Official Title of Study:

A Phase 1/2, Safety Confirmation, Placebo-controlled, Randomized Study of Nivolumab in Combination with Relatlimab and Bevacizumab in Treatment-naive Advanced/Metastatic Hepatocellular Carcinoma (RELATIVITY-106)

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CLINICAL PROTOCOL CA224106

A Phase 1/2, Safety Confirmation, Placebo-controlled, Randomized Study of Nivolumab in Combination with Relatlimab and Bevacizumab in Treatment-naive Advanced/Metastatic Hepatocellular Carcinoma (RELATIVITY-106)

Protocol Amendment 03

Incorporates Administrative Letter 03

Brief Title:

Phase 1/2 study of Nivolumab and Relatlimab in Combination with Bevacizumab in First-line HCC

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	05-Apr-2024	Major changes include: • Restricting enrollment only to participants without extrahepatic spread (EHS-No). • Endpoints updated to evaluate objective response rate (ORR) in All Comer and EHS-No populations. • Lymphocyte activation gene 3 (LAG-3) testing to be performed after randomization to decrease time to randomization. • Updates made to reflect transition to the EU Clinical Trial Directive.
Administrative Letter 03	11-Nov-2023	The purpose of this administrative letter is to report a change in the Medical Monitor for this study.
Protocol Amendment 02	20-Mar-2023	Major changes include: • Removal of Sponsor blinding. • Primary and secondary endpoints in Part 2 updated to objective response rate (ORR) and progression-free survival (PFS), respectively. • [redacted] • Extension of internal Safety Committee (SC) into Part 2 to replace Data Monitoring Committee (DMC) activities.
Administrative Letter 02	22-Aug-2022	Clarifies that bevacizumab vials may be obtained or supplied in quantities other than 400 mg/vial and that bevacizumab biosimilars are not permitted to be administered to participants treated under this protocol.
Administrative Letter 01	07-Jul-2022	Indicates that hepatitis serology assays may be performed by the designated central laboratory for sites where certain tests are unable to be routinely performed by the local laboratory. Also documents the relocation of the BMS office in Japan.
Protocol Amendment 01	16-Feb-2022	Protocol Amendment 01 for CA224106 includes a number of changes [redacted]. In addition, several minor changes were made at this time to align with current BMS program standards, to further clarify certain sections, [redacted].
Original Protocol	01-Nov-2021	Not applicable

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OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

The primary rationale for Protocol Amendment 03 is to make overall study design changes in Part 2 (Phase 2) of the study. The study population has been updated to exclude participants with extrahepatic spread of their disease (EHS-Yes) at the time of entry into the study. [redacted] As a result of this change, Phase 2 is split into 2 parts: Part 2a with the original inclusion criteria and Part 2b which restricts enrollment to participants without extrahepatic spread (EHS-No) status at study entry. In addition, the primary endpoint has been updated to evaluate objective response rate (ORR) in both All Comers as well as the EHS-No population. [redacted]

Additional changes include the removal of the requirement for lymphocyte activation gene 3 (LAG-3) testing of the screening tumor sample to be completed prior to randomization, however submission of tissue prior to randomization is still required. This will reduce the amount of time participants spend in screening and reduce the number of screen failures. Also, troponin monitoring requirements have been updated and sampling for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology and whole blood immunophenotyping have been removed, reducing unnecessary sampling.

Additional revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

This amendment also incorporates the changes from the approved Administrative Letter 03.

Minor editorial, formatting, and typographical corrections have been made and therefore have not been summarized.

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 Clinical Trial Physician name and contact information. • Updated European Union (EU) Trial Number.	Administrative update.
Table 2-1: Screening Procedural Outline (CA224106) Section 6.1: Inclusion Criteria Section 7.2: Method of Study Intervention Assignment Section 9.10.2: Tumor Samples Section 9.10.2.2: LAG-3 and PD-L1 Expression	Removed requirement for tumor lymphocyte activation gene 3 (LAG-3) expression status to be determined prior to randomization.	Adjusted to decrease time to randomization and associated delay in initiation of treatment, as LAG-3 expression is not required for stratification.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA224106) Section 6.1: Inclusion Criteria Section 7.2: Method of Study Intervention Assignment Section 9.10.2: Tumor Samples	Added clarification that the central laboratory must provide Interactive Response Technology (IRT) with confirmation of tissue receipt.	Updated to provide clarity on screening tissue submission requirements, where previously a LAG-3 result was required.
Table 2-2: On Study Treatment Procedural Outline (CA224106) [redacted] Table 9.4.4-1: Clinical Laboratory Assessments Section 9.4.6: Cardiac Evaluation	• Updated adverse event criteria for delay, resumption, and discontinuation of nivolumab and both nivolumab and relatlimab for increased cardiac troponin I or T. • Separated recommendations for asymptomatic and symptomatic cardiac troponin increases in Table 9.4.1-1. Added what constitutes a cardiac evaluation and when a cardiologist must be involved. • Added Section 9.4.6.	• To clarify adverse event management. • Aligned to BMS protocol standards and to provide clarity. • Aligned to BMS protocol standards and to provide clarity.
Table 2-2: On Study Treatment Procedural Outline (CA224106)	• Electrocardiogram (ECG) to be done predose, within 3 days of Day (D) 1 of each cycle (C). To be done at C1D1 predose, if not done at screening. To also be done with any abnormal troponin or as clinically indicated. • Updated troponin, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T.bili) testing, safety laboratory collections, and clinical evaluation windows from ± 1 day to ± 3 days. • Revised Clinical Observation to include "Non-dosing visit evaluations may be performed remotely by the Investigator/delegate." • Removed "in particular fatigue" from Clinical Observations.	• Clarification of ECG frequency. Updated to provide more flexibility and decrease burden to participants and site. • To provide more flexibility and decrease burden to participants and site. • To provide more flexibility and decrease burden to participants and site. • Updated to align with BMS program standard.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On Study Treatment Procedural Outline (CA224106) Table 2-3: Follow-up Assessments (CA224106)	Updated hepatitis testing: Hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) deoxyribonucleic acid (DNA) testing is required if participant tests positive for HBsAg or hepatitis B core antigen (HBcAg) at screening. Hepatitis C virus (HCV) ribonucleic acid (RNA) required if participant tests positive for anti-HCV at screening.	Updated to clarify protocol requirement and prevent unnecessary dosing delays.
Table 2-2: On Study Treatment Procedural Outline (CA224106) Table 2-3: Follow-up Assessments (CA224106) [redacted] Section 9.12: Other Assessments	Removed requirement for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology sampling.	Removed to decrease burden on site and participants as sample will not be used to determine study-related endpoint.
[redacted]		
Section 3.1: Study Rationale	Added a rationale for including participants without extrahepatic spread (EHS-No). Added background information about fibrinogen-like protein-1 (FGL-1).	Added to support study design change. Updated to reflect data available in currently published literature.
Section 3.2: Background	Information about Study CA224073 now reflects the primary analysis was performed.	The CA224073 primary analysis was reached. The complete report will be published at a later date.
Section 3.3.2: Benefit Assessment Figure 5-1: Study Design Schema	Updated enrollment to only allow participants with EHS-No. Added footnote i: "As of Protocol Amendment 03, enrollment will be restricted to EHS-No participants at study entry."	[redacted]

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 4-1: Objectives and Endpoints Table 4-2: Estimands for the Primary and Secondary Endpoints Figure 5-1: Study Design Schema Section 5.1: Overall Design	Updated the "all randomized participants" population to 2 distinct populations of interest, All Comers and participants with EHS-No status. Updated objectives and endpoints accordingly to reflect this change in populations. Removed endpoint "PFS assessed by BICR using RECIST v1.1 in all randomized participants." Relocated OS from a secondary endpoint to an exploratory endpoint. Removed the time point when final PFS was planned. Added secondary objective and endpoint to evaluate PFS in the populations of interest described above. Adjusted Estimands to align with updates to Objectives and Endpoints. • Added exploratory objective to investigate ORR and PFS by Barcelona-Clinic Liver Cancer (BCLC) status at study entry in both populations of interest. • Overall survival (OS) was moved to exploratory endpoints.	[redacted] To align with new objectives, endpoints, and study design.
Figure 5-1: Study Design Schema	Phase 2 of the study now reflects the split in study population and creation of Part 2A and Part 2B. Updated objectives to correspond with Table 4-1. Updated footnote g. Added footnotes h, i, and j.	To evaluate the updated study population, which excluded participants with EHS. In addition, the primary endpoint was updated to evaluate ORR in All Comers, as well as EHS-No participants, to evaluate this population more rigorously.
Section 5.1: Overall Design Section 5.2: Number of Participants	Updated the number of study participants.	To reflect the revised study design.
[redacted]		

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1: Overall Design Section 5.2: Number of Participants	Updated LAG-3 reference in the overall design to reflect "an expected" minimum of 32 LAG-3-positive participants.	Added flexibility to the number of LAG-3-positive participants identified during screening.
[redacted]		
Section 6: Study Population	Excluded individuals with extrahepatic spread/metastatic disease from being eligible for participation in the study.	To enrich population of participants without extrahepatic spread/metastases.
Section 6.1: Inclusion Criteria	• Inclusion criterion 2)d) is no longer applicable. • Inclusion criterion 2)e)ii)(4) was updated with directions for the central laboratory. • Updated inclusion criterion 2)j) for individuals with Barcelona-Clinic Liver Cancer (BCLC) staging C to include only those without EHS.	• Updated to reflect change in tissue screening process. • Updated to reflect change in tissue screening process. • Updated inclusion criteria as part of study design change to further explore subgroup of EHS-No participants.
Section 6.2: Exclusion Criteria	• Updated exclusion criterion 1)h)v) to specify that history of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment as an exclusion criterion must increase the risk of bleeding. • Added new exclusion criterion 1)q) for participants with known EHS of HCC. • Updated exclusion criterion 3)a)i) to state that participants must be evaluated by a cardiologist if troponin levels are between > 1 to 2× ULN within 24 hours. • Added exclusion criterion 3)a)ii).	• Updated to emphasize and clarify that history of abdominal inflammatory processes that increase risk of bleeding are excluded rather than all abdominal inflammatory processes. • Updated exclusion criteria to enrich population of participants without extrahepatic spread. • Updated to align with program standard. • Updated to align with program standard.
Section 6.4.1: Retesting During Screening or Lead-in Period	• Updated description of pretreatment failure.	• To provide clarity.
[redacted]		

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.2.4: Regulatory Reporting Requirements for SAEs Appendix 2: Study Governance Considerations	• Replaced requirement to adhere to the EU Directive 2001/20/EC with Regulation 536/2014.	• To align with new EU regulations.
Table 9.4.4-1: Clinical Laboratory Assessments	Separated requirements for human immunodeficiency virus (HIV) testing and hepatitis testing. Removed reflex to hepatitis C RNA if hepatitis C antibody is positive. Added label for hepatitis B and D.	Clarification of hepatitis testing requirements including requirement for hepatitis C RNA testing at screening.
Table 9.5-1: Pharmacokinetic [redacted] Schedule for Relatlimab, Nivolumab and Bevacizumab (CA224106)	Updated footnote b to specify that the sample should be drawn when "the nivolumab and relatlimab/placebo infusion has been completed."	Clarification.
[redacted]		
Section 10.1: Statistical Hypotheses Table 10.3-1: Analysis Sets Section 10.4: Statistical Analyses	Adapted statistical hypotheses, analysis sets, and primary and secondary endpoint descriptions.	Consistency with updates to Table 4-1 and Section 5.
Appendix 2: Study Governance Considerations	Made updates to the Institutional Review Board/Independent Ethics Committee section.	Changes required as a result of the European Union Clinical Trial Directive.

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1 PROTOCOL SUMMARY

Protocol Title:

A Phase 1/2, Safety Confirmation, Placebo-controlled, Randomized Study of Nivolumab in Combination with Relatlimab and Bevacizumab in Treatment-naive Advanced/Metastatic Hepatocellular Carcinoma (RELATIVITY-106)

Brief Title: Phase 1/2 study of Nivolumab and Relatlimab in Combination with Bevacizumab in First-line HCC

Study Phase: 1/2

Rationale: The study aims to provide evidence of clinical efficacy and to establish safety of triplet therapy of nivolumab, relatlimab, and bevacizumab in the first-line (1L) treatment of hepatocellular carcinoma (HCC) in the advanced/metastatic setting, relative to nivolumab in combination with bevacizumab. As of Protocol Amendment 03, the study population has been updated to exclude participants with extrahepatic spread of their disease (EHS-Yes) at study entry. [redacted] The 1L standard of care treatment for HCC has changed recently with the approval of atezolizumab and bevacizumab combination. There is also preliminary evidence of clinical benefit in treatment of patients with HCC with nivolumab and relatlimab combination therapy.

Despite the demonstrated benefit of immunotherapies on clinical outcome, a large proportion of patients with liver cancer do not respond or will relapse after an initial response to these agents in liver cancer. Substantial efforts are needed to provide therapy to patients who do not respond to currently approved immunotherapeutic combinations in 1L advanced/metastatic liver cancer.

An unmet need remains for novel treatment approaches after the approval of the combination therapy of atezolizumab and bevacizumab, which showed improved clinical benefit compared to sorafenib monotherapy. The disease control rate (DCR) was 73.6 % and there was around 20% of the patient population who did not respond to treatment at all. The median overall survival (OS) was 19.2 months (HR [hazard ratio] = 0.66, 95% confidence interval [CI]:0.52-0.85), median progression-free survival (mPFS) per Blinded Independent Central Review (BICR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was 6.9 months (HR = 0.65, 95% CI: 0.53-0.81)

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Objectives and Endpoints

Objectives	Endpoints
Primary • To determine the RP2D of relatlimab, nivolumab, and bevacizumab triplet combination in participants with advanced/metastatic HCC who have not received prior systemic therapy • To evaluate ORR of the relatlimab, nivolumab, and bevacizumab triplet combination relative to nivolumab and bevacizumab doublet combination in All Comers[b] and in participants with EHS-No[c] status at study entry with advanced/metastatic HCC who have not received prior systemic therapy	**Primary** • DLTs assessed by Investigator within a 6-week DLT window for the first approximately 12, 24, 36, or 48 treated participants in 2 arms combined, depending on data • ORR[a] assessed by BICR using RECIST v1.1 in the All Comer and EHS-No populations
Secondary • To estimate key efficacy endpoints of the relatlimab, nivolumab, and bevacizumab triplet combination and the nivolumab and bevacizumab in doublet combination in the All Comer and in EHS-No population with advanced/metastatic HCC who have not received prior systemic therapy and who express LAG-3 (≥ 1%) by IHC[d]	**Secondary** • PFS[a] assessed by BICR using RECIST v1.1 in the All Comer and in EHS-No population with LAG-3 positive status (≥ 1% by IHC) • ORR assessed by BICR using RECIST v1.1 in the All Comer and in EHS-No population with LAG-3 positive status (≥ 1% by IHC)
• To evaluate PFS of the relatlimab, nivolumab, and bevacizumab triplet combination relative to nivolumab and bevacizumab doublet combination in all randomized participants in the All Comer and in participants with EHS-No at study entry with advanced/metastatic HCC who have not received prior systemic therapy	• PFS[a] assessed by BICR using RECIST v1.1 in All Comer population and in all randomized participants with EHS-No at study entry
• To determine the safety and tolerability of the relatlimab, nivolumab, and bevacizumab triplet combination in all treated participants with advanced/metastatic HCC who have not received prior systemic therapy	• AEs, SAEs, select AEs, IMAEs, related or not, from first dose to 30- or 135-days after the last dose

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review; DLT, dose-limiting toxicity; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; IMAE, immune-mediated adverse

event; LAG-3, lymphocyte activation gene 3; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event.

[a] Refer to full protocol for more details on estimands.

[b] The "All Comer" population refers to all participants who were randomized using IRT in Part 1 and Part 2a of the study. Participants will be included in the treatment group to which they were randomized.

[c] The "EHS-No" population refers to all participants who were randomized using IRT in Part 1 and Part 2 of the study with EHS-No status at study entry.

[d] The "EHS-No LAG-3" population refers to all participants who were randomized using IRT in Part 1 and Part 2 of the study with EHS-No status at study entry with LAG-3 positive (≥ 1% by IHC) status at the time of randomization, as entered into the IRT.

Overall Design:

In this site and participant blinded (Sponsor will not be blinded) randomized Phase 1/2 study, approximately 124 participants, including an expected minimum of 32 lymphocyte activation gene 3 (LAG-3) positive (≥ 1% by immunohistochemistry [IHC]) participants, will be randomized in a 1:1 ratio to:

- Arm A: Relatlimab 360 mg + nivolumab 360 mg + bevacizumab 15 mg/kg intravenous (IV) infusions every 3 weeks (Q3W)
- Arm B: Placebo + nivolumab 360 mg + bevacizumab 15 mg/kg IV infusions Q3W

Participants will be stratified by alpha-fetoprotein (AFP) and Region (Asia [excluding Japan]) and Rest of World [including Japan]).

The Safety Lead-in will be considered the Phase 1 portion of the study, and enrollment following the confirmation of recommended Phase 2 dose (RP2D) will be considered the Phase 2 portion of the study.

[redacted] During the Safety Lead-in additional safety assessments will be performed according to the Schedule of Activities in the full protocol. In the Phase 2 part of the study, enrollment will continue up to 124 total randomized participants at the RP2D. Only participants who are randomized at RP2D in triplet therapy and respective participants who are randomized to doublet therapy contemporaneously from Safety Lead-in will count toward the 124. The stratification factors for randomization are Region and AFP. The primary endpoint for the Phase 2 part of the study is objective response rate (ORR) by RECIST v1.1 per BICR, assessed both in All Comers and in EHS-No participants. [redacted]

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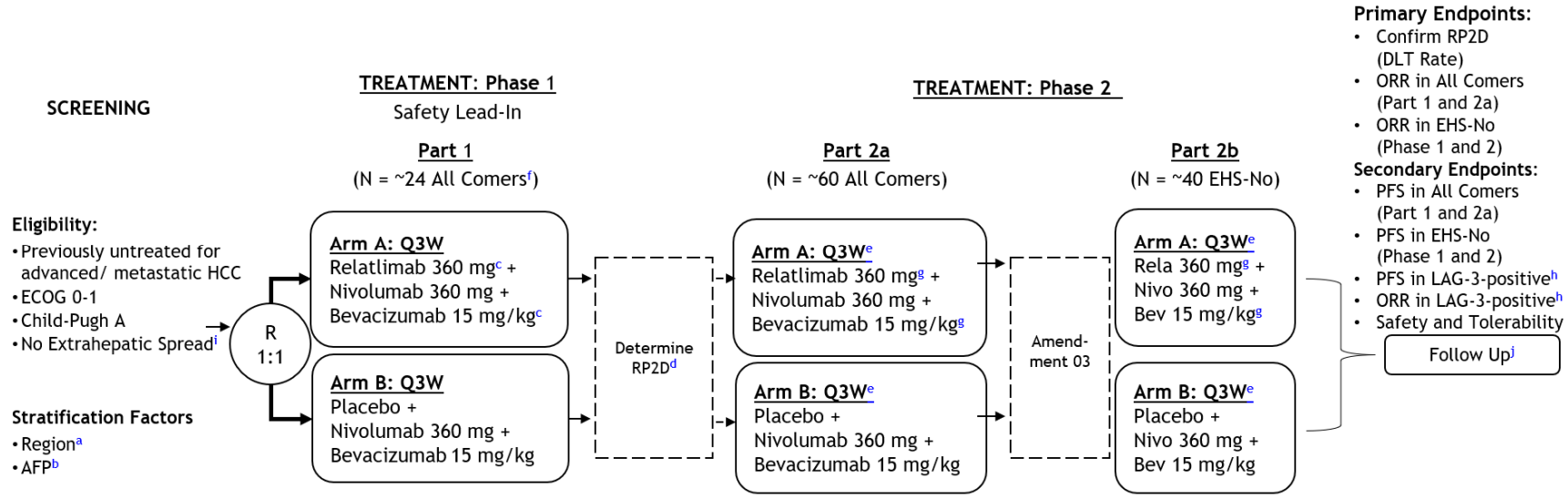
[redacted] The final ORR analysis is planned approximately 6 months (approximately 4 post-baseline scans) after 124 participants have been treated.

Study treatment will continue until progressive disease, unacceptable toxicity, or withdrawal of informed consent, whichever comes first. Treatment beyond initial radiographic progression will be allowed (described in the full protocol). In the event that bevacizumab is discontinued for toxicity, participants may continue treatment with immuno-oncology (IO) agents, in the event that IO agents are discontinued, participants may continue treatment with bevacizumab, if Investigator determines that participant is receiving clinical benefit and after discussion with the Medical Monitor if agreed upon by the Investigator and participant.

The study design schematic is presented below:

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Study Design Schema



Abbreviations: AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; LAG-3, lymphocyte activation gene 3; N, number of study participants; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RP2D, recommended Phase 2 dose.

[a] Asia (excluding Japan) versus Rest of World (including Japan).

[b] < 400 ng/mL versus ≥ 400 ng/mL.

[c] De-escalate if needed.

[d] [redacted]

[e] Treat until disease progression, unacceptable toxicity, or withdrawal of consent, whichever occurs first.

[f] If de-escalation of relatlimab or bevacizumab is required, additional participants will be randomized in this phase.

[g] RP2D will be utilized.

[h] ≥ 1% by IHC.

[i] As of Protocol Amendment 03, enrollment will be restricted to EHS-No participants at study entry.

[j] All participants will be followed until death, loss to follow-up, withdrawal of consent, conclusion of study, or a minimum of 5 years.

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Dose-limiting toxicities will be evaluated for relatlimab in combination with nivolumab, or nivolumab in combination with placebo (from the immunotherapy combination only relatlimab will be de-escalated) and bevacizumab separately. If the study is paused to fully evaluate the safety, then data from Arm B will be used for interpretation of safety, [redacted]. Study-independent Bristol-Myers Squibb Company (BMS) personnel comprising the Safety Committee will evaluate safety and confirm RP2D if the initial dose is RP2D or recommend dose de-escalation.

Participants who experience a DLT attributed to bevacizumab will be allowed to continue on relatlimab and nivolumab doublet or placebo and nivolumab, after consultation with the BMS Clinical Trial Physician. Participants who experience a DLT attributed to relatlimab and nivolumab combination or placebo and nivolumab therapy will be allowed to continue on bevacizumab, after consultation with the BMS Medical Monitor. To assess attributability of adverse events (AEs) to components of study drugs, bevacizumab vials will not be blinded.

Dose de-escalation will be performed if needed on a cohort level, intra-patient dose de-escalation is not permitted. Note that dose de-escalation will only occur in Arm A. Dose levels are presented below:

Dose De-escalation

Dose Level	Nivolumab Dose (Q3W)	Relatlimab Dose (Q3W)	Bevacizumab Dose (Q3W)
0 [a]	360 mg	360 mg	15 mg/kg
-1 [b]	360 mg	360 mg	7.5 mg/kg
-1 [c]	360 mg	120 mg	15 mg/kg
-1 [d]	360 mg	120 mg	7.5 mg/kg

Abbreviations: Q3W, every 3 weeks.

[a] Starting dose.

[b] If dose de-escalation is needed for bevacizumab related toxicity.

[c] If dose de-escalation is needed for immunotherapy related toxicity.

[d] If dose de-escalation is needed for both immunotherapy and bevacizumab related toxicity.

Number of Participants: If there is no dose de-escalation and the RP2D is the starting dose, then approximately 124 participants will be randomized, including all participants who are randomized from Safety Lead-in. If dose de-escalation occurs at Safety Lead-in Phase, then only participants who are randomized to triple therapy at the RP2D and respective participants who are randomized to doublet therapy contemporaneously will count toward the 124. It is estimated that approximately 200 enrolled participants will be required to achieve the 124 randomized. A minimum of 32 LAG-3 positive (≥ 1% by IHC) participants are expected to be randomized among the 124 patients at RP2D. Also, 124 participants provide adequate probability of success for the primary endpoint of ORR assuming a 20% difference between treatments. During enrollment, the proportion of

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participants with positive LAG-3 expression will be monitored in a pooled fashion. Additional participants may be enrolled to get the expected minimum of 32 LAG-3 positive [redacted] participants treated with the RP2D. [redacted]

Study Population: Adult (≥ 18 years) participants with histologically-confirmed advanced/metastatic HCC of any etiology (hepatitis C virus [HCV]-HCC, hepatitis B virus [HBV]-HCC, or nonviral related-HCC) who are naive to systemic therapies in advanced/metastatic setting. As of Protocol Amendment 03, study population is further limited to EHS-No participants at baseline.

Intervention Groups and Duration:

Arm A: Participants will receive masked IV infusion of relatlimab (360 mg) with nivolumab (360 mg) co-administered, followed by masked/unmasked* bevacizumab 15 mg/kg on Day 1 of every 3-week cycle.

Arm B: In order to maintain site and participant blinding, participants will receive masked IV infusion of nivolumab (360 mg) and placebo (normal saline solution) co-administered, followed by masked/unmasked* bevacizumab 15 mg/kg on Day 1 of every 3-week cycle.

*refer to Section 7.3 Blinding for details of bevacizumab blinding and unblinding.

Study intervention:

Study Intervention for CA224106		
Medication	**Potency**	**IP/Non-IP/AxMP**
Nivolumab (BMS-936558)	[redacted] mg/mL	IP
Relatlimab (BMS-986016)	[redacted] mg/mL	IP
Bevacizumab (biosimilars not permitted)	25 mg/mL	IP
Relatlimab Placebo	Normal Saline	IP

Abbreviations: AxMP, auxillary medicinal product; IP, investigational product.

Statistical Methods

The primary objective of Safety Lead-in Phase (beginning after randomization) is to determine the RP2D of relatlimab and nivolumab in combination of bevacizumab (triplet-therapy) based on DLT rate guided by the mTPI-2 design. No hypothesis testing will be performed for the Safety Lead-in Phase. After RP2D is determined, the study will then evaluate ORR by RECIST v1.1 as assessed per BICR of triplet therapy relative to the nivolumab and bevacizumab doublet therapy in 2 populations of primary interest, the All Comer population (Part 1 and Part 2a) and the population

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of all randomized subjects with EHS-No status at study entry (Part 1, Part 2a, and Part 2b). ORR using RECIST v1.1 as assessed per BICR will be assessed for participants receiving the triplet therapy relative to doublet-therapy. No formal hypothesis testing is planned. The difference in ORR between therapies, along with the 90% Clopper-Pearson CIs for each treatment, will be presented. Additionally, the posterior mean of the difference of ORR between the 2 arms and the corresponding 90% credible intervals will also be provided. [redacted]

Data Monitoring Committee: A Data Monitoring Committee will not be used in the study.

Brief Summary: This is a site and participant blinded, placebo-controlled, randomized, Phase 1/2 study in adult (≥ 18 years), male and female participants with treatment-naïve advanced/metastatic HCC.

Disease: Participants with treatment-naïve advanced/metastatic HCC.

Study Hypothesis: Relatlimab in combination with nivolumab and bevacizumab will demonstrate a favorable benefit/risk profile and larger ORR relative to nivolumab and bevacizumab doublet combination in treatment-naive advanced/metastatic HCC participants.

Study Duration: Participants will continue to be followed up to 5 years from last participant randomized.

Study Intervention Duration: Treatment will continue until progressive disease, unacceptable toxicity, or withdrawal of informed consent, whichever comes first.

Health Measurement/Observation: Participants will be followed for assessment of ORR, PFS, and OS.

Study Visit Frequency: Participants site visits will occur every week on treatment for the first 3 cycles; thereafter, participant site visits will occur every 3 weeks.

REFERENCES

[1] Guo W, Yang L. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2, Comtemporary Clinical Trials 2017 Jul;58;23-33.

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2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA224106)

Procedure	Screening Visit	Notes:[a] All windows are based on calendar days.
Pre-screening for Tumor Tissue Samples	X	If allowed by institutional practices, sites may use a pre-screening ICF for tumor tissue samples analysis (see below) to determine LAG-3 expression. The participant may proceed to additional screening procedures after signing the main study ICF.
Eligibility Assessments		
Informed Consent	X	Prior to any screening procedures. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Contact IRT	X	For participant number assignment at time main informed consent is obtained.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria including confirmation of screening tissue receipt by the central laboratory, must be determined prior to randomization.
Medical History	X	All medical history relevant to HCC (disease characteristics [including stratification factors], concomitant medications, prior cancer therapy, and alcohol history).
Prior Systemic Therapies	X	Includes all prior cancer treatment regimens, as well as medications administered within 4 weeks of study dose administration.
Risk Factors	X	See Section 6.
Child-Pugh Score	X	See Appendix 6.
Barcelona-Clinic Liver Cancer (BCLC) Staging	X	See Appendix 9.
Tumor Sample Submission	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 are not acceptable. Note the following for the required tumor sample: Samples should be collected within 3 months of enrollment, with no intervening systemic anti-cancer treatment between time of acquisition and randomization.

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Table 2-1: Screening Procedural Outline (CA224106)

Procedure	Screening Visit	Notes:[a] All windows are based on calendar days.
		If a recently collected tumor sample (as described above) is not available, then a fresh pretreatment biopsy may be obtained. This fresh biopsy should be excisional, incisional, or core needle. If the first two 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. Central laboratory must provide IRT with confirmation of tissue receipt for randomization/treatment. **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. Instructions for "freshly-cut" tumor slide preparation are included in the Covance Laboratory Manual.* Please see Section 9.10 (Biomarkers) for additional information.
Body Imaging	X	Contrast-enhanced CT of the chest, CT or MRI of the abdomen and pelvis (including required tri-phasic CT or MRI of the liver), and all other known and/or suspected sites of disease within 28 days prior to randomization. See Section 9.1.1 for further information.
Brain Imaging	X	MRI of the brain (without and with 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.
Safety Assessments		
Physical Examination, Measurements, Vital Signs, and Performance Status	X	Full Physical Examination, including height and weight. Vital signs including BP, heart rate, temperature, and oxygen saturation by pulse oximetry, collected within 14 days of randomization. ECOG Performance Status (See Appendix 7) must be collected within 3 days prior to randomization.
Assessment of Signs and Symptoms	X	Within 14 days of randomization.
Concomitant Medication Collection	X	Concomitant medication use within 28 days of randomization and vaccine use within 30 days prior to randomization.

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Table 2-1: Screening Procedural Outline (CA224106)

Procedure	Screening Visit	Notes:[a] All windows are based on calendar days.
SAE Assessment and AEs/SAEs related to SARS-CoV-2 or COVID-19	X	SAEs collected from time of consent. All AEs or SAEs following the signing of the informed consent that related to SARS-CoV-2 or COVID-19 must be reported (see Section 9.2).
ECG	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes, within 14 days of randomization.
2-D ECHO	X	LVEF assessment with documented LVEF ≥ 50% by either TTE (preferred test) or MUGA scan within 6 months from first study drug administration.
EGD	X	Patients who have undergone an EGD within 6 months prior to initiation of study treatment do not need to repeat the procedure.
Chest Radiograph	X	Posterior-anterior and lateral chest x-ray to establish baseline, within 24 hours of randomization.
Troponin T or I and CPK	X	Within 14 days prior to randomization.
Laboratory Tests		
Clinical Laboratory Assessments	X	On-site/local laboratory tests must be performed within 14 days prior to randomization. Refer to Section 9.4.4 for list of laboratory tests to conduct.
Urinalysis	X	To be performed within 7 days of the first dose.
Thyroid Function Tests	X	See Section 9.4.4. Within 14 days prior to administration of study intervention.
Serology	X	Perform within 28 days of randomization. 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). HIV (when required by local regulations [see Appendix 8]), must be done at local laboratory within 28 days prior to randomization. See Section 9.4.4. If local laboratory is unable to perform required testing, central laboratory may be utilized with Sponsor approval.
Coagulation Profile	X	Perform within 28 days of randomization. Include INR. If INR cannot be done by the local laboratory, then PT may be provided instead. Refer to Section 9.4.4 for list of laboratory tests to conduct.
Serum Alpha fetoprotein	X	Perform within 14 days of randomization.

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Table 2-1: Screening Procedural Outline (CA224106)

Procedure	Screening Visit	Notes:[a] All windows are based on calendar days.
Pregnancy Test (WOCBP Only)	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment.
Follicle-Stimulating Hormone	X	If needed to document post-menopausal status as defined in Appendix 4.

Abbreviations: 2-D ECHO, 2-D echocardiogram 2-dimensional; BCLC, Barcelona Clinic Liver Cancer; BMS, Bristol-Myers Squibb Company; BP, blood pressure; CPK, creatine phosphokinase; CT, computed tomography; CRF, case report form; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EGD, esophagogastroduodenoscopy; FFPE, formalin-fixed paraffin-embedded; HBV, hepatitis B virus; Hep B/C/D, hepatitis B/C/D; HCC, hepatocellular carcinoma; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; ICF, informed consent form; IHC, immunohistochemistry; INR, international normalized ratio; IRT, interactive response technology; LAG-3, lymphocyte activation gene 3; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multi-gated acquisition; PCR, polymerase chain reaction; PT, prothrombin time; RNA, ribonucleic acid; SAE, serious adverse event; TTE, transthoracic echocardiogram; WOCBP, women of childbearing 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.

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
Eligibility Assessments				
Inclusion/Exclusion Criteria	X			To be confirmed prior to C1D1 only.
Safety Assessment				
Targeted Physical Examination, Measurements, Vital Signs	X	X		BP, heart rate, temperature prior to dosing. Exam to be performed prior to dosing if clinically indicated.
Child-Pugh Score	X			See Appendix 6.
Physical Measurements and Performance Status	X			Weight and ECOG (Appendix 7), prior to dosing.
AE and SAE Assessment	Continuously			Record at each visit. 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

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
				hepatic and endocrinopathies in [redacted] and Table 7.4.2-1.
Concomitant Medications Use	Continuously			Record at each visit.
ECG	X (See Notes)	X		ECG to be done predose, within 3 days of Day 1 of each cycle. To be done at C1D1 predose, if not done at screening. Also to be done with any abnormal troponin or as clinically indicated.
Chest Radiograph	See notes.			As clinically indicated.
Laboratory Tests				
Clinical Laboratory Assessments	X	X	X	Perform on site/ local laboratory testing within 3 days prior to each dose. All labs should be checked prior to dosing. For the first treatment visit, labs need not be repeated if they were performed within 72 hours and the results are

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
				available and have been reviewed for eligibility. Additional safety laboratory collections should occur every week (± 3 days) up to and including Week 9 for all participants. These include troponin T or I, CPK, LDH, and AST/ALT/T.bili. The 1-day window only applies to these additional safety laboratory collections. In asymptomatic participants, these laboratory tests can be performed locally but treating Investigator must be notified on the same day. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.
Thyroid Function Tests	X	X	X	
Troponin T or I, CPK, LDH, and AST/ALT/T.bili	X (See notes.)			Will be collected weekly (± 3 days), up to and

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
				including Week 9, for all participants. After Week 9, collect if elevated or if new symptoms occur. No routine testing after Week 9. For elevated troponin, please refer to the immune-mediated adverse event (IMAE) management algorithms in Appendix 5 and dose delay [redacted] LDH and AST/ALT/T.bili are additional safety laboratory assessments collected for participants with HCC.
Clinical Observation	X (See notes.)			All participants should be clinically evaluated by qualified site personnel for any IMAEs. Non-dosing visit evaluations may be performed remotely by the Investigator/delegate.

