Official Title of Study:

A Randomized, Multi-center, Double-blinded, Placebo-controlled Phase 3 Study of Nivolumab and Ipilimumab, Nivolumab Monotherapy, or Placebo in Combination With Trans-arterial ChemoEmbolization (TACE) in Patients With Intermediate-stage Hepatocellular Carcinoma (HCC)

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Revised Date: 01-Dec-2021

CLINICAL PROTOCOL CA20974W

A Randomized, Multi-center, Double-blinded, Placebo-controlled Phase 3 Study of Nivolumab and Ipilimumab, Nivolumab Monotherapy, or Placebo in Combination with Trans-arterial ChemoEmbolization (TACE) in Patients with Intermediate-stage Hepatocellular Carcinoma (HCC)

(CheckMate 74W: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 74W)

Short Title: Nivolumab and Ipilimumab or Nivolumab or Placebo Plus TACE in Intermediate-stage Liver Cancer

Protocol Amendment Number: 01

Incorporates Administrative Letters 02, 03, and 04

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 01	01-Dec-2021	BMS determined [redacted] to stop the study. As a result, the study will be unblinded and the procedures for participants in treatment or in follow-up simplified.
Administrative Letter 04	16-Jul-2021	Updated study personnel information.
Administrative Letter 03	28-Apr-2021	Removed the 24-hr Emergency Telephone Number listed for Japan. This number will be retired, so Japan should use the provided international number instead.
Administrative Letter 02	26-Jan-2021	Updated study personnel information.
Administrative Letter 01	28-Jul-2020	Updated study personnel information.
Original Protocol	05-Aug-2019	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

[redacted]

Therefore, a decision was made by Bristol-Myers Squibb in September 2021 to stop the study. Importantly, there is no change to the understanding of the safety profile of nivolumab in combination with ipilimumab and trans-arterial chemoembolization (TACE) for the treatment of patients with intermediate-stage hepatocellular carcinoma (HCC).

Protocol Amendment 01 describes the modification to study procedures. All participants must be re-consented upon approval and implementation of Protocol Amendment 01. These changes affect all participants and should be implemented when Protocol Amendment 01 is implemented at the site.

Key changes in Protocol Amendment 01 include:

- Details of closure of the study with provision for participants currently on treatment or in the follow-up period to continue in the study as per the current protocol.
- The study will be unblinded.
- Removal of placebo infusions for participants in Arms B and C.
- Removal of pharmacokinetic (PK), immunogenicity (IMG), biomarker, and patient-reported outcome (PRO) assessments. **Only safety assessments will be conducted**.
- Removal of on-study imaging assessments. Sites should continue imaging assessments as per local standard of care.
- Removal of study-related efficacy assessments. Sites should continue efficacy assessments as per local standard of care.
- Align dose modification criteria and immuno-oncology agent management algorithms with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- Add the collection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-related adverse events (AEs) and serious adverse events (SAEs) to evaluate the impact of SARS-CoV-2 on participant safety and add coronavirus disease 2019 (COVID-19) vaccination information for study participants.
- Incorporate country-specific information for France, Czech Republic, and China; incorporate additional updates to improve alignment across protocol sections and/or clarify expectations for assessments, sample collections, and treatment administration.

This amendment incorporates the changes from the approved Administrative Letter 02, 03 and 04 that are detailed in the Document History but not listed in the Summary of Key changes below.

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

Changes instituted in Protocol Amendment 01 should override any existing protocol requirements in the event of any apparent discrepancies.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor editorial changes.	Minor, therefore have not been summarized.
All	Where applicable, "designee" was updated to "Clinical Scientist" in the text.	Clinical Scientist will be the designee for the Medical Monitor.
Section 2: Schedule of Activities Section 5.1.2: Treatment Period Section 6.1: Inclusion Criteria, 2) Type of Participant and Target Disease Characteristics Section 8.1: Discontinuation from Study Treatment Section 9.2.6: Pregnancy Section 9.5: Pharmacokinetics and Immunogenicity Section 9.6: Pharmacodynamics Section 9.8: Biomarkers	Added references to Appendix 9 where applicable. • Table 2-1: Screening Procedural Outline (CA20974W), Tumor Sample Submission Row. • Table 2-2: On-treatment Procedural Outline (CA20974W), Footnote c. • Table 2-3: Follow-up Procedural Outline (CA20974W), Footnote d. • Section 6.1, 2), c), ii). • Table 9.8-1: CA20974W Biomarker Sampling Schedule All Participants, Footnote d. • Text in Sections 5.1.2, 8.1, 9.2.6, 9.5, 9.6, and 9.8.	To provide a reference to the country-specific requirements where applicable.
Table 2-1: Screening Procedural Outline (CA20974W) Table 2-2: On-treatment Procedural Outline (CA20974W) Table 2-3: Follow-up Procedural Outline (CA20974W)	Language added to include the collection of SARS-CoV-2 infection-related AEs and SAEs.	To allow for the evaluation of the impact of SARS-CoV-2 infection on participant safety.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.2: Time Period and Frequency for Collecting AE and SAE Information Section 9.2.4: Follow-up of AEs and SAEs		
Table 2-1: Screening Procedural Outline (CA20974W) Table 2-2: On-treatment Procedural Outline (CA20974W) Table 2-3: Follow-up Procedural Outline (CA20974W)	AE language updated to mention CTCAE version 5.0 grading.	To identify the NCI CTCAE standards used in the study.
Table 2-2: On-treatment Procedural Outline (CA20974W) Section 5.1.2: Treatment Period Section 7.1.2: TACE Procedure	TACE timing should be 7 days (+ 3 days). Removed the minus.	To clarify the timing of the TACE procedure, as it was found to cause confusion.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On-treatment Procedural Outline (CA20974W)	1. Updated Column 2 header to indicate that ipilimumab is administered Q6W. 2. Pregnancy language updated to include a 72-hour extension. Additionally, "monthly" was updated to "every 28 days." 3. Added Urinalysis row. 4. Language for Efficacy, PK and IMG, Biomarker, and Outcomes Research Assessments, and Clinical Drug Supplies updated to reflect changes made to on-treatment study procedures as a result of study termination. 5. Added footnote d.	1. Correction. 2. To accommodate scenarios in which pregnancy test results cannot be obtained within the standard 24-hour window. Clarified the time period for monthly collection. 3. To clarify that urinalysis is required during on treatment as outlined in Section 9.4.4. 4. To describe the modifications made to study procedures as a result of study termination. 5. To clarify timing of nivolumab and ipilimumab dosing.
Table 2-3: Follow-up Procedural Outline (CA20974W)	Review of Subsequent Cancer Therapy; Efficacy, PK and IMG, Biomarker, and Outcomes Research Assessments; Survival Status; and Footnote b language updated to reflect changes made to follow-up study procedures as a result of study termination.	To describe the modifications made to study procedures as a result of study termination.
Section 3.1: Study Rationale	Removed "preliminary" to describe CA209040 data. Added approval of nivolumab with ipilimumab for the treatment of HCC in patients who previously received sorafenib.	Minor text updates.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1.1: Research Hypothesis	Updated to reflect changes made to the research hypothesis as a result of study termination.	To describe modifications made to the research hypothesis as a result of study termination.
Section 3.1.2: Changes Per Protocol Amendment 01	Added Section 3.1.2 to reflect changes made to the study procedures as a result of study termination.	To describe the modifications made to study procedures per Protocol Amendment 01 as a result of study termination.
Section 3.2.4: Nivolumab Mechanism of Action	Updated description of nivolumab mechanism of action.	Minor text updates.
Section 3.2.7: Nivolumab Combined with Ipilimumab Clinical Activity	Reference to additional information and description of the nivolumab/ipilimumab combination in the Investigator's Brochure (IB).	Minor text updates.
Section 3.2.8: Nivolumab Combined with Ipilimumab in HCC	Addition of CA2099DW to studies for the treatment of HCC.	Minor text updates.
Section 3.3: Benefit/Risk Assessment	Addition of COVID-19 vaccination language to the benefit/risk section.	To inform that non-live COVID-19 vaccination is considered a simple concomitant medication within the study and that the efficacy and safety of non-live vaccines in this patient population is unknown.
Section 4: Objectives and Endpoints Table 4-1: Objectives and Endpoints	Added a description of the changes made to the objectives and endpoints as a result of study termination. Removed all objectives and endpoints from Table 4-1 related to efficacy, quality of life (QoL), PRO, healthcare resource utilization (HCRU), PK, IMG, and biomarkers as a result of study termination.	To describe the modifications made to the study objectives and endpoints as a result of study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1: Overall Design Figure 5.1-1: Study Design Schematic Section 7.2: Method of Treatment Assignment	1. Language updated to reflect changes made to the study design as a result of study termination. 2. Updated description of West region in Section 5.1, Figure 5.1-1, and Section 7.2. 3. Updated figure and added Footnote c to reflect changes made to the study design as a result of study termination.	1. To describe the modifications made to the study design as a result of study termination. 2. To clarify countries grouped under the West region. 3. To visualize and clarify the study design modifications made as a result of study termination.
Section 5.1.2: Treatment Period Section 5.1.3: Follow-up Period Section 5.1.4: Treatment Beyond Progression Section 5.1.5.1: Data Monitoring Committee Section 5.1.5.2: Blinded Radiology Review Committee Section 5.2: Number of Participants Section 5.4.2: Rationale for TTTP as a Dual Primary Endpoint Section 5.4.3: Rationale for OS as a Dual Primary Endpoint Section 5.4.4: Rationale for EFS as a Secondary Endpoint Section 5.4.5: Rationale for PFS as a Secondary Endpoint Section 7: Treatment	Language in these sections updated to reflect changes made as a result of study termination.	To describe the modifications made to the study design and assessments as a result of study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 7-1: Study Treatments for CA20974W Section 7.1.1: Nivolumab and Ipilimumab Administration Section 7.1.2: TACE Procedure Section 7.2: Method of Treatment Assignment Section 7.3: Blinding Section 7.3.1: Unblinding at the Time of Disease Recurrence/Progression Section 8.1: Discontinuation from Study Treatment		
Section 5.4.2: Rationale for TTTP as a Dual Primary Endpoint	Added to list of new drug options for treatment of advanced HCC.	Minor text update.
Section 5.4.7: Rationale for Shorter Infusion Times (30 minutes) of Nivolumab and Ipilimumab	Updated with approval of shorter infusion time.	The 30-minute infusion time has been approved for nivolumab.
Section 5.4.9: Rationale for 2 Year Duration of Treatment with Nivolumab ± Ipilimumab	Removed references to Keynote 010 and Keynote 006.	Based on updated analyses for the 2 studies, they have been removed from this section.
Section 5.4.10: Rationale for Unblinding	Added section.	To continue safety monitoring after the decision to terminate the study.
Section 6: Study Population	Language updated to reflect enrollment closing as a result of study termination.	To describe patient enrollment closing as a result of study termination.
Section 7.1.1: Nivolumab and Ipilimumab Administration	1. Added the word "approximately" before infusion times. 2. Updated the text for weight-based dosing.	1. To allow for variations of infusion timing. 2. To clarify weight-based dosing calculations.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.2: TACE Procedure	Added text to reference new Appendix 11.	To align the protocol body with changes made to the appendices.
Section 7.4.2: Nivolumab and Ipilimumab Dose Delay Criteria	Updated text and added Table 7.4.2-1 outlining the delay, resume, and discontinuation criteria for nivolumab and ipilimumab.	To align with NCI CTCAE version 5.0 definitions and new terms. Tabular format done for ease of use.
Section 7.4.3: Treatment of Nivolumab- or Ipilimumab-related Infusion Reactions	Updated text to align with NCI CTCAE version 5.0.	To align with NCI CTCAE version 5.0.
Section 7.7.1: Prohibited and/or Restricted Treatments	Updated extensive non-palliative radiation therapy to palliative or non-palliative radiation therapy.	To prohibit and/or restrict palliative therapy during the study.
Section 7.7.3: Permitted Therapy	Added text for COVID-19 vaccine.	To include the risk that the efficacy and safety of COVID-19 vaccination in participants who are receiving nivolumab and/or ipilimumab are unknown.
Section 8.1: Discontinuation from Study Treatment	Added text about country-specific pregnancy requirements.	To clarify that pregnant participants must discontinue study treatment where locally mandated.
Section 8.1.1.1: Criteria for Nivolumab and Ipilimumab Treatment Discontinuation	Modified text to align criteria for dose delay, resume, and discontinuation with Table 7.4.2-1.	To align with NCI CTCAE version 5.0 definitions and new terms.
Section 8.1.2: Criteria to Resume Treatment	Removed redundant text and added criteria to resume treatment for participants with a confirmed or suspected SARS-CoV-2 infection.	To reduce redundancy and to manage the safety of participants with SARS-CoV-2 infection.
Section 8.1.3: Post Study Treatment Study Follow-up	Language updated to reflect changes made to follow-up study procedures as a result of study termination.	To describe the modifications made to study follow-up as a result of study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1: Efficacy Assessments Section 9.1.1: Imaging Assessment for the Study Section 9.1.1.1: Methods of Measurement Section 9.1.1.2: Imaging and Clinical Assessment Section 9.1.1.4: BICR Determination of Progression or Recurrence Section 9.1.2: Efficacy Assessments for TTTP Section 9.1.2.3: Definition of TTTP	Added language to specify that efficacy assessments will be conducted per the local standard of care.	To describe the modification made to study efficacy assessments as a result of study termination.
Section 9.1.1.4: BICR Determination of Progression or Recurrence Section 9.1.2: Efficacy Assessments for TTTP Section 9.1.2.3: Definition of TTTP Section 9.1.4: Outcomes Research Assessments Section 9.1.4.1: EQ-5D-5L Section 9.1.4.:2 FACT-Hep Section 9.6: Pharmacodynamics Section 9.8: Biomarkers Section 9.8.1: Tumor-based Biomarker Measures Section 9.8.1.1: Characterization of Tumor Infiltrating Lymphocytes and Tumor Antigens Section 9.8.1.2: Tumor Genomic Analysis Including Tumor Mutational	Added a statement that this section is not applicable per Protocol Amendment 01.	To describe the modifications made to efficacy, health-related QoL, HCRU, pharmacodynamic, and biomarkers assessments as a result of study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Burden and Gene Expression Analysis Section 9.8.2.1: Myeloid-derived Suppressor Cells Section 9.8.2.2: Soluble Biomarkers and Other Assessments in Serum Section 9.8.2.3: Genomic Analysis of Circulating Tumor DNA in Plasma Section 9.8.2.4: Whole Blood DNA and RNA Analyses Section 9.8.3: Microbiome Analysis Section 9.8.4: Additional Research Collection Section 9.9: Health Economics OR Medical Resource Utilization and Health Economics		
Section 9.2: Adverse Events	Added reference to NCI CTCAE version 5.0.	To identify the NCI CTCAE standards used in the study.
Section 9.2.2: Time Period and Frequency for Collecting AE and SAE Information	Removed reference to Sections 5.6.1 and 5.6.2 in the IB for Reference Safety Information.	Reference Safety Information has been moved from these sections in the IB.
Section 9.2.6: Pregnancy	Added text about country-specific pregnancy requirements.	To clarify that pregnant participants must discontinue study treatment where locally mandated.
Section 9.5: Pharmacokinetics and Immunogenicity Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for All Participants	Added a statement that PK/IMG sample collection is no longer necessary per Protocol Amendment 01 and if these are collected, they do not need to be analyzed. Included this statement as a note in Table 9.5-1.	To describe the modifications made to pharmacokinetic and immunogenicity assessments as a result of study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Included statement that original text in Section 9.5 is not applicable per Protocol Amendment 01.	
Table 9.8-1: CA20974W Biomarker Sampling Schedule for All Participants	Added footnote d to Table 9.8-1 clarifying biomarker sampling [redacted].	To clarify that [redacted] biomarker sample collection and analyses will not be performed except for PD-L1. [redacted]
Section 9.8.1.2: Tumor Genomic Analysis Including Tumor Mutational Burden and Gene Expression Analysis	Updated text describing the analyses to be conducted.	To clarify analyses to be conducted.
Section 9.8.2.2: Soluble Biomarkers and Other Assessments in Serum	Title updated to include "and Other Assessments."	To better reflect content of section.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10: STATISTICAL CONSIDERATIONS Section 10.1: Sample Size Determination Section 10.1.1: Sample Size Justification for Primary Endpoint of TTTP Section 10.1.2: Sample Size Justification for Primary Endpoint OS Section 10.1.3: Power Considerations in Nivolumab plus TACE vs Placebo plus TACE (Arm B vs Arm C) TTTP and OS Comparison as Secondary Endpoints Section 10.2: Populations for Analyses Table 10.2-1: Populations for Analyses Section 10.3: Statistical Analyses Section 10.3.1: Efficacy Analyses Section 10.3.3: Other Analyses Section 10.3.4: Interim Analyses	• Added a statement to Section 10 and Section 10.2 that only safety analyses will be conducted per Protocol Amendment 01. • Indicated in Section 10 that summary tables and listings will be provided to support the clinical study report and listings for efficacy data may be provided, if requested. • Added statement to Section 10.1 that sample size will be limited to participants enrolled as of 22-Sep-2021. • Added a statement to Sections 10.1.1, 10.1.2, 10.1.3, 10.3.3, and 10.3.4 that the section is not applicable per Protocol Amendment 01. • Added a statement in the table for PK, IMG, biomarker, and PRO that the populations are not applicable as per Protocol Amendment 01. • Removed reference to primary and secondary endpoints in Section 10.3. • Added a statement to Section 10.3.1 that a formal efficacy analyses will not be conducted per Protocol Amendment 01.	To describe the modifications made to statistical analyses as a result of study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3: Statistical Analyses Section 10.3.2: Safety Analyses Section 10.3.3: Other Analyses	Updated sentence to read "...before the first database lock...."	To clarify timing of the statistical analysis plan.
Table 10.3.1-1: Efficacy - Statistical Analyses	Correct a typo (TTTP should be OS).	Correction of a typo.
Appendix 1: Abbreviations and Trademarks	Added new terms and definitions.	To provide definitions for new terms introduced into the protocol with Protocol Amendment 01.
Appendix 2: Study Governance Considerations	Updated text under Monitoring. Added "Dissemination of Clinical Study Data" subheading.	To allow for alternative monitoring in circumstances where on-site monitoring is not advised. To clarify the dissemination of data for clinical trials.
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Updated the text for the "Definitions" and "Methods of Contraception" sections of the appendix.	To provide general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials.
Appendix 6: Management Algorithms for Studies Under CTCAE Version 5.0	Updated algorithms, including modified criteria for hepatic adverse events.	To be current with NCI CTCAE version 5.0 standards.
Appendix 9: Country-Specific Requirements	Updated appendix title and reformatted the tables. Added pregnancy- and biomarker-related country-specific requirements.	Reformatted for clarity. Inclusion of CA20974W country-specific protocol amendment changes for China (to provide clarity on which samples will be collected for biomarker analysis) and the Czech Republic [redacted].

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 11: France-specific General Guidance for Trans-arterial Chemo-embolization	Added France-specific appendix to include additional guidance on TACE.	Inclusion of CA20974W country-specific protocol amendment changes for France. The [redacted] additional guidance for TACE procedure, specifically authorized dose or dose ranges of anticancer agents that will be used in TACE procedures.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Randomized, Multi-center, Double-blinded, Placebo-controlled Phase 3 Study of Nivolumab and Ipilimumab, Nivolumab Monotherapy, or Placebo in Combination with Trans-arterial ChemoEmbolization (TACE) in Patients with Intermediate-stage Hepatocellular Carcinoma (HCC)

Short Title: Nivolumab and Ipilimumab or Nivolumab or Placebo Plus TACE in Intermediate-stage Liver Cancer

Study Phase: 3

Rationale:

Nivolumab is currently in development and has been registered in a variety of tumors. Development of nivolumab for hepatocellular carcinoma (HCC) was initiated in 2012 with CA209040, which is a Phase 1/2 clinical trial evaluating the safety and efficacy of nivolumab in advanced HCC. Data from the dose-escalation and expansion cohorts of this study led to the approval of nivolumab for the second-line (2L) therapy of advanced HCC patients who progressed on or were intolerant to sorafenib.

Combining immunotherapeutic agents with different mechanisms of action offers the possibility of an additive to synergistic response, and therefore represents an attractive therapeutic option that has proven to be effective in several cancer types. In advanced HCC, data from CA209040 shows promising results of the combination nivolumab and ipilimumab as 2L therapy, with durable antitumor activity and an acceptable and manageable safety profile and led to the Food and Drug Administration accelerated approval of nivolumab in combination with ipilimumab for the treatment of HCC patients who have been previously treated with sorafenib. These data provide support for evaluation of nivolumab and nivolumab and ipilimumab in an earlier stage of HCC (ie, intermediate-stage HCC).

Chemoembolization is recommended and widely used for the treatment of intermediate-stage HCC (Barcelona Clinic Liver Cancer [BCLC] Stage B), with conventional trans-arterial chemoembolization (TACE) being the most widely practiced embolotherapy for HCC. However, TACE is considered a palliative treatment and variable degrees of liver function impairment are observed post-TACE. The most common adverse effects of TACE include signs of liver injury and hepatic insufficiency. Elevated aminotransferases and negative changes in liver function tests are seen in almost all patients. The impact of treatment on liver function is problematic, particularly for patients who undergo repeated TACE sessions. The majority of patients with HCCs have underlying cirrhosis and preserving liver function is important. Physicians have to consider the risks of TACE and avoid adverse effects that will outweigh survival benefit. These have led to efforts to define when continuing TACE will be an ineffective therapeutic option.

The palliative nature of TACE and the need for a safer alternative for better liver function preservation has driven efforts to improve outcomes with TACE in patients with intermediate-stage HCC. Over the past decade, significant effort has been focused on clinical trials

combining TACE with systemic therapies, including sorafenib, brivanib, and orantinib. To date, these studies have been unsuccessful.

Despite these failures, the research on TACE is still ongoing. In particular, deeper investigation into combination strategies is recommended. The avidity with which this effort is pursued is reflected in the number of ongoing TACE studies. There are currently over 100 studies registered on ClinicalTrials.gov exploring combinations of TACE with systemic agents, including immunotherapy. At present, however, TACE remains the sole recommended treatment for intermediate-stage HCC. No systemic agent has been successfully developed for this stage of the disease.

Current data support the potential of immunotherapy for HCC therapy. Immune checkpoint inhibitors have clinical activity and are tolerable in advanced HCC, supporting their potential for use in other stages of the disease. Data on loco-regional therapy indicate that these procedures induce changes in the immune environment that suggest a synergistic potential for the combination of loco-regional therapy with immunotherapy. The preliminary data from tremelimumab in combination with ablation and from nivolumab in combination with TACE indicate that the combinations are feasible and tolerable. The combination of TACE with ipilimumab and/or nivolumab has the potential to address the need for better therapeutic options for intermediate-stage HCC, and support the further investigation of ipilimumab and nivolumab in combination with TACE in this setting.

[redacted] Therefore, a decision was made by Bristol-Myers Squibb in September 2021 to stop the study. Importantly, there is no change to the understanding of the safety profile of nivolumab alone or in combination with ipilimumab and TACE for the treatment of patients with intermediate-stage HCC.

As of 22-Sep-2021, enrollment for new participants was closed. The number of participants randomized was 26 as of 14-Oct-2021. **Per Protocol Amendment 01, there are no formal hypotheses or efficacy objectives for CA20974W. Only safety assessments will be conducted.** Following unblinding, study participants who are currently receiving nivolumab ± ipilimumab and tolerating study treatment may continue to receive study drug; however, placebo infusions will no longer be administered.

Study Population:

Male or female adults (≥ 18 years or age of majority) with histologically confirmed HCC who have intermediate-stage HCC by BCLC staging, have not previously received TACE, and whose tumor characteristics exceed the Beyond Milan and Up-to-7 (BMU7) criteria. Participants must not have extrahepatic spread (EHS), and disease characteristics must include no regional lymph node involvement, no portal vein thrombosis, and no macrovascular invasion (MVI).

Objectives and Endpoints:

Per Protocol Amendment 01, no analyses of efficacy, quality of life/patient-reported outcomes, healthcare resource utilization, biomarkers, pharmacokinetics, or immunogenicity are planned. Only safety assessments will be conducted. Previously collected biomarker samples may be analyzed, but no further biomarker collections are planned with this amended protocol.

Objective	Endpoint
• To evaluate the safety and tolerability of Arm A, Arm B, and Arm C in all treated participants.	• Incidence of AEs, SAEs, deaths, AEs leading to treatment discontinuation, and laboratory abnormalities in all treated participants.

Abbreviations: AE = adverse event; SAE = serious adverse event.

Overall Design:

This is a double-blind, placebo-controlled, 3-arm, randomized Phase 3 study of nivolumab and ipilimumab in combination with TACE and nivolumab in combination with TACE vs placebo in combination with TACE in participants with intermediate-stage HCC. Participants must have tumor characteristics that exceed the BMU7 criteria, no EHS, no regional lymph node involvement, no portal vein thrombosis, and no MVI must be present. As of 22-Sep-2021, enrollment for new participants was closed. The number of participants randomized was 26 as of 14-Oct-2021. Per **Protocol Amendment 01, there are no formal hypotheses or efficacy objectives for CA20974W. Only safety assessments will be conducted.** Following unblinding, study participants who are currently receiving nivolumab ± ipilimumab and tolerating study treatment may continue to receive study drug; however, placebo infusions will no longer be administered.

The study will consist of 3 periods: Screening, Treatment, and Follow-up. A complete list of study required procedures are provided within the Schedule of Activities section in the main protocol.

After signing an informed consent form, participants who have not previously received TACE will be evaluated for eligibility. If participants are eligible for receiving TACE and meet other eligibility criteria, they will be randomized in a 1:1:1 ratio to receive nivolumab and ipilimumab plus TACE (Arm A), nivolumab and ipilimumab placebo plus TACE (Arm B), or nivolumab placebo and ipilimumab placebo plus TACE (Arm C). Since TACE is the only recommended standard of care in clinical practice guidelines for the intended population, TACE plus nivolumab placebo and ipilimumab placebo will be used as a control. Both conventional TACE and TACE with drug-eluding beads (DEB-TACE) are acceptable treatment modalities in this study (see the TACE Procedure section within the main protocol for restrictions on TACE use) and first TACE will be administered 7 days (+ 3 days) after study drug administration. Stratification will occur by albumin-bilirubin (ALBI) grade (Grade 1 vs Grade 2), baseline alpha-fetoprotein (AFP) level (< 400 ng/mL vs ≥ 400 ng/mL), and Region (West [Europe, Americas, and Australia] vs Japan vs rest of Asia).

Participants will receive blinded treatment with 1 of the following regimens:

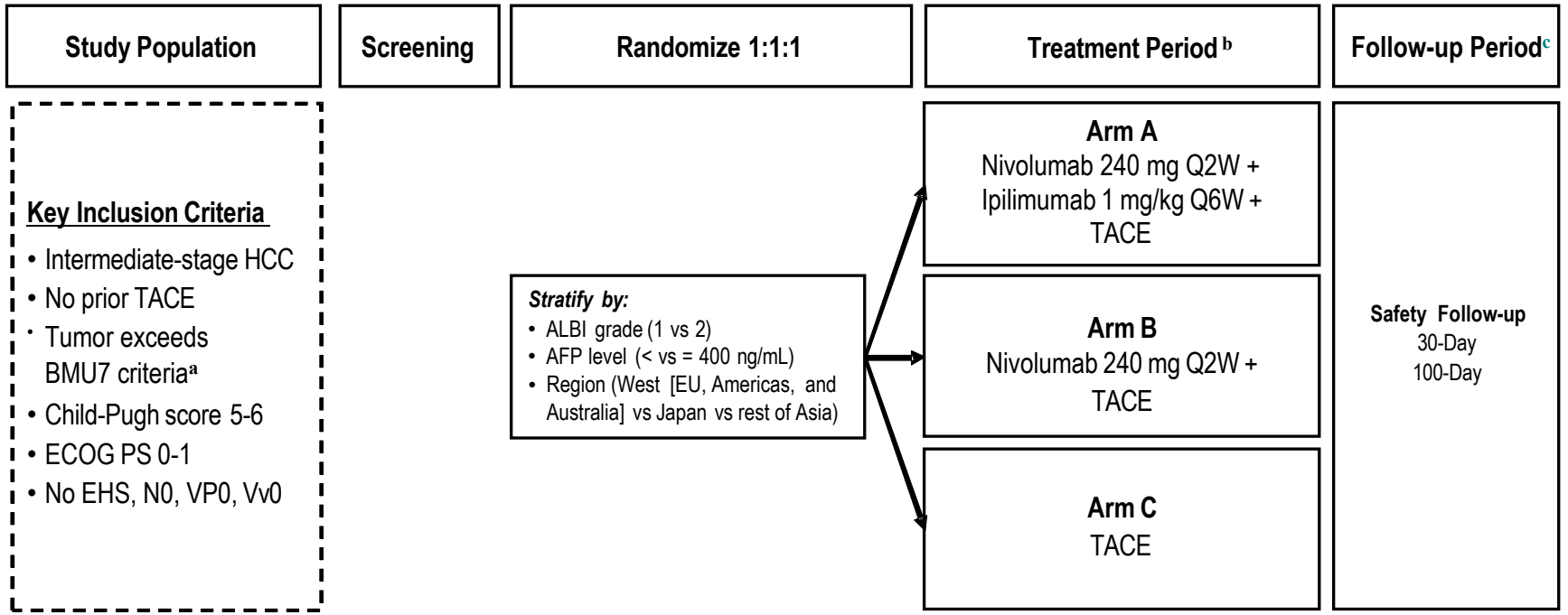
- Arm A: Nivolumab 240 mg every 2 weeks (Q2W) and ipilimumab 1 mg/kg every 6 weeks (Q6W) plus TACE
- Arm B: Nivolumab 240 mg Q2W and ipilimumab placebo Q6W plus TACE
- Arm C: Nivolumab placebo Q2W and ipilimumab placebo Q6W plus TACE

Per Protocol Amendment 01, this study will be unblinded and participants randomized to Arm B and Arm C will no longer receive placebo infusions following unblinding.

All randomized participants will receive treatment until progression as assessed by investigator, unacceptable toxicity, or consent withdrawal, for a maximum duration of treatment of 2 years. Participants will also receive on-demand TACE during the trial and can continue to receive TACE until they are not eligible for further TACE (see TACE Procedure section in main protocol). Participants in any arm may be treated with study therapy beyond progression as assessed by investigator under protocol-defined conditions (see Treatment Beyond Progression section in main protocol).

The study design schematic is presented in the figure below.

Study Design Schematic



Abbreviations: AFP = alpha-fetoprotein; ALBI = albumin-bilirubin; BMU7 = beyond Milan and up-to-7; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; EU = Europe; HCC = hepatocellular carcinoma; N0 = no regional lymph node metastasis; PS = performance status; Q2W = every 2 weeks; Q6W = every 6 weeks; TACE = trans-arterial chemoembolization; VP0 = no portal vein thrombosis; Vv0 = no macrovascular invasion.

[a] Number of nodules ≥ 1 cm + diameter of largest nodule in cm = 7.

[b] P**er Protocol Amendment 01, participants randomized to Arm B and Arm C will no longer receive placebo following unblinding.** Participants randomized to nivolumab and ipilimumab plus TACE (Arm A), nivolumab plus TACE (Arm B), or TACE alone (Arm C) will receive treatment until progression as assessed by investigator (unless treatment beyond progression was allowed), unacceptable toxicity, or consent withdrawal, for a maximum duration of treatment of 2 years.

[c] **Per Protocol Amendment 01, all participants randomized will have 30- and 100-day safety follow-up visits. No survival follow-up visits will occur.**

Number of Participants:

As of 22-Sep-2021, enrollment for new participants was closed. The number of participants randomized was 26 as of 14-Oct-2021.

Treatment Arms and Duration:

The selection and timing of dose for the study treatments is provided in the table below.

Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Nivolumab	240 mg	Q2W	IV
Ipilimumab	1 mg/kg	Q6W	IV
0.9% Sodium Chloride for Injection	NA	Q2W or Q6W	IV
5% Dextrose for Injection	NA	Q2W or Q6W	IV
TACE	NA	NA	Loco-regional

Abbreviations: IV = intravenous; kg = kilogram; mg = milligram; NA = not applicable; Q2W = every 2 weeks; Q6W = every 6 weeks; TACE = trans-arterial chemoembolization .

All participants should begin study treatment with nivolumab and ipilimumab in Arm A, nivolumab and ipilimumab placebo in Arm B, or nivolumab placebo and ipilimumab placebo in Arm C within 3 days after randomization. After nivolumab and ipilimumab (or placebo[s]) administration, first TACE will be administered 7 days (+ 3 days) after study drug administration. **Per Protocol Amendment 01, this study will be unblinded and participants randomized to Arm B and Arm C will no longer receive placebo infusions following unblinding.**

Study Treatment:

Study Drug for CA20974W

Medication	Potency	IP/Non-IP
Nivolumab (BMS-936558-01) Solution for Injection[a]	10 mg/mL	IP
Ipilimumab Solution for Injection	5 mg/mL	IP
0.9% Sodium Chloride for Injection[b]	NA	IP
5% Dextrose for Injection[b]	NA	IP

Abbreviations: IP = investigational product; mg = milligram; mL = milliliter; NA = not applicable.

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection.

[b] Diluents used for nivolumab and ipilimumab. These will be sourced by the investigative sites if available and permitted by local regulations.

