Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study official title	A Phase 1/2, Safety Lead-in and Dose Expansion, Open-label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Activity of Ivosidenib in Combination with Nivolumab and Ipilimumab in Previously Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation
Study brief title	Ivosidenib, Nivolumab, and Ipilimumab Combination in Previously Treated Subjects with Nonresectable or Metastatic IDH1-Mutant Cholangiocarcinoma
Study public title	A Phase 1/2, Safety Lead-in and Dose Expansion, Open-label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Activity of Ivosidenib in Combination with Nivolumab and Ipilimumab in Previously Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation
Test drug code	S95031 (formerly identified as AG-120)
Indication(s)	Second- or third-line treatment of IDH1-mutant cholangiocarcinoma
Development phase	Phase 1/2
Protocol code	CL1-95031-006
EU Trial Number	2023-503236-41-00
Universal Trial Number	Not applicable
Other register number (ISRCTN, CT. gov…)	NCT05921760
Investigational New Drug Application Number	166683
Sponsor	Institut de Recherches Internationales Servier (I.R.I.S.)
International Coordinator	Robin K. (“Katie”) Kelley, MD Professor of Clinical Medicine Helen Diller Family Comprehensive Cancer Center Division of Hematology/Oncology University of California, San Francisco
Date of the document	06 May 2024
Version of the document	Final Version
Version number	5.0
Substantial Amendment(s) integrated	1.0

VERSION LIST

Protocol No	Substantial amendment No	Final version date	Countries concerned	Nature of modifications
1.0	NA	13 March 2023	ALL	Not Applicable
2.0	NA	25 May 2023	ALL	Made modifications due to FDA feedback and information request
3.0	NA	16 June 2023	ALL	• Typographical were corrected globally. • Updated the information related to registration of ivosidenib in Section 2.2. • Exploratory objective and endpoints were added to safety lead-in phase to identify molecular and cellular biomarkers that may be indicative of clinical response/resistance, PD activity, and mechanism of action. • Exploratory endpoint was added to Expansion phase to align with the safety lead-in phase. • Specified that on C1D1, assessments should be conducted prior to IMP administration for the hematology, serum chemistry, and thyroid function test footnotes in Table (4.1.2) 1 (Schedule of Assessments for Subjects in the Safety Lead-in Phase and Expansion Phase). • Serum rather than plasma PK concentrations of nivolumab and ipilimumab will be collected. • Added drug diary for subjects to record the date and time of each dose, as well as the number and strength (mg) of tablets taken. • Blood collection method was updated in Section 9.2.2. • Added text regarding biomarker assessments in Section 9.5.
4.0	NA	07 December 2023	ALL	• Minor editorial changes including removing abbreviations no longer relevant were made globally. • Updated background information (Sections 2.1.2 and 2.2) to include recent approval of pembrolizumab +gemcitabine/cisplatin in 1st line locally advanced of metastatic CCA and new indication of ivosidenib in R/R MDS in the US. • Removed the following text from inclusion criterion #8 for clarity: with progression on the treatment that was most recently given at a minimum. • Corrected inclusion criterion #13 to AST and ALT ≤ 2.5 ULN to address the hepatic adverse event management guidelines for Nivolumab and Ipilimumab administration (per Protocol Appendix 8).

Protocol No	Substantial amendment No	Final version date	Countries concerned	Nature of modifications
				• Deleted the following text in Section 4.1.1.3 "Subjects in the Safety Lead-in phase may continue to receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met" to reduce redundancy. • Deleted the following text in Section 4.1.1.3 "Subjects in the Expansion phase may continue to receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met" to reduce redundancy. • Corrected the frequency of thyroid function tests in Table (4.1.2) 1 (Schedule of Assessments for Subjects in the Safety Lead-in Phase and Expansion Phase) and clarified that thyroid function test results obtained after a visit are acceptable so long as the value at Screening was normal or considered not clinically significant. • Specified that survival follow-up will occur every 12 weeks rather than every 3 months. • To improve protocol clarity with regards to the weekly ECG monitoring required per protocol for the 1st 3 cycles, a column was added for the ECG assessment at C1D8 in the schedule of assessments (Table (4.1.2) 1). • Specified that radiographic assessment can occur between D-7 to D0 during screening throughout the protocol. • The following statement about bone scans is deleted from Table (4.1.2) 1 (footnote #14): Bone scans will be performed at baseline if disease is suspected and on study at the same imaging time points as torso imaging; and the following statement is added: Additional anatomy should be imaged based on the signs and symptoms of individual subjects at baseline and follow-up. • Clarification that radiographic evaluation will occur every other cycle after Week 12 (assessment every 8 weeks) in the schedule of assessments (Table (4.1.2) 1). • Specified that 20 rather than 15 FFPE slides should be collected, and 1 H&E slide will be submitted at a later time together with the pathology report upon sponsor's request in Table (4.1.2) 1 and Section 9.5. • Added clarification about time between nivolumab and ipilimumab infusions (approximately 30 minutes). • Added clarification regarding radiographic assessment to include other imaging modalities as appropriate per RECIST v1.1 Appendix 4). • Clarified that response to treatment is to be assessed for reasons other than disease progression or start of another anticancer therapy in Table (4.1.2) 1 (footnote 15). • Updated Figure (8.10.1) 1 to remove events requiring immediate notification and align with current protocol template.

Protocol No	Substantial amendment No	Final version date	Countries concerned	Nature of modifications
				• Clarified predose PK/PD sampling in Table (4.1.2) 2, Table (4.1.2) 3, and globally.
4.1	NA	20 December 2023	GBR	• See Appendix 13
5.0	1.0	06 May 2024	ALL	• Updated the number of subjects/patients exposed to ivosidenib. • Updated risk language to align with IB v14.0: Guillain-Barré Syndrome, Leukoencephalopathy including Progressive Multifocal Leukoencephalopathy, Lumbosacral Plexopathy, and Posterior Reversible Encephalopathy Syndrome were removed. • Clarified that radiographic assessment of disease will occur between D-21 to Day -1 during the screening period. • Added optional analysis of biomarkers on tumor biopsy(ies) collected as per standard of care.

SYNOPSIS

Name of the Sponsor:
Institut de Recherches Internationales Servier (I.R.I.S.)