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
				Evaluations should occur every week (± 3 days) up to and including Week 9. Participants with any clinical symptoms should be immediately evaluated.
Coagulation profile	X	X	X	Include INR. If INR cannot be done by the local laboratory, then PT may be provided instead.
HBsAg, HBV DNA, HCV RNA	X* (See notes.)		X	HBsAg and HBV DNA required if participant tests positive for HBsAg or HBcAg at screening. HCV RNA required if participant tests positive for anti-HCV at screening. *Not required at C1D1 *Required every other Cycle beginning at Cycle 3 (C3D1, C5D1, C7D1, etc). If local laboratory is unable to perform required testing, central laboratory may be utilized with Sponsor approval. Results are not

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
				required to proceed with dosing.
Serum AFP	X		X	
Pregnancy Test (WOCBP only)	X			Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) within 24 hours prior to administration of first dose of study treatment and then every 4 weeks (± 7 days) regardless of dosing schedule.
Efficacy Assessments				
Body Imaging	See notes.			Contrast enhanced CT of the chest, CT/MRI of the 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 6 weeks starting from randomization (± 7 days)

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
				up to Week 60 and then every 12 weeks (± 14 days). Imaging should continue as per schedule until BICR confirmation of progression (including treatment beyond PD). 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 (without and with contrast) per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain (without or with contrast) can be performed if MRI is contraindicated. See Section 9.1.1.
Health Outcomes Assessments				
FACT-Hep	See notes.			To be completed prior to dosing on Day 1 of each

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
				treatment cycle. If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs or during a tumor assessment visit.
PROMIS Physical Function 8c	See notes.			To be completed prior to dosing on Day 1 of each treatment cycle. If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.
PGIS	See notes.			To be completed prior to dosing on Day 1 of each treatment cycle. If a dose is delayed, the administration of the

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
				patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.
PGIC	See notes.			To be completed prior to dosing on Day 1 of each treatment cycle starting with C2D1. If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.
[redacted]				
[redacted]				

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
[redacted]				
Pharmacokinetic Samples [redacted] **Assessments**				
Serum Sample	See notes.			See Section 9.5 and Table 9.5-1; as clinically

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Table 2-2: On Study Treatment Procedural Outline (CA224106)

Procedure	Cycle = 3 Weeks			Notes:[c]
	Day 1 of Each Cycle (± 3 days)[a]	Day 15 of Cycle 1 and 2 (Safety Lead-in Only) (± 3 days)	End of Treatment (EOT)[b]	
				indicated per local standards.
Study Intervention				
Randomize	X			Only C1D1 and with confirmation of eligibility and that treatment can be started.
Administer Study Intervention	X			See Section 7.1 for treatment administration details. Treatment should begin within 3 days of randomization/contacting IRT. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or study ends.

Abbreviations: AE, adverse event; AFP, alphafetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BICR, blinded independent central review; BP, blood pressure; C1D1, Cycle 1 Day 1; CPK, creatine phosphokinase; CRF, case report form; CT, computed tomography; CTCAE v5, Common Terminology Criteria for Adverse Events version 5; [redacted]; D, day; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FACT-Hep, Functional Assessment of Cancer Therapy – Hepatobiliary; HBcAb, hepatitis B core antibody test; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HCG, human chorionic gonadotropin; IgG, immunoglobulin G; IMAE, immune-mediated adverse event; INR, international normalized ratio; IRT, interactive response technology; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; [redacted]; PD, progressive disease; PGIC, Patient Global Impression of

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Change; PGIS, Patient Global Impression of Severity; PROMIS, Patient-Reported Outcomes Measurement Information System; PT, prothrombin time; RNA, ribonucleic acid; SAE, serious adverse event; T.bili, total bilirubin; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures schedule for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments and pregnancy testing, which must occur as scheduled.

[b] EOT is defined as the visit where a decision is made to discontinue the participant from treatment. The EOT visit will be the most recent on-treatment visit (with all available safety and response data), does not need to be repeated, and will be considered the start of the Week 1 Clinical/Safety Follow-up visit.

[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.

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Table 2-3: Follow-up Assessments (CA224106)

Procedure	Safety Follow-Up Visits 1 & 2[a] (± 7 days)	Survival Follow-Up[b]	Notes:[c]
Safety Assessment			
Targeted Physical Examination, Vital Signs, and Performance Status	X		Include weight, blood pressure, heart rate, temperature, ECOG Performance Status (see Appendix 7). Targeted physical examination to be performed only as clinically indicated.
AE and SAE Assessment	X	X*	Record at each visit. Collect continuously throughout the treatment period and for a minimum of 135 days following discontinuation of dosing. *Beyond 135 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent.
Concomitant Medications Review	X		Record at each visit.
Subsequent Cancer Therapy	X	X	Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy).
Laboratory Tests			
Pregnancy Test (WOCBP)	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.
Clinical Laboratory Assessments	X (see note)		To be performed at Follow-Up Visit 1, repeat at Follow-Up Visit 2 if study drug-related toxicity persists. Refer to Section 9.4.4 Clinical Safety Laboratory Assessments for the list of laboratory tests.
Coagulation profile	X		Refer to Section 9.4.4 for the list of laboratory tests to be conducted. Include INR. If INR cannot be done by the local laboratory, then PT may be provided instead.

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Table 2-3: Follow-up Assessments (CA224106)

Procedure	Safety Follow-Up Visits 1 & 2[a] (± 7 days)	Survival Follow-Up[b]	Notes:[c]
HBsAg, HBV DNA, HCV RNA	X		HBsAg and HBV DNA required if participant tests positive for HBsAg or HBcAg at screening. HCV RNA required if participant tests positive for anti-HCV at screening. If local laboratory is unable to perform required testing, central laboratory may be utilized with Sponsor approval.
Efficacy Assessments			
Survival Status	X	X	During Safety Follow-Up (Follow up Visits 1 and 2) and every 3 months (clinic visit or by telephone) during Survival Follow-Up. Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy). Participants will be followed until death, loss to follow-up, withdrawal of consent, conclusion of the study, or a minimum of 5 years.
Body Imaging		See notes	Contrast enhanced CT of the chest, CT/MRI of the 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 6 weeks starting from the date of randomization (± 7 days) up to Week 60 and then every 12 weeks (± 14 days). Imaging should continue as per schedule until treatment BICR confirmation of progression (including treatment beyond PD. 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 (without and with contrast) per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain (without or with contrast) can be performed if MRI is contraindicated.
Health Outcomes Assessments			
FACT-Hep	X		Administer at Safety Follow-up Visits 1 and 2.

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Table 2-3: Follow-up Assessments (CA224106)

Procedure	Safety Follow-Up Visits 1 & 2[a] (± 7 days)	Survival Follow-Up[b]	Notes:[c]
PROMIS Physical Function 8c	X		Administer at Safety Follow-up Visits 1 and 2.
PGIS	X		Administer at Safety-Follow-up Visits 1 and 2.
PGIC	X		Administer at Safety-Follow-up Visits 1 and 2.
[redacted]			
Pharmacokinetic Samples [redacted] Assessments			
PK [redacted] Blood Sample	X		See Table 9.5-1 for details.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BMS, Bristol-Myers Squibb Company; CRF, case report form; CT, computed tomography; DNA, deoxyribonucleic acid; ECOG, Eastern Cooperative Oncology Group; FACT-Hep, Functional Assessment of Cancer Therapy – Hepatobiliary; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MRI, magnetic resonance imaging; PD, progressive disease; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetics; PROMIS, Patient-Reported Outcomes Measurement Information System; PT, prothrombin time; RNA, ribonucleic acid; SAE, serious adverse event; WOCBP, women of childbearing potential.

[a] Participants must be followed for at least 135 days after last dose of study treatment. Follow-Up Visit 1 must occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 30 days after last dose. Follow-up Visit 2 occurs approximately 135 days (± 7 days) from last dose of study medication. Both follow-up visits should be conducted in person.

[b] Survival Follow-up visits to occur every 3 months (± 14 days) from Follow-Up Visit 2. Survival visit may be conducted in clinic or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3-month specified 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 contact.

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[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 regulation.

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In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest to low priority:

Safety electrocardiogram (ECG)

Safety (clinical labs)

Pharmacokinetic Sampling

Note: Safety assessment in response to adverse events (AEs) are not impacted by this priority list.

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3 INTRODUCTION

CA224106 is a site and participant blinded Phase 1/2 randomized study of the triplet combination of relatlimab (BMS-986016), nivolumab (BMS-936558), and bevacizumab as first-line (1L) therapy in advanced and/or metastatic hepatocellular carcinoma (HCC), relative to the doublet combination of nivolumab and bevacizumab.

Liver cancer may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. Immune checkpoint blockade has recently demonstrated clinical efficacy in several cancer types, including melanoma, HCC, gastric cancer, non-small cell lung cancer (NSCLC), and hematologic malignancies.[1,2,3]

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.[4,5] The immune checkpoint inhibitor nivolumab has demonstrated clinical activity via blockade of PD-1 in patients with a variety of malignancies, as described in the Investigator's Brochure (IB). Nivolumab is efficacious as a monotherapy and also as a combination therapy with other immunotherapeutics in patients with advanced HCC.

Targeting additional immune checkpoints enhances the anti-tumor activity of nivolumab. An immune checkpoint of interest is lymphocyte activation gene 3 (LAG-3, also known as cluster of differentiation 233[CD 223]). LAG-3 is a cancer immunotherapeutic target due to its negative regulatory effect on T cells.[6,7] Dual blockade of LAG-3 and PD-1 has shown the potential to improve efficacy in comparison with blocking PD-1 alone, potentially without adding significant toxicity. Preliminary single-arm HCC efficacy data from CA224020, which employed a combination regimen of immunotherapy (flat-dosing of relatlimab 80 mg once every two weeks [Q2W] + nivolumab 240 mg Q2W), showed improved efficacy in second-line (2L), immuno-oncology (IO) therapy-naive, patients with HCC [redacted]

Combining immune-checkpoint inhibition combinations with anti-vascular endothelial growth factor (VEGF) agents like bevacizumab has the potential to lead to greater depth of response and overall survival (OS) based on the preclinical data that presumes that bevacizumab can reverse abnormal vascularization that will allow nivolumab and relatlimab to inhibit the hypoxia-induced PD-L1 and LAG-3 expression. The combination of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) was approved by the Food and Drug Administration (FDA) in May 2020 for the treatment of patients in 1L, systemic treatment-naive, advanced/metastatic HCC setting. Since then, many patients with advanced metastatic HCC were treated with atezolizumab and bevacizumab combination therapy. However, there are no peer-reviewed publications on the efficacy of the combination of anti-PD-1 and bevacizumab in patients with HCC.

The triplet combination of nivolumab (anti-PD-1), relatlimab (anti-LAG3), and bevacizumab (anti-VEGF) will be evaluated based on the promising efficacy observed with nivolumab and relatlimab combination therapy as well as the efficacy with immune checkpoint inhibitor and bevacizumab combination. This proposed study will assess the efficacy of the triplet combination as a 1L treatment for participants with HCC.

Study intervention:

Relatlimab is a human LAG-3-specific antibody that was isolated from immunized transgenic mice expressing human immunoglobulin (Ig) gene.[9] 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 ligands, major histocompatibility complex (MHC) Class II, the peptide antigen presentation molecule recognized by CD4-positive (+) T cells.[10] 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). LAG-3 receptors expressed on T cells, its ligands are major histocompatibility complex (MHC) Class II[11] and fibrinogen-like protein-1 (FGL-1).[10] Relatlimab binding inhibits the negative regulatory function of LAG-3-mediated through its interaction with ligands in vitro. By blocking the inhibitory LAG-3 signaling pathway, relatlimab enhances the anti-tumor immune response and, thus, has the potential to inhibit the growth of multiple malignancies when administered in combination with other therapeutic immuno-oncology (IO) agents. Dual checkpoint inhibition with relatlimab and nivolumab results in enhanced T cell effector function that is greater than the effects of either antibody alone in murine syngeneic tumor models.[12]

PD-1 is a member of the CD28 family of T cell co-stimulatory receptors that also includes CD28, cytotoxic T-lymphocyte-associated protein 4 (CTLA 4), and inducible T-cell co-stimulator (ICOS). PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ, and 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. 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.[13]

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype monoclonal antibody that binds the programmed death-ligand 1 (PD-1) receptor on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and programmed death-ligand 2 (PD-L2) (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC.[14]

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assays. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian Chinese hamster ovary cell line.[15] There are preclinical and clinician evidences that bevacizumab synergizes with immune checkpoint blockade.

3.1 Study Rationale

The study aims to provide evidence of clinical efficacy and to establish safety of triplet therapy of nivolumab, relatlimab, and bevacizumab in 1L unresectable/metastatic HCC, versus nivolumab in combination with bevacizumab. The 1L standard of care for HCC has changed recently with the approval of atezolizumab and bevacizumab combination. The IMbrave150 trial demonstrated a statistically and clinically significant benefit. At the time of primary analysis the hazard ratio (HR) for death with atezolizumab and bevacizumab combination as compared to sorafenib was 0.58 (95% confidence interval [CI] 0.42 to 0.79, P = 0.0006), median progression-free survival (mPFS) was 6.8 months (95% CI, 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6) in the respective groups. This treatment regimen was also safe. Grade 3-4 AEs occurred in 56.5% of treated patients in the combination arm compared to 55.1% in the sorafenib treated arm.[16] With an additional 12 months follow-up time, this combination further confirmed the benefit versus sorafenib. The median OS was 19.2 months (HR = 0.66, 95% CI:0.52 to 0.85), mPFS per blinded-independent central review (BICR) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) was 6.9 months (HR = 0.65 [95% CI: 0.53-0.81]). The ORR was 30% with 8% complete response rate by RECIST v1.1. The ORR by modified RECIST (mRECIST) was 35% with 12% CR rate.[17]

There is preliminary evidence in HCC with the nivolumab and relatlimab combination therapy showing clinical benefit in LAG-3 positive (≥ 1% by IHC) population. Phase 3 evidence with the anti-programmed cell death-1-positive (PD-1+) anti-LAG-3 combination has been validated.[18]

Despite the demonstrated benefit of immunotherapies on clinical outcome, a large proportion of patients 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 immunotherapeutic combinations in 1L unresectable/metastatic liver cancer.

Although the combination therapy of atezolizumab and bevacizumab showed improved clinical benefit compared to sorafenib monotherapy, the disease control rate was 73.6% and there was approximately 20% of the patient population who did not respond to treatment at all. There is still a large unmet medical need in 1L advanced HCC.

As of Protocol Amendment 03, inclusion criteria have been updated to exclude participants with extrahepatic spread. This change will allow enrichment of the EHS-No population while preserving the ability to analyze safety and efficacy in both the All Comer, and EHS-No sub-populations. [redacted]

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LAG-3 (CD223) is a checkpoint receptor and expressed on several immune cell types including activated CD4+ and CD8+ T cells, memory T cells, Tregs, and natural killer cells.[11] Activation of the LAG-3 pathway occurs when LAG-3 interacts with its ligands, such as MHC Class II or other emerging ligands (eg, FGL-1), which triggers inhibitory activity that reduces the function of effector T cells.[10,11]

LAG-3 is often expressed on chronically exhausted T cells and is frequently co-expressed with PD-1 on tolerized tumor infiltrating lymphocytes (TILs) across many tumor types.[19,20,21] Increased expression of LAG-3 on TILs, especially in the context of PD-1 expression, further promotes T cell exhaustion, leading to an impaired ability to attack tumor cells and an increased potential for tumor growth.[11,22] Preclinical studies indicate that inhibition of the LAG-3 pathway may restore effector function of exhausted T cells, promoting proinflammatory cytokine signaling, and ultimately, an anti-tumor response. The combination of LAG-3 and PD-1 inhibition demonstrated enhanced anti-tumor activity by targeting independent pathways with distinct functions.[11]



3.1.1 Research Hypothesis

It is anticipated that relatlimab in combination with nivolumab and bevacizumab will demonstrate a favorable benefit/risk profile and larger ORR relative to nivolumab and bevacizumab doublet combination in systemic treatment-naive unresectable or metastatic HCC participants.

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3.2 Background

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; however, the majority of patients are not eligible due to 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. In 2020, the standard of care in 1L HCC changed following the approval of the combination regimen of atezolizumab and bevacizumab, providing an additional treatment option in addition to small molecule tyrosine kinase inhibitor monotherapies (TKIs) sorafenib and lenvatinib.[16]

The hypervascular nature of HCC tumors underscores the relevance of angiogenesis in the pathobiology of these tumors. Several angiogenic pathways have been identified as being dysregulated in HCC, suggesting a role in the development and pathogenesis of liver cancer.[27] Overexpression of VEGF has been observed in HCC [28, 29] and the concentration of the circulating VEGF is shown to correlate with advanced tumor stage, with the highest level observed with metastasis.[30] Tumor expression of VEGF has also been shown to correlate with vascular density, tumor invasiveness and prognosis in patients with HCC.[31]

Hypoxia is presumed to robustly stimulate tumor angiogenesis [32,33] but is also implicated in altering the immune microenvironment of HCC. Most preclinical models is investigating hypoxia-mediated mechanisms in HCC focused on inducible factor proteins (induce expression of proangiogenic factors), including VEGF which induce expression of proangiogenic factors, that induced angiogenesis in HCC tumors.[32,33,34] Noman et al. showed that hypoxia and hypoxia-inducible factors (HIFs) significantly increase PD-L1 expression on tumor-infiltrating myeloid derived suppressor cells (MDSCs), macrophages and tumor cells and suspected that the dual inhibition of hypoxia and PD-L-1 may show added benefit.[35] HIF has also shown to transactivate target genes such as VEGF, which is necessary for angiogenesis.[36] In addition, the surface expression of the inhibitory receptors like LAG-3 and anti-CTLA-4 was increased in wild-type CD8+ T cells.[37]

Clinical synergy between VEGF inhibition and immune modulation is hypothesized, as VEGF signaling has multiple effects on immune cells.[38] VEGF signaling can induce dendritic cells to impair T cell infiltration into tumors,[39] and cause upregulation of immune checkpoints on CD8+ T cells, [40] resulting in the modulation of T cell differentiation and cytotoxic T cell function.[41] Therefore, inhibition of VEGF signaling may abrogate some of these immunosuppressive effects, further enhancing immunotherapeutic treatments. Potential synergy between immune modulation and the VEGF pathways is demonstrated in the clinical setting by the positive IMbrave150 study.[16]

The treatment landscape for 1L HCC has rapidly evolved in the last few years. Both immunotherapies and anti-VEGF therapies have shown clinical activity. Until 2020, anti-VEGF

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small molecule tyrosine kinase inhibitor monotherapies were used in both 1L [42,43] and in 2L HCC, as well as anti-VEGF monoclonal antibody monotherapy.[44,45,46]

Nivolumab monotherapy has demonstrated statistically significant benefit in 2L HCC in patients who progressed on prior sorafenib monotherapy. Nivolumab 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. 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). Duration of response (DOR) was 91% at ≥ 6 months, 59% at ≥ 12 months, and 32% at ≥ 24 months.[5] Pembrolizumab (anti-PD1 monoclonal antibody) is also an approved immuno-oncology (IO) agent for 2L HCC.[47] Based on the study results of 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 data were evaluated by the FDA, based on ORR and DOR per RECIST v1.1. ORR was 17%, and DOR was 89% at 6 months and 56% at 12 months.

Nivolumab (anti-PD-1 monoclonal antibody) and ipilimumab (anti-CTLA-4 monoclonal antibody) combination received accelerated approval in 2L HCC, 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.[48]

Despite the demonstrated benefit of single or dual combinations of cancer immunotherapies and anti-VEGF single agent therapies on clinical outcome, a large proportion of cancer patients across many tumor types do not respond to these available therapies.

Preliminary efficacy of clinical activity in HCC was discussed earlier with the combination of relatlimab and nivolumab[8], as well as positive Phase 3 study with the combination regimen in 1L melanoma.[49] The combination of nivolumab (anti-PD-1 antibody) and bevacizumab (anti-VEGF antibody) was also studied before in NSCLC (ONO-4538-04)[50] and ovarian cancer (CA209323)[51] without identifying new safety signals.

Anti-VEGF monoclonal antibody (bevacizumab) monotherapy has demonstrated minimal clinical activity in HCC. Bevacizumab as a monotherapy was safe and well tolerated in the HCC population and safety findings were consistent with the HCC population and established safety profile of bevacizumab.[52,53] More information is available in Section 3.2.3 and Section 3.2.4.

After the approval of the combination of atezolizumab and bevacizumab combination therapy,[16] it can be hypothesized that combining dual immune-checkpoint inhibitors with anti-VEGF agents such as bevacizumab has the potential to lead to greater depth of response and OS. Preclinical data

of this combination suggests that bevacizumab is able to reverse abnormal vascularization[54,55,56] and will enable nivolumab and relatlimab to inhibit the hypoxia-induced PD-L1 and LAG-3 expression.

Based on the known safety profile of bevacizumab monotherapy,[56] as well as the data from IMbrave150 trial with the combination regimen of an anti-PD-L1 agent with bevacizumab in HCC,[57] in addition to the known safety profile of treatment with nivolumab in combination with relatlimab, a very small percentage of overlapping toxicities could be expected, if any. There are limited data available with relatlimab in combination with nivolumab in HCC (80 mg relatlimab/ 240 mg nivolumab Q2W), but there are existing data with the combination regimen up to [redacted] mg relatlimab/480 mg nivolumab every 4 weeks (Q4W) combination without added concerning safety signal in other indications. The most common TRAEs of any grade in the nivolumab and relatlimab program were fatigue (15.5%), pruritus (11.6%), diarrhea (8.6%), arthralgia (7.5%), while in the IMbrave150 study the most common TRAEs of any grade were hypertension (23.7%), proteinuria (18.8%), fatigue (15.2%) and aspartate aminotransferase increase (14%). Bevacizumab was shown to be withdrawn more frequently due to AE (14.6%) versus atezolizumab (8.5%) with an incidence of $\geq 1\%$ in either group. The most common reason of withdrawal of bevacizumab was gastrointestinal hemorrhage (0.9%) and esophageal varices hemorrhage (1.2%).

CA224073 study is currently enrolling in patients with second- or third-line liver cancer patients who are immunotherapy-naive and evaluating 480 mg relatlimab/480 mg nivolumab Q4W combinations versus 480 mg Q4W nivolumab monotherapy.[9] As of Protocol Amendment 03, this study has completed enrollment.

3.2.1 Mechanisms of Action of Each Agent

3.2.1.1 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.[12] 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], 0.25-0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its known ligands, MHC Class II (half maximal inhibitory concentration [IC50], 0.7 nM) and FGL1. 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.[12]

Refer to Relatlimab IB Section 4.1 and Section 4.2.[12]

3.2.1.2 Bevacizumab Mechanism of Action

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo

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assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF and has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian Chinese hamster ovary cell line. Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.[15]

3.2.1.3 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the downregulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab (OPDIVO^{TM}) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).[13]

3.2.2 Preclinical Activity

3.2.2.1 Relatlimab Combined with Nivolumab Pre-clinical Activity

LAG-3 has been shown to be expressed in TILs of several tumor types, including melanoma, HCC, breast, ovarian, and lung cancers, often in connection with increased PD-1+ T cells.[58] Preclinical data presented in recent years illustrate a clear synergy between the inhibitory receptors LAG-3 and PD-1 in controlling immune homeostasis, preventing autoimmunity, and enforcing tumor induced tolerance. [12,59] Importantly, combined treatment of mice with blocking antibodies against both receptors resulted in more robust immune responses than either single-treated group in these studies, and analyses of LAG-3−/−Pdcd1−/− double-knockout mice revealed a cooperative requirement for LAG-3 and PD-1 in maintaining immune homeostasis.

The single agent anti-tumor activity of anti-LAG-3 antibody (19C7) was evaluated in the very immunogenic Sa1N fibrosarcoma tumor model.[60] Compared with the isotype control group, all doses between 1 mg/kg and 30 mg/kg of anti-LAG-3 clone 19C7 demonstrated anti-tumor efficacy leading to between 30% and 60% of the mice being rendered tumor-free at the end of study.

Combined anti-PD1 and anti-LAG-3 activity was also assessed in the Sa1N model. In 2 different studies, anti-LAG-3 antibody, C9B7W, inhibited the growth of Sa1N tumors in mice when

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administered as monotherapy and when combined with anti-PD-1 antibody, 4H2.[61,62] The combination of these 2 antibodies resulted in 80% to 90% tumor-free mice and reductions in median tumor volumes superior to that of anti-PD-1 or anti-LAG-3 antibody monotherapy alone.[12]

Similarly, greater anti-tumor effect was also demonstrated for combined anti-PD1 and anti-LAG-3 in the MC38 colon adenocarcinoma models than with either agent alone.[12]

3.2.3 Clinical Activity

3.2.3.1 Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, SCCHN, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Details of the clinical activity in these various malignancies are provided in the United States Prescribing Information (USPI) and Summary of Product Characteristics (SmPC).[5]

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 showed clinical activity of nivolumab in 2L advanced HCC patients who progressed on or were intolerant to sorafenib. With 27 months of follow-up, with 154 participants treated with nivolumab 3 mg/kg every 2 weeks (Q2W), the ORR was 14%, the mPFS was 2.83 months, and the median overall survival (mOS) was 15.6 months.[63]

On 10-Mar-2020, the doublet combination of nivolumab and ipilimumab received accelerated approval from FDA in HCC patients who were previously treated with sorafenib. This approval was based on data from 28-month follow-up of CA209-040 [19-Jul-2019], demonstrating an ORR of 33% among the 49 participants treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W).[64] With a median follow up of 30.7 months in this trial, mOS was observed to be 22.8 months (95% CI: 9.4, NR), in those patients who had an objective response mOS was not reached.[65]

Nivolumab in HCC was further evaluated in CA209459, a randomized Phase 3 study of nivolumab (240 mg Q2W) versus sorafenib in first-line advanced HCC. With a minimum follow-up of 22.8 months, nivolumab monotherapy demonstrated a clinically meaningful improvement in 371 patients treated in OS (mOS 16.4 months [95% CI: 13.9-18.4]), PFS (mPFS 3.7 months [95% CI 3.1-3.9]), and ORR (15%), but the study did not meet statistical significance.[66]

3.2.3.2 Bevacizumab Clinical Activity

Bevacizumab has demonstrated clinical efficacy in recurrent glioblastoma in monotherapy and in combination therapy in metastatic CRC both for first- and 2L treatment in combination with chemotherapy, in unresectable, locally-advanced, recurrent or metastatic non-squamous NSCLC, in combination with carboplatin and paclitaxel for 1L treatment, metastatic RCC in combination

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with interferon-alfa, in persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. It is approved in epithelial ovarian, fallopian tube, or primary peritoneal cancer (1) in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent therapy, for stage III or IV disease following initial surgical resection, (2) in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens, (3) in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by bevacizumab as a single agent, for platinum sensitive recurrent disease.[15]

After small molecule tyrosine kinase inhibitors with activity against VEGF showed clinical efficacy in HCC, bevacizumab single agent trials were initiated. Siegel et al. conducted a Phase 2 trial of bevacizumab for the treatment of nonmetastatic HCC, excluding patients with extrahepatic disease, tumor invasion of the main portal vein or inferior vena cava, which led to the conclusion of many experts that this study enrolled patients with favorable prognostic values as opposed to traditional advanced/metastatic HCC studies. The ORR was 13% (95% CI: 3-23) and mPFS was 6.9 months (95% CI, 6.5-9.1), median survival was 12.4 months (95% CI: 9.4-19.9).[52] In another single agent bevacizumab Phase 2 study among 24 patients evaluable for efficacy, 3 partial responses (PR,13%) and seven stable diseases (SD, 29%) were reported of at least 16 weeks of follow up.[67] A retrospective study of 12 patients who were intolerant to or progressed during sorafenib therapy received bevacizumab monotherapy (5-10 mg/kg every 2-3 weeks). The mOS was 20.2 months (interquartile range [IQR], 7.0-43.5), with a median time to radiologic progression of 10.4 months (IQR, 2.8-16.1) and a disease control rate of 54%.[68] Subsequently, several Phase 2 trials studied bevacizumab in combination with erlotinib, capecitabine, or multi-agent chemotherapy and further demonstrated the potential of bevacizumab for the treatment of HCC.[69,70]

Boige at al. conducted a Phase 2 trial, eligible patients received bevacizumab, 5 mg/kg or 10 g/kg every 2 weeks with disease-control rate (DCR) at 16 weeks (16W) being the primary endpoint. There were 48 patients enrolled, 43 of whom received at least one dose of bevacizumab. The 16W-DCR was 42% (95% CI: 27%, 57%) in the overall population, 39% (95% CI: 19%, 59%) in patients treated with 5 mg/kg bevacizumab, and 45% (95% CI: 23%, 67%) in those treated at the 10 mg/kg dose. Among the 38 response-evaluable patients, 6 patients achieved a partial response (PR), the ORR was 14%;(95% CI: 4%, 24%), median duration of response (mDOR) was 148 days (range, 55-362 days), 18 patients had SD (DCR, 56%), including 12 patients who experienced SD for > 16 weeks. In the overall population (n = 43), mPFS was 3 months (95% CI: 2, 4); median OS was 8 months (95% CI: 4, 9).[53]

3.2.3.3 Relatlimab Monotherapy and Relatlimab Combined with Nivolumab Clinical Activity

[redacted]

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[redacted]

The Phase 1/2a study CA224020 is investigating the safety, tolerability, and effectiveness of relatlimab, with and without nivolumab, to treat various solid tumors. Initial results show encouraging clinical activity when relatlimab is combined with nivolumab in the treatment of participants with solid tumors.[12, 71, 72] [redacted]

More recently, CA224047, a global, double-blind, randomized, Phase 2/3 study comparing relatlimab + nivolumab FDC formulation (relatlimab 160 mg + nivolumab 480 mg Q4W [rela + nivo FDC]) 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. The study achieved its primary endpoint, demonstrating statistically significant improvement in PFS by BICR with rela + nivo FDC compared to nivolumab monotherapy in all randomized participants (N= 714) (PFS hazard ratio = 0.75 [95% CI: 0.62, 0.92], P-value = 0.0055). With a median follow-up of 13.2 months, the mPFS in the rela + nivo FDC 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 rela + nivo FDC and nivolumab monotherapy, respectively. The PFS benefit of rela + nivo FDC were consistent across key prespecified subgroups. Follow up for the secondary endpoints of OS and ORR is ongoing.[18]

3.2.3.4 Bevacizumab Combined with Nivolumab Clinical Activity

There is no clinical data with nivolumab in combination with bevacizumab in HCC.

The combination of nivolumab and bevacizumab has been studied before in NSCLC and ovarian cancer. Efficacy of this combination was explored in CA209012 study in patients with NSCLC as part of the maintenance therapy after 4 cycles of platinum-doublet therapy.[50] [redacted] participants were treated with [redacted] mg/kg nivolumab in combination with [redacted] mg/kg bevacizumab every 3 weeks

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(Q3W) as maintenance therapy. [redacted]

Liu et al published a study of 38 ovarian cancer (18 had platinum-resistant and 20 had platinum-sensitive disease) participants treated with nivolumab 240 mg and bevacizumab 10 mg/kg every Q2W. In this population, an ORR of 28.9% was observed, with a total clinical benefit (confirmed response + stable disease > 24 weeks) rate of 55.3%; these rates were enhanced in participants sensitive to platinum-based chemotherapy (ORR: 40.0%, clinical benefit rate [CBR]: 75.0%), platinum resistant participants demonstrated a comparatively reduced benefit (ORR: 16.7%, CBR: 33.3%).[51] The mPFS in all participants was 8.1 months (95% CI, 6.3-14.7 months), similarly PFS was improved in platinum sensitive patients (9.4 months) when compared to platinum resistant patients 5.3 months).

There are few case reports available with the nivolumab and bevacizumab combination in metastatic myxofibrosarcoma[73] and urothelial carcinoma.[74]

3.2.3.5 Bevacizumab Combined with Other Immune-checkpoint Inhibitors Clinical Activity (in HCC)

In a global, open-label, Phase 3 trial atezolizumab and bevacizumab combination therapy was evaluated (IMbrave150) in patients who had not previously received systemic treatment with advanced/metastatic HCC. There were 501 patients randomized to receive either atezolizumab and bevacizumab, or sorafenib treatment until unacceptable toxicity or loss of clinical benefit. This trial demonstrated statistically and clinically significant benefit with the combination regimen. At the time of primary analysis, the HR for death with the atezolizumab and bevacizumab combination as compared to sorafenib was 0.58 (95% CI 0.42 to 0.79, P = 0.006), mPFS was 6.8 months (95% CI, 5.7-to 8.3) and 4.3 months (95% CI, 4.0-to 5.6) in the respective groups. The OS benefit and PFS benefit with atezolizumab and bevacizumab combination therapy as compared with sorafenib were generally consistent across the clinically relevant subgroups analyzed.[16] The study further confirmed the benefit of the combination therapy versus. sorafenib with an additional 12 months follow-up time. The mOS was 19.2 months (HR = 0.66, 95% CI: 0.52-0.85), mPFS per BICR by RECIST v1.1 was 6.9 months (HR = 0.65, 95% CI: 0.53-0.81). ORR was 30% with 8% complete response (CR) rate by RECIST v1.1. The ORR by mRECIST 35% with 12% CR rate.[17]

3.2.4 Clinical Safety

3.2.4.1 Nivolumab Clinical Safety

Detailed clinical safety information is available in the Opdivo USPI and SmPC.[5] In patients with liver cancer, nivolumab monotherapy has been studied in 2L HCC in CA209040 study and in 1L CA209459 study.

