 only if study treatment-related toxicity persists.
Pregnancy Test (WOCBP only)	X		Serum or urine. Pregnancy testing is only required at Follow-up Visits 1 and 2, unless increased frequency and duration is required per local regulations.
[redacted]			
Coagulation Profile	X		Including PT/INR and aPTT.

Table 2-3: Follow-up Procedural Outline (CA224073)

Procedure	Safety Follow-up Visit 1 and 2[a]	Survival Follow-up visits[b]	Notes[c]
[redacted]			
[redacted]			
Efficacy Assessments			
Body Imaging	See notes.		Contrast-enhanced CT of the chest, CT or MRI of abdomen and pelvis (including required tri-phasic CT or MRI of the liver), and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days). Participants with SD, PR, or CR at the time of the EOT visit or at the time of study treatment discontinuation will continue to have radiologic and clinical tumor assessments every 8 weeks (± 7 days) after discontinuation of study treatment/EOT visit, until the start of subsequent therapy, disease progression (unless treatment beyond progression), or withdrawal of study consent. Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. See Section 5.1.3 and Section 9.1.1 for further details.
Brain Imaging	X	X	Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
Collection of Survival Status and Subsequent Therapy Information	X	X (see notes)	Collect every 3 months during survival visits until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit.
TSST/PFS2 Assessment	X	X	Following first progression, participants will continue to be followed during the safety and survival follow-up visits. Timing of objectively

Table 2-3: Follow-up Procedural Outline (CA224073)

Procedure	Safety Follow-up Visit 1 and 2[a]	Survival Follow-up visits[b]	Notes[c]
			documented progression after the next line of therapy per Investigator assessment will be documented. The start of the second next-line therapy will also be collected.
[redacted]			

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BMS = Bristol Myers Squibb; BP = blood pressure; CR = complete response; CRF = case report form; CT = computed tomography; [redacted] ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; [redacted] INR = international normalized ratio; MRI = magnetic resonance imaging; PE = physical examination; PFS2 = progression-free survival 2 (second progression); [redacted] PR = partial response; [redacted] PT = prothrombin time; SD = stable disease; [redacted] SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TSST = time to second subsequent therapy; WOCBP = women of child bearing potential.

[a] Follow-up visits occur as follows: Follow-up Visit 1 = 30 days from the last dose of study treatment (± 7 days) or coincides with the date of discontinuation (± 11 days) if date of discontinuation is greater than 42 days after last dose. Follow-up Visit 2 = 135 days (± 7 days) from last dose of study treatment. Participants must be followed for at least 135 days after last dose of study treatment. Both follow-up visits should be conducted in person.

[b] Survival follow-up visits may be conducted in clinic or by phone. Survival visits: first survival follow-up visit 3 months (± 14 days) after Follow-up Visit 2; subsequent survival follow-up visits every 3 months (± 14 days). BMS may request that survival data be collected on all treated participants outside of the 3 months-specified window. See Section 5.1.3.1 for participants with stable disease, complete response, or partial response.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

3 INTRODUCTION

[redacted] CA224073 is a Phase 2, randomized, open-label study of relatlimab (BMS-986016) in combination with nivolumab in participants with advanced HCC who are naive to prior immunotherapies, who have received one or two lines of tyrosine kinase inhibitor (TKI) therapies, and who have shown radiographic progression on or after the last line of TKI therapy in the advanced/metastatic setting.

Individually targeting immune checkpoint receptors, such as programmed death-1 (PD-1), has demonstrated clinical activity across multiple tumor types; several studies to date have demonstrated activity of therapeutic compounds aimed at the PD-1 receptor and its ligand, programmed death-ligand 1 (PD-L1). This benefit is further extended by dual combination therapy of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and PD-1 inhibitors, as well as combination of anti-PD-L1 (atezolizumab) and anti-vascular endothelial growth factor (VEGF; bevacizumab) monoclonal antibodies showing superior efficacy to sorafenib monotherapy. [5] Despite the demonstrated benefit of single or dual combinations of cancer immunotherapies on clinical outcome, a large proportion of patients with many tumor types do not respond or will relapse after an initial response to these agents. Substantial efforts are needed to provide therapy to patients who do not respond to currently approved single or dual combination immunotherapeutic agents.

Lymphocyte activation gene 3 (LAG-3; cluster of differentiation [CD] 223) is a checkpoint and a potential cancer immunotherapeutic target due to its negative regulatory role on T-cells and its regulatory capacity. [6, 7] Relatlimab is a human LAG-3-specific antibody that was isolated from immunized transgenic mice expressing human immunoglobulin (Ig) genes. [8] It is expressed as an immunoglobulin G4 (IgG4) isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. Relatlimab binds to LAG-3 with high affinity and inhibits the negative regulatory function of LAG-3 in vitro. Binding of relatlimab to LAG-3 prevents binding of this receptor to cells bearing its ligand, major histocompatibility complex (MHC) Class II, the peptide antigen presentation molecule recognized by CD4-positive (+) T cells. In addition, relatlimab enhances activation of human T cells in super-antigen stimulation assays when added alone or in combination with nivolumab (anti-PD-1 antibody).

3.1 Study Rationale

Despite the demonstrated benefit of single or dual combinations of cancer immunotherapies on clinical outcome, a large proportion of cancer patients across many tumor types do not respond to these available therapies. The most encouraging efficacy data are coming from trials with combination regimens. The IMbrave 150 trial of atezolizumab and bevacizumab vs sorafenib met its primary endpoint, with a median progression-free survival (mPFS) of 6.8 vs 4.3 months; however, Grade 3-4 treatment-related adverse events (AEs) were reported in 36% of participants in the combination arm and 16% of the participants had AEs leading to withdrawal of any study

component.[5] The combination of ipilimumab and nivolumab also showed improved efficacy (overall objective response rate [ORR]: 31%; median duration of response [DOR]: 17 months); 37% of participants had a Grade 3-4 treatment-related AEs and 5% had Grade 3-4 treatment-related AEs leading to discontinuation.[9] There is an unmet need to develop an efficacious combination regimen with an improved safety profile.

LAG-3 (CD223) is a checkpoint and a potential cancer immunotherapeutic target due to its negative regulatory role on T-cells and its regulatory capacity.[6,7] Relatlimab is a human LAG-3-specific antibody that was isolated from immunized transgenic mice expressing human Ig genes.[8]

1) HCC has a unique tumor microenvironment (TME) that is typically driven by either viral or other chronic infections/inflammations, which create a moderately inflamed environment.[10] Chronic inflammation causes a unique immune tolerogenic TME.[11] LAG-3 has been shown to play multiple roles in this context. In addition, relatlimab enhances activation of human T cells in super-antigen stimulation assays when added alone or in combination with nivolumab (anti-PD-1 antibody).[8]
   a) Comprehensive profiling of commercially sourced tumor specimens was performed to investigate and characterize expression of LAG-3 and MHC Class II in the context of inflammatory biomarkers (Bristol Myers Squibb [BMS] data on file). Relatlimab binds to LAG-3 with high affinity and inhibits the negative regulatory function of LAG-3 in vitro. Binding of relatlimab to LAG-3 prevents binding of this receptor to cells bearing its ligand, MHC Class II, the peptide antigen presentation molecule recognized by CD4+ T cells.[8] Fibrinogen-like protein 1 (FGL-1) is another potential ligand for LAG-3 that is highly expressed in the liver and is a tumor suppressor gene in HCC.[12] [redacted]
   b) To characterize the immune microenvironment in HCC, immunohistochemistry (IHC) staining was performed for CD8+ T lymphocytes, PD-1+ and LAG-3+ lymphocytes, CD163+ macrophages, and PD-L1 expression in tumor and liver backgrounds from 29 cases of resected HCC. LAG-3 and PD-L1, 2 inhibitory molecules implicated in CD8 T-cell tolerance, are increased in most HCC tumors, providing a basis for investigating combinatorial checkpoint blockade with LAG-3 and PD-L1 inhibitors in HCC.[13]
2) Immunotherapeutic compounds, such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 agents, either as monotherapy or as combination therapy, have already shown added benefit in different lines and settings of advanced/metastatic HCC.
   a) Nivolumab (anti-PD-1 monoclonal antibody) as a single agent or in combination with ipilimumab is indicated for the treatment of patients with HCC who have been previously treated with sorafenib.[14] These approvals were based on the CA209040 study. Nivolumab showed clinically meaningful efficacy in the pooled subgroup of 154 participants who were given 3 mg/kg nivolumab every 2 weeks (Q2W) until disease progression or unacceptable toxicity. With 27 months of follow-up, the ORR was 14% per blinded independent central review (BICR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and 18% per BICR by modified RECIST (mRECIST). DOR was 91% at ≥ 6 months, 59% at

≥ 12 months, and 32% at ≥ 24 months.[14] Pembrolizumab (anti-PD1 monoclonal antibody) is also an approved immuno-oncology (IO) agent for second-line (2L) HCC.[15] Based on the study result in KEYNOTE-224, 104 participants were treated with 200 mg/kg pembrolizumab every 3 weeks (Q3W) until unacceptable toxicity, progression, or 24 months of treatment in the same setting in HCC. The approval was based on ORR and DOR per RECIST v1.1. ORR was 17%, and DOR was 89% at 6 months and 56% at 12 months.

b) Nivolumab (anti-PD-1 monoclonal antibody) and ipilimumab (anti-CTLA-4 monoclonal antibody) combination received accelerated approval in 2L HCC,[16] showing promising efficacy. In CA209040, 49 participants received nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg Q3W for 4 doses, followed by single-agent nivolumab 240 mg Q2W until disease progression or unacceptable toxicity. The main efficacy outcome measures were ORR and DOR as determined by BICR using RECIST v1.1. ORR was 33% (n = 16; 95% confidence interval [CI]: 20, 48). DOR was 88% at ≥ 6 months, 56% at ≥ 12 months, and 31% at ≥ 24 months.

[redacted]

4) A systematic meta-analysis was conducted with 15 studies (n = 6306) exploring the effect of LAG-3 on overall survival (OS; for early-stage cancers) and disease-free survival (DFS) concluded that high expression of LAG-3 may be associated with favorable OS in several solid tumor types.[17]

[redacted]

This open-label, Phase 2 study will randomize participants with LAG-3+ [redacted] and LAG-3- [redacted] advanced HCC. The study will evaluate the efficacy of relatlimab 480 mg

and in combination with nivolumab 480 mg administered every 4 weeks (Q4W) compared to nivolumab 480 mg Q4W monotherapy. [redacted] Safety, [redacted] will also be evaluated for relatlimab 480 mg in combination with nivolumab 480 mg Q4W and for relatlimab 960 mg in combination with nivolumab 480 mg Q4W for participants who were treated prior to Protocol Amendment 03.

3.1.1 Research Hypothesis

It is anticipated that relatlimab in combination with nivolumab will demonstrate a favorable benefit/risk profile compared to nivolumab monotherapy to support further clinical testing in IO treatment-naive advanced/metastatic HCC patients.

3.2 Background

HCC is the fifth most common cancer worldwide and the second leading cause of cancer-related death. The incidence of HCC varies geographically, largely due to variations in hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. HCC incidence rates and death rates are increasing in many parts of the world, including North America, Latin America, and central Europe. In almost all populations, males have higher rates of liver cancer than females, with an overall sex ratio of around 2.4.[18]

Treatment of HCC is challenging because the disease is highly heterogeneous, with different etiologies, varying approaches to diagnosis and treatment, and variations in responses to therapy.[19] The patient's underlying liver function has an important influence on HCC treatment decisions. A total of 90% of HCC patients have an underlying cirrhosis requiring management of both the malignancy and the cirrhosis. Additionally, many patients require ongoing support for concomitant underlying disease, such as HBV or HCV, or non-viral related liver disease (eg, non-alcoholic steatohepatitis). Treatment strategies are therefore complex and best served by a multidisciplinary team.[20, 21, 22]

Relatively few patients are eligible for curative treatment because of the late appearance of symptoms.[20] For patients with liver-isolated disease who are not eligible for resection or liver transplantation, treatment options include local nonsurgical methods of liver-directed tumor ablation (radiofrequency ablation [RFA], microwave ablation, or cryoablation), irreversible electroporation (where available), embolization (including bland embolization, transarterial chemoembolization [TACE], and transarterial radioembolization), percutaneous injection therapy (with ethanol or acetic acid), and external beam radiation therapy. For patients who progress after locoregional liver-directed therapy, additional liver-directed therapy might be possible, depending upon tumor location and underlying liver function. However, the benefit of additional locoregional therapy vs early initiation of systemic therapy in these patients is unclear. The prognosis for these patients is poor.

Until 2008, no effective therapy existed for advanced HCC. In 2007, the multinational randomized SHARP trial demonstrated a modest but statistically significant survival benefit for sorafenib (a multitargeted TKI) over supportive care alone in participants with advanced HCC.

OS, the primary endpoint, was significantly longer in the sorafenib-treated participants (10.7 vs 7.9 months), as was time to radiologic progression (5.5 vs 2.8 months). A survival benefit was also demonstrated in Asian participants.[23, 24] These results established sorafenib monotherapy as a new reference standard systemic treatment for advanced HCC and formed the basis for approval of sorafenib for first-line (1L) treatment of unresectable HCC. Until May-2020, 2 TKIs, sorafenib and lenvatinib, were the only systemic agents approved to treat advanced HCC as 1L therapy. Lenvatinib demonstrated noninferiority to sorafenib in the REFLECT study, and is a treatment option, particularly for patients that do not tolerate sorafenib. [25] Post-marketing clinical studies of sorafenib showed that only a portion of patients show real benefits, while the incidence of drug-related significant adverse effects and the economic costs are relatively high.[26]

In 2019, the results of the CA209459 study were presented, showing meaningful clinical benefit with nivolumab therapy in 1L HCC compared to sorafenib therapy; although, results did not meet the statistical thresholds. Nivolumab compared to sorafenib was associated with a 2-fold higher ORR (15% vs 7%) and more complete responses (CRs; 4% vs 1%), but was not translated into statistical benefit with mPFS (3.7 vs 3.8 months) nor mOS (16.4 vs 14.7 months). In the sorafenib arm, 20% of participants received subsequent IO therapy after progressing on sorafenib. Grade 3 or 4 treatment-related AEs were reported in fewer nivolumab-treated participants than sorafenib-treated participants (22% vs 49%), who were also less likely to discontinue therapy because of side effects (4% vs 8%).[27]

In Oct-2019, preliminary data from the IMbrave 150 study (Phase 3) was presented with the combination of an anti-PD-L1 agent (atezolizumab) and an anti-VEGF monoclonal antibody (bevacizumab) for the 1L treatment of advanced HCC. There were significant improvements in mOS and mPFS with the combination therapy.[5] At a median follow-up of 8.6 months, mOS with combined therapy was not reached vs 13.2 months with sorafenib (estimated hazard ratio [HR] for survival, 0.58 [95% CI: 0.42, 0.79]). mPFS was also significantly better with combined therapy (6.8 vs 4.3 months; HR, 0.59 [95% CI: 0.47, 0.76). ORR was 2-fold higher with combined therapy (27.6% vs 12%). With this combination, 85% of participants had any-grade treatment-related AEs, 36% had Grade 3-4 treatment-related AEs, and 16% had AEs that led to discontinuation of any component of the regimen. In May-2020, the United States (US) Food and Drug Administration (FDA) granted approval to this regimen for patients with unresectable or metastatic HCC who have not received prior systemic therapy.[28]

Regorafenib is a TKI approved for patients with documented disease progression following sorafenib that showed moderate 2.8-month mOS improvement over placebo. A benefit for regorafenib in patients progressing after 1L treatment with sorafenib was suggested in the RESORCE trial, in which 573 participants were randomized to receive either regorafenib or placebo. Regorafenib was associated with significantly prolonged mOS (10.6 vs 7.8 months), as well as significantly higher rates of ORR (11 vs 4%).[29] Cabozantinib is also an approved TKI agent for patients who progressed on prior TKI therapy. In the CELESTIAL trial, 707 participants were enrolled to receive either cabozantinib or placebo. In the population of participants receiving 2L or third-line (3L) treatment after prior treatment with sorafenib, mOS was significantly better

with cabozantinib (10.2 vs 8.0 months), and the difference was more pronounced when the analysis was limited to participants whose only prior therapy was sorafenib (mOS: 11.3 vs 7.2 months).[30] Currently, 4 TKIs are approved for HCC globally: sorafenib, lenvatinib, regorafenib, and cabozantinib.

Ramucirumab is a recombinant vascular endothelial growth factor receptor (VEGFR)-2 monoclonal antibody that showed modest activity in the REACH trial in 2L HCC compared to placebo (mOS: 9.2 vs 7.6 months).[31] The follow-up REACH-2 trial in 2L HCC participants with ≥ 400 ng/mL alpha-fetoprotein (AFP) level was associated with significantly better OS compared to placebo (mOS: 8.5 vs 7.3 months),[32] and ramucirumab was approved for this patient population.[33]

Nivolumab was approved at a dose of 3 mg/kg Q2W for the treatment of HCC in patients who have been previously treated with sorafenib,[14] based on the escalation and expansion cohorts of the Phase 1/2 CA209040 study. Nivolumab monotherapy (at a dose of 3 mg/kg Q2W) in participants with advanced HCC produced durable responses and disease stabilization, irrespective of HCC etiology and regardless of prior therapy with sorafenib (see Section 3.1 [Study Rationale]).

In Mar-2020, the combination therapy of nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses was granted accelerated approval by FDA for HCC patients who have been previously treated with sorafenib, based on data from Cohort 4 of the CA209040 study (see Section 3.1 [Study Rationale]).[16] The combination regimen showed an ORR of 33%, with response durations ranging from 4.6 to 30.5+ months and 31% of responses lasting at least 2 years. With this combination, 94% of participants experienced any-grade treatment-related AEs (53% Grade 3-4) and 29% of the participants needed to discontinue treatment due to AEs.

After the approval of atezolizumab and bevacizumab combination in 1L HCC, the treatment recommendations shifted to indicate that previously approved 1L TKI therapies are now recommended after atezolizumab and bevacizumab therapies, and agents that were recommended after failure of 1L TKI therapies are now recommended in subsequent settings, according to the most recent guidelines. Although, for patients who are not eligible or cannot get access to atezolizumab and bevacizumab regimen, the recommendations remain the same. Recommendations for 2L therapy differ depending on which regimen was administered 1L.[34]

Based on these data, immunotherapies seem to play an important role in the treatment of HCC. Despite the recent approvals for patients diagnosed with advanced disease, the unmet medical need still remains for drugs with the potential to induce durable tumor responses and that can prolong mOS for advanced HCC patients as well as provide improved safety profile compared to existing therapeutic options in a patient population where liver function has already been compromised. [35]

Information for nivolumab (OPDIVO, BMS-936558, anti-PD-1 antibody) and relatlimab (BMS-986016, anti-LAG-3 antibody), is provided in the sections below; additional details are provided in the respective Investigator Brochures (IBs)/package inserts.[8,14, 36]

3.2.1 Relatlimab Mechanism of Action

Relatlimab is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human Ig genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. Relatlimab binds to a defined epitope on LAG-3 with high affinity (dissociation constant [Kd], 0.25 to 0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC Class II (half maximal inhibitory concentration [IC50], 0.7 nM). The antibody exhibits potent in vitro functional activity in reversing LAG-3-mediated inhibition of an antigen-specific murine T cell hybridoma overexpressing human LAG-3 (IC50, 1 nM). In addition, relatlimab enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti-PD-L1 antibody).