Data Monitoring Committee: Yes

Blinded Independent Central Review (BICR):

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Images will be submitted to a central imaging vendor for BICR on a rolling basis during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA20974W Imaging Manual provided by the central imaging vendor.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA20974W)

Procedure[a]	Screening Visit (Days -28 to -1)	Notes All windows are based on calendar days.
Eligibility Assessments		
Informed Consent	X	Original informed consent must be obtained before performing any protocol-related procedures that are not part of normal patient care. 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. Register in IRT system to obtain participant number.
Inclusion/Exclusion Criteria	X	Assessed during Screening Period and re-enrollment, if applicable. Must be confirmed prior to randomization. See Section 6 (Study Population).
Medical History	X	All medical history relevant to the disease under study.
Child-Pugh Score and ALBI score	X	Refer to Appendix 8 (Child-Pugh Score) and Section 5.4.8.3 (Albumin-bilirubin Grade) for additional details.
Tumor Sample Submission	X	An FFPE tissue block (preferred) or a minimum of 20 unstained slides of tumor tissue obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen prior to randomization (within 3 months of enrollment with no intervening systemic anticancer treatment between time of acquisition and randomization, or archival tissue [if above is not available]) must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable. 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 the BMS Medical Monitor or Clinical Scientist. Please see Appendix 9 for country-specific criteria for the collection of tumor tissue samples in China. The tissue submitted will be assessed for quality and only those participants who have met tissue quality thresholds can be randomized. Central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to participant randomization. See Section 9.8 (Biomarkers) for additional information.

Table 2-1: Screening Procedural Outline (CA20974W)

Procedure[a]	Screening Visit (Days -28 to -1)	Notes All windows are based on calendar days.
Safety Assessments		
Full PE, Physical Measurements, and ECOG PS	X	Height, weight, blood pressure (BP), heart rate, temperature, and ECOG PS (Appendix 5). Must be collected within 14 days prior to randomization.
Vital Signs	X	Obtain vital signs at the screening visit. Vital signs include temperature, respiratory rate, seated BP, and heart rate. BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Consider alternate position(s) for vital sign collection.
Assessment of Signs and Symptoms	X	Must be performed within 14 days prior to randomization.
Concomitant Medication Use	X	Must be collected within 14 days prior to randomization. Vaccine use within 30 days prior to randomization.
SAE Assessment	X	SAE collection from the time of consent. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection to be collected from time of consent. AEs will be graded according to the NCI CTCAE version 5.0.
12-lead ECG	X	Within 14 days prior to randomization.
Body Imaging	X	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, including pre- and post-contrast tri-phasic MRI or CT of the liver, and all other known and/or suspected sites of disease, within 28 days prior to randomization. See Section 9.1.1 (Imaging Assessment for the Study) for further details. Images must be submitted for BICR to confirm eligibility.
Brain Imaging	X	MRI of the brain without and with contrast is required for participants with suspected brain metastases, unless participant has completed an imaging study of the brain within 30 days of randomization. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 (Imaging Assessment for the Study) for further details.
Laboratory Tests		
Hematology and Chemistry/Endocrine	X	Must be performed locally within 14 days prior to randomization.

Table 2-1: Screening Procedural Outline (CA20974W)

Procedure[a]	Screening Visit (Days -28 to -1)	Notes All windows are based on calendar days.
		See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests.
Serology for Hep B, Hep C, Hep D, and HIV		**Testing for Viral Hepatitis** to be completed at the central laboratory within 28 days prior to randomization. In the event the central laboratory is unable to perform Hep D testing, local Hep D testing may be allowed until central laboratory testing resumes. Local testing requires approval from BMS along with supporting local laboratory documentation. **Testing for HIV** (when required by local regulations [refer to Appendix 9]) must be done at local laboratory within 28 days prior to randomization. See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests.
Pregnancy Test (WOCBP only)	X	See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests.
Urinalysis	X	See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests.
IRT		
Register Participant in IRT	X	A call must be made to the IRT to register participant after signing informed consent.

Abbreviations: AE = adverse event; ALBI = albumin-bilirubin; BP = blood pressure; BICR = blinded independent central review; BMS = Bristol-Myers Squibb; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FFPE = formalin-fixed, paraffin-embedded; HCG = human chorionic gonadotropin; Hep B = hepatitis B; Hep C = hepatitis C; Hep D = hepatitis D; HIV = human immunodeficiency virus; IRT = interactive response technology; IU = international unit; L = liter; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PE = physical examination; PS = performance status; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

[a] 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.

Table 2-2: On-treatment Procedural Outline (CA20974W)

Procedure[a]	Nivolumab Cycle 1 Day 1 and Q2W Thereafter (± 3 days) Ipilimumab Cycle 1 Day 1 and Q6W Thereafter (± 3 days) (1 Cycle = 2 weeks)	TACE Cycle 1 Day 7 (+3 days) and On-demand Thereafter	Notes[b]
Safety Assessments			
Targeted PE	X	X	Targeted PE must include, at a minimum, the following body systems, performed within 72 hours prior to dosing: cardiovascular, gastrointestinal, pulmonary, and skin.
Physical Measurements and ECOG PS	X	X	Physical measurements include weight and ECOG PS (Appendix 5), to be collected within 72 hours prior to dosing.
Vital Signs	X	X	Vital signs include BP, heart rate, temperature, and respiratory rate. Obtain vital signs within 72 hours prior to dosing.
Child-Pugh Score	X	X	Refer to Appendix 8 for further details.
AEs Assessment (including SAEs)	X	X	Record at each visit. Collect continuously throughout the Treatment Period and for a minimum of 100 days following discontinuation of dosing. SAEs must be collected from the time of consent. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from time of consent until 100 days following discontinuation of dosing. AEs will be graded according to the NCI CTCAE version 5.0.
Concomitant Medication Use	X	X	Record at each visit.
Laboratory Tests			
Hematology and Chemistry/Endocrine	X	X	Performed locally within 72 hours prior to dosing. See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests. TSH, with reflexive fT3 and fT4 if TSH is abnormal, (every third cycle [3, 6, 9, etc]).

Table 2-2: On-treatment Procedural Outline (CA20974W)

Procedure[a]	Nivolumab Cycle 1 Day 1 and Q2W Thereafter (± 3 days) Ipilimumab Cycle 1 Day 1 and Q6W Thereafter (± 3 days) (1 Cycle = 2 weeks)	TACE Cycle 1 Day 7 (+3 days) and On-demand Thereafter	Notes[b]
Serology for Viral Status (for HCV- and HBV-infected participants)	See Notes.		Testing to be completed at the central laboratory (see Table 9.4.4-1). Results of viral serologies are not required to continue study treatment. For HCV-infected participants: HCV RNA Q4W on treatment (every other cycle) through cycle 9, then every 6 cycles thereafter. For HBV infected participants, HBV DNA Q4W on treatment.
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24 hours prior to first dose, and then every 28 days, regardless of dosing schedule. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.
Urinalysis	X		See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests.
Efficacy Assessments			**Per Protocol Amendment 01, efficacy assessments should be conducted per the local standard of care.**
Body Imaging Assessments	See Notes.	See Notes	**Per Protocol Amendment 01, imaging should continue per local standard of care.** The following information refers to the original study design. Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, including pre- and post-contrast tri-phasic MRI or CT of the liver, and all other suspected sites of disease, should be performed. Tumor imaging assessments will occur 6 weeks from the date of randomization (± 1 week), then every 6 weeks (± 1 week) thereafter up to 48 weeks, then it will be every 12 weeks (± 1 week) until disease

Table 2-2: On-treatment Procedural Outline (CA20974W)

Procedure[a]	Nivolumab Cycle 1 Day 1 and Q2W Thereafter (± 3 days) Ipilimumab Cycle 1 Day 1 and Q6W Thereafter (± 3 days) (1 Cycle = 2 weeks)	TACE Cycle 1 Day 7 (+3 days) and On-demand Thereafter	Notes[b]
			progression (as assessed by investigator) or treatment is discontinued (whichever occurs later). See Section 9.1.1 (Imaging Assessment for the Study) for further details.
PK and IMG Assessments	See Notes.		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. See Section 9.5 (Pharmacokinetics and Immunogenicity) and Table 9.5-1 for PK/IMG sample collection schedule.
Biomarker Assessments[c]			
Serum Biomarkers, Whole Blood DNA and RNA, MDSC, Plasma (ctDNA)	See Notes.		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. See Table 9.8-1 for biomarker sample collection schedule.
Stool Samples for Microbiome Analysis	See Notes.		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. See Table 9.8-1 for biomarker sample collection schedule.
Collection of Tumor Upon TTTP or EOT	See Notes.		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. See Table 9.8-1 for biomarker sample collection schedule.

Table 2-2: On-treatment Procedural Outline (CA20974W)

Procedure[a]	Nivolumab Cycle 1 Day 1 and Q2W Thereafter (± 3 days) Ipilimumab Cycle 1 Day 1 and Q6W Thereafter (± 3 days) (1 Cycle = 2 weeks)	TACE Cycle 1 Day 7 (+3 days) and On-demand Thereafter	Notes[b]
Outcomes Research Assessments	See Notes.		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. Questionnaires should be administered at the start of the visit, before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). In the case of a delay in dosing, completion of the PRO measures will also be delayed to coincide with when dosing is resumed.
EQ-5D-5L	See Notes.		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. Complete prior to treatment on Day 1 of each treatment cycle through C13D1, and then every third cycle thereafter.
FACT-Hep	See Notes.		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. Complete prior to treatment on Day 1 of each treatment cycle through C13D1, and then every third cycle thereafter.
Healthcare Resource Utilization	X		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. HCRU to be assessed during clinical visit; must be completed by site staff and recorded on the eCRF. See Section 9.9 for additional details.

Table 2-2: On-treatment Procedural Outline (CA20974W)

Procedure[a]	Nivolumab Cycle 1 Day 1 and Q2W Thereafter (± 3 days) Ipilimumab Cycle 1 Day 1 and Q6W Thereafter (± 3 days) (1 Cycle = 2 weeks)	TACE Cycle 1 Day 7 (+3 days) and On-demand Thereafter	Notes[b]
Clinical Drug Supplies			
Contact Central Randomization IRT/Dispense Study Drug	See Notes[d]		**Per Protocol Amendment 01, after unblinding, participants in Arms B and C will no longer receive placebo infusions.** First dose of study medication to be administered within 3 calendar days following randomization. Participants will receive nivolumab 240 mg (flat dose) Q2W, ipilimumab 1 mg/kg (weight-based dosing) Q6W, and on-demand TACE. Participants may be dosed no less than 12 days and no more than 18 days between nivolumab doses and no less than 36 days and no more than 60 days between ipilimumab doses.

Abbreviations: AE = adverse event; BP = blood pressure; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; FACT-Hep = Functional Assessment of Cancer Therapy-Hepatobiliary; HBV = hepatitis B virus; HCRU = healthcare resource utilization; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; IMG = immunogenicity; IRT = interactive response technology; IU = international unit; L = liter; MDSC = myeloid-derived suppressor cell; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PE = physical examination; PK = pharmacokinetic; PRO = patient-reported outcome; PS = performance status; Q2W = every 2 weeks; Q4W = every 4 weeks; Q6W = every 6 weeks; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TACE = trans-arterial chemoembolization; TSH = thyroid-stimulating hormone; TTTP = time to TACE progression; WOCBP = women of childbearing potential.

[a] If a dose is delayed, the procedures schedule for that same timepoint should also be delayed to coincide with when that timepoint's dosing actually occurs.

[b] 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.

[c] Please see Appendix 9 for country-specific criteria for the collection and analyses of biomarker samples [redacted].

[d] The ± 3-day window should be used to align nivolumab and ipilimumab dosing for same-day administration and that participants must be dosed no less than 12 days and no more than 18 days between nivolumab doses and no less than 36 days and no more than 60 days between ipilimumab doses.

Table 2-3: Follow-up Procedural Outline (CA20974W)

Procedure	Safety Follow-up Visits 1 (FU1) and 2 (FU2)[a]	Survival Follow-up Visits[b]	Notes[c]
Safety Assessments			
Targeted PE, Physical Measurements, Vital Signs, and ECOG PS Assessment	X		Weight, BP, heart rate, temperature, and ECOG PS. Targeted PE must include, at a minimum, the following body systems: cardiovascular, gastrointestinal, pulmonary, and skin.
AEs Assessment (including SAEs)	X	X	Record at each visit. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the time of consent. All AEs (SAEs and non-serious AEs), including AEs associated with confirmed or suspected SARS-CoV-2 infection, must be collected continuously throughout the treatment period and for a minimum of 100 days following discontinuation of dosing. Participants will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out. AEs will be graded according to the NCI CTCAE version 5.0.
Review of Concomitant Medication Use	X		Record at each visit.
Review of Subsequent Cancer Therapy	X	X	**No longer applicable per Protocol Amendment 01.** Review and record any subsequent therapies received by the participant.
Laboratory Tests			
Hematology and Chemistry/Endocrine	X		To be performed locally. See Section 9.4.4 (Clinical Safety Laboratory Assessments) for a list of laboratory tests to conduct. Total T3/T4 are acceptable if free T3/T4 are not available.

Table 2-3: Follow-up Procedural Outline (CA20974W)

Procedure	Safety Follow-up Visits 1 (FU1) and 2 (FU2)[a]	Survival Follow-up Visits[b]	Notes[c]
Serology for Viral Status (for HCV- and HBV-infected participants)	X		Testing to be completed at the central laboratory (see Table 9.4.4-1). For HCV-infected participants: HCV RNA. For HBV-infected participants: HBV DNA.
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG).
Efficacy Assessments			**Per Protocol Amendment 01, efficacy assessments should be conducted by investigator per local standard of care.**
Body Imaging Assessments	X	X	**Per Protocol Amendment 01, imaging should continue per local standard of care**. The following information refers to the original study design. Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, including pre- and post-contrast tri-phasic MRI or CT of the liver, and all other suspected sites of disease, should be performed. Tumor imaging assessments will occur 6 weeks from the date of randomization (± 1 week), then every 6 weeks (± 1 week) thereafter up to 48 weeks, then it will be every 12 weeks (± 1 week) until disease progression (as assessed by investigator) or treatment is discontinued (whichever occurs later). See Section 9.1.1 (Imaging Assessment for the Study) for further details.

Table 2-3: Follow-up Procedural Outline (CA20974W)

Procedure	Safety Follow-up Visits 1 (FU1) and 2 (FU2)[a]	Survival Follow-up Visits[b]	Notes[c]
PK and IMG Assessments	See Notes.		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. See Section 9.5 (Pharmacokinetics and Immunogenicity) and Table 9.5-1 for PK/IMG sample collection schedule.
Biomarker Assessments[d]	See Notes.		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. See Table 9.8-1 for biomarker sample collection schedule.
Outcomes Research Assessments			**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. The EQ-5D-5L and FACT-Hep should be administered at the start of the visit, before the participant sees the physician and before any study-related procedures are done.
EQ-5D-5L	X	X	**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. EQ-5D-5L to be assessed during clinical visit or via a phone for survival follow-up visits.
FACT-Hep	X		**Not applicable per Protocol Amendment 01.**
Healthcare Resource Utilization	X		**Not applicable per Protocol Amendment 01.** The following information refers to the original study design. HCRU to be assessed during clinical visit; must be completed by site staff and recorded on the eCRF. See Section 9.9 for additional details.

Table 2-3: Follow-up Procedural Outline (CA20974W)

Procedure	Safety Follow-up Visits 1 (FU1) and 2 (FU2)[a]	Survival Follow-up Visits[b]	Notes[c]
Participant Status			
Survival Status		X	**Per Protocol Amendment 01, survival follow-up will stop after the second safety assessment (FU2) at 100 days.** **The following information is no longer applicable per Protocol Amendment 01 and refers to the original study design.** During safety follow-up and every 3 months (may be accomplished by clinic visit or by telephone contact) during the survival Follow-up Period. Include documentation of subsequent chemotherapy.

Abbreviations: AE = adverse event; BP = blood pressure; BMS = Bristol-Myers Squibb; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; FACT-Hep = Functional Assessment of Cancer Therapy-Hepatobiliary; FU1 = follow-up visit 1; FU2 = follow-up visit 2; HCG = human chorionic gonadotropin; HCRU = healthcare resource utilization; IMG = immunogenicity; IU = international unit; L = liter; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PE = physical examination; PK = pharmacokinetic; PS = performance status; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; WOCBP = women of childbearing potential.

[a] Participants must be followed for at least 100 days after last dose of study treatment. FU1 should occur 30 days from the last dose (±7 days) or can be performed on the date of discontinuation if that date is great than 42 days from the last dose. FU2 occurs approximately 100 days (±7 days) from last dose of study treatment. Both follow-up visits should be conducted in person.

[b] **Not applicable per Protocol Amendment 01.** The following information refers to the original study design. Survival Follow-up visits to occur every 12 weeks (± 14 days) from FU2. Survival visit may be conducted in person 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.

[c] 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.

[d] Please see Appendix 9 for country-specific criteria for the collection and analyses of biomarker samples [redacted].

3 INTRODUCTION

3.1 Study Rationale

Nivolumab is currently in development and has been registered in a variety of tumors.[1]Development of nivolumab for hepatocellular carcinoma (HCC) was initiated in 2012 with CA209040, which is a Phase 1/2 clinical trial evaluating the safety and efficacy of nivolumab in advanced[2]Data from the dose-escalation and expansion cohorts of this study led to the approval of nivolumab for the second-line (2L) therapy of advanced HCC patients who progressed on or were intolerant to sorafenib.

Combining immunotherapeutic agents with different mechanisms of action offers the possibility of an additive to synergistic response, and therefore represents an attractive therapeutic option that has proven to be effective in several cancer types[1]In advanced HCC, data from CA209040 shows promising results of the combination nivolumab and ipilimumab as 2L therapy, with durable antitumor activity and an acceptable and manageable safety profile and led to the Food and Drug Administration (FDA) accelerated approval of nivolumab in combination with ipilimumab for the treatment of HCC patients who have been previously treated with sorafenib.[3] These data provide support for evaluation of nivolumab and nivolumab and ipilimumab in an earlier stage of HCC (ie, intermediate-stage HCC).

3.1.1 Research Hypothesis

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Treatment with nivolumab and ipilimumab or nivolumab in combination with trans-arterial chemoembolization (TACE) will improve time to TACE progression (TTTP) and/or overall survival (OS) compared to TACE in participants with intermediate stage HCC.

3.1.2 Changes Per Protocol Amendment 01

[redacted] Therefore, a decision was made by Bristol-Myers Squibb (BMS) in September 2021 to stop the study. Importantly, there is no change to the understanding of the safety profile of nivolumab alone or in combination with ipilimumab and TACE for the treatment of patients with intermediate-stage HCC.

As of 22-Sep-2021, the following measures were put into effect:

- Enrollment of new participants was closed.
- Participants who signed study consent prior to this notification and were undergoing screening were permitted to be randomized to study treatment.
- Participants currently on treatment were allowed to continue study treatment.

- For participants currently in survival follow-up, it is at the discretion of the investigator and participant whether to continue follow-up until Protocol Amendment 01 is approved by the relevant Health Authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) at the site.

Protocol Amendment 01 describes the modification to study procedures. All participants must be re-consented upon approval and implementation of Protocol Amendment 01. These changes affect all participants and should be implemented when Protocol Amendment 01 is implemented at the site.

Key changes in Protocol Amendment 01 include:

- Details of closure of the study, with provision for participants currently on treatment or in the follow-up period to continue in the study per the current protocol amendment.
- The study will be unblinded.
- Removal of placebo infusions for participants in Arms B and C.
- Removal of pharmacokinetic (PK), immunogenicity (IMG), biomarker, and patient-reported outcome (PRO) assessments. **Only safety assessments will be conducted**.
- Removal of on-study imaging assessments. Sites should continue imaging assessments per local standard of care.
- Removal of study-related efficacy assessments. Sites should continue efficacy assessments per local standard of care.
- Align dose modification criteria and immuno-oncology agent management algorithms with the current National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- Add the collection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-related adverse events (AEs) and serious adverse events (SAEs) to evaluate the impact of SARS-CoV-2 on participant safety and add coronavirus disease 2019 (COVID-19) vaccine information for study participants.
- Incorporate country-specific information for France, Czech Republic, and China; incorporate additional updates to improve alignment across protocol sections and/or clarify expectations for assessments, sample collections, and treatment administration.

Changes instituted in Protocol Amendment 01 should override any existing protocol requirements in the event of any apparent discrepancies.

3.2 Background

3.2.1 The Unmet Need in Intermediate-Stage Hepatocellular Carcinoma

HCC is the seventh most common cancer in the world and the third most common cause of cancer-related death. There are more than 800,000 new cases a year and HCC causes approximately 700,000 to 800,000 deaths annually. Furthermore, its incidence and prevalence are increasing worldwide. The disease shows wide regional variations in incidence rates and etiology. HCC is particularly prevalent in Asian countries relative to Western countries. Over 80% of HCC cases occur in Africa and Asia. China alone accounts for more than 50% of cases worldwide.[4,5] Age-standardized (world) incidence rates in South-Eastern to Eastern Asia range from 21.0 to 26.8 per 100,000, distinctly higher than the rates in Northern Europe (EU) and North America, which range from 6.6 to 10.1 per 100,000. Age-standardized (world) mortality rates are similarly much higher in South and North Eastern Asia (17.2 to 34.0 per 100,000) than in Northern EU and North America (3.1 to 4.4 per 100,000).[6]

Virtually any cause of liver damage that leads to cirrhosis can predispose an individual to HCC. The main risk factors for primary liver cancer (PLC) are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin B1-contaminated foodstuffs, heavy alcohol intake, obesity, and type 2 diabetes mellitus.[7] Once cirrhosis is established, the annual incidence of HCC is 3% to 5% and one-third of these individuals will develop HCC over their lifetime.[8] Most cases of HCC arise in eastern Asia and sub-Saharan Africa, where the dominant risk factor is chronic HBV infection, together with exposure to aflatoxin B1.[9] In contrast, in North America, EU, and Japan, HCV infection is the main risk factor, together with alcohol use.[10]

Intermediate-stage HCC patients belong to the Barcelona Clinic Liver Cancer (BCLC) Stage B. The stage consists of patients with preserved liver function and performance status who are not eligible for curative treatments, such as surgery and liver transplantation. It includes a heterogeneous patient population that presents with a wide range of tumor extension and liver function (Child-Pugh compensated A5 cirrhosis to decompensated B9).[11]

Chemoembolization is recommended for the treatment of intermediate-stage HCC (BCLC Stage B). Transcatheter arterial therapies for HCC were first described in the 1970s[12] and include a variety of techniques (eg, TACE, bland embolization, trans-arterial embolization [TAE]). The use of TACE was adopted into practice guidelines based on 2 meta-analyses[13,14] and 2 seminal placebo-controlled randomized clinical trials (RCTs)[15,16] published in 2002. TACE has since been widely used, with conventional TACE being the most widely practiced embolotherapy for HCC.[12] The largest global HCC observational study (GIDEON) suggests that nearly half of all HCC patients receive TACE at some timepoint in the course of the disease.[17] Real-world data and clinical experience demonstrate TACE to be the method of choice for the treatment of intermediate-stage HCC, applied in about 50% to 60% of patients.[18,19]

However, TACE is considered a palliative treatment. Significant tumor response is achieved in 17-61.9% in individuals administered TACE, but TACE often fails to induce complete necrosis of the lesion. Even in cases where complete ablation is achieved, tumors commonly recur post-TACE

and repeated TACE treatments are usually required.[20] In the GIDEON study, 59.5% of patients received 2 or more TACE sessions.[17] Across different TACE studies, the majority of participants have received > 1 TACE session.[15,16,19,21,22,23,24,25,26]

In addition, TACE damages normal liver cells. Variable degrees of liver function impairment are observed post-TACE. The most common adverse effects of TACE include signs of liver injury and hepatic insufficiency. Elevated aminotransferases and negative changes in liver function tests (LFTs) are seen in almost all patients.[27,28] The impact of treatment on liver function is problematic, particularly for patients who undergo repeated TACE sessions. The majority of patients with HCCs have underlying cirrhosis and preserving liver function is important. Physicians have to consider the risks of TACE and avoid adverse effects that will outweigh survival benefit. These have led to efforts to define when continuing TACE will be an ineffective therapeutic option.[20,29,30]

The palliative nature of TACE and the need for a safer alternative for better liver function preservation has driven efforts to improve outcomes with TACE in patients with intermediate-stage HCC. Over the past decade, significant effort has been focused on clinical trials combining TACE with systemic therapies, including sorafenib, brivanib, and orantinib.[31] To date, these studies have been unsuccessful.

Despite these failures, the research on TACE is still ongoing. In particular, deeper investigation into combination strategies is recommended.[32] The avidity with which this effort is pursued is reflected in the number of ongoing TACE studies. There are currently over 100 studies registered on ClinicalTrials.gov exploring combinations of TACE with systemic agents, including immunotherapy.[33] At present, however, TACE remains the sole recommended treatment for intermediate-stage HCC. No systemic agent has been successfully developed for this stage of the disease.

3.2.2 Role of Immune Checkpoint Blockade in the Treatment of HCC

The immune system is a crucial player in the combat against malignancies. Since its introduction into clinical practice, immunotherapy has revolutionized cancer treatment. Among immunotherapy strategies, immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of oncology and is now considered as a cornerstone treatment regimen in cancer therapy. Agents targeting this mechanism via cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) has induced regressions in several types of cancer, and immune checkpoint blockade therapies are currently approved for the treatment of a broad range of tumor types.[34,35]

There is growing evidence to suggest that HCC can be considered an immunogenic tumor. However, different from other organs, liver shows its distinguished characteristics, such as an immune organ," and patients with HCC present with unique anti- or pro-tumor responses during the development and progression of HCC. Under physiological conditions, the liver induces immune tolerance by blocking activation of effector T cells in the liver microenvironment. This protective mechanism prevents organ autoimmune damage from ongoing immune stimulation due to continuous antigen exposure. While immune tolerance is beneficial in the case of cancer-free

liver, it may be detrimental in cancer-bearing host, as it might prevent an adequate immune response against malignant cells.[36,37,38] Moreover, the intrahepatic immunosuppressive environment is exacerbated by the chronic inflammation that underlies the development of fibrosis and cirrhosis. This chronic inflammation, characterized by the continued expression of different cytokines and recruitment of immune cells to the liver, may contribute to HCC carcinogenesis and disease progression by further activating immunosuppressive mechanisms, which results in an inability to escalate a meaningful antitumor response.[36,39] Indeed, immune changes reported in HCC, such as tumor-associated antigen-specific CD8+ T-cell immune responses, T-cell infiltration after loco-regional therapy, T regulatory cell (Treg) intratumoral accumulation, and myeloid-derived suppressor cells (MDSCs) accumulation have been correlated with disease progression and poor survival.[40,41,42] Overcoming this immune tolerance is thus an important challenge in the search for an effective immunotherapy against HCC.

Given the unique immunosuppressive tumor microenvironment, HCC is an attractive target for immunotherapy, particularly immune checkpoint inhibitors. In HCC, the negative regulatory target-immune checkpoints, such as CTLA-4, PD-1, and its ligand PD-L1, are often overexpressed to escape the host immune surveillance, and thus, treatment with immune checkpoint inhibitors can reactivate tumor-specific T cells and develop an antitumor effect by suppressing checkpoint-mediated signaling.[38,43,44]

The administration of CTLA-4 inhibitor has been demonstrated to increase antitumor immunity in a murine HCC model, with a tumor rejection rate of 90% and a curative rate of 50% in metastatic HCC.[45] Additionally, the clinical benefit of anti-CTLA-4 as a single-agent has been demonstrated in a Phase 2, non-controlled, open-label, multicenter trial.[46] In this trial, tremelimumab, a monoclonal antibody that blocks CTLA-4, was administered at a dose of 15 mg/kg intravenously (IV) every 90 days in 20 participants with HCV-associated HCC with Child-Pugh Stage A (57%) and Stage B (43%) who failed traditional HCC therapy. In terms of antitumor responses, this study reported a partial response (PR) rate of 17.6%, a disease control rate (DCR) of 76.4%, a time to progression (TTP) of 6.48 months, and a median OS of 8.2 months. Regarding safety, tremelimumab was generally well tolerated, with few participants experiencing Grade 3 disabling adverse events (AEs), being the most common side effects observed fatigue and anorexia, which occurred in almost one-half of participants. A remarkable rise in serum transaminases was observed after the first dose in more than half of the participants (Grade 3 or higher in 45% of cases), but with no other signs of liver dysfunction.

Similar to the role of CTLA-4 pathway inhibition, the role of PD-1/PD-L1 pathway in HCC has been investigated. PD-1 expression on effector phase cluster of differentiation (CD) 8-positive (+) T cells is increased in patients with HCC compared to cirrhotic patients or healthy controls.[47] Indeed, patients with HCC and higher numbers of tumor infiltrating and circulating PD-1+, CD8+ T cells showed earlier and more frequent disease progression after hepatic resection. PD-L1 is also highly expressed on peritumoral stromal cells (Kupffer cells, liver sinusoidal endothelial cells [LSECs], and monocytes) as well as cancer cells, promoting a PD-L1/PD-1 pathway-driven inhibition of antitumor T-cell responses.[48] These preclinical findings are further supported by results from CA209040, the first trial evaluating the safety and efficacy of an anti-PD-1 agent in advanced HCC. This Phase 1/2 study included 262 participants with unselected PD-L1 tumors,

including both treatment-naive and pretreated participants. Following confirmation of safety and tolerability in the dose-escalation phase, all participants in the dose-expansion phase received IV nivolumab 3 mg/kg every 2 weeks (Q2W) until disease progression or limiting toxicity. This trial showed convincing signs of efficacy, with objective tumor responses ranging from 15-20% in the escalation and expansion cohorts. Notably, responses were observed regardless of PD-L1 expression and were similar across different etiologies, and both in sorafenib-naive and sorafenib-exposed participants. Remarkably, responses were meaningful and durable (lasting for a median of 17 months) and the median OS in the sorafenib-treated group was 15.6 months in the expansion cohort, which compares favorably with sorafenib historical data (10.7 months)[49] and with results of the recently approved 2L molecular-targeted agents (median OS ranging from 8.5 to 10.6 months).[50,51,52] Overall, nivolumab was generally well tolerated with a manageable safety profile. Hepatic toxicity, consisting primarily of transaminase elevations, was generally mild, with Grade 3 or 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations observed in 7 (9%) and 7 (4%) of sorafenib-naive and pretreated participants, respectively; bilirubin elevations were infrequent (7 participants overall) and mostly mild, with only 1 Grade 3 or 4 elevation reported. In addition to nivolumab, other immune checkpoint inhibitors as single agents are being evaluated in HCC. Durvalumab (an anti-PD-L1 antibody) has shown clinical activity in a small Phase 1/2 study (N = 40), with response rates of 10% and a median OS of 13.2 months.[53] Similarly, most recently, pembrolizumab (an anti-PD-1 antibody) has also demonstrated clinical activity as 2L therapy with response rates of 17% and a median OS of 12.9 months in a Phase 1/2 including 104 participants with advanced HCC.[54]

Thus, there is a substantial body of scientific evidence that supports the rationale for the use of immune-based approaches to treat HCC. This theoretical rationale is further supported by a growing amount of clinical evidence, which indicates that immune checkpoint inhibitors are effective treatments for patients with advanced HCC.[43,44]

3.2.3 Rationale for Immune Checkpoint Inhibitors Combinations

While the efficacy of immune checkpoint inhibitors as single agents in HCC is promising, the majority of the patients remain refractory, due to the immunosuppressive mechanisms of HCC, comprising multiple humoral mediators and suppressive checkpoint molecules. Combination therapies may improve antitumor efficacy, and a number of studies evaluating different combination strategies are currently ongoing in the HCC field.[38,55]

Owing to the multiplicity of mechanisms used by tumors to evade the immune response, combining different immunotherapeutic agents with different mechanisms of action is an appealing approach to treat HCC, which offers the possibility of an additive to synergistic response. The most relevant example is dual CTLA-4 and PD-1/PD-L1 blockade. PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms to limit T cell activation. Preliminary indirect data from peripheral T cell assessments suggest that a given T-cell checkpoint inhibitor may modulate host immune cell phenotypes, rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing antitumor activity.[38,43,55]

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade is synergistic and may improve antitumor activity:

- In vitro, combinations of nivolumab and ipilimumab increase interferon-gamma (IFN-γ) production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction (MLR).[53]
- Several preclinical syngeneic tumor models showed that combined treatment with anti-murine PD-1 and anti-murine CTLA-4 monoclonal antibody resulted in increased antitumor responses over either monoclonal antibody alone, which were greatest when the antibodies were given together rather than sequentially.[53] In some instances, combined treatment resulted in tumor-free mice that exhibited long-lived tumor immunity when re-challenged with tumor cells.[53]
- In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor-infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral Tregs, as compared to either agent alone, suggesting a synergistic effect.[56]

In the clinic, combination therapies with monoclonal antibodies blocking PD-1 or PD-L1 and CTLA-4 have resulted in higher response rates and improved outcomes over monotherapy in a number of solid tumors.[1] In HCC, both durvalumab and tremelimumab[57] and nivolumab and ipilimumab[3] combinations were evaluated in Phase 1/2 clinical trials as 2L therapy in advanced HCC. While data are still limited, preliminary results demonstrate the antitumoral activity of these combinations, and show an acceptable safety profile, providing scientific rationale to further evaluate the role of dual checkpoint blockade in the treatment of advanced HCC.

Please see Section 3.2.7 (Nivolumab Combined with Ipilimumab Clinical Activity) and Section 3.2.8 (Nivolumab Combined with Ipilimumab in HCC) for information on the clinical activity and safety of the combination nivolumab and ipilimumab.

3.2.4 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immunosurveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[58,59,60] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[61] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, inducible T cell co-stimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA).[62]

PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, IFN-γ, and B-cell lymphoma-extra large (Bcl-xL). PD-1 expression 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.[63] 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.

Nivolumab (also referred to as BMS-936558) is a human monoclonal antibody (HuMab; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 CD279 cell surface membrane receptor. Binding of PD-1 to its ligands, PD-L1 and programmed death-ligand 2 (PD-L2), results in the downregulation of lymphocyte activation.

In vitro, nivolumab binds to PD-1 with high affinity (half-maximal effective concentration [EC50] 0.39-2.62 nM) and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (half-maximal inhibitory concentration [IC50] ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMCs), the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner vs isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[64]

3.2.5 Ipilimumab Mechanism of Action

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin (Ig) superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.[65] Ipilimumab (BMS-734016) is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on antigen-presenting cells, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4:B7 interaction.