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3.2.4.2 Bevacizumab Clinical Safety

Bevacizumab safety is summarized in the USPI and the SmPC in other indications.[15] Bevacizumab monotherapy has been studied in multiple Phase 2 studies in HCC. Siegel at al. published a Phase 2 trial of 46 patients with unresectable HCC who received bevacizumab monotherapy 5 mg/kg or 10 mg/kg (n = 34) every 2 weeks, and experienced Grade 3 to 4 AEs included hypertension (15%) and thrombosis (6%, including 4% with arterial thrombosis). Grade 3 or higher hemorrhage occurred in 11% of patients, including 1 fatal variceal bleed.[52] In another Phase 2 single-agent study of bevacizumab, among the 30 patients in advanced HCC treated at either dose (5-10 mg/kg bimonthly), 6 (20%) discontinued bevacizumab because of variceal hemorrhage (variceal banding successful in every case) (n = 3); Grade 3 transient ischemic attack (n = 1); Grade 3 hemorrhagic ascites (n = 1); and Grade 3 proteinuria (n = 1). Grade 1–2 toxicities included fatigue, epistaxis, hypertension, and proteinuria.[67] A retrospective study of 12 patients who were intolerant or progressed during sorafenib therapy received bevacizumab monotherapy (5-10 mg/kg every 2-3 weeks). Bevacizumab therapy was well tolerated with only 1/12 patients experiencing a Grade 3-4 TRAE (transient ischemic attack) and only 2/12 patients discontinued the therapy due to AEs.[75]

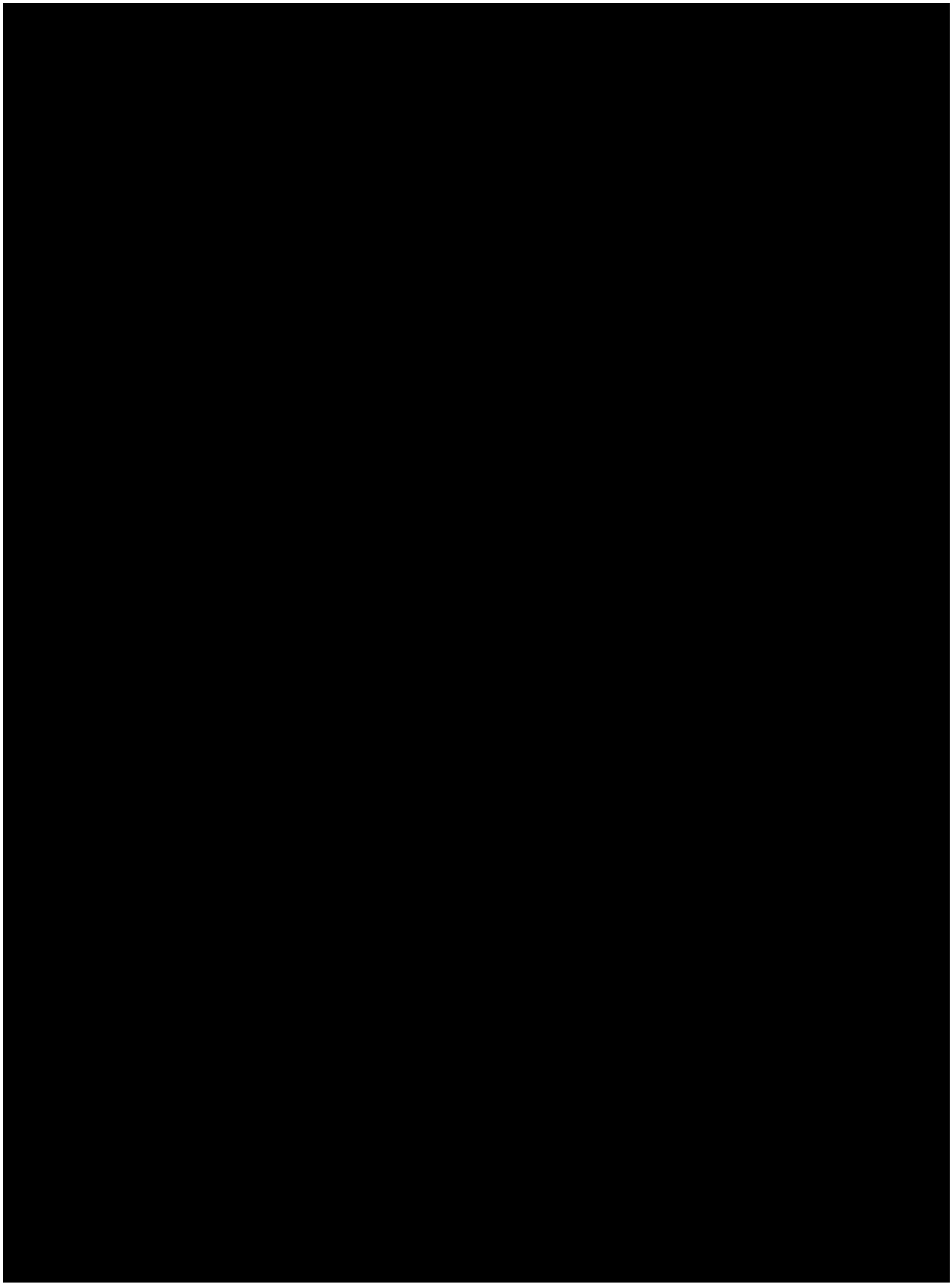
In another small, Phase 2 trial, eligible advanced HCC patients received bevacizumab, 5 mg/kg or 10 g/kg every 2 weeks. Out of the 48 patients who were enrolled, 43 patients received at least one dose of bevacizumab. Of those, 16 (37%) patients experienced Grade 3-4 toxicities (Grade 3-4 asthenia [12%], Grade 3-4 aminotransferase elevation [7%]), none of them were serious. Four patients (9%) had GI hemorrhage, although the study required upper GI endoscopy and propranolol treatment in case of medium or large gastro-esophageal varices were seen.[53]

3.2.4.3 Relatlimab monotherapy and Relatlimab combined with Nivolumab Clinical Safety

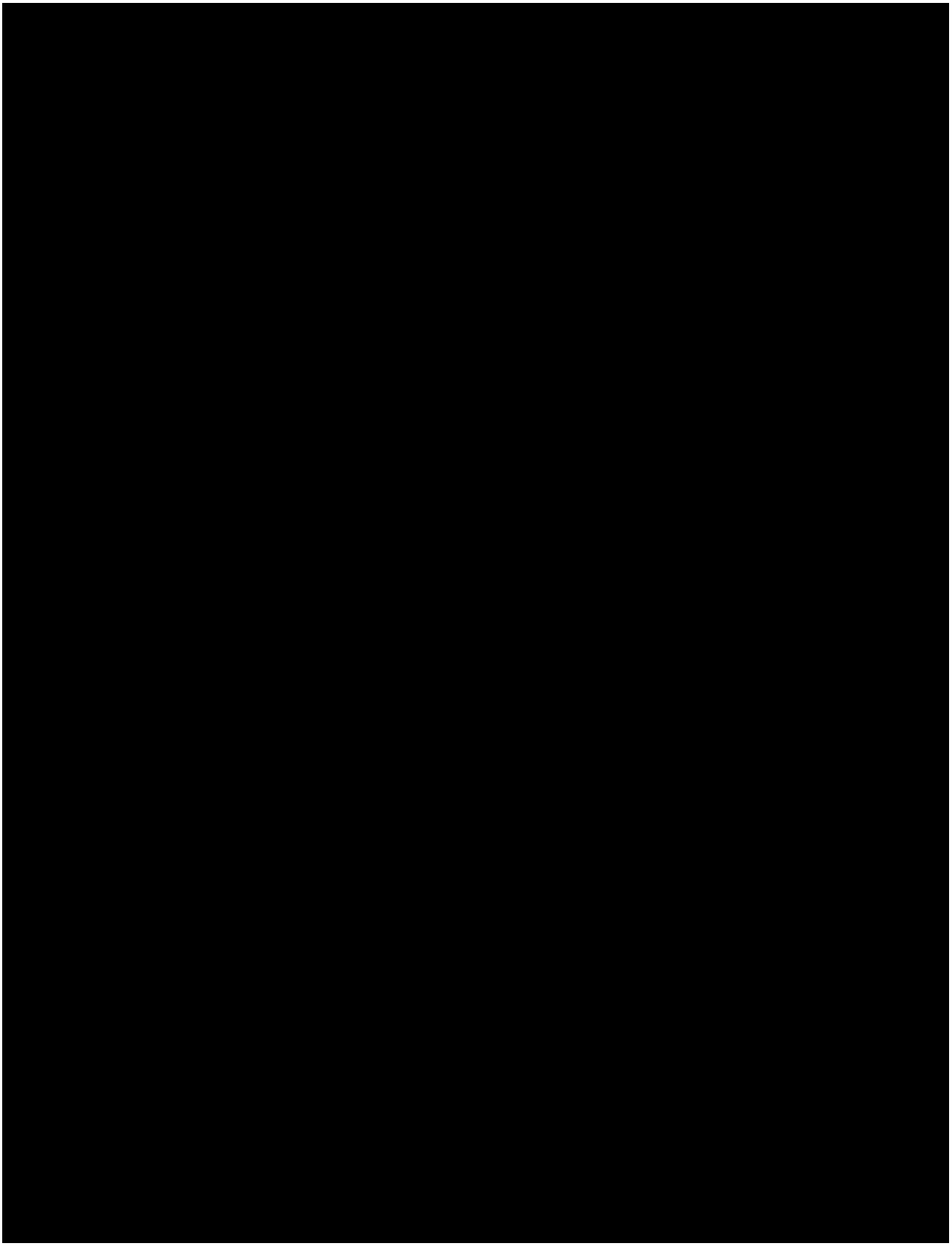
The safety profile of relatlimab appears manageable in the 3 ongoing studies with relatlimab monotherapy (clinical data cutoff date was 15-Jul-2020 for CA224020 and CA224022) with no maximum tolerated dose (MTD) reached at any dose tested up to an 800 mg flat-dose Q2W.[12]



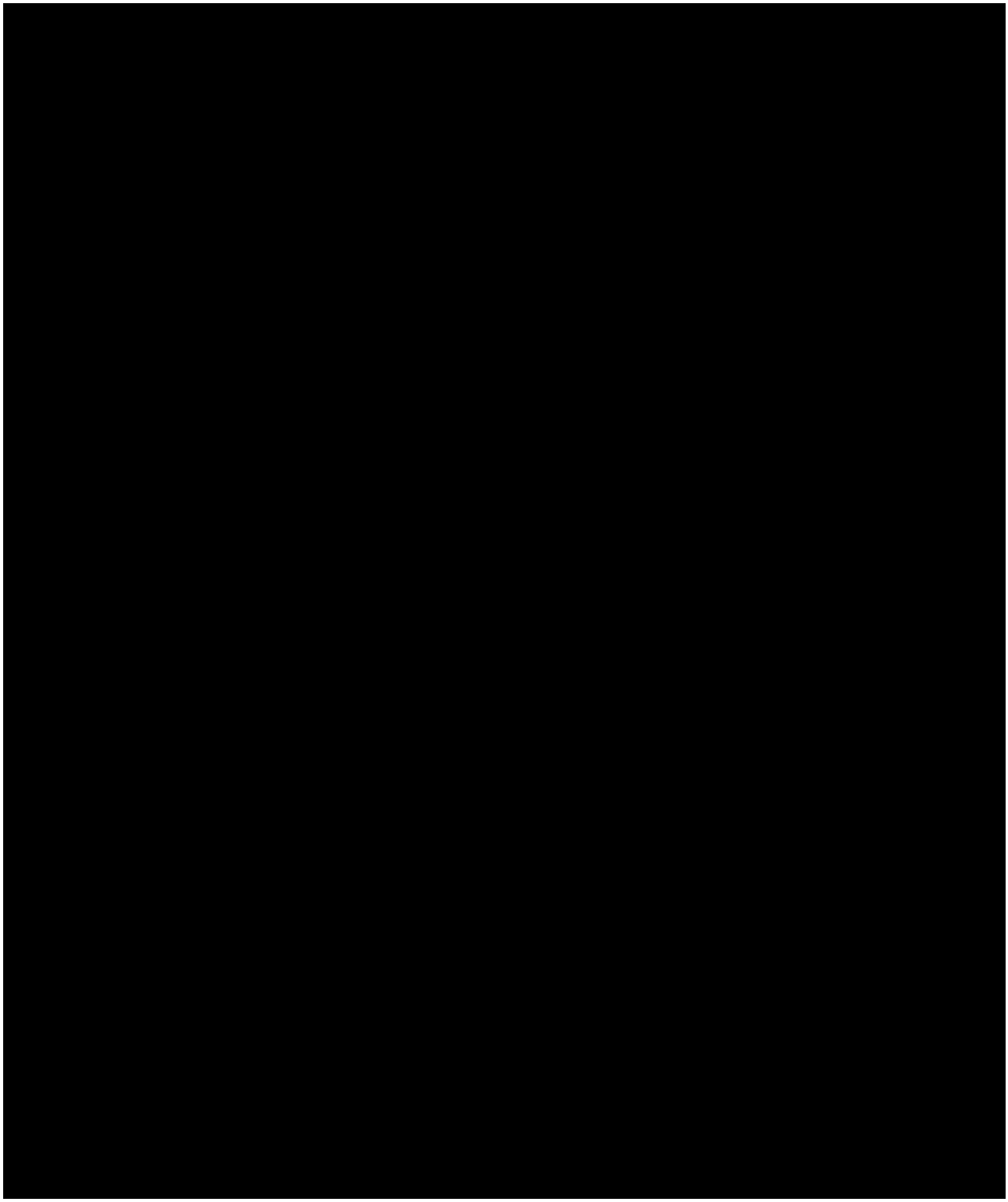
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More information can be found in the relatlimab IB.[12]

A safety update (11-Mar-2020 clinical data cutoff) of CA224020 suggests that the combination of nivolumab and relatlimab is well tolerated even at higher dose levels of relatlimab, with a safety profile similar to that of nivolumab monotherapy.[76]

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At the dose of 480 mg relatlimab + 480 mg nivolumab Q4W, of [redacted] participants treated, [redacted]% experienced any-grade AEs. The drug-related AEs were observed in [redacted]% of participants ([redacted]% experienced Grade 3-4 events). Of these, [redacted]% ([redacted] participants) discontinued treatment due to Grade 3-4 drug-related AEs. Of the [redacted] participants treated at dose level [redacted] mg relatlimab + 480 mg nivolumab Q4W, [redacted]% and [redacted]% of participants experienced a drug-related AE and drug-related Grade 3-4 AEs, respectively. Of these, [redacted]% ([redacted] participants) discontinued study therapy. At the dose level of [redacted] mg relatlimab + nivolumab 480 mg Q4W, of the [redacted] participants treated at the time of data cutoff (enrollment ongoing at data cutoff), [redacted]% experienced an AE. Drug-related AEs were reported in [redacted]% of treated participants; however, none of these were Grade 3-4 events. There were no drug-related AEs leading to treatment discontinuation at this dose level.[76]

Within the IO-naive advanced/metastatic HCC cohort of CA224020, safety in patients treated with 80 mg relatlimab in combination with 240 mg nivolumab Q2W was generally consistent with data from other trials. Related adverse events were observed in [redacted] of patients, [redacted] of which were Grade 3 or Grade 4 events. [redacted]

[redacted]

The safety profile of the combination of relatlimab (160 mg) + nivolumab (480 mg) FDC (n = 355) was confirmed in the pivotal Phase 2/3 global, multicenter study, CA224047, in previously

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untreated advanced melanoma participants. The study findings demonstrated a well-tolerated regimen with a manageable safety profile and without unexpected safety signals. The incidence of Grade 3-4 drug-related AEs was 18.9% in the rela + nivo FDC group versus 9.7% in the nivolumab monotherapy group. There were 3 treatment-related deaths with rela + nivo FDC and 2 with nivolumab-treated participants. Drug-related AEs (any grade) led to treatment discontinuation in 14.6% and 6.7% of patients in the rela + nivo FDC and nivolumab monotherapy groups, respectively. [18]

3.2.4.4 Bevacizumab Combined with Nivolumab Clinical Safety

The combination of nivolumab and bevacizumab has been studied before in NSCLC and ovarian cancer. Safety and tolerability of this combination was explored in CA209012 study in patients with NSCLC as part of the maintenance therapy after 4 cycles of platinum-doublet therapy.[50] [redacted] participants were treated with [redacted] mg/kg nivolumab in combination with [redacted] mg/kg bevacizumab every 3 weeks (Q3W) as maintenance therapy. No new safety concerns were identified, and no deaths were attributed to study drug toxicity. [redacted] patients experienced a drug-related adverse event (AE), [redacted] patients experienced Grade 3-4 AEs. The most frequent drug-related AE was skin toxicity followed by fatigue. Liu et al published the data of 38 participants with ovarian cancer treated with nivolumab 240 mg and bevacizumab 10 mg/kg every 2 weeks (Q2W).[51] Thirty-four participants (89.5%) experienced at least 1 treatment-related AE; 9 participants (23.7%) had a Grade 3 or higher treatment-related adverse event. No new safety concerns were identified, and no death were attributed to the study therapy. Pembrolizumab 200 mg (Q3W) and bevacizumab 10 mg/kg (Q3W) has been studied in patients with recurrent glioblastoma (GBM) and safety lead in results were published by Reardon et al. Six patients were treated. The most common AEs that were at least probably related to study therapy were fatigue (Grade 2, n = 2; Grade 1, n = 2) and hypertension (Grade 3, n = 2; Grade 1, n = 1). No patient experienced a DLT, and none required dose modification, interruption or discontinuation due to toxicity.[77]

3.2.4.5 Bevacizumab Combined with Other Immune-checkpoint Inhibitors Clinical Safety (in HCC)

Participants with Child-Pugh Class A cirrhosis with advanced/metastatic cancer, who had not previously been treated with systemic therapy, were given either sorafenib monotherapy or a combination regimen of atezolizumab and bevacizumab. The combination regimen had greater efficacy than sorafenib monotherapy. Due to the risk of bleeding, patients enrolled in this trial were required to have undergone esophagogastroduodenoscopy within 6 months of treatment initiation, and to have treatment of esophageal varices, when necessary. The trial excluded patients who had a myocardial infarction or stroke with the previous 3 months, were on therapeutic anticoagulation, or had coinfection with hepatitis C virus or hepatitis B virus (HCV or HBV).

Grade 3 or 4 AEs occurred in a similar percentage of participants in each group (57% versus 55%), but hypertension, pyrexia, alanine transaminase elevation, and proteinuria were more frequent with combined therapy. Overall, hypertension was the most common TRAE, with an incidence rate of > 10%. The second most-common TRAE was proteinuria. Both hypertension and proteinuria are

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consistent with the known safety profile of bevacizumab. Approximately 15% of participants in the combination group discontinued treatment as a result of AEs. The most common reason for discontinuation was gastrointestinal disorders, which are expected when individuals with liver cancer and underlying cirrhosis are treated with bevacizumab. Upper gastrointestinal bleeding is a common, life-threatening complication in patients with cirrhosis and HCC. Bleeding (including fatal events) is a known adverse reaction to bevacizumab. Therefore, participants with cirrhosis and HCC treated with bevacizumab are at increased risk of upper GI bleeds. In this trial, participants were evaluated for the presence of varices before enrollment, and varices of any size were treated according to local standards of care. Overall, the incidence of upper gastrointestinal bleeding observed in the combination group was 7%.[17]

3.3 Benefit/Risk Assessment

As described in Section 3.2.3.3, clinical activity was seen in multiple indications in the CA224020 study with the combination of relatlimab + nivolumab.[12] Preliminary clinical efficacy has been demonstrated in CA224020, where combination dosing of relatlimab 80 mg + nivolumab 240 mg Q2W showed responses in certain treatment-naïve and previously heavily-treated advanced solid tumors. The clinical efficacy of the combination was further confirmed in the CA224047 study, a global, double-blind Phase 2/3 randomized controlled trial, which demonstrated a statistically significant and clinically relevant PFS benefit of rela + nivo FDC Q4W compared to nivolumab 480 mg Q4W.[78]



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[redacted]

Furthermore, the rela + nivo FDC (relatlimab doses of 160 mg + nivolumab 480 mg FDC, administered Q4W) was confirmed to be well tolerated with a manageable safety profile in 355 participants treated in the CA224047 study. There were no unexpected safety signals from this combination.[79]

Given the safety profile of relatlimab as monotherapy and combination therapy observed to-date,[12] the positive benefit-risk of the pivotal Phase 2/3 study of rela + nivo FDC (CA224047) demonstrated in participants with previously untreated metastatic or unresectable advanced melanoma, and the significant unmet medical need in the advanced/metastatic HCC population, the continuing evaluation of the combination of relatlimab plus nivolumab is justified for the patient population in this protocol.[79]

[redacted]

The safety profile from the Phase 3 atezolizumab and bevacizumab combination study observed that the most common drug-related adverse events attributed to the combination therapy are hypertension, proteinuria, fatigue, aspartate aminotransferase increase, and pruritus, all of which are consistent with the well-known safety profiles distinct for each of those components. The most common drug-related AE that led to discontinuation of any of those study therapies were autoimmune hepatitis, GI hemorrhage, infusion-related reaction, and transaminase increase for atezolizumab. All AEs presented in 2 patients each (0.6%), which is very similar to the frequency of Grade 3/4 immune-mediated adverse events observed with the nivolumab and relatlimab combination: diarrhea (1.1%), aspartate aminotransferase increase (1.1%), amylase elevation, lipase elevation (asymptomatic, does not require dose discontinuation).[17]

The current study, CA224106, will also take preventive safety steps to evaluate patients who are at high-risk for bleeding and hypertension similar to the inclusion/exclusion criteria seen in the IMbrave150 study; these preventative measures include, but are not limited to: prospective evaluation for esophageal and gastric varices, detailed medical history that may increase the likelihood of a participant experiencing a bleeding complication, careful consideration of prior cardiac medical history, and specific constraints on concomitant therapies.

Investigators and the Sponsor will utilize continuous safety assessments to determine whether additional safety measures or termination from the study is required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the Sponsor's Medical Monitor and Worldwide Patient Safety (WS) representatives to monitor for any safety signals or trends. Additionally, safety will be routinely reviewed by the internal Safety Committee (SC). As relatlimab is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 5. Most high-grade AEs were manageable with the use

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of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of relatlimab and nivolumab, including results from other clinical studies, are also available in the relatlimab IB.[12]

3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) **Immunotherapy: Relatlimab, Nivolumab**		
[redacted]		

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Table 3.3.1-1: Risk Assessment		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
[redacted]		
Study Intervention(s) - Other **Study intervention: Bevacizumab** (anti-VEGF monoclonal antibody)		
Gastrointestinal perforation and fistula	USPI and SmPC for bevacizumab	I/E criteria; monitoring at every cycle. Recommended dose reductions and discontinuations - [redacted] Table 7.4.2-1 and Section 8.1,
Surgery and wound healing complications	USPI and SmPC for bevacizumab	I/E criteria, monitoring, physical examination at every cycle. Recommended dose reductions and discontinuations - [redacted] Table 7.4.2-1 and Section 8.1.
Hemorrhage	USPI and SmPC for bevacizumab	I/E criteria, monitoring with hematology profiles, physical examination at every cycle. Recommended dose reductions and discontinuations - [redacted] Table 7.4.2-1 and Section 8.1.
Arterial thromboembolic events	USPI and SmPC for bevacizumab	I/E criteria, monitoring with laboratory values, physical examination at every cycle. Recommended dose reductions and discontinuations - [redacted] Table 7.4.2-1 and Section 8.1
Venous thromboembolic events	USPI and SmPC for bevacizumab	I/E criteria, monitoring with laboratory values, physical examination at every cycle. Recommended dose reductions and discontinuations [redacted], Table 7.4.2-1, and Section 8.1
Hypertension	USPI and SmPC for bevacizumab	I/E criteria, blood pressure check, physical examination at every cycle. Recommended dose reductions and discontinuations - [redacted], Table 7.4.2-1 and Section 8.1
Posterior reversible encephalopathy syndrome	USPI and SmPC for bevacizumab	I/E criteria, blood pressure check, physical examination at every cycle. Recommended dose reductions and discontinuations - [redacted] Table 7.4.2-1 and Section 8.1

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Table 3.3.1-1: Risk Assessment		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Infusion related reactions	USPI and SmPC for bevacizumab	I/E criteria. Recommended dose reductions and discontinuations - [redacted] Table 7.4.2-1 and Section 8.1
Renal injury and proteinuria	USPI and SmPC for bevacizumab	I/E criteria, blood pressure check, dip stick test, physical examination at every cycle. Recommended dose reductions and discontinuations - [redacted], Table 7.4.2-1 and Section 8.1.
Embryo-fetal toxicity	USPI and SmPC for bevacizumab	Exclusion criteria, pregnancy testing, contraception per protocol -Sections 6.1, 9.2.5, and Appendix 4.
Ovarian failure	USPI and SmPC for bevacizumab	I/E criteria, physical examination at every cycle. Recommended dose reductions and discontinuations - [redacted] Table 7.4.2-1 and Section 8.1
Congestive heart failure	USPI and SmPC for bevacizumab	I/E criteria, physical examination at every cycle. Recommended dose reductions and discontinuations - [redacted] Table 7.4.2-1 and Section 8.1
Additional specific AEs (eg, electrolyte disturbances, hyperuricemia, cutaneous reactions, fluid retention, sepsis)	USPI and SmPC for bevacizumab	Recommended dose reductions and discontinuations - [redacted], Table 7.4.2-1 and Section 8.1
Study Procedures		
Tumor Biopsy (eg, pain, infection)	IB Section 7.1.3	Per institutional protocol/ investigator discretion.
Phlebotomy (eg, pain, ecchymosis, bleeding, syncope)	IB Section 7.1.3	Per institutional protocol/ investigator discretion.
Other (if applicable)		
Allergy to contrast agent (eg, reaction to anaphylaxis)	Contrast USPI and SmPC	Prophylaxis and/or treatment per institutional protocol/Investigator discretion.
SARS-CoV-2 Infection	Policy and Guidance for the conduct of BMS-sponsored clinical research in light of SARS-CoV-2	See Exclusion criteria (Section 6.2), Re-screening criteria (Section 6.4.1) and Dose Modifications section (Section 7.4) and the SARS-CoV-2 Safety Surveillance Plan.

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Table 3.3.1-1: Risk Assessment		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Dosing delay due to SARS-CoV-2 lockdowns	BMS SARS-CoV-2 Clinical Research Project Management Office	Specific measures have been considered to ensure the trial can continue should the hospital be subject to increased demands/restrictions due to the pandemic (travel restrictions, remote access / monitoring, preventative measures etc).

Abbreviations: AE, adverse event; BMS, Bristol-Myers Squibb Company; ECG, electrocardiogram; IB, Investigator Brochure; I/E, inclusion/exclusion; IMAE, immune-mediated adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SmPC, Summary of Product Characteristics; USPI, United States Prescribing Information; VEGF, vascular endothelial growth factor.

3.3.2 Benefit Assessment

As described in Section 3.2.3.3, clinical activity was seen in multiple indications in the CA224020 study with the combination of relatlimab + nivolumab.[12] Preliminary clinical efficacy has been demonstrated in CA224020, where combination dosing of relatlimab 80 mg + nivolumab 240 mg Q2W showed clinical benefit in advanced/metastatic liver cancer patients showing [redacted].

The Phase 2/3 study CA224047 evaluated the combination of relatlimab-nivolumab (160 mg/480 mg) versus nivolumab (480 mg) monotherapy in patients with previously untreated metastatic or unresectable melanoma highlighting the added benefit of relatlimab to nivolumab. Statistically significant efficacy has been reported with the combination of nivolumab and relatlimab, mPFS: 10.12 months (95% CI: 6.37, 15.74) versus nivolumab monotherapy 4.63 months (95% CI: 3.38-5.62), HR 0.75 (95% CI: 0.62, 0.92). Follow up for OS, a secondary endpoint, is ongoing.

The preliminary efficacy seen in HCC and the positive Phase 3 study result in 1L melanoma suggest that the addition of relatlimab to an anti-PD-1 agent in combination with bevacizumab can further improve efficacy over doublet therapy (established current standard of care) in 1L advanced/metastatic liver cancer.

As of Protocol Amendment 03, enrollment to CA224106 will be restricted only to participants without extrahepatic spread (EHS-No) of their disease, which will allow the Sponsor to assess efficacy and safety in both the All Comer and EHS-No sub-populations. [redacted] the IMbrave150 trial (Section 3.2.3.5), where participants without EHS

demonstrated a median OS of 22.8mo (95% CI: 17.1, 25.8) versus those with EHS who had a median OS of 17.8mo (95% CI: 16.1, 23.7),[81] among All Comers, mOS was 19.2mo (95% CI: 17.0, 23.7). [redacted]

3.3.3 Overall Benefit/Risk Conclusion

There is still a high unmet need in 1L systemic treatment-naive advanced/metastatic HCC. The following clinical efficacy data all support the rationale for relatlimab in combination with nivolumab and bevacizumab in patients with previously untreated advanced/metastatic HCC:

- The preliminary clinical evidence with relatlimab and nivolumab combination in HCC
- The Phase 3 data of PFS benefit of nivolumab and relatlimab combination in 1L melanoma
- The data from the Phase 3 IMbrave150 trial with immunotherapy (anti-PD-L1) and bevacizumab combination therapy in advanced/metastatic HCC
- The well-described immune biology in HCC.

The positive safety profile is supported by the following evidence:

- Nivolumab and relatlimab combination compared to nivolumab is acceptable and manageable from the Phase 3 1L melanoma study,
- The safety profile of immunotherapy from IMbrave150 trial is comparable to the available nivolumab and relatlimab combination therapy safety profile.
- The available clinical evidence and the anticipated acceptable safety profile of immunotherapy combination and bevacizumab as well as the proactive measures taken at enrollment to ensure that patients are not exposed additional risks.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with relatlimab and nivolumab in combination with bevacizumab are justified by the anticipated benefits that may be afforded to participants with 1L systemic treatment naive advanced/metastatic HCC.

The Sponsor will evaluate the risk/benefit profile of the study on an ongoing basis. The study will pause for an evaluation of DLTs and safety of the triplet regimen when approximately 12 participants have been treated per Section 5.1.1. The internal Safety Committee will evaluate if dose de-escalation is warranted. The safety evaluation will be based on all available data – with particular attention to:

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- AEs or other safety trends in this or any other clinical study in particular interest in HCC whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk
- Real-world data with immunotherapy and bevacizumab combination.

If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

BMS has given consideration regarding the benefit/risk of coronavirus disease 2019 (COVID-19) vaccination during participation in BMS-936558 (nivolumab) and BMS-986016 (relatlimab) clinical trials. Based on the review of current available data and evidence to date, knowledge of the mechanisms of action of the COVID-19 vaccines and nivolumab and Relatlimab Investigational Medicinal Product (IMP), a biological or pharmacological interaction occurring between the vaccine and the IMP that would negatively impact the benefit/risk for participants in BMS nivolumab and relatlimab clinical trials is not expected; however, data will continue to be reviewed. Therefore, at this time, a COVID-19 vaccine given to participants in this trial is considered a concomitant medication with no interaction.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary • To determine the RP2D of relatlimab, nivolumab, and bevacizumab triplet combination in participants with advanced/metastatic HCC who have not received prior systemic therapy • To evaluate ORR of the relatlimab, nivolumab, and bevacizumab triplet combination relative to nivolumab and bevacizumab doublet combination in All Comers[b] and in participants with EHS-No[c] status at study entry with advanced/metastatic HCC who have not received prior systemic therapy	**Primary** • DLTs assessed by Investigator within a 6-week DLT window for the first approximately 12, 24, 36, or 48 treated participants in 2 arms combined, depending on data • ORR[a] assessed by BICR using RECIST v1.1 in the All Comer and EHS-No population
Secondary	**Secondary**

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Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To estimate key efficacy endpoints of the relatlimab, nivolumab, and bevacizumab triplet combination and the nivolumab and bevacizumab in doublet combination in the All Comer and in EHS-No population with advanced/metastatic HCC who have not received prior systemic therapy and who express LAG-3 (≥ 1%) by IHC[d]	• PFS[a] assessed by BICR using RECIST v1.1 in the All Comer and in EHS-No population with LAG-3 positive status (≥ 1% by IHC) • ORR assessed by BICR using RECIST v1.1 in the All Comer and in EHS-No population with LAG-3 positive status (≥ 1% by IHC)
• To evaluate PFS of the relatlimab, nivolumab, and bevacizumab triplet combination relative to nivolumab and bevacizumab doublet combination in all randomized participants in the All Comer and in participants with EHS-No at study entry with advanced/metastatic HCC who have not received prior systemic therapy	• PFS[a] assessed by BICR using RECIST v1.1 in All Comer population and in all randomized participants with EHS-No at study entry
• To determine the safety and tolerability of the relatlimab, nivolumab, and bevacizumab triplet combination in all treated participants with advanced/metastatic HCC who have not received prior systemic therapy	• AEs, SAEs, select AEs, IMAEs, related or not, from first dose to 30- or 135-days after the last dose
Exploratory • To estimate exploratory efficacy endpoints of the relatlimab, nivolumab, and bevacizumab triplet combination and the nivolumab and bevacizumab in doublet combination in all randomized participants with advanced/metastatic HCC who have not received prior systemic therapy and all randomized participants	**Exploratory** • OS in All Comers and in all randomized participants that are EHS-No at study entry • PFS and ORR assessed by Investigator using RECIST v1.1 • DCR, TTR, and DOR assessed by Investigator and by BICR using RECIST v1.1 • PFS, ORR, DCR, TTR, and DOR assessed by BICR using mRECIST
• To evaluate ORR and PFS of the relatlimab, nivolumab, and bevacizumab triplet combination relative to nivolumab and bevacizumab doublet combination in all randomized participants with advanced/metastatic HCC who have not	• ORR assessed by BICR using RECIST v1.1 in all randomized participants with BCLC Stage B at study entry • PFS[a] assessed by BICR using RECIST v1.1 in all randomized participants with

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Table 4-1: Objectives and Endpoints

Objectives	Endpoints
received prior systemic therapy and have BCLC Stage B at study entry	BCLC Stage B at study entry
[redacted]	
• To assess participants' cancer-related QoL (using the FACT-Hep) of triplet versus doublet	• Change from baseline and the proportion of patients without meaningful symptomatic deterioration based on the FACT-Hep total and subscale scores
• To characterize the threshold for meaningful change for the FACT-Hep (total and subscale scores) and PROMIS Physical Function 8c	• Threshold for meaningful change, based on anchor (using PGIS and PGIC) and distribution-based approach
• To characterize the pharmacokinetics of relatlimab, nivolumab, and bevacizumab triplet combination and nivolumab and bevacizumab in doublet combination	• End of infusion concentration and trough concentrations
[redacted]	

Abbreviations: AE, adverse event; BCLC, Barcelona-Clinic Liver Cancer; BICR, blinded independent central review; BOR, best overall response; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; EHS, extrahepatic spread; FACT-Hep, Functional Assessment of Cancer Therapy - Hepatobiliary; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; IMAE, immune-mediated adverse event; IRT, interactive response technology; LAG-3, lymphocyte activation gene 3; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PROMIS, Patient-Reported Outcome Measurement Information System; QoL, quality of life; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event, TTR, time to response.