For additional details, refer to Section 4.1 (nonclinical pharmacology studies with relatlimab) and Section 4.2 (nonclinical pharmacokinetics with relatlimab) in the relatlimab IB.[8]

3.2.2 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses. [37, 38, 39] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR). [40] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, inducible T cell co-stimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA). [41] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, interferon-γ (IFN-γ), and B-cell lymphoma-extra large (Bcl-xL). PD-1 expression

has also been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice, which develop a variety of autoimmune phenotypes. [42] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (half-maximal effective concentration [EC50], 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and programmed death-ligand 2 (PD-L2; IC50, ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family, such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) restimulation assay with human peripheral blood mononuclear cells (PBMCs), the effect of nivolumab on antigen specific recall response indicated that nivolumab augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner vs isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the antitumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02). [43]

3.2.3 Relatlimab Combined with Nivolumab Clinical Activity

CA224047, a global, double-blind, randomized, Phase 2/3 study comparing a fixed-dose combination (FDC) formulation of nivolumab 480 mg + relatlimab 160 mg FDC Q4W to nivolumab 480 mg Q4W in participants with previously untreated advanced melanoma demonstrated a statistically significant and clinically meaningful benefit by dual inhibition of the LAG-3 and PD-1 pathways.[45, 46] The study achieved its primary endpoint, demonstrating statistically significant improvement in progression-free survival (PFS) by BICR with nivolumab 480 mg + relatlimab 160 mg FDC Q4W compared to nivolumab monotherapy in all randomized participants (N = 714) (PFS hazard ratio [HR] = 0.75 [95% CI: 0.62, 0.92], P-value = 0.0055). With a median follow-up of 13.2 months, the median PFS in the nivolumab + relatlimab FDC (3:1) group was 10.1 months (95% CI, 6.4–15.7) compared to 4.6 months (95% CI, 3.4–5.6) in the nivolumab monotherapy arm. PFS rates at 12 months were 47.7% (95% CI, 41.8–53.2) and 36.0% (95% CI, 30.5–41.6) for nivolumab + relatlimab FDC (3:1) and nivolumab monotherapy, respectively. The PFS benefit of nivolumab + relatlimab FDC (3:1) was consistent across key prespecified subgroups. The secondary endpoint of overall survival (OS) showed clinically meaningful improvement with nivolumab + relatlimab FDC over nivolumab monotherapy (median OS non-estimable [34.20, not reached {NR}]) versus 34.1 months [25.23, NR]; HR = 0.80 [0.64-1.01]; p = 0.0593) in all randomized participants but was not statistically significant.[45,46]

Due to the statistical non-significance of the secondary endpoint of OS, ORR was not formally tested per the statistical testing hierarchy; however, clinically meaningful numerical differences were observed with the nivolumab + relatlimab FDC arm over nivolumab monotherapy (43.1% vs 32.6%).[47]

3.3 Benefit/Risk Assessment

3.3.1 Introduction

Patients with advanced/metastatic HCC who experience progressive disease after TKI therapies have limited treatment options and poor overall prognosis, even with adequate liver reserve, as measured by Child-Pugh A status. Treatment options for patients who have not received a previous checkpoint-inhibitor therapy include single-agent anti-PD-1 therapy and TKIs. Nivolumab

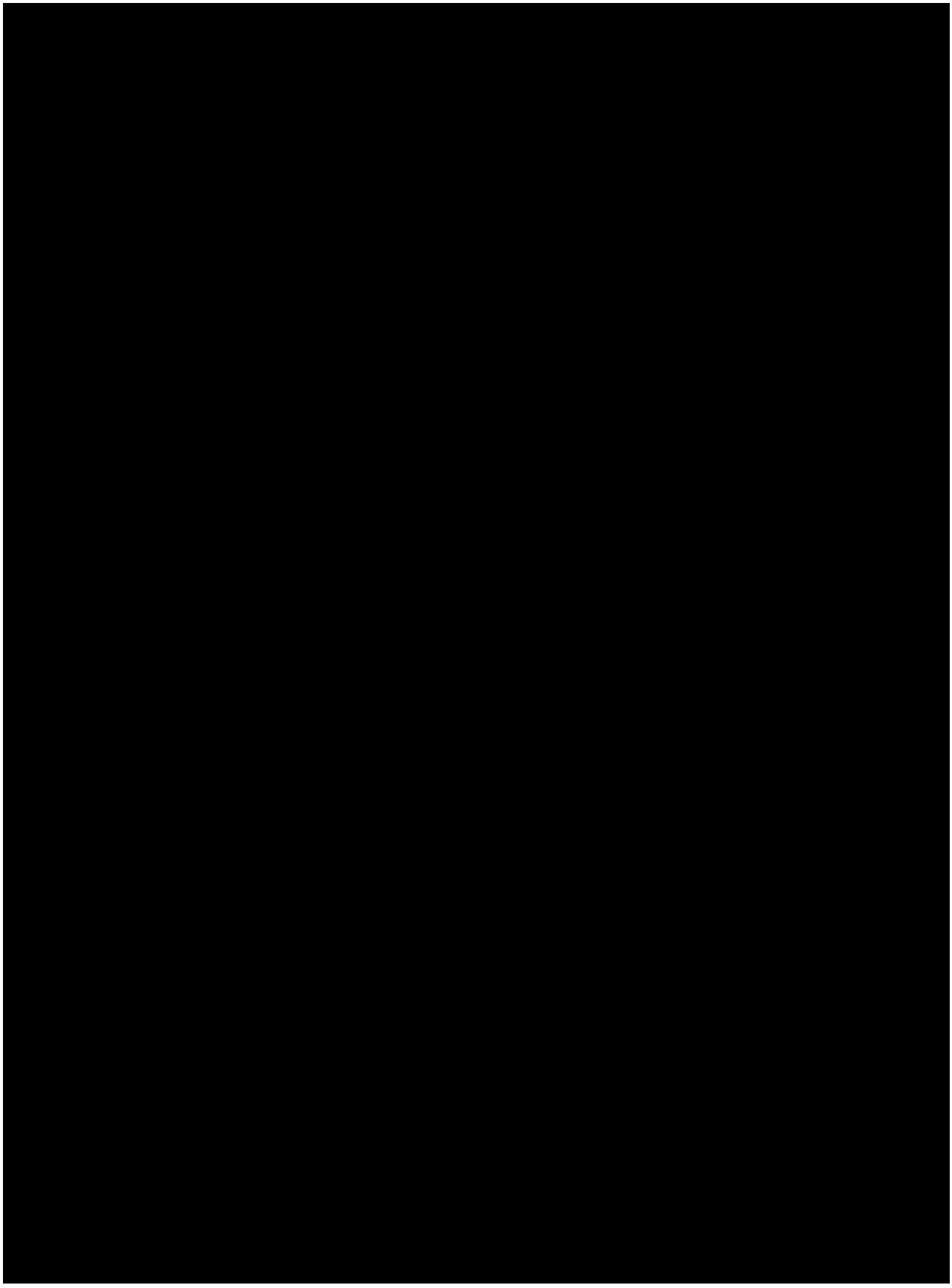
achieved an ORR of 14% and an mOS of 15 months (49% of participants experienced serious adverse events [SAEs]).[14] Pembrolizumab achieved an ORR of 17%, and an mOS of 14 months.[15] The TKIs cabozantinib and regorafenib achieved ORRs of had 4% and 11%, respectively, but with Grade 3-4 AEs reported in 85% of participants with cabozantinib and 44% of participants with regorafenib. The only IO combination regimen examined in 2L HCC (nivolumab and ipilimumab) showed improved efficacy compared to monotherapy agents, but presented with increased toxicity.[16] At present, other treatment modalities, such as the combination of IO with anti-VEGF therapies, are anticipated to be available only for patients without prior therapy; thus, the unmet need for patients who experience progressive disease after 1L and subsequent lines of TKI therapies remains.

HCC has a unique TME that is typically driven by either viral or other chronic infections/inflammations, which create a moderately inflamed environment.[10] Chronic inflammation causes a unique immune tolerogenic TME.[11] LAG-3 has been shown to play multiple roles in this context. In addition, relatlimab enhances activation of human T cells in super-antigen stimulation assays when added alone or in combination with nivolumab (anti-PD-1 antibody).[8]

There is strong preclinical support for the combination of relatlimab + nivolumab in HCC, evidence of clinical efficacy and tolerability of the combination at a lower dose, and extensive clinical experience with the dose of 480-mg relatlimab/480-mg nivolumab across a range of tumor types.

3.3.2 Safety

The combination of nivolumab and relatlimab has shown well-defined toxicity profiles based on a safety database comprised of participants treated with either relatlimab monotherapy or as a combination across multiple tumor types.



[redacted]

Safety results to date indicate that sequential, co-administration, and the FDC of nivolumab + relatlimab administration have similar manageable safety profiles that are consistent with the mechanisms of action of each agent, nivolumab and relatlimab. No new types of clinically important events have been identified.[8,45]

Given the safety profile of relatlimab as monotherapy and combination therapy observed to date,[8] the positive benefit/risk of the pivotal Phase 2/3 study of nivolumab + relatlimab FDC (3:1) demonstrated in participants with previously untreated metastatic or unresectable advanced melanoma,[46] and the significant unmet medical need in the advanced HCC population, the continuing evaluation of the combination of nivolumab + relatlimab is justified for the patient population in this protocol.

[redacted]

[redacted]

3.3.3 Safety Monitoring

A pattern of IMAEs has been defined, [redacted]. Most high-grade IMAEs, including hepatic and cardiac AEs, are manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed [redacted]. Additional extensive details on the safety profiles of relatlimab and nivolumab, including results from other clinical studies, are available in the respective IBs,[8,36]

and will not be repeated herein. As relatlimab is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur; however, data exists that the combination of relatlimab and nivolumab is safe and tolerable, even at higher doses in other tumor types, including those used in this study.

This protocol uses a Bayesian continuous monitoring strategy to assess criteria for stopping enrollment for each treatment arm.

The criteria of < 30% TRSAEs, as assessed by Investigator among the total participants, is proposed. This is slightly higher than the 22% rate that was observed in CA209040 HCC study for nivolumab 1 mg/kg and ipilimumab 3 mg/kg that has been approved by FDA.

The monitoring will be implemented by a monthly review of the CA224073 clinical trial data by the study team.

TRSAEs per treatment arm will be assessed and cumulative frequency per current enrollment will be determined. A broader review of safety for CA224073 will also take place by the study team.

If the posterior probability that the TRSAEs > 22% (resulting in the final boundary of 29 out of 100 total participants) is greater than 95%, a more in-depth safety analysis will start, and a report listing the SAEs, preferred term, grade, and outcome will be provided to the BMS Safety Committee (SC). The SC members have expertise in drug safety, clinical trial conduct, and oncology. The SC will convene an ad hoc meeting to review the safety data and provide a recommendation whether to continue enrollment or discontinue a treatment arm. In the event of a review, the totality of clinical data will be examined.

[redacted]

3.3.4 Efficacy

[redacted]

[redacted]

The available data with relatlimab and nivolumab and other immunotherapies in advanced HCC, as well as well-described immune biology in HCC, support the rationale for relatlimab in combination with nivolumab in patients with advanced/metastatic HCC who experience progressive disease after TKI therapies. This remains a high unmet need patient population; the available evidence and the anticipated acceptable safety profile support the benefit/risk of participation in this study.

4 OBJECTIVES AND ENDPOINTS

Objectives and endpoints are presented in Table 4-1.

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To evaluate the efficacy of relatlimab in combination with nivolumab relative to nivolumab monotherapy in IO therapy-naive participants after prior treatment with TKI therapy	• ORR assessed by BICR using RECIST v1.1
Key Secondary	
• To investigate safety and tolerability of relatlimab in combination with nivolumab in participants with advanced HCC	• Incidence of AEs, SAEs, and AEs leading to discontinuation, deaths, and clinical laboratory test abnormalities
• To further evaluate the preliminary efficacy of relatlimab in combination with nivolumab	• DCR, DOR, and PFS assessed by BICR per RECIST v1.1 • ORR, DCR, DOR, and PFS assessed by Investigator per RECIST v1.1 • OS
[redacted]	

Table 4-1: Objectives and Endpoints

Objective	Endpoint
[redacted]	

Abbreviations: AE = adverse event; BICR = Blinded Independent Central Review; DCR = disease control rate; DOR = duration of response; HCC = hepatocellular carcinoma; IO = immuno-oncology; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TKI = tyrosine kinase inhibitor.

5 STUDY DESIGN

5.1 Overall Design

This Phase 2 study will evaluate the safety and efficacy of relatlimab in combination with nivolumab in participants with 2L or 3L IO-naive HCC.

As of 19-July-2021, participants are being randomized 1:1 to receive:

- **Arm A:** Nivolumab 480 mg Q4W
- **Arm B:** Nivolumab 480 mg Q4W+ Relatlimab **480** mg Q4W

- [redacted]

Arm C: Nivolumab 480 mg Q4W+ Relatlimab **960** mg Q4W

[redacted] 24 participants were randomized to Arm C.

[redacted]

Stratification will occur by region (Asia [excluding Japan] vs Rest of the World [including Japan]) and macrovascular invasion and/or extrahepatic spread (MVI/EHS; present or absent). For the purposes of randomization, LAG-3 will also be treated as a stratification factor.

MVI is defined as:

- Hepatic vein tumor thrombus, OR
- Inferior vena cava tumor thrombus, OR
- Portal vein tumor thrombus; Vp3/Vp4 (presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe or first-order branches of the portal vein) participants are also eligible.

EHS is defined as presence of metastatic disease in lymph nodes or distant sites outside the liver.

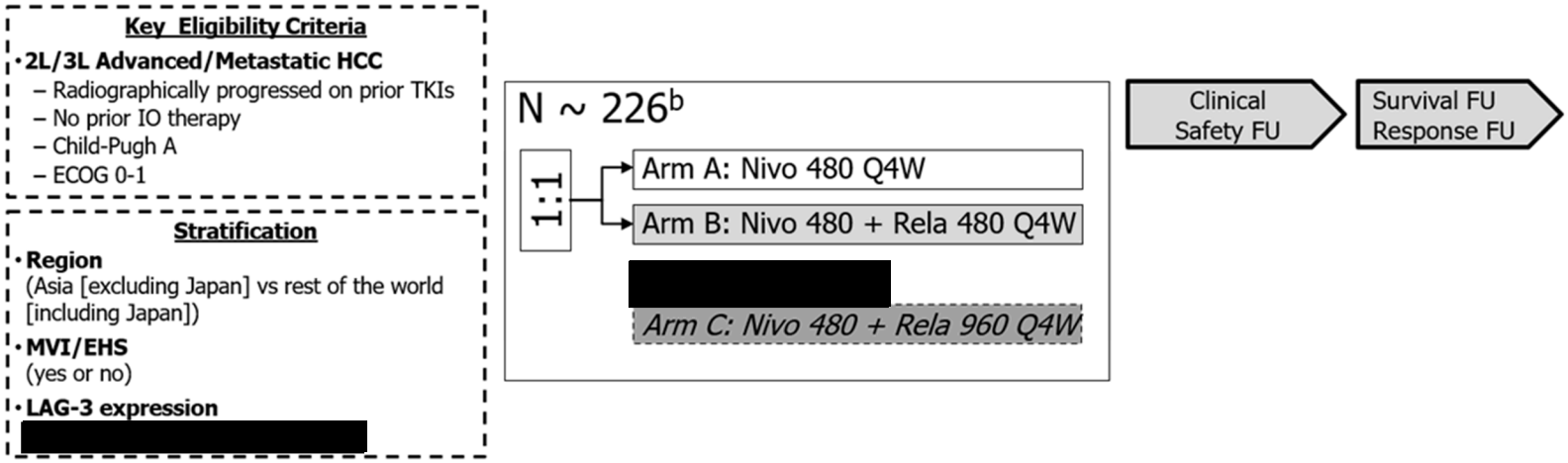
All participants will be treated until disease progression or unacceptable toxicity. Treatment beyond initial Investigator-assessed RECIST v1.1-defined progression is permitted if the participant has Investigator-assessed clinical benefit and is tolerating study treatment.

Individual participants with confirmed CR will be given the option to discontinue study therapy on a case-by-case basis, after specific consultation and agreement between the Investigator and BMS Medical Monitor, in settings where benefit/risk justifies discontinuation of study therapy.

Efficacy will be evaluated in the all-comer patient populations for 480-mg relatlimab in combination with 480-mg nivolumab Q4W compared to nivolumab 480 mg monotherapy. [redacted] Arm C (960-mg relatlimab in combination with 480-mg nivolumab) has [redacted] 24 patients [redacted]randomized. Approximately 226 participants will be randomized in Arm A and Arm B.

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

Figure 5.1-1: Study Design Schematic for CA224073



Abbreviations: [redacted] 2L = second line; 3L = third line; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; FU = follow-up; HCC = hepatocellular carcinoma; IO = immuno-oncology; LAG-3 = lymphocyte activation gene 3; MVI = macrovascular invasion; N = number; Nivo = nivolumab; Q4W = every 4 weeks; Rela = relatlimab; TKI = tyrosine kinase inhibitor.

[redacted]

b Total patients planned is approximately 250 with an additional 24 patients randomized to Arm C [redacted].

5.1.1 Screening Period

The Screening Period will be up to 28 days and begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF) or pre-screening ICF, if allowed. Informed consent will be obtained prior to any study-specific procedures. Participants will be evaluated based on the assessments as outlined in Table 2-1 and the Inclusion and Exclusion criteria (see Section 6). If a participant exceeds the 28-day Screening Period due to a study-related procedure (eg, scheduling of a tumor biopsy, waiting for a study-related laboratory value), the participant must be re-consented. If the subject is awaiting central laboratory results, then the participant does not have to re-consent until Day 42 (additional +14 days beyond screening window). Other screening procedures should be conducted within the windows specified in Table 2-1. A new participant identification number will be assigned by Interactive Response Technology (IRT) at the time of re-enrollment. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility. In these cases, the site should consult with the BMS Medical Monitor (or Clinical Scientist).

A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block (preferred) or a minimum of 20 freshly cut unstained slides of tumor tissue obtained from core biopsy, incisional biopsy, excisional biopsy, or surgical specimen prior to enrollment is required. Fine needle aspirates or other cytology samples and biopsies of bone lesions that do not have a soft tissue are not acceptable. Note the following for the required tumor sample:

- Samples should be collected within 3 months of enrollment. Biopsy can be taken on TKI treatment or after TKI treatment, with no intervening systemic anti-cancer treatment between time of acquisition and randomization.
- If a tumor sample (as described above) is not available, then a fresh pre-treatment biopsy may be obtained. This fresh biopsy should be excisional, incisional, or core needle.
- If the first 2 options are not feasible, then an archival tissue sample may be submitted if approval from BMS (Medical Monitor or Clinical Scientist) is obtained. This option should only be used in rare instances.

If despite best efforts, a minimum of 20 slides are not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with BMS Medical Monitor or Clinical Scientist. [redacted]

Tumor sample must be sent to the central laboratory. [redacted]

5.1.2 Treatment Period

- The treatment phase begins with the randomization call to the IRT system. The participant is randomly assigned to 1 of the 2 treatment arms:
  - Arm A: Nivolumab 480 mg Q4W

  - Arm B: Nivolumab 480 mg Q4W and Relatlimab 480 mg Q4W

- [redacted]
  - Arm C: Nivolumab 480 mg Q4W and Relatlimab 960 mg Q4W
- Administration of study treatment (see Table 7-1) should begin within 3 days of randomization/contacting IRT.
- Participants will receive treatment until disease progression (unless treatment beyond progressive disease is permitted), unacceptable toxicity, or withdrawn consent.
- Women of child bearing potential (WOCBP) must have a documented negative pregnancy test within 1 day prior to the start of study treatment. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window. For additional assessments see Table 2-2.
- On-study vital sign assessments should be performed at each on-treatment visit. Please see Table 2-2.
- On-study laboratory assessments should be performed within 3 calendar days prior to dosing at each on-treatment visit and will be assessed at the local laboratory. Please see Table 2-2.
- Tumor assessments will occur in accordance with Table 2-2, until disease progression (unless treatment beyond disease progression is permitted), or treatment discontinuation (including treatment beyond progression), whichever occurs later. Each site should submit scans on a rolling basis to a central vendor.

[redacted]

- Treatment Period ends when the participant is discontinued from study therapy for any reason. Please refer to Section 8 for a complete list of possible reasons for discontinuation.
- Individual participants with confirmed CR will be given the option to discontinue study therapy on a case-by-case basis, after specific consultation and agreement between the Investigator and BMS Medical Monitor, in settings where benefit/risk justifies discontinuation of study therapy.

5.1.3 Follow-up Period

Upon completion of study treatment, or once the decision is made to discontinue the participant from treatment, that is, at end of treatment (EOT), all participants will enter a Safety Follow-up Period.

EOT is defined as the last on-treatment visit or where a decision is made to discontinue the participant from treatment.

After the EOT visit, all participants will be evaluated for any new AEs for 135 days after the last dose of study treatment. Follow-up visits should occur at Days 30 and 135 (± 7 days for all study visits) after the last dose or at the date of discontinuation (± 11 days). All participants should complete the 2 clinical safety follow-up visits regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation.

Participants with SD, PR, or CR at the time of the EOT visit or at the time of study treatment discontinuation will continue to have radiologic and clinical tumor assessments every 8 weeks (± 7 days) after discontinuation of study treatment/EOT visit, until the start of subsequent therapy, disease progression, or withdrawal of study consent. Radiological assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the Survival Follow-up Period of the study. Participants who have disease progression after an initial course of study therapy will not be evaluated for response beyond the EOT visit and will be allowed to receive other tumor-directed therapy as required.

5.1.3.1 Survival Follow-up Period

In parallel with the safety follow-up period, all participants will start the Survival Follow-up Period. Participants will be followed until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Participants with SD, PR, or CR will have both the Response Follow-up Period and Survival Follow-up Period occur simultaneously during the Follow-up Period. The duration of this follow-up is 2 years following the first dose of study drug (and at least 1 year from last dose) for response assessment; although, a longer Follow-up Period may be considered in selected cases if an efficacy signal is apparent. Tumor assessment scans for participants who have ongoing clinical benefit beyond the 2-year period after the first dose of study treatment may continue to be collected as part of standard-of-care treatment, where permitted. Subsequent therapies will also be recorded in this Survival Follow-up Period.

5.1.4 Data Monitoring Committee and Other External Committees

5.1.4.1 Data Monitoring Committee

Relative to the exploratory nature of this Phase 2 open-label study and the experience that already exists around the use of relatlimab and nivolumab, a Data Monitoring Committee is not needed for this study. In addition to the comprehensive safety monitoring plan outlined below, the following key points were considered for this decision:

- This is an open-label study and there will be regularly scheduled Investigator meetings to review safety in an ongoing manner.
- Aggregate safety will be continuously monitored for Arm B and Arm C and will be informed by a Bayesian framework (see Section 10.3.4 [Interim Analyses]), which will consider overall safety measures if an excessive number of safety events are observed.
- The eligibility criteria exclude participants with disease characteristics that could predispose them to higher risk of morbidity.
- Exclusion of participants with known autoimmunity also applies because they could be at risk for exacerbation of their condition by the administration of therapies that relieve immune suppression, such as those used in this study.