3.2.6 Nivolumab Monotherapy for Hepatocellular Carcinoma

Nivolumab is currently being evaluated in 3 settings for HCC in BMS-sponsored studies for HCC (refer to the nivolumab Investigator's Brochure [IB][1] for additional details). CA209040 is a Phase 1/2 non-comparative study of nivolumab (alone or in combination with ipilimumab or cabozantinib) in participants with advanced HCC with or without chronic viral hepatitis. For first-line (1L) advanced HCC, CA209459 is a Phase 3 randomized study of nivolumab vs sorafenib as 1L treatment in participants with advanced HCC. For early-stage HCC, CA2099DX is a Phase 3

randomized, double-blind study of adjuvant nivolumab vs placebo for participants with HCC who are at high risk of recurrence after curative hepatic resection or ablation.

CA209040 showed that monotherapy with nivolumab in participants with advanced HCC produced durable responses and disease stabilization, irrespective of HCC etiology and regardless of prior therapy with sorafenib. Updated data from a 16-Nov-2017 database lock (minimum follow-up of 24 months) revealed a blinded independent central review (BICR)-confirmed objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 of 14.3% (95% confidence interval [CI]: 9.2, 20.8) in the 154 sorafenib-treated (2L) participants who received nivolumab 3 mg/kg IV Q2W. Responses were observed across participants with both viral and non-viral HCC. [redacted] despite the longer follow-up, a median DOR was not yet reached (95% CI: 9.69 months, not applicable [NA]) with 9 of 22 (41%) participants having an ongoing response. OS in 2L participants is promising, with a median OS of 15.15 months (95% CI: 13.04, 18.23). In addition to the clinical benefit observed in 2L participants, efficacy data in sorafenib-naive (1L) participants (n = 80) are even more compelling: ORR, 20% (95% CI: 11.9, 30.4) by BICR-confirmed RECIST v1.1; median DOR, not yet reached (95% CI: 11.1 months, NA); and median OS, 26.68 months (95% CI: 16.56, 35.48). Safety data support an acceptable and manageable safety profile (data on file).

These data indicate that nivolumab monotherapy has clinically meaningful antitumor activity in patients with advanced HCC with an acceptable and manageable safety profile. The observed durable responses and substantially longer OS relative to OS data from targeted agents, including historical data for sorafenib (10.7 months),[49] regorafenib (10.6 months),[50] lenvatinib (13.6 months),[66] and cabozantinib (10.2 months),[67] provide persuasive evidence to further evaluate nivolumab in HCC.

3.2.7 Nivolumab Combined with Ipilimumab Clinical Activity

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules. The following information describes the results of initial early phase clinical studies that were the basis for the nivolumab plus ipilimumab combination regimens that have been explored in late-phase clinical development. Additional information as well as a detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab and ipilimumab is provided in the IB.[1]

In the Phase 1 study CA209004, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab in participants with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks (Q3W) for 4 doses with nivolumab administered once Q3W for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks (Q12W) for 8 doses. The 3 initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg + ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1.0 mg/kg + ipilimumab 3 mg/kg; n = 17), and Cohort 3 (nivolumab 3 mg/kg + ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which

evaluated nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 16). The primary objective was to assess safety/tolerability; the secondary objective was to assess preliminary efficacy.

Of the 52 participants evaluable for response as of the 15-Feb-2013 clinical cut-off in CA209004, 21 participants (40%) had an objective response by modified World Health Organization (mWHO) criteria. In an additional 2 participants (4%), there was an unconfirmed objective response. In Cohort 1 (0.1 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 14 evaluable participants had an objective response by mWHO (21%), including 1 complete response (CR) and 2 PRs. In Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 9 out of 17 (53%) evaluable participants had an objective response by mWHO, including 3 CRs (18%) and 6 PRs (35%). In Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab), 6 out of 15 (40%) evaluable participants had an objective response by mWHO, including 1 CR (7%) and 5 PRs (33%). In Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 6 (50%) evaluable participants had an objective response by mWHO, all 3 of which were PRs (50%).

Preliminary analysis revealed 16 of the 52 evaluable participants (31%) had > 80% reduction in the size of target tumor lesions by the week 12 evaluation. This is compared to < 2% for 3 mg/kg ipilimumab monotherapy based on CA184020 (N = 540) and < 3% for nivolumab monotherapy based on CA209003 (N = 94, 0.1-10 mg/kg).

The following dose-limiting toxicities (DLTs) were observed: in Cohort 1, Grade 3 elevated AST/ALT (1 participant); in Cohort 2, Grade 3 uveitis (1 participant) and Grade 3 elevated AST/ALT (1 participant) and in Cohort 3, Grade 4 elevated lipase (2 participants), and Grade 3 elevated lipase (1 participant). Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

A total of 53 melanoma participants were treated with nivolumab combined with ipilimumab in CA209004 across Cohorts 1, 2, 2a, and 3. At least 1 AE, regardless of causality, has been reported in 98% of participants treated. The most common (reported at > 10% incidence) treatment-related AEs (any Grade 93%; Grade 3-4 53%) are rash (55%; 4%), pruritus (47%; 0%), vitiligo (11%; 0%), fatigue (38%; 0%), pyrexia (21%; 0%), diarrhea (34%; 6%), nausea (21%; 0%), vomiting (11%; 2%), ALT increased (21%; 11%), AST increased (21%; 13%), lipase increased (19%; 13%), amylase increased (15%; 6%), headache (11%; 0%), and cough (13%; 0%).

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3 or 4 (reported in 11 of 53 participants, 21%). Grade 3 events included lipase increased, ALT increased, AST increased, troponin I increased, colitis, diverticular perforation, pancreatitis, tachycardia, renal failure acute, choroiditis, autoimmune disorder, and pneumonitis. One participant each discontinued due to Grade 4 events of blood creatinine increased and AST increased. No drug-related deaths were reported.[53]

The combination of nivolumab with ipilimumab is being studied in the Phase 1 study CA209016. Participants with metastatic renal cell carcinoma (RCC; Karnofsky performance status ≥ 80%; untreated or any number of prior therapies) were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3)

IV Q3W for 4 doses followed by nivolumab 3 mg/kg IV Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; secondary objective was to assess antitumor activity.

Participants were randomized to N3 + I1 (n = 47) and N1 + I3 (n = 47). Approximately half (n = 46; 51%) had prior systemic therapy (N3 + I1: 22; N1 + I3: 26).

After a median follow-up of 22.3 months, the confirmed ORR per RECIST v1.1 was 40.4% (N = 47) in both arms N3 + I1 and N1 + I3; 42.1% (n = 8) and 36.8% (n = 7) had an ongoing response, with a median DOR of 88.7 weeks (95% CI: 37.14, NA) and 85.9 weeks (95% CI: 35.14, NA), respectively. Median progression-free survival (PFS) was 7.7 months (95% CI: 3.71, 14.29) and 9.4 months (95% CI: 5.62, 18.63) in Arms N3 + I1 and N1 + I3, respectively. OS at 12 months was 80.9% and 85.0% in arms N3 + I1 and N1 + I3, respectively, and at 24 months was 67.3% and 69.6%, respectively.

The safety of nivolumab combined with ipilimumab was assessed in study CA209016. Treatment-related AEs were seen in 88 of 94 participants (94%), including 43 of 47 (92%) in N3 + I1 and 45 of 47 (96%) in N1 + I3. The most frequently reported drug-related AEs in N3 + I1 included fatigue (66%), cough (53.2%), and arthralgia (51.1%), the majority of which were Grade 1-2. The most frequently reported drug-related AEs in N1 + I3 included fatigue (74.5%), nausea (55.3%), and diarrhea (53.2%). The majority were Grade 1-2.

Treatment-related AEs leading to discontinuation (31.9% vs 10.6%), and treatment-related serious adverse events (SAEs; 34% vs 23.4%) occurred more commonly in participants in the N1 + I3 arm than in the N3 + I1 arm, respectively.[3]

CA209012 was a multi-arm Phase 1b trial evaluating the safety and tolerability of nivolumab in participants with chemotherapy-naive advanced non-small cell lung cancer (NSCLC), as either a monotherapy or in combination with other agents including ipilimumab, at different doses and schedules. The primary endpoint of the study was safety with secondary endpoints of ORR per RECIST v1.1 and 24-week progression-free survival (PFS). Participants were assigned to receive nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W (n = 38), nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg every 6 weeks (Q6W; n = 39) and nivolumab 3 mg/kg Q2W (n = 52). The confirmed ORR was 47% (N3 Q2W + I1 Q12W), 39% (N3 Q2W + I1 Q6W), and 23% (N3 Q2W). The median DOR was not reached in any of these groups.

The rate of treatment-related AEs in the Q12W (82%) and Q6W (72%) arms were comparable to monotherapy (72%). In the study, Grade 3 to 4 AEs 37%, 33%, and 19% for the Q12W, Q6W, and nivolumab monotherapy arms, respectively. Treatment-related Grade 3 to 4 AEs led to discontinuation in 5% and 8% of participants in the Q12W and Q6W cohorts, respectively, and were similar to nivolumab monotherapy. There were no treatment-related deaths. The treatment-related select AEs in participants administered the optimized dosing schedule (3 mg/kg of nivolumab Q2W plus 1 mg/kg of ipilimumab Q6W) were skin related (36%), gastrointestinal (23%), endocrine (20%), and pulmonary (5%) and there were ≤ 5% treatment related Grade 3 and Grade 4 AEs per category.[68] Nivolumab in combination with ipilimumab is FDA approved for the

treatment of unresectable or metastatic melanoma, advanced RCC, and microsatellite instability (MSI)-high metastatic colorectal cancer (CRC).[69,70]

3.2.8 Nivolumab Combined with Ipilimumab in HCC

Nivolumab and ipilimumab combination is currently being evaluated as 2L therapy for advanced HCC in CA209040, a Phase 1/2 non-comparative, multi-cohort study of nivolumab (alone or in combination with ipilimumab or cabozantinib) as 1L/2L treatment in participants with advanced HCC with or without chronic viral hepatitis and in CA2099DW, a Phase 3 randomized study of nivolumab in combination with ipilimumab vs sorafenib or lenvatinib as 1L treatment in participants with advanced HCC.

CA209040 was initially designed as a Phase 1 dose-escalation study to investigate the safety, immuno-regulatory activity, pharmacokinetics (PK), and preliminary antitumor activity of nivolumab monotherapy in advanced HCC. Dose escalation occurred in 3 parallel cohorts by etiology (uninfected, HBV-infected, and HCV-infected). Participants (n = 48) with histologically confirmed advanced HCC and Child-Pugh score ≤ 7, who previously failed or were intolerant of sorafenib, received nivolumab at doses ranging from 0.1 to 10 mg/kg for up to 2 years. Following preliminary data showing responders in all cohorts, the study was expanded to confirm the safety and efficacy of nivolumab monotherapy in a diverse group of participants with advanced HCC. In this phase (EXP Cohort), 214 participants were enrolled in 4 parallel cohorts (uninfected sorafenib-naive/intolerant, uninfected sorafenib progressors, HCV-infected, and HBV-infected), and received nivolumab 3 mg/kg IV Q2W.[3] Please refer to Section 3.2.6 (Nivolumab Monotherapy for Hepatocellular Carcinoma) for information on the clinical activity and safety of nivolumab monotherapy in HCC.

Once the safety and efficacy of nivolumab monotherapy was established, the study was amended to add a cohort aimed to evaluate the safety and efficacy of the combination of nivolumab and ipilimumab as 2L therapy. A total of 148 participants with histologically confirmed advanced HCC (87.8% had vascular invasion [VI] or extrahepatic spread [EHS]; and 43.9% had alpha-fetoprotein [AFP] ≥ 400 ng/mL) and Child-Pugh score ≤ 6, who had previously failed or were intolerant of sorafenib, were randomized to 1 of the following 3 dose arms:

- Arm A (N1+I3 Q3W): nivolumab 1 mg/kg and ipilimumab 3 mg/kg Q3W for 4 doses, followed by nivolumab 240 mg Q2W (n = 50)
- Arm B (N3+I1 Q3W): nivolumab 3 mg/kg and ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 240 mg Q2W (n = 49)
- Arm C (N3 QW2+I1 Q6W): nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W (n = 49)

Results from CA209040 (interim analysis; database lock, 22-Mar-2019)[3] show that treatment with nivolumab and ipilimumab in participants with advanced HCC produced durable responses and prolonged survival, irrespective of HCC etiology. Overall, the confirmed ORR by BICR assessment (using RECIST v1.1 criteria) was 31.0%, with response rates fairly comparable, regardless of dose arm (32% for Arm A, 31% for Arm B, and 31% for Arm C). However, a higher

rate of CR was observed with N1+I3 QW3 (4 [8%] CR for Arm A, 3 [6%] CR for Arm B, and no CR for Arm C). An additional 26.4% of participants had PR (24%, 24%, and 31% in Arm A, Arm B, and Arm C, respectively).

Responses were meaningful and durable with a median DOR of 17.5 months (range: 4.6, 30.5) in Arm A, 22.2 months (range: 4.2, 29.9) in Arm B, and 16.6 months (range: 4.1, 32.0) in Arm C. Of note, responses were observed across all HCC etiologies (overall ORR of 15.2%, 30.7%, and 39.4% for uninfected [n = 33], HBV-infected [n = 75], and HCV-infected [n = 33], respectively) and regardless of dosing arm. Participants who received treatment with N1+I3 Q3W (Arm A) showed a more consistent response rate across etiological subgroups (30.8%, 32.1%, and 28.6% for uninfected [n = 13], HBV-infected [n = 28], and HCV-infected [n = 7]) but the small size of some subgroups in other treatment arms precludes drawing any definitive conclusion.

With regards to OS, with a minimum follow-up of 28.0 months, participants treated with N1+I3 Q3W had longer OS (22.80 months [95% CI: 9.4, N.A]) compared to those randomized to Arm B (12.48 months [95% CI: 7.6, 16.4]) or Arm C (12.75 months [95% CI: 7.43, 33.0]), with 2-year survival rates of 48.2%, 30.2%, and 42.3%, respectively.

The preliminary safety data from CA209040 (n = 146) indicate that nivolumab and ipilimumab was generally well tolerated, with a safety profile similar to the observed in other tumor types in terms of type of reported events; no new safety concerns were identified for nivolumab and ipilimumab. One death (reported in Arm A) was attributed to study drug by Investigator (pneumonitis, which occurred 79 days after last dose of study drug). Overall, as previously reported in other tumor types, the frequency of treatment-related AEs for the combination nivolumab and ipilimumab was higher compared to nivolumab monotherapy. By dosing arm, a higher frequency of treatment-related AEs (any grade or high grade) were reported in Arm A (93.9%; 53.1%) compared to Arm B (69.4%; 28.6%) and Arm C (79.2%; 31.0%). Similarly, the frequency of AEs leading to discontinuation was slightly higher in Arm A (n = 11; 22.0%) relative to Arm B (n = 3; 6.1%) and Arm C (n = 1; 2.1%), with diarrhea (n = 2) and liver test abnormalities (n = 2) being the most frequent reasons for discontinuation. Across the 3 arms, treatment-related AEs of increased AST (20.4% of participants in the N1+I3 Q3W and N3+I1 Q3W arms, and 13.0% in the N3+I1 Q6W arm) and increased ALT (16.3%, 14.3%, and 8.3% of participants in the N1+I3 Q3W, N3+I1 Q3W, and N3+I1 Q6W arms, respectively) were observed. These AEs were infrequently associated with treatment-related increased bilirubin (11.6% of participants across all arms; 6.1%, 0%, and 4.2% of participants in Arm A, Arm B, and Arm C, respectively), and infrequently led to treatment discontinuation (n = 2), being most of them manageable with established algorithms.

Therefore, data from CA209040 demonstrate that nivolumab and ipilimumab has clinically meaningful antitumor activity with a manageable safety profile.

3.2.9 Immunotherapy and Loco-regional Therapy for HCC

3.2.9.1 Impact of Loco-regional Therapy on the HCC Immune Environment

Loco-regional therapy has been shown to modulate the immune environment. Tregs are the dominant cells inducing tumor immune tolerance and thus have a significant role in the

development of HCC. An increased quantity of circulating Tregs in patients with HCC is associated with a high mortality rate and reduced survival.[40] Spontaneous regression of untreated lesions has been reported after loco-regional treatment of liver tumors ("abscopal effect"). The latter is attributed to the induction of antitumor immunity by the loco-regional therapy.[71,72,73] Data on the effect of TACE on immune function are limited but suggest that TACE results in immune environment change. In a study on the impact of TACE on immune function in 47 participants, significant increases in CD4+ T cells and decreases in CD8+ T cells were seen post-TACE, with a significant change in the ratio of CD4+/CD8+ T cells from 1.03 ± 0.14 vs 1.29 ± 0.14 ($p < 0.05$). The percentage of CD4+, CD25+ Tregs in CD4+ T cells and CD4+, CD25-high T cells post-TACE was reduced from 11.12 ± 3.58% prior to TACE to 7.58 ± 2.65% following TACE ($p < 0.05$) and from 3.34 ± 0.79% prior to TACE to 2.11 ± 0.67% following TACE ($p < 0.05$), respectively. This indicates that the proportion of Tregs following TACE treatment decreased with a reduction in its immunosuppressive function,[74] and suggests a partial restoration of cellular immune function post-TACE. In another study in 51 participants, CD4+ cells and CD4/CD8 ratio decreased but CD8+ cells increased post-TACE in the subset of participants treated only with TACE ($p < 0.05$). This, in turn, suggested that TACE lowered immunologic function to a certain extent.[75]

Despite variable reports, the data suggest immune environment modulation post-TACE and support clinical interest in combining loco-regional therapies with immune checkpoint blockade. Local tumor destruction via ablation, chemoembolization, or radioembolization all have the potential to differentially alter and enhance tumor-specific antigen presentation. Therefore, there exists a synergistic potential for immunotherapy and TACE and it will be of critical importance to assess how different methods of local tumor destruction and their timing can augment or be augmented by checkpoint blockade.[76]

3.2.9.2 Data on the Combination of Loco-regional Therapy with Checkpoint Inhibitors

Preliminary clinical data for loco-regional therapy in combination with checkpoint inhibitors demonstrates a good safety profile and promising efficacy. In a study to evaluate whether tremelimumab could be combined safely and feasibly with TACE, radiofrequency ablation (RFA), or chemoablation in participants with advanced HCC, no DLTs were encountered. Of the 19 evaluable participants, 5 (26.3% [95% CI: 9.1, 51.2]) achieved a confirmed PR. Six- and 12-month probabilities of tumor PFS for this refractory HCC population were 57.1% and 33.1%, respectively, with median TTP of 7.4 months (95% CI: 4.7, 19.4). Median OS was 12.3 months (95% CI: 9.3, 15.4). The authors concluded that tremelimumab in combination with tumor ablation is a potential new treatment for patients with advanced HCC and leads to the accumulation of intratumoral CD8+ T cells.[77]

3.2.9.3 Nivolumab in Combination with TACE

CA209731 is a multicenter study designed to test the hypothesis that nivolumab is safe in combination with TACE with drug-eluding beads (DEB-TACE) in unresectable HCC patients (BCLC Stage B) who are not candidates for hepatic transplantation and have Child-Pugh A hepatic function (ClinicalTrials.gov: NCT03143270).[78] A modified 3 + 3 design sequentially enrolled

participants to define the safety and tolerability of nivolumab given at different times related to DEB-TACE. DEB-TACE was performed on Day 0. Nivolumab at 240 mg/m^2 was administered every 14 days, but at 3 different schedules related to DEB-TACE (Cohort 1-sequential; Cohort 2-interrupted; and Cohort 3-continuous) for up to 1 year. DLTs were monitored for 4 weeks after combination treatment.

As of 18-July-2019, 10 participants have been accrued on the study: 4 participants to Cohort 1, 3 participants to Cohort 2, and 3 participants to Cohort 3. One participant was withdrawn from study due to the combination of mixed HCC-cholangiocarcinoma on pretreatment biopsy. Five participants have been removed from study due to progression of disease, and 2 remain on active treatment, while 2 remain on study in surveillance. Evaluable participants (9) were a median 65 years of age (range: 54-76), male (89%), with a mixture of etiologic factors (viral [44%, 1 HBV, 3 HCV] and non-viral [55.6%]), and all with Child-Pugh A liver function. HCC substage included 3 B1 (33%), 4 B2 (44%), and 2 C (22%). Most participants received prior surgery (44%) and/or regional therapy (44%), while 3 (33%) were treatment naive. Median AFP for the study population was 22.5 (range: 6-5914) ng/mL. No cases of treatment-related liver failure or DLT in the 3 cohorts have occurred. There were no Grade 4 or higher AEs. Grade 3 events at least possibly related to nivolumab, DEB-TACE, or both, included: transaminases (AST or ALT) elevation (n = 4), post-embolization syndrome (PES; n = 1), lipase increase (n = 1), hypothyroidism (n = 1), and post-procedural groin hematoma (1). Regarding 4 AEs of Grade 3 increase in AST/ALT, 2 occurred immediately post-embolization and were attributed to DEB-TACE; the other 2 AEs occurred outside the DLT window and were attributed to be possibly related to nivolumab. All Grade 3 events resolved with appropriate medical management. The efficacy data is still immature at the time of reporting.

In summary, current data support the potential of immunotherapy for HCC therapy. Immune checkpoint inhibitors have clinical activity and are tolerable in advanced HCC, supporting their potential for use in other stages of the disease. Data on loco-regional therapy indicate that these procedures induce changes in the immune environment that suggest a synergistic potential for the combination of loco-regional therapy with immunotherapy. The preliminary data from tremelimumab in combination with ablation and from nivolumab in combination with TACE indicate that the combinations are feasible and tolerable. The combination of TACE with nivolumab and ipilimumab has the potential to address the need for better therapeutic options for intermediate-stage HCC and support further investigation of nivolumab and ipilimumab in combination with TACE in this setting.

3.3 Benefit/Risk Assessment

The current standard of care (SOC) for intermediate-stage HCC patients, unsuitable for potentially curative therapy, is loco-regional therapy with TACE.[79,80,81] Although significant tumor response can be achieved, TACE often fails to induce complete necrosis of the lesion. Even in cases where complete ablation is achieved, tumors commonly recur post-TACE. Thus, TACE is considered a palliative treatment and preventing tumor recurrence in this population remains a significant unmet medical need, as there are no other established therapeutic options available.

The overall benefit-risk of nivolumab and ipilimumab or nivolumab in combination with TACE over TACE in patients with intermediate-stage HCC is not yet known. However, in clinical trials, nivolumab and ipilimumab and nivolumab alone have demonstrated an acceptable benefit-risk ratio with clinical activity and a tolerable AE profile across multiple tumor types including HCC.

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 nivolumab and ipilimumab or nivolumab alone are unknown.

3.3.1 Nivolumab and Ipilimumab Safety Profile

Extensive details on the safety profile of nivolumab and nivolumab in combination with ipilimumab in multiple tumors are available in the IBs.[1,82]

Overall, the safety profile of nivolumab monotherapy as well as in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.[1]

The recently reported clinical trial CA209040 Cohort 4 characterized the safety and efficacy of different doses of nivolumab and ipilimumab in participants with advanced HCC who progressed on sorafenib. The overall frequency of AEs (any Grade, Grade 3-4) were similar in all 3 treatment arms. Frequencies of drug-related AEs (any Grade, Grade 3-4) were numerically higher in the N1+I3 Q3W arm relative to the N3+I1 Q3W, and N3+I1 Q6W arms. The overall frequencies of SAEs were consistent between the N1+I3 Q3W, N3+I1 Q3W, and N3+I1 Q6W arms, but a trend for higher drug-related SAEs was seen in the N1+I3 Q3W arm. The overall frequencies of all-causality AEs leading to discontinuation and drug-related AEs leading to discontinuation were also numerically higher in the N1+I3 Q3W arm relative to the N3+I1 Q3W and N3+I1 Q6W arms. The most frequent drug-related AEs across the 3 dose arms were in the skin and subcutaneous tissue disorders (48-61%), investigations (31-49%), and GI disorders (35-37%) system organ classes; however, these infrequently led to discontinuations due to drug-related AEs. Drug-related AST/ALT increases were observed in 20.4%/16.3%, 20.4%/14.3%, and 12.5%/8.3%, in the N1+I3 Q3W, N3+I1 Q3W, and N3+I1 Q6W arms, respectively. However, drug-related increases in bilirubin were typically not associated with aminotransferase increases and occurred in 6.1%/0%/4.2%, respectively, and were all low-grade. Drug-related hepatic discontinuations within 30 days of last dose of study drug were infrequent and occurred in 3 of 49 (6.1%), 2 of 49 (4%), and 0 of 48 (0%) subjects in the N1+I3 Q3W, N3+I1 Q3W, and N3+I1 Q6W arms, respectively. Please refer to Section 3.2.8 (Nivolumab Combined with Ipilimumab in HCC) for further details.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 6. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.[1] Additional details on the safety profile of nivolumab and ipilimumab, including results from other clinical studies, are also available in the nivolumab and ipilimumab IBs.[1,82]

3.3.2 Clinical Experience with Nivolumab and Ipilimumab in HCC

In HCC, the clinical activity of nivolumab monotherapy observed to date includes data from the Phase 1/2 study CA209040, which demonstrated clinically meaningful antitumor activity in the advanced setting, regardless etiology and prior therapy with sorafenib.[3] The observed durable responses and substantially longer OS relative to historical data is particularly remarkable considering the unfavorable characteristics of the study population. Additionally, safety data showed a safety profile similar to that observed in other tumor types, in terms of the type, frequency, and severity of reported events, with no new safety concerns. Treatment-related AEs most frequently reported (mostly Grade 1 or 2) were fatigue, pruritus, rash, and diarrhea. Of particular interest in the context of HCC is the observed hepatic toxicity. Treatment-related AST, ALT, and bilirubin elevations were observed at a slightly increased frequency as compared to the nivolumab program overall, but were generally mild, manageable with established treatment algorithms, and reversible, with very few discontinuations due to hepatic events. In addition, AST/ALT increases typically occurred without change in other hepatic parameters and were more frequently observed in participants with higher values at baseline. Taken together, these results suggest the potential for improved clinical outcomes with nivolumab in the intermediate-stage setting, without impacting the overall safety profile.

Nivolumab and ipilimumab demonstrated clinically meaningful activity in participants with advanced HCC in the 2L or higher setting after sorafenib treatment. The ORR was 32%, 30.6%, and 30.6% and DOR was 17.48, 22.21, and 16.59 months by BICR for N1+I3 Q3W, N3+I1 Q3W, and N3+I1 Q6W arms, respectively. This compares favorably with other approved therapies for post-sorafenib 2L advanced HCC: 14.3% with nivolumab monotherapy, 7% with regorafenib, 5% with ramucirumab, and 4% with cabozantinib.

In summary, based on the high unmet medical need in this clinical setting, the robust clinical activity demonstrated by nivolumab and ipilimumab in advanced HCC, and the manageable safety profile, the overall potential benefits of a combination of nivolumab and ipilimumab or nivolumab with TACE in this population outweigh the potential clinical risks. Nevertheless, in order to mitigate potential risks, a Data Monitoring Committee (DMC) will be involved in the study to periodically evaluate the emerging data and trends (see Section 5.1.5.1 [Data Monitoring Committee]).

4 OBJECTIVES AND ENDPOINTS

Per Protocol Amendment 01, no analyses of efficacy, quality of life (QoL)/PROs, healthcare resource utilization, PK, or IMG are planned. Only safety assessments will be conducted. Previously collected biomarker samples may be analyzed, but no further biomarker collections are planned with this amended protocol.

Table 4-1: Objectives and Endpoints

Objective	Endpoint
• To evaluate the safety and tolerability of Arm A, Arm B, and Arm C in all treated participants.	• Incidence of AEs, SAEs, deaths, AEs leading to discontinuation, and laboratory abnormalities in all treated participants.

Abbreviations: AE = adverse event; SAE = serious adverse event.

5 STUDY DESIGN

5.1 Overall Design

This is a double-blind, placebo-controlled, 3-arm, randomized Phase 3 study of nivolumab and ipilimumab in combination with TACE and nivolumab in combination with TACE vs placebo in combination with TACE in patients with intermediate-stage HCC. Participants must have tumor characteristics that exceed the Beyond Milan and Up-to-7 (BMU7) criteria, no EHS, no regional lymph node involvement, no portal vein thrombosis, and no macrovascular invasion (MVI) must be present. As of 22-Sep-2021, enrollment for new participants was closed. The number of participants randomized was 26 as of 14-Oct-2021. **Per Protocol Amendment 01, there are no formal hypotheses or efficacy objectives for CA20974W. Only safety assessments will be conducted.** Following unblinding, study participants who are currently receiving nivolumab ± ipilimumab and tolerating study treatment may continue to receive study drug; however, placebo infusions will no longer be administered.

The study will consist of 3 periods: Screening, Treatment, and Follow-up. For a complete list of study required procedures, please see Section 2 (Schedule of Activities).

After signing an informed consent form (ICF), participants who have not previously received TACE will be evaluated for eligibility. If participants are eligible for receiving TACE and meet other eligibility criteria, they will be randomized in a 1:1:1 ratio to receive nivolumab and ipilimumab plus TACE (Arm A), nivolumab and ipilimumab placebo plus TACE (Arm B), or nivolumab placebo and ipilimumab placebo plus TACE (Arm C). Since TACE is the only recommended SOC in clinical practice guidelines for the intended population, TACE plus nivolumab placebo and ipilimumab placebo will be used as a control. Both conventional TACE and DEB-TACE are acceptable treatment modalities in this study (see Section 7.1.2 [TACE Procedure] for restrictions on TACE use) and will be administered 7 days (+3 days) after study drug administration. Randomization will be stratified by ALBI grade (Grade 1 vs Grade 2), baseline AFP level (< 400 ng/mL vs ≥ 400 ng/mL), and Region (West [EU, Americas, and Australia] vs Japan vs rest of Asia).

Participants will receive blinded treatment with 1 of the following regimens:

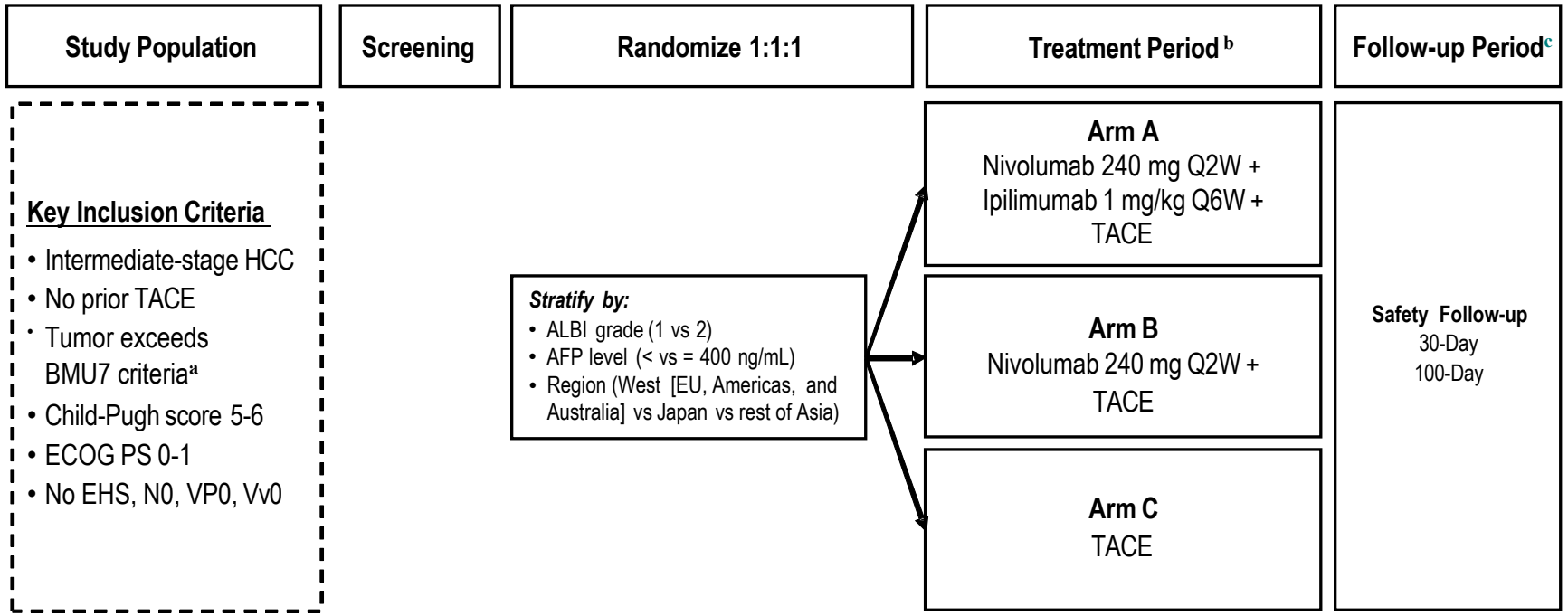
- Arm A: Nivolumab 240 mg Q2W and ipilimumab 1 mg/kg Q6W plus TACE
- Arm B: Nivolumab 240 mg Q2W and ipilimumab placebo Q6W plus TACE
- Arm C: Nivolumab placebo Q2W and ipilimumab placebo Q6W plus TACE

Per Protocol Amendment 01, this study will be unblinded and participants randomized to Arm B and Arm C will no longer receive placebo infusions following unblinding.

All randomized participants will receive treatment until progression as assessed by investigator, unacceptable toxicity, or consent withdrawal, for a maximum duration of treatment of 2 years. Participants will also receive on-demand TACE during the trial and can continue to receive TACE until they are not eligible for further TACE (see Section 7.1.2 [TACE Procedure]). Participants in any arm may be treated with study therapy beyond progression as assessed by investigator under protocol-defined conditions (see Section 5.1.4 [Treatment Beyond Progression]).

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

Figure 5.1-1: Study Design Schematic



Abbreviations: AFP = alpha-fetoprotein; ALBI = albumin-bilirubin; BMU7 = beyond Milan and up-to-7; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; EU = Europe; HCC = hepatocellular carcinoma; N0 = no regional lymph node metastasis; PS = performance status; Q2W = every 2 weeks; Q6W = every 6 weeks; TACE = trans-arterial chemoembolization; VP0 = no portal vein thrombosis; Vv0 = no macrovascular invasion.