[a] Please refer to Table 4-2 for more details on estimands.

[b] The "All Comer" population refers to all participants who were randomized using IRT in Part 1 and Part 2a of the study. Participants will be included in the treatment group to which they were randomized (see Table 10.3-1).

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[c] The "EHS-No" population refers to all participants who were randomized using IRT in Part 1 and Part 2 of the study with EHS-No status at study entry (see Table 10.3-1).

[d] The "EHS-No LAG-3" population refers to all participants who were randomized using IRT in Part 1 and Part 2 of the study with EHS-No status at study entry with LAG-3 positive (≥ 1% by IHC) status at the time of randomization, as entered into the IRT.

The estimands corresponding to the primary and secondary objectives are specified in Table 4-2.

Table 4-2: Estimands for the Primary and Secondary Endpoints

Endpoint	Population	Treatment	Intercurrent events (IE) /strategy	Population level summary	Note
Primary Objective					
RP2D	All DLT evaluable participants in triplet therapy and who had advanced/metastatic HCC and have not received prior systemic therapy	Triplet	[redacted]	Percent of participants with DLT among DLT evaluable population at each dose level	
ORR assessed by BICR using RECIST v1.1	All Comer population (Part 1 and Part 2a) at RP2D[a] with advanced/metastatic HCC who have not received prior systemic therapy	Triplet versus doublet		Difference of response rate and 90% Clopper-Pearson confidence interval by treatment group	Primary Estimand
ORR assessed by BICR using RECIST v1.1	All randomized participants (Part 1 and Part 2) at RP2D[a] with advanced/metastatic HCC who have not received prior systemic therapy with EHS-No status at study entry	Triplet versus doublet		Difference of response rate and 90% Clopper-Pearson confidence interval by treatment group	Primary Estimand

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Table 4-2: Estimands for the Primary and Secondary Endpoints

Endpoint	Population	Treatment	Intercurrent events (IE) /strategy	Population level summary	Note
Secondary Objective[b]					
PFS assessed by BICR using RECIST v1.1	All Comer population (all randomized in Part 1 and Part 2a) at RP2D[a] with advanced/metastatic HCC who have not received prior systemic therapy	Triplet versus doublet	[redacted]	Stratified HR based on Cox proportional hazard model	
PFS assessed by BICR using RECIST v1.1	All randomized (in Part 1 and Part 2) participants at RP2D[a] with advanced/metastatic HCC who have not received prior systemic therapy with EHS-No status at study entry	Triplet versus doublet		Stratified HR based on Cox proportional hazard model	

Abbreviations: BICR, Blinded Independent Central Review; DLT, dose-limiting toxicity; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; HR, hazard ratio; IE, intercurrent events; NA, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase 2 dose.

[a] If starting dose is RP2D, then all randomized participants; if dose de-escalation occurs during Safety Lead-in, all participants who are randomized at RP2D in triplet therapy and respective participants who are randomized to doublet therapy contemporaneously.

[b] The estimands for PFS, ORR and OS in all randomized LAG-3 positive (≥ 1% by IHC) participants are similar to corresponding endpoints in all randomized participants, except that these endpoints in all randomized LAG-3 positive participants are considered as subgroup analysis and unstratified HR for PFS and OS, and unstratified ORR difference will be applied.

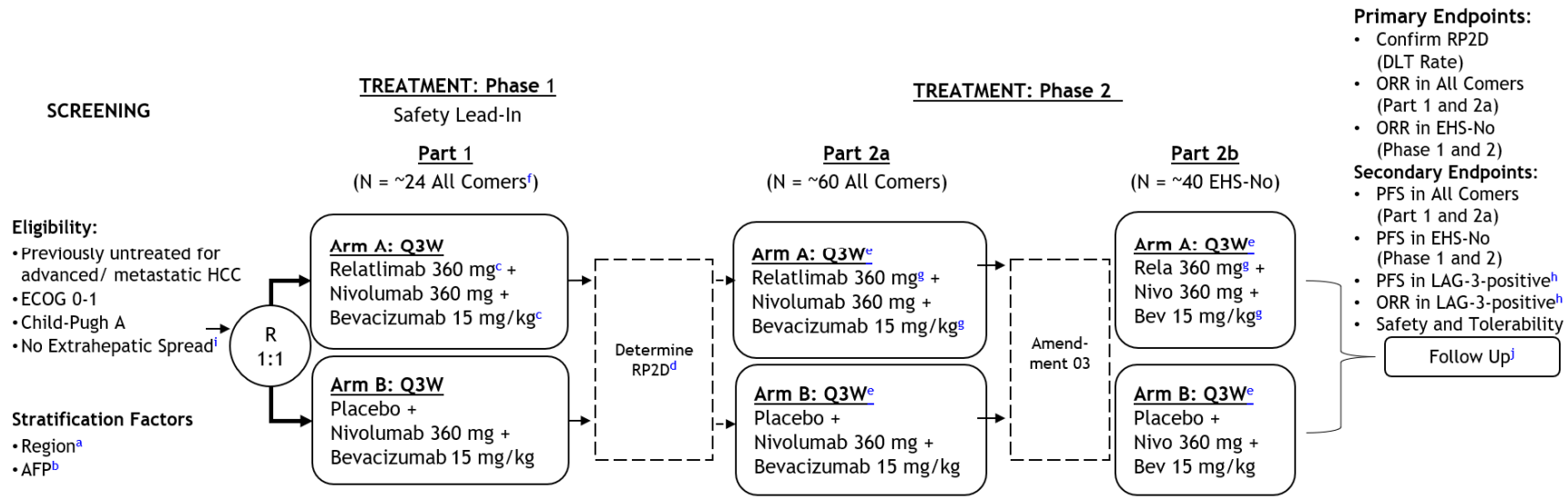
5 STUDY DESIGN

This is a site and participant blinded, placebo-controlled, randomized, Phase 1/2 study in adult participants (≥ 18 years) with advanced/metastatic HCC who have not received prior systemic therapy in the advanced/metastatic setting.

The study design schematic is presented in Figure 5-1.

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Figure 5-1: Study Design Schema



Abbreviations: AFP, alphafetoprotein; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; LAG-3, lymphocyte activation gene 3; N, number of study participants; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RP2D, recommended Phase 2 dose.

[a] Asia (excluding Japan) versus Rest of World (including Japan).

[b] < 400 ng/mL versus ≥ 400 ng/mL.

[c] De-escalate if needed.

[d] [redacted]

[e] Treat until disease progression, unacceptable toxicity, or withdrawal of consent, whichever occurs first.

[f] If de-escalation of relatlimab or bevacizumab is required, additional participants will be randomized in this phase.

[g] RP2D will be utilized.

[h] ≥ 1% by IHC.

[i] As of Protocol Amendment 03, enrollment will be restricted to EHS-No participants at study entry.

[j] All participants will be followed until death, loss to follow-up, withdrawal of consent, conclusion of study, or a minimum of 5 years.

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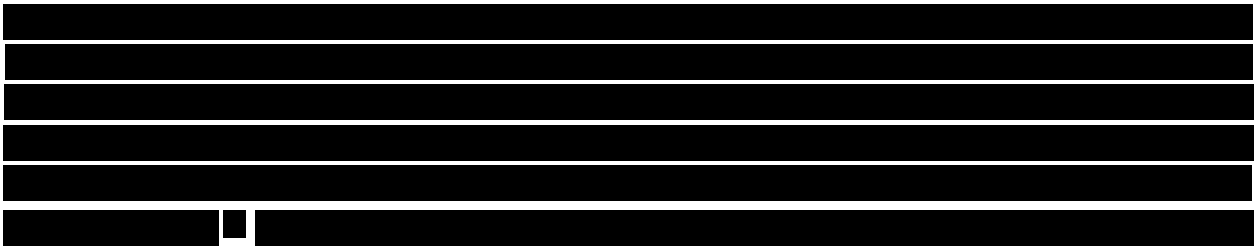
5.1 Overall Design

In this site and participant blinded randomized Phase 1/2 study, approximately 124 participants, including an expected minimum of 32 LAG-3 positive (≥ 1% by IHC) participants, will be randomized in a 1:1 ratio across 2 arms, and stratified by Region (Asia [excluding Japan] versus Rest of World [including Japan]) and alpha-fetoprotein (AFP). The two treatment arms are:

- **Arm A:** Relatlimab 360 mg + nivolumab 360 mg + bevacizumab 15 mg/kg IV infusions dose in 3-week cycles (Q3W)
- **Arm B:** Placebo + nivolumab 360 mg + bevacizumab 15 mg/kg IV infusions dose in 3-week cycles (Q3W).

Study Treatment will continue until progressive disease, unacceptable toxicity, or withdrawal of informed consent, whichever comes first. Treatment beyond initial radiographic progression will be allowed. In the event that bevacizumab is discontinued for toxicity, participants may continue treatment with IO agents, in the event that IO agents are discontinued, participants may continue treatment with bevacizumab, if Investigator determines that participant is receiving clinical benefit and after discussion with the medical Monitor if agreed upon by the Investigator and participant.

The Safety Lead-in will be considered the Phase 1 portion of the study, and enrollment following determination of the RP2D will be considered the Phase 2 portion of the study.



DLTs are evaluated for relatlimab in combination with nivolumab, and bevacizumab separately, so one drug might be de-escalated and the other might be expanded/stay. Note that dose de-escalation will only occur in Arm A. If the study is paused to fully evaluate the safety, then data from Arm B will supplement the interpretation of safety. No intra-patient dose de-escalation is allowed. Dose levels for de-escalated cohorts are described in Table 5.1-1.

Participants who experience a DLT attributed to bevacizumab will be allowed to continue on relatlimab and nivolumab doublet, after consultation with the BMS Medical Monitor. Participants who experience a DLT attributed to relatlimab and nivolumab combination therapy will be allowed to continue on bevacizumab, after consultation with the BMS Medical Monitor.

During the Safety Lead-in, additional safety assessments will be performed according to the Schedule of Activities in the full protocol. In the Phase 2 part of the study, enrollment will continue up to 124 total randomized participants at the RP2D. Only participants who are randomized at RP2D in triplet therapy and respective participants who are randomized to doublet therapy contemporaneously from the Safety Lead-in will count toward the 124. The primary endpoint for the Phase 2 part of the study is ORR by RECIST v1.1 per BICR, and will be assessed in both the

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All Comer population and in participants with EHS-No at study entry. [redacted] The trial is expected to continue irrespective of the efficacy outcome in this analysis. Sites and participants will remain blinded. The final ORR analysis is planned when approximately 124 participants have been treated and followed for at least 6 months (approximately 4 post-baseline scans).

Table 5.1-1: Arm A Dose Levels

Dose Level	Nivolumab Dose (Q3W)	Relatlimab Dose (Q3W)	Bevacizumab Dose (Q3W)
0[a]	360 mg	360 mg	15 mg/kg
-1[b]	360 mg	360 mg	7.5 mg/kg
-1[c]	360 mg	120 mg	15 mg/kg
-1[d]	360 mg	120 mg	7.5 mg/kg

Abbreviations: Q3W, every 3 weeks.

[a] Starting dose.

[b] If dose de-escalation is needed for bevacizumab related toxicity.

[c] If dose de-escalation is needed for immunotherapy related toxicity.

[d] If dose de-escalation is needed for both immunotherapy and bevacizumab related toxicity.

Tumor tissue must be obtained and submitted to central laboratory prior to randomization. See Section 6.1 (Inclusion Criteria) and Section 9.10 (Biomarkers) for specifications.

5.1.1 Dose Limiting Toxicities

For the purpose of guiding dose selection, DLTs will be defined based on the incidence, intensity, and duration of AEs that are possibly related to study treatment. The DLT period will be 6 weeks after initiation of study drug during the Safety-Lead in portion of the study. Toxicities that occur beyond the DLT period, and the overall safety profile of the combination, will be considered during safety review. The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

For the Safety Lead-in, participants must receive at least 1 dose of nivolumab, bevacizumab, and relatlimab (if randomized to Arm A) to be considered DLT-evaluable. Participants who withdraw from the study during the DLT evaluation period or have received less than the specified number of doses for reasons other than an AE that is at least possibly related to study treatment will not be considered as DLT-evaluable. Participants who are dose delayed during the DLT evaluation period for an AE that is at least possibly related to the study treatment should be considered as DLT-

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evaluable if they received at least 1 dose of the assigned regimen and were followed for at least 6 weeks after the first dose.

For the purpose of participant management, potential DLTs that occur at any time, will result in all study drug(s) being held pending evaluation of the event's relatedness to study drug, severity, and duration, and in accordance with Section 7.4.1 and Section 7.4.2. Participants must meet criteria for retreatment prior to reinitiation of study treatment (See Section 7.4.3).

Due to the distinct AE profiles of immunotherapy versus anti-VEGF monoclonal antibody therapy, DLT criteria will be defined for each component of the regimen separately based on the criteria below. Dose de-escalation decisions will be based on distinct DLTs in accordance with the DLT rules described below.

The Investigator may attribute the DLT to relatlimab + nivolumab, bevacizumab, or all three drugs.

If the DLT cannot be definitively attributed to any of the three drugs, then conservatively, they can be attributed to all three drugs based on Investigator's assessment.

If the Investigator believes a DLT is attributable to nivolumab, they may assign attributability to relatlimab due to the similarity in the known safety profiles based on Investigator's assessment. The Investigator may consult the BMS Medical Monitor and/or Worldwide Patient Safety Lead if needed. The incidence of DLT(s) during the 6-week DLT evaluation period will be used to help guide de-escalation decisions and to define RP2D.

5.1.1.1 DLTs Attributed to Bevacizumab

In addition to events specified below, any toxicity related to bevacizumab that results in a dosing delay > 42 days shall be considered a DLT.

General Toxicity

- GI perforation, any grade
- Nephrotic syndrome (any grade) or proteinuria (any grade) if associated with nephrotic syndrome (any grade)
- Infusion-related reaction, Grade 3/4
- Any Grade 5 event

[redacted]

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[redacted]

Neurologic Toxicity

- Posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS), any grade

Cardiovascular Toxicity

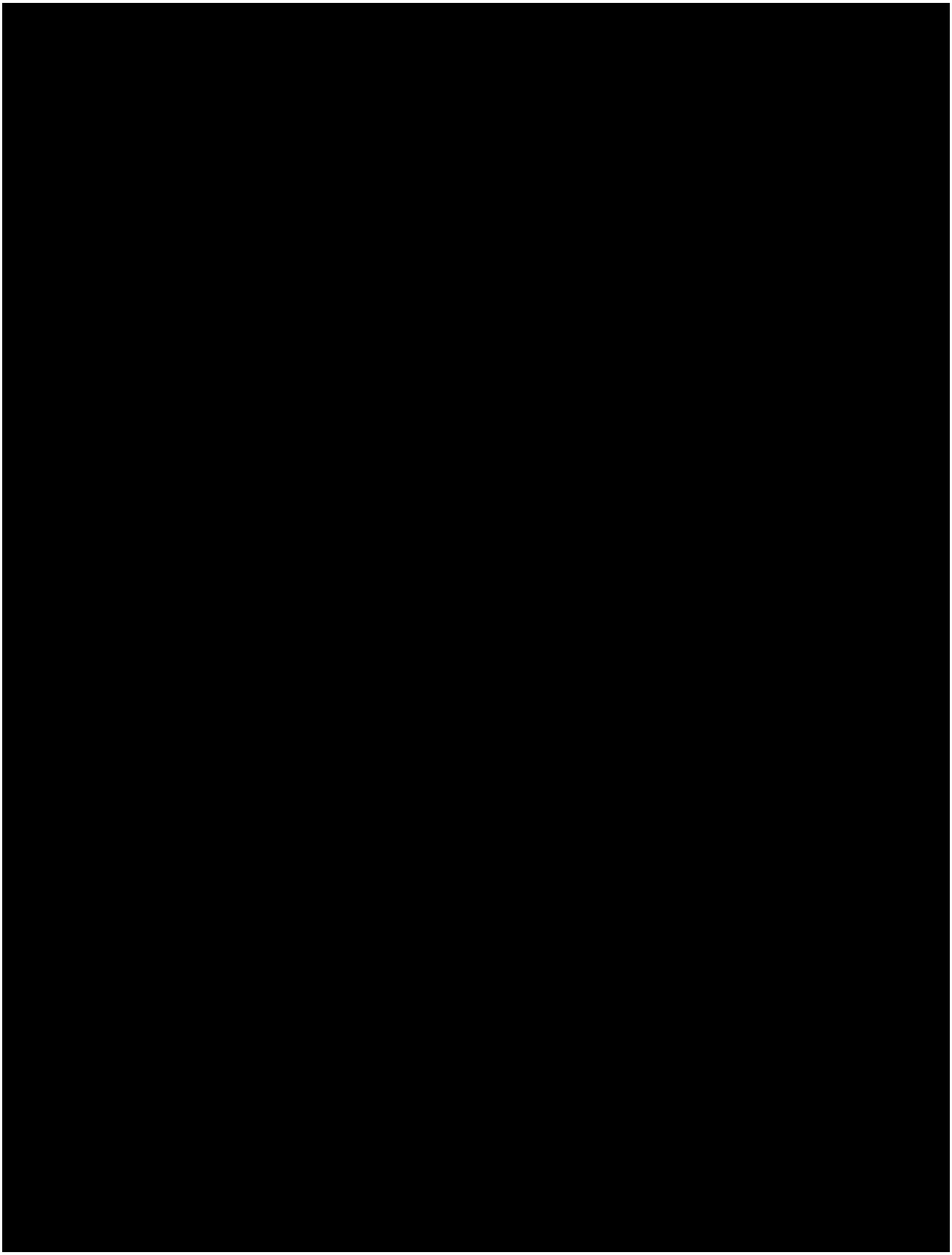
- Grade 3 uncontrolled hypertension
- Grade 4 hypertension
- Hypertensive crisis
- Hypertensive encephalopathy
- Any grade congestive heart failure or worsening of pre-existing heart failure

Bleeding/Thromboembolic Toxicity

- Arterial Thromboembolic Event, any grade
- Venous Thromboembolic Event, any grade
- Hemorrhage Grade 3 (noncerebral)
- Hemorrhage Grade 4 (or any cerebral)
- Wound dehiscence, any grade requiring medical or surgical therapy
- Necrotizing fasciitis, any grade
- Fistula formation involving any internal organ, any grade

[redacted]

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5.1.2 Follow-up Phase

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. Safety Follow-up Visit 1 occurs approximately 30 days (± 7 days) from the last dose of study treatment. Safety Follow-up Visit 2 occurs approximately 135 days (± 7 days) from 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, and those who have not yet had progressive disease (PD) as confirmed by BICR at the time of the End of Treatment (EOT) visit or at the time of study treatment discontinuation will continue to have radiologic and clinical tumor assessments per the protocol schedule (Section 2) after discontinuation of study treatment/EOT visit, until the start of subsequent therapy, BICR-confirmed 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 confirmed 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 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. The duration of this follow-up is up to 5 years following the last participant randomized for survival assessment. Subsequent therapies will also be recorded in this Survival Follow-up Period.

5.1.4 Data Monitoring Committee and Other Committees

5.1.4.1 Data Monitoring Committee

The original design of Study CA224106 was a double-blinded study utilizing an independent Data Monitoring Committee (DMC) to provide general oversight and safety considerations during Part 2. The protocol has been updated to unblind the Sponsor while keeping both sites and participants blinded, therefore eliminating the need for external committee oversight, allowing direct safety oversight from study team and enabling exploratory ORR assessments to support future decision-making. The internal Safety Committee's responsibility for assessing safety and efficacy in Part 1 will be extended to Part 2 and is described below in Section 5.1.4.2.

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5.1.4.2 Internal Safety Committee

An internal Safety Committee (SC) consisting of BMS research and development representatives (including clinical development, drug safety, and statistics) will regularly meet to evaluate the accumulating safety data of participants on the dose selection of the study and provide input to interpret safety signals and make a decision of dose de-escalation/stay. Decisions on safety, toxicity, and benefit-risk regarding each dose level in Phase 1 will be the responsibility of BMS and will take account of the totality of the data available, including data from other studies within the program. The SC will be responsible for determining the RP2D prior to transitioning into the Phase 2 portion of the study, where the SC will continue to be utilized to provide general oversight and safety considerations related to the conduct of Study CA224106.

The SC charter will further describe the procedures related to the committee operations in greater detail.

5.1.4.3 Blinded Independent Radiology Central Review

A blinded independent central review (BICR) is recommended by regulatory agencies in situations where clinical site image interpretation is variable, and results of image measurements are important for eligibility determination, safety, and/or efficacy endpoints. Specifically, BICR of scans may mitigate bias regarding endpoint assessment due to the subjectivity involved in lesion measurement and interpretation of ORR and PFS. Sites should submit all images to BICR on a continuing basis.

However, should the BICR interpretation be in conflict with the local evaluation, treatment decisions will be based on investigator assessment and not the BICR results provided to the site. See Section 9.1.1.3 for more information on BICR confirmation of progression.

5.1.4.4 Study Steering Committee

A Study Steering Committee (SSC), consisting of investigators and personnel members representing the Sponsor of the study, will be established to obtain scientific guidance and advice for the protocol and conduct of the study. Details of the SSC responsibilities and procedures will be specified in the SSC charter.

5.2 Number of Participants

If no dose de-escalation occurs and RP2D is the starting dose, then approximately 124 participants will be randomized, including all participants who are randomized from Safety Lead-in. If dose de-escalation occurs during the Safety Lead-in Phase, then only participants who are randomized to triple therapy at RP2D and respective participants who are randomized to doublet therapy contemporaneously will count toward the 124. It is estimated that approximately 200 enrolled participants will be required to achieve the 124 randomized. A minimum of 32 participants with LAG-3 positive (≥ 1% by IHC) tumors are expected to be randomized. During enrollment, the proportion of participants with positive LAG-3 expression will be monitored in a pooled fashion. Additional participants may be enrolled to get the expected minimum of 32 LAG-3 positive (≥ 1% by IHC) participants.

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5.3 End of Study Definition

The start of the trial is defined as the first participant first visit. End of trial is defined as the last participant last visit. Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected if this is not the same. A participant is considered to have completed the study if he/she has completed the last visit or the last procedure shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

Randomized 1:1 study designs are well established for Phase 2 studies. Nivolumab and bevacizumab doublet was chosen as the control arm in order to clearly demonstrate the added benefit of relatlimab as an add-on to this regimen.

The Safety Lead-in portion of the study uses a modified toxicity probability interval-2 (mTPI-2) design, which addresses many issues identified in its original toxicity probability interval (TPI) and mTPI designs. The mTPI-2 design, along with a similar Bayesian optimal interval (BOIN) design are part of a class of interval-based statistical designs for oncology dose escalation studies and are widely cited in the statistical literature. The mTPI-2 design was chosen for its flexibility with cohort sizes and easy-to-use table escalation/stay/de-escalation decision rule prospectively specified. For this study, escalation and stay will be combined as stay since escalation is not allowed in dose selection.

5.4.1 Rationale for Blinding

The study will be site and participant blinded in order to:

1) Minimize bias including but not limited to reporting, classification, and management of AEs
2) Limit bias for classification of progression between the arms (which could subsequently affect treatment duration between the arms and have an impact on the primary endpoint of PFS)

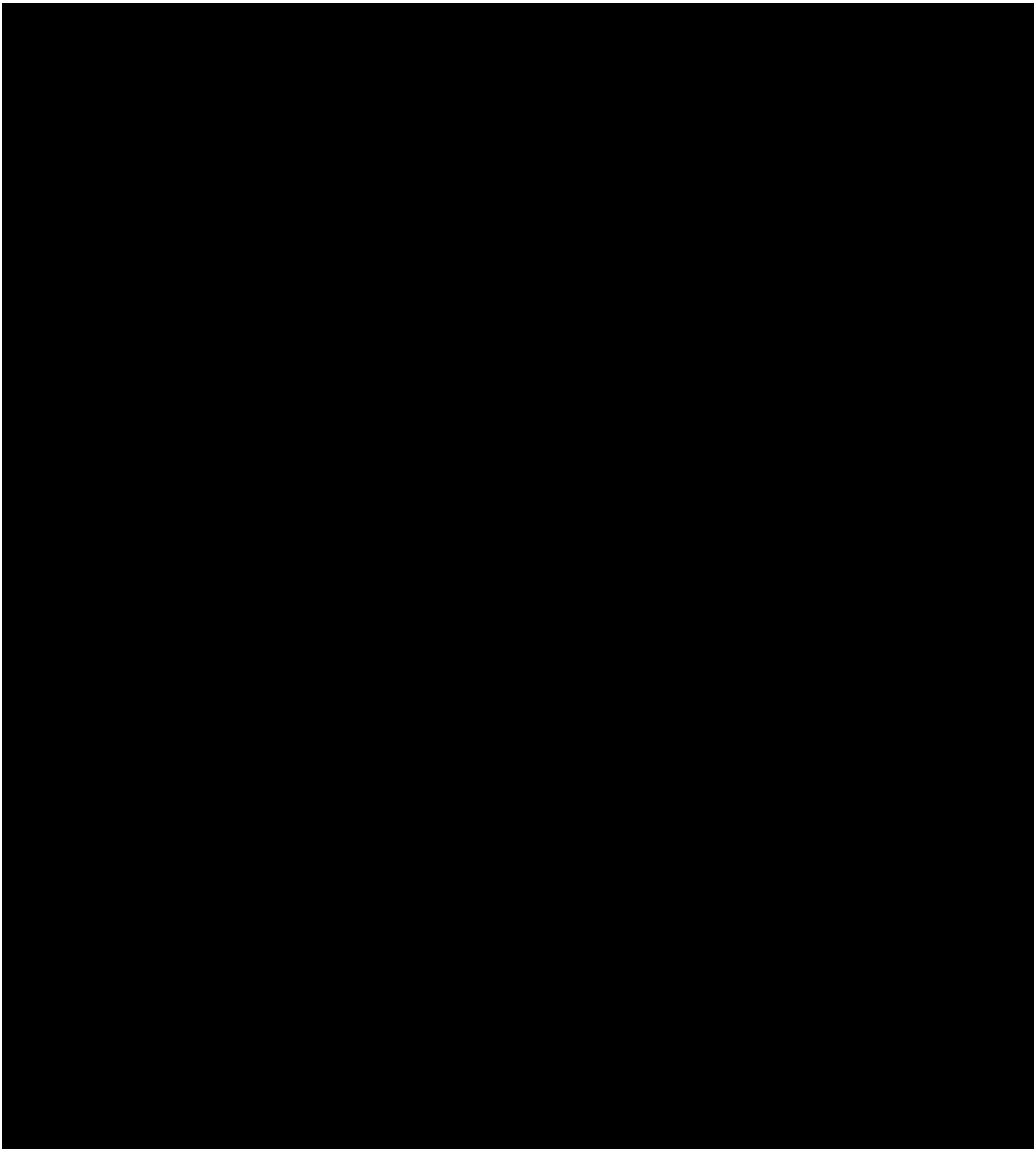
As participants who progress will not require knowledge of which treatment arm they were assigned to for selection of subsequent therapies, blinding will be maintained even after disease progression since the subsequent therapy would be the same for both arms. The Sponsor's central protocol team (including but not limited to clinical, statistics, and data management) will not be blinded to treatment assignment throughout the duration of the study. Safety Lead-in will be operated by an independent BMS team to determine RP2D. Measurement of the primary and secondary endpoints of ORR and PFS will be conducted by BICR (see Section 5.1.4.3), minimizing any bias from unblinded Sponsor personnel.

5.4.2 Rationale for Objective Response Rate as Primary Endpoint

Based on the current treatment landscape in treatment naive unresectable/metastatic HCC, ORR seems to be to the appropriate primary endpoint for this Phase 2 study because:

[redacted]

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5.4.3 Rationale for Choice of Comparators

Nivolumab and bevacizumab combination was selected as comparator arm to establish dose, efficacy, and safety of this combination as well as to provide contribution of component of relatlimab in this line and setting of liver cancer.

Atezolizumab in combination with bevacizumab is the current first line treatment for patients with unresectable HCC. IMbrave150 trial showed the improved OS as mentioned in Section 5.4.2 with

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manageable safety profile. The nivolumab and bevacizumab combination is expected to have similar efficacy and safety as atezolizumab plus bevacizumab according to similar mechanism of action.

5.4.4 Rationale for Use of Relatlimab in Combination with Nivolumab

The rationale for combining a LAG-3 inhibitor and an anti-PD-1/PD-L1 agent is based on the potential role of LAG-3 in T cell exhaustion and anti-PD-1 resistance.[20] Addition of the LAG-3 inhibitor, relatlimab to the PD-1 inhibitor nivolumab, may further enhance the overall clinical activity of single agent PD-1 pathway blockade, without significant addition of toxicity. The mechanism of action for both agents and preclinical data support the potential for producing clinical benefit. See Section 3.2 for more details on the mechanism of action and preclinical data of relatlimab and nivolumab. Preliminary data from a Phase 1/2a study of relatlimab (anti-LAG-3) and nivolumab (anti-PD-1) in combination showed promising clinical activity in participants with previously treated recurrent or metastatic melanoma, with a safety profile similar to nivolumab monotherapy.

5.4.5 Rationale for Duration of Treatment

The optimal duration of treatment is well established with immuno-monotherapies. There are data supporting 2 immunotherapy combinations, but currently there is no established evidence with anti-PD-L1 and bevacizumab combination regimen duration of treatment and also currently there is not enough data to support duration of treatment estimation with nivolumab and relatlimab combination regimen.

This study will be conducted until patients are experiencing clinical benefit in the opinion of Investigator, or unacceptable toxicity is evidenced or withdrawal of informed consent.

5.4.6 Rationale for Stratification Factors

Participants will be stratified treatment arms by:

Region (Asia [excluding Japan] versus rest of the world [including Japan])
AFP (< 400 ng/mL versus ≥ 400 ng/mL).

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 versus non-infectious etiology. Based on World Health Organization data, the prevalence of HCV is highest in the eastern Mediterranean region (> 2%), and HBV prevalence is 2% to 7% in Mediterranean countries, Japan, central Asia, the Middle East, and parts of South America. 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.[92] The IMbrave 150 and CHECKMATE-459 studies stratified by region, including Japan to the rest of the world. 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.

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Higher AFP levels are related to more aggressive cancer phenotypes and linked with hepatic cancer cells that have stem/progenitor features. Depending on the clinical setting, AFP cutoff levels of 20, 200, 400, and 1000 ng/mL have been examined to assess the prognostic effect of AFP on long-term survival, mostly in a retrospective setting. A prospective propensity model study analyzed the prognostic ability of 4 different cutoffs of AFP in 2,579 unselected HCC patients. The study showed the independent predictive ability of baseline serum AFP levels. Patients with baseline AFP levels ≥ 400 ng/mL had notably lower survivals than patients with lower values. The researchers recommended AFP cutoff levels of 20 and 400 ng/mL as feasible cutoffs to predict long-term survival outcome in unselected patients.[93] The lower cut-off of 20 ng/mL is the upper limit of normal (ULN) for AFP and is more relevant to studies in early-stage HCC. Patients with intermediate-stage disease are more likely to have elevated AFP levels. In addition to AFP being a well-known prognostic factor, results from REFLECT trial suggest a differential treatment effect of lenvatinib and sorafenib according to AFP values, with worse survival outcomes observed in those patients with higher levels in both arms but a higher survival benefit observed with lenvatinib compared to sorafenib in patients with higher AFP values.[94] In IMbrave150 trial better OS and PFS benefit was observed patients with < 400 ng/ml. This study will use a cut-off level of 400 ng/mL for stratification.

[redacted]

5.5 Justification for Dose

The relatlimab dose of 360 mg Q3W was selected to be evaluated in co-administration with 360 mg nivolumab Q3W + bevacizumab 15 mg/kg Q3W. Additionally, 360 mg Q3W of nivolumab will be evaluated in combination with bevacizumab 15 mg/kg Q3W regimen to determine the contribution of components.

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5.5.1 Justification for Nivolumab Dose

The nivolumab dose of 360 mg Q3W was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) was used.

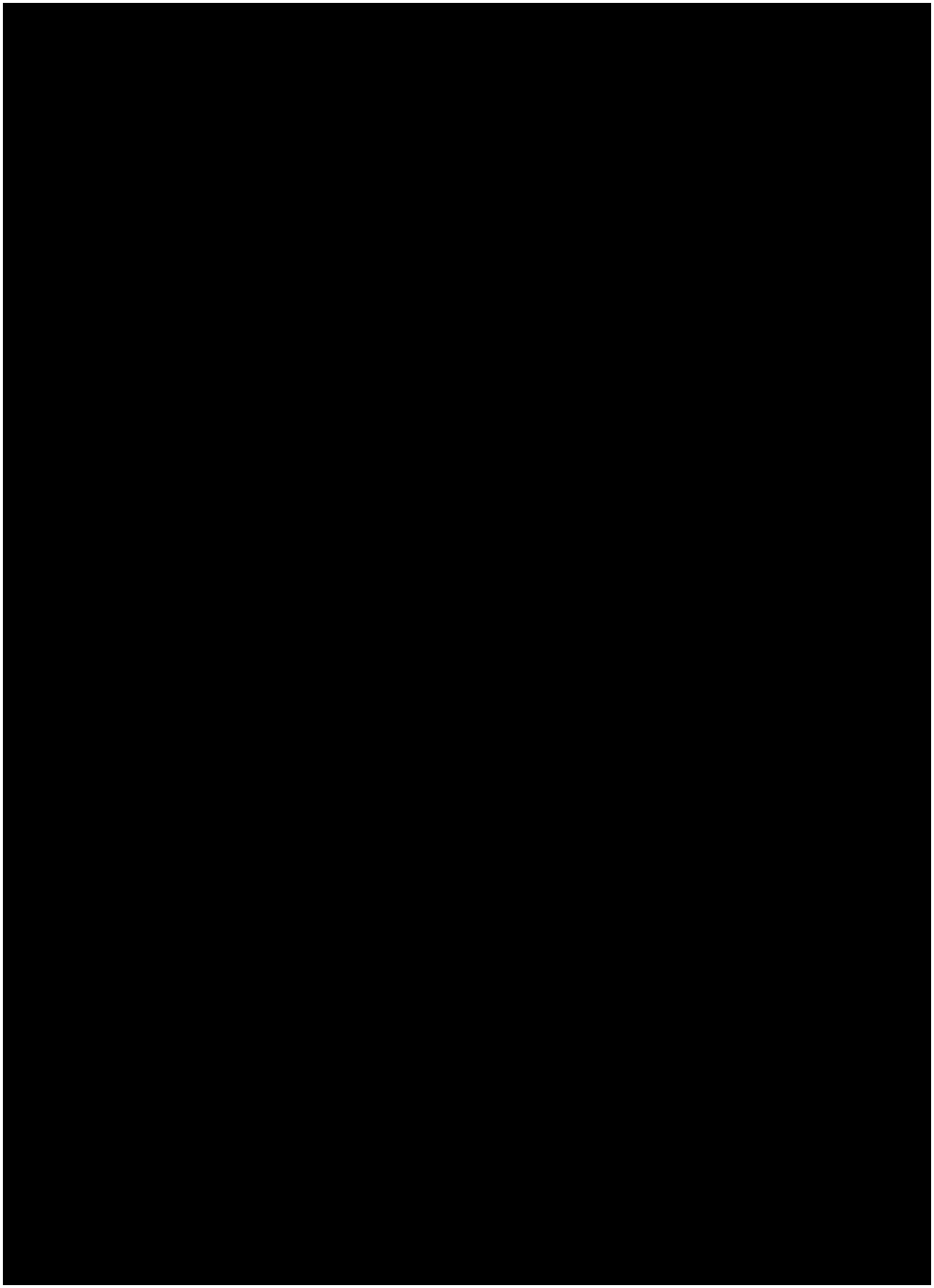
Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W, and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications.[5, 95] Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

The benefit-risk profiles of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and exposure-response relationships across indications. Population PK (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W. The simulated average serum concentration at steady state [Cavgss] following administration of nivolumab 360 mg Q3W and 480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to patients over a wide body weight range (34-180 kg) across tumor types.