- Participants will be observed frequently for clinical evaluation and blood counts during the Treatment Period.
- Well-defined discontinuation criteria are established in the protocol for individual participants for safety, with clear criteria for treatment discontinuation, dose delay, and toxicity management.
- BMS has in place a multilayered process for ensuring participant safety through close collaboration of study site Investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team (SMT). This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below.
- Study safety is evaluated continuously by representatives of BMS WWPS, who operate independently from the clinical team and monitor safety across all BMS protocols. AEs are monitored continuously by WWPS. Signal detection is performed at least monthly and ad hoc throughout the study by the SMT, composed, at a minimum, of the WS medical safety assessment physician (Chairman of the SMT) and WWPS single-case review physician, the study Medical Monitor(s), the study biostatistician, and epidemiologist. The SMT monitors actual or potential issues related to participant safety that could result in a significant change in the medical benefit/risk balance associated with the use of study treatments. Furthermore, Investigators will be kept updated of important safety information during teleconferences between Investigators and the BMS clinical team, which will be held on a regularly scheduled basis. If appropriate, select safety issues may be escalated to a senior level, multidisciplinary, BMS-wide Medical Review Group for further evaluation and action. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label study, the BMS Medical Monitor and the Investigators will have access to all data necessary for safety evaluation.
- All participants in this study represent individuals with high unmet medical need because the prognosis for advanced/metastatic solid tumors is generally very poor.

5.2 Number of Participants

Approximately 250 participants will be randomized (226 to Arm A and B, and 24 in Arm C).

It is estimated that approximately 357 enrolled participants will be needed to achieve these 250 randomized.

[redacted]

5.3 End of Study Definition

The start of the study is defined as first participant screened. End of study is defined as the end of the survival follow-up period for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

Additional follow-up for OS may be conducted up to approximately 5 years after the randomization of the last participant.

5.4 Scientific Rationale for Study Design

Preliminary efficacy was seen with a lower dose of relatlimab and nivolumab combination in a single-arm study. [redacted] To further evaluate and understand these data, this study aims to:

- Understand the added benefit of relatlimab to nivolumab monotherapy.

[redacted]

5.4.1 Rationale for Choice of Comparators

Nivolumab was chosen to be the comparator treatment to explore efficacy in 2L and subsequent settings. Nivolumab initially received accelerated approval for use in HCC patients who have failed sorafenib treatment.[14] Currently, the National Comprehensive Cancer Network (NCCN) guidelines recommend nivolumab in subsequent lines of therapy in certain circumstances.[34]

5.4.2 Rationale for Use of Relatlimab in Combination with Nivolumab

Several studies conducted and consequent approvals of immunotherapy agents support the use of immunotherapies in HCC, as previously described. HCC is a primary liver tumor that typically develops a pattern of chronic liver disease, particularly in patients with cirrhosis or chronic viral infection. The viral association makes it suitable for combination therapy BMS-986016 (relatlimab) and nivolumab. On one hand, it has been shown that LAG-3 is selectively up-regulated on tumor infiltrating CD8+ T cells and that HBV-specific CD8+ tumor-infiltrating lymphocytes (TILs) have an impaired effector function in participants with HCC.[49] [redacted]

Besides the already proven benefit of immunotherapies in HCC, [redacted] Phase 1/2 studies are supporting the efficacy of LAG-3 mechanism of action in HCC. Lymphocytic infiltration of the tumor and a high CD4+:CD8+ T-cell ratio have been associated with reduced risk of tumor recurrence following liver transplantation for HCC.[50] Adoptive immunotherapy with autologous lymphocytes activated with recombinant-2 and antibody to CD3 in patients who had undergone curative resection resulted in significantly longer recurrence-free and disease-specific survival, although OS did not differ significantly between treated and control groups.[51] The data nonetheless imply a central role of T cells in modulating tumor progression and provide strong justification for T-cell immunotherapy.[20] There is also evidence that FGL-1, a liver-secreted protein, is a major LAG-3 functional ligand independent from MHC-II. FGL-1 inhibits antigen-specific T-cell activation, and ablation of FGL-1 in mice promotes T-cell immunity. Blockade of the FGL-1:LAG-3 interaction by monoclonal antibodies stimulates tumor immunity and is therapeutic against established mouse tumors in a receptor-ligand, inter-dependent manner. FGL-

1 is highly produced by human cancer cells, and elevated FGL-1 in the plasma of cancer patients is associated with a poor prognosis and resistance to anti-PD-1/B7-H1 therapy.[52]

[redacted]

5.4.3 Rationale for Duration of Treatment

All participants will be treated until progression or appearance of intolerable toxicities, or if confirmed CR is achieved. Continuous tumor assessment every 8 weeks and safety evaluation will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

Tumor assessments should continue until disease progression or treatment discontinuation, whichever occurs later. Participants with unconfirmed progressive disease, SD, or PR at the end of a given cycle will continue to the next treatment cycle.

Individual participants with confirmed CR will be given the option to discontinue study therapy on a case-by-case basis, after specific consultation and agreement between the Investigator and BMS Medical Monitor, in settings where benefit/risk justifies discontinuation of study therapy.

Participants will be allowed to continue study treatment until the first occurrence of any of the following situations:

- Progressive disease defined by RECIST v1.1, unless participants meet criteria for treatment beyond progression (see Section 8.1.2).
- Clinical deterioration suggesting that no further benefit from treatment is likely.
- Intolerability to therapy.
- Participant meets criteria for discontinuation of study treatment.

5.4.4 Rationale for Stratification Factors

Stratification will occur by:

- Region (Asia [excluding Japan] vs rest of the world [including Japan])
- MVI/EHS (yes or no)
- LAG-3 expression [redacted]

Recent pivotal studies in this indication and line/setting of therapy used the following stratification factors: the CA209040 study that led to the approval in 2L stratified by HCC HCV vs non-HCV and presence of Investigator-assessed vascular invasion (VI) or EHS vs absence of VI/EHS; while the KEYNOTE-240 study, which did not meet its endpoints with pembrolizumab monotherapy

approval, stratified by geographic region (Asia excluding Japan, vs non-Asia including Japan), MVI (yes or no) and AFP (< 200 ng/mL vs > 200 ng/mL).

A number of randomized Phase 3 trials in HCC that followed the sorafenib pivotal trials have failed to demonstrate positive outcomes. These include 4 Phase 3 trials in the 1L setting with sunitinib, brivanib, linifanib, and erlotinib.[53, 54, 55, 56] The reasons for trial failure are considered heterogeneous and include lack of understanding of critical drivers of tumor progression/dissemination, liver toxicity, flaws in trial design, or marginal antitumor potency.[57] With respect to trial design, publications have cited potential imbalances in prognostic baseline factors.

The randomized Phase 3 trials were mostly stratified by the presence or absence of VI and/or EHS, geographic region, and Eastern Cooperative Oncology Group (ECOG) performance status. Despite stratification and randomization, notable differences were observed in the outcomes. Subset analysis of the 2 pivotal sorafenib trials showed differences in the outcomes of participants who had VI/EHS compared to those who did not have VI/EHS. Participants who had VI/EHS had worse outcomes than participants without VI/EHS.[58, 59] This study will therefore stratify by VI/EHS.

The impact of differing HCC patient populations and different approaches to clinical practice in the different regions is still important to consider. Based on pivotal trial results, differences in outcome are also captured in outcome by infectious vs non-infectious etiology. Based on World Health Organization (WHO) data, the prevalence of HCV is highest in the eastern Mediterranean region (>2%),[60] and HBV prevalence is 2-7% in Mediterranean countries, Japan, central Asia, the Middle East, and parts of South America.[61] These regions where HBV and HCV infection and consequent HCC is prevalent are in the Asian region. The Japanese HCC population is different from the other non-Japanese Asian HCC populations, with a higher prevalence of HCV-HCC and a better screening system. The KEYNOTE-224 and IMbrave 150 studies stratified by region, including Japan to the rest of the world.[62] Therefore, this study will not stratify by etiology, assuming the majority of HCC with infectious origin comes from the Asian countries. This study will therefore stratify by region.

[redacted] To balance the expression across arms, LAG-3 will also be treated as a stratification factor.

[redacted]

5.5 Justification for Dose

5.5.1 Justification for Nivolumab Dose

Nivolumab 480 mg Q4W has been approved in Europe for use as monotherapy in patients with melanoma and renal cell carcinoma (RCC) and in the US for use as monotherapy in patients with melanoma, RCC, non-small cell lung cancer (NSCLC), and other indications, including HCC.

The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response (E-R) analyses of data from studies in multiple tumor types (melanoma, NSCLC, RCC, squamous cell carcinoma of the head and neck [SCCHN], urothelial carcinoma [UC], and classical Hodgkin lymphoma [cHL]), where body weight-normalized dosing (mg/kg) has been used. The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance (CL) and volume of distribution were found to increase as the body weight increases, but less than proportionally with increasing weight, indicating that mg-per-kg dosing represents an over adjustment for the effect of body weight on nivolumab PK.

The PPK model previously developed using data from NSCLC participants has recently been updated, using data from 3,203 participants from 19 studies investigating nivolumab in the treatment of melanoma, NSCLC, RCC, SCCHN, UC, and cHL. In this dataset, the median (minimum - maximum) weight was 76.7 kg (34.1 kg - 180 kg) and thus, an approximately equivalent dose of 3 mg/kg Q2W for an 80-kg participant, nivolumab 480 mg Q4W was selected for future studies.

Nivolumab 480 mg Q4W is predicted to produce similar exposures to those of 3 mg/kg Q2W and 240 mg Q2W regimens. The overall distributions of nivolumab average steady state exposures are comparable after treatment with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W, although the flat-dose regimen of 480 mg Q4W is predicted to result in approximately 43% higher steady-state peak concentration (Cmaxss) and approximately 16% lower steady-state trough concentrations compared to the reference regimen of 3 mg/kg Q2W. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Although nivolumab Cmaxss is predicted to be higher following 480 mg Q4W, these exposures are predicted to be lower than or within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program and are not considered to put patients at increased risk. In addition, there was no difference in AE profile by body weight groups when extensive evaluations were performed with available 3 mg/kg Q2W and 10 mg/kg Q2W data. The exposures predicted following administration of nivolumab 480 mg Q4W are on the flat part of the E-R curves for previously investigated tumors (melanoma and NSCLC) and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W. For lower body weight patients, given the relatively flat E-R relationship of nivolumab, the increased exposures from 480 mg Q4W are not expected to pose an increased risk.

Nivolumab 480 mg Q4W is currently being evaluated in various studies across the nivolumab clinical development program. Preliminary results from pooled analyses, including 310 participants who received nivolumab 480 mg IV over 30 minutes Q4W, showed that the safety profile is consistent with the established safety profile of nivolumab (240 mg Q2W or 3 mg/kg Q2W administered IV over 60 minutes) across multiple indications, and no new safety concerns were identified. In HCC, this dose schedule is currently approved for the treatment of advanced HCC in the US and it is also under evaluation in an ongoing trial of nivolumab monotherapy in the adjuvant setting (CA2099DX). Therefore, in this study, 480 mg Q4W will be used for the nivolumab dose; this dose will provide a more convenient dosing regimen for participants, without compromising safety.

5.6 Clinical Pharmacology Summary

5.6.1 Nivolumab Clinical Pharmacology Summary

The PK of single-agent nivolumab was studied in participants over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute IV infusion every 2 or 3 weeks. Nivolumab CL decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%), resulting in a geometric mean steady-state clearance (CLss; CV%) of 8.2 mL/h (53.9%) in participants with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab CL does not decrease over time in participants with completely resected melanoma, as the geometric mean population CL is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (Vss; CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The predicted exposure (average concentration [Cavg] and maximum concentration [Cmax]) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Specific Populations: The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the CL of nivolumab was evaluated by a PPK analysis in participants with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the CL of nivolumab were found between participants with renal impairment and participants with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the CL of nivolumab was evaluated by PPK analyses in participants with HCC and in participants with other tumors with mild hepatic impairment (total bilirubin less than or equal to the upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than 1 to 1.5× ULN and any AST) and in HCC participants with moderate hepatic impairment (total bilirubin greater than 1.5 to 3× ULN and any AST). No clinically important differences in the CL of nivolumab were found between participants with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the IB.[36]

[redacted]

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF, in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, tumor biopsies, and other requirements of the study.

c) Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a screen failure (ie, participant has not been randomized). If re-enrolled, the participant must be re-consented.

d) For Protocol Amendment 03, all participants in Arm B and Arm C were re-consented due to updated safety information obtained in this study.

2) Type of Participant and Target Disease Characteristics

a) Participants must have a diagnosis of HCC based on histological confirmation.

i) Participants with only a radiologic diagnosis of HCC may be enrolled for screening in the study but histological confirmation is mandatory prior to the start of study therapy. Note: If tumor samples are not available, participants must consent to a pre-treatment fresh biopsy for histological confirmation as a condition of protocol participation.

b) Participants must have advanced/metastatic (Barcelona Clinic Liver Cancer stages B and C, Appendix 10) 2L or 3L HCC, defined as:

i) ***Not Applicable per Protocol Amendment 02 (see new criterion iii) below):*** *Progressive disease after sorafenib or lenvatinib therapies in the advanced/metastatic setting.*

ii) Disease not eligible for curative surgical and/or locoregional therapies.

(1) If local or locoregional therapy of intrahepatic tumor lesions (eg, surgery, radiation therapy, hepatic arterial embolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) was provided, it must have been completed ≥ 4 weeks before the first dose of study medication [redacted]

iii) Progressive disease in participants who received one or two lines of TKI therapies and who have evidence of radiographic progression on or after the last line of TKI therapy in the advanced/metastatic setting. Washout period between end of TKI treatment and start of dosing is 10 days for sorafenib, 6 days for lenvatinib, 6 days for regorafenib, and 21 days for cabozatinib.[1,2,3,4] The washout period for any other TKI therapies can

be discussed with the Medical Monitor. Participants who have had prior systemic treatment with cytotoxic chemotherapy are not eligible.

c) Participants with MVI are allowed to enroll, and MVI is defined as:
   i) Hepatic vein tumor thrombus, OR
   ii) Inferior vena cava tumor thrombus, OR
   iii) Portal vein tumor thrombus; Vp3/Vp4 (presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe or first-order branches of the portal vein) participants are also eligible.

d) Participants with extrahepatic spread (EHS) are allowed to enroll. EHS is defined as presence of metastatic disease in lymph nodes or distant sites outside the liver.

e) Participants have to be immunotherapy treatment-naive in the advanced/metastatic setting: No prior immunotherapies are permitted (such as, but not limited to anti-LAG-3, anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody, oncolytic viruses, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) for the treatment of the advanced/metastatic disease.
   i) Therapies with immunotherapy in early and intermediate stage are allowed if at least 6 months between the last dose and date of recurrence occurred prior to initiating 1L systemic therapy.

[redacted]

g) Participants must be LAG-3+ [redacted] or LAG-3- [redacted]. Both LAG-3+ and LAG-3- participants will be allowed to enroll.

h) Tumor tissue from an unresectable or metastatic site of disease that has not been previously irradiated must be provided [redacted].
   i) ***Not applicable per Protocol Amendment 02 (see new criterion iv) below):*** *An FFPE tumor tissue block (preferred) or a minimum of 20 freshly cut unstained slides of tumor tissue obtained from core biopsy, incisional biopsy, excisional biopsy, or surgical specimen prior to enrollment is required. Fine needle aspirates or other cytology samples are not acceptable. Preferably, the tumor sample will be recently collected within 3 months of enrollment. Biopsy can be taken any time after the end of TKI treatment, with no intervening systemic anti-cancer treatment between time of acquisition and randomization. If a recently collected tumor sample (as described above) is not available, then a fresh pre-treatment biopsy (excisional, incisional, or core needle) may be obtained. If the first 2 options are not feasible, then an archival tissue may be submitted if approval from BMS (Medical Monitor or Clinical Scientist) is obtained. Central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. The tissue submitted will be assessed for quality with a hematoxylin and eosin (H&E) stain and only those participants who have met tissue quality thresholds can be randomized. If despite best efforts, a minimum of 20 slides are not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with BMS Medical Monitor or Clinical Scientist.*

ii) If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, participants must consent to allow the acquisition of additional tumor tissue during the Screening Period for performance of [redacted] analyses.

iii) Biopsies of bone lesions that do not have a soft tissue component are not acceptable.

ii) An FFPE tumor tissue block (preferred) or a minimum of 20 freshly cut unstained slides of tumor tissue obtained from core biopsy, incisional biopsy, excisional biopsy, or surgical specimen prior to enrollment is required. [redacted] If there is only 1 measurable lesion, and a core-needle biopsy is done (instead of excisional), the lesion may be used as a measurable lesion. Fine needle aspirates or other cytology samples and biopsies that do not have a soft tissue component are not acceptable. The tumor sample should be collected within 3 months of enrollment. Biopsy can be taken on TKI treatment or after TKI treatment, with no intervening systemic anti-cancer treatment between time of acquisition and randomization. If a tumor sample (as described above) is not available, then a fresh pre-treatment biopsy (excisional, incisional, or core needle) may be obtained. If the first 2 options are not feasible, then an archival tissue sample (collected > 3 months prior to enrollment) may be submitted as a third option if approval from BMS (Medical Monitor or Clinical Scientist) is obtained. The third option should be used only in rare instances. Central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. The tissue submitted will be assessed for quality with a hematoxylin and eosin (H&E) stain and only those participants who have met tissue quality thresholds can be randomized. If despite best efforts, a minimum of 20 slides are not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with BMS Medical Monitor or Clinical Scientist.

i) Participants must have at least 1 RECIST v1.1 measurable untreated lesion.

i) The lesion must be accurately measured in at least one dimension by contrast-enhanced spiral computed tomography (CT) or contrast-enhanced dynamic magnetic resonance imaging (MRI) as ≥10 mm. Note: Malignant lymph nodes must be ≥15 mm on short axis.

ii) The lesion must not have been previously treated with surgery, radiotherapy, and/or locoregional therapy (eg, RFA, percutaneous ethanol injection [PEI] or percutaneous acetic acid injection [PAI], cryoablation, high-intensity focused ultrasound [HIFU], TACE, transarterial embolization [TAE], etc.).

j) Child-Pugh score of 5 or 6 (ie, Child-Pugh A; Appendix 5).

k) ECOG performance status 0 or 1 for ECOG performance status scale (Appendix 6).

l) Life expectancy of ≥ 3 months.

m) Participants are eligible to enroll if they have non-viral HCC, or if they have HBV-HCC, or HCV-HCC defined as follows:

i) HBV-HCC: Resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV deoxyribonucleic acid (DNA), and undetectable HBV surface antigen) or chronic HBV infection (as

evidenced by detectable HBV surface antigen or HBV DNA). Participants with chronic HBV infection must have HBV DNA < 500 IU/mL and must be on antiviral therapy.

ii) HCV-HCC: Active or resolved HCV infection as evidenced by detectable HCV ribonucleic acid (RNA) or antibody.

n) Adequate cardiac function with LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration.

o) All participants: Ability to comply with treatment, [redacted] sample collection and required study follow-up.

p) Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to randomization:

i) Adequate hematologic function:

(1) White blood cells ≥ 2000/μL (SI: ≥ 2.00 × 10^9/L; stable, off any growth factor within 4 weeks of study treatment administration)

(2) Neutrophils ≥ 1500/μL (SI: ≥ 1.50 × 10^9/L; stable, off any growth factor within 4 weeks of study treatment administration)

*(3) **Not Applicable per Revised Protocol 01 (see new criterion (5) below):** Platelets ≥ 60×10^3/μL (SI: ≥ 100 × 10^9/L; transfusion or the use of platelet-stimulating agents to achieve this level is not permitted)*

(4) Hemoglobin ≥ 8.5 g/dL (SI: ≥ 85 g/L; may be transfused to meet this requirement; recombinant human erythropoietin not permitted within 3 weeks of first study drug administration)

(5) Platelets ≥ 60×10^3/μL (SI: ≥ 60 × 10^9/L; transfusion or the use of platelet-stimulating agents to achieve this level is not permitted)

ii) Adequate hepatic function as documented by:

(1) Serum albumin ≥ 2.8 g/dL (SI: ≥ 28 g/L; transfusion to meet this level is not permitted)

(2) Serum total bilirubin < 2 mg/dL

(3) AST/ALT: ≤ 5.0× ULN

iii) Prothrombin time (PT)-international normalized ratio (INR) ≤ 2.3 or PT ≤ 6 seconds above control.

iv) Adequate renal function, defined as a serum creatinine < 1.5× ULN, or creatinine clearance (CrCl) > 40 mL/min (measured or calculated using the Cockcroft-Gault formula):

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

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

3) Age and Reproductive Status (age ≥ 18 years or local age of majority)

a) Female Participants

i) Females, ages ≥ 18 years or local age of majority.

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

iii) Women participants must have documented proof that they are not of childbearing potential.

iv) Women of childbearing potential (WOCBP) must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 1 day prior to the start of study treatment.

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

(2) An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

v) Additional requirements for pregnancy testing during and after study intervention are located in Section 2 (Schedule of Activities).

vi) The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

vii) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF. See criterion x) (2) below for additional details.

viii) WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

ix) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

x) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

(1) Is not a WOCBP

OR

*(2) **Not Applicable per Revised Protocol 01 (see new criterion (3) below):** Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 4 during the intervention period and for at least 24 weeks after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for nivolumab and relatlimab to undergo approximately 5 half-lives) and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.*

(3) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 4 during the intervention period and for at least 5 months after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for nivolumab and relatlimab to undergo approximately 5 half-lives) and

agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

b) Male Participants

i) Males, ages ≥ 18 years or local age of majority. No contraception is required for male participants.

ii) ***Not Applicable per Revised Protocol 01:*** *Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 for the duration of treatment with study treatment(s) plus 33 weeks after the last dose of the study treatment (ie, 90 days [duration of sperm turnover] plus the time required for nivolumab and relatlimab to undergo approximately 5 half-lives), and as described below. In addition, male participants must be willing to refrain from sperm donation during this time.*

iii) ***Not Applicable per Revised Protocol 01:*** *Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.*

iv) ***Not Applicable per Revised Protocol 01:*** *Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the intervention period and for at least 33 weeks after the last dose of study intervention.*

v) ***Not Applicable per Revised Protocol 01:*** *Female partners of males participating in the study should be advised to use highly effective methods of contraception during the intervention period and for at least 33 weeks after the last dose of study intervention in the male participant.*

vi) ***Not Applicable per Revised Protocol 01:*** *Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) even if the participants have undergone a successful vasectomy, during the intervention period and for at least 33 weeks after the last dose of study intervention.*

vii) ***Not Applicable per Revised Protocol 01:*** *Male participants must refrain from donating sperm during the intervention period and for at least 33 weeks after the last dose of study intervention.*

viii) ***Not Applicable per Revised Protocol 01:*** *Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.*

Investigators shall counsel WOCBP on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study drug to a developing fetus.