Name of Finished Product:
Ivosidenib
Nivolumab
Ipilimumab

Name of Active Ingredient:
S95031 (ivosidenib)

Title of Study:
A Phase 1/2, Safety Lead-in and Dose Expansion, Open-label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Activity of Ivosidenib in Combination with Nivolumab and Ipilimumab in Previously Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation

Study Brief Title:
Ivosidenib, Nivolumab, and Ipilimumab Combination in Previously Treated Subjects with Nonresectable or Metastatic IDH1-Mutant Cholangiocarcinoma

Study Public Title*:*
A Phase 1/2, Safety Lead-in and Dose Expansion, Open-label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Activity of Ivosidenib in Combination with Nivolumab and Ipilimumab in Previously Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation

Coordinator(s) *or* **Investigator** *or* **Steering Committee Chairman**
National coordinators and Investigators: listed in a separate document

Study Center(s):
This is an international multicenter study to be conducted in centers in the United States (US), Europe (EU), and United Kingdom.
For the Safety Lead-in phase, approximately 10 sites will be opened.
For the Expansion phase, additional countries and sites will be included and activated.

Study Period:
Study duration for the participants: including treatment period until progression of disease, unacceptable toxicity, or Investigator's or subject's decision to discontinue and additional follow-up for progression-free survival (PFS), safety, or overall survival (OS).

- Target study initiation: June 2023
- Target study completion: Estimated 2026

Study Development Phase:
Phase 1/2

Objective(s), Endpoints(s), and Estimand(s):

Objectives and Endpoints of the Safety Lead-in Phase

	Objectives	Endpoints
Primary	To evaluate the safety and tolerability of ivosidenib in combination with nivolumab and ipilimumab and determine the recommended combination dose (RCD) of ivosidenib, nivolumab, and ipilimumab	• Dose limiting toxicities (DLTs) associated with ivosidenib in combination with nivolumab and ipilimumab during the first 2 cycles of treatment • Adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)
Secondary	To evaluate the pharmacokinetics (PK) of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma concentrations and PK parameters including, but not limited to, area under the concentration-*vs*-time curve (AUC) from 0 to time of last measurable concentration (AUC_{0-t}), AUC over 1 dosing interval at steady state ($AUC_{tau,ss}$), time to maximum concentration (T_{max}), maximum concentration (C_{max}), trough concentration (C_{trough}), apparent volume of distribution (Vd/F), and apparent clearance (CL/F)

	To evaluate the pharmacodynamic (PD) effects of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma 2-hydroxygluturate (2-HG) concentration
Exploratory	To evaluate ivosidenib exposure in tumor tissue	Tumor tissue concentrations of ivosidenib
	To evaluate the PK of nivolumab and ipilimumab when given in combination with ivosidenib	Serum concentrations of nivolumab and ipilimumab
	To evaluate immunogenicity of nivolumab and ipilimumab when given in combination with ivosidenib	Measurement of anti-drug antibody (ADA) to nivolumab and ipilimumab
	To evaluate the PD effects of ivosidenib when given in combination with nivolumab and ipilimumab	Tumor tissue 2-HG concentration
	To identify molecular and cellular biomarkers that may be indicative of clinical response/resistance, PD activity, and the mechanism of action	• Associations of pre-treatment molecular and cellular markers with patient outcome • Differences in molecular and cellular markers between on-treatment and/or pre-treatment samples

Objectives, Endpoints, and Estimands of the Expansion Phase

	Objectives	**Endpoints**	**Other Estimand Attributes**
Primary	To assess the clinical activity of ivosidenib in combination nivolumab and ipilimumab using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	Objective response (confirmed complete response [CR] or confirmed partial response [PR]) of anti-tumor activity using RECIST v1.1)	The primary estimand of interest is the objective response rate (ORR). The attributes of the primary estimand are defined as follows: • Treatment: ivosidenib plus nivolumab and ipilimumab • Population: Safety Analysis Set • Summary measure: objective response (Yes, No) • Intercurrent events (IE): 1. Early treatment discontinuation 2. Administration of further anti-cancer therapy
Secondary	To confirm the safety and tolerability of the recommended combination dose (RCD) of ivosidenib, nivolumab, and ipilimumab	Adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)	Not applicable

	To evaluate additional efficacy parameters to assess anti-tumor activity of ivosidenib in combination with nivolumab and ipilimumab	Duration of response (DOR), progression-free survival (PFS) and disease control (CR, PR, or stable disease [SD] maintained for at least 5 months), time to response (TTR) according to RECIST v1.1 Overall survival (OS)	Not applicable
	To evaluate the pharmacokinetics (PK) of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma concentrations and PK parameters including, but not limited to, area under the concentration-*vs*-time curve (AUC) from 0 to time of last measurable concentration (AUC_{0-t}), AUC over 1 dosing interval at steady state ($AUC_{tau,ss}$), time to maximum concentration (T_{max}), maximum concentration (C_{max}), trough concentration (C_{trough}), apparent volume of distribution (Vd/F), and apparent clearance (CL/F)	Not applicable
	To evaluate the pharmacodynamic (PD) effects of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma 2-hydroxyglutarate (2-HG) concentration	Not applicable
Exploratory	To evaluate ivosidenib exposure in tumor tissue	Tumor tissue concentrations of ivosidenib	Not applicable
	To evaluate the PK of nivolumab and ipilimumab when given in combination with ivosidenib	Serum concentrations of nivolumab and ipilimumab	Not applicable
	To evaluate immunogenicity of nivolumab and ipilimumab when given in combination with ivosidenib	Measurement of anti-drug antibody (ADA) to nivolumab and ipilimumab	Not applicable
	To evaluate the PD effects of ivosidenib when given in combination with nivolumab and ipilimumab	Tumor tissue 2-HG concentrations	Not applicable
	To identify molecular and cellular biomarkers that may be indicative of clinical response/resistance, PD activity, and the mechanism of action	Associations of pre-treatment molecular and cellular markers with patient outcome Differences in molecular and cellular markers between on-treatment and/or pre-treatment samples	Not applicable

Methodology:
This is a Phase 1/2, non-comparative, multicenter, open-label study of ivosidenib, an oral mutant isocitrate dehydrogenase-1 (IDH1) inhibitor, administered in combination with nivolumab and ipilimumab. Subjects are required to have a histologically confirmed diagnosis of cholangiocarcinoma (CCA), a local molecular IDH1 gene-mutation and not eligible for curative resection, transplantation, or ablative therapies. The study will be conducted in adult subjects with nonresectable or metastatic CCA. Subjects must have progression of disease or treatment intolerance and have received at least 1 but not more than 2 prior treatment regimens for advanced

disease (nonresectable or metastatic). All subjects must have received either a gemcitabine- or a 5-fluorouracil (5-FU)–based chemotherapy regimen.
Radiological tumor assessments will be based on Investigator assessments according to RECIST v1.1. These assessments will be conducted at Screening (Day -21 to Day -1), every 6 weeks beginning at C1D1 (± 7 days) for the first 2 assessments (*i.e.*, through Week 12), and then every 8 weeks (± 7 days) thereafter independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected; tumor assessment frequency may be reduced to every 12 weeks after two years of study treatment initiation.