Extensive exposure-response (E-R) analyses of multiple PK measures (maximum serum concentration at Day 1 [Cmax1], average serum concentration at Day 28 [Cavg28], and trough serum concentration at Day 28 [Cmin28]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen are similar to that of 3 mg/kg Q2W IV regimen. In E-R efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using Cavg28 as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV 480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade 3+, and immune-mediated AEs (IMAEs) Grade 2+ are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

Additional details on nivolumab posologies and risk-benefit can be found in the IB.

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[redacted]

5.5.3 Justification for Bevacizumab Dose

Bevacizumab, at a dose of 15 mg/kg Q3W, in combination with atezolizumab is the currently approved dose regimen for the treatment of 1L advanced/metastatic HCC. In this study, the same dose of bevacizumab will be administered in combination with relatlimab and nivolumab, as well as in combination with nivolumab only to determine the contribution of components.

In the event of a bevacizumab-related dose-limiting toxicity, the bevacizumab dose will be de-escalated to 7.5 mg/kg Q3W. Based on the linear kinetics of bevacizumab observed between 1-20 mg/kg dose range, a Q3W dose of 7.5 mg/kg is expected to have roughly half of the exposure of the 15 mg/kg Q3W dose[54] Bevacizumab, at a dose of 7.5 mg/kg Q3W, has been approved for the treatment of metastatic colorectal cancer (CRC) in combination with chemotherapy.

5.6 Clinical Pharmacology Summary

5.6.1 Nivolumab Clinical Pharmacology Summary

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for single-agent nivolumab.

Nivolumab as a single agent: The PK of single-agent nivolumab has been studied in patients 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 intravenous infusion every 2 or 3 weeks. Nivolumab clearance (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 patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance 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 (Versuss) (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 every 2 weeks, 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 every 2 weeks. The predicted exposure (Cavg and Cmax) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Specific Populations: The population PK analysis suggested that the following factors had no clinically important effect on the clearance 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 clearance of nivolumab was evaluated by a population PK analysis in patients with mild (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 clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (T.bili less than or equal to the ULN and AST greater than ULN or T.bili greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (T.bili greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment. Full details on the clinical pharmacology aspects of nivolumab can be found in the IB and product label.



6 STUDY POPULATION

Adult (≥ 18 years) participants with Child-Pugh A cirrhosis and with histologically confirmed advanced/metastatic HCC of any etiology (hepatitis C virus [HCV]-HCC, hepatitis B virus [HBV]-

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HCC, or non-viral related-HCC) who are naive to systemic therapies in the advanced/metastatic setting. **Note**: As of Protocol Amendment 03, participants with extrahepatic spread (EHS) of disease are not eligible. EHS is defined as presence of metastatic disease in lymph nodes or distant sites outside the liver.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

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

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

2) Type of Participant and Target Disease Characteristics

a) Naïve to systemic therapy for advanced/metastatic HCC

i) Note: Prior neo-adjuvant or adjuvant immunotherapy is permitted if recurrence occurs ≥ 6 months after treatment completion and the case is discussed with the BMS medical monitor or designee

b) Participants must have advanced/metastatic HCC, defined as:

i) Disease must not be amenable to curative surgical and/or locoregional therapies, or experienced progressive disease after surgical and/or locoregional therapies

ii) Patients who received prior local therapy (eg, radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) are eligible provided the target lesion(s) have not been previously treated with local therapy or the target lesion(s) within the field of local therapy have subsequently progressed in accordance with RECIST version 1.1.

(1) Note: For those participants who progressed after locoregional therapy, the locoregional procedure must have been completed at least 4 weeks prior to the screening imaging tests. In addition, all acute toxic effects of the locoregional procedure must have resolved to NCI CTCAE version 5.0 Grade ≤ 1.

c) Participants must have histologic confirmation of advanced/metastatic HCC.

d) **Not applicable per Protocol Amendment 03:** Participants who are LAG-3 evaluable by IHC. Participants with indeterminate or unevaluable LAG-3 status results will not be permitted to receive study treatment or randomize to a treatment arm (pre-screening ICF is suggested).

e) Tumor Tissue Requirements

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

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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.

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] Fine needle aspirates or other cytology samples and biopsies of bone lesions are not acceptable. Note the following for the required tumor sample:

(1) Samples should be collected within 3 months of enrollment with no intervening systemic anti-cancer treatment between time of acquistion and randomization.

(2) If a recently collected tumor sample (as described above) is not available, then a fresh pretreatment biopsy may be obtained. This fresh biopsy should be excisional, incisional, or core needle.

(3) 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.

(4) Tumor sample must be sent to the central laboratory. Central laboratory must provide IRT with confirmation of tissue receipt for randomization/treatment.

**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.*

Please see Section 9.10 (Biomarkers) for additional information.

f) Participants must have at least 1 measurable lesion as defined by RECIST v1.1 criteria (see Appendix 10) for response assessment.

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) Participants with previously locally treated lesions as the sole site of measurable disease will be permitted to enroll provided that the lesion(s) have demonstrated clear progression prior to the time of informed consent and can be measured accurately.

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

i) HBV-HCC:

(1) Resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen), OR

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

ii) HCV-HCC:

(1) Resolved HCV infection as evidenced by detectable antibody and undetectable HCV RNA, OR

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(2) Chronic HCV infection as evidenced by detectable HCV RNA.

h) Child-Pugh score of 5 or 6 (ie, Child-Pugh A).

i) Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1.

j) Barcelona Clinic Liver Cancer (BCLC) staging B or BCLC staging C without extrahepatic spread (EHS). EHS is defined as presence of metastatic disease in lymph nodes or distant sites outside the liver.

k) Life expectancy ≥ 3 months.

3) Age of Participant

a) Participant must be 18 years of age, or age of majority, at the time of signing the informed consent.

4) Laboratory Values

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

b) Adequate hematologic function:

i) WBC ≥ 2,000/μL (stable, off any growth factor within 4 weeks of study treatment administration)

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

iii) Hemoglobin ≥ 9.0 g/dL (without transfusion for at least 2 weeks)

iv) Platelet count ≥ 75 × 10^3/μL (transfusion or the use of platelet-stimulating agents to achieve this level is not permitted).

c) Adequate hepatic function:

i) Serum albumin ≥ 2.8 g/dL (transfusion to meet this level is not permitted)

ii) Serum T.bili ≤ 3 mg/dL

iii) Serum Aspartate Aminotransferase (AST) ≤ 5× ULN

iv) Alanine Aminotransferase (ALT) ≤ 5× ULN

d) Prothrombin time (PT)-international normalized ratio (INR) or aPTT ≤ 2.0× ULN for patients not receiving anticoagulation

e) Adequate renal function, defined as a serum creatinine of ≤ 1.5× ULN OR a creatinine clearance (CrCl) ≥ 50 mL/min (Cockcroft-Gault formula):

i) Female CrCl (mL/min) = [(140- age in years) x weight in kg x 0.85] / [72× serum creatinine in mg/dL]

ii) Male CrCl (mL/min) = [(140- age in years) x weight in kg x 1.00] / [72× serum creatinine in mg/dL]

iii) Proteinuria < 2+ measured by urine dipstick (within 7 days prior to initiation of study treatment). Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate < 1 g of protein in 24 hours.

f) 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

5) Reproductive Status

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Investigators shall counsel women of childbearing potential (WOCBP), and male participants who are sexually active with 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 intervention.

a) Female Participants

i) Female participants must have documented proof that they are not of childbearing potential.

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

iii) WOCBP must have a negative highly sensitive urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study intervention. 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.

iv) Additional requirements for pregnancy testing during and after study intervention are located in Schedule of Activities.

v) 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.

vi) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

vii) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP, OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 6 months and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

b) Male Participants

i) Male participants should maintain their usual practice regarding contraception (if any); however, no specific or additional contraceptive measures are required.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply.

1) Medical Conditions

a) Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.

b) Prior allogenic stem cell or solid organ transplantation.

c) 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

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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.

d) Leptomeningeal metastases.

e) Uncontrolled tumor-related pain

f) Participants with clinically significant ascites as defined by:

   i) Prior ascites that required treatment and requires on-going prophylaxis, OR

   ii) Current ascites requiring treatment.

g) Participants with evidence of portal hypertension as defined by:

   i) Episode of hepatic encephalopathy (≥ Grade 2) within 12 months prior to randomization.

   ii) Presence of portal hypertension with history of high-risk of bleeding due to untreated or incompletely treated esophageal or gastric varices within 6 months of randomization. Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone an EGD within 6 months of prior to initiation of study treatment do not need to repeat the procedure.

h) Prior disease history with increased risk of bleeding as defined by:

   i) Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).

   ii) A prior bleeding event due to esophageal and/or gastric varices within 6 months prior study treatment initiation.

   iii) History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment.

   iv) History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction including sub-occlusive disease related to the underlying disease or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding prior to initiation of study treatment. Patients with signs/symptoms of sub-/occlusive syndrome/intestinal obstruction at time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.

   v) History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment that increases risk of bleeding, including but not limited to active peptic ulcer disease, diverticulitis, or colitis.

   vi) Radiographic evidence of metastatic disease of large volume with high risk of rupture of major blood vessels or airways with the bevacizumab treatment.

   vii) Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study.

   viii) Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture

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ix) History of hemoptysis (half tablespoon [≥ 2.5 mL] of bright red blood per episode) within 1 month prior study initiation)

x) Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to the first dose of bevacizumab

i) Cardiovascular Disease

i) Inadequately controlled arterial hypertension (defined as systolic blood pressure (BP) ≥ 150 mmHg and/or diastolic blood pressure > 100 mmHg), based on an average of ≥ 3 BP readings on ≥ 2 sessions

(1) Anti-hypertensive therapy to achieve these parameters is allowable.

ii) Prior history of hypertensive crisis or hypertensive encephalopathy

iii) Elevated Troponin (See Exclusion Criteria 3a)

iv) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

(1) History of myocarditis, regardless of etiology

(2) Myocardial infarction or stroke/transient ischemic attack within 3 months prior to consent

(3) Uncontrolled angina

(4) Unstable arrhythmias

(5) Significant vascular disease, including but not limited to recent peripheral arterial thrombosis, aortic aneurysm requiring surgical repair within 6 months prior to study initiation.

j) Infections

i) Participants with active co-infection with:

(1) Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV deoxyribonucleic acid (DNA) and HCV ribonucleic acid (RNA), OR

(2) Hepatitis D infection in participants with HBV.

ii) Active bacterial or fungal infections requiring systemic treatment within 7 days prior to study drug dosing.

iii) 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.

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(5) NOTE: Testing for HIV must be performed at sites where mandated locally. HIV-positive participants must be excluded where mandated locally (refer to country-specific Appendix 8).

iv) Active SARS-CoV-2 infection.

v) 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.

k) 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.

l) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the patient 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.

m) 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.

n) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

o) Participants with serious or uncontrolled medical disorders, other than the disease under study.

p) Reproductive Status
   i) Women who are breastfeeding.
   ii) Women with a positive pregnancy test at enrollment or prior to administration of study medication.

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

2) Prior/Concomitant Therapy

a) Prior treatment with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways in advanced/metastatic setting (prior adjuvant/neoadjuvant immunotherapies are allowed if recurrence occurs ≥ 6 months after treatment completion).

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

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c) Radiotherapy within 28 days and abdominal/ pelvic radiotherapy within 60 days prior to initiation of study treatment, except palliative radiotherapy to bone lesions within 7 days prior to initiation of study treatment. Participants must have recovered (ie, Grade ≤1 or at baseline) from radiation-related toxicities prior to first study treatment.

d) 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]).

e) 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).

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

g) 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.

h) Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1 for prohibited therapies.

i) Anticoagulant therapies

   i) Use of warfarin or Coumadin-like products is not permitted at all (includes for prophylactic use). See Section 7.7.1 (Prohibited Concomitant Treatment).

   ii) Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose.

   iii) Prophylactic anticoagulation for the patency of venous access devices is allowed so long as the activity of the agent results in an INR < 1.5x ULN and aPTT is within normal limits within 14 days prior to initiation of study treatment. Prophylactic use of unfractionated heparin or low molecular-weight heparin (ie, enoxaparin 40 mg/day) is allowed. *For prophylactic use of anticoagulants or thrombolytic therapies, local label approved dose levels may be used.*

   iv) Current or recent (within 10 days of first dose of study treatment) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol.

   v) Concomitant chronic use of NSAIDs while receiving study drugs is prohibited. However, for the symptomatic relief of medical conditions (eg, headache, fever) sporadic or short-term intake of oral NSAIDs is allowed, when co-administered proton pump inhibitors to reduce potential GI damage.

vi) Current use of full dose anticoagulants or thrombolytic therapy at therapeutic doses. However, if a patient experiences a venous thromboembolism (VTE) event while still receiving study drug treatment, it may still be possible for the patient to remain on study medication despite anticoagulation treatment (See Table 7.4.2-1).

3) Physical and Laboratory Test Findings

a) Troponin T (TnT) or I (TnI) > 2× institutional ULN.

i) Participants with TnT or TnI levels between > 1 to 2× ULN will be permitted if repeat levels within 24 hours are ≤ 1 ULN. If TnT or TnI levels are between >1 to 2× ULN within 24 hours, the participant must be evaluated by a cardiologist. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT or TnI repeat levels beyond 24 hours are < 2× ULN, the participant must be evaluated by a cardiologist.

ii) After cardiologist evaluation, the participant may be considered for randomization if the Investigator assesses a favorable benefit/risk. Notification of the decision to enroll the participant has to be made to the BMS Medical Monitor or designee.

b) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population.c) Positive pregnancy test at enrollment or prior to administration of study medication.

4) Allergies and Adverse Drug Reaction

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

5) Other Exclusion Criteria

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

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.

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6.4.1 Retesting During Screening or Lead-in Period

Participant Re-enrollment: This study permits the re-enrollment of a participant who was considered a pretreatment failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in 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, because 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,
  - At least 24 hours have passed since last fever without the use of fever-reducing medications,
  - Acute symptoms (eg, cough, shortness of breath) have resolved,
  - In the opinion of the Investigator and in consultation with the Medical Monitor or Clinical Scientist, there are no COVID-19-related sequelae (eg, cardiovascular) that may place the participant at a higher risk of receiving investigational treatment,
  - Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local, or regional guidelines.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1.1-1.

An IP, also known as IMP in some regions, is defined 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 from the

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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 -IPs/AxMPs.

7.1 Study Interventions Administered

Begin study treatment within 3 calendar days of randomization.

Arm A: Participants will receive masked relatlimab (360 mg) nivolumab (360 mg) and, followed by masked/unmasked* bevacizumab 15 mg/kg on Day 1 of every 3-week cycle. Relatlimab will be co-administered with nivolumab in a single bag IV over 30 minutes, participants weighing less than 45 kg will receive infusion over 90 minutes. Bevacizumab will be administered over a duration of 90 minutes following immunotherapy until safety is established (infusion tolerated by participant without infusion-related reaction); once safety is established subsequent infusions will be shortened to 60 minutes and then to 30 minutes if tolerated. If needed, flush the intravenous line with an appropriate amount of diluent (eg. 0.9% sodium chloride) to ensure that the complete dose is administered.

Arm B: In order to maintain site and participant blinding, participants will receive masked nivolumab (360 mg) and placebo (normal saline solution 0.9) IV also over 30 minutes, participants weighing less than 45 kg will receive infusion over 90 minutes, followed by masked/unmasked* bevacizumab 15 mg/kg on Day 1 of every 3-week cycle. Bevacizumab will be administered over a duration of 90 minutes following immunotherapy until safety is established; once safety is established subsequent infusions will be shortened to 60 minutes and then to 30 minutes if tolerated. If needed, flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride) to ensure that the complete dose is administered.

Participants should be carefully monitored for infusion reactions during co-administration. Bevacizumab 15 mg/kg is administered following immunotherapy with a minimum of 5 minutes between dosing.

There will be no intra-participant dose escalations or reductions of nivolumab and relatlimab or bevacizumab combination therapy is allowed. For Q3W dosing cycles, participants may be dosed no less than 19 days from the previous dose. Premedications are not recommended for the first dose of any study therapy.

Monitor participants carefully for infusion reactions during administration. If an acute infusion reaction is noted, manage participants according to Section 7.4.5.

Doses of study drug(s) may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Care must be taken to ensure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

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All windows related to dosing or procedures should always be based on calendar days versus business days.

For details regarding relatlimab and nivolumab and bevacizumab storage, preparation and administration, please refer to the current respective IBs and/or Pharmacy Manuals.

*Refer to Section 7.3 for details of bevacizumab blinding and unblinding.

7.1.1 Nivolumab Combined with Bevacizumab and/or Relatlimab Administration

Participants will receive nivolumab and relatlimab, followed by bevacizumab on Day 1 of every 3-week cycle. In Arm A nivolumab will be co-administered with relatlimab in a single bag IV over approximately 30 minutes. In Arm B nivolumab will be co-administered with placebo in a single bag IV over approximately 30 minutes. Participants should be carefully monitored for infusion reactions during co-administration. If an acute infusion reaction is noted, participant should be managed according to Section 7.4.5. There will be no dose escalations or reductions of immunotherapy allowed unless the Safety Committee makes the decision based on DLT assessment.

Premedications are not recommended for the first dose of immunotherapy.

Participants should be carefully monitored for infusion reactions during immunotherapy administration.

If an acute infusion reaction is noted, participants should be managed according to Section 7.4.5.

Participants should receive immunotherapy until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Doses of immunotherapy and bevacizumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment according to [redacted] and Table 7.4.2-1.

Dosing visits must not be skipped, only delayed. See Sections 7.4.1, 7.4.2, and Section 8.1 (Discontinuation Criteria).

The assessment for discontinuation of immunotherapy (nivolumab + relatlimab/nivolumab + placebo) should be made separately from the assessment to discontinue bevacizumab therapy.

If criteria for discontinuation of immunotherapy (nivolumab + relatlimab/nivolumab + placebo) are met, bevacizumab therapy may continue until progression, unacceptable toxicity, or withdraw of informed consent, whichever occurs first.

If criteria for discontinuation of bevacizumab therapy are met, immunotherapy (nivolumab + relatlimab/nivolumab + placebo) may continue until progression, unacceptable toxicity, the study ends, or withdraw of informed consent, whichever occurs first.

If a participant meets criteria for discontinuation and the Investigator is unable to determine whether the event is related to all or any 1 study drug, the participant should discontinue all study treatment and be taken off the treatment phase of the study.

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The immunotherapy (nivolumab + relatlimab/nivolumab + placebo) injections can be infused diluted. All infusions must be promptly followed by a diluent flush to clear the line of investigational (IP) before starting the bevacizumab infusion(s).

The second infusion will always be bevacizumab and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred. The time between immunotherapy (nivolumab + relatlimab/nivolumab + placebo) and bevacizumab infusions is expected to be approximately 5 minutes, but may be more depending on the situation (ie, infusion reactions and/or safety assessments). Instructions for dilution and infusion of immunotherapy 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 and/or Pharmacy Manual. The selection and timing of dose for each participant is provided in Table 7.1.1-1 and Table 7.1.1-2.

Study treatment will be dispensed by IRT at the study visits as listed in Section 2 (Schedule of Activities). Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

Table 7.1.1-1: Study Interventions: Arm A

Arm A	Nivolumab	Relatlimab	Bevacizumab
Intervention Name	Nivolumab (BMS-936558)	BMS-986016	Bevacizumab (biosimilars not permitted)
Type	Biological	Biological	Biological
Dose Formulation	Injection	Injection	Injection
Unit Dose Strength(s)	[redacted] mg/mL	[redacted] mg/mL	25 mg/mL
Dosage Level(s)	360 mg Q3W	360 mg Q3W or 120 mg Q3W	15 mg/kg Q3W or 7.5 mg/kg Q3W
Route of Administration	IV infusion	IV infusion	IV infusion
Use	Experimental	Experimental	Experimental
IMP and Non-IMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Central sourcing / Local sourcing hybrid (based on region)
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement

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Table 7.1.1-1: Study Interventions: Arm A

Arm A	Nivolumab	Relatlimab	Bevacizumab
Current/Former Name(s) or Alias(es)	BMS-936558 Nivolumab	BMS-986016 Relatlimab	Bevacizumab

Abbreviations: AxIMP, auxiliary medicinal product; BMS, Bristol-Myers Squibb Company; IMP, investigational medicinal product; IV, intravenous; Q3W, every 3 weeks.

Table 7.1.1-2: Study Interventions: Arm B

Arm B	Placebo	Nivolumab	Bevacizumab
Intervention Name	Normal Saline (not provided by Sponsor)	Nivolumab (BMS-936558)	Bevacizumab (biosimilars not permitted)
Type	NA	Biological	Biological
Dose Formulation	NA	Injection	Injection
Unit Dose Strength(s)	NA	[redacted] mg/mL	25 mg/mL
Dosage Level(s)	NA	360 mg Q3W	15 mg/kg Q3W
Route of Administration	NA	IV infusion	IV infusion
Use	NA	Experimental	Experimental
IMP and Non-IMP/AxMP	NA	IMP	IMP
Sourcing	NA	Provided centrally by the Sponsor	Central sourcing / Local sourcing hybrid (based on region)
Packaging and Labeling	NA	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement
Current/Former Name(s) or Alias(es)	NA	BMS-936558 Nivolumab	Bevacizumab

Abbreviations: AxIMP, auxiliary medicinal product; BMS, Bristol-Myers Squibb Company; IMP, investigational medicinal product; IV, intravenous; NA, not applicable; Q3W, every 3 weeks.

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.[96] 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 radiation 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) 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 Study Intervention Assignment

All participants will be centrally randomized using Interactive Response Technology (IRT). Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by calling the IRT to obtain a participant number. Every participant that signs the ICF must be assigned a participant number in IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document. The Investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS.

The following information is required for enrollment:

Date that informed consent was obtained

Date of birth, where applicable by local regulations

Gender at birth

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

- Participant number

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- Year of birth
- Region (Asia [excluding Japan] versus Rest of world [including Japan])
- Confirmation from central laboratory that screening tissue sample has been received
- Baseline AFP level (< 400 ng/mL versus ≥ 400 ng/mL)

Participants will be randomized in 1:1 ratio and stratified by following factors:

- Region (Asia [excluding Japan] versus Rest of world [including Japan])
- Baseline AFP level (< 400 ng/mL versus ≥ 400 ng/mL)

The randomization procedures will be carried out via permuted blocks within each stratum. The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

Both Part 1 and Part 2 in the study are site and participant blinded. The Sponsor will not be blinded. Access to treatment codes will be restricted from all participants and site personnel. As this is a Phase 1/2 signal-seeking study, assessment of preliminary safety and efficacy signals for further development planning is essential. In order to assess and understand emerging safety and efficacy data, the study will remain unblinded to the Sponsor. Bevacizumab will be administered as open label if bevacizumab dose is the same between triplet and doublet therapies. If bevacizumab is de-escalated in triplet therapy, then bevacizumab will be blinded in order to keep trial site and participant blinded.

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

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

For this study, the method of unblinding for emergency purposes is through the IRT. Please consult the IRT manual for further information on how to unblind in an emergency.

Any request to unblind a participant for nonemergency purposes should be discussed with the Medical Monitor.

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7.4 Dose Modification

No dose modifications for relatlimab, nivolumab, or bevacizumab are permitted. Causality of adverse events should be assessed for immunotherapy (nivolumab and relatlimab combination) and for bevacizumab therapy separately. Dose delay and discontinuation criteria should be applied separately for nivolumab and relatlimab combination therapy and for bevacizumab therapy.

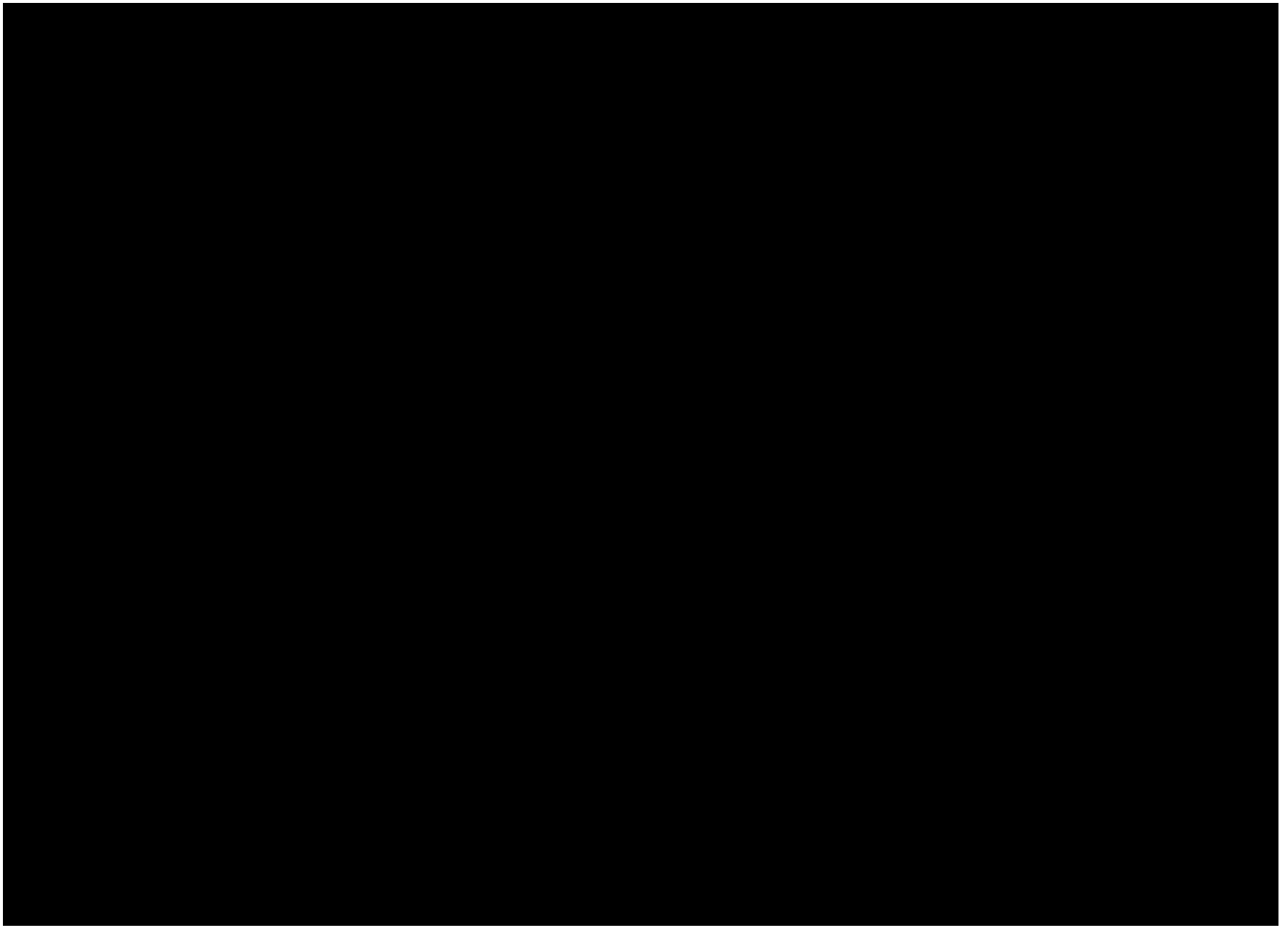
Delay dosing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, either confirmed or suspected.

7.4.1 Dose Delay/Discontinuation Criteria for Relatlimab and Nivolumab

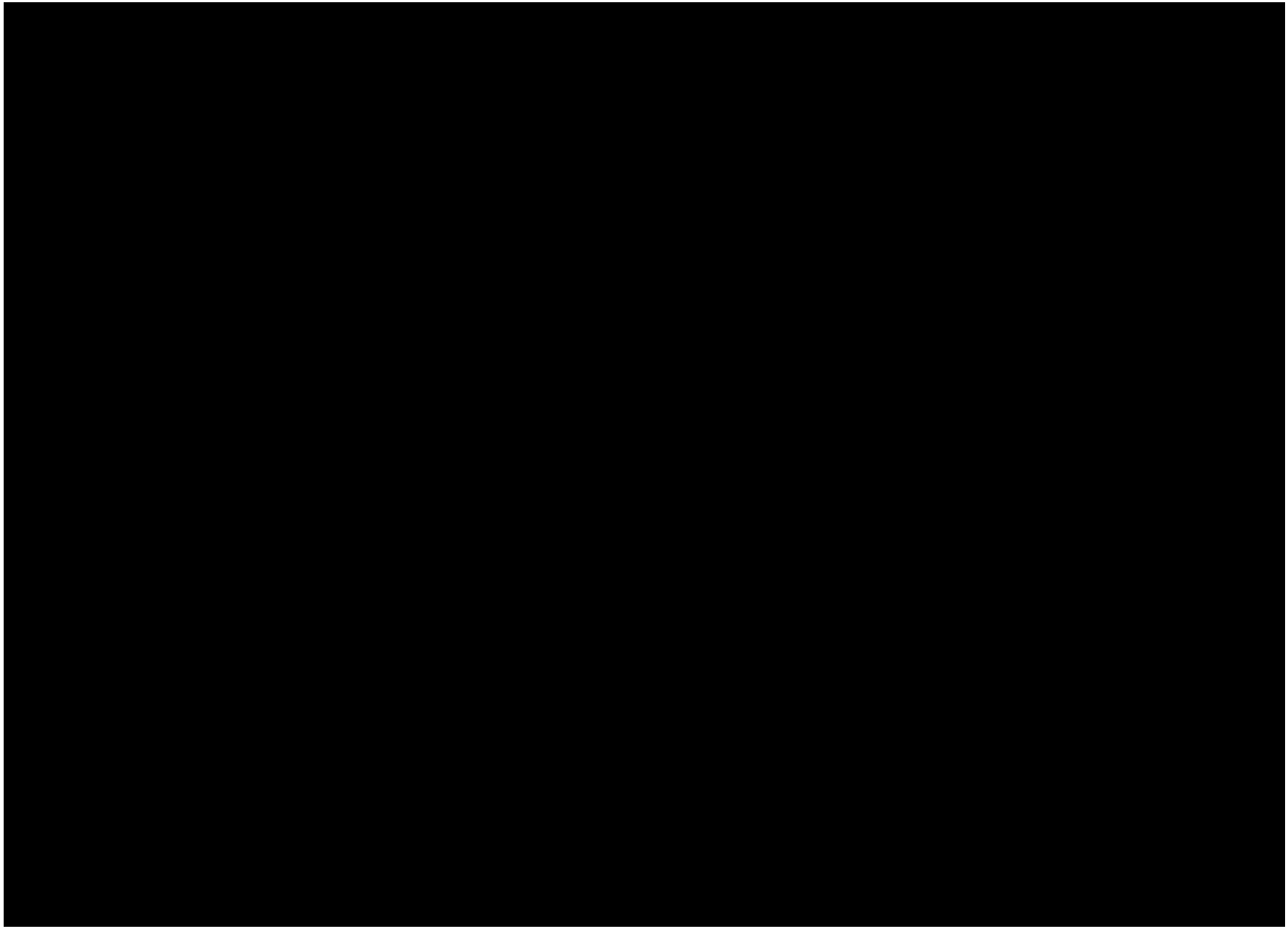
Dose delay and discontinuation criteria apply for all drug-related AEs. Delay or discontinue administration of both relatlimab and nivolumab if any of the delay criteria [redacted] are met. Delay relatlimab and nivolumab dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the Investigator, warrants delaying the dose of study medication. Delay or discontinuation of nivolumab or relatlimab dosing independent of the other is not permitted.

For participants who require delay of relatlimab and nivolumab, re-evaluate weekly, or more frequently, if clinically indicated, and resume dosing when criteria to resume treatment are met (see Section 7.4.3). Continue tumor assessments per protocol even if dosing is delayed.