[a] Number of nodules ≥ 1 cm + diameter of largest nodule in cm = 7.

[b] **Per Protocol Amendment 01, participants randomized to Arm B and Arm C will no longer receive placebo following unblinding.** Participants randomized to nivolumab and ipilimumab plus TACE (Arm A), nivolumab plus TACE (Arm B), or TACE alone (Arm C) will receive treatment until progression as assessed by investigator (unless treatment beyond progression was allowed), unacceptable toxicity, or consent withdrawal, for a maximum duration of treatment of 2 years.

[c] **Per Protocol Amendment 01, all participants randomized will have 30- and 100-day safety follow-up visits. No survival follow-up visits will occur.**

5.1.1 Screening Period

The screening assessments are shown in Table 2-1.

- Screening procedures are to occur within 28 days prior to first dose.
- Screening begins by establishing the participant's initial eligibility and signing of the ICF.
- Participant is enrolled using the interactive response technology (IRT) system.
- Participant is assessed for study eligibility according to the inclusion (Section 6.1) and exclusion (Section 6.2) criteria.
- Sufficient, recent tumor tissue obtained within 3 months prior to randomization from a lesion from an unresectable primary tumor lesion that has not been previously irradiated (formalin-fixed, paraffin-embedded [FFPE] block or minimum of 20 slides, obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen) will be submitted to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable. 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. The central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Participants should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained. Please see Appendix 9 for country-specific criteria for the collection of tumor tissue samples in China.
- Images must be submitted for BICR to confirm eligibility.
- The Screening Period either ends with confirmation of full eligibility and randomization for the participant, or with the confirmation that the participant is a screen failure.
- This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure prior to randomization (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented. A new participant identification number will be assigned by IRT at the time of re-enrollment (see Section 6.4.1 [Retesting During Screening or Lead-in Period]).

5.1.2 Treatment Period

The on-treatment procedures are shown in Table 2-2.

- The Treatment Period begins with the randomization call to the IRT system. The participant is randomly assigned to 1 of the 3 treatment arms:
  - Arm A: Nivolumab 240 mg Q2W and ipilimumab 1 mg/kg Q6W plus TACE
  - Arm B: Nivolumab 240 mg Q2W and ipilimumab placebo Q6W plus TACE
  - Arm C: Nivolumab placebo Q2W and ipilimumab placebo Q6W plus TACE

  Note: **The study will be unblinded per Protocol Amendment 01.** After unblinding, participants in Arms B and C will no longer receive placebo.
- Administration of study treatment must begin within 3 calendar days after randomization.
- First TACE will be administered 7 days (+3 days) after study drug administration. Participants will receive study treatment until progression as defined by investigator (unless treatment beyond progression is permitted), unacceptable toxicity, or consent withdrawal for a maximum duration of treatment of 2 years. See Section 5.1.4 (Treatment Beyond Progression).

- On-demand TACE is allowed and should be given with at least a 7-day window for systemic therapy. See Section 7.1.2 (TACE Procedure) for further details on TACE.
- Specific requirements for participants treated in any arm, including dose delays or interruptions and treatment discontinuation criteria, are described in Section 7.4 (Dosage Modification) and Section 8.1.1 (Treatment Discontinuation Criteria), respectively.
- Women of childbearing potential (WOCBP) must have a documented negative pregnancy test within 24 hours prior to the start of study treatment. For additional assessments, see Table 2-2.
- On-study vital sign assessments should be performed at each on-treatment visit (see Table 2-2).
- On-study laboratory assessments should be performed at each on-treatment visit and will be assessed at the local laboratory (see Table 2-2).
- Efficacy assessments will occur in accordance with Table 2-2 per local standard of care until progression as assessed by investigator (unless treatment beyond progression is permitted) or treatment discontinuation (including treatment beyond progression), whichever occurs later.
- **Not applicable per Protocol Amendment 01:** Biomarker sample collection will be done according to the schedule in Table 9.8-1. Please see Appendix 9 for country-specific criteria for the collection of biomarker samples [redacted].
- **Not applicable per Protocol Amendment 01:** PK and immunogenicity (IMG) samples are to be collected predose and according to Table 9.5-1.
- **Not applicable per Protocol Amendment 01:** Outcomes research assessments instruments (EuroQol-5 Dimensions-5 Levels [EQ-5D-5L] and Functional Assessment of Cancer Therapy-Hepatobiliary [FACT-Hep]) will be completed prior to treatment at the start of each cycle for the first 6 months, and then every third cycle thereafter during the Treatment Period (see Table 2-2).
- The Treatment Period ends when the participant is discontinued from study therapy for any reason, or a maximum of 2-years total duration of study medication (if treatment not discontinued before). Please see Section 8 (Discontinuation Criteria) for a complete list of possible reasons for discontinuation.

5.1.3 Follow-up Period

The follow-up procedures are shown in Table 2-3.

- The Follow-up Period begins when the decision is made to discontinue a participant from study therapy (eg, due to toxicity or progression) or after study drug discontinuation (due to toxicity or progression) or treatment completion (2-years total duration), whichever comes first.
- Participants will have 2 follow-up visits, follow-up visit 1 (FU1) and follow-up visit 2 (FU2) for safety within approximately 30 and 100 days from the last dose of study treatment, respectively. Both follow-up visits should be conducted in person, according to Table 2-3.
  - Follow-up visits include targeted physical examination, laboratory tests, tumor assessments (if applicable), and AE and concomitant medication assessments. Additional details and requirements are outlined in Table 2-3.

- Participants who discontinue study treatment for reasons other than radiographic disease progression (as assessed by investigator) will continue to have tumor assessments (if clinically feasible), according to the schedule in Table 2-3.
- After completion of the first 2 follow-up visits, participants will be followed for ongoing treatment-related AEs until these events have resolved, returned to baseline, or are deemed irreversible. All toxicities will be documented for a minimum of 100 days after the last dose of study medication. Please refer to Section 9.2.4 for further details regarding follow-up of AEs and SAEs.
- **Not applicable per Protocol Amendment 01:** Participants will be followed for survival status Q12W (±14 days) until death, withdrawal of consent for any further contact, lost to follow-up, or end of study.
  - Survival status may be ascertained by telephone contact if the participant is unable to return to the site for a visit.
  - If new antitumor therapy is initiated for disease progression or for a secondary malignancy at any time during this period, this and all other pertinent data obtained should be recorded on the appropriate electronic case report form (eCRF).

5.1.4 Treatment Beyond Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[83]

Participants will be permitted to continue treatment beyond progression (as assessed by investigator) up to a maximum of 24 months from the date of randomization, as long as the following criteria are considered:

- Investigator-assessed clinical benefit.
- Tolerance of study drug(s).
- Stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Participant provides written informed consent prior to receiving additional treatment 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.
- Should be documented in the study records.

Radiographic assessment/scan(s) should continue in accordance with Section 2 (Schedule of Activities) for the duration of the treatment beyond progression.

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

The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with study therapy.

5.1.5 Data Monitoring Committee and Other External Committees

5.1.5.1 Data Monitoring Committee

A DMC will be established to provide oversight and safety and efficacy considerations in the CA20974W study. On 22-Sep-2021, enrollment was closed and a total of 26 participants have been randomized. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled/treated in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit-risk profile for nivolumab and ipilimumab or nivolumab in combination with TACE. A safety review will be conducted by the DMC after all participants have been randomized and have been followed for a minimum of 6 weeks, unless decided otherwise by the DMC chair. After participants are unblinded as per Protocol Amendment 01, the Sponsor will continue safety monitoring of remaining participants on the study. No subsequent DMC meeting will occur after the first safety monitoring meeting.

The BMS clinical study leadership will have responsibility for the overall conduct of the study, including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, providing guidance regarding the continuation or termination of the study, and determining whether amendments to the protocol or changes to the study conduct are required.

Details of the DMC responsibilities and procedures will be specified in the DMC Charter.

5.1.5.2 Blinded Radiology Review Committee

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

In addition to local tumor assessments by mRECIST, images from this study will undergo a BICR to assess TTTP and to assess response based on the modified RECIST assessment criteria (mRECIST) and RECIST v1.1 criteria. The centrally reviewed response data will be used in the analyses of TTTP, ORR, PFS, DOR, DCR, and time to response. All final determinations on centrally reviewed image-based endpoints will be made based on the independent assessments, for a uniform and unbiased assessment of outcome. Details of the procedures and the criteria for the central review are defined in a separate Imaging Charter.

5.2 Number of Participants

As of 22-Sep-2021, enrollment for new participants was closed. The number of participants randomized was 26 as of 14-Oct-2021.

5.3 End of Study Definition

The start of the trial is defined as the first participant's first visit. End of trial is defined as the last participant's last study visit or scheduled procedure shown in the Schedule of Activities (Section 2)

for the last participant. Study completion is defined as the final date on which data for the primary endpoint and survival follow-up was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Study Population

In clinical practice, TACE is used not only as a palliative therapy for patients with intermediate-stage HCC, but also a preoperative adjuvant therapy in patients with HCC to improve survival, and as a bridging therapy for the purposes of downstaging prior to liver transplantation or as bridging therapy while on the transplant waiting list.[84,85,86,87] In addition, TACE is also used in clinical practice for advanced-stage HCC. This is premised on the fact that more than two-thirds of patients with advanced HCC die of liver failure or intrahepatic tumor progression, rather than from progression of metastatic disease.[88,89,90] Investigations on the use of TACE in advanced HCC report a survival benefit in patients with vascular involvement or extrahepatic metastasis who underwent TACE instead of receiving best supportive care (BSC).[90,91,92,93,94] The participant inclusion and exclusion criteria (see Section 6 [Study Population]) are intended to specify inclusion of only patients whose disease falls into the BCLC B category for intermediate-stage HCC, for whom TACE is recommended in treatment guidelines.

Tumor characteristics must exceed the BMU7 criteria. The Milan criteria identify early-stage patients who are eligible for liver transplantation. There are, however, patients who present with HCC beyond the Milan criteria and can be downstaged for transplantation using loco-regional therapy. The tumor characteristics of the latter patients fulfill the Up-to-7 criteria and are therefore currently considered for transplantation and not the subject of this research.

5.4.2 Rationale for TTTP as a Dual Primary Endpoint

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Long OS in the TACE setting necessitates the use of a dual primary endpoint for an earlier assessment of clinical benefit.

TACE treatment affords patients with long survivals. A 2016 meta-analysis review of conventional TACE in a large sample size of patients with HCC reported survivals in line with those from the seminal RCTs. Median OS was 19.4 months (95% CI: 16.2, 22.6).[95] A 2017 network meta-analysis projected a similar median survival of 18.1 months (95% CI: 15.6, 21.6) for conventional TACE and a reduction in the hazard of death in the range of 24%.[96] These data are aligned with the expected median survival of 20 months quoted in the 2012 European Society for Medical Oncology and the European Society of Digestive Oncology (ESMO-ESDO) guidelines.[80] However, a clear trend of progressively improving survival outcomes over the years has been observed.[97] Various clinical studies and TACE analyses have reported median OS values higher than 19.4 months, ranging from 26.1 to 61 months.[15,23,98,99,100,101,102]

The long OS poses challenges for demonstrating OS in the intermediate-stage TACE setting. This is not an uncommon challenge for earlier-stage cancer studies, given the relatively long survival

relative to later disease stages. The evaluation of OS in settings with long baseline survival commonly requires very long study durations and large numbers of participants.

In addition, there has been an advent of new drug options for the treatment of advanced HCC; including atezolizumab in combination with bevacizumab, nivolumab in combination with ipilimumab, cabozantinib, lenvatinib, nivolumab, pembrolizumab, ramucirumab and regorafenib. These options are now available for HCC patients (in clinical studies or in clinical practice) after they migrate from an intermediate to an advanced stage. This raises concerns that efficacy of drugs administered in conjunction with TACE, as measured by OS, may be confounded by subsequent therapy in the advanced setting, thereby underestimating their true clinical benefit.[103] Available data from studies using TACE in combination with systemic agents reflects the fact that both systemic and non-systemic therapies are used after patients discontinue from TACE studies and progress to the advanced stage of the disease.[23,26]

The situation for TACE is not dissimilar to the challenges faced by earlier-stage cancer studies, where demonstration of OS is difficult given the relatively long OS relative to later stages of the disease. In the adjuvant setting for early stage HCC, alternative endpoints, such as relapse-free survival (RFS) and disease-free survival (DFS), have become increasingly important surrogate endpoints that have been broadly used and accepted by Investigators and regulators as meaningful primary endpoints.[104,105,106,107] In a TACE setting, however, these exact endpoints do not have the same relevance and carry fundamental issues.

Treatment with TACE follows a different paradigm for discontinuation of treatment. For systemic therapies, treatment is generally stopped when disease recurs or progresses. TACE treatment, however, can continue in the case of tumor progression (ie, in cases where there is regrowth of an initially responsive tumor or the appearance of a new lesion). In actual clinical practice, repeated TACE sessions are felt to increase the efficacy of TACE. Patients commonly receive multiple TACE treatments.[25,108,109,110,111,112] The continued use of TACE in the face of progression raises the question of the suitability of endpoints such as DFS, RFS, and PFS in a TACE setting.

Furthermore, the relevance of traditional tumor assessment-based endpoints, such as ORR and TTP, is questionable in a TACE setting. The application of RECIST-assessed ORR and TTP in a TACE setting is complicated by the nature of the TACE procedure and its continued application in the presence of disease progression or recurrence. In RECIST v1.1, target lesions are designated at participant entry into a clinical study and a sum of the diameters for all target lesions are calculated and reported as the baseline sum of diameters. The baseline sum of diameters then serves as the comparator for subsequent measurements. A CR is based on disappearance of all target lesions. A PR is based on a $\geq$ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.[113]

This poses a dilemma in a TACE study setting because TACE destroys tumor tissue each time it is administered. TACE responses can be complete or partial, and is complete in as many as one-third of patients (28.2%).[114,115] Pathology studies have shown that palliative trans-arterial lipiodol-based treatments may achieve > 90% tumor necrosis in 26-70% of the treated nodules, depending on technique, lesion size, and arterial anatomy.[116,117] In a TACE setting, therefore, a

response soon after TACE (ie, CR or PR) is mainly attributable to the TACE treatment. An objective response post-TACE is the norm and the highest quality studies of conventional TACE show a clear trend of progressively improving ORRs over a 15-year period.[95] In this setting, a systemic agent administered concurrently will not have sufficient time to further improve ORR. This is particularly true for immunotherapy agents that require time to stimulate the immune system and are known for their delayed cure effect.[118,119] Even in a setting where immunotherapy agents are administered as monotherapy, there are advocates for a change in the established paradigm of response assessment and reconsideration of conventional efficacy endpoints for monotherapy immuno-oncology (IO) studies.[118,119,120,121,122] A traditional RECIST-defined response may therefore not capture the effect of a systemic IO treatment appropriately, particularly in a TACE setting.

These challenges have been observed in clinical studies. Two Phase 3 TACE studies in intermediate-stage HCC reported no correlation of ORR by RECIST or mRECIST with OS. In the exploratory analysis of the brivanib Phase 3 BRISK-TA study, the ORR was 48% in the brivanib group and 42% in the placebo group, with an odds ratio favoring brivanib (odds ratio, 1.28 [95% CI: 0.90, 1.83]).[23] Although sorafenib demonstrated improved OS in the 1L setting, in the sorafenib Phase 3 TACE-2 study, response assessments by both RECIST v1.1 and mRECIST showed no difference in participants treated with TACE + sorafenib vs TACE + placebo. The definition of an endpoint needs to have a biological rationale for its use and must take into context the setting in which it is applied. The RECIST guidelines for solid tumors were developed in the context of the ability of anticancer cytotoxic agents to generate varying degrees of tumor shrinkage and that a change in tumor burden was an important feature of the clinical evaluation of these drugs.[113] In a TACE setting, the TACE treatment destroys tumor and changes the tumor burden independent of the effects of a systemic agent. Evaluating the added benefit of systemic agents to TACE therefore requires special considerations. In addition, the added benefit of systemic agents is best assessed in patients who can receive a series of TACE treatments.

The relevance of TTP, PFS, and ORR in a TACE setting are not established. While applicable to studies using only systemic agents, these endpoints do not take into account the impact of the TACE procedure and raise the question of their suitability as an endpoint in a TACE study. This is an important consideration because surrogates may fall short in their ability to predict outcomes in hard endpoints (eg, OS) for 2 broad categories of reasons: (1) technical factors in measuring the surrogate introduce such uncertainty that their association with the hard endpoints becomes weak; and (2) factors in the relationship between the surrogate, hard endpoint, and drug weakens a direct causal link between the surrogate and the hard endpoint.[123] The destructive effects of TACE, coupled with continued TACE with tumor regrowth or the appearance of new lesions, challenges the conventional approach to assessing ORR, TTP, and PFS.

This study will utilize TTTP, which is based on the time to tumor progression. The elements of the TTTP endpoint take into consideration: (1) the impact of TACE on tumor lesions; and (2) its application in a clinical study that includes participants that can receive more than 1 TACE treatment. TTTP is defined as the time from randomization to the appearance of evidence of tumor progression that is characterized by the first of any of the following: (1) A 20% increase in dynamic

tumor burden over baseline scan (see Section 9.1.1 [Imaging Assessment for the Study] for the operational elements of a dynamic tumor burden assessment); (2) development of MVI; (3) development of EHS; and (4) death.

TTTP has been retrospectively evaluated in 3 TACE datasets. Arizumi and colleagues evaluated 592 Japanese participants treated with conventional TACE.[124] Correlation analysis showed a moderate positive correlation between OS and TTTP for both B1 ($R^2 = 0.6563$; $p = 0.0045$) and B2 ($R^2 = 0.6433$; $p = 0.0052$) substages. The authors concluded that TTTP showed a moderate correlation with OS after TACE therapy, where participants with short TTTP represented short OS, indicating that TTTP is a potential alternative parameter for benefit analysis of HCC patients undergoing TACE. Izumoto and colleagues subsequently evaluated 192 Japanese participants treated with conventional TACE.[125] Similarly, their data showed a modest correlation between TTTP and OS ($r = 0.527$; 95% CI: 0.416, 0.622; $p < 0.001$). The third evaluation was conducted on the placebo arm of the brivanib TACE study.[23] To evaluate whether TTTP could be used as a survival predictor, landmark analyses of TTTP and OS were conducted that showed that TTTP was correlated with OS. Notable differences were seen in the probability of survival at 2, 4, 6, 8, and 10 months relative to whether or not participants had reached TTTP. Participants who did not reach TTTP at the specified timepoints had longer survivals than those who had reached TTTP. In addition, participants who took longer to progress by TTTP had longer survivals than those who reached TTTP earlier.

A fourth evaluation is ongoing in collaboration with TARGET-HCC[126] to assess TTTP in a real-world population. Preliminary data indicate a median TTTP for BCLC Stage B of 366 days. A majority (80.9%) of the participants in the TARGET-HCC database achieved TTTP due to an increase in tumor burden, as defined by TTTP parameters. The study was started in Dec-2016 and the data are currently too immature to provide a correlation with OS. Essentially, only participants who had their first TACE around the time of enrollment could be included for an initial OS analysis. The study is ongoing and a robust analysis of OS could be possible in another year.

Improvement in TTTP may also lead to a clinical benefit in these participants, as defined by EFS. If study treatment leads to a delay in development of EHS/VI, these participants do not progress to advanced stage and start subsequent 1L systemic therapy. In addition, they may require fewer TACE procedures, which limits damage to the liver and may prevent hepatic decompensation. This could lead to prolongation in EFS, which is a key secondary endpoint of the study.

In summary, TTTP differs from previous TACE-specific endpoints as it takes into consideration the impact of the TACE procedure on tumor lesions, is an endpoint based on tumor lesion changes, is applicable to the population of intermediate-stage HCC that can be treated with a series of TACE, and can potentially reflect the added effect of a systemic agent. It also differs from previous TACE-specific endpoints in that it has been evaluated in different TACE populations and datasets. This is in contrast to previous TACE-specific endpoints that were applied in TACE clinical studies without prior evaluation of their relevance. Of note, the 3 evaluations presented used varying approaches to assess whether there is a correlation of TTTP with survival, and yet the results showed similar trends. The data are of special significance in light of the absence of data

supporting the relevance of TTP, PFS, and ORR in a TACE setting. The TTTP data provide support for the utilization of TTTP as a more relevant endpoint for assessment of tumor burden changes in a TACE setting.

The TTTP endpoint reasonably reflects both the impact of TACE on tumor lesions and the added effect of a systemic agent. Based on the evaluation of TTTP in intermediate-stage HCC TACE datasets, TTTP can be considered as a reasonable tumor assessment-based endpoint for a TACE study. Therefore, TTTP as a dual primary endpoint in the proposed study can provide insight into the benefit of ipilimumab and nivolumab or nivolumab alone added to TACE prior to subsequent therapies.

TTTP is defined as the time from randomization to the first occurrence of any of the following:

- A 20% increase in dynamic tumor burden (see Section 9.1.2.2) over baseline scan
- Development of MVI
- Development of EHS
- Death

5.4.3 Rationale for OS as a Dual Primary Endpoint

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

OS, defined as the time from randomization to death from any cause, is a dual primary endpoint for this study. As an endpoint, OS is easily measured, unambiguous, objective, and unaffected by the timing of assessment. It is considered the gold standard among efficacy endpoints (clinically and regulatory accepted), and an appropriate measure of treatment benefit for immune checkpoint inhibitors.

5.4.4 Rationale for EFS as a Secondary Endpoint

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

EFS is defined as the time from randomization to initiation of first-line systemic therapy or the date of progression of cirrhosis from Child Pugh A to Child Pugh C score, or death, whichever occurs first. Prolongation of EFS may lead to clinical benefit since it takes into consideration liver decompensation, as measured by Child-Pugh score, which is a composite of clinical and laboratory factors. Delaying start of 1L systemic therapy may also lead to a clinical benefit in a patient, due to shorter survival and significant AEs seen with 1L systemic therapy in HCC.

5.4.5 Rationale for PFS as a Secondary Endpoint

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

PFS is defined as the time from randomization to the first documented disease progression as assessed by BICR, using mRECIST or death due to any cause, whichever occurs first. PFS was

chosen as a secondary endpoint in order to support extrapolation of this study with other completed and ongoing studies using PFS in the intermediate stage HCC.

5.4.6 Rationale for Nivolumab and Ipilimumab Dose and Schedule

The nivolumab and ipilimumab combination dosing regimen selected for evaluation in this study is nivolumab 240 mg (flat dose) Q2W and ipilimumab 1 mg/kg Q6W. The combination dosing and schedule was selected based on the overall benefit-risk observed in CA209040, a Phase 1/2 study evaluating safety and efficacy of nivolumab, alone or in combination with ipilimumab or cabozantinib, in participants with advanced HCC.[3]

Exposure-response (E-R) analysis of nivolumab monotherapy across dose ranges of 1 mg/kg to 10 mg/kg revealed similar clinical activity regardless dose, while E-R analysis of different doses of ipilimumab monotherapy (0.3 mg/kg, 3 mg/kg, and 10 mg/kg) in the Phase 2 study CA184022 have demonstrated an increase in antitumoral activity by increasing ipilimumab dose.[1,82] The combination of dual checkpoint blockade with both of these agents administered together has demonstrated an efficacy advantage over either single agent alone.

In HCC, results from CA209040 demonstrate antitumor activity of the combination of nivolumab and ipilimumab as 2L therapy in the advanced setting, with a manageable safety profile. In this trial, participants were treated with nivolumab in combination with either high-dose (3 mg/kg) or low-dose (1 mg/kg) ipilimumab at different schedules. Efficacy outcomes were mostly similar between the different regimens; however, the nivolumab 3-mg/kg Q2W and ipilimumab 1-mg/kg Q6W arm was associated with the most favorable safety profile. Treatment-related AEs leading to discontinuation, treatment-related elevations in AST and ALT, and the incidence of hepatic immune-mediated adverse events (IMAEs) occurred less frequently in the nivolumab 3-mg/kg Q2W and ipilimumab 1-mg/kg Q6W arm compared to the other 2 arms. Most of the AEs were Grade 1-2 and manageable with treatment algorithms, leading to treatment discontinuation in 2 out of 49 participants (~ 4%) randomized to this arm; none of the participants discontinued due to liver function abnormalities (AST/ALT elevation).[3]

A flat nivolumab dose of 240 mg Q2W was selected for Arm A and Arm B in this trial, based on a less than 15% difference in exposures of nivolumab after 3 mg/kg and 240 mg Q2W dosing, using simulations conducted in an HCC population that used 80 kg as a reference body weight.

Taken together, these data suggest that combination therapy with nivolumab 240 mg and ipilimumab 1 mg/kg may provide the most appropriate benefit-risk and support the further development of this combination in intermediate-stage HCC.

5.4.7 Rationale for Shorter Infusion Times (30 minutes) of Nivolumab and Ipilimumab

Nivolumab has been approved for the shorter 30-minute infusion.[69,127]

Long infusion times place a burden on patients and treatment centers. Thus, establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30-minute duration will diminish the burden, provided that there is no change in the safety profile.

Establishing that nivolumab and ipilimumab can be safely administered using a shorter infusion time (30 minutes) is still under investigation. Previous clinical studies have used a 60-minute infusion duration for nivolumab and 90-minute infusion duration for ipilimumab (1-3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been safely administered at up to 10 mg/kg with the same infusion duration with no safety concerns:

- Nivolumab has been safely administered up to 10 mg/kg over long treatment periods, and infusion reactions, including high-grade hypersensitivity reactions, have been uncommon across the nivolumab clinical program. In study CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 240 mg and 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) or for 480 mg of nivolumab (~ 60% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dosing infused over a 60-minute duration. The safety of nivolumab 3 mg/kg administered as a 30-minute infusion was assessed in CA209153 in participants (n = 322) with previously treated advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in participants administered nivolumab over a 30-minute infusion compared with that reported for participants with the 60-minute infusion. Additionally, preliminary safety data from 310 participants who received 480 mg Q4W over a 30-minute infusion have showed no substantive differences in the safety profile compared to nivolumab 3 mg/kg or 240 mg given IV over 60 minutes, further supporting that nivolumab 3 mg/kg or nivolumab 480 mg (flat dose) can be safely infused over 30 minutes.
- Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In participants with advanced Stage II or Stage IV melanoma (CA184022), where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug-related hypersensitivity events (Grade 1/2) were reported in 1 participant (1.4%) in the 0.3 mg/kg group and in 2 participants (2.8%) in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3/4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as a 90-minute infusion in a large Phase 3 study in prostate cancer (CA184043) and as adjuvant therapy for Stage III melanoma (CA184029), with infusion reactions occurring in participants. Administering 3 mg/kg of ipilimumab represents approximately one-third of the 10 mg/kg dose, and thus, a shortened infusion duration of 30 minutes for ipilimumab is not expected to present additional safety concerns.

Overall, infusion reactions, including high-grade hypersensitivity reactions, have been uncommon across clinical studies of nivolumab, ipilimumab, and nivolumab/ipilimumab combinations. A change in safety profile is not anticipated with 30-minute infusions of nivolumab, ipilimumab, or nivolumab and ipilimumab. Furthermore, a 30-minute break after the first infusion for the combination will ensure appropriate safety monitoring before the start of the second infusion. Similar infusion times are currently being used in trials evaluating nivolumab and ipilimumab at similar dosing schedules in several tumor types and no safety concerns have been identified.

5.4.8 Rationale for Stratification Factors

Not applicable per Protocol Amendment 01, as enrollment has been stopped for the study. The following information refers to the original study design.

5.4.8.1 Region

Differences in patient populations and clinical practice patterns in the different regions are well known and can impact OS outcomes. The systematic review of the literature on lipiodol TACE for HCC reported significantly higher median OS in Japan (31.3 months [95% CI: 22.9, 39.8]) than in the West (18.3 months [95% CI: 13.7, 22.9]) or Asia-Pacific (15.6 months [95% CI: 13.7, 22.9]) regions (Japan vs West region, p = 0.007; Japan vs Asia-Pacific region, p = 0.0007; West vs Asia-Pacific regions: p = 0.3632).[95] As such, the impact of differing HCC patient populations and different approaches to clinical practice in the different regions is still important to consider. This study will therefore stratify by region.

5.4.8.2 Alpha-fetoprotein

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.[128] 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. This study will use a cutoff level of 400 ng/mL for stratification.

5.4.8.3 Albumin-bilirubin Grade

Assessment of liver function is particularly important in HCC trials because cirrhosis is a competing cause of death. The ALBI grade[129] was developed to assess liver function in patients with HCC that involved serum bilirubin and albumin levels. Data from a global database of 3,887 patients demonstrated that objective measures of liver dysfunction, as measured by the ALBI grade, influence survival in patients with HCC in the Japan, US/EU, and China cohorts. Patients in the US/EU cohort with an ALBI Grade 1 had a median survival of 24.5 months compared to 14.7 months for those with ALBI Grade 2 and 4.7 months for those with ALBI Grade 3. Similarly, patients with ALBI Grade 1 in the Japan and China cohorts had better median survival than those with ALBI Grade 2 and 3.[130] These data show that ALBI grade can be used to stratify patients with HCC into 3 risk categories. This study will use ALBI Grade 1 and 2 as a stratification factor. Participants with Grade 3 ALBI are not eligible for TACE and therefore these patients are excluded.

5.4.9 Rationale for 2 Year Duration of Treatment with Nivolumab ± Ipilimumab

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggest that benefit can be maintained in the absence of continued treatment. A retrospective pooled analysis of two melanoma studies suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[131] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long-term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[132]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in participants with previously treated advanced solid tumors (including 129 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[133] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2-year OS rates of 23% and 29%, and 3-year OS rates of 16-18% for squamous and non-squamous NSCLC, respectively).[134]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, participants with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 participants still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively (HR, 0.42 [95% CI: 0.25, 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR, 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[135]

Collectively, these data suggest that there is minimal, if any, benefit derived from continuing IO treatment beyond 2 years in advanced tumors. Even though immunotherapy is well tolerated,

patients will be at risk for additional toxicity with longer-term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

5.4.10 Rationale for Unblinding

[redacted] Therefore, a decision was made by BMS in September 2021 to stop the study.

Upon implementation of Protocol Amendment 01, participants will be unblinded to allow BMS to continue safety monitoring the remaining participants on study without blinding while streamlining other study procedures. All investigators, ethics committees, and health authorities have been informed.

5.5 Justification for Dose

The doses of nivolumab and ipilimumab in this study were based on the overall clinical pharmacology profile of nivolumab and ipilimumab and clinical assessment of the combination in HCC.

5.5.1 Nivolumab Clinical Pharmacology Summary

The PK of nivolumab were studied in participants over a dose range of 0.1 to 10 mg/kg, administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (coefficient of variation [%CV], %) CL was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose-proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The CL of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline lactate dehydrogenase (LDH), and PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG performance status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab was administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the CL of ipilimumab. Additionally, PPK and E-R analyses have been performed to support use of 240-mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at a 240-mg flat dose was identical to a dose of 3 mg/kg for participants weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials.

Full details on the clinical pharmacology aspects of nivolumab can be found in the IB.[1]

5.5.2 Ipilimumab Clinical Pharmacology Summary

The PPK of ipilimumab, when administered alone or in combination with nivolumab, to participants with melanoma, NSCLC, RCC, small cell lung cancer (SCLC), HCC, and CRC has been assessed previously. The PK of ipilimumab in combination with nivolumab was well described by a linear 2-compartment model with time-varying CL. Ipilimumab CL decreased with time and the decrease was ~ 22% in participants receiving ipilimumab in combination with nivolumab. The CL of ipilimumab was higher when administered in combination with nivolumab 1 mg/kg Q2W, 1 mg/kg Q3W, or 3 mg/kg Q2W compared to ipilimumab monotherapy; however, the magnitude of these differences are not considered to be clinically relevant (< 20%). Ipilimumab CL, when given in combination with nivolumab 0.3 mg/kg or 3 mg/kg Q3W, was not significantly different from that seen with ipilimumab monotherapy. The CL of ipilimumab in participants with NSCLC, RCC, HCC, and CRC was not significantly different relative to participants with melanoma. The CL of ipilimumab was lower in participants with SCLC relative to participants with melanoma; however, the magnitude of the difference was not considered to be clinically relevant. Ipilimumab CL was not significantly different in the presence of anti-ipilimumab antibodies.

Full details on the clinical pharmacology aspects of ipilimumab can be found in the IB.[82]

5.5.3 Justification for Dose of Nivolumab

The nivolumab dose of 240 mg Q2W was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and E-R analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) has been used. (See Section 5.4.6 [Rationale for Nivolumab and Ipilimumab Dose and Schedule] for additional clinical data in HCC for justification of the selected treatments.)

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance (CL) and volume of distribution were found to increase as the body weight increases, but less than proportionally with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC participants has recently been updated, using data from 1,544 participants from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35-160 kg), and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg participant, nivolumab 240 mg Q2W, was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W, the PPK model was used to simulate nivolumab 3 mg/kg Q2W and 240 mg Q2W. In the simulations, the simulated patient populations consisted of 1,000 participants per treatment arm randomly sampled from the aforementioned pooled database of cancer participants. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data will be applicable to participants with other tumor types. The simulated measure of exposure of interest, steady-state average concentrations (Cavgss) for

240 mg Q2W are predicted to be similar for all participants in reference to 80-kg participants receiving 3 mg/kg Q2W.

Nivolumab is safe and well tolerated up to a 10 mg/kg Q2W dose level. AEs have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or E-R relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35-160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab (ie, 95th percentile following nivolumab 10 mg/kg Q2W from clinical study CA209003). Thus, while participants in the lower body weight ranges would have greater exposures than 80-kg participants, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg Q2W) used in the nivolumab clinical program and are not considered to put participants at increased risk. For participants with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of a 240 mg Q2W are on the flat part of the E-R curves for previously investigated tumors, melanoma and NSCLC. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240-mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Thus, nivolumab 240 mg Q2W over 30 minutes will be used in this study.