The study will consist of 2 phases:

Safety Lead-in Phase

The Safety Lead-in phase will evaluate the safety and tolerability of ivosidenib in combination with nivolumab and ipilimumab in order to determine the RCD. This phase will enroll approximately 6-12 DLT-evaluable subjects with nonresectable or metastatic CCA with an IDH1 mutation.

The first 6 subjects enrolled will receive a dose of 500 mg once daily (QD) of ivosidenib in combination with nivolumab 3 mg/kg IV infusion and ipilimumab 1 mg/kg IV infusion concurrently once every 3 weeks (Q3W) for 4 doses followed by nivolumab at 480 mg IV once every 4 weeks (Q4W) until progression or unacceptable toxicity (up to a maximum of 24 months of nivolumab). DLTs will be evaluated through Cycle 2 (*i.e.*, during the first 42 days, 21 days/cycle). Based on the DLT evaluation of 500 mg QD, an additional 6 subjects may be enrolled to test an alternative dose of 250 mg QD. DLT evaluability is determined by subjects who have received the combination therapy and experienced a DLT through Cycle 2 or who have received at least 2 doses of nivolumab and ipilimumab, respectively, and at least 75% of ivosidenib at the assigned dose through Cycle 2 without experiencing a DLT through Cycle 2. There will be no intra-subject dose escalations or reductions of nivolumab or ipilimumab allowed. Subjects must be dosed with nivolumab and/or ipilimumab no fewer than 19 days from the previous dose for the first 4 cycles and no fewer than 25 days from the last dose in Cycle 5 and beyond. A minimum of 6 DLT-evaluable subjects will be required to evaluate the safety and tolerability of the combination. Subjects who are not DLT evaluable will be replaced. A data review team (DRT) composed of Sponsor medical, safety, and statistical representatives, together with Principal Investigator(s), will review the available safety data when at least 6 DLT-evaluable subjects have completed at least 2 cycles of treatment or experienced a DLT within the first 2 cycles.

Dose Stopping Criteria and De-escalation

At the end of Cycle 2, if ≥ 33% of DLT-evaluable subjects have experienced a DLT, further dosing in that cohort will be halted and the dose of ivosidenib will be reduced to 250 mg for all subjects in that cohort. The DRT may recommend enrolling up to an additional 6 subjects to receive ivosidenib at a 250 mg QD dose level, and the same dose stopping rules will be applied after review of the safety data through Day 42 (through Cycle 2). The DRT may decide to cease enrollment in a dosing cohort if fewer than 2 subjects experience DLTs, but the nature of the event(s) is deemed a significant risk to subjects at that dose level. Because the immune-modulating regimen of nivolumab and ipilimumab itself may give rise to Grade 3 or 4 toxicity, the DRT will also consider the aggregate treatment-emergent data in relation to the known toxicity profile of nivolumab and ipilimumab and determine the acceptability of the safety profile of the combination. If 0 or 1 of the 6 evaluable subjects experience DLTs during the first 2 cycles at the 500 mg or the 250 mg QD dose levels, the study may proceed to the Expansion phase.

Expansion Phase

Once the RCD of ivosidenib in combination with nivolumab and ipilimumab has been determined, the Expansion phase of the study will begin. This phase will evaluate the clinical activity of ivosidenib in combination nivolumab and ipilimumab in this disease. Safety and tolerability data of ivosidenib in combination with nivolumab and ipilimumab will be reviewed on an ongoing basis during the study.

This part will be conducted in 2 IDH1-mutated (IDH1m) CCA subpopulations:

- Cohort 1: anti-programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1)–naïve subpopulation: This subpopulation will include up to approximately 40 participants with nonresectable or metastatic CCA who have not received any anti-PD-1/L1 therapy.
- Cohort 2: anti-PD-1/L1 previously treated subpopulation: This subpopulation will include up to approximately 40 participants with nonresectable or metastatic CCA who have received anti-PD-1/L1 therapy.

Statistical Methods

Each expansion cohort will enroll up to approximately 40 subjects to provide reasonable certainty in estimating the primary estimand ORR for the primary endpoint of objective response. CCI [redacted]

CCI [redacted]

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

A Bayesian 2-stage design with a futility interim analysis will be implemented for each expansion cohort. Futility analysis will be conducted for each cohort when approximately 20 response-evaluable subjects have completed at least 4 cycles of treatment or discontinued study treatment. The following futility rule will be considered for the futility analysis:

1. Cohort 1: anti-PD1/L1–naïve subpopulation: If there are 2 or fewer responders (based on unconfirmed CR or unconfirmed PR) of 20 subjects, enrollment may stop; otherwise, enrollment will continue.
2. Cohort 2: anti-PD1/L1 previously treated subpopulation: If there are 0 or 1 responders (based on unconfirmed CR or unconfirmed PR) of 20 subjects, enrollment may stop; otherwise, enrollment will continue.

Additional interim analyses may be conducted during the Expansion phase if necessary. The Sponsor may determine to terminate or further expand cohorts after the interim analyses.
Details of the planned analyses will be prespecified in a statistical analysis plan. Statistical analyses will be primarily descriptive in nature. Summary statistics will be presented for the relevant study analysis populations and by subgroups where appropriate.

Number of Enrolled Participants:
Planned:
Safety Lead-in phase: approximately 6 to 12 DLT-evaluable participants
Expansion phase: approximately 80 participants

Diagnosis and Main Criteria for Inclusion:
Inclusion Criteria:
Subjects must meet all the following criteria to be enrolled in the study:

Demographic Characteristics
1. Male or female participant age ≥ 18 years old.

General Criteria
2. Estimated life expectancy ≥ 12 weeks.
3. Eastern Cooperative Oncology Group performance status ≤ 1.

Sex and Contraceptive/Barrier Requirements
4. Women of childbearing potential (WOCBP) must agree to abstain from sexual intercourse or to use 2 highly effective (Appendix 7) forms of contraception, at least one of which must be a barrier method, from the time of giving informed consent throughout the study, and for 5 months after the last dose of study treatment. Ivosidenib, nivolumab, and ipilimumab may have adverse effects on a fetus in utero. Furthermore, it is not known if nivolumab and ipilimumab have transient adverse effects on the composition of sperm. Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. Egg donation (ova, oocytes), for the purpose of reproduction, will not be allowed during the study and for 3 months after the last dose of study treatment.
   - Male subjects with WOCBP partners must use a condom during the study and until at least 3 months after the last dose of study treatment. In addition, contraception should be considered for their female partners. Contraceptive measures do not apply if the subject is sterile, vasectomized, or sexually

abstinent. Sperm donation from male subjects will not be allowed during the study and for 3 months after the last dose of study treatment.
Please refer to Appendix 7 for further contraception considerations.