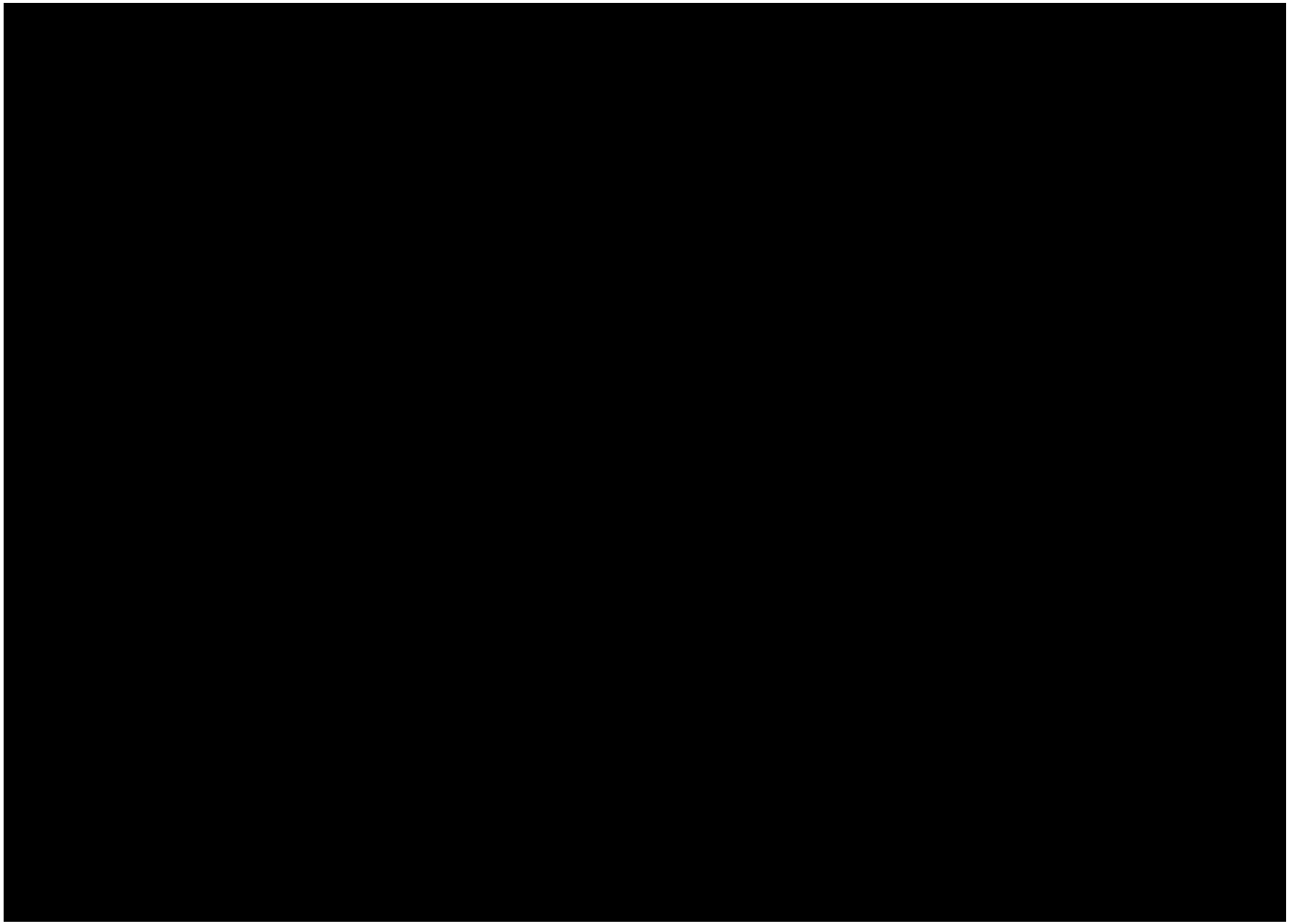
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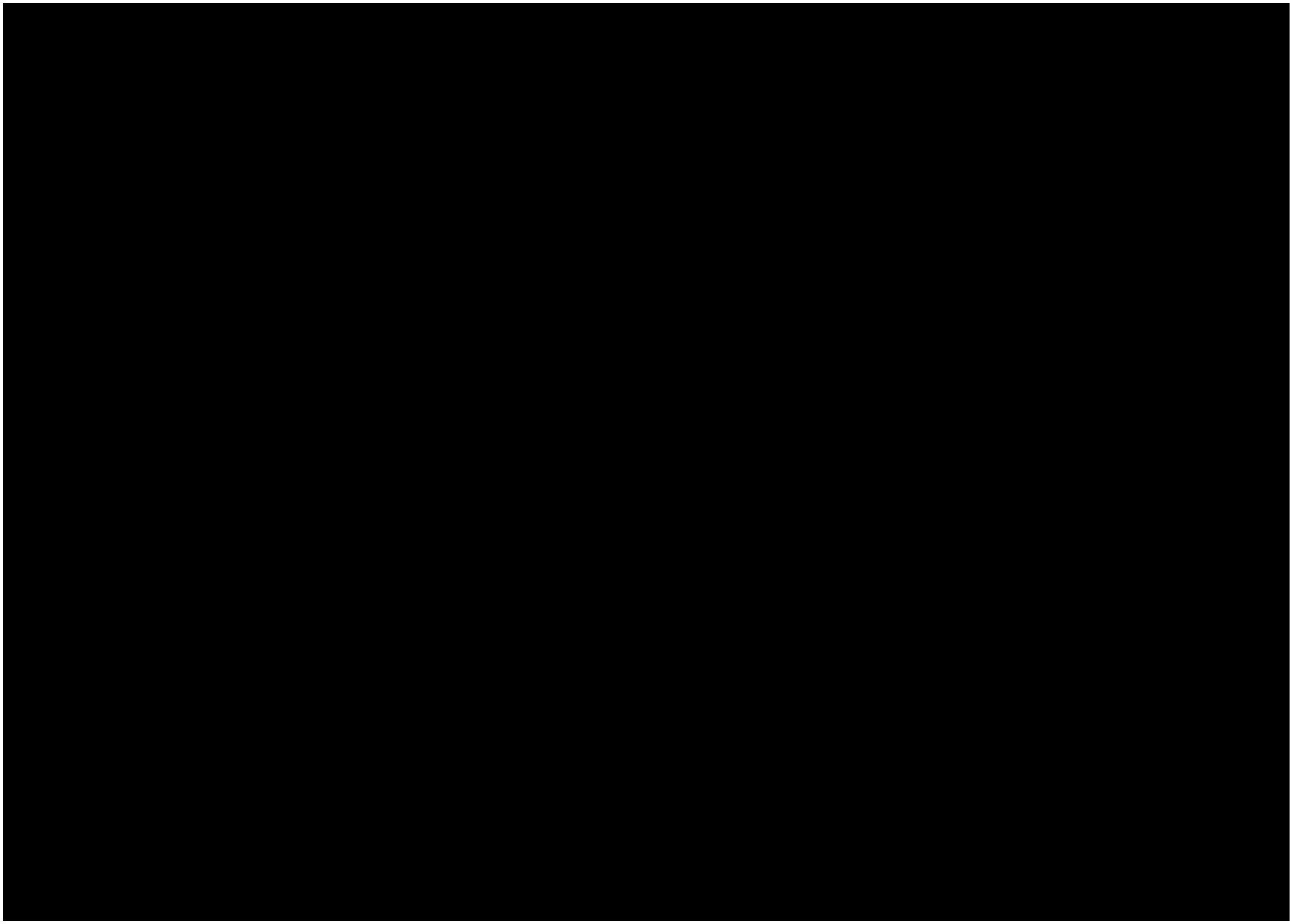
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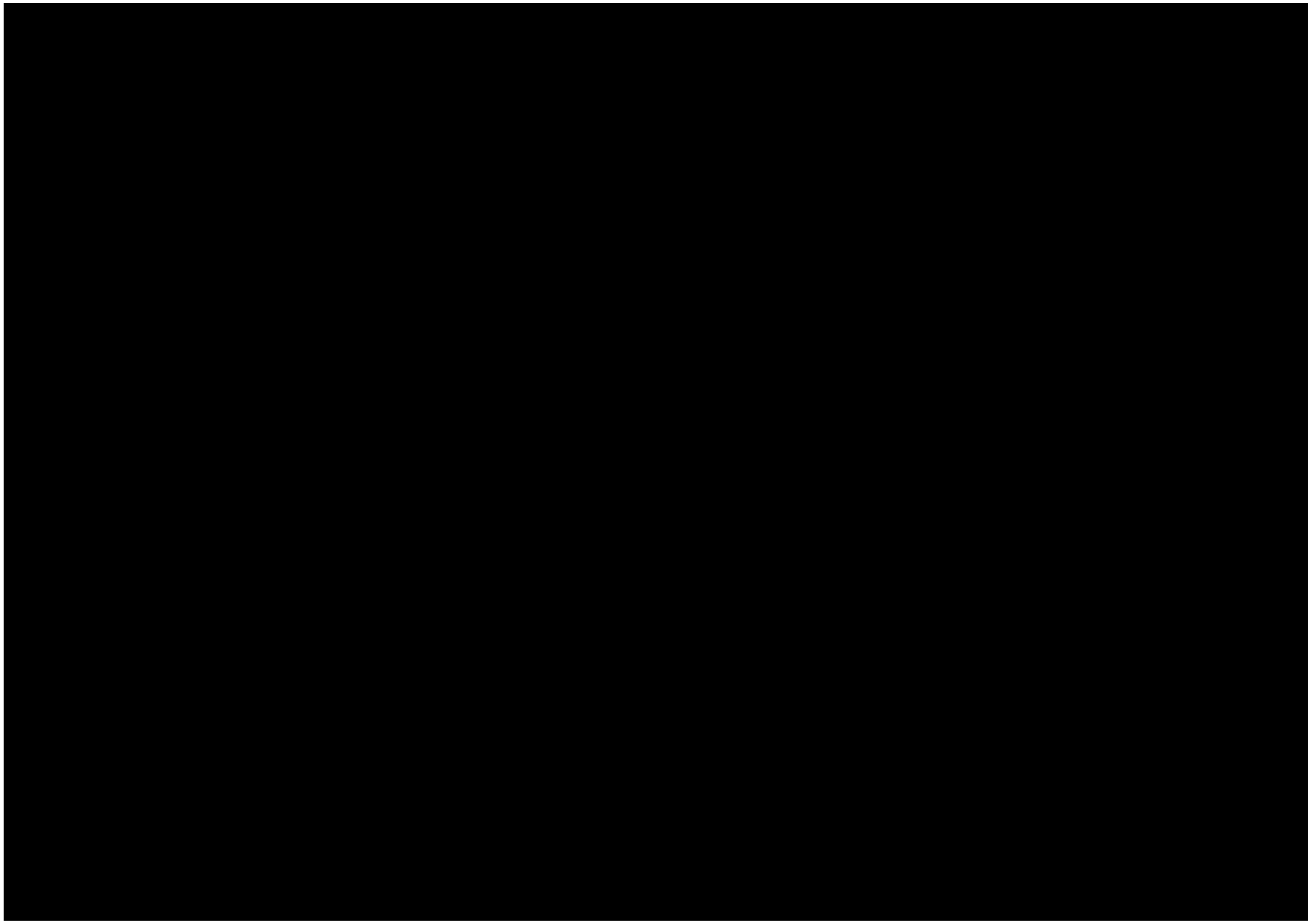
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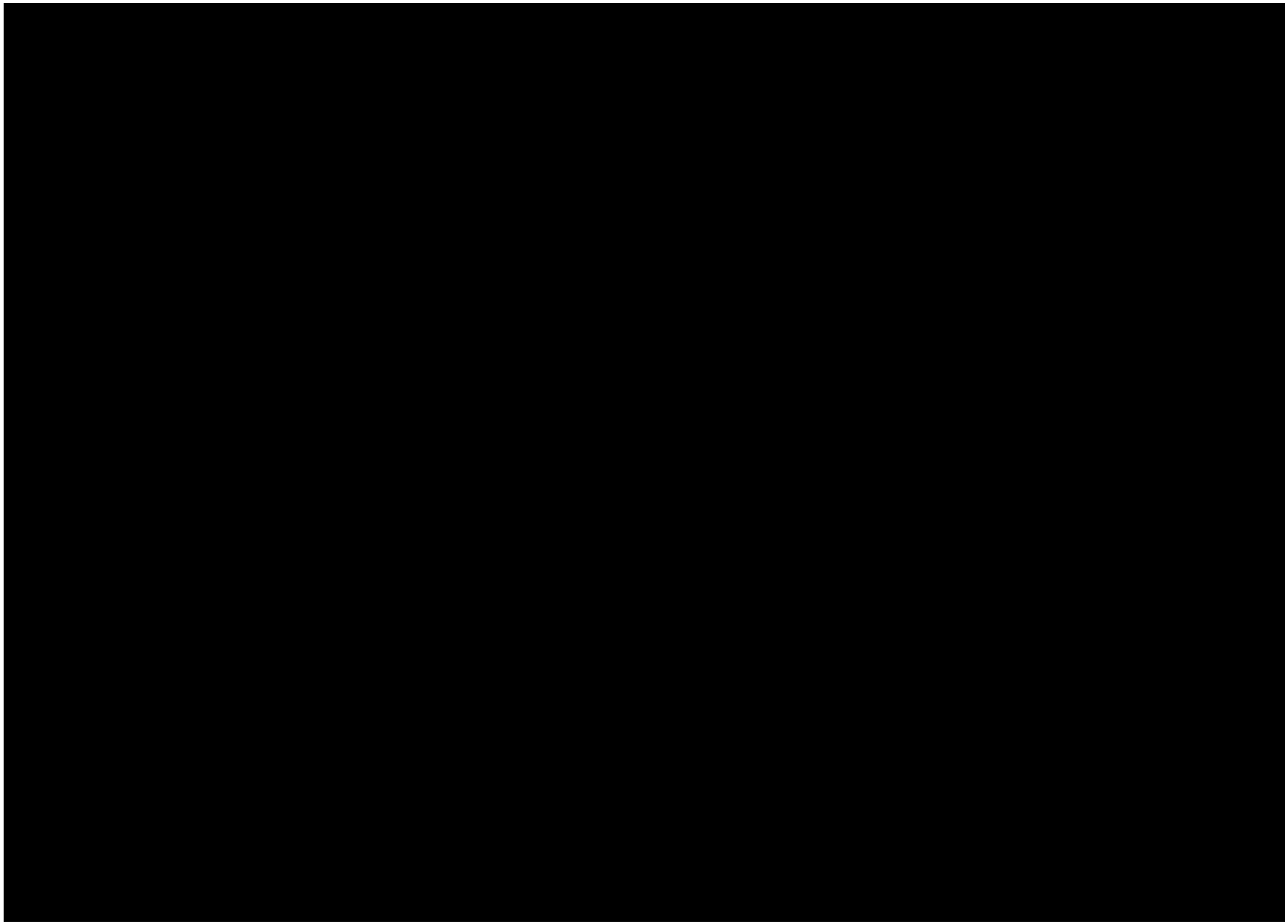
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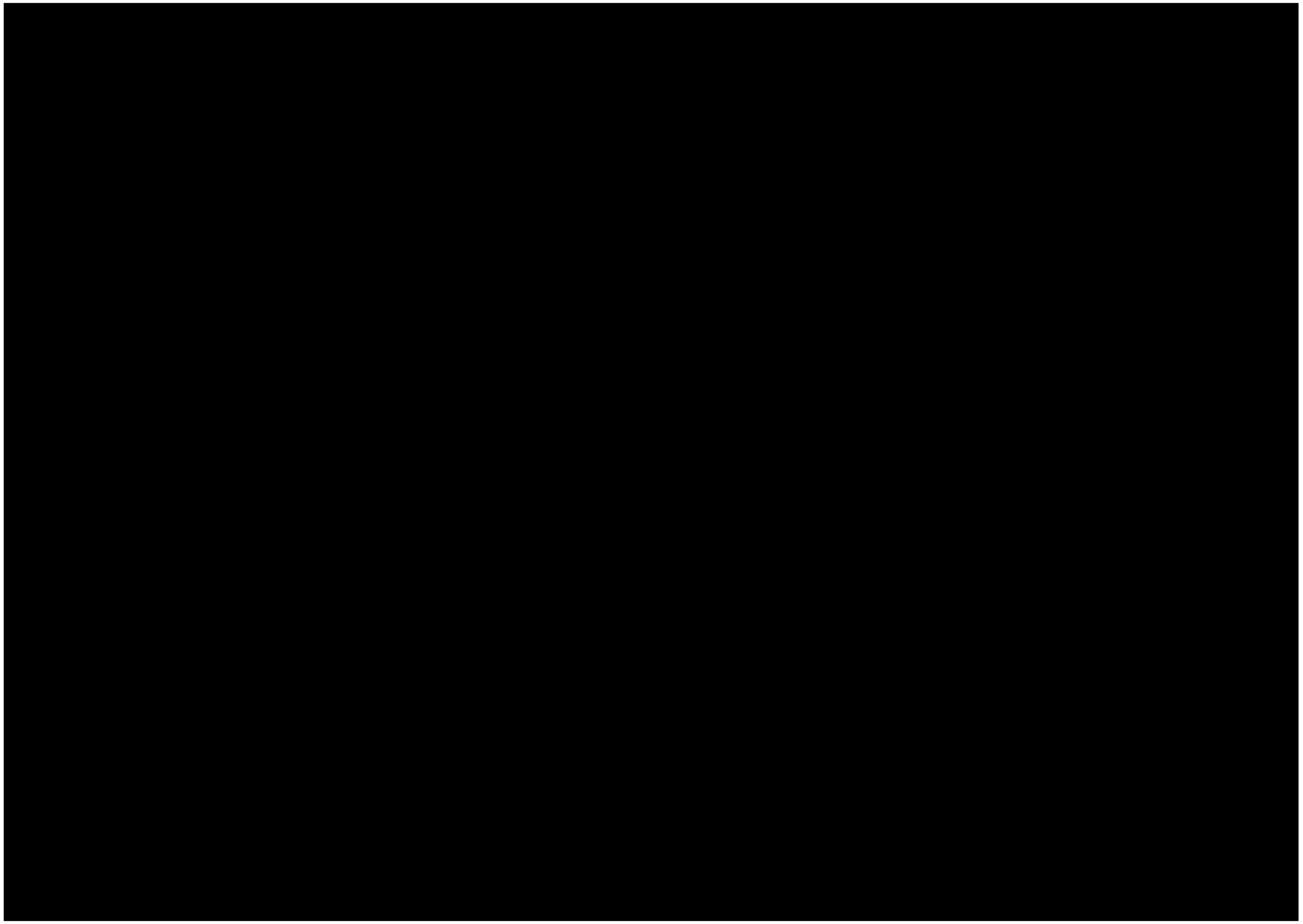
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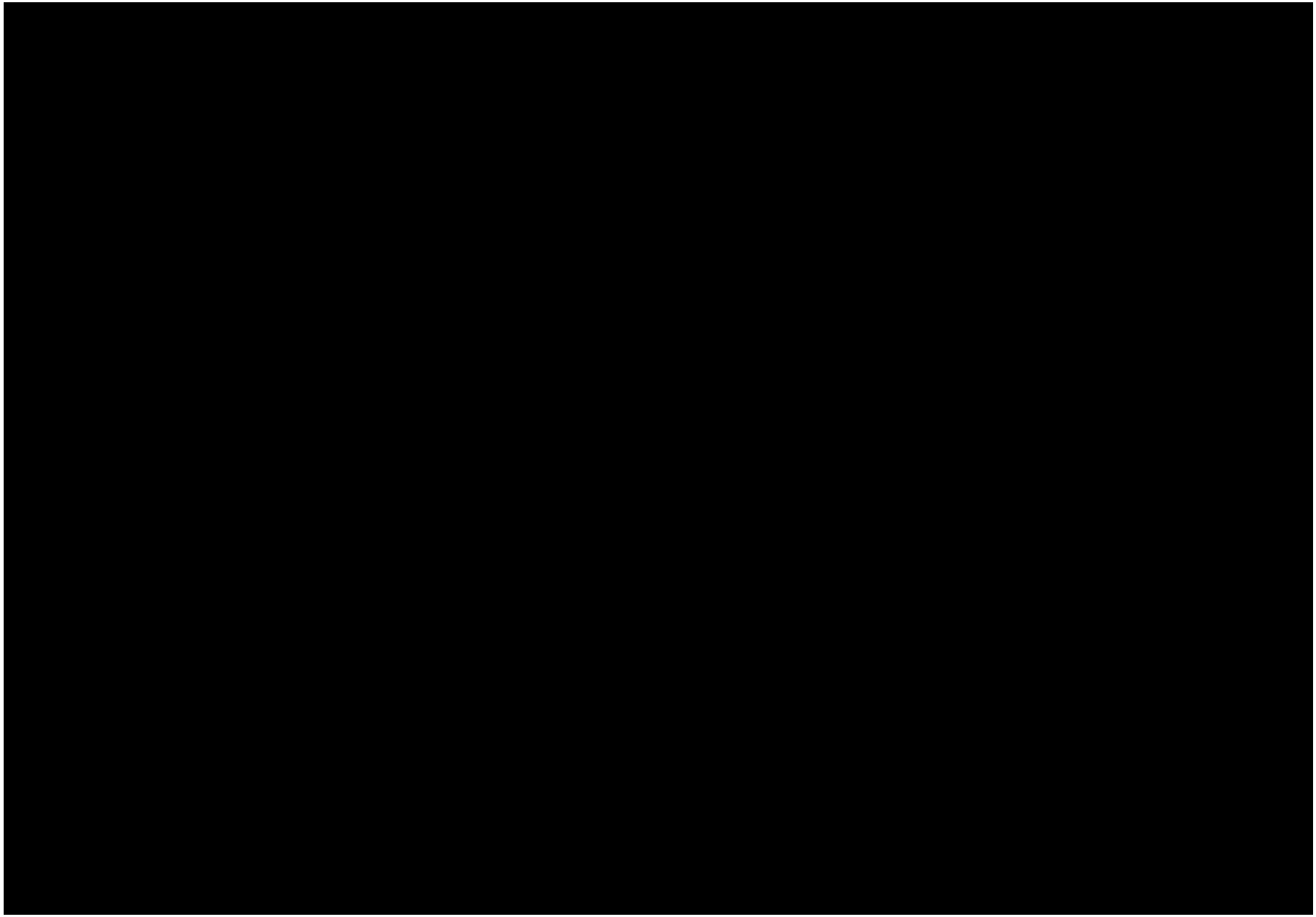
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[redacted]

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Abbreviations: AE, adverse event; [redacted]

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7.4.2 Dose Delay/Discontinuation Criteria for Bevacizumab

Dose delay criteria apply for all drug-related AEs. Delay bevacizumab dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the Investigator, warrants delaying the dose of study medication. Delay administration of bevacizumab if any of the delay criteria in Table 7.4.2-1 are present.

For participants who require delay of bevacizumab, re-evaluate weekly, or more frequently, if clinically indicated, and resume dosing when criteria to resume treatment are met (See Section 7.4.3). Continue tumor assessments per protocol even if dosing is delayed.

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Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Bevacizumab

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
GI Perforation	Any Grade	Permanently discontinue bevacizumab	
Bowel Obstruction	Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention	Bevacizumab may be restarted upon completion resolution of event
	Grade 3/4	Hold bevacizumab for complete obstruction	If surgery is necessary, patient may restart bevacizumab after full recover from surgery and at Investigator's discretion
Hypertension[a]			
Hypertension	Grade 2	Hold bevacizumab	Once blood pressure is ≤ 150/100 mmHg, patient may resume treatment.
	Grade 3	Hold bevacizumab	If blood pressure not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
	Grade 4	Discontinue bevacizumab	
	Hypertensive Crisis	Discontinue bevacizumab	
	Hypertensive Encephalopathy	Discontinue bevacizumab	
Arterial Thromboembolic Events			
Arterial Thromboembolic Events	Any Grade	Discontinue bevacizumab	

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Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Bevacizumab

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Venus Thromboembolic Event			
Venus Thromboembolic Event	Grade 3	Hold bevacizumab > 3 weeks	For Grade 3 thromboembolic events, hold bevacizumab for > 3 weeks. Bevacizumab treatment may be resumed during the period of therapeutic-dose anticoagulant therapy once the level of anticoagulation therapy is stabilized. *Please follow local anti-coagulation therapy guidelines.* After administration of bevacizumab is restarted, if the patient experiences another Grade 3+ venous thromboembolic event, bevacizumab should be discontinued.
	Grade 4	Discontinue bevacizumab	
Hemorrhage			
Hemorrhage	Grade 3 (non-cerebral)	Discontinue bevacizumab	
	Grade 4 (or any cerebral)	Discontinue bevacizumab	
Hemoptysis			
Hemoptysis	Half tablespoon (≥ 2.5 mL)	Hold bevacizumab	
Fistula			
Tracheoesophageal fistula	Any Grade	Discontinue bevacizumab	
Non-tracheoesophageal fistula	Grade 4	Discontinue bevacizumab	
Involves internal organs	Any Grade	Discontinue bevacizumab	

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Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Bevacizumab

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Wound Healing Complication			
Wound healing complication	Any Grade	Discontinue bevacizumab	Any wound healing complication including wound dehiscence requiring medical or surgical therapy and necrotizing fasciitis requires discontinuation.
Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome			
PRES/RPLS	Any Grade	Discontinue Bevacizumab	PRES/RPLS must be confirmed by MRI prior to discontinuation.
Proteinuria			
Proteinuria	First occurrence, no diagnosis of nephrotic syndrome	• For proteinuria 2 + or 3 + by dipstick, administer bevacizumab as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled bevacizumab administration. • If 24-hour proteinuria ≤ 2 g, the next bevacizumab dose can be administered as scheduled. • If 24-hour proteinuria > 2 g, hold bevacizumab treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose, and continue to hold scheduled bevacizumab until proteinuria has decreased to ≤ 2 g/24 hours. • When proteinuria has decreased to ≤ 2 g/24 hours, scheduled bevacizumab may be administered as planned. However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose until proteinuria has improved to ≤ 1 g/24 hours.	
	Second and subsequent occurrences, no diagnosis of nephrotic syndrome	• For proteinuria 2+ or 3+ by dipstick, administer bevacizumab as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled bevacizumab administration. • If 24-hour proteinuria ≤ 2 g, the next bevacizumab dose can be administered as scheduled. • If 24-hour proteinuria ≥ 2 g, hold bevacizumab treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose, and continue to hold scheduled bevacizumab until proteinuria has decreased to ≤ 2 g/24 hours.	

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Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Bevacizumab

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
		• When proteinuria has decreased to ≤ 2 g/24 hours, scheduled bevacizumab may be administered as planned. However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose until proteinuria has improved to ≤ 1 g/24 hr.	
	With diagnosis of nephrotic syndrome	Discontinue Bevacizumab	
Infusion Reactions[b]			
Infusion Related Reaction	Grade 1 or 2	Reduce infusion rate to ≤ 50% or interrupt infusion at the discretion of the Investigator per medical judgment	If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
	Grade 3/4	Stop infusion, permanently discontinue bevacizumab	

Abbreviations: AE, adverse event; CTCAE v5, Common Terminology Criteria for Adverse Events version 5; GI, gastrointestinal; hr, hour; MRI, magnetic resonance imaging; PRES/RPLS, posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome.

[a] Grade 2 and above - start antihypertensive therapy

[b] Manifested by [redacted]

Note: If bevacizumab is delayed due to toxicity for > 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for > 42 days if the Medical Monitor agrees that the patient is likely to derive clinical benefit.

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7.4.3 Criteria to Resume Treatment

Participants may resume treatment with study drug if they have completed AE management (ie corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per [redacted] Table 7.4.2-1 prior to re-initiating treatment in a participant with a dosing delay lasting > [redacted] weeks, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every 3 weeks or more frequently if clinically indicated during such dosing delays.

7.4.4 Management Algorithms for Nivolumab and Relatlimab

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and relatlimab are considered IO agents and the management algorithms in Appendix 5 provide guidance on assessing and managing the following groups of AEs:

[redacted]

The above algorithms are found in Appendix 5 of this protocol. Note that the program management algorithm for hepatic AEs has been modified for this HCC protocol.

7.4.4.1 Protocol-specific Recommendations for Management of Hepatic Events

The nivolumab program has developed a standardized approach for the management of hepatic events based on cumulative data across the program in participants with normal hepatic function. Participants with advanced HCC generally have underlying cirrhosis with decreased hepatic function. They may also have a concomitant chronic viral infection. For CA224106, the upper limits for inclusion were therefore adjusted to account for baseline liver dysfunction. Participants included in prior nivolumab studies have had no higher than a ≤ 3× ULN AST or ALT elevation. Criteria for dose delay, resumption, and discontinuation are provided in [redacted] Table 7.4.2-1. [redacted] (Section 8.1).

7.4.5 Treatment of Related Infusion Reactions

Since nivolumab and relatlimab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with [redacted]

[redacted] Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

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

[redacted]

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[redacted]

7.5 Preparation/Handling/Storage/Accountability

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

The product storage manager should ensure that the study intervention 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 intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

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

IP/AxMP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure the 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).

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual and in Appendix 2.

For study interventions not provided by BMS and obtained commercially by the site, storage should in accordance with the product label.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Relatlimab, nivolumab, and bevacizumab 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

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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.[96]

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines including non-live COVID-19 vaccines) in participants receiving BMS-936558 or BMS-986016 is unknown.

7.7.1 Prohibited and/or Restricted Treatments

The following medications and treatments are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids. 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.
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of HCC)
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted.
- 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.
- Any live / attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.
- Live COVID-19 vaccines should not be administered to a participant during the study, including during the treatment, safety follow-up period and within 3 months following the last dose of IMP. In addition, the administration of a live COVID-19 vaccine is prohibited up to 30 days prior to initiation of study treatment.
- Locoregional therapies
- Any therapeutic use of anticoagulant therapy (See Section 6.1)
    - Use of warfarin or Coumadin-like products is not permitted at all (includes for prophylactic use).
    - Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose.

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- Prophylactic anticoagulation for the patency of venous access devices is allowed so long as the activity of the agent results in an INR < 1.5x ULN and aPTT is within normal limits within 14 days prior to initiation of study treatment. Prophylactic use of unfractionated heparin or low molecular-weight heparin (ie, enoxaparin 40 mg/day) is allowed. *For prophylactic use of anticoagulants or thrombolytic therapies, local label approved dose levels may be used.*
- Current or recent (within 10 days of first dose of study treatment) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol.
- Concomitant chronic use of oral NSAIDs while receiving study drugs is prohibited (topical and transdermal applications [patches] are acceptable). However, for the symptomatic relief of medical conditions (eg, headache, fever) sporadic or short-term intake of oral NSAIDs is allowed, when co-administered with proton pump inhibitors to reduce potential GI damage.
- Current use of full dose anticoagulants or thrombolytic therapy at therapeutic doses. However, if a patient experiences a venous thromboembolism (VTE) event while still receiving study drug treatment, it may still be possible for the patient to remain on study medication despite anticoagulation treatment (See Table 7.4.2-1).

7.7.2 Other Restrictions and Precautions

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

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, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image manual.

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

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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 + 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 for maximum treatment duration as specified in 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 study drug 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

If a participant receiving nivolumab + relatlimab combination [redacted] or bevacizumab therapy (Table 7.4.2-1) meets criteria for discontinuation, they may continue on the other component of the regimen.

8.1 Discontinuation From Study Intervention

Participants MUST discontinue investigational product (and non-investigational 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

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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 adverse event (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 Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary 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.)
- Any event meeting DLT criteria/dose modification criteria, patient may continue with the other component of study therapy at Investigator's discretion.
- Pregnancy

Refer to the 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/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2. 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 (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention 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 per local regulatory requirements in each region/country and entered on the appropriate CRF page.

Nivolumab and relatlimab or bevacizumab treatment must be permanently discontinued per criteria in on Sections 7.4.1 and 7.4.2.

Discontinue nivolumab and relatlimab or bevacizumab for any AE, laboratory abnormality, or intercurrent illness which in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab and relatlimab or bevacizumab dosing.

[redacted]

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[redacted]

The assessment for discontinuation of immunotherapy should be made separately from the assessment to discontinue bevacizumab.

8.1.1 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[97] Participants will be permitted to continue treatment beyond initial RECIST v1.1 defined PD, as assessed by the Investigator, as long as the following criteria are considered:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)

Note: Participants with signs of rapid disease progression, threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression), or who require urgent alternative medical intervention should be excluded from consideration of treatment beyond disease progression. In all cases, judgement of the treating investigator is integral to evaluating whether continuing treatment beyond disease progression is in the best interest of the participant.

- Participant provides written informed consent prior to receiving additional treatment with the study drug regimen. 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 PD. 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 PD. It is recommended that study treatment should be discontinued permanently upon documentation of further progression.

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New lesions are considered measurable 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-measurable at the time of initial progression may become measurable 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.

8.1.2 Post-study Intervention Study Treatment Follow-up

In this study, PFS 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 intervention 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 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 (See Section 2). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact or is lost to follow-up.

8.2 Discontinuation from the Study

Participants who request to discontinue study intervention 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 intervention 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.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.

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- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- 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 (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) 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 the Investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

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- 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 the Schedule of Activities.
- Safety, laboratory, and analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Perform additional measures, including non-study required laboratory tests, 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 on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.
- Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate or changes from baseline) or symptoms (eg. dyspnea, cough, chest pain, fatigue, palpitations).
- Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

9.1.1 Efficacy Assessment for the Study

Images will be submitted to a central imaging vendor for BICR at any time 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.

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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 timepoint of tumor assessments will be reported on the eCRF based on the Investigator's assessment using RECIST v1.1 criteria (See Appendix 10 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. A Best Overall Response (BOR) of SD requires a minimum of 35 days on study from randomization to the date of the first imaging assessment.

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9.1.1.3 BICR Confirmation of Progression

Sites should submit all scans to the central imaging vendor on a rolling basis, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and Investigator assessment of submitted scans. When progression per RECIST v1.1 criteria is assessed by the Investigator, the site will inform the central imaging vendor, in order for BICR assessment of progression to be performed. The BICR will be completed and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol−specified schedule as noted in Section 2 (Schedule of Activities) until progression has been confirmed by BICR.

All study treatment decisions will be based on the Investigator's assessment of tumor images and not on the BICR assessment.

9.1.2 Clinical Outcome Assessments

The evaluation of patient-reported outcomes (PROs) is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting.[98] Participants will be asked to complete the Functional Assessment of Cancer Therapy - Hepatobiliary (FACT-Hep), Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function 8c short-form, Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC) at designated study visits. When possible, participants should complete the PRO measures prior to any other assessments or study procedures when they are being administered during study visits. Assessments will be completed prior to dosing on Day 1 of each cycle and at designated time points during the safety follow-up period. The questionnaires will be provided in the participant's preferred language, if available. See Section 2 (Schedule of Activities) for timing of assessments. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with Sponsor or the Sponsor's representative.