5.5.4 Justification for Dose of Ipilimumab

The preliminary safety data from CA209040 cohort 4, which evaluated 3 dosing schedules of nivolumab + ipilimumab (N1+I3 Q3W, N3+I1 Q3W, and N3+I1 Q6W) in advanced HCC, shows a lower rate of drug-related AEs, SAEs, and AEs leading to discontinuation with the N3+I1 Q6W dose compared with the N1+I3 Q3W dose.[3] The response rate and DOR are similar for all dosing arms. Nivolumab 240 mg Q2W and ipilimumab 1 mg/kg Q6W dosing is being chosen for this study to be combined with TACE as it has a lower rate of AEs with comparable efficacy. Please see Section 5.4.6 (Rationale for Nivolumab and Ipilimumab Dose and Schedule) for further details.

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met. As of 22-Sep-2021, enrollment into this study was closed.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care. In situations where the participant is unable to sign the ICF, a legally acceptable representative would be expected to sign (according to country-specific guidelines; refer to Appendix 2 and Appendix 9).

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

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

2) Type of Participant and Target Disease Characteristics

a) Participant has intermediate-stage HCC by BCLC staging criteria[11] whose tumor characteristics exceed the BMU7 criteria and is eligible for TACE as per disease management team.

i) Up-to-seven criteria, with 7 being the result of the sum of size (in cm) of the largest lesion and number of tumors. This includes all combinations of a given HCC disease, from 1 nodule up to 6 cm in size (1 + 6 = 7) to many tumors fulfilling 7 as the sum of the size plus number (ie, 2 tumors up to 5 cm in size, 3 tumors up to 4 cm in size, etc; refer to Appendix 7).[136]

b) Participant has no EHS, no regional lymph node involvement, no main, left main, or right main portal vein thrombosis, and no MVI. (Segmental bland portal vein thrombosis is allowed).

c) Participant has histologic confirmation of HCC.

i) Participants with only a radiologic diagnosis of HCC may be enrolled for screening in the study but histological confirmation is mandatory prior to the start of study therapy.

ii) Either a FFPE tissue block (preferred) or a minimum of 20 unstained slides of tumor tissue sections obtained within 3 months prior to randomization or archived (if above is not available) with an associated pathology report must be submitted to the central laboratory for inclusion. The central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration or other cytology samples are unacceptable for submission. 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 Appendix 9 for country-specific criteria for the collection of tumor tissue samples in China.

d) Participant has cirrhotic status of Child-Pugh Class A (refer to Appendix 8).

e) Participant has an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1 (refer to Appendix 5 for ECOG PS scale).

f) 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) Non-HBV, non-HCV related HCC

ii) HBV-HCC

(1) Resolved HBV infection, as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV deoxyribonucleic acid (DNA), and undetectable HBV surface antigen [HBsAg]); OR

(2) Chronic HBV infection, as evidenced by detectable HBsAg or HBV DNA. Participants with chronic HBV infection must be on antiviral therapy [redacted]

iii) HCV-HCC

(1) Resolved HCV infection as evidenced by detectable antibody; OR

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

3) Age and Reproductive Status

a) Males and Females, ages ≥ 18 years or age of majority.

b) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study treatment.

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatments plus approximately 5 half-lives of the study treatments plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (Appendix 4) for the duration of treatment with study treatments plus approximately 5 half-lives of the study drugs plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy and when applicable, the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

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

b) Prior liver transplant or participants who are on the waiting list for liver transplantation.

c) Prior history of or current hepatic encephalopathy.

d) Tumor >10 cm in size and other contra-indications for angiography or embolization.

e) Clinically significant ascites as defined by:

i) Any ascites by physical examination at screening; OR

ii) Prior ascites that required treatment and require on-going prophylaxis; OR

iii) Current ascites requiring treatment.

f) Diffuse pattern of disease on computed tomography (CT)/magnetic resonance imaging (MRI).

g) Infections:

i) Active co-infection with:

(1) Both hepatitis B and C as evidenced by detectable HBsAg or HBV DNA and HCV RNA, OR

(2) Hepatitis D infection in participants with hepatitis B.

ii) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally (refer to Appendix 9).

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

h) Interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity.

i) Prior organ allograft or allogeneic bone marrow transplantation.

j) Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.

k) 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.

l) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease, with the exception of those allowed as per exclusion criterion k) above.

m) Prior malignancy active within the previous 3 years, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

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

o) WOCBP who are pregnant or breastfeeding.

p) Women with a positive pregnancy test at enrollment or prior to administration of study medication.

2) Prior/Concomitant Therapy

a) Any previous TACE or TAE (trans-arterial embolization without instillation of chemotherapy agent) procedure for HCC.

b) Prior use of systemic agents for HCC, including prior chemotherapy, immune therapy, and targeted kinase inhibitors.

c) Prior treatment with radioactive isotope yttrium (Y90).

i) RFA, microwave ablation (MWA), including other forms of ablation and resection, are permitted, provided TACE is indicated at the time of relapse/recurrence. TACE as combination treatment with the above is not permitted.

d) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

e) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support to treat the disease under study within 2 weeks prior to randomization. Refer to Section 7.7.1 (Prohibited and/or Restricted Treatments for Nivolumab) for prohibited therapies.

f) Participants who have received a live/attenuated vaccine within 30 days of randomization.

3) Physical and Laboratory Test Findings

a) Positive pregnancy test.

b) Screening laboratory values must not meet the following criteria, and be without continuous supportive treatment (such as, growth factor administration, blood transfusion, coagulation factors and/or platelet transfusion, or albumin transfusion):

i) Inadequate hematologic function:

(1) WBC < 2,000/μL.

(2) Neutrophils < 1500/μL.

(3) Platelets < 60×10^3/μL.

(4) Hemoglobin < 8.5 g/dL.

ii) Prothrombin time (PT)-international normalized ratio (INR) ≥ 1.7 or PT ≥ 4 seconds above control.

iii) Inadequate hepatic function as documented by:

(1) Serum albumin < 2.8 g/dL.

(2) Total bilirubin > 2 mg/dL.

(3) AST > 5 × institutional ULN.

(4) ALT > 5 × institutional ULN.

iv) Inadequate renal function, with a serum creatinine > 1.5 × ULN, unless creatinine CL ≥ 40 mL/min (measured or calculated using the Cockcroft-Gault formula).

4) Allergies and Adverse Drug Reaction

a) Known or suspected allergy to nivolumab, ipilimumab, or any agents given in association with this trial.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

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

d) Inability to tolerate contrast-enhanced CT and MRI, including, but not limited to, known or suspected allergy to both CT and MRI contrasts.

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 BMS approval is required.)

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

This study permits the re-enrollment of a participant that has discontinued the study as 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, as it represents the participant's most current, clinical state.

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

7 TREATMENT

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

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

- Nivolumab
- Ipilimumab
- Nivolumab-Placebo (0.9% Sodium Chloride Injection or 5% Dextrose Injection)
- Ipilimumab-Placebo (0.9% Sodium Chloride Injection or 5% Dextrose Injection)

The normal saline or dextrose to be used as placebo will not be provided by the Sponsor.

Per Protocol Amendment 01, participants will no longer receive placebo infusions following unblinding.

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

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the SOC for a given diagnosis, may be considered as non-IPs. In this study, the TACE procedure is not considered to be a study treatment.

Premedications used to treat infusion reactions should be sourced by the investigative sites if available and permitted by local regulations.

Table 7-1: Study Treatments for CA20974W

Product Description/ Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01) Solution for Injection[a]	10 mg/mL	IP	Open Label[b]	Vial	Refer to the label on container and/or Pharmacy Manual
Ipilimumab Solution for Injection	5 mg/mL	IP	Open Label[b]	Vial	Refer to the label on container and/or Pharmacy Manual
0.9% Sodium Chloride for Injection[c]	NA	IP	Open Label[b]	Various (local commercial product)	As per package insert
5% Dextrose for Injection[c]	NA	IP	Open Label[b]	Various (local commercial product)	As per package insert

Abbreviations: BMS = Bristol-Myers Squibb; IMP = investigational medicinal product; IP = investigational product; mg = milligram; mL = milliliter; NA = not applicable.

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection.

[b] The term “open-label” refers to the medication as it is upon receipt at the pharmacy.

[c] Diluents used for nivolumab and ipilimumab. These will be sourced by the investigative sites if available and permitted by local regulations.

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Nivolumab	240 mg	Q2W	IV
Ipilimumab	1 mg/kg	Q6W	IV
0.9% Sodium Chloride for Injection	NA	Q2W or Q6W	IV
5% Dextrose for Injection	NA	Q2W or Q6W	IV
TACE	NA	NA	Loco-regional

Abbreviations: IV = intravenous; kg = kilogram; mg = milligram; NA = not applicable; Q2W = every 2 weeks; Q6W = every 6 weeks; TACE = trans-arterial chemoembolization.

7.1.1 Nivolumab and Ipilimumab Administration

Per Protocol Amendment 01, participants in Arm B (nivolumab + placebo + TACE) and Arm C (placebos + TACE) will no longer receive placebo following unblinding.

Participants should receive treatment with nivolumab (240 mg Q2W) and ipilimumab (1 mg/kg Q6W), or their matching placebos, as an approximately 30-minute infusion on Cycle 1 Day 1 until progression as assessed by investigator (unless treatment beyond progression was allowed), unacceptable toxicity, withdrawal of consent, completion of 2 years of study medication, or the study ends, whichever occurs first.

Participants should begin study treatment within 3 calendar days after randomization. Dosing calculations for ipilimumab should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant's weight is within 10% of the baseline weight or the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram per institutional standard.

After the first cycle, subsequent dosing should be based on the actual date of administration of the previous cycle. Participants may be dosed no less than 12 days and no more than 18 days between nivolumab or matching placebo doses and no less than 36 days and no more than 60 days between ipilimumab or matching placebo doses. Doses may be administered within 3 days before or after the scheduled date, if necessary. All TACE related toxicities must have resolved to baseline or Grade 1 before study treatment is resumed.

When study treatments (nivolumab and ipilimumab or their matching placebos) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start

after the infusion line has been flushed, filters changed, and participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

Premedications are not recommended for the first dose of treatment. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.2 (Nivolumab and Ipilimumab Dose Delay Criteria).

There will be no dose escalations or reductions of study treatment allowed. Doses of nivolumab and/or ipilimumab and their matching placebos may be interrupted, delayed, or discontinued, depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. If dosing is delayed, all study treatments planned to be administered on the same day should be delayed at the same time. If dosing is resumed after a delay, all study treatments planned must be resumed on the same day. For more details, see Section 7.4.2 (Nivolumab and Ipilimumab Dose Delay Criteria) and Section 8.1.1.1 (Criteria for Nivolumab and Ipilimumab Treatment Discontinuation).

Nivolumab injection, 10 mg/mL is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line. Instructions for preparation of nivolumab infusion may be provided in the Pharmacy Manual or IB. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Separate infusion bags and filters should be used when administering nivolumab and ipilimumab on the same day.

Ipilimumab is to be administered as an approximately 30-minute IV infusion and may be infused using a volumetric pump with a 0.2-micron to 1.2-micron, low-protein binding in-line filter at the protocol-specified dose. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of diluent.

Please refer to the current version of the IBs[1,82] and/or Pharmacy Manual for complete preparation, storage, and handling information for nivolumab and ipilimumab.

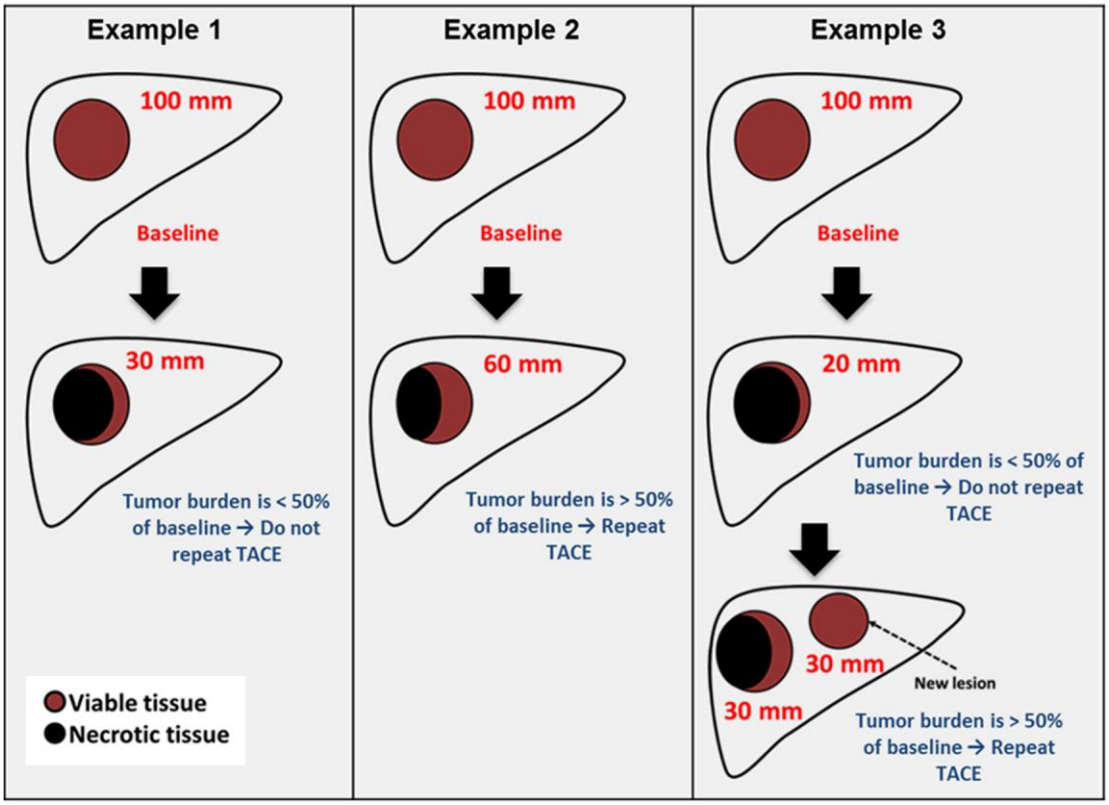
7.1.2 TACE Procedure

No significant differences in efficacy and safety have been observed between conventional TACE and DEB-TACE.[137,138] This trial allows the use of conventional TACE and DEB-TACE and the choice of procedure to use is left to the Investigator's discretion. However, once the participant starts receiving either conventional TACE or DEB-TACE, the same TACE procedure must be followed throughout the study for that participant. Switching to conventional TACE for participants that started the trial with DEB-TACE and to DEB-TACE for participants who received conventional TACE is not permitted. Additionally, once conventional TACE has been administered with a select chemotherapy agent, switching to a different chemotherapy agent is not

permitted. For participants receiving DEB-TACE or conventional TACE, the TACE technique should be maintained consistently throughout the study.

First TACE should be administered no later than 7 days (+ 3 days) after study drug administration. All drug-related toxicities must have resolved to Grade 1 or baseline before TACE is administered. TACE sessions can be continued until all the liver lesions are adequately treated. Evaluation for additional on-demand TACE will occur at each imaging as per Section 2 (Schedule of Activities). In general, imaging is repeated 4-8 weeks after TACE to assess the need for repeat TACE. Since scheduled imaging occurs every 6 weeks for the first 48 weeks, imaging on study will fall within the 4- to 8-week window. Ad-hoc imaging can be performed if clinically necessary at any time. TACE can be repeated if the dynamic tumor burden is at least 50% of the total tumor burden at baseline or earlier, as per Investigator discretion, if it is felt to be in the best interest of the participant or as per local practice and guidelines (see Figure 7.1.2-1). Once a determination is made to perform TACE, it should be performed within 4 weeks.

Figure 7.1.2-1: Criteria to Re-TACE: Tumor Burden > 50% of the Baseline Tumor Burden



Abbreviations: mm = millimeter; TACE = trans-arterial chemoembolization.

Once randomized, participants should receive first TACE in 7 days (+3 days) after study drug administration and then TACE as needed, until participant is no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Once progression has been met as assessed by the investigator, the participant may continue to receive

additional TACE until the participant is no longer eligible for further TACE, per Investigator discretion, if it is felt to be in the best interest of the participant.

TACE should be administered as per local practices and guidelines. TACE should be given with at least a 7-day window of systemic therapy. All drug-related toxicities must have resolved to Grade 1 or baseline before TACE is administered, and participants must be evaluated as per Table 2-2 prior to TACE procedure.

Premedications for TACE, such as analgesics, antiemetics, sedatives, etc, are allowed and are left to the discretion of the Investigator; however, the use of corticosteroids for the prophylaxis of PES is not permitted (see Section 7.7 [Concomitant Therapy] for additional details).

France Only: Please refer to Appendix 11 (France-specific General Guidance for Trans-arterial Chemo-embolization) for additional information on the TACE procedure.

7.2 Method of Treatment Assignment

CA20974W is a double-blind, placebo-controlled, randomized trial. Participants with intermediate-stage HCC whose tumor characteristics exceed the BMU7 criteria will be eligible to participate. All participants will be randomized using an IRT system. 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 other delegated and trained site personnel 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

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

- Participant number
- Date of birth, where applicable per local regulations
- ALBI grade (Grade 1 vs Grade 2)
- Baseline AFP level (< 400 ng/mL vs ≥ 400 ng/mL)
- Region (West [EU, Americas, and Australia] vs Japan vs rest of Asia)
- Confirmation of tumor tissue sample receipt and acceptability at the central laboratory
- Confirmation of eligibility by BICR

Participants meeting all eligibility criteria will be randomized into one of the treatment arms in a 1:1:1 ratio. Randomization will be stratified by the following factors:

- ALBI grade (Grade 1 vs Grade 2)
- Baseline AFP level (< 400 ng/mL vs ≥ 400 ng/mL)
- Region (West [EU, Americas, and Australia] vs Japan vs rest of Asia)

Blinded study treatment was dispensed at the study visits as listed in Schedule of Activities (Section 2). The exact procedures for using the IRT will be detailed in the IRT Manual.

As of 22-Sep-2021, enrollment for new participants was closed and the study will be unblinded per Protocol Amendment 01.

7.3 Blinding

The Sponsor, participants, Investigator, and site staff will be blinded to the study therapy administered. Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned to provide oversight of drug supply and other unblinded study documentation.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the 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 active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the BMS Medical Monitor or Clinical Scientist, 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 should only call in for emergency unblinding AFTER the decision to discontinue the participant has been made.

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

In cases of accidental unblinding, contact the BMS Medical Monitor or Clinical Scientist and ensure every attempt is made to preserve the blind.

Any request to unblind a participant for non-emergency purposes should be discussed with the BMS Medical Monitor or Clinical Scientist.

Designated staff of BMS Research & Development (R&D) may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and IMG. A bioanalytical scientist in the Bioanalytical Sciences department of BMS R&D (or a designee in the external

central bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

As of 22-Sep-2021, enrollment for new participants was closed. **Per Protocol Amendment 01, the objectives of this study have been amended to safety only**. The study will be unblinded to facilitate ongoing safety monitoring.

7.3.1 Unblinding at the Time of Disease Recurrence/Progression

As of 22-Sep-2021, enrollment for new participants was closed. **Per Protocol Amendment 01, the objectives of this study have been amended to safety only.** The study will be unblinded to facilitate ongoing safety monitoring.

If a participant is assessed by the Investigator to have HCC disease recurrence/progression (Section 9.1.1 [Imaging Assessment for the Study]), and unblinding is considered necessary to inform the appropriate subsequent anti-cancer therapy, the study treatment assignment for the participant can be obtained by the Investigator through IRT for non-emergency unblinding. The Investigator should follow the procedures outlined in the IRT Manual to obtain the participant's study treatment assignment. The BMS central study team (including, but not limited to, clinical, statistics, and data management) will remain blinded to treatment assignment.

Investigators must wait for confirmation of recurrence/progression from the BICR prior to non-emergency unblinding for the purpose of initiating subsequent anti-cancer therapy, unless clinical considerations require immediate intervention (eg, symptomatic brain metastases). If subsequent anti-cancer therapy (including systemic cancer therapy, radiotherapy, or tumor-directed surgery) is planned prior to BICR confirmation of recurrence/progression, the Investigator must contact the BMS Medical Monitor or Clinical Scientist to discuss the case prior to the start of any of such therapy.

If a participant is diagnosed with a non-HCC secondary cancer, blinding should be preserved unless specific circumstances, to be discussed with the BMS Medical Monitor or Clinical Scientist, require that the blind be broken (eg, participant has metastases and could enroll on a clinical trial but would be ineligible if he or she had prior checkpoint inhibitor therapy).

For this study, the method of unblinding for emergency purposes is through the IRT. For information on how to unblind in an emergency, please see Section 7.3 (Blinding).

7.4 Dosage Modification

7.4.1 Nivolumab and Ipilimumab Dose Modifications

No dose modifications for nivolumab or ipilimumab are allowed.

7.4.2 Nivolumab and Ipilimumab Dose Delay Criteria

Dose delay criteria summarized in Table 7.4.2-1 apply for all drug-related AEs, regardless of whether the event is attributed to nivolumab or ipilimumab or both. Delay administration of both nivolumab and ipilimumab if any of the delay criteria in Table 7.4.2-1 are met.

Delay nivolumab and ipilimumab for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication. Delay study therapy also in cases of confirmed or suspected SARS-CoV-2 infection.

Participants receiving nivolumab plus ipilimumab who have drug-related toxicities that meet the criteria for dose delay should have both drugs (nivolumab and ipilimumab) delayed until retreatment criteria are met, regardless of whether or not the event is attributed to 1 of the drugs. Tumor assessments for all participants should continue as per protocol even if dosing is delayed.

Participants who require delay of nivolumab and ipilimumab should be re-evaluated weekly, or more frequently if clinically indicated, and resume study treatment when re-treatment criteria are met (see Section 8.1.3 [Post Study Treatment Study Follow-up]). Please see also Appendix 6 (IO Management Algorithms) for guidance on appropriate management and follow-up of AEs.

Table 7.4.2-1 summarizes criteria for delaying, resuming, and discontinuing dose of both nivolumab and ipilimumab.

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

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Permanently discontinue	
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.Bili) increased	AST/ALT • *If Baseline AST/ALT is within normal limits:* – AST or ALT > 3× upper limit of normal (ULN) • *If Baseline AST/ALT > ULN and up to 3× ULN:* – AST or ALT > 5× ULN	Delay dose	• Dosing may resume when AST or ALT values return to normal or ≤ 3× ULN • Exceptions: – If baseline AST or ALT > 3× and ≤ 5× ULN, dosing may resume when AST or ALT values return to ≤ 5× ULN – Participants with AST or ALT meeting discontinuation criteria should have treatment permanently discontinued

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

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	• *If Baseline AST/ALT > 3× and ≤ 5× ULN:* – AST or ALT 2-fold increase OR AST or ALT of 8× ULN (whichever is lower)		
	Total Bilirubin • *If Baseline T.Bili is within normal limits:* – T.Bili > 1.5× ULN • *If Baseline T Bili > ULN and up to 1.5× ULN:* – T. Bili > 3× ULN • *If Baseline T.Bili > 1.5× and ≤ 3× ULN:* – T.Bili 2-fold increase	Delay dose	• Dosing may resume when laboratory values return to normal or ≤ 1.5× ULN • Exceptions: – If baseline T.Bili > 1.5× and ≤ 3× ULN, dosing may resume when T.Bili values return to ≤ 3× ULN – Participants with T.Bili meeting discontinuation criteria should have treatment permanently discontinued
	• AST or ALT > 10× ULN for > 2 weeks • AST or ALT > 15× ULN irrespective of duration • T.Bili > 5× ULN for participants with normal T.Bili at entry OR > 8× ULN for participants with elevated T.Bili at study	Permanently discontinue	

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

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	entry, irrespective of duration • Potential drug-induced liver injury; Concurrent ALT > 10× ULN AND T.Bili ≥ 2× ULN or baseline value (if elevated bilirubin at study entry), and no other immediately apparent cause of hepatic lab abnormalities.		
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the BMS Medical Monitor/Clinical Scientist needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the BMS Medical Monitor/Clinical Scientist needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.

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

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the BMS Medical Monitor/Clinical Scientist needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the BMS Medical Monitor/Clinical Scientist needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤ 10% body surface area

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

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	

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

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Clinical AE			
Pancreatitis:	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay.
			Dosing may resume when patient becomes asymptomatic.
Amylase or Lipase increased	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If patient requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-Related AE (not listed above)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	
Other Lab abnormalities			
Other Drug-Related lab abnormality **(not listed above)**	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.

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

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.3 on Treatment of Related Infusion Reactions

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; CTCAE V5 = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; DRESS = drug reaction with eosinophilia and systemic symptoms; GBS = Guillain-Barre syndrome; MG = myasthenia gravis; SJS = Stevens-Johnson syndrome; T.Bili = total bilirubin; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

7.4.3 Treatment of Nivolumab- or Ipilimumab-related Infusion Reactions

Since nivolumab and ipilimumab contains only human Ig 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 fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor or Clinical Scientist and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 guidelines.

Treatment recommendations are provided below based on NCI CTCAE version 5.0 grading definitions and may be modified based on local treatment standards and guidelines, as appropriate.

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional study treatment administrations.

For Grade 2 symptoms (therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours):

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before study treatment infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms (severe reaction, Grade 3: prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life threatening consequences; urgent intervention indicated).

- Immediately discontinue infusion of study treatment. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and the CA20974W Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability / Bioequivalence / Biocomparability

Not applicable.

7.6 Treatment Compliance

Study treatment will be administered in the clinical facility. Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF.

7.7 Concomitant Therapy

Prohibited and/or restricted treatments are outlined below.

7.7.1 Prohibited and/or Restricted Treatments

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

- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]), within 30 days prior to randomization, during treatment, and until 100 days after the last dose.
- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.2 [Exclusion Criteria] criterion 1) subcriterion 1) and Section 7.7.3 [Permitted Therapy]).
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, molecular targeted therapy, locoregional therapy, hormonal therapy, immunotherapy, palliative or non-palliative radiation therapy, or standard or investigational agents for treatment of HCC). TACE on demand is allowed as per protocol-defined criteria.
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Concurrent use of antiviral therapy containing interferon (IFN).

7.7.2 Other Restrictions and Precautions

- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Investigators are strongly encouraged to wait for confirmation of recurrence/progression from the BICR prior to initiating subsequent systemic cancer therapy, loco-regional therapy, or tumor-directed surgery for suspected recurrence/progression unless clinical considerations require immediate intervention (eg, symptomatic brain metastases). If subsequent systemic cancer therapy, loco-regional therapy, or tumor-directed surgery is planned prior to BICR confirmation of recurrence/progression, the Investigator must contact the BMS Medical Monitor or Clinical Scientist to discuss the case prior to the start of any of these procedures.

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate.

Specific to MRI, participants with severe renal insufficiency (ie, eGFR < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis; therefore, MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the Imaging Manual.

Gentle hydration before and after IV contrast should follow local SOC. 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 IEC.

7.7.3 Permitted Therapy

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

Supportive care for disease-related symptoms may be offered to all participants on the trial.

COVID-19 vaccines that are NOT live (not replication competent) are permitted during the study and after the last dose of IP. No data are available on the response to COVID-19 vaccines. The efficacy and safety of vaccination in participants who are receiving nivolumab and ipilimumab or nivolumab alone are unknown. Please contact the BMS Medical Monitor or Clinical Scientist with any questions related to COVID-19 vaccines.

7.7.3.1 Antiviral Therapy

Participants on antiviral therapy for hepatitis B or C should continue the treatment during the study, providing the regimen is IFN-free. 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 study treatment temporarily held. The participant may resume study treatment once virologic control is reestablished [redacted].

For any participant who continues to be HCV RNA positive after receiving study treatment, current guidelines for management of chronic HCV infection, including those from American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (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.

7.7.3.2 Other Systemic Therapy

- **Hormone replacement therapy:** participants may continue to receive hormonal replacement therapy if initiated prior to randomization.

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 the maximum treatment duration specified in Section 7.1 (Treatments Administered)**. 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:

- The study is terminated due to safety concerns.
- The development of nivolumab/ipilimumab is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives.
- The participant can obtain medication from a government-sponsored or private health program.

In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Criteria listed in Section 8.1.1 (Treatment Discontinuation Criteria).
- Participants meeting progression as assessed by investigator, unless eligible to continue with treatment beyond progression (see Section 5.1.4 [Treatment Beyond Progression]).

- Disease progression or occurrence of a secondary malignancy which requires systemic therapy or radiotherapy for treatment.
- Pregnancy, if locally mandated (see Appendix 9 for country-specific requirements).

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

In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/Clinical Scientist of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Study treatment must be permanently discontinued where locally mandated. See Section 9.2.6 (Pregnancy).

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

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

8.1.1 Treatment Discontinuation Criteria

8.1.1.1 Criteria for Nivolumab and Ipilimumab Treatment Discontinuation

Nivolumab and ipilimumab treatment must be permanently discontinued per criteria in Table 7.4.2-1 in Section 7.4. Discontinue nivolumab and ipilimumab for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab and ipilimumab dosing. Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
- Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or Clinical Scientist).

Tumor assessments should continue as per protocol, even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q6W, or more frequently if clinically indicated during such dosing delays.

8.1.2 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 Table 7.4.2-1.

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after all of the following conditions are met:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, reverse transcription-polymerase chain reaction [RT-PCR] or viral antigen), and
- Resolution of acute symptoms (including at least 24 hours have passed since last fever without fever-reducing medications), and
- Evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment

For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.

When criteria to resume treatment are met, resume both nivolumab and ipilimumab on the same day.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor (or designee) must be consulted (see Section 8.1.1.1 [Criteria for Nivolumab and Ipilimumab Treatment Discontinuation]). In addition, see Appendix 6 (IO Management Algorithms) for guidance on appropriate management and follow-up of AEs.

8.1.3 Post Study Treatment Study Follow-up

Per Protocol Amendment 01, survival follow-up is not required. However, participants in the follow-up period at the time of Protocol Amendment 01 implementation are permitted to continue in the study. Participants will be followed for assessment of safety through 100 days after the last dose of study treatment. Participants will not be followed for survival.

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

BMS may request that survival data be collected on all randomized participants outside of the protocol-defined window (see Section 2 [Schedule of Activities]). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

Participants who discontinue study treatment may continue to be followed. Subsequent therapies received by the participant will also be reviewed and recorded.

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain the 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 (Section 2).

- 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 (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, baseline scans) 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 (Section 2).
- Additional measures, including non-study-required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug-induced liver enzyme evaluations) will be monitored during the Follow-up Period via on-site/local laboratories until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.
- If a participant shows pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) IB.[1]
- 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

Study evaluations will take place in accordance with the Schedule of Activities in Section 2. **Per Protocol Amendment 01, efficacy assessments will be conducted per the local standard of care.**

9.1.1 Imaging Assessment for the Study

Per Protocol Amendment 01, imaging should continue per local standard of care. The following information refers to the original study design.

Images will be submitted to a central imaging vendor for BICR on a rolling basis 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 CA20974W 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 timepoints 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 (eg, most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI) should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

9.1.1.1 Methods of Measurement

Per Protocol Amendment 01, imaging should continue per local standard of care. The following information refers to the original study design.

Contrast-enhanced CT of the chest, MRI or CT of the abdomen, pelvis (including pre- and post-contrast tri-phasic MRI or CT 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 timepoints. 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 BICR using the TTTP 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 pre- and post-contrast tri-phasic MRI of the liver), and other known/suspected sites of disease should be obtained.

Positron emission tomography (PET) scan are not adequate for assessment of mRECIST response.

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

9.1.1.2 Imaging and Clinical Assessment

Per Protocol Amendment 01, imaging should continue per local standard of care. The following information refers to the original study design.

Tumor assessments should continue even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the Investigator using mRECIST 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 mRECIST criteria (refer to Appendix 10 for specifics of mRECIST criteria for HCC[139] 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.

9.1.1.3 Assessment of Baseline Disease Status

Screening imaging must be submitted to the central imaging vendor for BICR assessment for participant eligibility (arterially enhancing HCC exceeding the BMU7 criteria as defined in

Section 9.1.2.1 [Definition of Baseline Tumor Burden], no EHS [including regional lymph node involvement], no portal vein thrombosis, and no VI), prior to randomization. Randomization must occur within 4 weeks from screening imaging.

9.1.1.4 BICR Determination of Progression or Recurrence

Not applicable per Protocol Amendment 01. Tumor assessments will be conducted by the investigator per local standard of care. The following information refers to the original study design.

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. The BICR will be completed and the results (TTTP reached or not) 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 by TTTP criteria is not determined 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 (TTTP as assessed by BICR), tumor assessments will continue according to the protocol-specified schedule, as noted in Section 2 (Schedule of Activities), until progression (TTTP as assessed by BICR), has been confirmed by BICR.

9.1.2 Efficacy Assessments for TTTP

Not applicable per Protocol Amendment 01. Tumor assessments will be conducted by the investigator per local standard of care. The following information refers to the original study design.

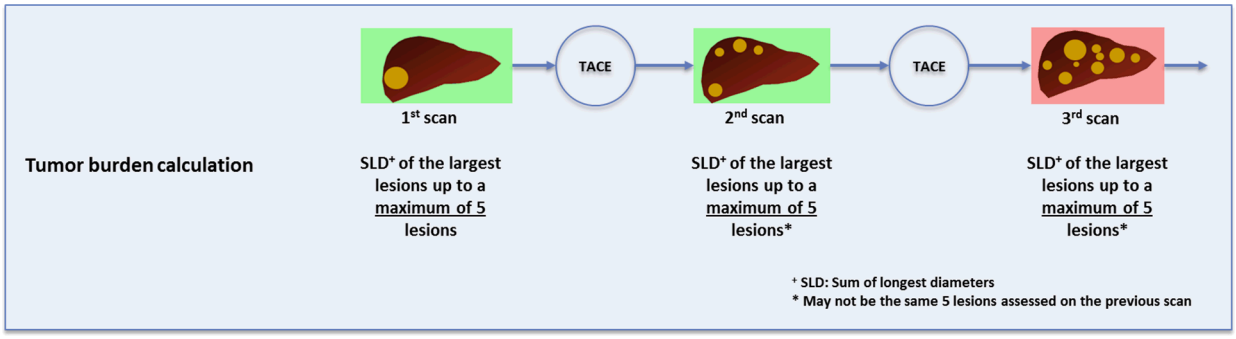
9.1.2.1 Definition of Baseline Tumor Burden

The baseline tumor burden in this design will be the tumor burden recorded on imaging at the time of screening. The 5 largest (arterially enhancing portion measuring at least 10 mm) liver lesions will be selected for the calculation of tumor burden at baseline.