Informed Consent

5. Obtained prior to any study-specific procedure as described in Section 13.3 of the protocol.

Medical and Therapeutic Criteria

6. Have a histopathological diagnosis consistent with nonresectable or metastatic cholangiocarcinoma and are not eligible for curative resection, transplantation or ablative therapies.
7. Have documented IDH1 gene-mutated disease based on local testing procedure (R132C/L/G/H/S mutations variants tested). Preferably using a tumor biopsy sample collected within the last 3 years.
8a. Have disease progression or treatment intolerance following at least 1 and no more than 2 prior systemic regimens for advanced disease (nonresectable or metastatic) including the following:
   i. For Cohort 1: subjects who have not received any prior immune checkpoint inhibitor therapy but received at least 1 gemcitabine- or 5-FU-containg regimen for advanced cholangiocarcinoma.
   ii. For Cohort 2: subjects must have received at least two doses of anti-PD1/L1 therapy in first or second line, which may include combination with chemotherapy which should include at least 1 gemcitabine- or 5-FU-containg regimen for advanced cholangiocarcinoma. Combination therapy with other checkpoint inhibitors or investigational agents must be excluded.
   iii. Safety Lead-in phase: subjects eligible for either Cohort 1 or Cohort 2.

   Prior capecitabine or gemcitabine containing adjuvant chemotherapy will be considered a line of treatment if there is documented disease progression during or within 12 months of completing the therapy.
9. Participants must have at least one measurable lesion, as defined by RECIST v1.1. Subjects who have received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) are eligible provided measurable disease falls outside of the treatment field or if within the field but has shown ≥ 20% growth in size post-treatment assessment.
10. Adequate hematological function, defined as:
   i. WBC ≥ 2 x 10^9/L.
   ii. Absolute neutrophil count ≥ 1.5 x 10^9/L.
   iii. Hemoglobin ≥ 9 g/dL. In case of blood transfusion, the hemoglobin assessment must be performed 2 weeks or more after the transfusion.
   iv. Platelet count ≥ 100 x 10^9/L.
11. Adequate coagulation function as defined by International Normalization Ratio (INR), or Prothrombin Time (PT) or Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 upper limit of normal (ULN); Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study. Subjects receiving a factor Xa inhibitor who have abnormal PT/ partial thromboplastin time (PTT) may be eligible after discussion with the Sponsor.
12. Adequate renal function defined as: calculated creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault formula:

   (140 − Age) × (weight in kg) × (0.85 if female)/72 × serum creatinine
13. Adequate hepatic function, defined as:
   i. Total serum bilirubin and direct bilirubin ≤ 1.5 x ULN (total serum bilirubin ≤ 3.0 x ULN for confirmed Gilbert disease).
   ii(a) Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × ULN, exception to this range will need to be discussed and approved by the study medical monitor.
   iii. Serum albumin ≥ 2.8 g/dL.

Exclusion Criteria:

Subjects meeting any of the following criteria may not be enrolled in the study:

General Criteria

14. Inability to swallow oral medication.
15. Pregnant and lactating women.
16. WOCBP who tested positive in a serum pregnancy test within 24 hours prior to the first day of IMP administration, unless hCG has been determined to be elevated due to tumor production only with no

evidence of pregnancy by ultrasound and/or gynecologic evaluation. An extension up to 72 hours prior to the start of study treatment is permissible in situations where the results cannot be obtained within the standard 24-hour window.

17. Unlikely to cooperate in the study.
18. Participation in another interventional study at the same time or within 2 weeks prior to the first IMP administration. Participation in non-interventional registries or epidemiological studies is allowed. In addition, the first dose of ivosidenib should not occur before a period greater than or equal to 5 half-lives or 28 days, whichever is shorter, of the last dose of the investigational product.

Medical and Therapeutic Criteria

19. Subjects who received prior treatment with an IDH inhibitor or prior treatment with an immune checkpoint inhibitor other than anti-PD1/L1.
20. Have a history of another primary cancer, with the exception of: a) curatively resected nonmelanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid or liquid tumor within 2 years prior (*i.e.*, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before and the subject has no evidence of disease), with no known active disease present that, in the opinion of the Investigator, will not affect subject outcome in the setting of current cholangiocarcinoma diagnosis.
21. Subjects with prior Grade ≥ 3 immune-related AE resulting from immune checkpoint inhibitors (ICI) therapy or have history of life-threatening toxicity related to prior immune therapy (ICI or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (*e.g.*, hypothyroidism).
22. Subjects with active autoimmune disease or any condition requiring systemic treatment with either corticosteroids (> 10 mg daily of prednisone equivalents) or other immunosuppressive medications within 14 days of study treatment. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
23. Known prior severe hypersensitivity to investigational products or any component in their formulations.
24. Participants who have not recovered from toxicity of previous anti-cancer therapy, including Grade ≥ 1 non-hematologic toxicity, according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0, prior to the first IMP administration. Residual Grade ≤ 2 toxicity from chemotherapy (*e.g.*, alopecia, neuropathy) may be allowed.
25. Major surgery within 4 weeks prior to the first IMP administration or participants who have not recovered from side effects of the surgery.
26. Have left ventricular ejection fraction (echocardiogram, multiple gated acquisition scan, or by other method according to institutional practice) < 40% by ECHO scan (or by other methods according to institutional practice) obtained within 28 days prior to the start of study treatment.
27. Subjects who have heart rate-corrected QT interval using Fridericia's formula (QTcF) of ≥ 450 msec or with other factors that increase the risk of QT prolongation or arrhythmic events (*e.g.*, heart failure, hypokalemia, family history of long QT interval syndrome). Subjects with bundle branch block and prolonged QTcF should be reviewed by the Sponsor for potential inclusion.
28. History of motor neuropathy considered to be of autoimmune origin (*e.g.*, Guillain-Barre syndrome, myasthenia gravis).
29. Known immunodeficiency or HIV, hepatitis B, or hepatitis C infection. Antibody to hepatitis B or C without evidence of active infection may be allowed. Subjects with chronic hepatitis B virus that is adequately controlled per institutional guideline will be permitted.
30. Severe or uncontrolled active acute or chronic infection.
31. Have known symptomatic brain metastases requiring steroids. Subjects with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and have radiographically stable disease for at least 3 months prior to study entry. Note: Up to 10 mg per day of prednisone equivalent will be allowed.
32. Subjects who have received systemic anti-cancer treatment or palliative radiotherapy to bone metastases or other non-liver lesions less than 2 weeks before the first dose of ivosidenib. Arterial therapies and radiation to liver lesions less than 4 weeks before the first dose of ivosidenib.
33. Treatment with a live/attenuated vaccine withing 30 days of first study treatment.
34. History of non-infectious pneumonitis that required steroids, current pneumonitis, or history of interstitial lung disease.
35. Subjects who discontinued prior treatment with ICIs for toxicity, irrespective of the grade of the event that triggered discontinuation.