- The Investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Local laws and regulations may require the use of alternative and/or additional contraception methods.

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Known fibrolamellar HCC, sarcomatoid HCC, or combined hepatocellular cholangiocarcinoma.

b) Prior organ allograft or allogeneic bone marrow transplantation.

c) Episodes of hepatic encephalopathy (≥ Grade 2) within 12 months prior to randomization.

d) Clinically significant ascites as defined by:

i) ***Not applicable per Protocol Amendment 02 (see new criterion iii) below):*** *Prior ascites that required treatment and require ongoing prophylaxis, OR*

ii) ***Not applicable per Protocol Amendment 02:*** *Current ascites requiring treatment.*

iii) Any prior (within 1 year) or current clinically significant ascites as measured by physical examination and that requires active paracentesis for control.

e) Presence of portal hypertension with history of bleeding due to esophageal or gastric varices within the past 6 months prior to randomization.

f) ***Not applicable per Revised Protocol 01 (see new criterion g) and h) below):*** *Active brain metastases or leptomeningeal metastases. Participants with treated brain metastases are eligible if the following criteria are fulfilled:*

i) ***Not applicable per Revised Protocol 01:*** *The brain lesions have been treated and there is no MRI evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to randomization. (If an MRI is contraindicated, a CT scan is acceptable after discussion with the study Medical Monitor or designee).*

ii) ***Not applicable per Revised Protocol 01:*** *There is no requirement for immunosuppressive doses of corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.*

iii) ***Not applicable per Revised Protocol 01:*** *The case is discussed with the study Medical Monitor or designee.*

g) Untreated symptomatic central nervous system (CNS) metastases. Participants are eligible if CNS metastases are asymptomatic and do not require immediate treatment, or have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants must have been either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization. Imaging performed within 28 days prior to randomization must document radiographic stability of CNS lesions and be performed after completion of any CNS-directed therapy.

h) Leptomeningeal metastases.

2) Medical Conditions

a) Women who are pregnant or breastfeeding.

b) Infections
   i) Active co-infection with:
      (1) Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV DNA and HCV RNA, OR
      (2) Hepatitis D infection in participants with hepatitis B.
   ii) ***Not Applicable per Revised Protocol 01 (see new criterion iv) below):*** *Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally (see Appendix 7).*
   iii) Active bacterial or fungal infections requiring systemic treatment within 7 days prior to study drug dosing.
   iv) Known human immunodeficiency virus (HIV) positive with an acquired human immunodeficiency syndrome (AIDS)-defining opportunistic infection within the last year, or a current CD4 count < 350 cells/µL. HCC participants with HIV are eligible if:
      (1) They do not have another active viral infection.
      (2) They have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization, as clinically indicated.
      (3) They continue on ART as clinically indicated while enrolled on study.
      (4) CD4 counts and viral load are monitored per standard of care by a local health care provider.
      (5) NOTE: Testing for HIV must be performed at sites where mandated locally. HIV-positive participants must be excluded where mandated locally (refer to Appendix 7).
   v) ***Not applicable per Protocol Amendment 02 (see new criterion vii) below):*** *Active SARS-CoV-2 infection.*
      (1) Additionally, in the case of prior SARS-CoV-2 infection, acute symptoms must have resolved and based on Investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment (see Section 6.4.1).
   vi) Other active viral infection.
   vii) Symptomatic SARS-CoV-2 infection.
      (1) Additionally, in the case of prior SARS-CoV-2 infection, acute symptoms must have resolved and based on Investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment (see Section 6.4.1).
c) Participants with a history of myocarditis, regardless of etiology.
d) Interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity.
e) Participants with an active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

*g) **Not applicable per Revised Protocol 01 (see new criterion i) below):** Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.*

h) Participants with any serious or uncontrolled medical disorders that in the opinion of the Investigator may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

i) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

j) All toxicities attributed to prior anticancer therapy other than hearing loss, alopecia, and fatigue must have resolved to Grade 1 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5) or baseline before administration of study drug.

3) Prior/Concomitant Therapy

a) Prior treatment with relatlimab or any other LAG-3 targeted agents.

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

c) Participants with history of life-threatening toxicity related to prior systemic anti-cancer therapy, except those that are unlikely to re-occur with standard countermeasures.

d) Radiotherapy within 4 weeks prior to start of study drug. Palliative radiotherapy for symptomatic control is acceptable (if completed at least 2 weeks prior to study drug administration) and no additional radiotherapy for the same lesion is planned.

e) Participants who have received a live/attenuated vaccine within 30 days of randomization (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]).

f) Any of the following procedures or medications within 4 weeks prior to study drug administration:

i) Any investigational cytotoxic drug. Exposure to any non-cytotoxic drug within 4 weeks or 5 half-lives (whichever is shorter) is prohibited. If 5 half-lives are shorter than 4 weeks, agreement with Sponsor/Medical Monitor is mandatory.

ii) Growth factors (eg, granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor, erythropoietin).

iii) Major surgery.

g) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7 (Concomitant Therapy).

h) ***Not Applicable per Revised Protocol 01 (see new criterion j) below):*** *Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. See Section 7.7.1 for prohibited therapies.*

i) Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine prior to screening, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the Investigator and the Medical Monitor.

j) Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.

k) If participants who are currently enrolled in other BMS studies in HCC are being considered for enrollment in CA224073, they cannot enroll in CA224073 until the other BMS study has completed the analysis of the primary endpoint.

4) Physical and Laboratory Test Findings

a) Positive pregnancy test at enrollment or prior to administration of study medication.

b) Participants who do not meet criteria for screening laboratory values described in Section 6.1 (Inclusion Criteria).

c) [redacted]

d) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, electrocardiograms (ECGs), or clinical laboratory determinations beyond what is consistent with the target population.

5) Allergies and Adverse Drug Reaction

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

6) Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding.

7) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a screen failure (ie, participant has not been randomized). If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single Screening Period will be permitted (in addition to any parameters that require a confirmatory value).

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

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

Testing for asymptomatic COVID-19, for example by reverse transcription polymerase chain reaction (RT-PCR) or viral antigen, is not required. However, some participants may develop suspected or confirmed symptomatic COVID-19 or be discovered to have asymptomatic COVID-19 during the screening period. In such cases, participants may be considered eligible for

the study after meeting all inclusion/exclusion criteria related to symptomatic infection and after meeting the following criteria:

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

7 TREATMENT

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

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

- Nivolumab
- Relatlimab

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

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 non-IPs.

IPs used in this trial are provided in Table 7-1. There are no non-IPs in this study.

Table 7-1: Study Treatments for CA224073

Product Description/ Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
Relatlimab[a] Injection (10 mg/mL)	10 mg/mL	IP	Open-label, 4 vials per carton/ 80 mg/vial (8 mL vial)	Colorless to pale yellow liquid, clear to opalescent, light (few) particulates (consistent in appearance to protein particulates) may be present.	Refer to the label on container and/or Pharmacy Manual.
Nivolumab[a] Injection (10 mg/mL)	10 mg/mL	IP	Open-label, 4 vials per carton/ 100 mg/vial (10 mL vial)	Clear to opalescent, colorless to pale yellow liquid. Light (few) particulates may be present.	Refer to the label on container and/or Pharmacy Manual.

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

[a] Relatlimab is sometimes referred to as BMS-986016; Nivolumab is sometimes referred to as BMS-936558.

7.1 Treatments Administered

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

Table 7.1-1: Treatments Administered

Study Arm	Study Treatment	Dose Level	Frequency of Administration and Duration of Treatment	Route of Administration	Approximate Infusion Time, minutes
Arm A	Nivolumab	480 mg	Q4W Until progression, unacceptable toxicity, or withdrawal of consent	IV	30
Arm B	Nivolumab/ Relatlimab[a]	480 mg/ 480 mg	Q4W Until progression, unacceptable toxicity, or withdrawal of consent	IV	60
Arm C	Nivolumab/ Relatlimab[a]	480 mg/ 960 mg	Q4W Until progression, unacceptable toxicity, or withdrawal of consent	IV	60[b]
[redacted]					

Abbreviations: IV = intravenous; mg = milligram; Q4W = every 4 weeks.

[a] Nivolumab and relatlimab are co-administered.

[b] Infusions will occur over approximately 60 minutes for participants weighing equal to or greater than 45 kg, and for participants weighing less than 45 kg, infusions will occur over approximately 90 minutes.

7.1.1 Relatlimab Combined with Nivolumab Dosing

Relatlimab and nivolumab will be administered on Day 1 of each Q4W treatment cycle. For Q4W dosing cycles, participants may be dosed no less than 26 days from the previous dose.

Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, the participant should be managed according to Section 7.4.4.

Participants should receive relatlimab and nivolumab until progression, unacceptable toxicity, withdrawal of consent/assent by the participant, or the study ends, whichever occurs first.

There will be no dose escalations or reductions of relatlimab or nivolumab. Premedication for potential infusion reaction is not recommended for the first dose of either treatment.

Doses of relatlimab or nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits must not be skipped, only delayed. See Section 7.4 (Dosage Modification) and Section 8.1 (Discontinuation from Study Treatment).

The relatlimab and nivolumab injections can be infused undiluted or diluted. The infusion must be promptly followed by a flush of diluent to clear the line. Instructions for dilution and infusion of relatlimab and nivolumab injections will be provided in the Pharmacy Manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

For details on prepared drug storage, preparation, and administration, please refer to the IBs[8,36] and/or Pharmacy Manual. The selection and timing of dose for each participant is provided in Table 7.1-1.

For the 960-mg relatlimab/480-mg nivolumab dose, infusions will occur over approximately 60 minutes for participants weighing equal to or greater than 45 kg, and for participants weighing less than 45 kg, infusions will occur over approximately 90 minutes.

Study treatment will be dispensed by IRT at the study visits as listed in Section 2 (Schedule of Activities).

7.1.2 Best Supportive Care

Recommendations for best supportive care (BSC) can be found in the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of HCC.[64] These include up to 3 g/day acetaminophen (paracetamol) for management of mild pain. Nonsteroidal anti-inflammatory medications should be avoided in participants with cirrhosis. Pain of intermediate or severe intensity can be managed with opioids, with care taken to avoid opioid-induced constipation.

7.1.3 Palliative Therapy

Palliative local therapy for clinically symptomatic tumor sites (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) including palliative (limited-field) radiation and palliative surgical resection may be considered during trial therapy if the following criteria are met:

- The participant is considered to have progressed at the time of palliative therapy and meets criteria to continue with treatment beyond progression.
- OR
- The lesion for palliative local therapy is a non-target lesion which has not met criteria for progression.
- Tumor lesions requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy. The potential for overlapping toxicities with radiotherapy and nivolumab/nivolumab plus relatlimab currently is not known; however, anecdotal data suggest that radiotherapy with nivolumab is tolerable. If palliative radiotherapy is required, then study drugs should be withheld for at least 1 week before, during, and 1 week after radiation. Palliative therapy must be clearly documented in the source records and case report form (CRF). Details in the source records should include dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs.

7.2 Method of Treatment Assignment

Study treatment will be dispensed at the study visits as listed in Section 2 (Schedule of Activities). Before the study is initiated, each user will receive login information and instructions on how to access the IRT. After the participant's ICF has been obtained and initial eligibility is established, the participant must be enrolled into the study by using IRT to obtain the participant number. Every

participant who signs the ICF must be assigned a participant number in IRT. The Investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. All procedures will be clarified in the IRT manual.

Study treatment will be dispensed at the study visits per the Section 2 (Schedule of Activities). During the screening visit, the investigative site will call into the enrollment option of the IRT designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted]. The participant identification (PID) number will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID o[redacted]. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to assign the participant into the open dose level.

Treatment assignments for eligible participants will alternate among the arms, with screened participants assigned to different parts through IRT. If a treatment arm becomes overly enrolled because of screen failures in alternate arms, it can be temporarily closed to allow enrollment in the other arms. Once balance is achieved, the temporary hold can be lifted. If there are no openings available in the part to which the participant would be assigned by this algorithm, the participant will be assigned to the next open part/cohort until respective dose levels or cohorts have completed accrual according to principles outlined in Section 5.1.2 (Treatment Period).

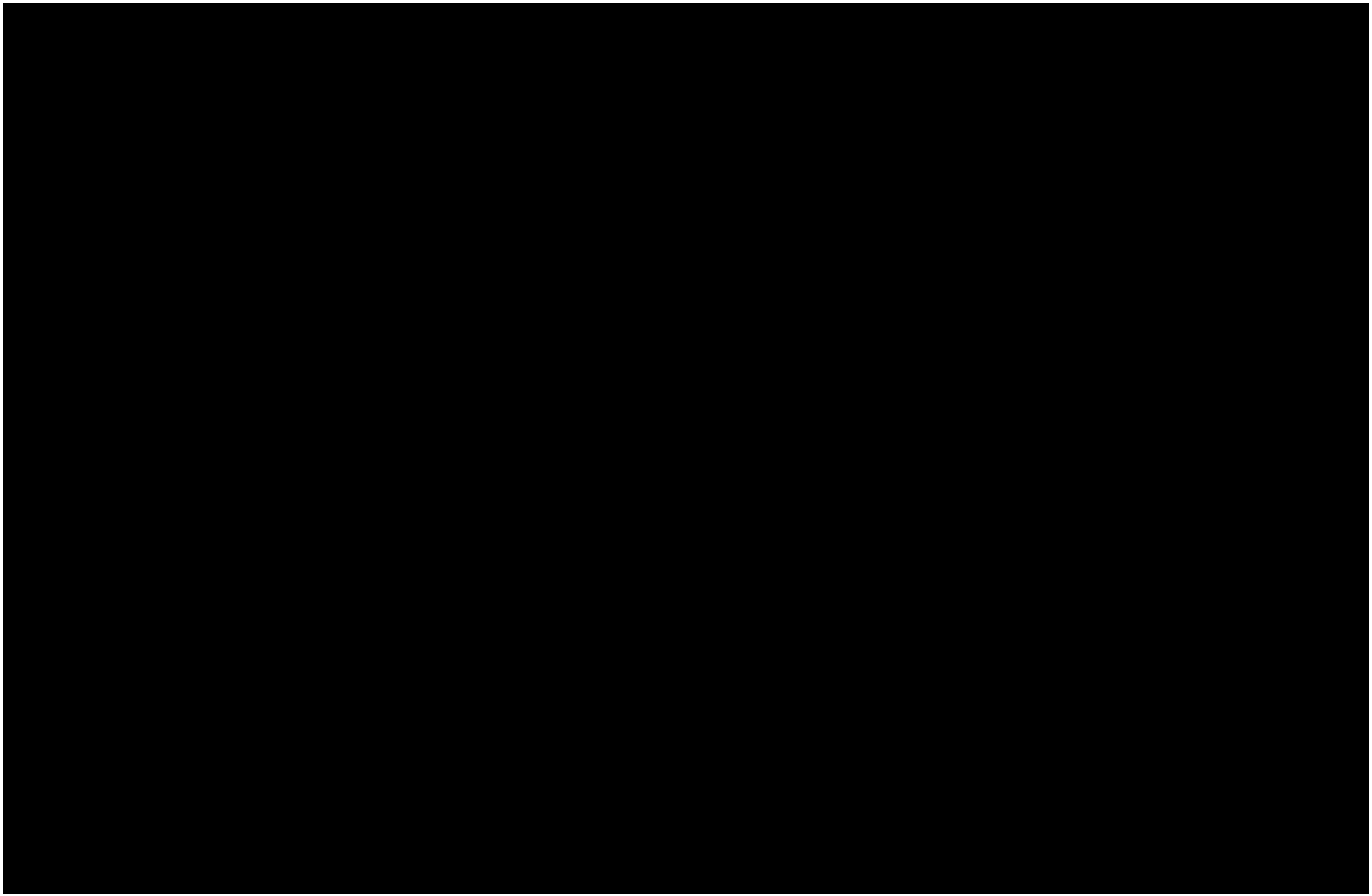
Participants will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment.

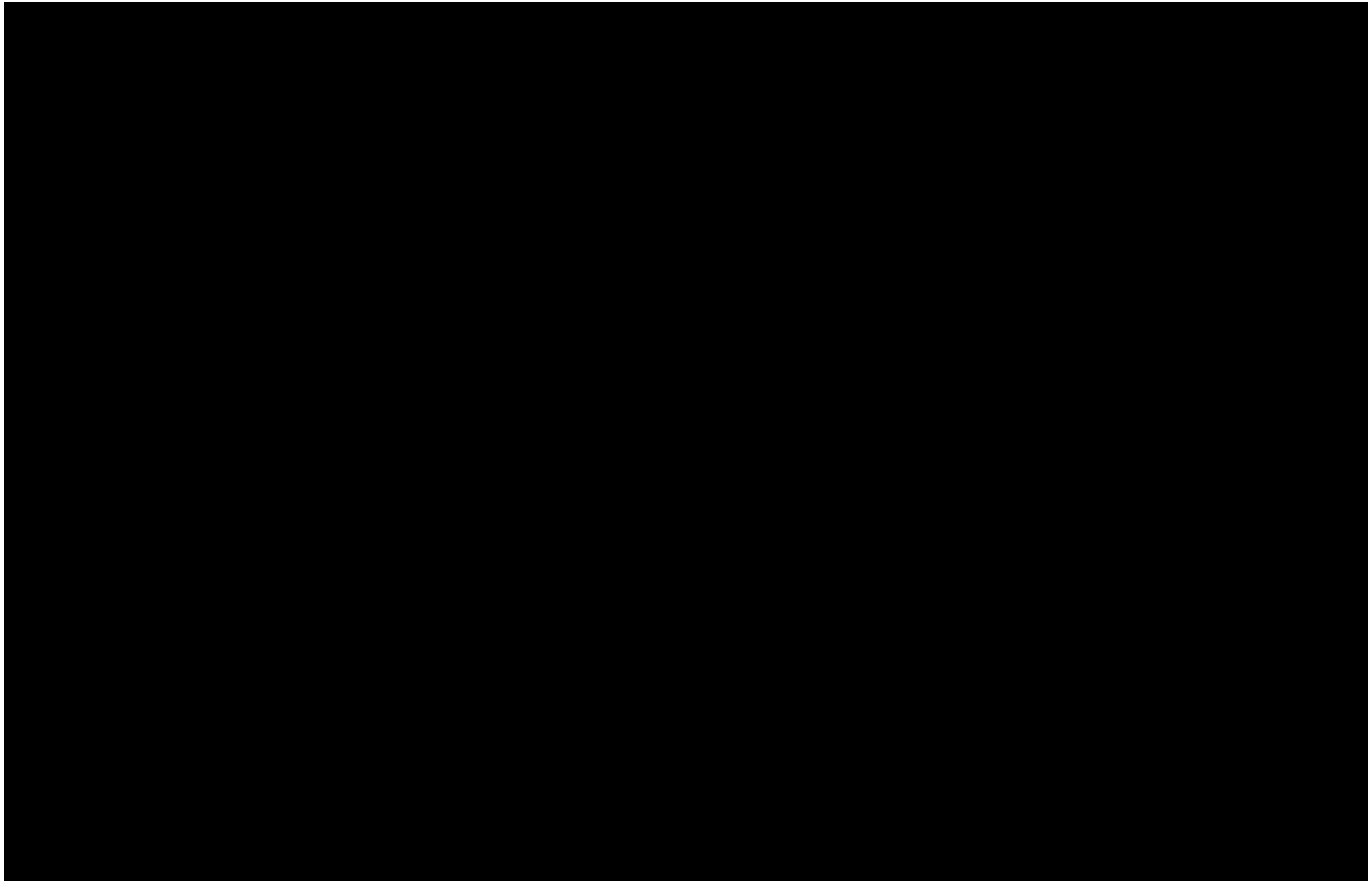
7.3 Blinding

This is a randomized, Phase 2a study, that is open label to Sponsor and site. It has been determined that blinding is not required to meet study objectives. Blinding procedures are not applicable and access to treatment assignment information is unrestricted. The specific treatment to be taken by a participant will be assigned using IRT. The site will contact the Interactive Response system prior to the start of study intervention administration for each participant. The site will record the treatment assignment on the applicable Case Report Form (CRF).

7.4 Dosage Modification

AE criteria for delaying, resuming, and discontinuing of study treatment is provided [redacted].





[redacted]

[redacted]

[redacted]

[redacted]

7.4.2 Dose Delay Criteria

For participants receiving nivolumab monotherapy or combination relatlimab and nivolumab, dose delay criteria apply for all drug-related AEs (regardless of whether the event is attributed to nivolumab, relatlimab, or both). Delay administration of nivolumab or both nivolumab and relatlimab if any of the delay criteria [redacted] are met. Delay nivolumab or combined nivolumab and relatlimab dosing for any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, warrants delaying the dose of study medication.