9.1.2.2 Dynamic Assessment of Tumor Burden

During screening (see Section 9.1.2.1 [Definition of Baseline Tumor Burden]) and at each prescribed imaging timepoint the 5 largest liver lesions will be selected for the calculation of tumor burden. These may be lesions exhibiting regrowth or any new (arterially enhancing portion measuring at least 10 mm) liver lesions. This assessment of tumor burden is therefore a dynamic one and is more clinically relevant in a TACE setting, particularly when compared to a static assessment where tumor burden continues to be assessed based on the initial target lesions selected, which may no longer be there after a TACE procedure. Figure 9.1.2.2-1 illustrates the concept of a dynamic assessment of tumor burden.

Figure 9.1.2.2-1: Dynamic Tumor Burden Assessment



Abbreviations: SLD = sum of longest diameters; TACE = trans-arterial chemoembolization.

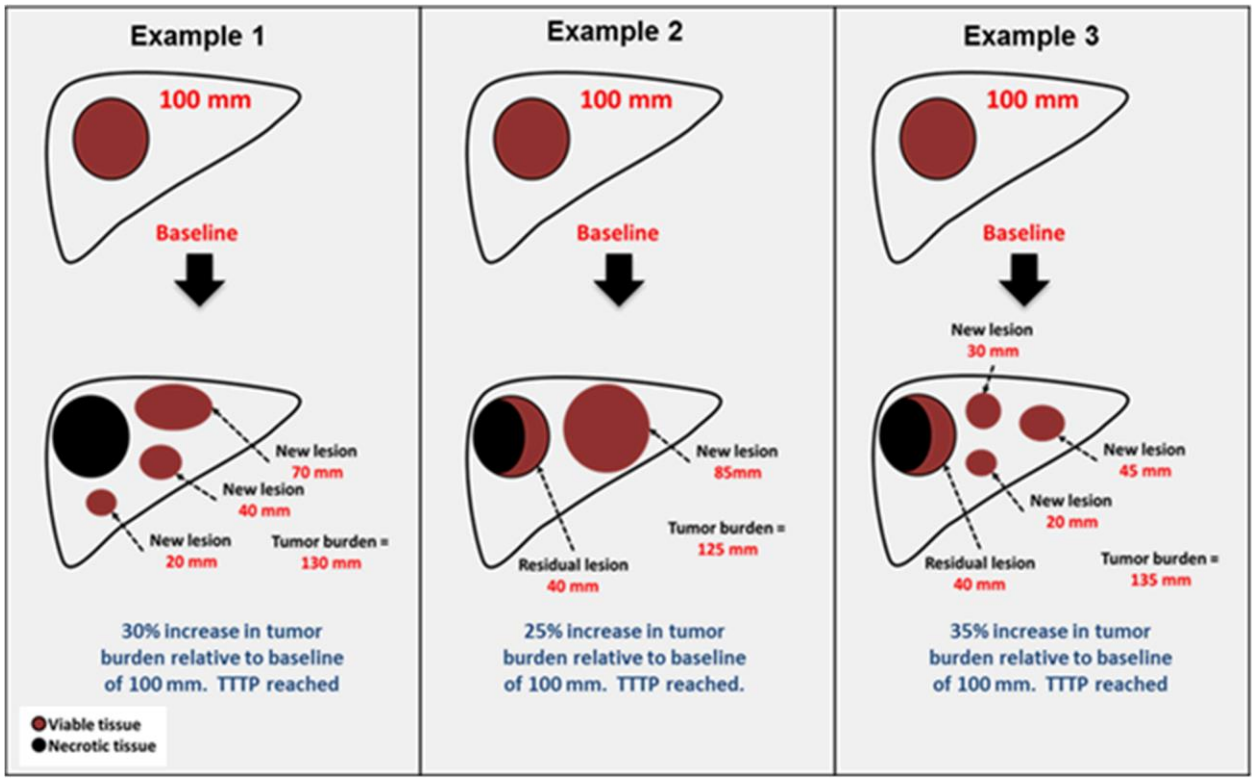
Finally, intermediate-stage HCC does not include patients with lesions outside of the liver. So the recorded measurable lesions will be solely defined based on liver lesions. The development of lesions outside of the liver will be captured as an EHS.

9.1.2.3 Definition of TTTP

Not applicable per Protocol Amendment 01. Progression will be assessed by the investigator per local standard of care. The following information refers to the original study design.

TTTP by imaging will be defined as a 20% increase in dynamic tumor burden over the baseline tumor burden, development of macroscopic evidence of MVI, extrahepatic tumor spread, or death (see Figure 9.1.2.3-1).

Figure 9.1.2.3-1: Criteria to Reach TTTP Based on Tumor Burden



Abbreviations: TACE = trans-arterial chemoembolization; TTTP = time to TACE progression; mm = millimeters.

9.1.3 Efficacy Assessments using mRECIST

As with traditional tumor assessment-based endpoints, a baseline tumor burden is needed in order to have a reference to compare changes in tumor burden during treatment. Tumor burden quantification should also follow the basic principles defined by mRECIST (refer to Appendix 10). As such, liver lesions will be categorized as "measurable" if the arterially enhancing portion can be accurately measured in at least 1 dimension, with a minimum size of 10 mm by CT or MRI scan.

9.1.4 Outcomes Research Assessments

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

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. Additionally, generic health-related quality of life (HRQL) measures provide data needed for calculating utility values to inform health economic models.

Participants will be asked to complete the both the EQ-5D-5L and FACT-Hep in the participant's preferred language when available. Participants will complete both measures prior to any other

assessments or study procedures when they are being administered during study visits. The PRO measures will also be completed at designated timepoints during the follow-up period. In addition, the EQ-5D-5L can be captured during survival follow-up visits by telephone administration. There exists a standardized guide that can be used to facilitate telephone administration of the EQ-5D-5L. See Section 2 (Schedule of Activities) for timing of assessments.

9.1.4.1 EQ-5D-5L

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

The EQ-5D-5L is a standardized instrument used to measure self-reports of health status and functioning.[140] The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels, reflecting no problems, slight problems, moderate problems, severe problems, and extreme problems. A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Thus, the vectors 11111 and 55555 represent the best health state and the worst health state, respectively, as described by the EQ-5D-5L. Altogether, the instrument describes $5^5 = 3,125$ health states.

Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate an index measuring the value to society of his or her current health.[141] Utility index values range from a 1 (full health) to 0 (dead) with negative values indicating a state considered worse than being dead. In addition, the EQ-5D-5L includes a visual analog scale (VAS) that allows respondents to rate their own current health on a 0-100 point scale ranging from "the worst health you can imagine" to the "best health you can imagine."

The EQ-5D-5L uses a recall period of "today."

9.1.4.2 FACT-Hep

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

The FACT-Hep questionnaire will be used to assess the effects of HCC and its treatment HRQL.[142] The FACT-Hep includes the 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 hepatobiliary cancer subscale (HCS) that assesses back and stomach pain, gastrointestinal symptoms, anorexia, weight loss, and jaundice. A subset of items from the FACT-Hep can also be scored as the National Cancer Care Network (NCCN)-FACT Hepatobiliary-Pancreatic Symptom Index (FHSI).[143] The GP5 item of the FACT-Hep can also be used to assess the bother associated with the side effects of treatment. 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 HRQL, 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 HRQL. Higher scores indicate better HRQL. 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; 8-9 points for the FACT-Hep total score; and 2-3 points for the FHSI-8.[144]

The FACT-Hep uses a recall period of the "past 7 days".

9.2 Adverse Events

Use the NCI CTCAE version 5.0 definitions and grading for safety reporting of all AEs and SAEs on the CRF.

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

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

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

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Immune-mediated Adverse Events

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

9.2.2 Time Period and Frequency for Collecting AE and SAE Information

All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of dosing, at the timepoints specified in Section 2 (Schedule of Activities).

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and for a minimum of 100 days of discontinuation of dosing. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the time of signing the consent until 100 days following discontinuation of dosing.

The Investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- All SAEs will be recorded and reported to the 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 the updated information being available.

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

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

9.2.3 Method of Detecting AEs and SAEs

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

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

9.2.4 Follow-up of AEs and SAEs

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

All SAEs and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, the event is deemed irreversible, until the participant is lost to follow-up (as defined in Section 8.3 [Lost to Follow-up]), or for suspected cases, until SARS-CoV-2 infection is ruled out.

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

9.2.5 Regulatory Reporting Requirements for SAEs

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

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws, including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and will be reported to the appropriate regulatory authorities and Investigators following local and global guidelines and requirements.

9.2.6 Pregnancy

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

If the Investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the Investigator and the BMS Medical Monitor/Clinical Scientist must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/Sponsor/IRB/EC, as applicable. Study treatment must be permanently discontinued where locally mandated; see Appendix 9 for country-specific requirements.

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

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

In cases where a study drug can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner,

the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.7 Laboratory Test Result Abnormalities

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

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

9.2.8 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 2 and Appendix 3 for reporting details).

Potential DILI is defined as:

- Concurrent ALT $\geq 10 \times$ ULN, AND
- Total bilirubin $\geq 2 \times$ ULN or baseline value (if elevated bilirubin at study entry), AND
- No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, pre-existing hepatic disease or the administration of other drug(s), herbal medications, and substances known to be hepatotoxic.

9.2.9 Other Safety Considerations

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

9.2.10 Management Algorithms for Immuno-oncology Agents

IO agents are associated with IMAEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered IO agents in this protocol. Early recognition and management of IMAEs associated with IO agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with ipilimumab and nivolumab to assist Investigators in assessing and managing the following groups of IMAEs:

- Gastrointestinal

- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological
- Myocarditis

The algorithms recommended for the management of IMAEs in this protocol are in Appendix 6.

- Checkpoint inhibitor molecules have been uncommonly associated with ocular drug-related AEs. Inflammation of components within the eye (eg, episcleritis, uveitis) are uncommon events of nivolumab monotherapy (< 1% of cases). These events are usually of low or intermediate grade, reversible, detected early in the course of therapy, and manageable with topical or systemic steroids.
  - Routine eye examinations should be performed in participants receiving immune checkpoint inhibitors (Section 2 [Schedule of Activities]). Upon clinical suspicion of an ocular event, consider ophthalmic consult, dose omission, or dose discontinuation.
  - Permanently discontinue for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids for severe immune-mediated adverse reactions.
  - Permanently discontinue for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.
  - Administer corticosteroid eye drops to participants who develop uveitis, iritis, or episcleritis.

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 (refer to Appendix 3).

9.4 Safety

Planned timepoints for all safety assessments are listed in Section 2 (Schedule of Activities). Additional procedures and assessments may be performed as part of SOC; however, data for these assessments should remain in the participant's medical record and should not be provided to BMS, unless specifically requested. Both AEs and laboratory tests will be graded according to the NCI CTCAE version 5.0.

9.4.1 Physical Examinations

See the Schedule of Activities (Section 2).

9.4.2 Vital Signs

See the Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

See the Schedule of Activities (Section 2).

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

A list of the clinical laboratory analyses to be tested is provided in Table 9.4.4-1 below.

Table 9.4.4-1: Clinical Safety Laboratory Assessments

Hematology - CBC	
Hemoglobin Hematocrit Total leukocyte count, including differential Platelet count Coagulation profile: International normalized ratio (INR). If INR cannot be done by the local laboratory, then PT may be provided instead.	
Chemistry/Endocrine	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) or serum urea Glucose Alpha-fetoprotein (AFP) Amylase Lipase	Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on-treatment. For TSH assessments, total T3/T4 are acceptable if free T3/T4 are not available.
Serology	
Hepatitis B/C/D ***Screening:*** HBsAg, HBV surface antibody, HBV core antibody, HBV DNA vial load [PCR], HCV viral load [PCR], HCV antibody or HCV RNA, HDV antibody ***On-treatment:*** For HCV-infected participants, HCV RNA; for HBV-infected participants, HBV DNA.	
HIV Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG) FSH screening - only required to confirm menopause in women < age 55	
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick.	

Abbreviations: CBC = complete blood count; DNA = deoxyribonucleic acid; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HDV = hepatitis D virus; HIV = human immunodeficiency virus; IU = international unit; L = liter; PCR = polymerase chain reaction; PT = prothrombin time; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing 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.

9.5 Pharmacokinetics and Immunogenicity

Upon implementation of Protocol Amendment 01, PK and immunogenicity sample collection is no longer necessary for any participant who is on study treatment. In the event samples are collected following implementation of Protocol Amendment 01, samples do not need to be analyzed.

The following information refers to the original study design and is not applicable per Protocol Amendment 01.

Samples for PK and IMG assessments will be collected for all participants, as described in Table 9.5-1. Only samples collected from nivolumab- and ipilimumab-treated participants will be analyzed; samples collected from placebo participants will not be analyzed. All timepoints are relative to the start of study treatment administration. All on-treatment timepoints 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 the predose sample 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. Further details of sample collection, processing, and shipment will be provided in the Laboratory Procedures Manual.

Serum concentration analyses for nivolumab will be performed by a validated immunoassay bioanalytical method for participants treated with nivolumab. Samples collected from participants treated with nivolumab will be evaluated for the development of anti-drug antibody (ADA) to nivolumab by validated immunoassays. Samples with a positive ADA response may also be analyzed for nivolumab neutralizing ADA characterization by a validated cell-based assay.

Serum concentration analyses for ipilimumab will be performed by a validated immunoassay bioanalytical method for participants treated with ipilimumab. Samples collected from participants treated with ipilimumab will be evaluated for the development of ADA to ipilimumab by validated immunoassays. Samples with a positive ADA response may also be analyzed for ipilimumab neutralizing ADA characterization by a validated cell-based assay.

In addition, selected serum samples may be analyzed by exploratory methods that measure nivolumab or ipilimumab, or detect ADAs for technology exploration purposes; exploratory results will not be reported. The corresponding serum samples designated for either PK, IMG, or biomarker assessments may also be used for any of those analyses, if required (eg, insufficient sample volume to complete testing or to follow up on suspected IMG-related AE).

Please see Appendix 9 for country-specific criteria for the collection and analyses of biomarker samples [redacted].

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for All Participants

Study Day of Sample Collection (1 Cycle = 2 weeks)	Event	Time Relative to Start of Nivolumab Infusion (hr:min)	Nivolumab Pharmacokinetic Serum Sample	Ipilimumab Pharmacokinetics Serum Sample	Nivolumab Immunogenicity Serum Sample	Ipilimumab Immunogenicity Serum Sample
Cycle 1 Day 1	Predose[a]	00:00	X	X	X	X
	End of infusion[b]	See note.[c]	X	X		
Cycle 2 Day 1	Predose[a,d]	00:00	X	X	X	X
Cycle 4 Day 1	Predose[a]	00:00	X	X	X	X
Cycle 5 Day 1	Predose[a,d]	00:00	X	X	X	X
Cycle 9 Day 1	Predose[a,d]	00:00	X	X	X	X
Cycle 13 Day 1	Predose[a]	00:00	X	X	X	X
Cycle 19 Day 1	Predose[a]	00:00	X	X	X	X
Cycle 25 Day 1	Predose[a]	00:00	X	X	X	X
Cycle 29 Day 1	Predose[a]	00:00	X	X	X	X
Cycle 37 Day 1	Predose[a,d]	00:00	X	X	X	X
Cycle 45 Day 1	Predose[a]	00:00	X	X	X	X

Abbreviations: hr = hour; min = minute; PK = pharmacokinetic.

Note: Upon implementation of Protocol Amendment 01, PK and immunogenicity sample collection is no longer necessary for any participant who is on study treatment. In the event samples are collected following implementation of Protocol Amendment 01, samples do not need to be analyzed.

[a] Predose: All pre-dose samples for nivolumab and ipilimumab should be taken just before the start of nivolumab infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample 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] End of infusion samples for both nivolumab and ipilimumab should be collected at the end of (preferably within 2 minutes prior to the end of) ipilimumab infusion.

[c] On days where nivolumab and ipilimumab will be administered sequentially, the End of infusion sample collection for both nivolumab and ipilimumab at the end of ipilimumab infusion is 1:30, (0:30 for nivolumab infusion + 0:30 break + 0:30 ipilimumab infusion).

[d] Ipilimumab pharmacokinetics/immunogenicity samples will be collected, even though ipilimumab infusion will not be administered at these visits.

9.6 Pharmacodynamics

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Pharmacodynamic parameters will be evaluated in this study. Systemic immune monitoring of MDSCs, cytokines/chemokines, and other related soluble factors to investigate the immunomodulatory properties of nivolumab, ipilimumab, and TACE will be assessed. See Section 9.8 (Biomarkers) for a detailed description of the analyses and Table 9.8-1 for the sample collection schedule.

Please see Appendix 9 for country-specific criteria for the collection and analyses of samples in China.

9.7 Pharmacogenomics

Not applicable.

9.8 Biomarkers

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

A variety of factors that could potentially predict clinical response to nivolumab, ipilimumab, and/or TACE will be investigated in tumor specimens, peripheral blood, and stool taken from all participants as described below. Data from these investigations will be evaluated for association with efficacy endpoints. In addition, analyses of markers in all 3 treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs prognostic value.

A detailed description of each biomarker analysis is described below and a schedule of biomarker sample collections is provided in Table 9.8-1. Tumor tissue, peripheral blood, and a stool sample will be collected prior to therapy. Peripheral blood samples and a stool sample will also be collected at selected timepoints on-treatment. If a biopsy or surgical resection is performed at the time of TTTP by BICR or end of treatment, tumor sample (block or slides) should also be submitted for analysis. If biomarker samples are drawn but study treatment(s) are not administered, samples will be retained. Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Procedure Manual at the time of study initiation.

Please see Appendix 9 for country-specific criteria for the collection and analyses of samples in China.

Table 9.8-1: CA20974W Biomarker Sampling Schedule All Participants

Study Day of Sample Collection (1 Cycle = 2 weeks)	Serum Biomarkers[a]	Whole Blood DNA[a]	Whole Blood RNA[a]	MDSC[a]	Plasma (ctDNA)[a]	Stool[b]	Tumor[c,d]
Screening							X
Cycle 1 Day 1	X	X	X	X	X	X	
Cycle 3 Day 1	X		X	X	X	X	
Cycle 7 Day 1	X			X		X	
Cycle 13 Day 1					X		
Cycle 19 Day 1					X		
Cycle 25 Day 1					X		
Cycle 31 Day 1					X		
Cycle 37 Day 1					X		
Cycle 43 Day 1					X		
Cycle 49 Day 1					X		
Upon TTTP by BICR or EOT	X			X	X		X

Abbreviations: BICR = blinded independent central review; ctDNA = circulating tumor DNA; DNA = deoxyribonucleic acid; EOT = end of treatment; MDSC = myeloid-derived suppressor cells; RNA = ribonucleic acid; TACE = trans-arterial chemoembolization; TTTP = time to TACE progression.

[a] Prior to dosing (when applicable).

[b] Stool collection is optional and should be collected within 7 days prior to dosing. Stool should not be collected in China and in other geographies if restricted by local requirements.

[c] Tumor tissue submission during screening is required for randomization. Upon TTTP by BICR or end of treatment, tumor tissue submission is highly recommended if clinically feasible

[d] Biomarker samples will not be collected [redacted] except for tumor samples during Screening. See Appendix 9.

9.8.1 Tumor-based Biomarker Measures

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Tumor tissue will be obtained at baseline and upon TTTP by BICR or end of treatment (if clinically feasible) to characterize immune cell populations, expression of selected tumor markers, expression of inflammatory genes, and genetic analyses mentioned below in detail. Tumor block (preferred) or slides must be sent to the central laboratory prior to randomization. Biopsy samples should be excisional, incisional, or core needle. Fine needle aspirates or other cytology samples are not acceptable. A tumor block is preferred, but if a block is not feasible, a minimum of 20 unstained slides is required. Slides should be unstained, have a recommended tissue section thickness of 4 microns, and must be positively charged. Tumor tissue must contain adequate tumor content (≥ 100 tumor cells), as determined by hematoxylin and eosin (H&E) review at the central laboratory. If the initial tumor sample submission does not meet this criterion, an additional tissue submission (if available) is allowed. Participants must have an evaluable tumor tissue specimen to be eligible for randomization. A tumor biopsy upon TTTP by BICR or end of treatment is also highly recommended, if clinically feasible.

Tumor samples may be used for the assessments described below. Please see Appendix 9 for country-specific criteria for the collection and analyses of tumor-tissue samples in China.

9.8.1.1 Characterization of Tumor Infiltrating Lymphocytes and Tumor Antigens

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Immunohistochemistry (IHC) may be used to assess tumor markers as well as the number and composition of immune infiltrates in order to define the immune cell subsets present within FFPE tumor tissue before therapy and upon TTTP by BICR or end of treatment. IHC analyses may include, but not necessarily be limited to, the following markers: major histocompatibility complex (MHC) class I/II, CD8, PD-1, PD-L1, PD-L2, and lymphocyte activating 3 (LAG3).

9.8.1.2 Tumor Genomic Analysis Including Tumor Mutational Burden and Gene Expression Analysis

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

DNA from tumor samples will be analyzed using platforms, including, but not limited to, whole-exome sequencing to identify and quantify somatic mutations by using the whole blood DNA sample as a germline reference. Mutations that are detected may be analyzed for their ability to bind the MHC class I and MHC class II proteins using prediction algorithms. Evaluating the ability of tumor mutations to bind MHC molecules may provide evidence that these mutations are serving as antigens that are recognized by the immune system and are potential rejection antigens. MSI or MSI status may be derived from whole-exome sequencing data if MSI status is not already known. Lastly, RNA expression within tumor biopsies may be examined using RNAseq, whole-

transcriptome sequencing, or other next-generation sequencing technologies to detect expression of all genes.

9.8.2 Peripheral Biomarkers

9.8.2.1 Myeloid-derived Suppressor Cells

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

MDSCs are an immune cell population capable of suppressing T cell activation and proliferation. MDSCs will be measured prior to dosing on Cycle 1 Day 1, on-treatment, and upon TTTP by BICR or end of treatment to assess pharmacodynamic changes as well as associations with outcome.

9.8.2.2 Soluble Biomarkers and Other Assessments in Serum

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Serum will be collected prior to dosing on Cycle 1 Day 1, on-treatment, and upon TTTP by BICR or end of treatment to measure levels of cytokines, chemokines, other immune mediators, and extracellular matrix fragments. These factors will be assessed by techniques that may include, but are not limited to, enzyme-linked immunosorbent assay (ELISA) or multiplex assays. Analyses may include, but are not limited to, IFN-γ, C-X-C motif chemokine ligand (CXCL) 9, CXCL10, soluble PD-L1, collagen, and other extracellular matrix fragments. These analyses may identify potential biomarkers with prognostic and predictive value for outcomes.

9.8.2.3 Genomic Analysis of Circulating Tumor DNA in Plasma

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Plasma will be collected prior to dosing on Cycle 1 Day 1, on-treatment, and upon TTTP by BICR or end of treatment to enable genomic analysis of circulating tumor DNA (ctDNA).

9.8.2.4 Whole Blood DNA and RNA Analyses

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

DNA in the whole blood samples may be used to examine germline (predisposing) characteristics as well as to help identify genetic information specific to the participant's tumor, such as somatic DNA alterations. RNA in the whole blood sample may be used to assess the expression of genes associated with inflammation. These blood samples will be obtained prior to dosing on Cycle 1 Day 1 (whole blood DNA and whole blood RNA) and on-treatment (whole blood RNA only) unless restricted by local requirements.

9.8.2.5 Viral Safety Biomarkers

At screening, HBV DNA, qualitative and quantitative hepatitis B surface antigen (qHBsAg), hepatitis B e-antigen (qHBeAg), hepatitis B surface antibody (HBsAb), HCV RNA,

HCV antibody, and hepatitis D antibody (if chronic HBV infection) samples will be collected for all participants. On-treatment and during follow-up visits FU1 and FU2, HBV DNA will only be collected for HBV chronic-infected participants, and HCV RNA will only be collected for HCV chronic-infected participants. Details regarding sample collection timepoints can be found in Section 2 (Schedule of Activities). These analyses will be performed at the central laboratory. Results of HBV DNA and HCV RNA will be provided to sites for management of virologic breakthrough (see Section 7.7.3.1 [Antiviral Therapy]).

9.8.3 Microbiome Analysis

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

An optional stool sample will be collected prior to dosing and while on-treatment to assess microbiome diversity and composition, unless restricted by local requirements.

9.8.4 Additional Research Collection

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

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

For All US sites:

AR is required for all study participants, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where 1 or more of these exceptions occurs, participation in the AR should be encouraged but will not be a condition of overall study participation.

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

For non-US Sites

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

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

Sample Collection and Storage

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

- Residual PK/IMG, tumor tissue, and serum, plasma, whole blood, and stool samples from collections (see Table 9.8.4-1 [Residual Sample Retention for Additional Research Schedule]) will also be retained for AR purposes.

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 the 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.

Table 9.8.4-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for Which Residual Samples will be Retained
PK/IMG	All
Tumor tissue	All
Serum biomarkers	All
Plasma for ctDNA	All
Whole blood DNA	C1D1
Whole blood RNA	C1D1
Stool	All

Abbreviations: C = cycle; ctDNA = circulating tumor DNA; D = day; DNA = deoxyribonucleic acid; IMG = immunogenicity; PK = pharmacokinetics; RNA = ribonucleic acid.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Healthcare resource utilization (HCRU) data will be collected for all randomized participants using an internal CRF developed for use in previous trials. The form, which is completed by study staff, records information about hospital admissions, including number of days spent in various wards and discharge diagnosis, as well as non-protocol specified visits related to study therapy, including date of visit, reason for visit, and type of visit. The HCRU data will be used to support subsequent economic evaluations.

10 STATISTICAL CONSIDERATIONS

Per Protocol Amendment 01, only safety analyses will be conducted. Summary tables and listings for baseline, disposition, and safety data will be provided to support the Clinical Study Report (CSR) and study data disclosure. Listings for efficacy data may be provided, if requested, per regional data disclosure requirement. Details of the analysis and outputs will be provided in the SAP.

10.1 Sample Size Determination

Per Protocol Amendment 01, sample size will be limited to the participants randomized as of 22-Sep-2021. The following information refers to the original study design.

For the comparison of nivolumab and ipilimumab plus TACE (Arm A) vs nivolumab placebo and ipilimumab placebo plus TACE (Arm C), both TTTP and OS are primary endpoints. For sample size determination purpose, the family-wise error rate of 5% will be controlled using Bonferroni split: comparison of TTTP with alpha of 1% and comparion of OS with alpha of 4%.

Approximately 765 participants will be randomized to 3 treatment arms in a 1:1:1 ratio in approximately 36 months. Approximately 94% and 89% power will be achieved for TTTP and OS, respectively, under the detailed assumptions described in following subsections. EAST v6.4.1 was used to conduct simulations for sample size calculation.

10.1.1 Sample Size Justification for Primary Endpoint of TTTP

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Assumpations for sample size justification for TTTP include:

- Exponential distribution in Arm C, with a median of [redacted].
- Piecewise-exponential distribution in Arm A as determined by a 2-piece HR with a delay effect of HR of 1 in the first [redacted], followed by a constant HR o[redacted] (see Table 10.1.1-1). This results in an averaged target HR of [redacted] at the TTTP final analysis.
- Anticipated dropout rate of [redacted] by month 3 and [redacted] by month 24.

Table 10.1.1-1: TTTP Hazard Rates and HRs (Arm A vs Arm C)

Starting at Time (month)	Hazard Rates for TACE (Arm C)	Hazard Rates for Nivolumab and Ipilimumab plus TACE (Arm A)	HR
[redacted]			

Abbreviations: HR = hazard ratio; TACE = trans-arterial chemoembolization.

Based on simulation under the assumptions stated above, approximately 510 participants will be randomized to Arm A and Arm C and followed until at least 418 TTTP events are observed, in order to provide 94% power for an average HR of [redacted] with a 2-sided type I error of 1%. The number of events is expected to be reached after approximately 55 months from the first participant randomized (see Table 10.1.1-2).

Table 10.1.1-2: Summary of Sample Size Parameters and Schedule of Analyses for TTTP (Arm A vs Arm C)

Parameter	Value
Number of randomized participants	510
Hypothesized delayed period	[redacted]
Hypothesized HR after delayed period	
Hypothesized median in control arm	
Significance level (2-sided)	0.01
Enrollment period[a]	36 months
Number of events	418
Projected TTTP analysis time[a]	55 months
Power	94%
Average HR	[redacted]
Median in experimental arm time	14.9 months

Abbreviations: HR = hazard ratio; TACE = trans-arterial chemoembolization; TTTP = time to TACE progression.

[a] Time is calculated from the time the first participant is randomized.

It is projected that an observed HR of [redacted] or less would results in a statistically significant improvement of nivolumab and ipilimumab plus TACE at the final analysis of TTTP.

10.1.2 Sample Size Justification for Primary Endpoint OS

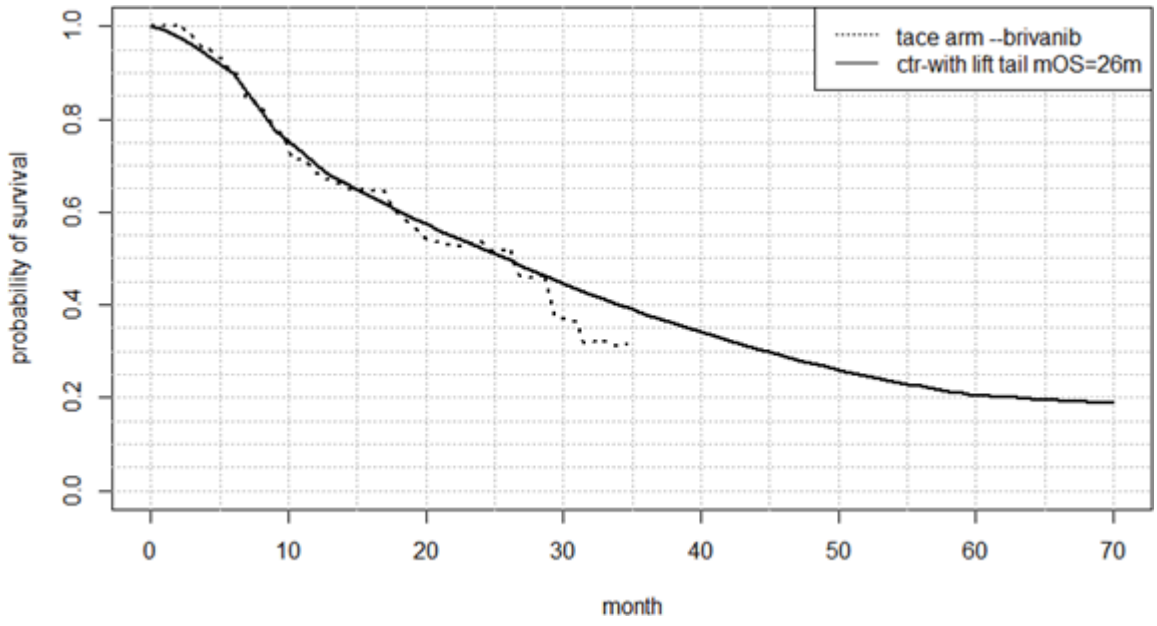
Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Assumptions for sample size justification for OS include:

- Piecewise-exponential distribution in both control and experimental arms.
- When viewing the OS data from the BRISK-TA study, the TACE arm was considered as the most relevant to this study's control arm, Arm C. Based on such data, a [redacted] exponential distribution is assumed for OS of Arm C. The assumed piecewise-exponential model fits the OS data of TACE in the BRISK-TA study up to [redacted] months. Starting from month 26, the tail of the control OS curve rose to have higher OS rates, with a 5-year OS [redacted] (see Figure 10.1.2-1). The flattened tail of the OS curve intends to indicate that the longer-term OS should be improved with current and future available 1L, 2L, and later lines of therapies.
- The median OS of the control arm is [redacted] based on above assumptions.
- Anticipated dropout rate of [redacted] by month 3 and [redacted] by month [redacted]

The target average HR of [redacted] is assumed for Arm A vs Arm C and is modeled as an [redacted] HR with a delay effect of HR of [redacted] in the first [redacted] months, followed by multiple pieces of HR. These HRs start with [redacted] after separation, and HRs are gradually increased thereafter to reflect the belief that the overall treatment effect will be compromised when participants who progress in the control arm have a higher chance to select immunotherapies as their subsequent therapies (see Table 10.1.2-1).

Figure 10.1.2-1: OS for TACE from External Data (BRISK-TA study) and Assumed Probability of OS for Placebo plus TACE (Arm C)



Abbreviations: ctr = control; m = months; mOS = median overall survival; OS = overall survival; TACE = trans-arterial chemoembolization.

Table 10.1.2-1: OS Hazard Rates and HRs (Arm A vs Arm C)

Starting at Time (month)	Hazard Rates for TACE (Arm C)	Hazard Rates for Nivolumab and Ipilimumab plus TACE (Arm A)	HR
[redacted]			

Abbreviations: HR = hazard ratio; OS = overall survival; TACE = trans-arterial chemoembolization.

Based on simulation under the assumptions stated above, approximately 510 participants will be randomized to the nivolumab and ipilimumab plus TACE and placebo plus TACE arms and followed until at least 371 OS events are observed, in order to provide 89% power for an average HR of [redacted] with a 2-side type I error of 4%. This accounts for a group sequential testing procedure with 2 interim analyses and 1 final analysis. The first OS interim analysis will be conducted at the time of TTTP final analysis, when approximately 72% of OS events (267 events) are expected. The second OS interim analysis will be conducted when 88% of OS events (326 events) are expected. The alpha allocation for the interim and final analyses is based on Lan-DeMets alpha spending function approach using an O'Brien-Fleming stopping boundary, controlling for a 2-sided overall type I error of 4%. The stopping boundary will depend on the actual number of deaths at the time of the interim analyses and the final analysis (see Table 10.1.2-2).