36. Any clinically significant medical condition (*e.g.*, organ dysfunction) or laboratory abnormality likely to jeopardize the participant's safety or to interfere with the conduct of the study, in the Investigator's opinion.
37. Any contraindication to the use of nivolumab or ipilimumab as per standard labelling and local guidance.
38. Are taking known strong cytochrome P450 (CYP) 3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing.
    Note: Please refer to Appendix 10, Table 2 and Table 5, for further drug-drug interaction considerations.

Test Drug:
Ivosidenib (test drug), combined with nivolumab and ipilimumab.

Ivosidenib

Ivosidenib will be supplied as 250 mg strength tablets to be administered orally QD for a 21-day cycle. After the first 4 cycles, the cycle length will increase to 28 days.

In the Safety Lead-In phase, ivosidenib will be administered orally at a starting dose of 500 mg QD. Depending on the DLT evaluation by the DRT, an alternative dose of 250 mg QD may be evaluated.

Subjects enrolled in the Expansion phase will receive ivosidenib at the RCD in combination with nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) concurrently Q3W for 4 doses followed by nivolumab (480 mg) Q4W until progression (up to a maximum of 24 months from date of first dose).

In both phases, subjects will receive ivosidenib at the assigned dose on Days 1 through 21 in 21-day cycles for first 4 cycles followed by 28-day cycles starting with Cycle 5. Dosing is continuous, there are no planned rest periods. On days when subjects are receiving nivolumab and ipilimumab, ivosidenib should be administered approximately 30 minutes before the start of the infusion. It is recommended that each dose should be taken with or without food. Subjects taking ivosidenib with food should be advised to avoid grapefruit or grapefruit products and avoid consuming a high-fat meal (Please refer to examples of low-fat and high-fat meals in Appendix 11).

No premedication is required prior to subjects receiving the first dose of ivosidenib.

Nivolumab

Nivolumab will be administered as an approximately 30-minute infusion at 3 mg/kg IV Q3W for the first 4 doses followed by 480 mg Q4W until progression and for up to a maximum of 24 months. Nivolumab infusion is to be administered prior to ipilimumab.

Infusion duration: Nivolumab is to be infused over an approximately 30-minute (-5/+10 minutes) period. Subjects should be monitored for infusion reactions for 30 to 60 minutes after completing the nivolumab infusion. If a subject has an infusion reaction, a follow-up call approximately 24 hours after completion of infusion is recommended to ensure that the event is resolved. Premedications are not recommended for the first dose of nivolumab.

Ipilimumab

Ipilimumab will be administered as an approximately 30-minute infusion at 1 mg/kg IV Q3W for 4 total doses.

Infusion duration: Ipilimumab is to be infused within 30 minutes after the end of nivolumab infusion over an approximately 30-minute (-5/+10 minutes) period. The time in between nivolumab and ipilimumab infusions is expected to be within approximately 30-minutes.

Subjects should be monitored for infusion reactions for 30 to 60 minutes after completing the ipilimumab infusion. If a subject has an infusion reaction, a follow-up call approximately 24 hours after completion of infusion is recommended to ensure that the event is resolved.

Duration of Treatment:
Active treatment period: The planned duration of treatment is until disease progression. Subjects may be discontinued from treatment earlier due to unacceptable toxicity or other discontinuation criteria are met. End of Treatment (EOT) evaluations will be performed at the time of decision to discontinue treatment (or as close to the decision day as possible). Subjects may continue to receive up to a maximum of 24 months of nivolumab. Subjects who are still deriving clinical benefit after 24 months may continue to receive ivosidenib monotherapy until disease progression, unacceptable toxicity, or other discontinuation criteria are met.

Safety Follow-up period: Following discontinuation from study treatment, all subjects will have a 30-day Safety Follow-up visit. During the 30 (+5)-day Safety Follow-up period, all AEs and new medications (including new anti-cancer therapy) will be reported. Following the 30 (+5)-day Safety Follow-up period, subjects will be followed for safety for an additional 100 (+5) days after their last dose of immunotherapy or until they begin any other anti-cancer therapy, whichever is earlier.

Overall Survival (OS) Follow-up period: Subjects will be followed for OS. Subjects will be contacted every 12 weeks (±2 weeks) beginning at the EOT visit for up to 2 years after the last subject has been enrolled, or until death, lost to follow-up, withdrawal of consent from overall study participation, or Sponsor ending study, whichever occurs first.

Data Review Team: A DRT composed of Sponsor medical, safety, and statistical representatives and study Investigator(s) will review the available safety data in all subjects enrolled in the 500 mg QD dose cohort of the Safety Lead-in phase in order to determine whether 500 mg QD is the ivosidenib RCD or whether the 250 mg QD dose level will be tested. If the 250 mg QD dose cohort is opened, the DRT will review the safety data in order to determine whether 250 mg QD is the RCD for the Expansion phase.

Contractual signatories	
I, the undersigned, have read the foregoing protocol and the "Participant information and consent form" document attached to the protocol and agree to conduct the study in compliance with such documents, Good Clinical Practice and the applicable regulatory requirements.	
INVESTIGATOR	
NAME	
CENTER NUMBER	
DATE	
SIGNATURE	
VICE PRESIDENT, CLINICAL DEVELOPMENT HEAD OF CANCER METABOLISM GLOBAL DEVELOPMENT	
NAME	PPD
DATE	06 May 2024
SIGNATURE	PPD

Other Sponsor's signatories	
BIOSTATISTICS HEAD OR DESIGNEE:	
NAME	PPD
DATE	06 May 2024
SIGNATURE	PPD

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List of abbreviations

Abbreviation	Definition
2-HG	Plasma 2-hydroxygluturate
5-FU	5-fluorouracil based chemotherapy
ADA	Anti-Drug Antibody
ADL	Activities of daily living
AE	Adverse Events
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
AST	Aspartate aminotransferase
AUC	Area under the concentration
$AUC_{0-\infty}$	Area under the concentration from 0 to infinity
AUC_{0-t}	0 to time of last measurable concentration
$AUC_{tau,ss}$	Area under the concentration over 1 dosing interval at steady state
BOR	Best overall response
BTC	Biliary tract cancer
C1D1	Cycle 1 Day 1
CCA	Cholangiocarcinoma
CD	Combination Dose
cHL	classical Hodgkin Lymphoma
CI	Confidence Interval
CL	Clearance
CL/F	Apparent Clearance
C_{max}	Maximum Concentration
CR	Confirmed complete response
CRC	Colorectal Cancer
CRO	Contract research organizations
CSR	Clinical study report
CT	Cytotoxic T
ctDNA	Circulating tumor DNA
CTLA4	Cytotoxic T-lymphocyte associated protein 4
C_{trough}	Trough concentration
CV	Curriculum vitae
CYP	Cytochrome p450
DCR	Disease control rate
DLT	Dose limiting toxicities
DOR	Duration of response
DRT	Data review team
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European economic area
EOT	End of Treatment
EU	European union