Study treatment must also be delayed for SARS-CoV-2 infection, either confirmed or suspected.

For participants who require delay of relatlimab or nivolumab, re-evaluate weekly, or more frequently if clinically indicated, and resume relatlimab or nivolumab dosing when the retreatment criteria are met [redacted]. Continue tumor assessments per protocol, even if dosing is delayed.

[redacted]

[redacted]

7.4.4 Management of Treatment-related Infusion Reactions

Since relatlimab and nivolumab contain only human Ig protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions; however, if such a reaction were to occur, it might manifest with [redacted]. All Grade 3 or 4 infusion reactions should be reported within 24 hours and reported as an SAE if it meets the criteria.

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

[redacted]

7.5 Preparation/Handling/Storage/Accountability

For relatlimab and nivolumab, refer to the current version of the IBs[8,36] and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information.

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

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

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

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

- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and the Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Relatlimab and nivolumab IV infusions will be administered to the participant in the clinical facility. Trained medical personnel will dispense study treatments to the participants. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance.

7.7 Concomitant Therapy

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over-the-counter medications) continued at the start of the study or started during the study and different from the study treatment must be documented in the concomitant therapy section of the CRF.

Care should be taken when using benzodiazepines in participants with advanced cirrhosis due to an increased risk of falls, injuries, or altered mental status. Participants should be provided with appropriate psychological and nutritional support.[64]

The effect of COVID-19 vaccines on participants taking relatlimab and nivolumab is currently unknown.

7.7.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3 [Permitted Therapy]).
- Loco-regional therapies for HCC.
- Any concurrent anti-neoplastic therapy (ie, systemic chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of HCC).
  - Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any live/attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) within 30 days of initiating study treatment, during treatment, and until 135 days post last dose.

7.7.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization are excluded.

Participants who need anticoagulation treatment due to concomitant cardiovascular disease should be monitored closely; a maintenance of INR > 2 is recommended.

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and, if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, eGFR < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis; therefore, MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image manual. Site-specific imaging requirements that are different than those captured in the imaging manual may be considered after discussion with the BMS Medical Monitor or Clinical Scientist.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the Investigator, and standards set by the local Ethics Committee.

7.7.3 Permitted Therapy

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

7.7.4 Antiviral Therapy

Participants on antiviral therapy for hepatitis B or C should continue the treatment during the study. Changing of dosage and regimens of antiviral therapy will be at the discretion of the Investigator.

If a participant has a > 1 log IU/mL increase in HBV DNA, then virologic breakthrough should be considered and HBV DNA confirmed. Adherence to current antiviral therapy should be assessed, and resistance testing performed according to local practices. If a participant has documented virologic breakthrough due to antiviral resistance, then this should be managed based on standardized regional guidelines and treatment with relatlimab and nivolumab temporarily held. The participant may resume treatment with relatlimab and nivolumab or nivolumab (monotherapy phase) once virologic control is reestablished (HBV DNA < 500 IU/mL).

For any participant who continues to be HCV RNA positive after receiving relatlimab plus nivolumab, current guidelines for management of chronic HCV infection, including those from American Association for the Study of Liver Disease (AASLD), EASL, or Asian Pacific Association for the Study of the Liver (APASL) may be consulted. Initiation of direct-acting antivirals (DAAs) for HCV is allowed at the discretion of the Investigator after discussion with the BMS Medical Monitor or Clinical Scientist.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment specified in protocol Section 7.1. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and Ethics Committee, or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986016 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Documented radiographic disease progression per RECIST v1.1, unless the participant meets criteria for treatment beyond progression (Section 8.1.2).

Refer to the Section 2 (Schedule of Activities) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/Clinical Scientist of this event. In most cases (all cases in Czech Republic, Argentina, or other countries where it is required), the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 (Pregnancy).

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

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

8.1.1 Relatlimab and Nivolumab Treatment Discontinuation

If a participant in any of the nivolumab/relatlimab combination arms meets criteria for discontinuation [redacted], the participant must discontinue both nivolumab and relatlimab and be taken off the treatment phase of the study.

Both nivolumab and relatlimab treatment must be permanently discontinued per criteria [redacted] in Section 7.4 (Dosage Modification). Discontinue nivolumab (Arm A) or both nivolumab and relatlimab (Arm B or Arm C) for any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

Study treatment must also be permanently discontinued for the following:

[redacted]

- Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

8.1.2 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[43]

Participants treated with study therapy in any arm will be permitted to continue treatment beyond initial RECIST v1.1-defined progressive disease, assessed by the Investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Tolerance of study treatment.
- Stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Participant provides written informed consent prior to receiving additional treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

Radiographic assessment/scan(s) should continue in accordance with the Section 2 (Schedule of Activities) for the duration of the treatment beyond progression and should be submitted to the central imaging vendor.

If the Investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to Section 2 (Schedule of Activities).

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial progressive disease. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial progressive disease. Treatment should be discontinued permanently upon documentation of further progression.

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 non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden 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 which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.3 Criteria to Resume Treatment

[redacted]

[redacted] Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every 6 weeks or more frequently if clinically indicated during such dosing delays.

When criteria to resume treatment are met, resume nivolumab and relatlimab on the same day for participants receiving combination therapy or resume nivolumab in participants receiving monotherapy.

Participants may also resume treatment with study drug under the following criteria:

[redacted]

- Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after all of the following: 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen); 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever-reducing medications); 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment; **and** 4) consultation by the Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.

[redacted]

[redacted]

8.1.4 Post Study Treatment Study Follow-up

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

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol-defined window. At the time of this request, each participant will be contacted to determine their survival status, unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation from the Study

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

- Participants should notify the Investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails, as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If Investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the Investigator may use a

Sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.

- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in Section 2 (Schedule of Activities).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in Section 2 (Schedule of Activities), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes, provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in Section 2 (Schedule of Activities).

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the [redacted] BMS-936558 (nivolumab) IB[36] [redacted].

[redacted]

Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or

assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor for BICR during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor.

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

Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example, most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, CT or MRI of abdomen and pelvis (including required tri-phasic CT or MRI of the liver), and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same Investigator or radiologist for each assessment, whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST v1.1 criteria.

If a participant has a contraindication for CT IV contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the, abdomen, pelvis (including required tri phasic CT or MRI of the liver), and other known/suspected sites of disease should be obtained.

Bone scan or positron emission tomography (PET) scan are not adequate for assessment of RECIST v1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

MRI of brain should be acquired as outlined in Section 2 (Schedule of Activities). CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

Use of CT component of a PET-CT scanner: Combined modality scanning, such as with PET-CT, is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use

in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically-based RECIST v1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an Investigator if it is not routinely or serially performed.

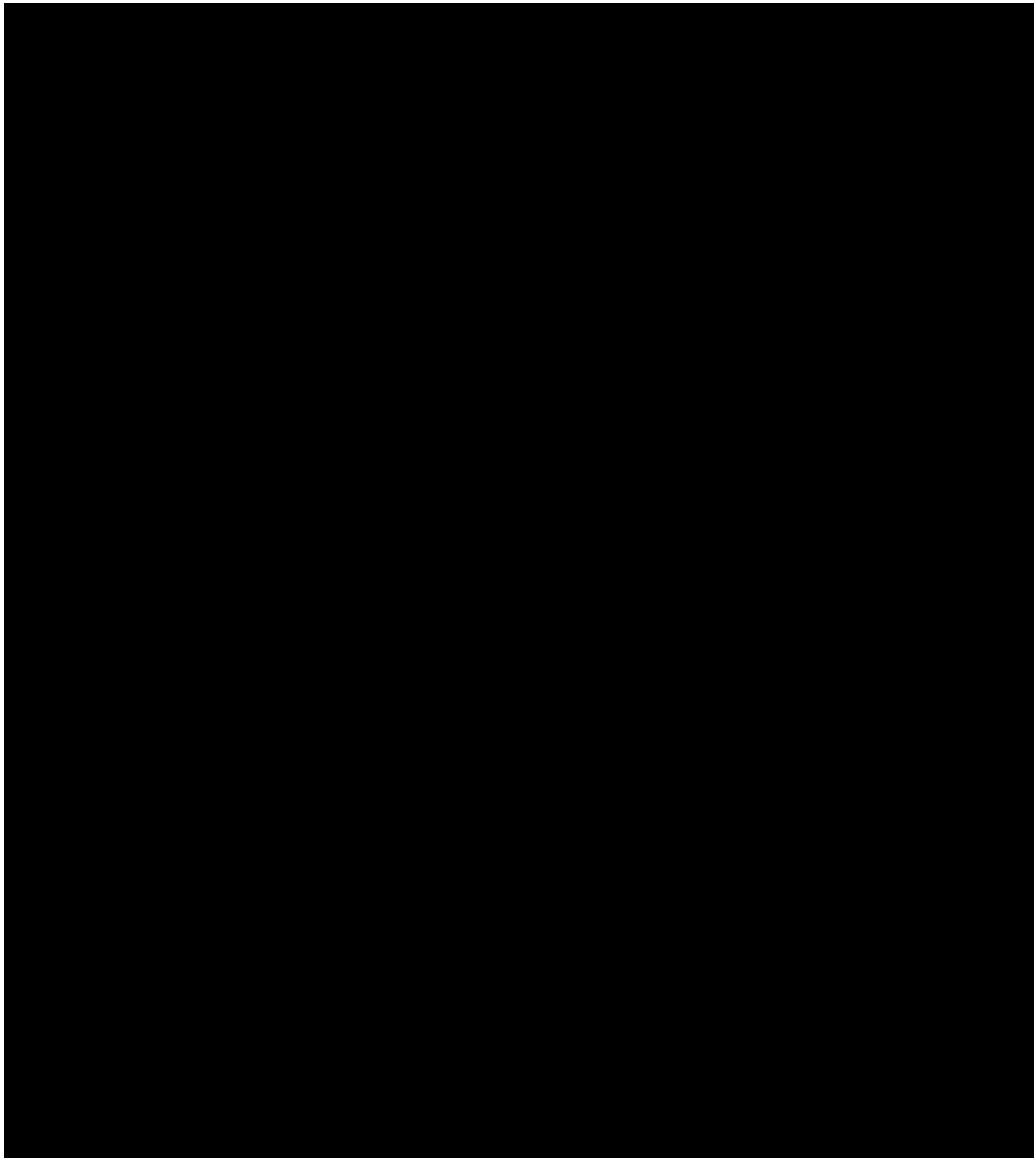
Bone scans may be collected per local standards, as clinically indicated.

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue on the protocol-defined imaging schedule, regardless if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same Investigator or designee using RECIST v1.1 criteria. Investigators will 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 9 for specifics of RECIST v1.1 criteria to be used in this study). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. [redacted]

Imaging should continue as per schedule until treatment stop (including treatment beyond progressive disease) or start of subsequent systemic therapy, whichever is later.

[redacted]



9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

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

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment until the time points specified in the Section 2 (Schedule of Activities). See Section 9.2.3 for additional details on Follow-up.

- All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection, must be collected from the date of the participant's written consent until 135 days following discontinuation of dosing.
- All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 135 days of discontinuation of dosing, except in cases where a study participant has started a new anti-neoplastic therapy. However, any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the Investigator will be reported, and any deaths occurring within the 135-day follow-up period must be reported regardless of initiation of new anti-neoplastic therapy.
  - For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.
- The Investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure (eg, a follow-up skin biopsy).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours of site awareness, as indicated in Appendix 3.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

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

9.2.2 Method of Detecting AEs and SAEs

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

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

All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 135 days following discontinuation of study treatment.

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, non-serious AEs of special interest (as defined in Section 9.2), and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, the event is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

The Sponsor or designee will be reporting AEs 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. A suspected, unexpected serious adverse

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

9.2.5 Pregnancy

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

If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the Investigator and the BMS Medical Monitor/Clinical Scientist must occur. In the Czech Republic and Argentina (or other countries where it is required), all pregnancies will require the participant to discontinue treatment.

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.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious 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 participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI (p-DILI) event. All occurrences of p-DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

[redacted]

[redacted]

9.2.8 Other Safety Considerations

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

9.3 Overdose

For this study, any dose of relatlimab or nivolumab greater than the protocol-specified dose will be considered an overdose.

- In the event of an overdose, the Investigator should do the following:
  - Contact the Medical Monitor immediately.
  - Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
  - Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

9.4 Safety

Planned time points for all safety assessments are listed in Section 2 (Schedule of Activities). Safety assessments include AEs, physical examinations, vital signs, performance status, assessment of signs and symptoms, laboratory tests, and pregnancy tests as outlined in Section 2 (Schedule of Activities).

9.4.1 Physical Examinations

Refer to Section 2 (Schedule of Activities).

9.4.2 Vital signs

Refer to Section 2 (Schedule of Activities).

9.4.3 Electrocardiograms

Refer to Section 2 (Schedule of Activities).

9.4.4 Clinical Safety Laboratory Assessments

Laboratory assessments are listed in Table 9.4.4-1.

Investigators must document their review of each laboratory safety report.

All clinical safety laboratory assessments will be performed locally per Section 2 (Schedule of Activities).

Table 9.4.4-1: Laboratory Assessment Panels

Hematology - Complete Blood Count (CBC)	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Amylase Alpha-fetoprotein (AFP) Lactate dehydrogenase (LDH) Lipase Creatinine Blood urea nitrogen (BUN)/serum urea Glucose Liver laboratory tests: Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Total bilirubin (T.bili) Direct bilirubin Albumin	Total protein Sodium Potassium Chloride Calcium Phosphorus Magnesium TSH, free T3 and free T4 - screening; if free T3 is not available, total T3 is acceptable TSH, with reflexive free T3 and free T4 if TSH is abnormal - on treatment Creatinine clearance (CrCl) - if used, at screening only
[redacted]	
[redacted]	
Urinalysis	
Protein Glucose Blood Leukocyte esterase Specific gravity pH Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
Serology	
Hepatitis C antibody (if Hepatitis C antibody is positive reflex to hepatitis C RNA), hepatitis C RNA viral load (PCR), hepatitis B surface antigen (if hepatitis B surface antigen is positive reflex to hepatitis D), hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA viral load (PCR), HIV-1 and -2 antibody (screening only; testing for HIV must be performed at sites where mandated by local requirements [see Appendix 7]).	

Table 9.4.4-1: Laboratory Assessment Panels

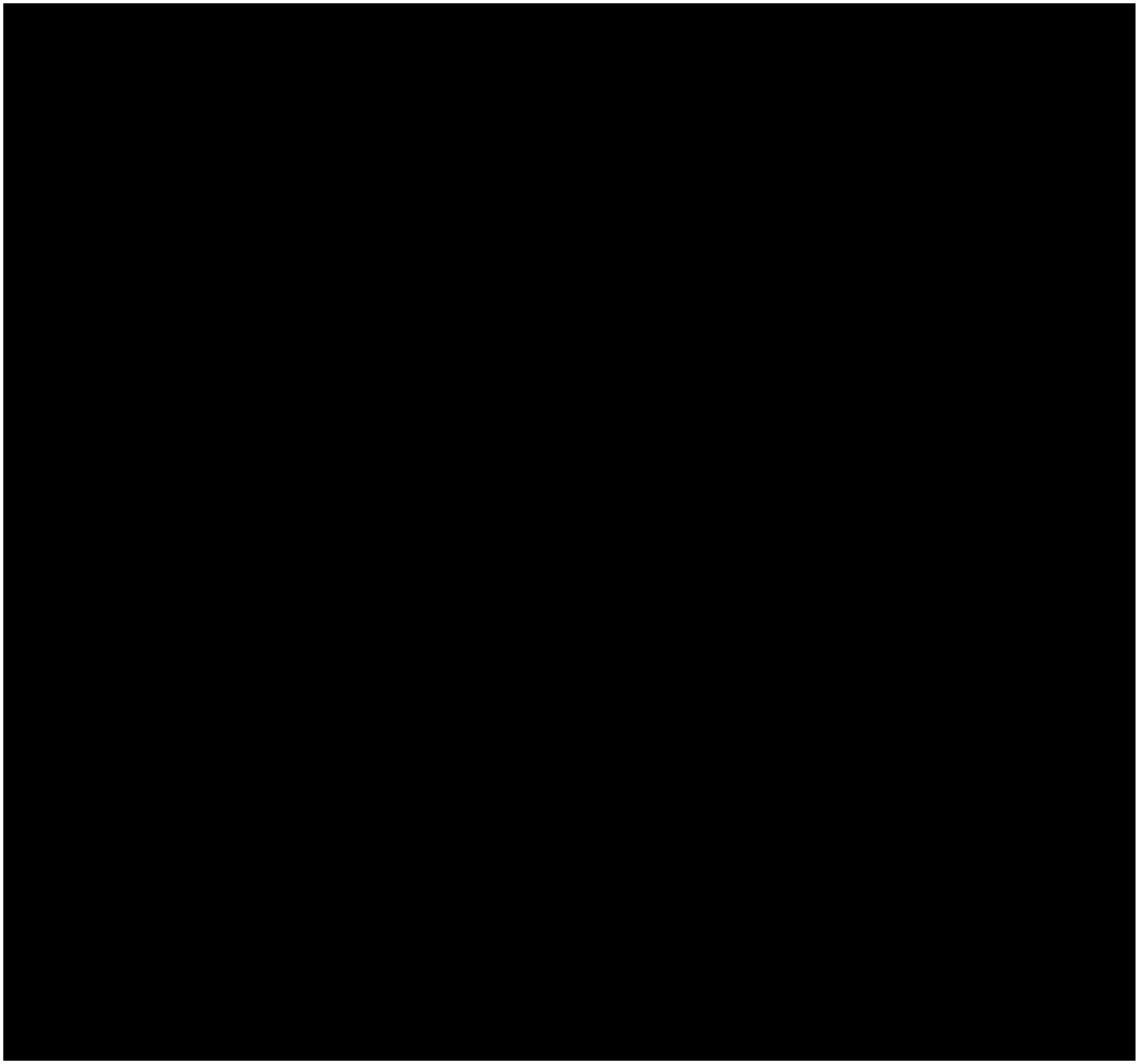
Other Analyses
Pregnancy test, serum or urine (WOCBP only; minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin (HCG); screening, predose, safety follow-up
Follicle stimulating hormone (FSH) screening -only required to confirm menopause in women < age 55)
Coagulation profile (INR or PT, and aPTT)
SARS-CoV-2 viral test

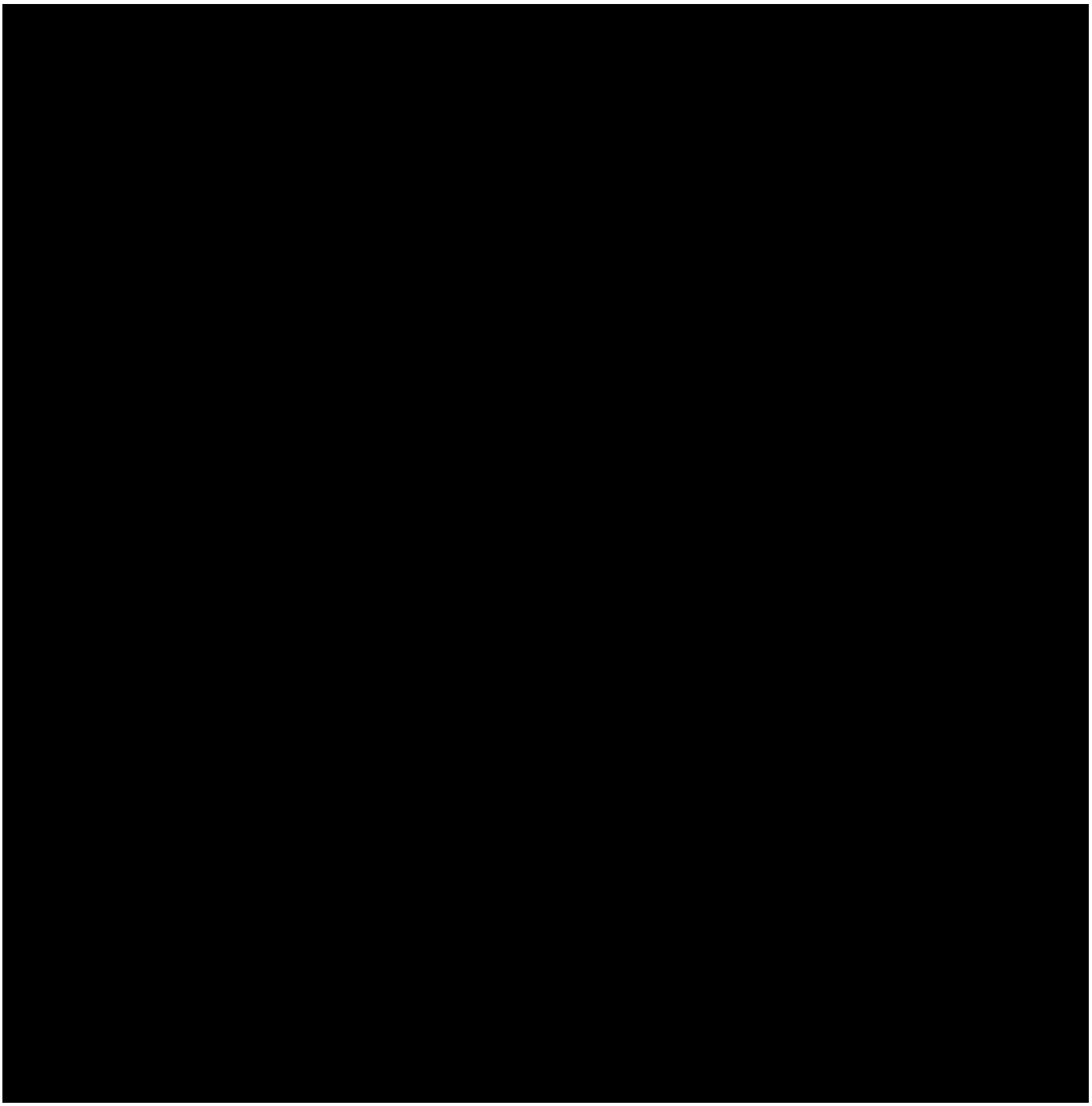
Abbreviations: aPTT = activated partial thromboplastin time; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = prothrombin time; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of child bearing potential.