Table 10.1.2-2: Summary of Sample Size Parameters and Schedule of Analyses for OS (Arm A vs Arm C)

Parameter	Value
Number of randomized participants	510
Hypothesized delayed period	[redacted]
Hypothesized HR after delayed period	
Hypothesized median in control arm	
Significance level (2-sided)	0.04
Enrollment period[a]	36 months
Interim Analysis #1 for OS	
Number of events	267
Projected analysis time[a]	55 months
Interim Analysis #2 for OS	
Number of events	326
Projected analysis time[a]	68 months
Final Analysis	
Number of events	371
Projected analysis time[a]	87 months
Power	89%
Average HR	[redacted]
Median in experimental arm	37.7 months

Abbreviations: HR = hazard ratio; OS = overall survival.

[a] Time is calculated from the time the first participant is randomized.

It is projected that an observed HR of 0.74/[redacted] or less would result in a statistically significant improvement of nivolumab and ipilimumab plus TACE at the first/second interim analyses of OS, and an observed HR of 0.8 or less would result in a statistically significant improvment of nivolumab and ipilimumab plus TACE at the final analysis of OS.

10.1.3 Power Considerations in Nivolumab plus TACE vs Placebo plus TACE (Arm B vs Arm C) TTTP and OS Comparison as Secondary Endpoints

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

TTTP between nivolumab plus TACE (Arm B) vs placebo plus TACE (Arm C) will be tested following a hierachical procedure. This comparison will be tested when the primary objective of TTTP of nivolumab and ipilimumab plus TACE vs placebo plus TACE meets statistical

significance. The testing will be conduced at the same significance level of 1%. The TTTP comparison in Arm B vs Arm C will be conducted at the same time of TTTP comparison of Arm A vs Arm C. At the time of the TTTP analysis for Arm A and Arm C, it is projected 421 events will be observed in Arm B and Arm C. Under the piecewise HR assumption for Arm B (see Table 10.1.3-1), the comparison will have approximately 86% power (see Table 10.1.3-2).

Table 10.1.3-1: TTTP Hazard Rates and HRs (Arm B vs Arm C)

Starting at Time (month)	Hazard Rates for TACE (Arm C)	Hazard Rates for Nivolumab plus TACE (Arm B)	HR
[redacted]			

Abbreviations: HR = hazard ratio; TACE = trans-arterial chemoembolization; TTTP = time to TACE progression.

Table 10.1.3-2: Summary of Design Parameters and Schedule of Analyses for TTTP (Arm B vs Arm C)

Parameter	Value
Number of randomized participants	510
Hypothesized delayed period	[redacted]
Hypothesized HR after delayed period	
Hypothesized median in control arm	
Significance level (2-sided)	0.01
Enrollment period[a]	36 months
Number of events	421
Projected TTTP analysis time[a]	55 months
Power	86%
Average HR	[redacted]
Median in experimental arm	14.3 months

Abbreviations: HR = hazard ratio; TACE = trans-arterial chemoembolization; TTTP = time to TACE progression.

[a] Time is calculated from the time the first participant is randomized.

OS between nivolumab plus TACE (Arm B) vs placebo plus TACE (Arm C) will be tested following a hierarchical procedure. This comparison will be tested when the primary objective of OS of Arm A vs Arm C meets statistical significance. The testing will be conduced at the same significance level of 4%. At the time of OS final analysis for Arm A and Arm C, it is projected 376 events will be observed in Arm B and Arm C. Under the piecewise HR assumption for Arm B (see Table 10.1.3-3), the comparison will have approximately 83% (see Table 10.1.3-4). A graphical approach will be used to control the overall alpha of 4% among the primary endpoint

of OS, secondary endpoint of OS, and their interim and final analyses. Detailed will be documented in the statistical analysis plan (SAP).

Table 10.1.3-3: OS Hazard Rates and HRs (Arm B vs Arm C)

Starting at Time (month)	Hazard Rates for TACE (Arm C)	Hazard Rates for Nivolumab plus TACE (Arm B)	HR
[redacted]			

Abbreviations: HR = hazard ratio; OS = overall survival; TACE = trans-arterial chemoembolization.

Table 10.1.3-4: Summary of Design Parameters and Schedule of Analyses for OS (Arm B vs Arm C)

Parameter	Value
Number of randomized participants	510
Hypothesized delayed period	[redacted]
Hypothesized HR after delayed period	
Hypothesized median in control arm	
Significance level (2-sided)	0.04
Enrollment period[a]	36 months
Interim Analysis #1 for OS	
Number of events	271
Projected analysis time[a]	55 months
Interim Analysis #2 for OS	
Number of events	327
Projected analysis time[a]	68 months

Table 10.1.3-4: Summary of Design Parameters and Schedule of Analyses for OS (Arm B vs Arm C)

Parameter	Value
Final Analysis	
Number of events	376
Projected analysis time[a]	87 months
Power	83%
Average HR	[redacted]
Median in experimental arm	36.2 month

Abbreviations: HR = hazard ratio; OS = overall survival.

[a] Time is calculated from the time the first participant is randomized.

10.2 Populations for Analyses

Per Protocol Amendment 01, only safety assessments wll be conducted.

For purposes of analysis, the following populations are defined in Table 10.2-1.

Table 10.2-1: Populations for Analyses

Population	Description
All Enrolled	All participants who signed an ICF and were registered into the IRT.
All Randomized	All participants who were randomized to any treatment arm in the study. Participants are grouped within the All Randomized population by the treatment to which they were randomized. This is the primary analysis set for demography, protocol deviations, and baseline characteristics.
All Treated	All enrolled participants who receive at least 1 dose of study drug. Participants are grouped within the All Treated population according to the treatment they actually received. This is the analysis set for all safety analyses and study drug administration.
PK	**Not applicable per Protocol Amendment 01.** All participants who receive at least 1 dose of nivolumab or ipilimumab and have available serum concentration data that allow for computation of meaningful PK parameter values.
IMG	**Not applicable per Protocol Amendment 01.** All nivolumab- or ipilimumab-treated participants with baseline and at least 1 post-baseline IMG assessment.
Biomarker	**Not applicable per Protocol Amendment 01.** All Treated participants who have available biomarker data. For predictive biomarkers, biomarker population includes all randomized participants who have biomarker data available at baseline. For pharmacodynamic biomarkers, the biomarker population includes all randomized participants who have baseline and at least 1 post-baseline biomarker data available.

Table 10.2-1: Populations for Analyses

Population	Description
PRO Analysis	**Not applicable per Protocol Amendment 01.** All Treated participants who have a valid baseline assessment (prior to treatment on Cycle 1 Day 1) and at least 1 post-baseline assessment during the treatment period.

Abbreviations: ICF = informed consent form; IMG = immunogenicity; IRT = interactive response technology; PK = pharmacokinetics; PRO = patient-reported outcome.

10.3 Statistical Analyses

The SAP will be developed and finalized before the first 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.

10.3.1 Efficacy Analyses

Per Protocol Amendment 01, formal efficacy analyses will not be conducted. Descriptive summary statistics may be provided for internal dissemination only.

A Bonferroni-based graphical approach[145] will be used for primary and key secondary endpoint analyses. Details will be provided in the SAP. The following secondary endpoints will be tested sequentially in the following order at the allocated alpha inherited from the primary endpoint of TTTP:

- TTTP in Arm B vs Arm C
- EFS in Arm A vs Arm C
- EFS in Arm B vs Arm C
- PFS in Arm A vs Arm C
- PFS in Arm B vs Arm C

Statistical analyses for efficacy are shown in Table 10.3.1-1.

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
Primary	
TTTP nivolumab and ipilimumab plus TACE vs placebo plus TACE	**TTTP** is defined as the time from the date of randomization to appearance of any of the following: a 20% increase in dynamic tumor burden over baseline scan; development of MVI; development of EHS; or death. Participants who are alive and with no HCC tumor progression by TTTP will be censored at the last tumor assessment date prior to or on first subsequent therapy date. The distribution of TTTP of nivolumab and ipilimumab plus TACE and placebo plus TACE will be compared via a 2-sided, log-rank test stratified by the stratification factors. The HR and corresponding 99% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The TTTP curves for each arm will be estimated using the Kaplan-Meier produce limit method. The 2-sided 95% CIs for median TTTP will be computed by Brookmeyer and Crowley method (using log-log transformation).

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
OS nivolumab and ipilimumab plus TACE vs placebo plus TACE	**OS** is defined as the time from the date of randomization to the date of death due to any cause in all randomized participants. Participants who are alive will be censored at the last known alive dates. The distribution of OS of nivolumab and ipilimumab plus TACE and placebo plus TACE will be compared via a 2-sided, log-rank test stratified by the stratification factors. The HR and corresponding 100×(1-adjusted alpha)% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The OS curves for each arm will be estimated using the Kaplan-Meier produce limit method. The 2-sided 95% CIs for median OS will be computed by Brookmeyer and Crowley method (using log-log transformation). In addition, survival rates at select milestones will be computed as well as the corresponding 2-sided 95% CIs using the log-log transformation.
Secondary	
TTTP nivolumab plus TACE vs placebo plus TACE	Similar to primary endpoint analysis. Hierarchical testing of TTTP in nivolumab plus TACE and placebo plus TACE will be performed upon demonstration of superiority in TTTP in nivolumab and ipilimumab plus TACE and placebo plus TACE. Descriptive analysis will be performed if superiority is not demonstrated.
OS nivolumab plus TACE vs placebo plus TACE	Similar to primary endpoint analysis. Hierarchical testing of OS in nivolumab plus TACE and placebo plus TACE will be performed upon demonstration of superiority in OS in nivolumab and ipilimumab plus TACE and TACE plus placebo. Descriptive analysis will be performed if superiority is not demonstrated.

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
EFS nivolumab and ipilimumab plus TACE vs placebo plus TACE and nivolumab plus TACE vs placebo plus TACE	**EFS** is defined as the time from randomization to initiation of first-line systemic therapy or the date of progression of cirrhosis from Child Pugh A to Child Pugh C score, or death, whichever occurs first. Participants who are alive and received no first-line systemic therapy or are not progressed to Child Pugh C will be censored at the last Child-Pugh score assessment date. The distribution of EFS in randomized arms will be compared via a 2-sided, log-rank test stratified by the stratification factors. The HR and corresponding 99% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The EFS curves for each arm will be estimated using the Kaplan-Meier produce limit method. The 2-sided 95% CIs for median EFS will be computed by Brookmeyer and Crowley method (using log-log transformation). Hierarchical testing of EFS will be performed upon demonstration of superiority in TTTP. Descriptive analysis will be performed if superiority is not demonstrated in TTTP.
PFS nivolumab and ipilimumab plus TACE vs placebo plus TACE and nivolumab plus TACE vs placebo plus TACE	**PFS** is defined as the time from the randomization date to the first documented disease progression as assessed by BICR using mRECIST or death due to any cause, whichever occurs first. Participant who are alive and not progressed will be censored on the date of last tumor assessment prior to or on first subsequent therapy date. The distribution of PFS in randomized arms will be compared via a 2-sided, log-rank test stratified by the stratification factors. The HR and corresponding 100×(1-adjusted alpha)% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The PFS curves for each arm will be estimated using the Kaplan-Meier produce limit method. The 2-sided 95% CIs for median PFS will be computed by Brookmeyer and Crowley method (using log-log transformation). Hierarchical testing of PFS will be performed upon demonstration of superiority in TTTP and EFS. Descriptive analysis will be performed if superiority is not demonstrated in TTTP and EFS.
Exploratory	
All exploratory endpoints	The exploratory endpoints and their analyses will be described in the SAP finalized prior to database lock.

Abbreviations: BICR = blinded independent central review; CI = confidence interval; EFS = event-free survival; EHS = extrahepatic spread; HCC = hepatocellular carcinoma; HR = hazard ratio; mRECIST = modified Response Evaluation Criteria in Solid Tumors; MVI = macrovascular invasion; OS = overall survival; PFS = progression-free survival; SAP = statistical analysis plan; TACE = trans-arterial chemoembolization; TTTP = time to TACE progression.

10.3.2 Safety Analyses

Safety analyses will be described in the SAP finalized before the first database lock.

10.3.3 Other Analyses

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

PK, pharmacodynamic, biomarker, IMG, and outcomes research exploratory analyses will be described in the SAP finalized before the first database lock.

10.3.4 Interim Analyses

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Two interim analyses and 1 final analysis of OS are planned for this study. The first interim analysis of OS is planned at the time of final TTTP analysis (with approximately 267 OS events expected in Arm A and Arm C). TTTP final analysis is expected to occur when there are 418 events (approximately 55 months after the first participant's randomization date) in Arm A and Arm C. First OS interim analysis will be conducted at the same time (with approximately 267 OS events expected in Arm A and Arm C). The second OS interim analysis is expected to occur when there are 326 OS events in Arm A and Arm C (approximately 68 months after the first participant's randomization date). These formal comparisons of OS will allow for early stopping for superiority. Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary will be used. The stopping boundary will depend on the actual number of deaths at the time of the interim analyses. An independent statistical group supporting the DMC, external to BMS, will perform the analyses. Formal interim analyses for OS and final analysis for TTTP in Arm B and Arm C will be performed at the same time of TTTP and OS analysis in Arm A and Arm C. EFS and PFS analysis will also be conducted at the TTTP final analysis if TTTP is superior in both Arm A and Arm B.

The SAP will further describe the planned interim analyses.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
°C	degrees Celsius
µL	microliter
+	positive
1L	first line
2L	second line
AASLD	American Association for the Study of Liver Diseases
AC	anthracycline + cyclophosphamide
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AFP	alpha-fetoprotein
ALBI	albumin-bilirubin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APASL	Asian Pacific Association for the Study of the Liver
AR	additional research
AST	aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
Bcl-xL	B-cell lymphoma-extra large
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BMU7	Beyond Milan and Up-to-7
BOR	best overall response
BP	blood pressure
BSC	best supportive care
BTLA	B- and T-lymphocyte attenuator
BUN	blood urea nitrogen
C	cycle
Cavgss	steady-state average concentration

Term	Definition
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
cm	centimeter
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTAg	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
ctl	control
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
CV	coefficient of variation
CXCL	C-X-C motif chemokine ligand
D	day
DAA	direct-acting antiviral
DCR	disease control rate
DEB-TACE	trans-arterial chemoembolization with drug-eluding beads
DFS	disease-free survival
DILI	drug-induced liver injury

Term	Definition
dL	deciliter
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
E-R	exposure-response
EASL	European Association for the Study of the Liver
EC	ethics committee
EC50	half-maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EHR	electronic health record
EHS	extrahepatic spreading
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMR	electronic medical record
EOI	end of infusion
EOT	end of treatment
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ESMO-ESDO	European Society for Medical Oncology and the European Society of Digestive Oncology
etc	et cetera
EU	Europe
EWB	emotional well-being
FACT-Hep	Functional Assessment of Cancer Therapy-Hepatobiliary

Term	Definition
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FHSI	FACT Hepatobiliary-Pancreatic Symptom Index
FSH	follicle-stimulating hormone
FU1	follow-up visit 1
FU2	follow-up visit 2
FWB	functional well-being
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H&E	hematoxylin and eosin
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCRU	healthcare resource utilization
HCS	hepatobiliary cancer subscale
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
Hep B	hepatitis B
Hep C	hepatitis C
Hep D	hepatitis D
HIV	human immunodeficiency virus
hr	hour
HR	hazard ratio
HRQL	health-related quality of life
HuMab	human monoclonal antibody
IB	Investigator's Brochure
IC50	half-maximal inhibitory concentration

Term	Definition
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICOS	inducible T cell co-stimulator
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	interferon
IFN-γ	interferon-gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMAE	immune-mediated adverse event
IMG	immunogenicity
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IO	immuno-oncologic
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
IU	international unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	interactive voice response system
kg	kilogram
L	liter
LAG3	lymphocyte activating 3
LAM	lactation amenorrhea method
LDH	lactate dehydrogenase

Term	Definition
LFT	liver function test
LSEC	liver sinusoidal endothelial cell
m	month
m^2	meters squared
MD	medical doctor
MDSC	myeloid-derived suppressor cell
mg	milligram
MHC	major histocompatibility complex
MID	minimally important difference
min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
MMR	measles, mumps, rubella
mOS	median overall survival
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI	microsatellite instability
MTD	maximum tolerated dose
MVI	macrovascular invasion
MWA	microwave ablation
mWHO	modified World Health Organization
N	number of subjects or observations
N0	no regional lymph node metastasis
NA	not applicable
NCCN	National Cancer Care Network
NCI	National Cancer Institute
nM	nanomolar
NSCLC	non-small cell lung cancer

Term	Definition
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death-1
PD-1+	programmed cell death-1-positive
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PE	physical examination
PES	post-embolization syndrome
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival 2
PK	pharmacokinetic
PLC	primary liver cancer
PPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	prothrombin time
PWB	physical well-being
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
Q12W	every 12 weeks
qHBeAg	qualitative and quantitative hepatitis B e-antigen
qHBsAg	qualitative and quantitative hepatitis B surface antigen
QoL	quality of life

Term	Definition
R&D	research and development
RCC	renal cell carcinoma
RCT	randomized clinical trial
RECICL	Response Evaluation Criteria in Cancer of the Liver
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
RFS	relapse-free survival
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SLD	sum of longest diameters
SOC	standard of care
SOP	standard operating procedures
SUSAR	suspected, unexpected serious adverse reaction
SWB	social/family well-being
t1/2	half-life
TACE	trans-arterial chemoembolization
TAE	trans-arterial embolization
TM	trademark
Treg	T regulatory cell
TSH	thyroid-stimulating hormone
TTP	time to progression
TTDP	time to disease progression
TTTP	time to TACE progression
TTUP	time to unTACEable progression

Term	Definition
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VAS	visual analog scale
VI	vascular invasion
VP0	no portal vein thrombosis
vs	versus
Vss	mean volume of distribution at steady state
Vv0	no vascular invasion
WBC	white blood cell
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
Y90	radioactive isotope yttrium

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will

be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

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

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

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

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

RECORDS RETENTION

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

investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

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

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

RETURN OF STUDY TREATMENT

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The

method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.

- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

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

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

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

SCIENTIFIC PUBLICATIONS

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

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (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; 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 9.2.8 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.6 for reporting pregnancies).

EVALUATING AES AND SAES

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

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

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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 post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

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

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

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

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

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

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the 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

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*

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

Highly Effective Contraceptive Methods That Are User Dependent *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 (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b]
- Intrauterine device (IUD)[c]
- Intrauterine hormone-releasing system (IUS) (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b,c]
- Bilateral tubal occlusion

- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to: calendar, symptothermal, 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 participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. 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] Intrauterine devices and 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 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, post-ovulation methods) • Withdrawal(coitus interruptus) • Spermicide only • Lactation amenorrhea method (LAM)

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

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of study treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.6 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[a]	
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, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

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

APPENDIX 6 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

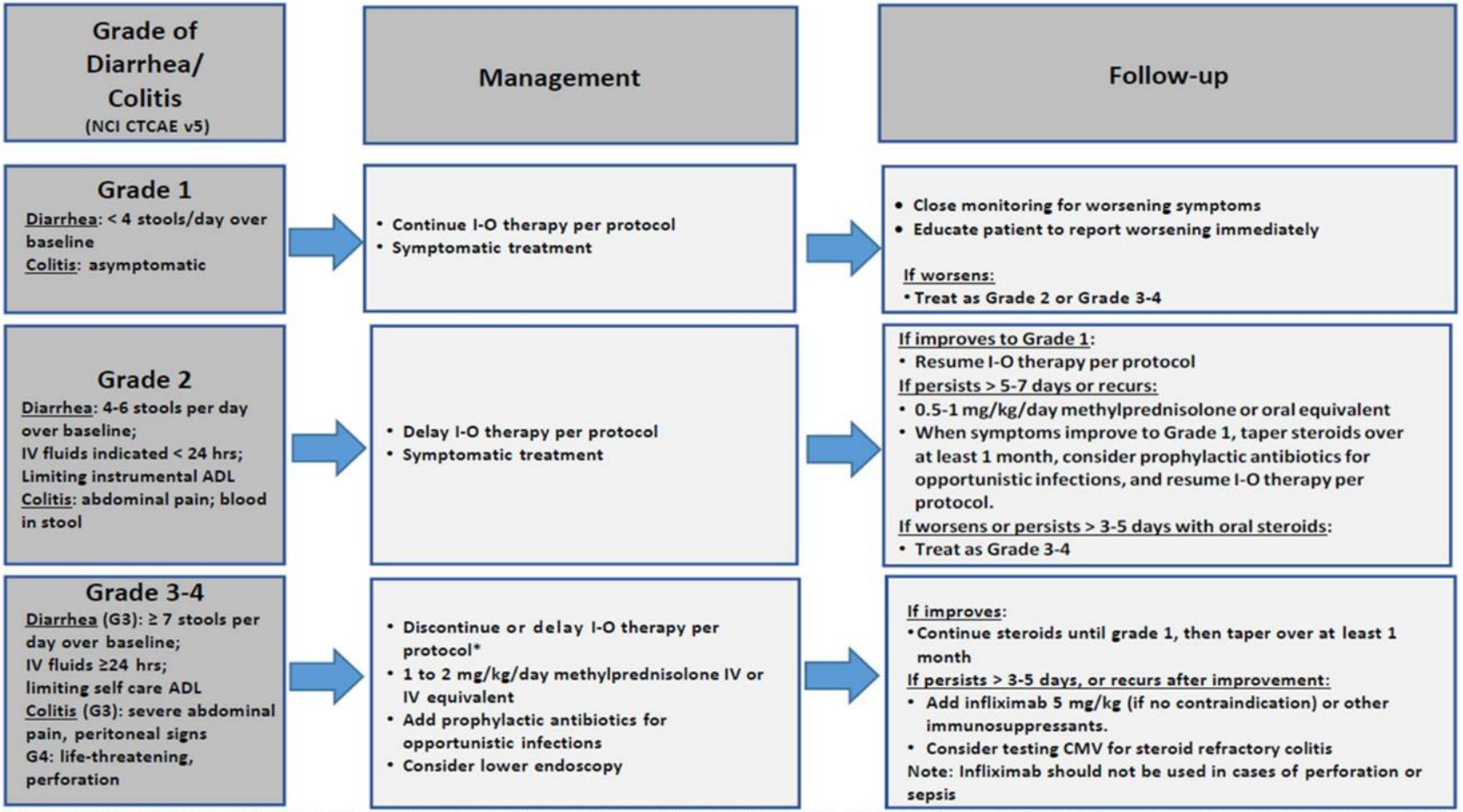
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



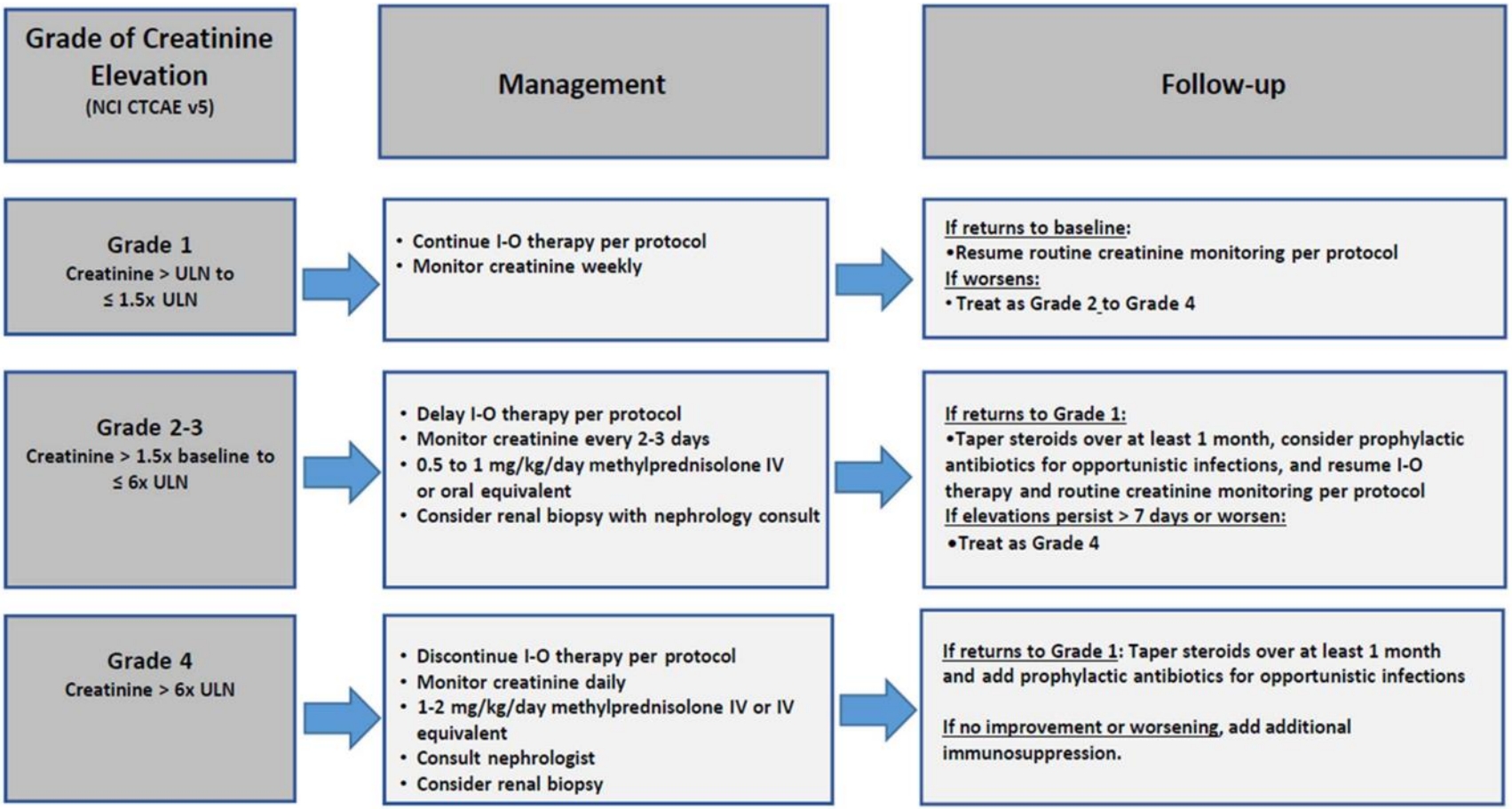
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

02-Jul-2021

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

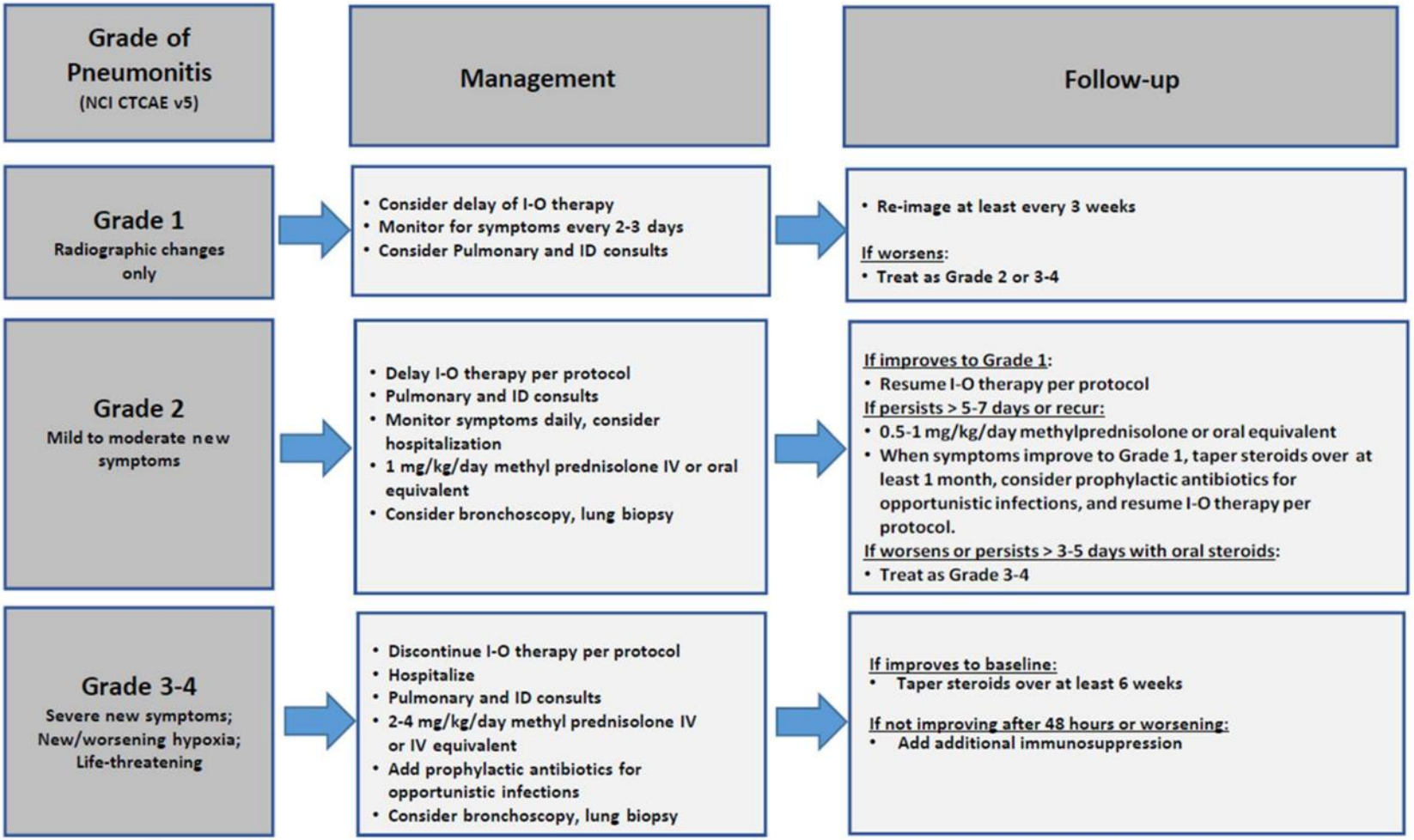


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

02-Jul-2021

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



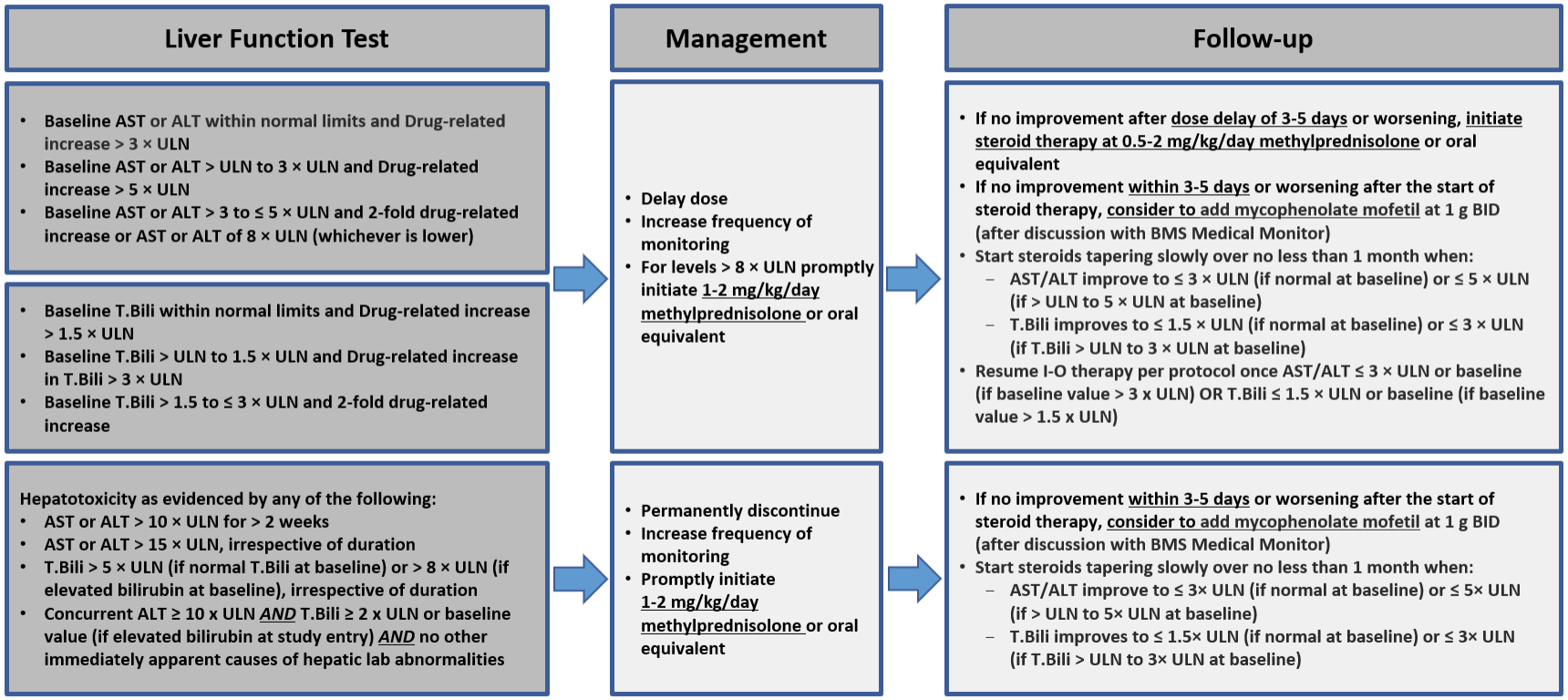
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

02-Jul-2021

Hepatic Adverse Event Management

(For HCC Studies Only)

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



For all participants initiating steroids, consult the BMS Medical Monitor within 24 hours after initiation of steroids, and gastroenterology consult is recommended.