FDA	Food and drug administration
FDG	Fluorodeoxyglucose
FGFR	Fibroblast growth factor receptor
FSP	Full service provider
GCP	Good clinical practice
GLP	Good laboratory practice
HCC	Hepatocellular Carcinoma
HPBL	Human peripheral blood lymphocyte
HR	Hazard ratio
IB	Investigator brochure
iCCA	Intrahepatic
ICF	Informed consent form
ICI	Immune checkpoint inhibitors
IDH1	Isocitrate dehydrogenase 1
IE	Intercurrent events
IEC	Independent ethics committee
Ig	Immunoglobulin
IMAE	Immune-mediated adverse events
IMP	Investigational medicinal product
INR	International normalization ratio
IO	Immuno-oncology
irAE	Immune-related adverse events
IRB	Institutional review board
IV	Ivosidenib
LEVF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic
PD-L1	Programmed death-ligand 1
PD-L	Programmed death 1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PT	Prothrombin time
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
Q4W	Once every 4 weeks
QD	Once daily
QTcF	QT interval using Fridericia's formula

R/R	Relapsed or refractory
RCC	Renal cell carcinoma
RCD	Recommended combination Dose
RECIST	Response evaluation criteria in solid tumors
RTSM	Randomization and trial supply management
SAP	Statistical analysis plan
SAE	Serious adverse events
SCCHN	Squamous cell carcinoma of head and neck
SCLC	Small cell lung cancer
SD	Stable disease
SmPC	Summary of product characteristics
$T_{1/2}$	Time required for drug concentration
TEAE	Treatment-emergent adverse events
T_{max}	Time to maximum concentration
TTR	Time to response
ULN	Upper limit of normal
US	United States
USPI	US prescribing information
Vd/F	Apparent volume of distribution
WMA	World medical association
WOCBP	Women of childbearing potential
WT	Wild-type tumors

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Non-Sponsor parties, Sponsor parties, and contract research organizations (CROs) responsible for local management of the study are described in a separate document entitled "Administrative Part of Clinical Study Protocol." The list of Investigators is given in a separate document attached to the protocol and entitled "Investigators."

2. BACKGROUND INFORMATION

2.1. Cholangiocarcinoma

2.1.1. Overview of Cholangiocarcinoma

Cholangiocarcinomas (CCAs) are rare cancers (accounting for 3% of all gastrointestinal malignancies) that arise from biliary epithelium and are typically diagnosed at advanced stages for which curative surgery is not feasible. The classification of CCAs is divided anatomically as extrahepatic, intrahepatic (iCCA), and perihilar (Saha *et al*, 2014; Van Dyke *et al*, 2019). The disease is often advanced and incurable at the time of diagnosis. Common presentation includes symptoms related to biliary tract obstruction including jaundice, abdominal pain, weight loss, fever, fatigue, and abnormal liver function tests. The prognosis for subjects with CCA is poor; regardless of stage at diagnosis, the 5-year survival rates associated with both intrahepatic (iCCA) and extrahepatic CCA are 9% to 10% and only 2% in subjects with distant metastases (ACS, 2021). CCA (intrahepatic and extrahepatic) affects approximately 8,000 people in the US annually (ACS, 2019) and approximately 1.3 in 10,000 people in the EU (Agency, 2018).

Isocitrate dehydrogenase-1 (IDH1) mutations occur globally in approximately 16%, and up to 29% in some reports, of iCCAs and approximately 0% to 7% of extrahepatic CCAs. Using a maximum incidence of 14% (13% for intrahepatic + 1% for extrahepatic) for IDH1 mutations in CCA indicates an overall prevalence of 0.182 in 10,000 people (Kendre *et al*, 2022). Based on majority of available literature, IDH1 mutations do not have a prognostic impact on clinical outcomes including progression-free survival (PFS) and overall survival (OS) (Boscoe *et al*, 2019). Therefore, outcomes in this biomarker-selected population can be compared to those reported among the general advanced, previously treated CCA population (Boscoe *et al*, 2019; Goyal *et al*, 2015).

2.1.2. Current Treatment of Cholangiocarcinoma

As early-stage disease is commonly asymptomatic, only a minority of CCA subjects are diagnosed with resectable disease, while most of the subjects present with locally nonresectable or metastatic disease (Rizzo *et al*, 2021). The first-line standard of care treatment for subjects with CCA, including subjects with IDH1 mutation-positive CCA, in a locally nonresectable or metastatic setting is a combination of durvalumab with gemcitabine/cisplatin and a combination of pembrolizumab with gemcitabine/cisplatin. Approval of durvalumab in combination with gemcitabine/cisplatin was granted starting in 2022 in the US, EU, UK and other parts of the world and was based on the Phase 3 TOPAZ-1 trial evaluating the durvalumab and gemcitabine/cisplatin combination *vs.* gemcitabine/cisplatin. The addition of durvalumab resulted in an improved OS of 12.8 months compared with a gemcitabine/cisplatin OS of 11.5 months (hazard ratio [HR]: 0.80, confidence interval [CI]: 0.66-0.97, p = 0.021) (Oh *et al*, 2022). Approval of pembrolizumab in combination with gemcitabine/cisplatin was granted in

2023 in the US and was based on the Phase 3 Keynote-966 trial evaluating pembrolizumab and gemcitabine/cisplatin combination vs. gemcitabine/cisplatin. The addition of pembrolizumab resulted in an improved OS of 12.7 months compared to a gemcitabine/cisplatin OS of 10.9 months (HR: 0.83, CI: 0.72–0.95, p = 0.0034) (Kelley *et al*, 2023).

Second-line chemotherapy regimens produce an incrementally smaller therapeutic benefit, with an average median PFS of 2 to 3 months (Brieau *et al*, 2015; Lamarca *et al*, 2021). Overall survival outcomes are also limited to approximately 6 months (Kim *et al*, 2017; Lamarca *et al*, 2021; Matsuyama *et al*, 2018; Ying and Chen, 2019), demonstrating the need for novel treatment options in subjects with CCA.

Recent years have seen the advent of novel treatments in the biliary tract cancer (BTC) landscape, including targeted therapies (ivosidenib, pemigatinib, infigratinib, and futibatinib) and immune checkpoint inhibitors (ICIs), as monotherapy or in combination (Rizzo *et al*, 2021).