9.1.2.1 FACT-Hep

The FACT-Hep questionnaire will be used to assess the effects of HCC and its treatment on health-related quality of life (HRQoL).[99,100,101] The FACT-Hep includes the Functional Assessment of Cancer Therapy-General version (FACT-G) generic cancer-related core questionnaire to assess symptoms and treatment-related effects impacting physical well-being (PWB; 7 items), social/family well-being (SWB; 7 items), emotional well-being (EWB; 6 items), and functional well-being (FWB; 7 items). In addition, the FACT-Hep includes an 18-item disease-specific

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hepatobiliary cancer subscale (HCS) that assesses back and stomach pain, gastrointestinal symptoms, anorexia, weight loss, and jaundice. The GP5 item (FACT-G single item ["I am bothered by side effects of treatment"]) of the FACT-Hep can also be used to assess the bother associated with the side effects of treatment.[102] Each item is rated on a 5-point scale ranging from 0 (not at all) to 4 (very much).

Scores for the PWB, FWB, SWB, and EWB subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic HRQoL, while the FACT-G and HCS scores can be combined to produce a total score for the FACT-Hep, which provides a composite measure of general and targeted HRQoL. Higher scores indicate better HRQoL. Minimally important differences (MIDs) have been estimated for the various FACT-Hep subscale and total scores. These are as follows: 2-3 points for the PWB, FWB, SWB, and EWB subscales; 5-6 points for the HCS subscale; 6-7 points for the FACT-G total score; and 8-9 points for the FACT-Hep total score.[101]

9.1.2.2 PROMIS Physical Function 8c

Physical function has been identified as a key domain for assessing symptom-related impacts and HRQoL in patients with cancer in clinical trials. Physical function, along with symptoms of specific tumor types and symptomatic AEs, can provide important data to support the safety and efficacy of a cancer treatment. PROMIS is a set of self-report measurement tools that was developed by the US National Institutes for Health (NIH). PROMIS contains an item bank of physical function items that assess a range of physical abilities.[103,104] The PROMIS Physical Function Short Form 8c (PROMIS PF 8c) contains a subset of 8 items selected from the PROMIS Physical Function item bank, which were determined to be relevant to cancer patients. Each item assesses the difficulty a respondent has in performing different activities using a 5-level verbal rating scale. The PROMIS PF 8c uses a recall period of the past 7 days.

9.1.2.3 PGIS and PGIC

PGIS and PGIC will be included as exploratory endpoints. The PGIS is a single item that assesses participants' perceptions of overall severity of cancer symptoms for the last 7 days with response options ranging from "none" to "very severe." The PGIC assesses participants' perceptions of overall change in symptom severity since before treatment, and assesses whether or not participants feel such a change is meaningful. Response options for this item range from "much worse" to "much improved." Data collected via the PGIS and PGIC will be used as anchor measures for use in assessing the psychometric measurement properties and the threshold for meaningful change for the FACT-Hep and PROMIS PF 8c.

9.2 Adverse Events

The definitions of an AE or serious adverse event (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).

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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.

Immune-mediated adverse events 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 case report form.

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

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

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 must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 135 days following discontinuation of dosing.
- For participants randomized to treatment and never treated with study drug, collect SAEs for 30 days from the date of randomization.
- The Investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure (eg, a follow-up skin biopsy).
- Medical occurrences that begin before the start of study intervention 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, 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 intervention 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.

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- Collect all nonserious adverse events (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of 135 days following discontinuation of study treatment.

Refer to Appendix 3 for SAE reporting.

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 adverse event 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 case report form.

9.2.3 Follow-up of AEs and SAEs

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).

Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.

All identified nonserious AEs must be recorded and described on the nonserious 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, and nonserious 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, 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 toward 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.

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The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations, including European Regulation 536/2014 and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of SAEs and must be reported to the appropriate regulatory authorities and Investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

This section is not applicable for women not of childbearing potential.

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives (6 months, which reflects the longest elimination period for each IMP administered) after study intervention administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In all cases, the study intervention will be discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety).

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. Protocol-required procedures for study discontinuation and follow-up must be performed.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE eCRF, 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 intervention 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 versus low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

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

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Potential DILI is defined as hepatotoxicity, evidenced by the following:

[redacted]

This is the standard DILI definition across the BMS HCC program.

- The key responsibilities for Investigators during p-DILI assessment include: (i) early detection, medical evaluation (including the exclusion of other potential causes), and rapid laboratory confirmation of liver-related abnormalities, and (ii) BMS notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information BMS is responsible for: (i) timely evaluation and triaging of p-DILI cases, (ii) expedited reporting of p-DILI cases, and (iii) expanded review of p-DILI cases including a detailed assessment of all available clinical information, investigations and biochemical data.
- Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a participant meets p-DILI criteria. They are expected to promptly notify BMS of all p-DILI cases. Potential DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur [redacted]. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to BMS as an SAE within 24 hours of confirmation.
- [redacted]

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9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3). 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:

1) Contact the Medical Monitor immediately.
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
3) 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 the 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 Schedule of Activities.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to 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). If local laboratory is unable to perform required serology assessments in Section 2, central laboratory may be utilized with Sponsor approval.

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Table 9.4.4-1: Clinical Laboratory Assessments

<table>
<tr><td colspan="2">Hematology - Complete Blood Count (CBC)</td></tr>
<tr><td colspan="2">Hemoglobin</td></tr>
<tr><td colspan="2">Hematocrit</td></tr>
<tr><td colspan="2">Total leukocyte count, including differential</td></tr>
<tr><td colspan="2">Platelet count</td></tr>
<tr><td colspan="2">Chemistry</td></tr>
<tr><td>Amylase
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Alpha-fetoprotein (AFP)
Total bilirubin (T.bili)
Direct bilirubin
Alkaline phosphatase (ALP)
Lactate dehydrogenase (LDH)
Lipase
Creatinine
Blood urea nitrogen (BUN)/serum urea
Glucose
Creatine phosphokinase (CPK)</td><td>Total protein
Albumin
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</td></tr>
<tr><td colspan="2">Troponin (local standard to be used/allowed)
Cardiac Troponin T (cTnt) or I (cTnI):
• The first troponin elevation in asymptomatic patients requires a dose delay until a cardiac evaluation has been completed (see Section 9.4.6 for details) and a favorable risk/benefit assessed by the Investigator.
• Troponin elevations in symptomatic patients requires a dose delay and a consult with a cardiologist. See Section 9.4.6 for details.
Following evaluation(s), determination of further treatment will be based on the discretion of the Investigator and, if applicable, the cardiologist.</td></tr>
<tr><td colspan="2">Urinalysis</td></tr>
<tr><td colspan="2">Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick</td></tr>
<tr><td colspan="2">Serology</td></tr>
<tr><td colspan="2">Hepatitis C: Hepatitis C antibody, hepatitis C RNA viral load (PCR)
Hepatitis B/D: Hepatitis B surface antigen (if hepatitis B surface antigen is positive reflex to hepatitis D antibody), hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA viral load (PCR)

HIV (Screening only): HIV-1 and -2 antibody (Testing for HIV must be performed at sites where mandated by local requirements [see Appendix 8]).</td></tr>
<tr><td colspan="2">Other Analyses</td></tr>
<tr><td colspan="2">Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units HCG.</td></tr>
<tr><td colspan="2">Follicle stimulating hormone (FSH) screening - If needed to document post-menopausal status as defined in Appendix 4.</td></tr>
</table>

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Table 9.4.4-1: Clinical Laboratory Assessments

Coagulation profile (INR or PT, and aPTT)
SARS-CoV-2 viral test

Note: For countries that require it, HIV testing should be added to the protocol in an appendix. Consider specifying that total T3 may be allowed if collection of free T3 is not feasible. Refer to program laboratory testing plan (LTP) for list of nivolumab / relatlimab specific procedures

Abbreviations: aPTT, activated partial thromboplastin time; DNA, deoxyribonucleic acid; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; INR, international normalized ratio; IU/L, international units per liter; PCR, polymerase chain reaction; PT, prothrombin time; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 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.

9.4.6 Cardiac Evaluation

The first asymptomatic troponin elevation on treatment requires a cardiac evaluation as noted below and a dose delay until the cardiac evaluation has been completed. Dosing may be resumed after the cardiac evaluation if the investigator assesses a favorable benefit/risk. Subsequent asymptomatic troponin elevations while on study should be evaluated as clinically indicated.

All symptomatic elevations required a dose delay and a consult with a cardiologist. Dosing may be resumed when AE resolves to baseline and all symptoms resolved, unless myocarditis has been diagnosed, at which point the study drug must be discontinued.

[redacted]

A cardiac evaluation must include an ECG and echocardiogram, but may also include the following or more as deemed necessary by the Investigator and/or cardiologist:

- Laboratory testing: repeat serum troponin levels and CPK levels
- Cardiac imaging: chest radiograph, cardiac MRI, coronary angiogram
- Cardiac biopsy
- Cardiology consult

9.5 Pharmacokinetics

Collect samples for PK [redacted] assessment for participants at the time points indicated in Table 9.5-1. All on-treatment PK time points are intended to align with days on which study treatment is administered. If it is known that a dose is going to be delayed, then collect the predose sample just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, do not collect an additional predose sample.

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Draw blood samples from a site other than the infusion site (ie, contralateral arm) on days of infusion for all pre-dose and end of infusion-PK (EOI-PK) samples. Please ensure accurate documentation of the time and date of sample collection. If the infusion was interrupted, the interruption details will also be documented on the CRF.

PK of relatlimab, nivolumab, and bevacizumab will be derived from serum concentration versus time. The PK parameters to be assessed, depending on the availability of data, include the following:

Ctrough: Trough observed serum concentration

Ceoinf: Observed concentration at the end of infusion

Table 9.5-1 lists the sampling schedule to be followed for the assessment of PK. Further details of blood collection and processing will be provided to the site in the procedure manual.

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK/[redacted] samples.

Concentration analyses for relatlimab, nivolumab and bevacizumab will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments (eg, [redacted] PK, or [redacted]) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, [redacted] etc).

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including, but not limited to, [redacted], metabolite analyses, etc) and or for additional method purposes (including, but not limited to, cross-validation, [redacted]/PK selectivity, cutpoint, etc).

[redacted]

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

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Table 9.5-1: Pharmacokinetic [redacted] Sampling Schedule for Relatlimab, Nivolumab and Bevacizumab (CA224106)

Study Day of Sample Collection (1 Cycle = 3 weeks)	Event	Time Relative to start of Infusion (Hour:Min)	Nivolumab PK Serum Samples	[redacted]	Relatlimab PK Serum Samples	[redacted]	Bevacizumab PK Serum Samples	[redacted]
Cycle 1 Day 1	Predose[a]	0:00	X		X		X	
	EOI[b]	See note	X		X			
Cycle 2 Day 1	Predose[a]	0:00	X		X		X	
Cycle 4 Day1	Predose[a]	0:00	X		X			
Cycle 6 Day 1	Predose[a]	0:00	X		X			
	EOI[b]	See note	X		X			
Cycle 9 Day 1	Predose[a]	0:00	X		X		X	
Cycle 12 Day 1	Predose[a]	0:00	X		X			
Cycle 18 Day 1	Predose[a]	0:00	X		X		X	
Cycle 24 Day 1	Predose[a]	0:00	X		X			
Cycle 30 Day 1	Predose[a]	0:00	X		X		X	
Follow Up Visit 1			X		X			
Follow Up Visit 2			X		X		X	

Abbreviations: [redacted]; EOI, end of infusion; HR, hazard ratio; [redacted]; IV, intravenous; min, minute; PK, pharmacokinetic.

[a] All predose samples should be collected just before starting the infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose samples should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[b] Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, the EOI-PK sample should be drawn when the nivolumab and relatlimab/placebo infusion has been completed. If the site infuses drug without a flush, then collect the EOI-

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PK sample within approximately 5 minutes after end of infusion (30 minutes). If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered.

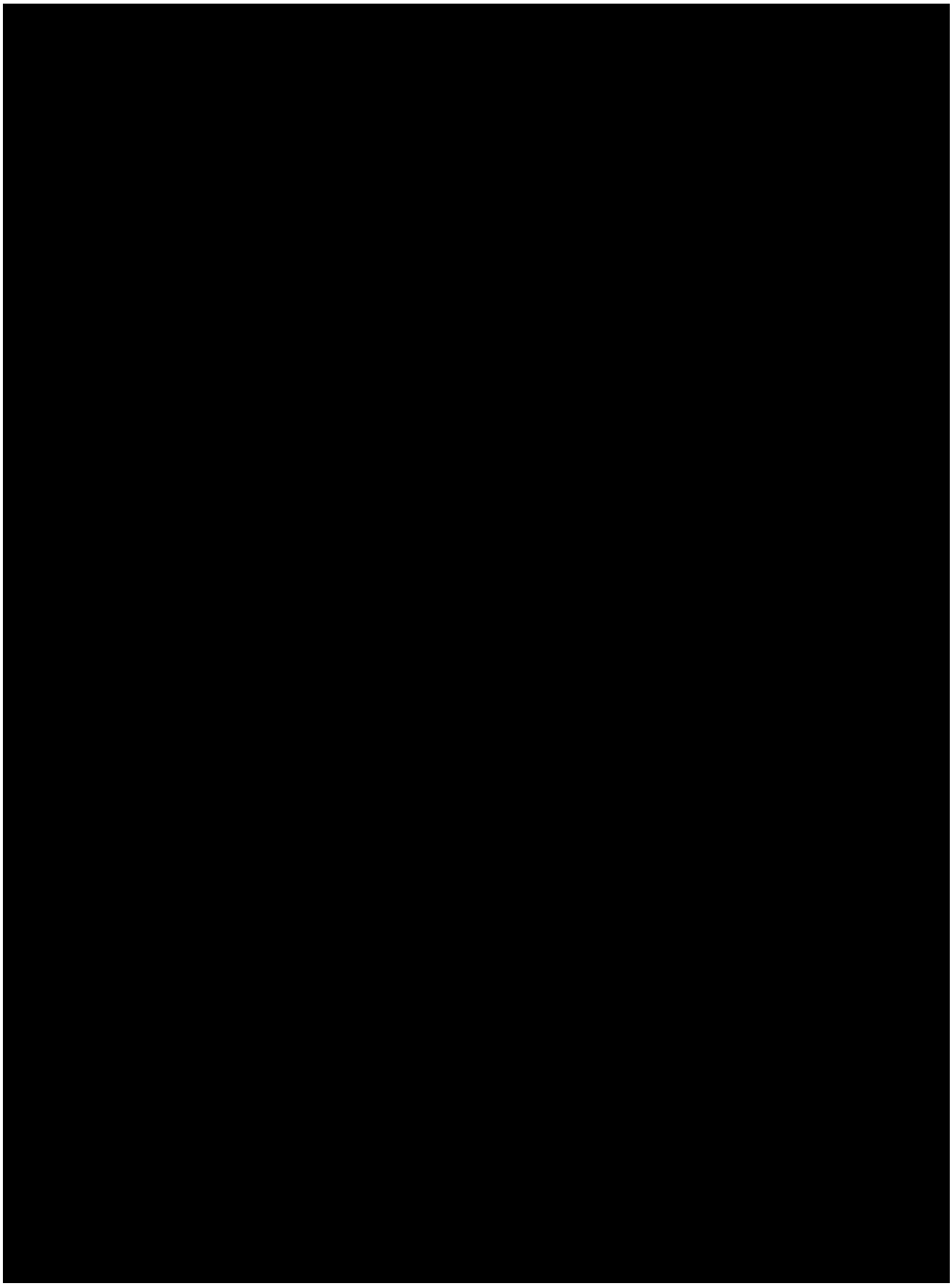
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[redacted]

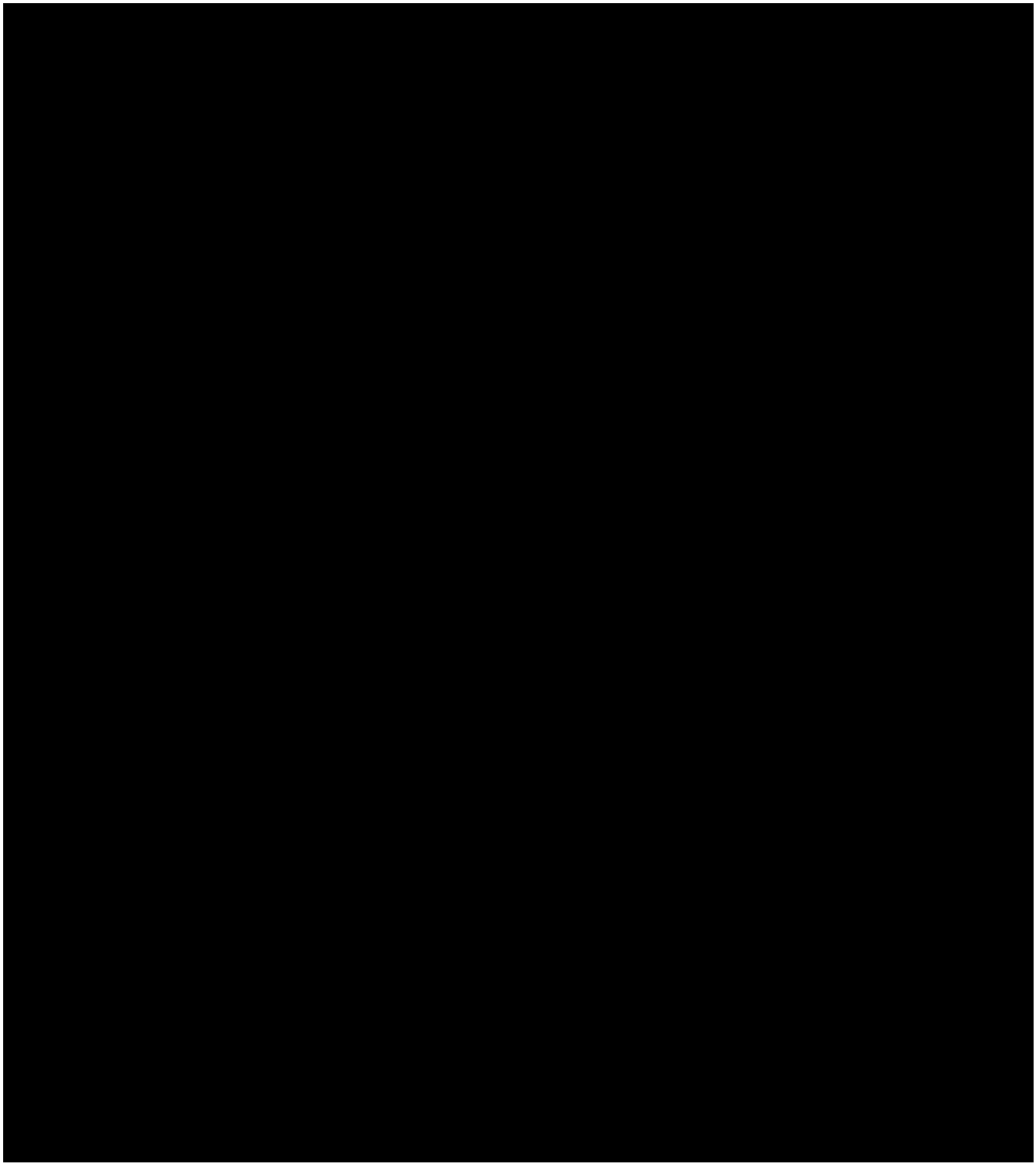
9.10 Biomarkers

[redacted]

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9.10.2 Tumor Samples

Tumor biopsy specimens will be obtained from consenting participants prior to treatment to characterize immune cell populations, evaluate expression of selected tumor and immune markers, . 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

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aspirates or other cytology samples and biopsies of bone lesions are not acceptable. Note the following for the required tumor sample:

- Samples should be collected within 3 months of enrollment, 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 pretreatment 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. Central laboratory must provide IRT with confirmation of receipt for randomization/treatment.

*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.

Submission of on-treatment and upon progression biopsy samples are required if medically feasible.

[redacted]

9.10.2.1 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.

9.10.2.2 LAG-3 and PD-L1 Expression

LAG-3 expression on immune cells and PD-L1 expression on tumor and immune cells will be measured [redacted].

[redacted]

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9.11 Additional Research Collection

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

For All US sites:

Additional research 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 additional research should be encouraged but will not be a condition of overall study participation.

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

- **For non-US Sites:**
- Additional research 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 additional research is intended to expand the translational R&D capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health

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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.

Additional research is intended to expand the R&D capability at Bristol Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

[redacted]

Sample Collection and Storage

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

Residual PK samples, [redacted] from scheduled and unscheduled collections (See Table 9.5-1 and Table 9.10-1) will also be retained for additional research purposes. This includes all materials derived and extracted from these samples including but not limited to [redacted] proteins, and other soluble factors.

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.

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Table 9.11-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
PK[redacted]	All
[redacted]	

Abbreviations: [redacted]; PK, pharmacokinetics; [redacted].

9.12 Other Assessments

Not applicable per Protocol Amendment 03: Serum will be collected for potential future measurements of anti-SARS-CoV-2 antibodies by serology (anti-SARS-CoV-2 total or IgG) to explore potential association with safety, efficacy, [redacted].

9.13 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

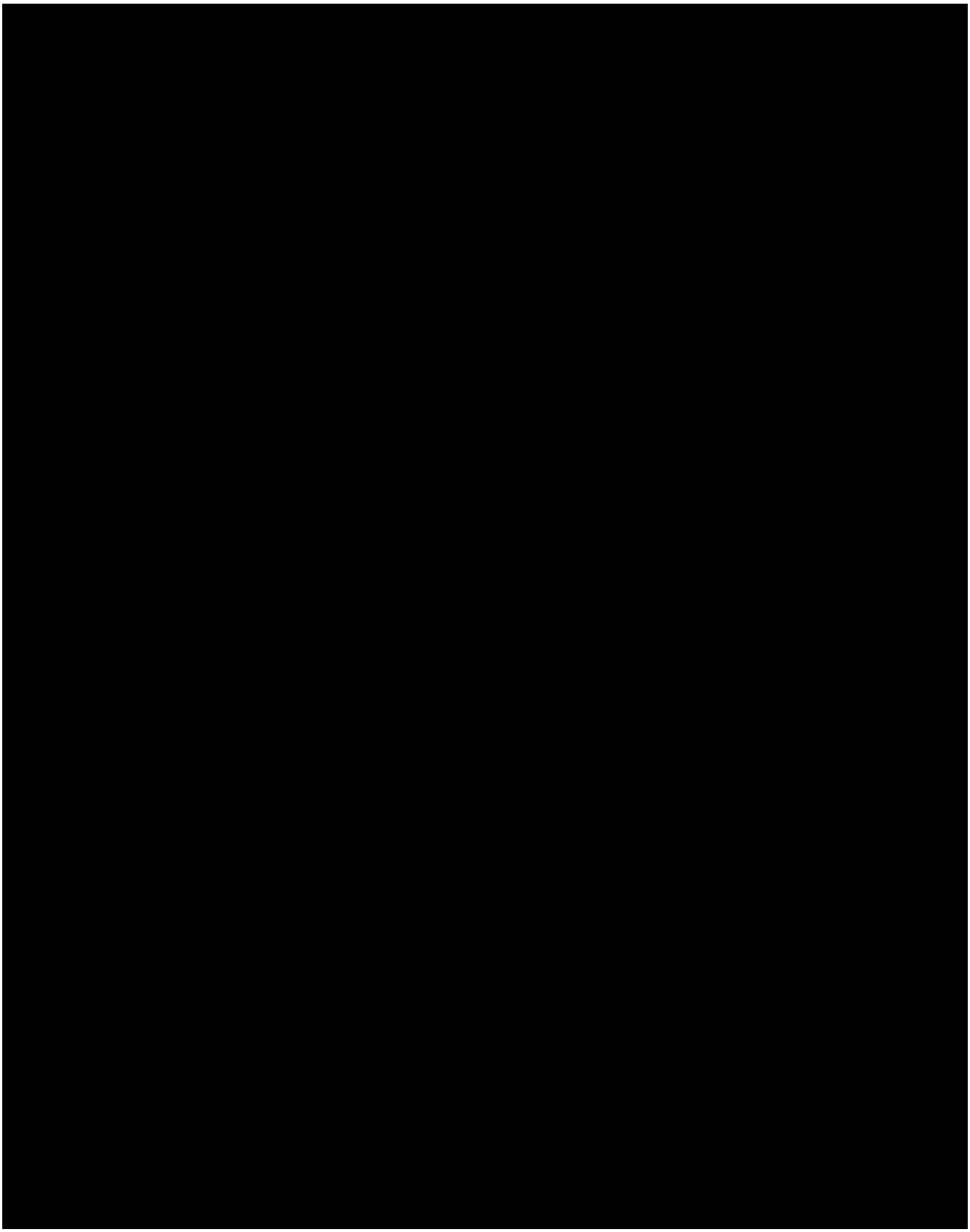
10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

The primary objective of Safety Lead-in is to determine RP2D of relatlimab and nivolumab in combination with bevacizumab (triplet therapy) based on DLT rate. No hypothesis testing will be performed for the Safety Lead-in. After RP2D is determined, then the study will evaluate ORR by RECIST v1.1 as assessed per BICR of triplet therapy relative to the nivolumab and bevacizumab doublet therapy in 2 populations of primary interest, the All Comer population and the population of all randomized subjects with EHS-No status at study entry. No formal hypothesis testing is planned, and an estimation approach will be used for both ORR and PFS analyses.

[redacted]

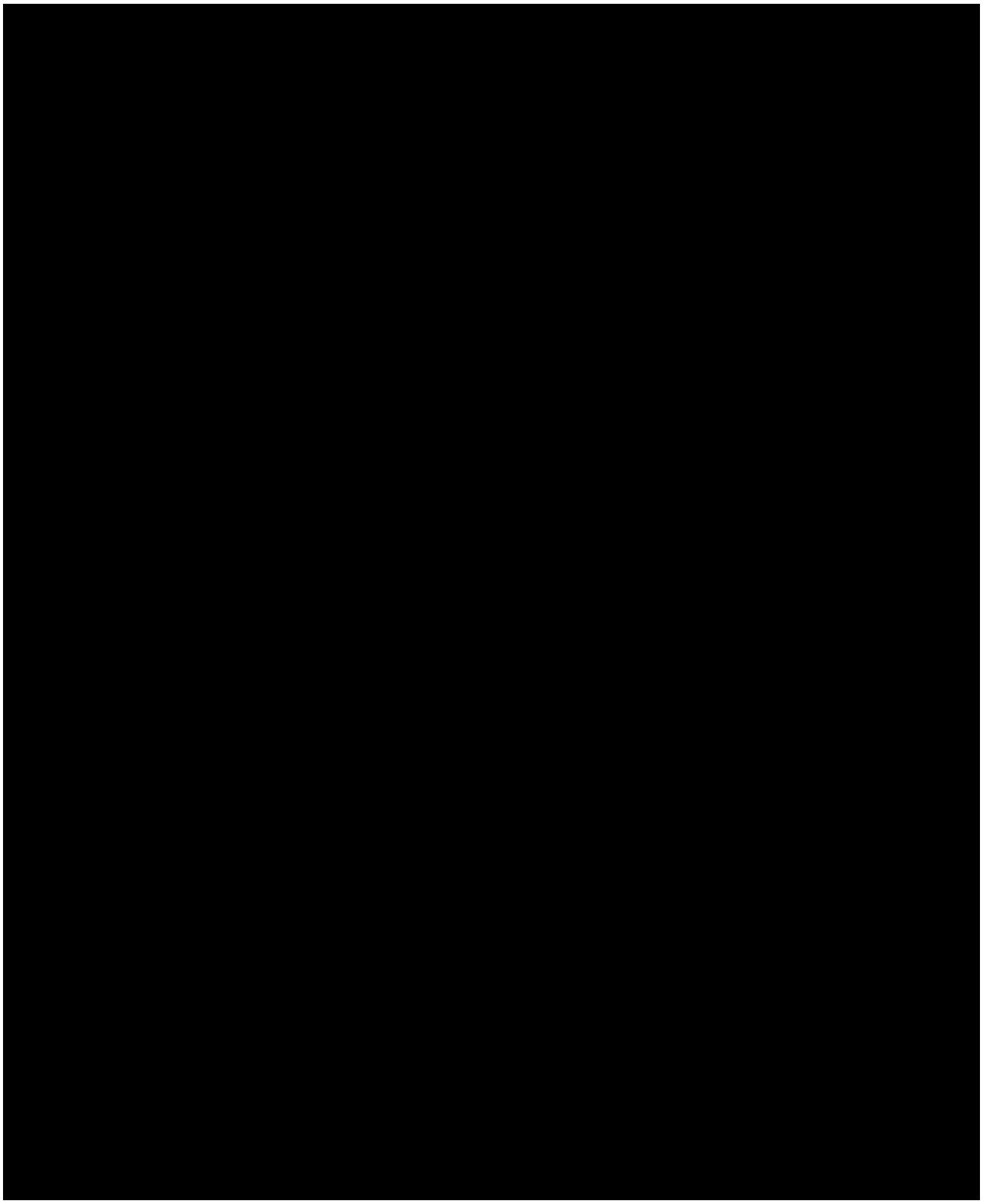
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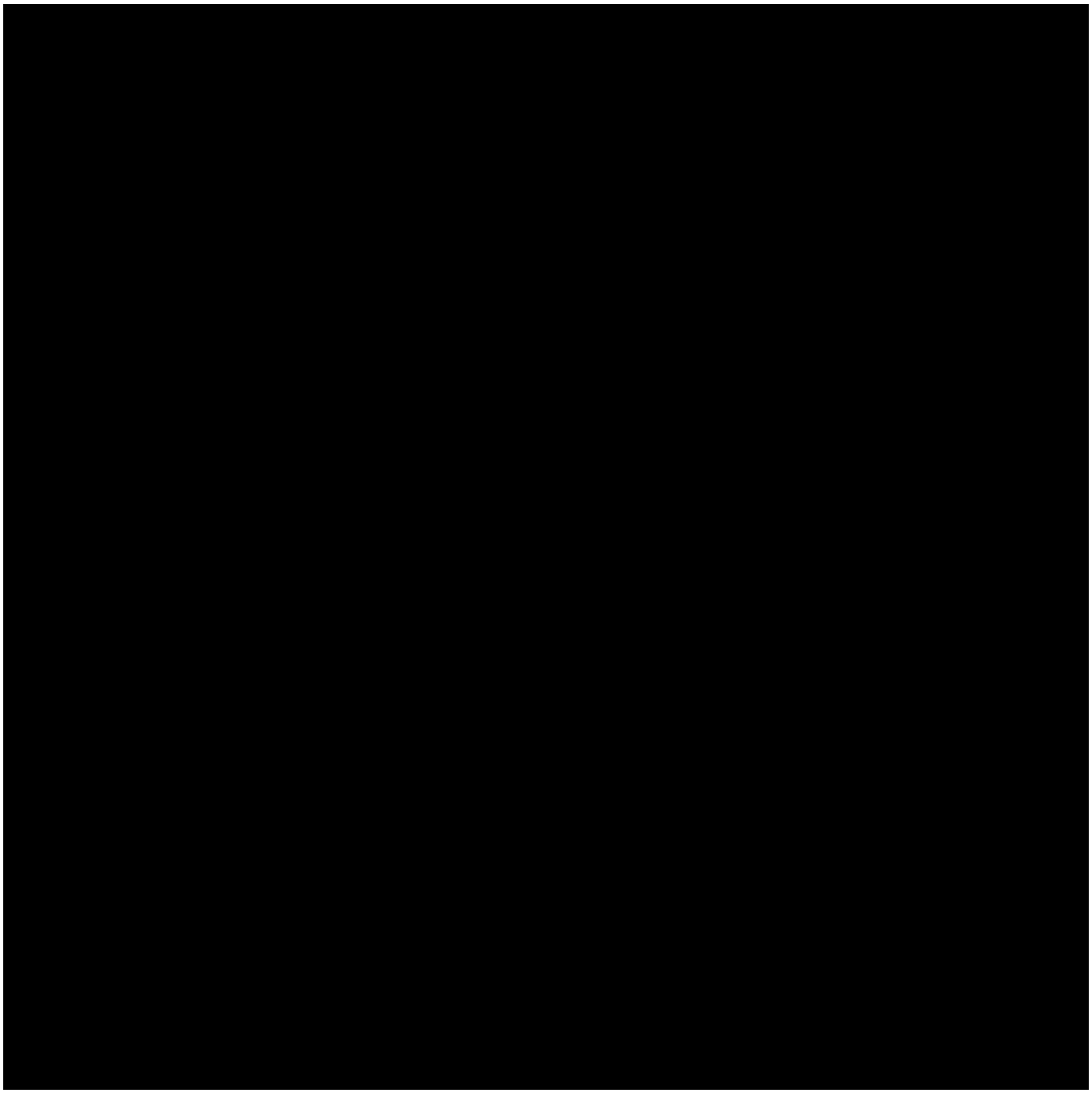
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[redacted]

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10.3 Analysis Sets

For the purposes of analysis, the following populations are defined in Table 10.3-1

Table 10.3-1: Analysis Sets

Population	Description
DLT Evaluable	DLT-evaluable is defined as treated (at least 1 dose) with all 3 drugs within the triplet regimen and followed during a 6-week DLT window or until a DLT is observed in both drugs (in less than 6 weeks). Participants who receive only 1 or 2 out of the 3-drug regimen will not be DLT evaluable for the triplet.
Enrolled	All participants, or their legally acceptable representative, if applicable, has agreed to participate in a clinical study following completion of the informed consent process, unless otherwise specified by the protocol.
Treated	All participants who received at least 1 dose of any study intervention. Participants will be included in the treatment group to which they were actually treated.
All Comers	All participants who were randomized using IRT in Part 1 and Part 2a of the study. Participants will be included in the treatment group to which they were randomized.
All Comers LAG-3	All participants who were randomized using IRT in Part 1 and Part 2a of the study with LAG-3 positive (≥ 1% by IHC) status at the time of randomization, as entered into the IRT.
Randomized EHS-No	All participants who were randomized using IRT in Part 1 and Part 2 of the study with EHS-No status at study entry
Randomized EHS-No, LAG-3	All participants who were randomized using IRT in Part 1 and Part 2 of the study with EHS-No status at study entry with LAG-3 positive (≥ 1% by IHC) status at the time of randomization, as entered into the IRT.

Abbreviations: DLT, dose limiting toxicity; IHC, immunohistochemistry; IRT, interactive response technology; LAG-3, lymphocyte activation gene 3.

10.4 Statistical Analyses

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

A description of the participant population will be included in the clinical study report, including subgroups of age, gender, race and other study specific populations and demographic

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characteristics. A description of participant disposition will also be included in the clinical study report.

10.4.1 General Considerations

The estimands for primary and secondary endpoints are described in Table 4-2.

10.4.2 Primary Endpoints

The primary endpoint for Safety Lead-in part is to determine RP2D using DLT rate, which is defined as the incidence of DLTs within the 6-week DLT window among DLT-evaluable participants in Arm A cohort. The incidence of DLTs will be calculated for DLTs attributable to relatlimab in combination with nivolumab and DLTs attributable to bevacizumab, separately, and compared to the decision rules in the mTPI-2 design to guide the dose de-escalation/stay decision for each drug.