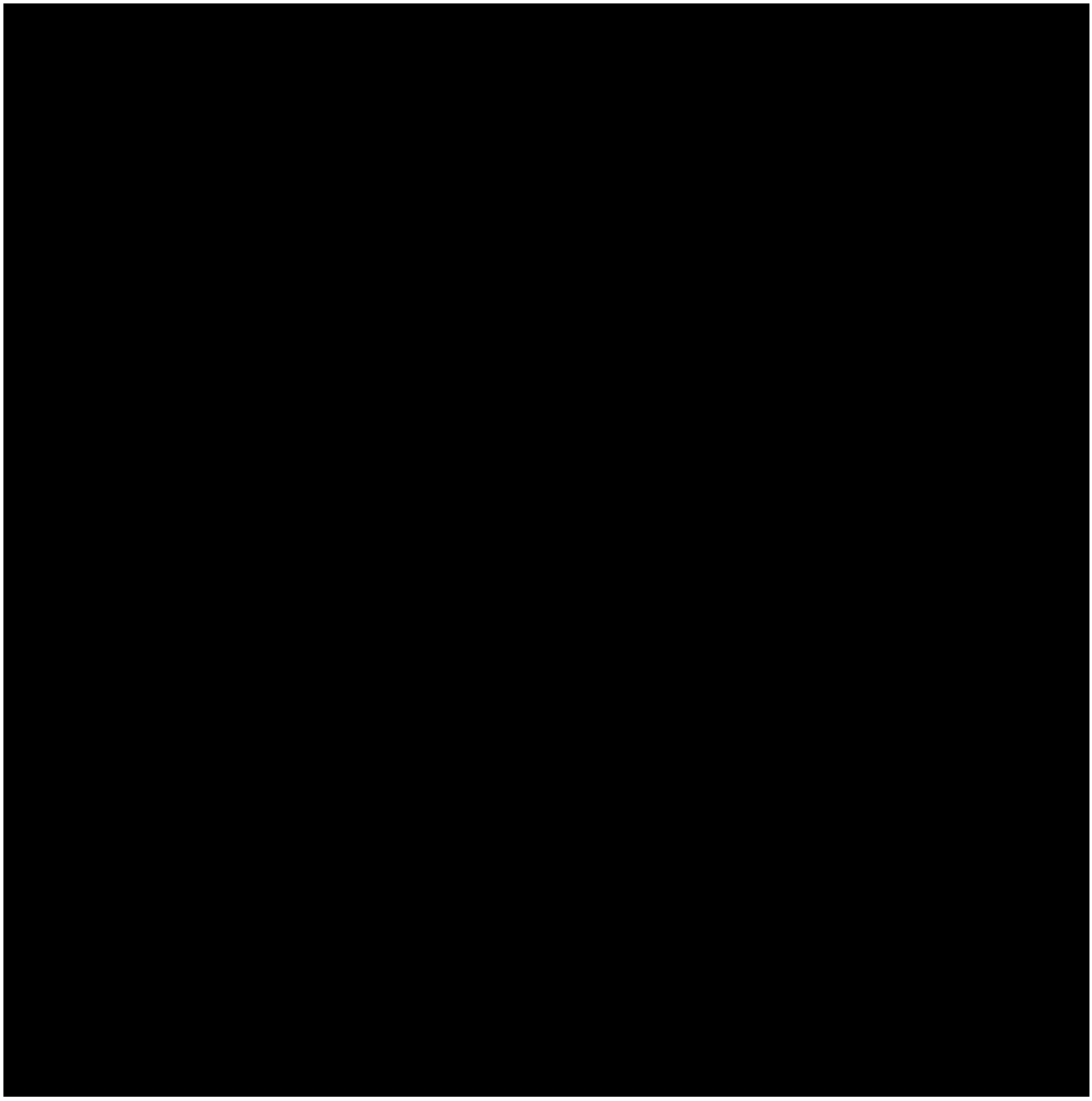
9.4.5 Imaging Safety Assessment

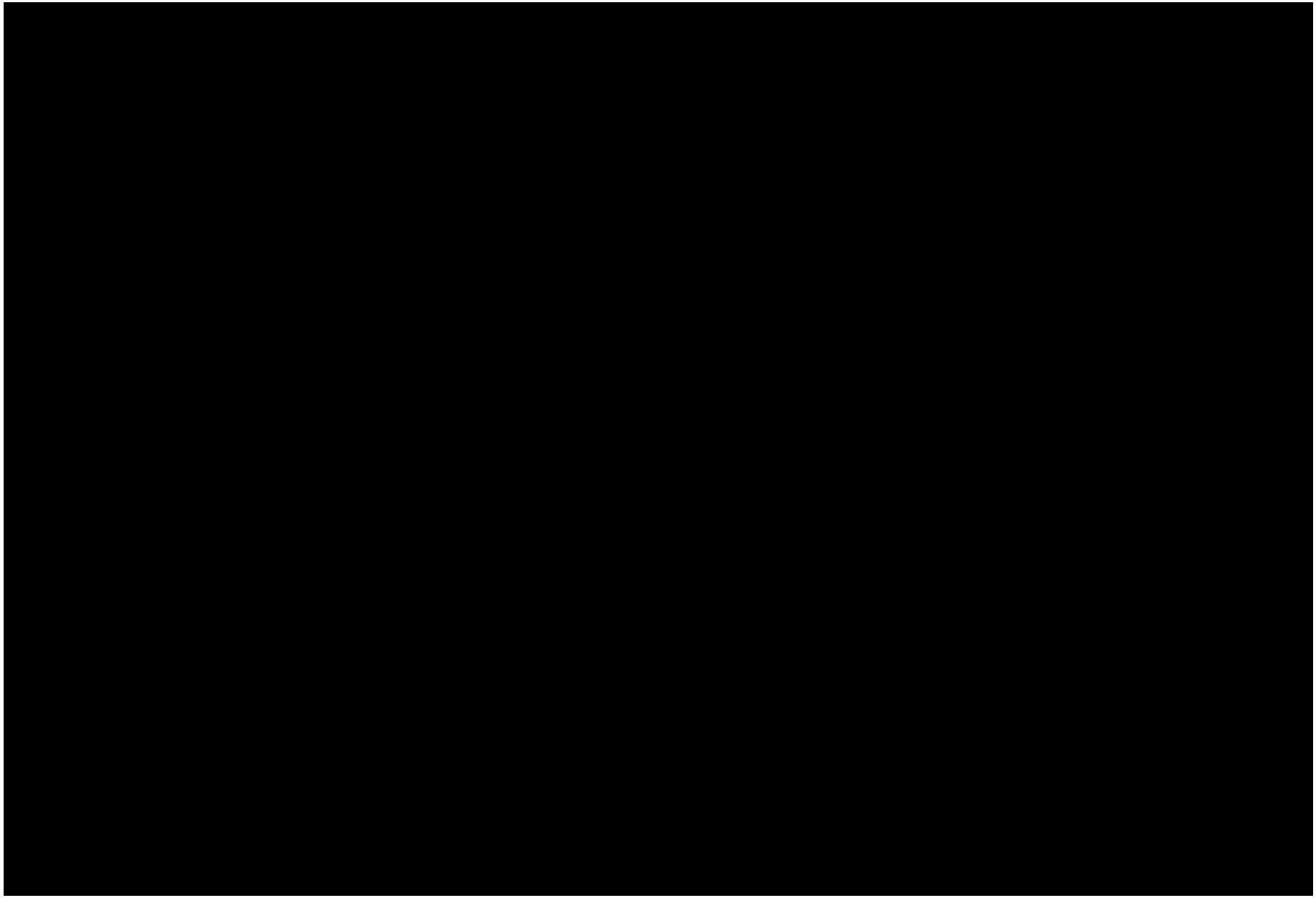
Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study Investigator as per standard medical/clinical judgment.

[redacted]

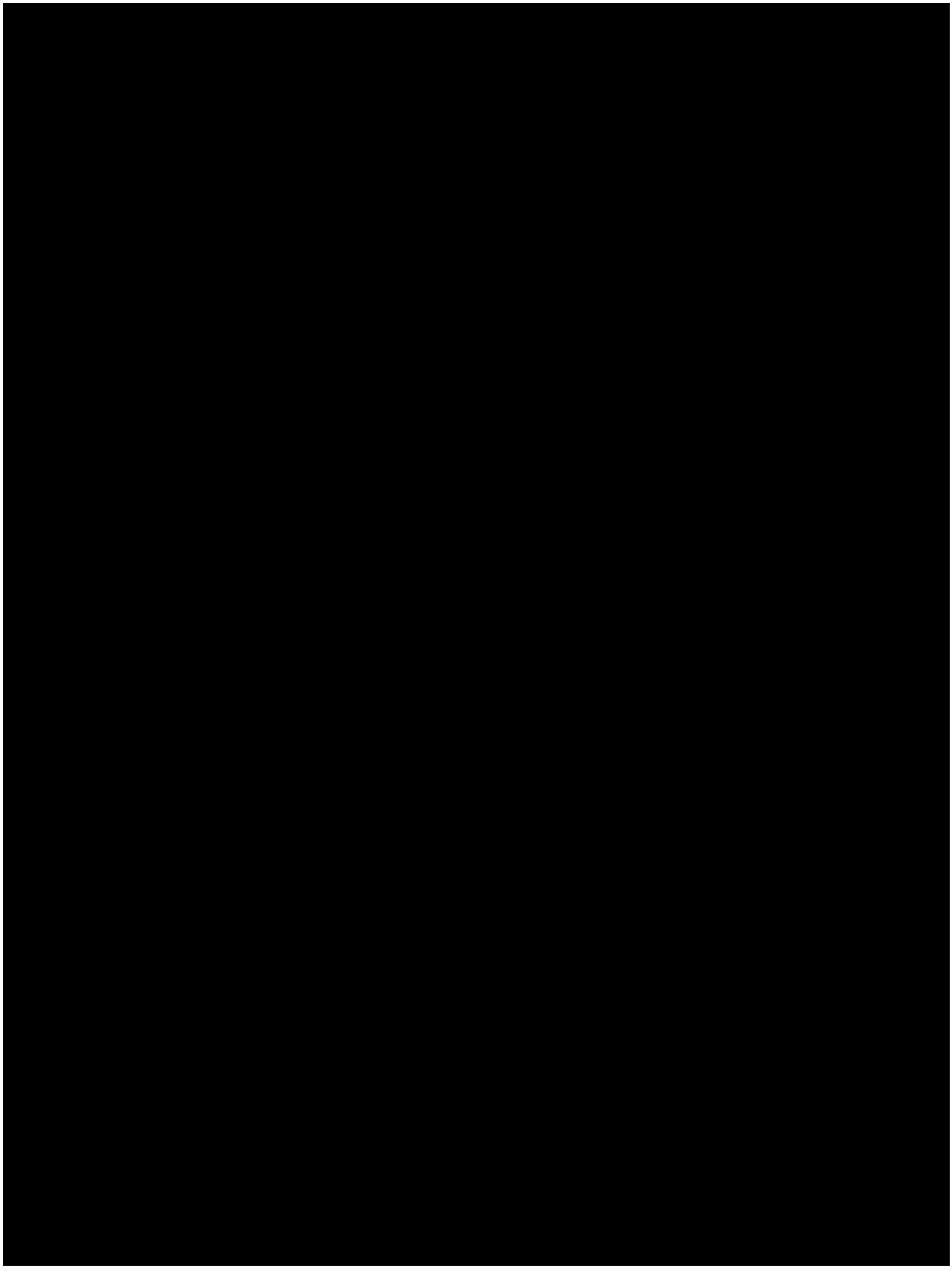








[redacted]



[redacted]

9.8.2 Tumor Samples

Tumor biopsy specimens will be obtained as stated in Table 2-1.

[redacted]

9.8.2.1 Tumor Sample Collection

The Investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen; however, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the participant. Detailed instructions of the obtaining, processing, labeling, handling, storing, and shipping of specimens will be provided in a separate Laboratory Manual.

9.8.2.2 *LAG-3 and PD-L1 Expression*

Entry to this study requires assessment for LAG-3 expression in tumor specimens. LAG-3 expression on immune cells and PD-L1 expression on tumor and immune cells will be measured

using analytically validated immunohistochemical assays. LAG-3 status, as determined using a [redacted] threshold, will be stratification criteria for randomization.

[redacted]

9.8.4 Additional Research Collection

This protocol will include residual sample storage for additional research (AR).

For All US sites:

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

- If the IRB/Ethics Committees and site agree to the mandatory AR retention and/or collection, then the study participant must agree to the mandatory AR as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the AR retention and/or collection.

For non-US Sites

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

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

Note: Additional Research collection and analysis will not occur [redacted] as per Protocol Amendment 04.

Sample Collection and Storage

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

[redacted]

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

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

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

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

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

[redacted]

9.8.6 Other Assessments

Serum will be collected for potential future measurements [redacted].

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health care resource utilization data will not be collected in this study.

10 STATISTICAL CONSIDERATIONS

[redacted]

[redacted]

[redacted]

10.2 Populations for Analyses

For purposes of analysis, populations for primary and secondary objectives are defined in Table 10.2-1. [redacted]

Table 10.2-1: Populations for Analyses

Population	Description
Enrolled	All participants who sign informed consent and obtain a participant number.
Randomized	All participants who are randomized.
Randomized LAG-3+	All participants who are randomized and have LAG-3+ status.
Treated	All participants who take at least 1 dose of any study treatment.
Treated LAG-3+	All participants who take at least 1 dose of any study treatment and is LAG-3+.

Abbreviations: + = positive; LAG-3 = lymphocyte activation gene 3.

10.3 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

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

10.3.1 Efficacy Analyses

Efficacy Analyses are described in Table 10.3.1-1 and will be performed on the randomized population. If Arm C is closed or dropped and number of participants randomized in Arm C is small, the primary efficacy comparison will be performed between Arm B vs Arm A and the efficacy analysis in Arm C will be descriptive.

Table 10.3.1-1: Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The difference in ORR between relatlimab in combination with nivolumab (Arm B) vs nivolumab (Arm A) will be presented by BICR using RECIST v1.1 computed using a simple proportion and 95% Clopper-Pearson confidence interval for this study. In addition, posterior probability of the true difference of ORR assessed by BICR using RECIST v1.1 to fall in the activity interval given the data will be provided. Also, the posterior mean of the difference of ORR between the two arms and the corresponding 90% credible intervals will also be provided. The efficacy analysis in Arm C will be descriptive.
Secondary	ORR assessed by Investigator and DCR will be computed and analyzed using frequency statistics. DOR, PFS, and OS will be analyzed using the Kaplan-Meier method.
[redacted]	

Abbreviations: BICR = Blinded Independent Central Review; DCR = disease control rate; DOR = duration of response; LAG-3 = lymphocyte activation gene 3; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors.

10.3.2 Safety Analyses

All safety analyses described in Table 10.3.2-1 will be performed on the treated population.

Table 10.3.2-1: Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable.
Secondary	Incidence of AEs, SAEs, AEs leading to discontinuation, death, and laboratory abnormalities will be analyzed using frequency statistics.
[redacted]	

Abbreviations: AE = adverse event; IMAE = immune-mediated adverse event; SAE = serious adverse event.

[redacted]

[redacted]

10.3.4 Interim Analyses

[redacted]

10.3.4.2 Bayesian Continuous Monitoring for Safety

A Bayesian continuous monitoring framework[72] will be utilized to detect safety signals that occur during the study that may lead to termination of Arm B or Arm C. [redacted].

[redacted]

These boundaries can be applied in a continuous basis (does not require the exact number of participants) and is intended to assist on the recommendation to the BMS SC for clinical interpretation. Other parameters may be considered, and other posterior probabilities and boundaries may be calculated, as deemed appropriate by the SC, without amending the protocol.

The SAP will further describe the planned interim analyses.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
–	negative
+	positive
°C	degrees Celsius
µg	microgram
µL	microliter
1L	first line
2D	2-dimensional
2L	second line
3L	third line
AASLD	American Association for the Study of Liver Disease
[redacted]	
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APASL	Asian Pacific Association for the Study of the Liver
aPTT	activated partial thromboplastin time
AR	additional research
ART	antiretroviral therapy
AST	aspartate aminotransferase
[redacted]	
BCLC	Barcelona Clinic Liver Cancer
Bcl-xL	B-cell lymphoma-extra large
BIC	Bayesian information criterion
BICR	blinded independent central review
BMI	body mass index
BMS	Bristol Myers Squibb
[redacted]	

Term	Definition
BP	blood pressure
BSC	best supportive care
BTLA	B- and T-lymphocyte attenuator
BUN	blood urea nitrogen
Cavg	average concentration
CBC	complete blood count
CD	cluster of differentiation
[redacted]	
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
CLss	steady-state clearance
Cmax	maximum concentration
Cmaxss	steady-state maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
[redacted]	
CR	complete response
CrCl	creatinine clearance
CRF	case report form, paper or electronic
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTAg	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	

Term	Definition
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
[redacted]	
CV	coefficient of variation
[redacted]	
D	day
DAA	direct-acting antiviral
DCR	disease control rate
DFS	disease-free survival
DILI	drug-induced liver injury
dL	deciliter
[redacted]	
DNA	deoxyribonucleic acid
DOR	duration of response
[redacted]	
E-R	exposure-response
EASL	European Association for the Study of the Liver
EC50	half-maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EHR	electronic health record
EHS	extrahepatic spreading
[redacted]	
EMR	electronic medical record
[redacted]	
EOT	end of treatment
E-R	exposure-response
etc	et cetera

Term	Definition
[redacted]	
EUDRACT	European Union Drug Regulating Authorities Clinical Trials Database
[redacted]	
FDA	Food and Drug Administration
FDC	fixed-dose combination
FFPE	formalin-fixed, paraffin-embedded
FGL-1	fibrinogen-like protein 1
[redacted]	
FSH	follicle-stimulating hormone
FU	follow-up
[redacted]	
g	gram
[redacted]	
GC	gastric cancer
GCP	Good Clinical Practice
GFR	glomerular filtration rate
[redacted]	
h	hour
[redacted]	
H&E	hematoxylin and eosin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
[redacted]	
HCV	hepatitis C virus
Hep B	hepatitis B
Hep C	hepatitis C

Term	Definition
Hep D	hepatitis D
[redacted]	
HIFU	high-intensity focused ultrasound
HIV	human immunodeficiency virus
HR	hazard ratio
[redacted]	
IB	Investigator's Brochure
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICOS	inducible T cell co-stimulator
ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
Ig	immunoglobulin
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IL	interleukin
IMAE	immune-mediated adverse event
[redacted]	
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IO	immuno-oncology
IP	investigational product
Ipi	ipilimumab
IRB	Institutional Review Board
IRT	interactive response technology

Term	Definition
ITT	intent-to-treat
IU	international unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
[redacted]	
IV	intravenous
kg	kilogram
Kd	dissociation constant
L	liter
LAG-3	lymphocyte activation gene 3
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
m^2	meters squared
mg	milligram
MG	myasthenia gravis
MHC	major histocompatibility complex
[redacted]	
mL	milliliter
MLR	mixed lymphocyte reaction
MMR	measles, mumps, rubella
mOS	median overall survival
mPFS	median progression-free survival
mRECIST	modified Response Evaluation Criteria in Solid Tumors
[redacted]	
MRI	magnetic resonance imaging
msec	millisecond
[redacted]	
MUGA	multiple-gated acquisition

Term	Definition
MVI	macrovascular invasion
N	number of subjects or observations
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not estimable
ng	nanogram
[redacted]	
Nivo	nivolumab
[redacted]	
nM	nanomolar
NR	not reached
NSCLC	non-small cell lung cancer
O2	oxygen
ORR	objective response rate
OS	overall survival
PAI	percutaneous acetic acid injection
[redacted]	
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death-1
PD-1+	programmed cell death-1-positive
p-DILI	potential drug-induced liver injury
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PE	physical examination
PEI	percutaneous ethanol injection
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival 2

Term	Definition
[redacted]	
PID	participant identification
PK	pharmacokinetic
PPK	population pharmacokinetics
PR	partial response
[redacted]	
PT	prothrombin time
[redacted]	
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
Q12W	every 12 weeks
[redacted]	
R&D	research and development
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
Rela	relatlimab
RFA	radiofrequency ablation
RNA	ribonucleic acid
[redacted]	
RT-PCR	reverse transcription polymerase chain reaction
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan

Term	Definition
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	
SC	safety committee
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SDR	Safety Data Review
SI	International System of Units
[redacted]	
SMT	Safety Management Team
SOP	standard operating procedures
SUSAR	suspected, unexpected serious adverse reaction
[redacted]	
t1/2	half-life
T3	T3 = triiodothyronine
T4	thyroxine
TACE	transarterial chemoembolization
TAE	transarterial embolization
T.bili	total bilirubin
TCR	T-cell receptor
[redacted]	
TKI	tyrosine kinase inhibitor
TIL	tumor-infiltrating lymphocyte
[redacted]	
TME	tumor microenvironment
[redacted]	
TSH	thyroid-stimulating hormone

Term	Definition
TTE	transthoracic echocardiogram
TSST	time to second subsequent therapy
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
UTN	Universal Trial Number
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VI	vascular invasion
vs	versus
Vss	mean volume of distribution at steady state
WHO	World Health Organization
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The Investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the Investigator or qualified physician who is a sub-Investigator and who is delegated this task on the Delegation of Authority Form. Sub-Investigators in Japan may not be delegated the CRF approval task. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

CLINICAL STUDY REPORT

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

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

- Participant recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal Investigator, sub-Investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.