Ivosidenib, a potent and selective inhibitor of the IDH1 mutant protein, is the only drug approved for the treatment of adult subjects with previously treated, locally nonresectable or metastatic CCA with an IDH1 mutation (approval granted in the US in 2021). Pemigatinib, infigratinib, and futibatinib, selective inhibitors of fibroblast growth factor receptor (FGFR), are approved for treatment of adult subjects with previously treated, locally nonresectable or metastatic CCA who have *FGFR2* fusions or rearrangements (approved in the US in 2020, 2021, and 2022, respectively). Pemigatinib is also approved in EU (approval granted in 2021). FGFR fusions are detected in 10% to 15% of subjects with iCCA (Saborowski *et al*, 2020), however they rarely co-occur (less than 1% of subjects) with mutations of IDH1 (Abou-Alfa *et al*, 2020).

The activity of ICIs (programmed death-1 [PD-1], programmed death-ligand 1 [PD-L1]) in previously treated BTC has been tested with heterogenous results. Results with ICI monotherapy in unselected BTCs, including CCA, suggest limited activity in recurrent disease; the objective response rate (ORR) of single-agent anti-PD-1 is approximately 10% (Doki *et al*, 2022; Kim *et al*, 2020; Klein *et al*, 2020; Piha-Paul *et al*, 2020).

Two Phase 1/2 studies testing the combination of a PD-1 or PD-L1 inhibitor with an anti–cytotoxic T-lymphocyte associated protein 4 (CTLA4) agent showed superior efficacy than any compound alone. Durvalumab (anti-PD-L1) in combination with tremelimumab (anti-CTLA4) was tested in Asian subjects resulting in an ORR of 10.8% and a median OS of 10.1 months (Doki *et al*, 2022). In the second trial, nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA4) (Klein *et al*, 2020) was administrated to 39 Australian subjects (16 with iCCA) resulting in an ORR of 23% (31% iCCA), and median PFS and median OS of 2.9 and 5.7 months, respectively. These preliminary results appear to suggest that combination of anti-PD-1 with anti-CTLA4 has superior efficacy compared with anti-PD-1 monotherapy and warrants further investigation in larger clinical trials.

2.2. Overview of Ivosidenib

Ivosidenib (also known as S95031, AG-120, and AGI-16678) is a potent, selective, orally active small molecule inhibitor of mutated IDH1. The clinical development of ivosidenib is being conducted worldwide, focusing on advanced hematologic malignancies as a single agent

and in combination with other standard chemotherapies, and on advanced solid tumor malignancies as a single agent.

Ivosidenib (TIBSOVO) is an IDH1 inhibitor indicated for subjects with a susceptible IDH1 mutation as detected by a US Food and Drug Administration (FDA)-approved test:

- In combination with azacitidine or as a monotherapy for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
- For the treatment of adult subjects with relapsed or refractory (R/R) AML.
- For the treatment of adult patients with relapsed or refractory myelodysplastic syndromes.
- For the treatment of adult subjects with locally advanced or metastatic CCA who have been previously treated.

TIBSOVO is also registered in the EU, in combination with azacitidine for the treatment of adult patients with newly diagnosed AML with an IDH1 mutation who are not eligible to receive standard induction chemotherapy, or as monotherapy for the treatment of adult subjects with locally advanced or metastatic CCA with an IDH1 mutation, who have been previously treated.

Details about the indication-specific safety information are provided in Section 6.5 and Section 6.6 of the Investigator's Brochure (IB).

Two studies investigated ivosidenib as a single agent in subjects with IDH1-mutated CCA. The results from the Phase 3 ClarIDHy study (AG120-C-005) and the supportive Phase 1 AG120-C-002 study demonstrate clinically meaningful and durable efficacy in subjects who received at least 1 prior line of chemotherapy.

2.2.1. Description of the Investigational Medicinal Product Ivosidenib

2.2.1.1. Nonclinical Data

Details of the nonclinical development program for ivosidenib are provided in the IB.

2.2.1.2. Toxicology Summary of Ivosidenib

The toxicity profile of ivosidenib was evaluated in vitro in a Good Laboratory Practice (GLP) bacterial reverse mutation assay, a GLP human peripheral blood lymphocyte micronucleus assay, and a GLP BALB/c 3T3 mouse fibroblast phototoxicity assay. In vivo GLP toxicology studies included repeat-dose 28-day and 3-month Sprague Dawley rat and cynomolgus monkey studies, dose range–finding and definitive embryo-fetal development studies in Sprague Dawley rats and New Zealand white rabbits, and a micronucleus study in Sprague Dawley rats. Based on the results of the nonclinical toxicology program conducted to date, ivosidenib has an acceptable safety profile for continued use in humans.

2.2.2. Clinical Pharmacokinetics and Pharmacodynamics

A total of 12 clinical studies have contributed to the characterization of the pharmacokinetics (PK) and pharmacodynamics (PD) of ivosidenib. Five of these studies were conducted in healthy subjects (all single-dose studies), and 7 of these studies were conducted in subjects with advanced hematologic malignancies and solid tumor malignancies (single and multiple doses). Ivosidenib demonstrated good oral bioavailability, rapid absorption, and a long

elimination half-life ($t_{½}$) in subjects with IDH1-mutated AML and solid tumor malignancies, supporting a once daily (QD) dosing regimen. The mean terminal $t_{½}$ at steady state of ivosidenib in subjects with CCA is 129 hours (102%). After multiple doses of ivosidenib, steady state was reached within 14 days, with approximately 2-fold accumulation in plasma exposure. Plasma exposure of ivosidenib increased less than dose proportionally from 100 to 1,200 mg.

Results from studies in subjects with advanced hematologic malignancies (AG120-C-001, AG120-221-C-001, and AG221-AML-005) and solid tumor malignancies (AG120-C-002, AG120-881-C-001, and AG120-C-005) indicate that plasma 2-hydroxyglutarate (2-HG) levels were substantially reduced in subjects with an IDH1 mutation (achieving levels similar to those in healthy subjects) at doses ranging from 200 to 1,200 mg QD. Multiple doses of ivosidenib also decreased 2-HG levels in bone marrow (AML) and tumor biopsies (CCA and chondrosarcoma) at doses ranging from 200 to 1,200 mg QD. Maximal plasma inhibition of 2-HG occurred at 500 mg QD in most subjects, with no additional inhibition observed at higher doses.

2.3. Overview of Nivolumab and Ipilimumab

2.3.1. Nivolumab

2.3.1.1. Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (mAb) (immunoglobulin [Ig]G4-S228P) that targets the PD-1 cluster of differentiation (CD)279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies.

Nivolumab (marketed in the US and EU under the trade name Opdivo®) is approved for the treatment of several types of cancer in multiple regions including the US (December 2014), the EU (June 2015), and Japan (July 2014).