The primary endpoint for Phase 2 part is to evaluate ORR of the triplet relative to the doublet therapies. ORR is defined as the number of randomized participants who achieve a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) based on BICR using RECIST v1.1 assessments divided by the number of all randomized participants. The primary endpoint ORR will be investigated in both populations, All Comers as well as by EHS status at study entry with focus on the 'EHS-No' subgroup.

Table 10.4.2-1: Primary Endpoint

Primary Endpoint	Description	Timeframe
Incidence of dose limiting toxicity (DLT)	Percent of participants with DLT among DLT evaluable participants	6-week DLT window after first dose date or until a DLT is observed in both relatlimab and bevacizumab (if it occurs less than 6 weeks)
Objective response rate (ORR)	ORR is defined as the number of randomized participants in the population of interest who achieve a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) based on BICR assessments divided by the number of all randomized participants in the analyzed population of interest. ORR is assessed by BICR using RECIST v1.1. Populations of interest are All Comers (Part 1 and Part 2a) and participants with EHS-No Status at study entry (Part 1 and Part 2)	Tumor assessments should continue until disease progression (including progression on treatment beyond initial progression) or death, whichever is earlier

Abbreviations: BICR, blinded independent central review; DLT, dose limiting toxicity; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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ORR will be assessed in each population of primary interest in the 2 treatment groups, using a simple proportion and 90% Clopper-Pearson confidence intervals by treatment group for this study.

The difference in ORR in the triplet therapy relative to the doublet therapy will be presented. Additionally, the posterior mean of the difference of ORR between the 2 arms and the corresponding 90% credible intervals will also be provided. [redacted]

10.4.3 Secondary Endpoints

The secondary endpoints and statistical analysis methods are described in Table 10.4.3-1. There is no adjustment for multiplicity for secondary endpoints.

Table 10.4.3-1: Secondary Endpoints

Secondary Endpoint	Description	Timeframe	Statistical Analyses Methods
PFS	PFS is defined as the time from randomization to first documented progression or death due to any cause, whichever is earlier. Participants without PFS events will be censored at last evaluable tumor assessment. PFS is assessed by BICR using RECIST v1.1 and will be evaluated in the populations of interest (All Comers [Part 1 and Part 2a] and participants with EHS-No status at study entry [Part 1 and Part 2] and complement).	When 6-month follow-up available for all randomized participants	HR from unstratified Cox regression model will be presented. Median PFS will be estimated for each arm, along with the respective 90% CIs. PFS rates at specific points (ie, 6 months, 12 months, etc) will be computed along with their 90% CIs.
PFS in all randomized LAG-3 positive (≥ 1% by IHC) participants	Same definition as PFS (ie, will be evaluated in the same populations of interest), but in LAG-3-expressing participants.	When 6-month follow-up available for all randomized participants	HR from unstratified Cox regression model will be presented, along with 90% CIs for each treatment group.
ORR in LAG-3 positive (≥ 1% by IHC) participants	Same definition as primary endpoint (ie, will be evaluated in the same populations of interest), but in LAG-3-expressing participants.	Same timeframe as primary endpoint.	Estimates of response rate, along with its exact 2-sided 90% Clopper-Pearson CIs for each treatment group will also be presented.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; EHS, extrahepatic spread; HR, hazard ratio; IHC, immunohistochemistry; LAG-3, lymphocyte activation gene 3; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

10.4.4 Exploratory Endpoint(s)

The exploratory endpoints, including OS, and corresponding analyses will be described in the SAP finalized before database lock.

10.4.5 Other Safety Analysis

Unless specified otherwise, safety analyses will be performed on all Treated Participants. The assessment of safety will be based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, select AEs, IMAEs, and abnormalities in specific clinical laboratory assessments. See Section 9.2 for details. AEs from first dose date (of any study medication) to 30 or 135 days after last dose date will be summarized by treatment arm. AEs will be coded using the most current version of the MedDRA. AEs and laboratory values will be graded for severity according to the NCI CTCAE v5.0.

10.4.6 Other Analyses

10.4.6.1 Pharmacokinetic Analyses

The relatlimab and nivolumab concentration data obtained in this study will be pooled with data from other studies in the clinical development program to develop or refine the relatlimab and nivolumab population PK models. These models will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of relatlimab and nivolumab and to determine measures of individual exposure. The model determined exposures of relatlimab and nivolumab may be used for exposure-response analyses for safety endpoints (eg, Gr3+ DRAEs and Gr2+ IMAEs) and efficacy endpoints (eg, PFS, ORR, and OS). Results of the population PK and exposure-response analyses will be reported separately.

[redacted]

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12 APPENDICES

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APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
µL	microliter
1L	first-line
2L	second-line
AASLD	American Association for the Study of Liver Disease
[redacted]	
AE	adverse event
AFP	alpha-fetoprotein
AIDS	acquired immunodeficiency syndrome
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]	
AxMP	auxiliary medicinal product
β-HCG	beta-human chorionic gonadotrophin
Bcl-xL	B-cell lymphoma-extra large
BICR	Blinded Independent Central Review
BMS	Bristol-Myers Squibb Company
BOIN	Bayesian optimal interval
BOR	best overall response
BP	blood pressure
BSC	best supportive care
BTLA	B- and T-lymphocyte attenuator
BUN	blood urea nitrogen
Cavg	average concentration
Cavgss	average serum concentration at steady state
CBC	complete blood count

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Term	Definition
CBR	Clinical benefit rate
CD	cluster of differentiation
Ceoinf	observed concentration at the end of infusion
Ceoinf	observed concentration at the end of infusion
CFR	Code of Federal Regulations
cHL	Classical Hodgkin's Lymphoma
CI	confidence interval
CPK	Creatine phosphokinase
CL	clearance
CLss	steady-state clearance
Cmax	maximum concentration
Cmin	minimum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CrCl	creatine clearance
CRF	Case Report Form, paper or electronic
CT	computed tomography
CTAg	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
[redacted]	[redacted]
Ctrough	trough-observed plasma concentration
CV	coefficient of variation
[redacted]	[redacted]
D	day
DAA	direct-acting antiviral
DC	discontinuation
DCR	disease control rate
DILI	drug-induced liver injury

Term	Definition
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
[redacted]	
E-R	exposure-response
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
eg	exempli gratia (for example)
EGD	Esophagogastroduodenoscopy
eGFR	estimated glomerular filtration rate
EHS	extrahepatic spread
EHS-No	without extrahepatic spread
EHS-Yes	with extrahepatic spread
[redacted]	[redacted]
EOI	end of infusion
EOT	end of treatment
E-R	Exposure-response
etc	et cetera
EU	European Union
EUDRACT	European Union Drug Regulating Authorities Clinical Trials Database
EWB	emotional well-being
FACT-G	Functional Assessment of Cancer Therapy-General version
FACT-Hep	Functional Assessment of Cancer Therapy - Hepatobiliary
FDA	Food and Drug Administration
FDC	fixed dose combination
FFPE	formalin-fixed, paraffin-embedded
FGL1	fibrinogen like ligand-1
[redacted]	[redacted]
FSH	follicle-stimulating hormone

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Term	Definition
FU	follow-up
FWB	functional well-being
g	gram
[redacted]	[redacted]
GCP	Good Clinical Practice
GI	gastrointestinal
GP5	Functional Assessment of Cancer Therapy-General version (FACT-G) single item (“I am bothered by side effects of treatment”)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCS	hepatobiliary cancer subscale
HCV	hepatitis C virus
HIV	human immunodeficiency virus
[redacted]	[redacted]
hr	hour
HR	hazard ratio
HRQoL	health related quality of life
HRT	hormone replacement therapy
[redacted]	[redacted]
IB	Investigator 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
[redacted]	[redacted]
ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
Ig	immunoglobulin
IgG	immunoglobulin G
IHC	immunohistochemistry

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Term	Definition
IL	interleukin
[redacted]	[redacted]
IMAE	immune-mediated adverse event
[redacted]	[redacted]
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IO	immuno-oncology
IP	investigational product
IQR	Interquartile range
IRB	Institutional Review Board
IRT	interactive response technology
IU	international unit
IUS	intrauterine hormone-releasing system
IV	intravenous
kD	dissociation constant
kg	kilogram
L	liter
LAG-3	lymphocyte activation gene-3
LAM	lactation amenorrhea method
LCM	lifecycle management
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
m^2	meters squared
[redacted]	[redacted]
mDOR	Median duration of response
MDSC	myeloid derived suppressor cells
MedRA	Medical Dictionary for Regulatory Activities
MEL	melanoma
mg	milligram
[redacted]	[redacted]
MHC	major histocompatibility complex
MID	minimally important difference

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Term	Definition
min	minute
mL	milliliter
mmHg	millimeters of mercury
MMR	measles, mumps, rubella
MOA	mode of action
mOS	median overall survival
mPFS	median progression-free survival
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval-2
MUGA	multigated acquisition
N	number of participants or observations
N/A	not applicable
NCI	National Cancer Institute
NE	not estimable
ng	nanogram
[redacted]	[redacted]
NIH	National Institutes of Health
Nivo	nivolumab
[redacted]	[redacted]
nM	nanomolar
Non-IMP	Noninvestigational Medicinal Product
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
[redacted]	[redacted]
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-1+	programmed cell death-1-positive
p-DILI	potential drug-induced liver injury

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Term	Definition
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival 2
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
PPK	population pharmacokinetics
PR	partial response
PRES/RPLS	Posterior reversible encephalopathy syndrome/ Reversible Posterior Leukoencephalopathy Syndrome
PRO	patient-reported outcome
PROMIS	Patient-reported Outcome Measurement Information System
PROMIS PF 8c	Patient-reported Outcome Measurement Information System Physical Function Short Form 8c
PT	prothrombin time
PWB	physical well-being
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QSP	quantitative systems pharmacology
R&D	research and development
RP2D	recommended Phase 2 dose
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
Rela	relatlimab
RNA	ribonucleic acid
[redacted]	[redacted]
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	[redacted]

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Term	Definition
SCCHN	squamous cell carcinoma of the head and neck
SC	Safety Committee
SD	standard deviation
SJS	Stevens-Johnson syndrome
[redacted]	[redacted]
SmPC	summary of products characteristics
SSC	Study Steering Committee
SUSAR	suspected, unexpected serious adverse reaction
SWB	social/family well-being
t1/2	half-life
T3	triiodothyronine
[redacted]	[redacted]
T4	thyroxine
TB	total bilirubin
T.bili	total bilirubin
TEN	toxic epidermal necrolysis
[redacted]	[redacted]
TILs	tumor-infiltrating lymphocytes
TnI	troponin I
TnT	troponin T
TRAE	Treatment-related adverse event
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiogram
TSST	time to second subsequent therapy
ULN	upper limit normal
US	United States
USPI	United States Prescribing Information
UTN	Universal Trial Number
VEGF	vascular endothelial growth factor
vs	versus
Vss	apparent volume of distribution at steady state
VTE	venous thromboembolism
WBC	white blood cell

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Term	Definition
[redacted]	[redacted]
WHO	World Health Organization
WOCBP	women of childbearing potential
WWPS	Worldwide Patient Safety

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APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

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- ICH guidelines
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Regulation 536/2014 for clinical studies
- European Medical Device Regulation 2017/745 for clinical device research
- the IRB/IEC
- and all other applicable local regulations.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, also by the local Health Authority, must be sent to Bristol-Myers Squibb (BMS).

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant or his/her legally acceptable representativeand answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant or his/her legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant or his/her legally acceptable representativeto inquire about the details of the study.

Obtain an ICF signed and personally dated by participant or his/her legally acceptable representativeand by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

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

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

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

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

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

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

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assess and improve its ability to protect, detect, and respond to cyberattacks 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

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in the Site Process and Source Documentation (SPSD) form.

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

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

STUDY INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention integrity and traceability from receipt, preparation, administration,

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and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

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

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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.

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

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- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reas4on for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases

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in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

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

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

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

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

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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.

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

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

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SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality

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

- **Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term[s] initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic case report form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed facsimile transmission.

SAE Email Address: [redacted]

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

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APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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

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

End of Relevant Systemic Exposure

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

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 (rings) – 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.

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• 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. A vasectomy is a highly effective contraception method provided that the participant 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 participant chooses to forego complete abstinence. • Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants 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. For information specific to this study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this

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study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol..

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, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • 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 Appendix 3.

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[redacted]

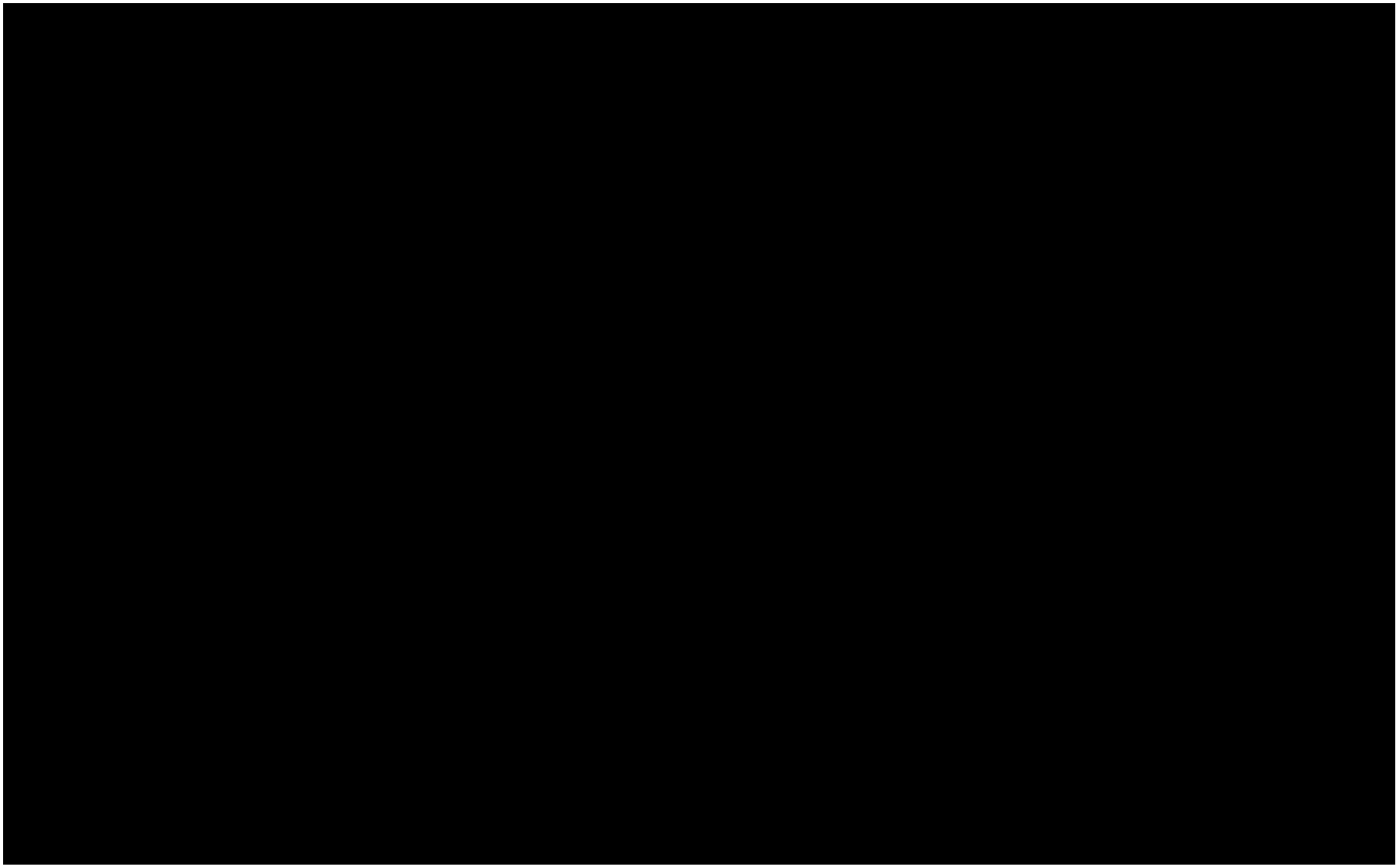
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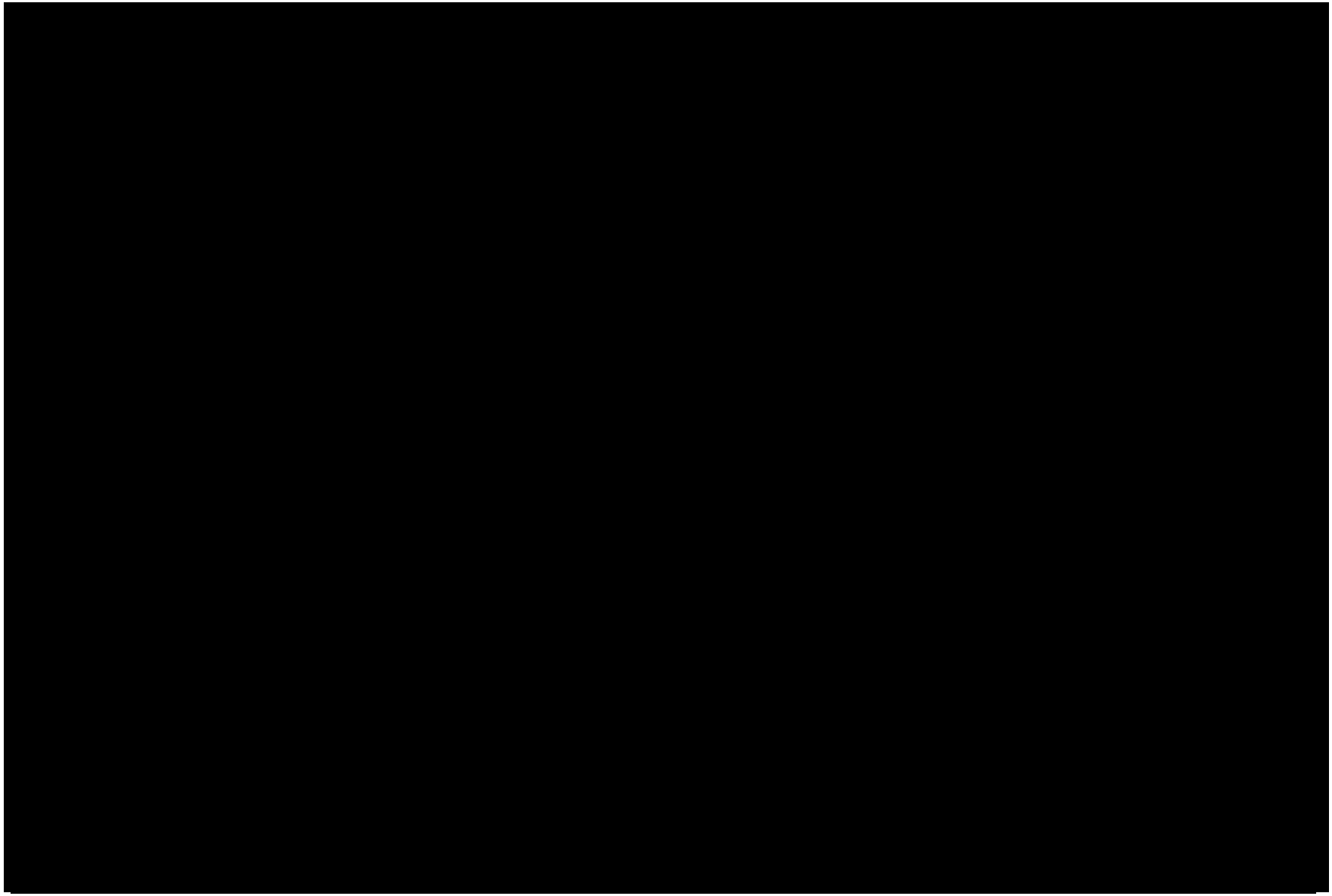


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[redacted]

14-Jan-2022

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APPENDIX 6 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

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APPENDIX 7 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.

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APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES

Country/Location Requirement	Original Language/ Section Number	Country-specific Language or Differences
Germany	Table 2-1, Screening Procedural Outline (CA224106)	Add human immunodeficiency virus to the list of laboratory tests.
France	Section 6.2: Exclusion Criteria	Add new Exclusion Criteria (EC) 1) q) and 1) r) to EC 1) Medical Conditions: 1) q) Prior history of pneumonitis and/or interstitial lung disease (ILD). 1) r) Prior history of Stevens-Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN).
France	Table 2-2: On Study Treatment Procedural Outline (CA224106)	Add "X" to End of Treatment (EOT) column for electrocardiogram (ECG).
France	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." The following statement is deleted: "If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/Clinical Scientist must occur."
		Add to discontinuation criteria bullets an item for D/C due to severe infection.
France/Italy	Section 8.1: Discontinuation from Study Treatment	Add to discontinuation criteria bullets an item for discontinuation due to product inefficacy.

Japan	Appendix 4
	Contraception Guidance for Female Participants of Child Bearing Potential
		Following methods of contraception are not approved/certified in Japan:
		Highly Effective Contraceptive Methods That Are User Dependent
		• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation
		  • intravaginal (vaginal birth control suppositories, rings, creams, gels)
		  • transdermal
		• Progestogen-only hormonal contraception associated with inhibition of ovulation
		  • oral
		  • injectable
		• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation

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Country/Location Requirement	Original Language/ Section Number	Country-specific Language or Differences
		Less Than Highly Effective Contraceptive Methods That Are User Dependent • Female condom with or without spermicide. • 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 **Unacceptable Methods of Contraception** Spermicide only

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APPENDIX 9 BARCELONA-CLINIC LIVER CANCER (BCLC) STAGING

Stage	Performance Status	Tumor Stage	Okuda Stage	Liver function
A1	0	Single, < 5 cm	I	No portal hypertension, normal bilirubin
A2	0	Single, < 5 cm	I	Portal hypertension, normal bilirubin
A3	0	Single, < 5 cm	I	Portal hypertension, abnormal bilirubin
A4	0	3 tumors, < 3 cm	I-II	Child-Pugh A-B
Stage B: Intermediate HCC	0	Large, multinodular	I-II	Child-Pugh A-B
Stage C: Advanced HCC	1-2	Vascular invasion or extrahepatic spread	I-II	Child-Pugh A-B
Stage D: End-Stage HCC	3-4	Any	I-II	Child-Pugh C
Stage A and B: All criteria need to be fulfilled Stage C: At least one of the following criteria needs to be filled: performance status 1-2 or vascular invasion/extrahepatic spread. Stage D: At least one of the following criteria needs to be filled: performance status 3-4 or Okuda Stage III/Child Pugh C.				

Reference: Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis.* 1999 19 (3)329-38.

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APPENDIX 10 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 < 10mm 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.

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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.

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- **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.

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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 (< 10mm 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

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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.

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2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

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
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

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

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

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.

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APPENDIX 11 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02, 20-Mar-2023

The primary rationale for Protocol Amendment 02 is to make overall study design changes in Part 2 (Phase 2) of the study.

The primary and secondary endpoints in Part 2 have been updated to objective response rate (ORR) and progression-free survival (PFS), respectively. ORR has been selected as the primary endpoint after analysis of recently available clinical data of immunotherapy in first-line metastatic hepatocellular carcinoma (HCC) that suggest that ORR is more closely associated with overall survival (OS) and may be a better surrogate than PFS, which exhibits suboptimal performance as a surrogate for OS.

[redacted]

The original design of Study CA224106 was a double-blinded study utilizing an independent Data Monitoring Committee (DMC) to provide general oversight and safety considerations during Part 2. The protocol has been updated to unblind the Sponsor while keeping both sites and participants blinded, therefore eliminating the need for external committee oversight, allowing direct safety oversight from the study team and enabling exploratory ORR assessments to support future decision-making. The internal Safety Committee's (SCs) responsibility for assessing safety and efficacy in Part 1 will be extended to Part 2. As of the date of this amendment, Part 2 has not started and the previously described DMC has not been initiated.

Additional revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

This amendment incorporates the changes from the approved Administrative Letters 01 and 02, which are detailed in the Document History but not listed in the Summary of Key Changes below.

Minor editorial, formatting, and typographical corrections have been made and therefore have not been summarized.

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	Protocol title was revised to reflect removal of Sponsor blinding. Added credentials for the Clinical Scientist.	Due to study design update, title has been modified. For completeness.
Table 2-1: Screening Procedural Outline (CA224106)	In the note for "Thyroid Function Tests", added that this testing will be	Thyroid function testing collection window was added to clarify the

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	performed within 14 days prior to administration of study intervention.	allowable timing for sample collection.
	In the row for "Serology" added that if a local laboratory was unable to perform the required testing, a central laboratory may be utilized with Sponsor approval.	Utilization of a central laboratory for some sampling requirements added to assist with site operations, where needed.
Table 2-2: On Study Treatment Procedural Outline (CA224106)	The row for "2-D ECHO" was removed.	2-D ECHO was included erroneously and was removed to reduce patient burden of unnecessary assessments.
	In the row for hepatitis testing, removed "quantitative" from the procedure type and added that if a local laboratory was unable to perform the required testing, a central laboratory may be utilized with Sponsor approval.	Qualitative testing is acceptable for this assessment.
	[redacted]	
Table 2-3: Follow-up Assessments (CA224106)	In the row for hepatitis testing, removed "quantitative" from the procedure type and added that if a local laboratory was unable to perform the required testing, a central laboratory may be utilized with Sponsor approval.	Qualitative testing is acceptable for this assessment.
	In the row for "Tumor Tissue Sample Collection Upon Progression", added that tumor collection upon progression will be done only for those participants who progressed after a CR or PR, if medically feasible.	Tumor biopsies collected upon progression will aid in understanding acquired resistance to these therapies.
Section 3: Introduction Section 5: Study Design Section 5.1: Overall Design Section 5.4.1: Rationale for Blinding	Study design was changed from double-blind to site and participant blinded.	Updated due to changes in study design.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1: Study Interventions Administered Section 7.3: Blinding		
Section 3.1.1: Research Hypothesis	Revised to reflect that the primary endpoint is objective response rate (ORR) as opposed to progression-free survival (PFS).	Updated due to changes in study design.
Section 3.3: Benefit/Risk Assessment	The Data Monitoring Committee will now be replaced by an internal Safety Committee (SC).	As this study is no longer Sponsor-blinded, external oversight is no longer required to ensure participant safety and scientific integrity.
Section 3.3.3: Overall Benefit/Risk Conclusion	Added that the Sponsor will evaluate dose-limiting toxicities and safety of the triplet regimen when approximately 12 total participants have been treated and then when approximately 24 total participants are treated, and the internal SC will evaluate if dose de-escalation is warranted.	Updated due to changes in study design.
Table 4-1: Objectives and Endpoints	The primary objective and endpoint were updated to ORR rather than PFS. Secondary endpoints were updated. Table footnote ‘a’ was updated.	Updated due to changes in study design.
Table 4-2: Estimands for the Primary and Secondary Endpoints	Updated to reflect the change in primary and secondary objectives to ORR and PFS, respectively. Adverse event (AE)/serious adverse event (SAE)/immune-mediated adverse event (IMAE) estimands were removed.	Updated due to changes in study design. Estimands for AE/SAE/IMAEs are not required.
Figure 5-1: Study Design Schema	Figure was replaced with an updated study design schema.	Updated due to changes in study design.
Section 5.1: Overall Design [redacted]	[redacted] The analysis for the primary endpoint of ORR was updated.	Language updated to improve clarity. Updated due to changes in study design.
Section 5.1.4.1: Data Monitoring Committee	Section no longer applicable.	Updated due to changes in study design.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.4.2: Internal Safety Committee	Section was updated with SC responsibilities.	Updated due to changes in study design.
Section 5.1.4.3: Blinded Independent Radiology Central Review	Newly created section providing details for blinded independent central review (BICR) of images.	Section created to document the role of the radiology BICR.
Section 5.1.4.4: Study Steering Committee	Newly created section giving details of who comprises the Study Steering Committee (SSC) and their role.	Section created to document the formation of the SSC and describe its role.
Section 5.4: Scientific Rationale for Study Design	Removed “double-blind”.	Due to change in study design.
Section 5.4.1: Rationale for Blinding	Added that measurement of primary and secondary endpoints of ORR and PFS will be conducted by BICR.	To confirm minimal bias from unblinding Sponsor.
Section 5.4.2: Rationale for Objective Response Rate as Primary Endpoint	The section was updated to reflect the rationale for ORR as the primary endpoint.	Updated due to changes in study design.
Section 6.1: Inclusion Criteria	Criterion #5 updated to remove language relating to male participants who are sexually active with women of childbearing potential. Criterion #5)b)i) was updated for male participants.	Updated to align with program standards.
Table 7.1.1-1: Study Interventions: Arm A Table 7.1.1-2: Study Interventions: Arm B	Added that biosimilars for bevacizumab are not permitted. In the row for “Unit Dose Strength(s)”, removed the dose/vial for all study interventions.	Updated for clarity. Updated to allow for various bevacizumab vial availability in different regions.
Section 7.3: Blinding	Section was updated with blinding details, and language regarding data monitoring committee (DMC) was removed.	Updated due to changes in study design.
Section 7.7.1: Prohibited and/or Restricted Treatments	Added that while concomitant chronic use of oral nonsteroidal anti-inflammatory drugs is prohibited, topical and transdermal patches are acceptable.	Clarified prohibited and/or restricted treatments.
Section 9.2.5: Pregnancy	Added language that this is not applicable for women not of childbearing potential and the procedure to follow if a participant discovers they are pregnant.	Updated to align with program standards.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.1: Statistical Hypotheses [redacted] Section 10.4.2: Primary Endpoints	[redacted]	Updated due to changes in study design.
[redacted]		
Table 10.4.2-1: Primary Endpoint	Table was updated.	Updated due to changes in study design.
Table 10.4.3-1: Secondary Endpoints	Table was updated.	Updated due to changes in study design.
[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 Bristol-Myers Squibb (BMS) Company commitment to diversity in clinical trials and to comply with European Union Clinical Trials Regulation requirement.
Appendix 8: Country Specific Requirements/Differences	Added Germany-specific requirements. Added France-specific requirements.	To document the requirement to perform human immunodeficiency virus testing during screening for participants in Germany. To eliminate the need for a French-specific version of the protocol.

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Overall Rationale for Protocol Amendment 01, 16-Feb-2022:

Protocol Amendment 01 for CA224106 includes a number of changes made [redacted], including revisions to the dose-limiting toxicity criteria for relatlimab and bevacizumab, and reducing the target toxicity rate from 45% to 25%. The revised toxicity rate will more appropriately reflect the expected incidence of treatment-related Grade 3 or higher adverse events during the first 6 weeks of treatment and reduce the chance of selecting a Phase 2 dose with an unacceptable safety profile. Changes made to dose-limiting toxicity criteria will make the selection of the recommended Phase 2 dose more conservative and further reduce the chances of selecting an inappropriate/toxic dose. Additional clarifying revisions were made [redacted], as detailed in the following table.

In addition, several minor changes were made at this time to align with current BMS program standards, to further clarify certain sections, [redacted].

CA224106 has not yet started enrollment as of the time of Protocol Amendment 01, and no participants will be enrolled under the original protocol.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	• [redacted] - Medical Monitor changed.	Change to staff.
Protocol Summary	• Revised to reflect the revisions in the body of the protocol.	For consistency throughout the protocol document.
Table 2-1: Screening Procedural Outline (CA224106)	• Simplified table columns, moved timing instructions to notes column.	Increase clarity and readability.
Table 2-1: Screening Procedural Outline (CA224106) Table 4-1: Objectives and Endpoints Section 6.1: Inclusion Criteria: 2)e)ii) [redacted] Section 9.10.2: Tumor Samples 9.10.2.2: LAG-3 and PD-L1 Expression [redacted]	[redacted]	[redacted].

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted] Section 9.11: Additional Research Collection		
Table 2-2: On Study Treatment Procedural Outline (CA224106)	• Revised the safety lead-in collection from Day 14 to Day 15. • Updated to include weekly collection up to and including Week 9 of Troponin T or I, CPK, LDH, and AST/ALT/T.bili. • Removed the up to 7 days prior to dosing testing allowance for Quantitative HBsAG, HBV DNA, HCV RNA. • Home pregnancy testing option removed.	• Adjusted for increased clarity. • Updated to align with increased participant safety monitoring for IMAEs. • Removed to align BMS HCC Program standards. • Removed to align BMS Program standards.
Figure 5-1: Study Design Schema	• Revised schema and footnotes for treatment Phase 2 doses for Arm A relatlimab and bevacizumab to clarify further that the recommended Phase 2 dose will be used.	Increase clarity within the study schematic.
Section 5.1: Overall Design	• Additional clarification added for Arm A dose de-escalation.	Increase clarity for sites.
Section 5.1.1: Dose Limiting Toxicities	• Clarification added for determining DLT-evaluable participants.	[redacted].

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.1.2: DLTs Attributed to Immunotherapy		
Section 5.1.1.1: DLTs Attributed to Bevacizumab	• Updated list of toxicities.	Updated to align with bevacizumab package insert.
Section 6.1: Inclusion Criteria	• Revised 4)b)iii) to clarify time from transfusion. • Corrected creatinine clearance to greater than or equal to 50 mL/min.	[redacted].
Section 7.1: Study Interventions Administered	• Revised to clarify and provide link to guidance for masking and unmasking bevacizumab.	[redacted]
Section 7.1.3: Palliative Therapy	• Revised to clarify palliative local radiation therapy considerations.	[redacted].
Section 7.4.1: Dose Delay/Discontinuation Criteria for Relatlimab and Nivolumab	• Revised to clarify discontinuation.	[redacted].
[redacted]		
Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Bevacizumab	• Added and/or revised adverse event guidance.	[redacted].
Section 8.1.1: Treatment Beyond Disease Progression	• Added note with additional guidance to clarify treatment beyond disease progression for	[redacted].

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	participants requiring urgent alternative medical intervention.	
Table 9.5-1: Pharmacokinetic [redacted] Sampling Schedule for Relatlimab, Nivolumab and Bevacizumab (CA224106)	• Sample collection on Cycle 4 Day 1 Predose has been added.	[redacted].
[redacted]		
Section 10.4.6.1: Pharmacokinetic Analyses [redacted]	• New sections added under Section 10.4.6: Other Analyses.	[redacted].

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 5: Management Algorithms for Studies Under CTCAE Version 5.0	• Removed nivolumab myocarditis algorithm. • Revised relatlimab myocarditis algorithm.	• Not required in appendix. • [redacted].
All	• Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

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