  The required method for SAE data reporting is through the eCRF.

  The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).

  In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission

  When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:

  Documented hysterectomy

  Documented bilateral salpingectomy

  Documented bilateral oophorectomy

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

- Postmenopausal female

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

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

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

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

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • oral (birth control pills) • intravaginal (vaginal birth control suppositories, rings, creams, gels) • transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)b • oral • injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b,c] • Bilateral tubal occlusion

• Vasectomized partner Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence • Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide

• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 CHILD-PUGH SCORE

Score	Points
Child-Pugh A	5 - 6
Child-Pugh B	7 - 9
Child-Pugh C	> 9

Scoring

	Score		
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dl)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
PT prolongation or INR	< 4 sec < 1.7	4 - 6 sec 1.7 - 2.3	> 6 sec > 2.3
Encephalopathy grade	None	1 - 2	3 - 4

Encephalopathy Grading

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unrousable coma, no personality/behavior, decerebrate

APPENDIX 6 ECOG PERFORMANCE STATUS

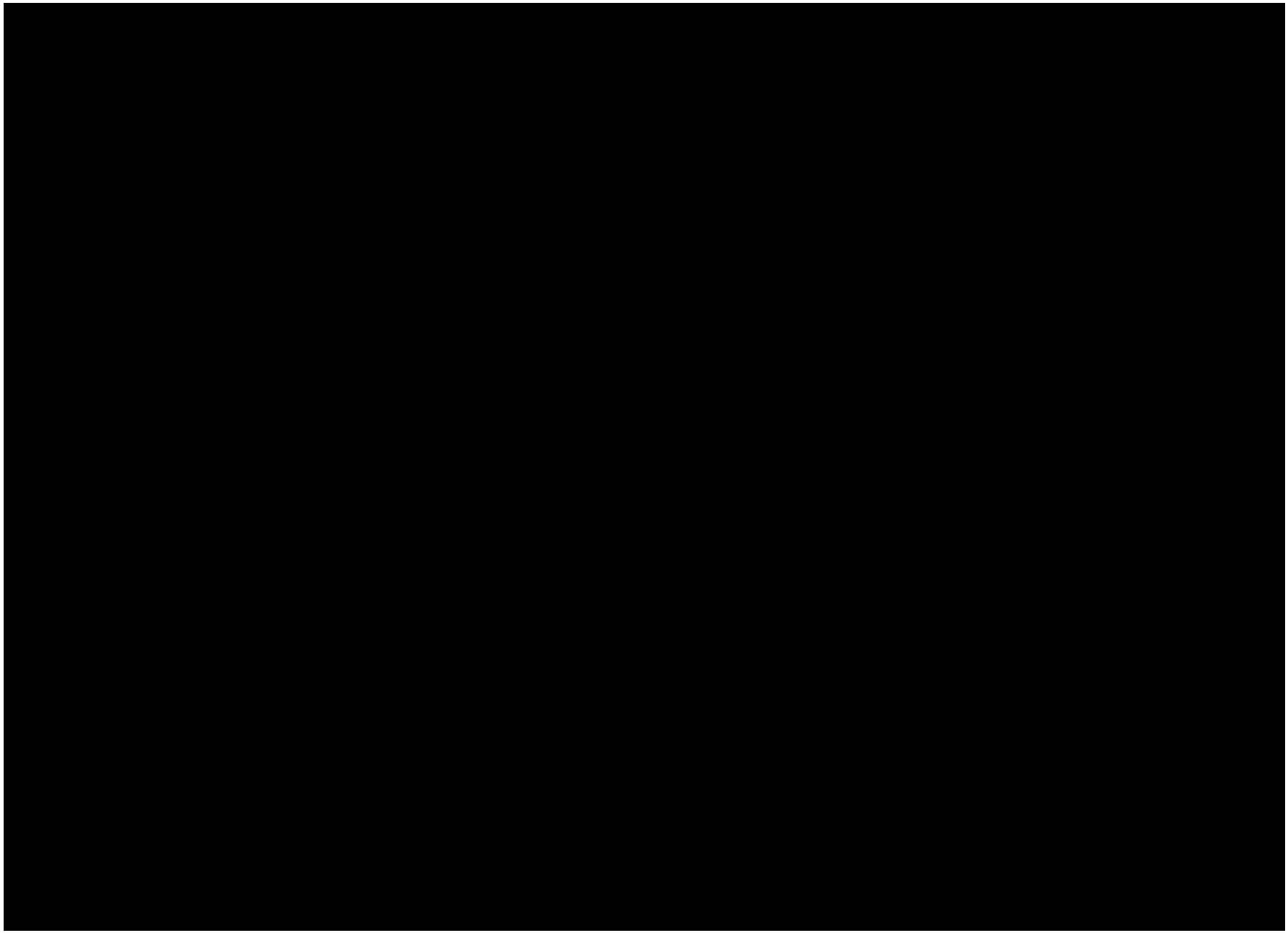
ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	dead

[1] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–655.

APPENDIX 7 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES

Country/Location Requirement	Original Language/ Section Number	Country-specific Language or Differences
Argentina, Czech Republic, Germany, Romania	Section 2 Schedule of Activities Table 2-1: Screening Procedural Outline (CA224073); Laboratory Tests	Add "HIV" to the list of laboratory tests.
	Section 6.2: Exclusion Criteria Exclusion criterion 2)b)iv)(5)	Standard language in exclusion criterion add: "Countries where exclusion of HIV positive participants is locally mandated."
	Table 9.4.4-1: Clinical Safety Laboratory Assessments	Serology information modified to read: • Serum for hepatitis C antibody, HCV RNA. • Hepatitis B surface antigen (screening only). • HIV testing must be performed at sites where mandated by local or country regulations (see Appendix 7).
France, Germany	Section 8.1: Discontinuation from Study Treatment	Second paragraph following bulleted text modified to read: "In the case of pregnancy, the Investigator must immediately notify the BMS Medical Monitor/Clinical Scientist of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy."
France		Add to discontinuation criteria bullets an item for discontinuation due to product inefficacy.
France		Add to discontinuation criteria bullets an item for discontinuation due to severe infection.
Czech Republic		Second paragraph following bulleted text modified to read: "In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/Clinical Scientist of this event. In all cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 (Pregnancy)."
Czech Republic	Section 9.2.5: Pregnancy	Second paragraph modified to read: "In the Czech Republic, all pregnancies will require the participant to discontinue treatment."
[redacted]		

Country/Location Requirement	Original Language/ Section Number	Country-specific Language or Differences
[redacted]		



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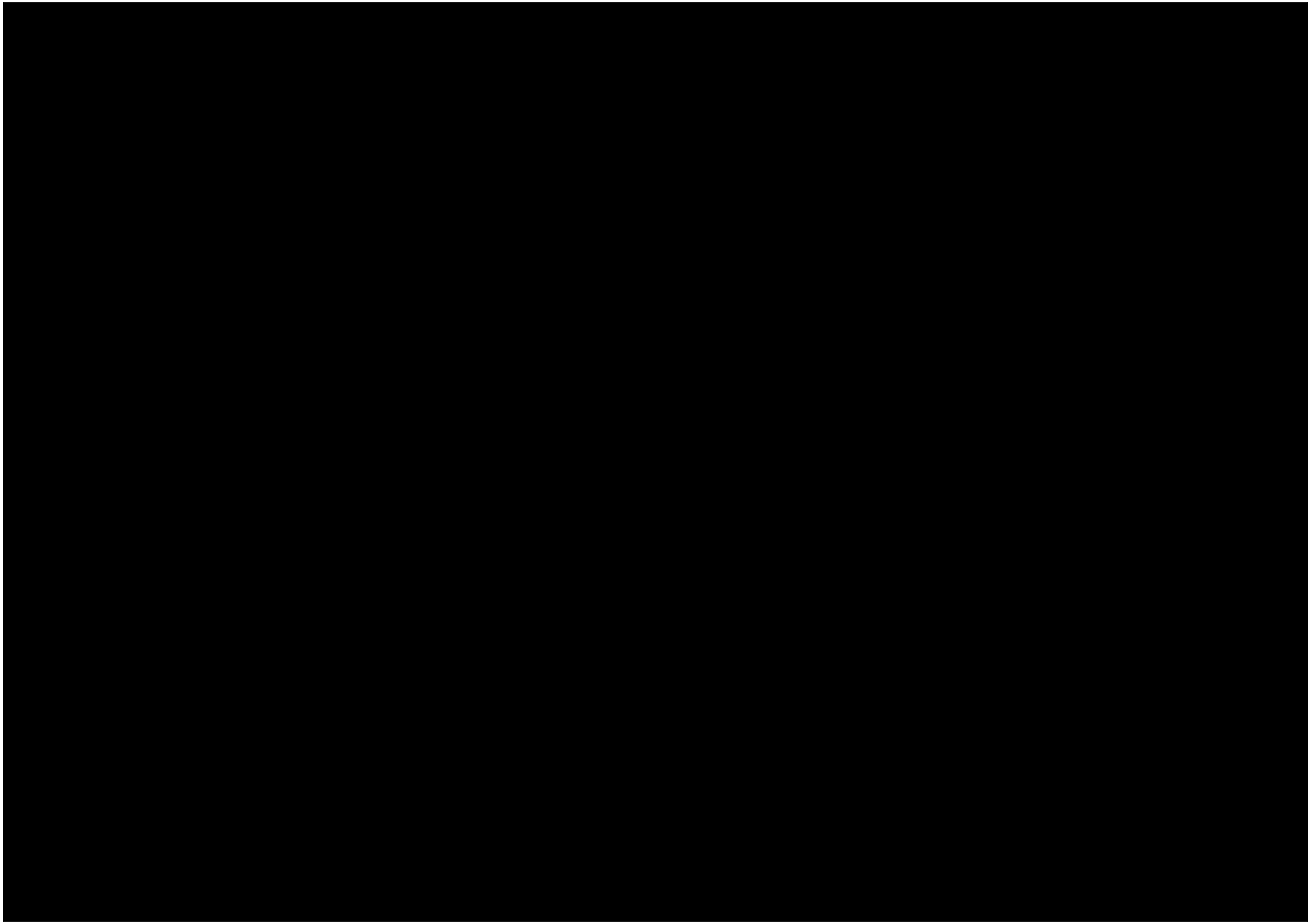
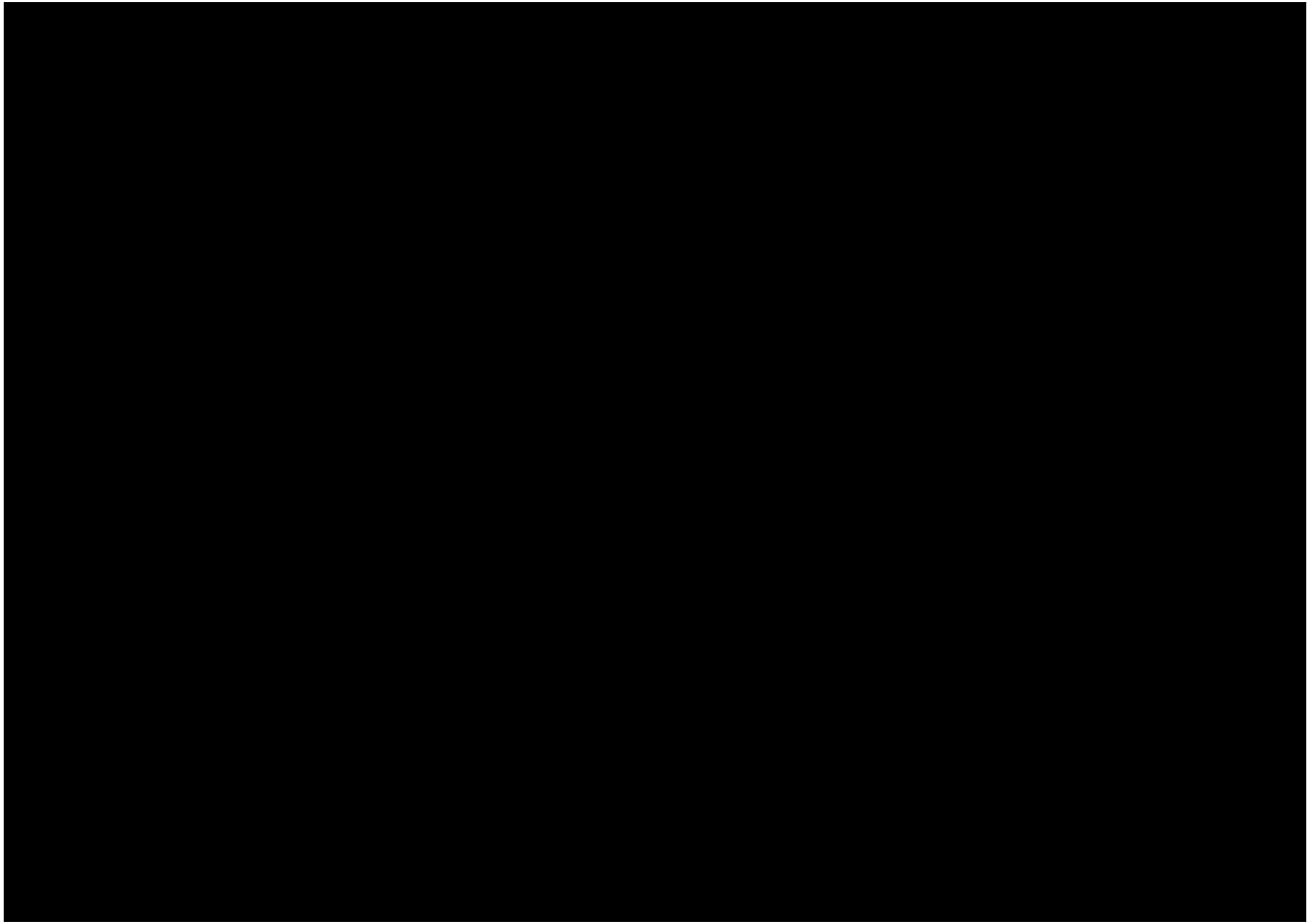
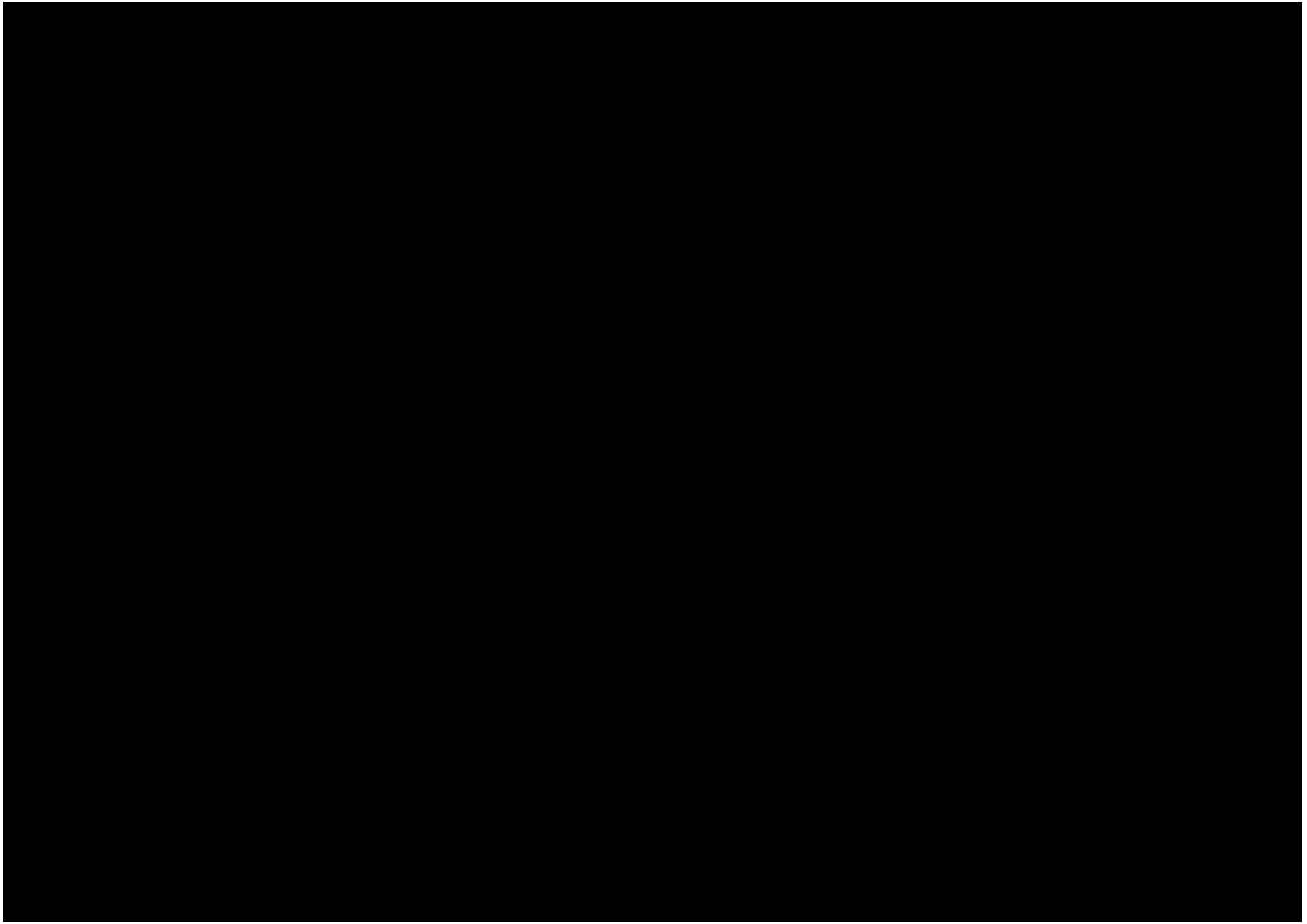
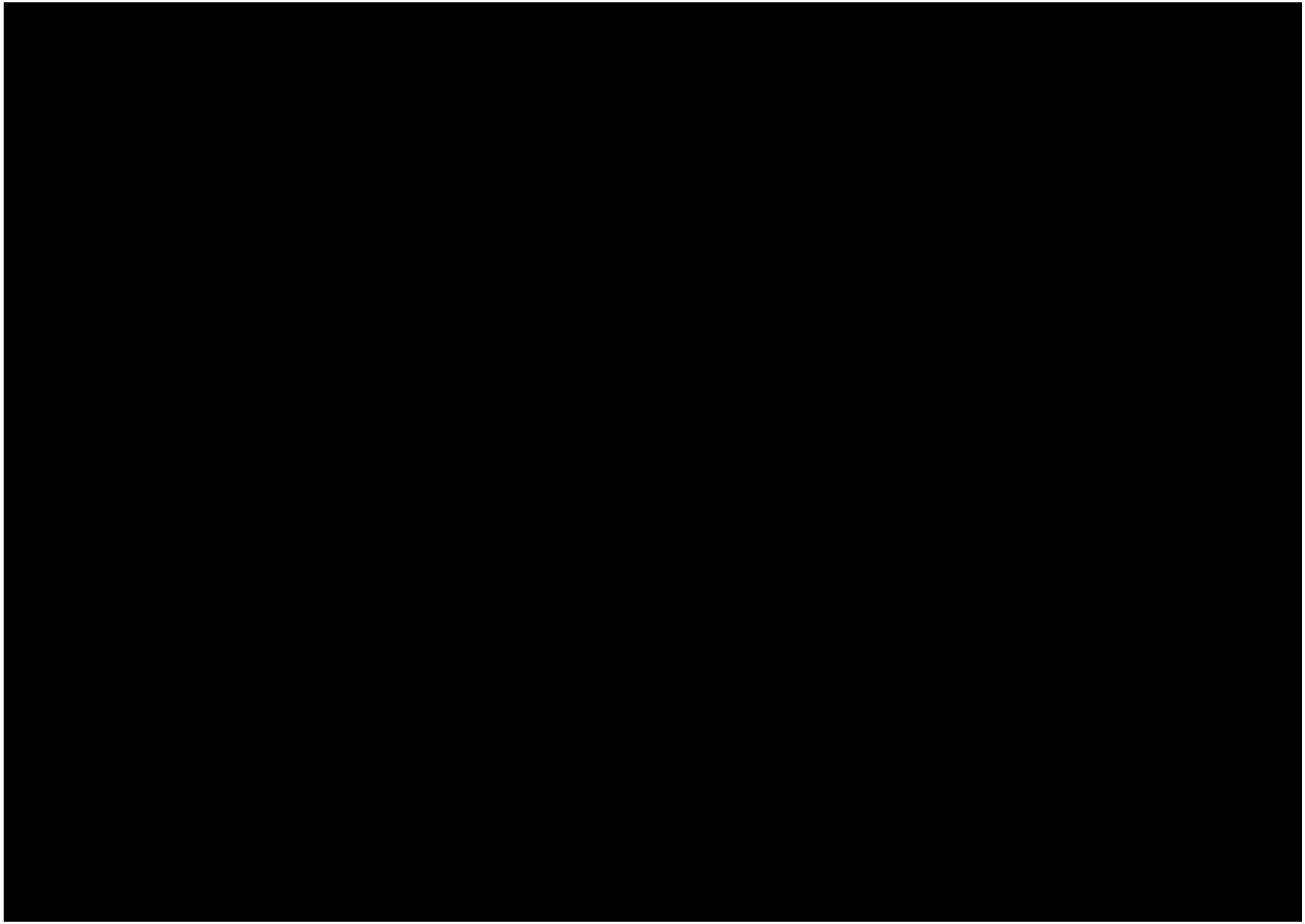