14-Jun-2021

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

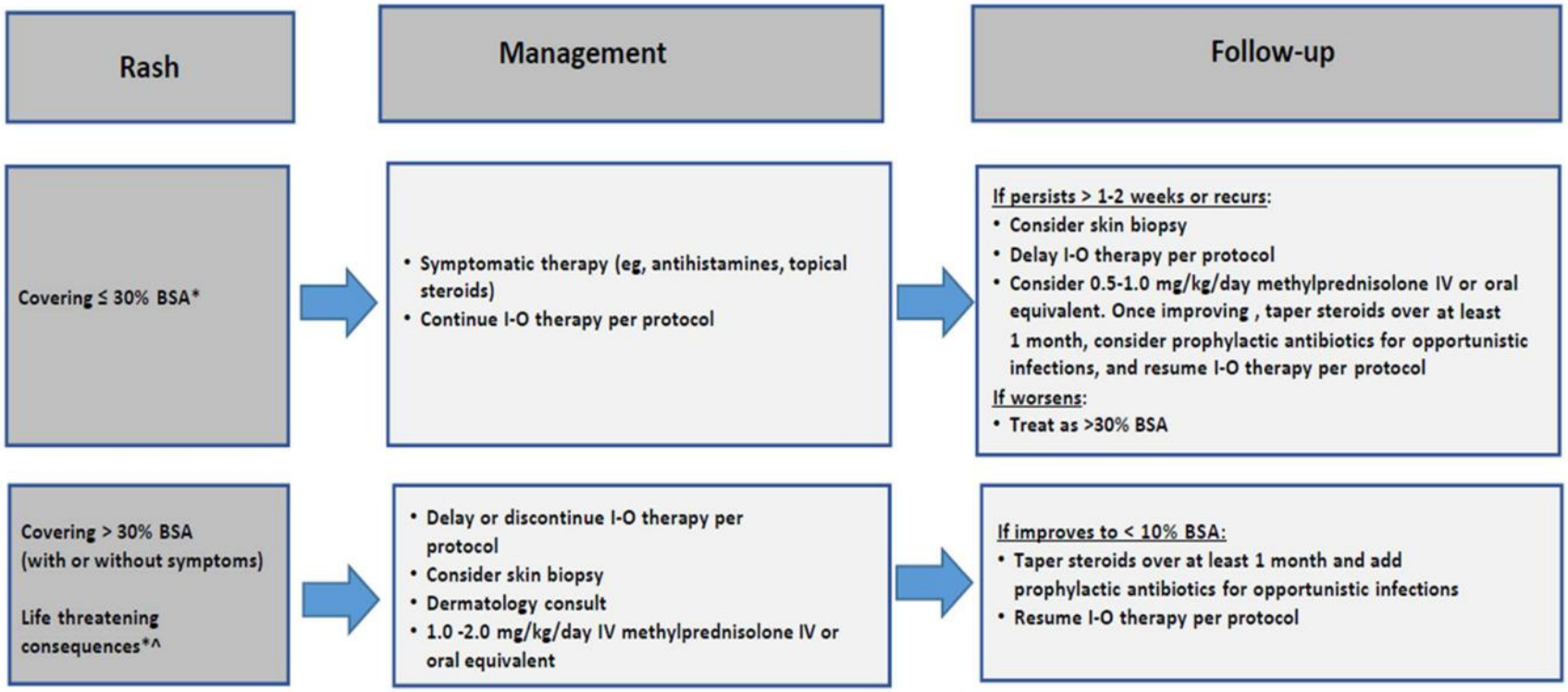
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: ○ include fT4 at subsequent cycles as clinically indicated; ○ consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

02-Jul-2021

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

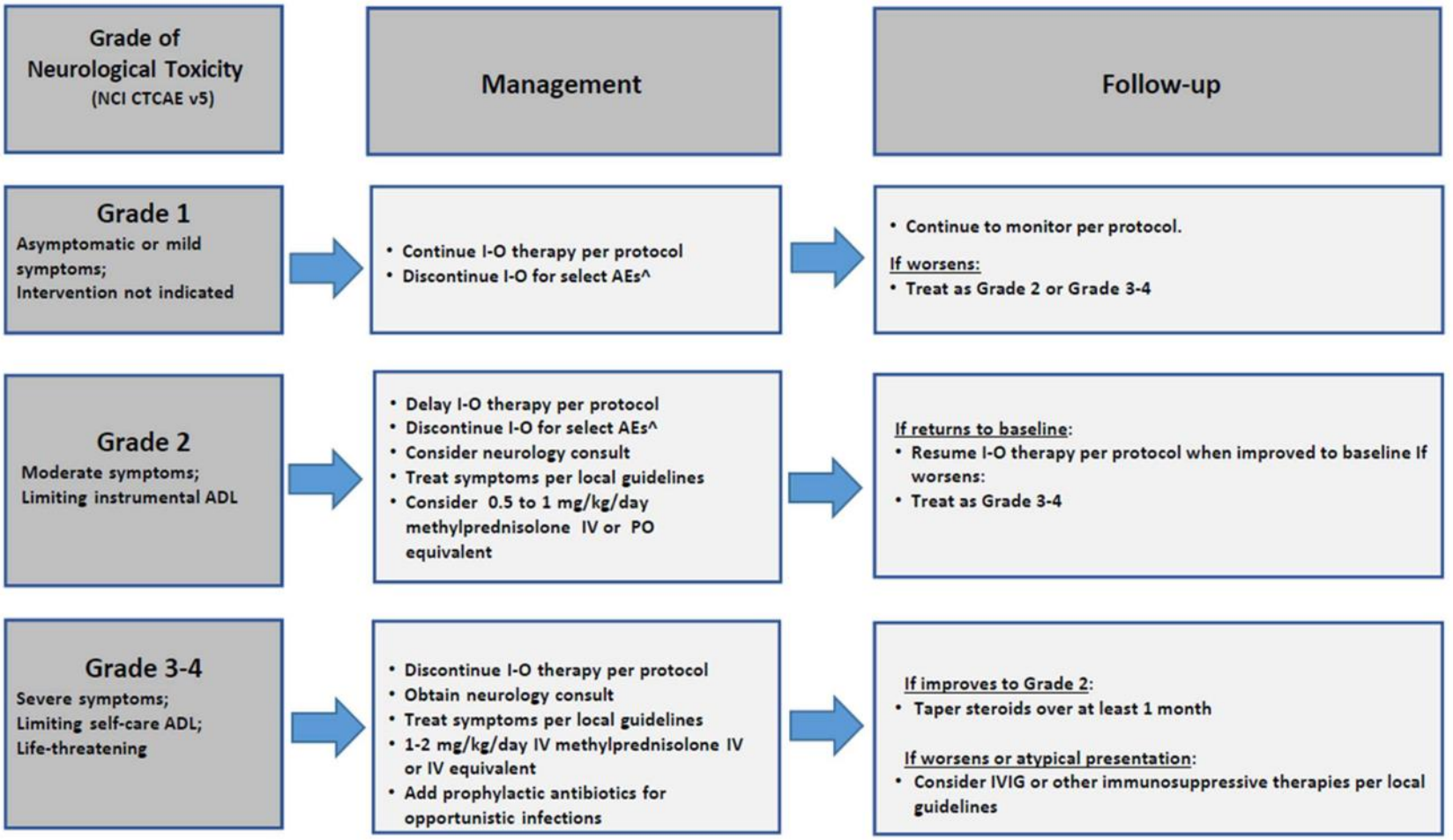
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

02-Jul-2021

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



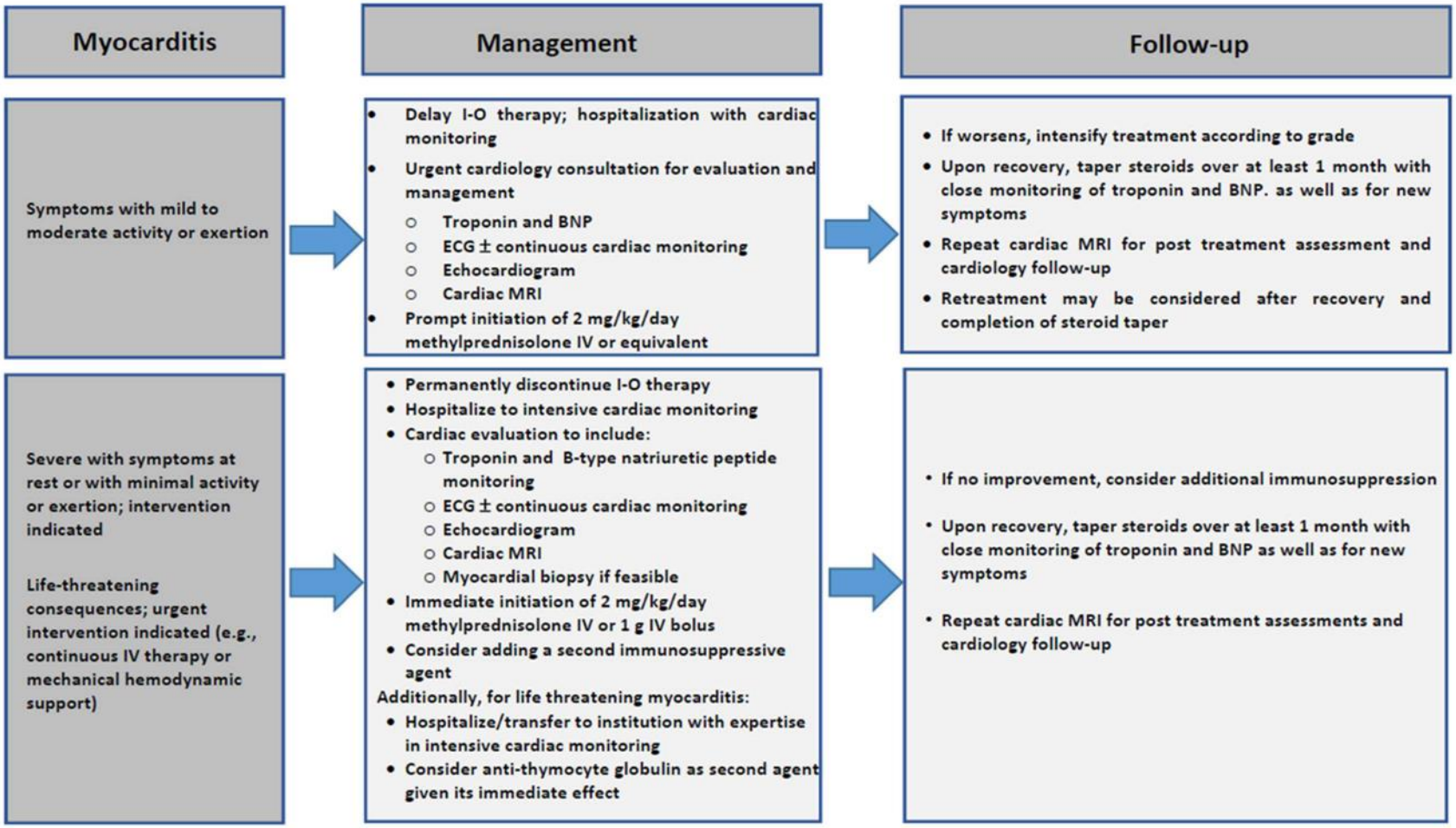
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

02-Jul-2021

Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

02-Jul-2021

APPENDIX 7 BEYOND MILAN AND UP-TO-7 CRITERIA

Up-to-7 Criteria	7 being the result of the sum of size (in cm) and number of tumors for any given hepatocellular carcinoma. For example: 1 nodule up to 6 cm in size (1 + 6 = 7) to many tumors fulfilling 7 as the sum of the size of the largest lesion plus the number (ie, 2 tumors up to 5 cm in size, 3 tumors up to 4 cm in size, 4 tumors up to 3 cm in size, and 5 tumors up to 2 cm in size). Liver lesions must have an arterially enhancing lesion measuring at least 10 mm in size to be counted as a tumor.

APPENDIX 8 CHILD-PUGH SCORE

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

Scoring

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

Encephalopathy Grading

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

APPENDIX 9 COUNTRY-SPECIFIC REQUIREMENTS

Criteria for exclusion of HIV-positive participants in Argentina, Czech Republic, Germany, Italy, Spain, and any other countries where exclusion of HIV-positive participants is locally mandated.

Protocol Section	Current Protocol Text	Revised Protocol Text
Table 2-1: Screening Procedural Outline (CA20974W)	**Testing for HIV** (when required by local regulations [refer to Appendix 9]) must be done at local laboratory within 28 days prior to randomization.	**Testing for HIV** must be done at local laboratory within 28 days prior to randomization.
Section 6.2: Exclusion Criteria, 1) Medical Conditions, g) Infections ii)	Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally (refer to Appendix 9).	Positive test for HIV.
Table 9.4.4-1: Clinical Safety Laboratory Assessments	Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.	Testing for HIV-1 and HIV-2 must be performed.

Criteria for discontinuation of treatment due to pregnancy in the Czech Republic and any other countries where discontinuation of pregnancy participants is locally mandated.

Protocol Section	Current Protocol Text	Revised Protocol Text
Section 8.1: Discontinuation from Study Treatment	Pregnancy, if locally mandated (see Appendix 9 for country-specific requirements).	Pregnancy
Section 9.2.6 Pregnancy	If the Investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the Investigator and the BMS Medical Monitor/Clinical Scientist must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/Sponsor/IRB/EC, as applicable. Study treatment must be permanently discontinued where locally mandated; see Appendix 9 for country-specific requirements.	Remove this text

Criteria for collection and analyses of biomarker samples [redacted] and any other countries where applicable.

Protocol Section	Current Protocol Text	Revised Protocol Text
Section 2 Schedule of Activities, Table 2-1 Screening Procedural Outline (CA20974W), Tumor Sample Submission notes	An FFPE tissue block (preferred) or a minimum of 20 unstained slides of tumor tissue obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen prior to randomization (within 3 months of enrollment with no intervening systemic anticancer treatment between time of acquisition and randomization, or archival tissue [if above is not available]) must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable. 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 the BMS Medical Monitor or Clinical Scientist. Please see Appendix 9 for country-specific criteria for the collection of tumor tissue samples in China.	An FFPE tissue block (preferred) or a minimum of 5 unstained slides of tumor tissue obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen prior to randomization (within 3 months of enrollment with no intervening systemic anticancer treatment between time of acquisition and randomization, or archival tissue [if above is not available]) must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable.
Section 2 Schedule of Activities, Table 2-2 On-treatment Procedural Outline (CA20974W) and Table 2-3 Follow-up Procedural Outline (CA20974W)	Table 2.2 Biomarker Assessments, including procedures for Serum Biomarkers, Whole Blood DNA and RNA, MDSC, Plasma (ctDNA); Stool Samples for Microbiome Analysis; Collection of Tumor Upon TTTP or EOT; and SARS-CoV-2 serology Table 2-3 Biomarker Assessments	Remove Biomarker Assessments from table.
Section 4 Objectives and Endpoints	**Removed in Protocol Amendment 01** Objective: To analyze biomarkers in tumor, peripheral blood, and stool to evaluate association with clinical efficacy and/or incidence of AEs in all randomized participants. Endpoint: Correlation of selected biomarkers with efficacy (TTTP, OS, EFS, PFS) and safety (incidence of AEs) endpoints.	Objective: To analyze PD-L1 to evaluate association with clinical efficacy in all randomized participants. Endpoint: Correlation of PD-L1 with efficacy (TTTP, OS, EFS, PFS) endpoints.
Section 4 Objectives and Endpoints	**Removed in Protocol Amendment 01** Objective: To investigate the association between tumor inflammation and clinical efficacy measures, including OS, in all randomized participants. Endpoint: Correlation of inflammatory biomarkers with efficacy (TTTP, OS, EFS, PFS) endpoints	Remove objective and endpoint.
Section 5.1.1 Screening Period	Sufficient, recent tumor tissue obtained within 3 months prior to randomization from a lesion from an unresectable primary tumor lesion that	Sufficient, recent tumor tissue obtained within 3 months prior to randomization from a lesion from an

Protocol Section	Current Protocol Text	Revised Protocol Text
	has not been previously irradiated (formalin fixed, paraffin-embedded [FFPE] block or minimum of 20 slides, obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen) will be submitted to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable. 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. The central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Participants should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained. Please see Appendix 9 for country-specific criteria for the collection of tumor tissue samples in China.	unresectable primary tumor lesion that has not been previously irradiated (formalin-fixed, paraffin-embedded [FFPE] block or minimum of 5 slides, obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen) will be submitted to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable. The central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Participants should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained.
Section 5.1.2 Treatment Period	Biomarker sample collection will be done according to the schedule in Table 9.8-1. Please see Appendix 9 for country-specific criteria for the collection of biomarker samples [redacted].	Remove this text.
Section 6.1 Inclusion Criteria – 2, c, ii)	Either a FFPE tissue block (preferred) or a minimum of 20 unstained slides of tumor tissue sections obtained within 3 months prior to randomization or archived (if above is not available) with an associated pathology report must be submitted to the central laboratory for inclusion. The central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration or other cytology samples are unacceptable for submission. 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 Appendix 9 for country-specific criteria for the collection of tumor tissue samples in China.	Either a FFPE tissue block (preferred) or a minimum of 5 unstained slides of tumor tissue sections obtained within 3 months prior to randomization or archived (if above is not available) with an associated pathology report must be submitted to the central laboratory for inclusion. The central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration or other cytology samples are unacceptable for submission.

Protocol Section	Current Protocol Text	Revised Protocol Text
Section 9.5 Pharmacokinetics and Immunogenicity	In addition, selected serum samples may be analyzed by exploratory methods that measure nivolumab or ipilimumab, or detect ADAs for technology exploration purposes; exploratory results will not be reported. The corresponding serum samples designated for either PK, IMG, or biomarker assessments may also be used for any of those analyses, if required (eg, insufficient sample volume to complete testing or to follow up on suspected IMG-related AE). Please see Appendix 9 for country-specific criteria for the collection and analyses of biomarker samples [redacted].	In addition, selected serum samples may be analyzed by exploratory methods that measure nivolumab or ipilimumab, or detected ADAs for technology exploration purposes; exploratory results will not be reported. The corresponding serum samples designated for either PK or IMG may also be used for any of those analyses, if required (eg, insufficient sample volume to complete testing or to follow-up on suspected IMG-related AE).
Section 9.6 Pharmacodyamics	Not applicable per Protocol Amendment 01. The following information refers to the original study design. Pharmacodynamic parameters will be evaluated in this study. Systemic immune monitoring of MDSCs, cytokines/chemokines, and other related soluble factors to investigate the immunomodulatory properties of nivolumab, ipilimumab, and TACE will be assessed. See Section 9.8 (Biomarkers) for a detailed description of the analyses and Table 9.8-1 for the sample collection schedule. Please see Appendix 9 for country-specific criteria for the collection and analyses of samples in China.	Not applicable.
Section 9.8 Biomarkers	**Not applicable per Protocol Amendment 01. The following information refers to the original study design.** A variety of factors that could potentially predict clinical response to nivolumab, ipilimumab, and/or TACE will be investigated in tumor specimens, peripheral blood, and stool taken from all participants as described below. Data from these investigations will be evaluated for association with efficacy endpoints. In addition, analyses of markers in all 3 treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs prognostic value. A detailed description of each biomarker analysis is described below and a schedule of biomarker sample collections is provided in Table 9.8-1. Tumor tissue, peripheral blood, and a stool sample will be collected prior to therapy. Peripheral blood samples and a stool sample will also be collected at selected timepoints on-treatment. If a biopsy or surgical resection is performed at the time of TTTP by BICR or end of treatment, tumor sample (block or slides)	Remove text and table. Leave Level 2 header.

Protocol Section	Current Protocol Text	Revised Protocol Text
	should also be submitted for analysis. If biomarker samples are drawn but study treatment(s) are not administered, samples will be retained. Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Procedure Manual at the time of study initiation. Please see Appendix 9 for country-specific criteria for the collection and analyses of samples in China. Table 9.8-1: CA20974W Biomarker Sampling Schedule All Participants.	
Section 9.8.1 Tumor-based Biomarker Measures	9.8.1 Tumor-based Biomarker Measures **Not applicable per Protocol Amendment 01. The following information refers to the original study design.** Tumor tissue will be obtained at baseline and upon TTTP by BICR or end of treatment (if clinically feasible) to characterize immune cell populations, expression of selected tumor markers, expression of inflammatory genes, and genetic analyses mentioned below in detail. Tumor block (preferred) or slides must be sent to the central laboratory prior to randomization. Biopsy samples should be excisional, incisional, or core needle. Fine needle aspirates or other cytology samples are not acceptable. A tumor block is preferred, but if a block is not feasible, a minimum of 20 unstained slides is required. Slides should be unstained, have a recommended tissue section thickness of 4 microns, and must be positively charged. Tumor tissue must contain adequate tumor content (≥ 100 tumor cells), as determined by hematoxylin and eosin (H&E) review at the central laboratory. If the initial tumor sample submission does not meet this criterion, an additional tissue submission (if available) is allowed. Participants must have an evaluable tumor tissue specimen to be eligible for randomization. A tumor biopsy upon TTTP by BICR or end of treatment is also highly recommended, if clinically feasible. Tumor samples may be used for the assessments described below. Please see Appendix 9 for country-specific criteria for the collection and analyses of tumor-tissue samples in China.	9.8.1 Tumor for PD-L1 Analysis Tumor tissue will be obtained at baseline to assess PD-L1. Tumor block (preferred) or slides must be sent to the central laboratory prior to randomization. Biopsy samples should be excisional, incisional, or core needle. Fine needle aspirates or other cytology samples are not acceptable. A tumor block is preferred, but if a block is not feasible, a minimum of 5 unstained slides is required. Slides should be unstained, have a recommended tissue section thickness of 4 microns, and must be positively charged. Tumor tissue must contain adequate tumor content (≥ 100 tumor cells), as determined by hematoxylin and eosin (H&E) review at the central laboratory. If the initial tumor sample submission does not meet this criteria, an additional tissue submission (if available) is allowed. Participants must have an evaluable tumor tissue specimen to be eligible for randomization.

Protocol Section	Current Protocol Text	Revised Protocol Text
Section 9.8.1.1 Characterization of Tumor Infiltrating Lymphocytes and Tumor Antigens	**Not applicable per Protocol Amendment 01. The following information refers to the original study design.** Immunohistochemistry (IHC) may be used to assess tumor markers as well as the number and composition of immune infiltrates in order to define the immune cell subsets present within FFPE tumor tissue before therapy and upon TTTP by BICR or end of treatment. IHC analyses may include, but not necessarily be limited to, the following markers: major histocompatibility complex (MHC) class I/II, CD8, PD-1, PD-L1, PD-L2, and lymphocyte activating 3 (LAG3).	Remove section.
Section 9.8.1.2 Tumor Genomic Analysis Including Tumor Mutational Burden and Gene Expression Analysis	**Not applicable per Protocol Amendment 01. The following information refers to the original study design.** DNA from tumor samples will be analyzed using platforms, including, but not limited to, whole-exome sequencing to identify and quantify somatic mutations by using the whole blood DNA sample as a germline reference. Mutations that are detected may be analyzed for their ability to bind the MHC class I and MHC class II proteins using prediction algorithms. Evaluating the ability of tumor mutations to bind MHC molecules may provide evidence that these mutations are serving as antigens that are recognized by the immune system and are potential rejection antigens. MSI or MSI status may be derived from whole-exome sequencing data if MSI status is not already known. Lastly, RNA expression within tumor biopsies may be examined using RNAseq, whole-transcriptome sequencing, or other next-generation sequencing technologies to detect expression of all genes.	Remove section.
Section 9.8.2 Peripheral Biomarkers	Heading only	Remove section
Section 9.8.2.1 Myeloid-derived Suppressor Cells	**Not applicable per Protocol Amendment 01. The following information refers to the original study design.** MDSCs are an immune cell population capable of suppressing T cell activation and proliferation. MDSCs will be measured prior to dosing on Cycle 1 Day 1, on-treatment, and upon TTTP by BICR or end of treatment to assess pharmacodynamic changes as well as associations with outcome.	Remove section.

Protocol Section	Current Protocol Text	Revised Protocol Text
Section 9.8.2.2 Soluble Biomarkers and Other Assessments in Serum	**Not applicable per Protocol Amendment 01. The following information refers to the original study design.** Serum will be collected prior to dosing on Cycle 1 Day 1, on-treatment, and upon TTTP by BICR or end of treatment to measure levels of cytokines, chemokines, other immune mediators, and extracellular matrix fragments. These factors will be assessed by techniques that may include, but are not limited to, enzyme-linked immunosorbent assay (ELISA) or multiplex assays. Analyses may include, but are not limited to, IFN-γ, C-X-C motif chemokine ligand (CXCL) 9, CXCL10, soluble PD-L1, collagen, and other extracellular matrix fragments. These analyses may identify potential biomarkers with prognostic and predictive value for outcomes.	Remove section.
Section 9.8.2.3 Genomic Analysis of Circulating Tumor DNA in Plasma	**Not applicable per Protocol Amendment 01. The following information refers to the original study design.** Plasma will be collected prior to dosing on Cycle 1 Day 1, on-treatment, and upon TTTP by BICR or end of treatment to enable genomic analysis of circulating tumor DNA (ctDNA).	Remove section.
Section 9.8.2.4 Whole Blood DNA and RNA Analyses	**Not applicable per Protocol Amendment 01. The following information refers to the original study design.** DNA in the whole blood samples may be used to examine germline (predisposing) characteristics as well as to help identify genetic information specific to the participant's tumor, such as somatic DNA alterations. RNA in the whole blood sample may be used to assess the expression of genes associated with inflammation. These blood samples will be obtained prior to dosing on Cycle 1 Day 1 (whole blood DNA and whole blood RNA) and on-treatment (whole blood RNA only) unless restricted by local requirements.	Remove section.
Section 9.8.2.5 Viral Safety Biomarkers	At screening, HBV DNA, qualitative and quantitative hepatitis B surface antigen (qHBsAg), hepatitis B e-antigen (qHBeAg), hepatitis B surface antibody (HBsAb), HCV RNA, HCV antibody, and hepatitis D antibody (if chronic HBV infection) samples will be collected for all participants. On-treatment and during follow-up visits FU1 and FU2, HBV DNA will only be collected for HBV chronic-infected participants, and HCV RNA will only be collected for HCV chronic-infected	Move to become a subsection of Section 9.4.

Protocol Section	Current Protocol Text	Revised Protocol Text
	participants. Details regarding sample collection timepoints can be found in Section 2 (Schedule of Activities). These analyses will be performed at the central laboratory. Results of HBV DNA and HCV RNA will be provided to sites for management of virologic breakthrough (see Section 7.7.3.1 [Antiviral Therapy]).	
Section 9.8.3 Microbiome Analysis	**Not applicable per Protocol Amendment 01. The following information refers to the original study design.** An optional stool sample will be collected prior to dosing and while on-treatment to assess microbiome diversity and composition, unless restricted by local requirements.	Remove section.
Section 9.8.4 Additional Research Collection	Residual PK/IMG, tumor tissue, and serum, plasma, whole blood, and stool samples from collections (see Table 9.8.4-1 [Residual Sample Retention for Additional Research Schedule]) will also be retained for AR purposes.	Residual PK/IMG and tumor tissue (see Table 9.8.4-1 [Residual Sample Retention for Additional Research Schedule]) will also be retained for AR purposes.”

APPENDIX 10 RESPONSE EVALUATION CRITERIA MODIFIED FOR HEPATOCELLULAR CARCINOMA (mRECIST) WITH BMS ADAPTATIONS

1 EVALUATION OF LESIONS

In this protocol, the response criteria modified for the assessment of HCC (mRECIST), published in the Journal of the National Cancer Institute (JNCI 2010) will be applied. This modified RECIST for HCC criteria is based on RECIST v1.1 but introduces the concept of the longest diameter of the viable tumor tissue for "typical" intrahepatic HCC lesions. Intrahepatic lesions are considered "typical" if they display hypervascularity in the arterial phase and a wash-out in the portal or late venous phase in dynamic contrast-enhanced CT or MRI. Differentiating between viable vs necrotic liver tumor tissue may allow a more accurate representation of anti-cancer treatment effects. In the context of this protocol, these criteria will be termed 'Modified RECIST for HCC (mRECIST)'. At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

2 MEASURABLE

Liver lesions: Must be well-delineated, arterially enhancing lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- contrast enhancement at least 10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm).

Extrahepatic 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 × 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.

3 NON-MEASURABLE

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm, liver lesions with atypical enhancement, 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.

3.1 Special considerations regarding lesion measurability

3.1.1 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.

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

The selection of target lesions will be initially guided by the presence of 'typical' intrahepatic lesions.

'Typical' intrahepatic lesions MUST meet the following criteria:

- Lesions can be classified as measurable lesion
- Lesions are suitable for repeated measurements
- Lesion shows typical vascular pattern of HCC in contrast-enhanced spiral CT or MRI studies, defined as:
  - Well delineated intrahepatic lesions
  - Hypervascularity in the arterial phase
  - Contrast agent wash-out in the portal and late venous phase

Measurable lesions in the liver meeting the criteria for 'typical' target lesions present at baseline, should be chosen as the sole intrahepatic target lesions. Up to five 'typical' intrahepatic lesions will be selected as target lesions. Measurement of the longest viable diameter, which is the longest diameter of the viable tumor lesion, will be applied to these lesions.

HCC lesions that show local recurrence and/or residual disease after loco-regional therapy and have typical hypervascular patterns of HCC can be selected as target lesions. All other 'atypical' intrahepatic lesions will NOT be considered as target lesions.

If measurable extrahepatic lesions are present in addition to the 'typical' intrahepatic lesions at baseline, up to five lesions (and a maximum of two lesions per organ), representative of all involved organs, will be identified as target lesions.

Note: Outside of the liver, 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.

All measurable intrahepatic lesions (up to a maximum of five lesions) and extrahepatic lesions (up to five lesions and a maximum of two lesions per organ) should be identified as target lesions to be measured and recorded at baseline. 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, up to ten total, 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. Non-target lesions may include:

Intrahepatic lesions:

- Poorly delineated HCC lesions including infiltrative-type and diffuse HCC
- HCC lesions with atypical contrast-agent enhancement patterns
- HCC lesions showing local recurrence after previous loco-regional treatment without meeting the criteria for 'viable' lesions (ie, lack of clear-cut hypervascular recurrence and/or well-delineation from the surrounding liver tissue)
- Portal vein tumor invasion and/or thrombosis
- Intrahepatic viable lesions in excess to the 5 lesions in the liver selected as target lesions

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').

5 RESPONSE CRITERIA

5.1 Evaluation of Target Lesions

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

5.1.1 Special Notes on the Assessment of Target Lesions

5.1.1.1 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.

5.1.1.2 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.

5.1.1.3 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'.

5.2 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):** For typical intrahepatic non-target lesions, complete disappearance of any intratumoral contrast-agent enhancement in the arterial phase of CT or MRI. For atypical intra- and extrahepatic non-target lesions, complete disappearance of all 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.

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

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

5.2.1.1 When the Participant 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.

5.2.1.2 When the Participant has Only Non-measurable Disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

5.2.2 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.

New hepatic lesion with the longest diameter of at least 10 mm with the vascular pattern characteristic for HCC (ie, hypervascularization) in the arterial phase with wash-out in the portal venous (or late venous) phase of contrast-enhanced CT or MRI imaging denotes disease progression.

New hepatic lesions larger than 10 mm without the vascular pattern characteristic for HCC but evidence of growth of at least 10 mm in subsequent scans will also denote disease progression.

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 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. [redacted]

5.3 Response Assessment

5.3.1 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.

5.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 5.3.2-1 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 5.3.2-2 is to be used.

Table 5.3.2-1: Time Point Response

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

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 5.3.2-2: Time Point Response

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

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease.

[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.

5.3.3 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 5.3.3-1. 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 5.3.3-1: 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

Table 5.3.3-1: Best Overall Response (Confirmation of CR and PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	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

Abbreviations: CR = complete response NE = inevaluable, PD = progressive disease; PR = partial response; SD = stable disease.

[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.

5.3.4 Confirmation Scans

[redacted]

Verification of Progression: [redacted]

6 REFERENCES

[1] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30(1):52-60.

APPENDIX 11 FRANCE-SPECIFIC GENERAL GUIDANCE FOR TRANS-ARTERIAL CHEMO-EMBOLIZATION

1 PURPOSE

This guidance provides information regarding the Trans-arterial Chemo-Embolization (TACE) procedure and is based on TACE procedure commonalities worldwide. For CA20974W, it is required that the same procedure technique, chemotherapy agent(s), and embolizing agent are used for each patient enrolled in this study.

2 PROCEDURE

TACE will be performed following a standard procedure in each investigational site. The same chemotherapy agent(s) must be used for all TACE procedures on a patient.

The general recommendation of TACE procedures are as follows:

1) Confirm tumor enhancement and feeding artery by abdominal angiography.
2) Insert a catheter into the feeding artery of the HCC, which is technically accessible, as close to the lesion as possible.
3) EITHER
   a) Inject the emulsion of the anticancer agent(s) with lipiodol or another contrast agent. Drugs that may be considered include doxorubicin, epirubicin, idarubicin, oxaliplatin, cisplatin and mitomycin (see Table 2-1).
4) Embolize the feeding artery with an embolization agent (eg, gelatin sponge), and complete the therapy.

OR

   a) Inject Drug Eluting Beads (DEB). Only DEBs with single-agent chemotherapy, are allowed. The use of DEBs must be in accordance with the registered indication (see Table 2-2).
5) The end of TACE procedure is the cessation of arterial blood flow to the tumor.

Table 2-1: Dose Ranges in Conventional TACE (per session)

Drug	Dose Range Per Session
Doxorubicin	30 - 150 mg
Idarubicin	5 - 20 mg
Epirubicin	30 - 60 mg
Mitomycin	5 - 20 mg
Cisplatin	30 - 100 mg
Oxaliplatin	50 - 100 mg

Table 2-2: Dose Ranges in DEB-TACE (per session)

Drug	Dose Range per Session
Doxorubicin	30 - 150 mg