[redacted]







APPENDIX 9 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

- 10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, 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, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

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

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. 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)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

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

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

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change

in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

[redacted]

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

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

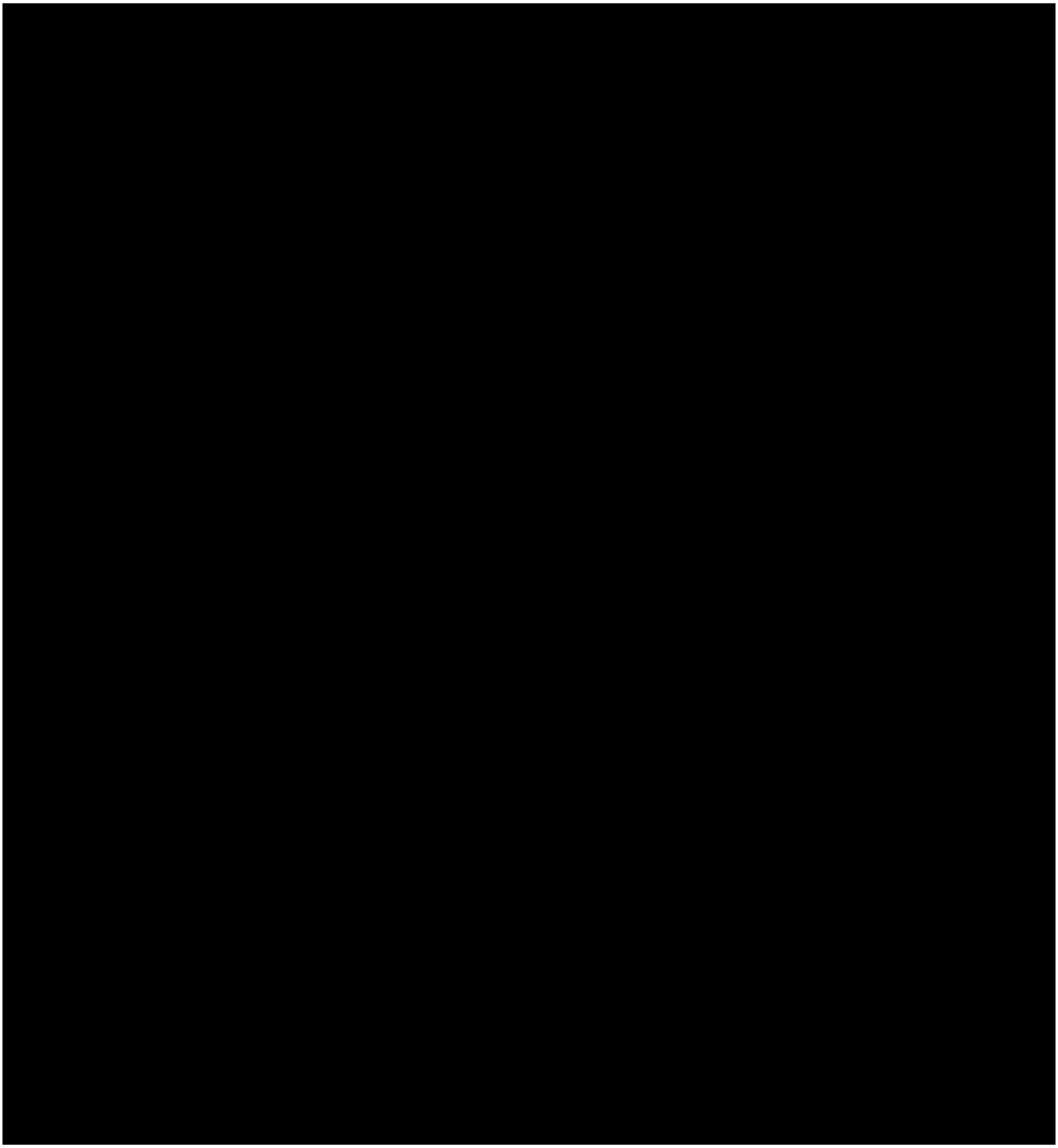
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.



2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES

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

APPENDIX 10 BARCELONA CLINIC LIVER CANCER (BCLC) CLASSIFICATION

Stage	Performance Status*	Tumor Stage	Liver Function Status
A	0	Single	Child-Pugh A-B
B	0	Large multinodular	Child-Pugh A-B
C	1-2	Vascular invasion/ extrahepatic spread	Child-Pugh A-B
D	3-4	Any	Child-Pugh C

REFERENCE:

Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999;19:329-38.

APPENDIX 11 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 03, 29-Jul-2021

Additional updates, including to sections of the Synopsis, have been made to align the protocol with respect to these changes. This protocol amendment applies to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated contact information for Medical Monitor.	Provided current contact information for the study.
[redacted]		
Section 2: Schedule of Activities; Section 6.1: Inclusion Criteria; Appendix 10: Barcelona Clinic Liver Cancer (BCLC) Classification	Added BCLC staging for advanced/metastatic hepatocellular carcinoma (HCC) to Table 2-1 and inclusion criterion 2) b) and included new Appendix for BCLC.	Clarified eligibility expectations for advanced/metastatic HCC.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 4: Objectives and Endpoints		Updated objectives and endpoints to align with study design change
[redacted]		
Section 5.1: Overall Design	Added language describing dose options for participants who were already enrolled [redacted] prior to Protocol Amendment 03.	Clarified treatment expectations for participants who have already received relatlimab 960 mg + nivolumab 480 mg Q4W.
Section 5.1: Overall Design	Updated number of participants planned for the study.	Aligned approximate number of participants with study design change [redacted]
Section 6.1: Inclusion Criteria	Added new criterion 1) d): "For amendment Protocol Amendment 03, all participants in Arm B and Arm C will be re-consented [redacted]"	Provided expectations for participant consent for Protocol Amendment 03.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

Overall Rationale for Protocol Amendment 02, 15-Apr-2021

The primary reasons for these changes are to include participants with advanced immuno-oncology (IO) therapy-naive hepatocellular carcinoma (HCC) who have received one or two lines of tyrosine kinase inhibitor (TKI) therapies and have shown radiographic progression on or after the last line of TKI therapy; clarify expectations for sample collection, study assessments, and participant eligibility; [redacted]

Additional amendments, including to sections of the Synopsis, have been made to align the protocol with respect to these changes. This protocol amendment applies to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page; Section 3: Introduction; Section 5.1: Overall Design; Section 6.1: Inclusion Criteria	Broadened eligibility to include participants with advanced IO therapy-naive HCC who have received one or two lines of TKI therapies and have shown radiographic progression on or after the last line of TKI therapy.	Updated study indication to include participants who are IO therapy-naive with ≤ 2 prior lines of TKI therapies with advanced/metastatic HCC.
Section 2: Schedule of Activities	The following modifications were made: • Table 2-1: Updated Notes for Chest Radiograph row to clarify either side for lateral chest x-ray. • Table 2-2: – Column headers: Updated windows from 2 days to 3 days. – Vital Signs row: Removed "within 3 days." – Laboratory Tests row: Removed note for liver function tests. – Body Imaging and Brain Imaging rows: Updated "first dose" to "randomization." • Table 2-2 and Table 2-3: [redacted]	Clarified expectations for on-treatment and follow-up assessments.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities; Section 5.1.1: Screening Period; Section 6.1: Inclusion Criteria	The following modifications were made: • Updated screening procedures and inclusion criteria for required tumor tissue samples to clarify expectations for collection and use of archival tissue. • Table 2-2 and inclusion criterion 2) b) iii): Provided washout periods between end of TKI treatment and beginning of study treatment for specific TKIs.	These changes were made to clarify: • Expectations for tumor tissue sample collection at screening. • Timing for initiating treatment administration.
Section 2: Schedule of Activities; Section 6.2: Exclusion Criteria; Section 6.4.1: Retesting During Screening Period	Updated testing and exclusion criteria for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from "active" to "symptomatic."	Changed considerations for SARS-CoV-2 from "active" to "symptomatic" infection.
Section 2: Schedule of Activities; Section 9.4.4: Clinical Safety Laboratory Assessments	The following udpates were made: • Added serum alpha-fetoprotein (AFP) testing to on-treatment assessments. • Removed Epstein-Barr virus antibody serology testing.	These changes were made to: • Include on-treatment serum AFP testing. • Remove Epstein-Barr virus antibody testing because it is no longer applicable to this study.
Section 3: Introduction; Section 3.2: Background; Section 3.3.1: Introduction; Section 3.3.4: Efficacy; Section 6.1: Inclusion Criteria	The following updates were made: • Updated "sorafenib or lenvatinib" to "TKI" and provided list of currently approved TKIs. • Added paragraph describing current treatment recommendations for 1L and 2L therapies in HCC.	These changes were made to: • Generalize the description of TKI therapies. • Provide additional background information on current treatment guidelines for HCC.
[redacted]		
Section 5.4.1: Rationale for Choice of Comparators	Added text describing current National Comprehensive Cancer Network (NCCN) guidelines recommendations for use of nivolumab in subsequent lines of therapy in HCC after disease progression.	Clarified recommended use of nivolumab in HCC per current treatment guidelines.
Section 6.1: Inclusion Criteria	Added new criterion 2) e) i) related early- and intermediate-stage immunotherapy.	Clarified eligibility for participants with early- or intermediate-stage immunotherapy.
Section 6.2: Exclusion Criteria	The following updates were made: • Replaced criterion 1) d) i) related to prior ascites with new criterion 1) d) iii) and removed criterion 1) d) ii). • Added new criterion 3) k) related to enrollment in other BMS studies.	These changes were made to: • Provide more permissive language for clinically significant ascites. • Clarify eligibility of participants who are currently enrolled in other BMS studies in HCC.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1: Treatments Administered; Section 7.1.1: Relatlimab Combined with Nivolumab Dosing	Removed information related to administering relatlimab and nivolumab sequentially and added footnote describing expectations for co-administration infusions.	Updated treatment administration of relatlimab and nivolumab to co-administration only.
Section 7.4: Dosage Modification; Section 7.4.2 Dose Delay Criteria; Section 8.1.3: Criteria to Resume Treatment	Updated descriptions of combination relatlimab and nivolumab to reflect co-administration.	Aligned language with updated treatment administration of relatlimab and nivolumab to co-administration only.
Section 7.7: Concomitant Therapy	Added text: "The effect of COVID-19 vaccines on participants taking relatlimab and nivolumab is currently unknown."	Included considerations for COVID-19 vaccines.
Section 7.7.2.1: Imaging Restriction and Precautions	Added text: "Site-specific imaging requirements that are different than those captured in the imaging manual may be considered after discussion with the BMS Medical Monitor or Clinical Scientist."	Clarified expectations for site-specific imaging requirements.
Section 9.2.5: Pregnancy	Removed last 2 paragraphs related to pregnancy surveillance and contraception measures for male participants.	Updated section to fully align with the rest of the protocol, which does not include male contraceptive requirements.
[redacted]		
Section 9.8.2: Tumor Samples	Updated paragraph to refer to Table 2-1 only.	Removed repetitive text to improve readability.
Appendix 2: Study Governance Considerations	Updated first paragraph for Monitoring section to further describe that details on monitoring can be found in the monitoring plan.	Clarified expectations for monitoring.
Appendix 7: Country Specific Requirements/ Differences	Added country-specific differences for Czech Republic related to Section 8.1 and Section 9.2.5.	Aligned Appendix 7 with country-specific differences for Czech Republic described in the main text.
[redacted]		

Overall Rationale for Revised Protocol 01, 28-Oct-2020

[redacted]

improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, sample collections, treatment administration, and country-specific requirements.

Additional amendments, including to sections of the Synopsis, have been made to align the protocol with respect to these changes. This Revised Protocol applies to all participants.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	The following changes were made: • Removed Investigational New Drug (IND) number. • Updated "Study Director" to "Clinical Scientist."	Changes were made for these reasons: [redacted] • Role name at Bristol Myers Squibb (BMS) has changed.
Section 2: Schedule of Activities	• Added/updated the following rows with notes related to SARS-CoV-2 within Section 2 tables: [redacted] o Adverse Event and/or Serious Adverse Event Assessments • Added or updated details to Notes columns for the following rows: o Table 2-1: Inclusion/Exclusion Criteria, Medical History, Required Tumor Tissue Samples, Concomitant Medication Use, Serious Adverse Events Assessment, Laboratory Tests, Serology, Disease Assessment: Serum Alpha-fetoprotein, Pregnancy Test (WOCBP only) o Table 2-2: Procedure, Inclusion/Exclusion Criteria, Targeted Physical Examination, Vital Signs, Adverse Event and Serious Adverse Event Assessments, Laboratory Tests, Thyroid Function Tests, Pregnancy Test (WOCBP only), Body Imaging, Brain Imaging, [redacted] o Table 2-3: Laboratory Tests	• Serum and AE/SAE collection in the context of [redacted] was added in the event that coronavirus disease 2019 (COVID-19) sequelae may increase toxicity or impact interpretation of study events/results. • Updated or corrected Notes as needed to clarify expectations and/or to better align with protocol text.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities (continued)	• Added a footnote for the Notes column in each Section 2 table to indicate that assessments may not be captured as data in the case report form (CRF). • Added reference to Section 5.1.3.1 in footnote b of Table 2-3.	• Clarified expectations for capturing assessments in the CRF. • Clarified expectations for survival follow-up in participants with stable disease, complete response, or partial response.
Section 3.2: Background	Added information for the CA209459 study on participants with subsequent IO therapy.	Provided additional context for findings from the CA209459 study.
Section 3.3.3: Safety Monitoring	Added text referring to other sections in the protocol for risk mitigation for SARS-CoV-2.	Aligned with updates to other parts of the protocol related to SARS-CoV-2.
Section 4: Objectives and Endpoints	[redacted]	
Section 5.1.1: Screening Period	Added to tumor sample language that biopsy can be taken any time after the end of tyrosine kinase inhibitor treatment.	Clarified expectations the required tumor sample.
Section 5.1.2: Treatment Period; Section 6.1: Inclusion Criteria	Added to pregnancy text language in Section 5.1.2 and added new sub-criterion 3) a) iv) (2) for women of childbearing potential (WOCBP): "An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window."	Clarified expectations for eligibility related to pregnancy testing and results.
[redacted] Section 5.6.1: Nivolumab Clinical Pharmacology Summary; [redacted]	Updated text per more recent data [redacted] in the context of specific populations/medical conditions.	Updated pharmacology information for nivolumab and relatlimab to align with more recent clinical experience.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria	The following updates were made: • Added new sub-criterion 2) b) ii) (1) related to local or locoregional therapy. • Added new sub-criterion 2) h) iii) related to biopsies of bone lesions. • Replaced criterion 2) p) (3) with new criterion 2) p) (5) to update platelet requirements to SI: $\geq 60 \times 10^9$/L. • Added age requirements to 3) header. • Replaced criterion 3) x) (2) with new criterion 3) x) (3) to update "24 weeks" to "5 months." • Criteria 3) b) ii) through 3) b) viii) are no longer applicable; removed text related to male contraception in last paragraph.	These changes were made to: • Clarified expectations for eligible advanced HCC disease. • Clarified expectations for required tumor tissue sample. • Corrected platelet values in inclusion criteria. • Clarified age requirements. • Update timing of contraceptive use for WOCBP-based study treatment half-lives. • Remove contraceptive requirements for male participants based on current safety information.
Section 6.2: Exclusion Criteria	The following updates were made: • Replaced criterion 1) f) with new criteria 1) g) and 1) h) related to central nervous system (CNS) and leptomeningeal metastases, respectively. • Replaced criterion 2) b) ii) with new criteria 2) b) iv) related to human immunodeficiency virus. • Added new criteria 2) b) v) for active infection with SARS-CoV-2 and 2) b) vi) for other active viral infection. • Replaced criterion 2) g) with new criterion 2) i) related to concurrent or prior malignancy. • Added new criterion 2) j) related to resolution of AEs related to prior anticancer therapy. • Replaced criterion 3) h) with new criterion 3) j) related to complementary medications. • Added new criterion 3) i) for participants currently in other interventional trials, including those for COVID-19.	These changes were made to include new clinical approaches for eligibility related to CNS metastases, viral infections, and concurrent or prior malignancies, prior anticancer therapy AEs, supportive care, and eligibility criteria for participants in interventional trials.
Section 6.4.1: Retesting During Screening Period	Added text describing testing and retesting for participants who may develop suspected or confirmed symptomatic COVID-19.	Included language to clarify expectations for eligibility and retesting for participants with suspected or confirmed symptomatic COVID-19.
Section 7.1: Treatments Administered	Added text to footnote b of Table 7.1-1 clarifying that nivolumab and relatlimab will be co-administered once allowable.	Updated co-administration language to better align with Section 7.1.1.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.1: Relatlimab Combined with Nivolumab Dosing	The following updates were made: • Added "approximately" for timing of administration. • Added text: "For Q4W dosing cycles, participants may be dosed no less than 26 days from the previous dose." • Added language describing potential co-administration infusion times for participants ≥ 45 kg and < 45 kg.	These changes were made to: • Allow more flexibility for the timing of infusion administration. • Clarify expectations for dosing cycles. • Distinguish infusion times for co-administration based on weight.
Section 7.1.3: Palliative Therapy	The following updates were made: • Updated definition and lesion for palliative local therapy. • Moved last paragraph to Section 7.7: Concomitant Therapy.	These changes were made to: • Clarify expectations for palliative therapy. • Relocate information related to concomitant therapy to a more appropriate location in the protocol.
[redacted]		
Section 7.4.2: Dose Delay Criteria	Added suspected or confirmed SARS-CoV-2 infection as a criterion to delay treatment.	Updated dose delay criteria to include expectations in cases of confirmed or suspected SARS-CoV-2 infection.
[redacted]		
Section 7.7.1: Prohibited and/or Restricted Treatments	Updated language related to herbal supplements and traditional Chinese medicines for supportive care.	Aligned section with new exclusion criterion 3) j) in Section 6.2.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1: Discontinuation for Study Treatment; Section 9.2.5: Pregnancy	The following changes were made: • Section 8.1: Updated second sentence in second paragraph after bulleted list, related to pregnancy cases, to "In most cases (all cases in Czech Republic Argentina, or other countries where it is required), the study treatment will be permanently discontinued..." • Section 9.2.5: o Added text: In the Czech Republic and Argentina (or other countries where it is required) all pregnancies will require the participant to discontinue treatment. o Updated 24 weeks to 5 months.	Clarified expectations for discontinuation in the case of pregnancy, including for countries in which it is required that the study treatment be permanently discontinued in all pregnancy cases.
Section 8.1.3: Criteria to Resume Treatment	Added text describing scenarios in which participants with suspected or confirmed SARS-CoV-2 infection may resume treatment.	Included language to clarify expectations for resuming treatment in participants with suspected or confirmed SARS-CoV-2 infection.
Section 9.1.1.2: Imaging and Clinical Assessment	Removed all but last sentence from second paragraph.	Removed repetitive text.
[redacted]		
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	The following updates were made: • Removed bullet related to Reference Safety Information in Investigator's Brochure (IB). • Added text to describe collection of AEs and SAEs in the context of SARS-CoV-2 infection. • Removed bullet related to SAE collection for participants who signed a pre-screening consent.	These changes were made to: • Align references to IB in the protocol with current IB template. • Include language for AE/SAE collection in the context of SARS-CoV-2 in the event that COVID-19 sequelae may increase toxicity or impact interpretation of study events/results. • Remove inconsistent text to ensure alignment of this section with Table 2-1.
Section 9.2.3: Follow-up of AEs and SAEs	Updated last paragraph to include details related to follow-up of SAEs and non-serious AEs associated with confirmed or suspected SARS-CoV-2 infection.	Included language for AE/SAE follow-up in the context of SARS-CoV-2 in the event that COVID-19 sequelae may increase toxicity or impact interpretation of study events/results.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.4.4: Clinical Safety Laboratory Assessments	The updates below were made to Table 9.4.4-1: • Updated "Blood Urea Nitrogen (BUN)" to "Blood Urea Nitrogen (BUN)/serum urea." • Added hepatitis C RNA viral load and hepatitis B DNA viral load under Serology. • Added "serum or urine" for pregnancy test. • Added SARS-CoV-2 viral test.	Clarified expectation for assessments related to urea (when urea measurements are required instead of BUN), serology, pregnancy testing, and added SARS-CoV-2 viral test to align with related changes made in Section 6.2 and Section 6.4.1.

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.8.6: Other Assessments	Added section to describe potential use of [redacted] collections.	Included language for potential use of [redacted] collections, in alignment with the endpoint/objective added to Table 4-1.
Appendix 4: Women Of Childbearing Potential Definitions and Methods of Contraception	Updated vasectomized partner row in methods of contraception table.	Aligned methods of contraception with updates made to male contraceptive requirements in Section 6.1.
Appendix 7: Country Specific Requirements/ Differences	The following updates were made: • Removed Czech Republic from modifications for Section 8.1: Discontinuation from Study Treatment modifications. • Added difference [redacted] for Section 6.2: Inclusion Criteria.	[redacted]
[redacted]		
All	Minor formatting and typographical corrections.	These changes were minor, and therefore have not been summarized.