2.3.1.2. Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), small cell lung cancer (SCLC), gastric cancer, squamous cell carcinoma of head and neck (SCCHN), urothelial cancer, hepatocellular carcinoma (HCC), and colorectal cancer (CRC). In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with nonresectable or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Details of the clinical activity in these various malignancies are provided in the US Prescribing Information (USPI) and Summary of Product Characteristics (SmPC), see Section 2.4.2.

2.3.2. Ipilimumab

2.3.2.1. Mechanism of Action

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal IgG1 kappa specific for human CTLA4 (CD152), which is expressed on a subset of activated T cells. CTLA4 is a negative regulator of T-cell activity. Ipilimumab is a mAb that binds to CTLA4 and blocks the interaction of CTLA4 with its ligands, CD80/CD86. Blockade of CTLA4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

2.3.2.2. Ipilimumab Clinical Activity

Ipilimumab (marketed in the US and EU under the trade name Yervoy®) is a recombinant, fully human mAb that binds to CTLA4 and is approved as monotherapy and in combination with nivolumab for the treatment of subjects with unresectable or metastatic melanoma; for the treatment of subjects with intermediate/poor-risk, previously untreated advanced RCC; for the first-line treatment of subjects with metastatic or recurrent NSCLC with no epidermal growth factor receptor or ALK receptor tyrosine kinase genomic tumor aberrations; and for the first-line treatment of subjects with unresectable malignant pleural mesothelioma.

2.3.3. Nivolumab Combined with Ipilimumab Clinical Activity

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules. Based on Phase 3 data showing improved survival over standard of care therapies, nivolumab combined with ipilimumab has been approved in multiple countries for the treatment of subjects with unresectable or metastatic melanoma, intermediate or poor risk, previously untreated advanced RCC, and microsatellite instability-high or mismatch repair deficient CRC. Details of the clinical activity in these various malignancies are provided in the USPI and SmPC. The combination has been studied in subjects with biliary tract cancers with activity and safety summarized in Sections 2.4.2 and 2.5.

2.4. Rationale for the Combination of Ivosidenib with Nivolumab and Ipilimumab in Cholangiocarcinomas

2.4.1. Nonclinical Data for Ivosidenib in Combination with Nivolumab and Ipilimumab

Mutations in the metabolic enzyme IDH1 occur in approximately 14% of subjects with iCCA and result in overproduction of the oncometabolite 2-HG (Dang *et al*, 2009; Figueroa *et al*, 2010). IDH1 mutations may play a role in the pathogenesis of the CCA by blocking the differentiation of liver progenitor cells, promoting cellular proliferation (Valle *et al*, 2010), and activating a dual immunoevasion program reducing T-cell recruitment and interferon γ expression and response (Notarangelo *et al*, 2022; Wu *et al*, 2022).

Ivosidenib is a novel, first-in-class, small molecule targeted selectively to inhibit the mutated IDH1 enzyme and reduce the production of the oncogenic metabolite 2-HG. It inhibits 2-HG production by > 95% in nonclinical studies (in vitro and in vivo) and reduces plasma 2-HG up to 98% in clinical studies (see the IB). Recent studies suggest a role for high 2-HG in repressing key immune-related genes and impairing lymphocyte infiltration both in glioma and CCA (Kohanbash et al, 2017; Notarangelo *et al*, 2022; Thorsson et al, 2018 ; Wu *et al*, 2022).

Mutant IDH1 CCA subject samples exhibit a T-cell-deficient tumor microenvironment compared with IDH1 wild-type (WT) tumors (Wu et al, 2022; Xiang *et al*, 2021). In pre-treatment CCA biopsies obtained in the Phase 3 study testing ivosidenib *versus* placebo in subjects with previously treated advanced CCA with IDH1 mutations (NCT02989857), an artificial intelligence–based histological analysis showed less lymphocyte infiltration pattern in IDH1-mutated tissue sections compared with IDH1 WT samples. The pattern was more pronounced in subjects with higher 2-HG, supporting a role for elevated 2-HG in immune-quiescence.

Direct effects of 2-HG on T cells and combination benefit between ivosidenib and immune checkpoint inhibition have been demonstrated in mouse models. In a mouse model of IDH1-mutated CCA, ivosidenib treatment stimulated T-cell recruitment and effector function in the tumor and was synergistic in combination with CTLA4 inhibition, with the combination resulting in complete tumor regression in the majority of animals receiving a 26-day treatment course (Wu *et al*, 2022). In a second study, 2-HG was shown to directly impact the metabolism of CD8 T cells resulting in impaired effector function, and this effect was recapitulated in clinical samples from subjects with IDH-mutant glioma (Notarangelo *et al*, 2022).

2.4.2. Clinical Data for Ivosidenib in Combination with Nivolumab and Ipilimumab

The activity of ICIs (PD-1, PD-L1) in metastatic and recurrent BTC has been tested with heterogenous results. Monotherapy in unselected BTCs, including CCA, has had disappointing results and limited activity in recurrent disease; the ORR of a single-agent anti-PD-1 is approximately 10% (Doki *et al*, 2022; Kim *et al*, 2020; Klein *et al*, 2020; Piha-Paul *et al*, 2020).

Two Phase 1/2 studies testing the association of a PD-1 or PD-L1 inhibitor with an anti-CTLA4 showed superior efficacy than any compound alone. Durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA4) was tested in Asian subjects resulting in an ORR of 10.8% and a median OS of 10.1 months (Doki *et al*, 2022). In the second trial, nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA4) (Klein *et al*, 2020) was administrated to 39 Australian subjects (16 with iCCA) obtaining an ORR of 23% (31% iCCA) and a median PFS and median OS of 2.9 and 5.7 months, respectively. These preliminary results showed that combination of an anti-CTLA4 and an anti-PD-1 seemed to have superior efficacy than anti-PD-1 monotherapy and warrants further investigation from larger clinical trials.

Additionally, an Investigator-initiated trial of ivosidenib in combination with nivolumab in IDH1-mutated advanced solid tumors is active with ongoing subject accrual in the US (NCT04056910).

2.5. Overall Benefit/Risk

The safety profile for ivosidenib is manageable based on the cumulative safety data from approximately 13,812 subjects/patients who have been exposed to 1 or more doses of ivosidenib. Important identified risks associated with ivosidenib administration based on the current safety profile include Electrocardiogram QT prolonged (all subjects) and Differentiation syndrome (hematologic malignancies only).

The primary endpoint in the ClarIDHy study, PFS by IRC demonstrated a highly statistically significant and clinically meaningful reduction in the risk of progression or death (HR, p-value). This benefit in PFS was also apparent at the 6 and 12-month timepoints. Additionally, the benefit of OS in the ivosidenib arm compares favorably with chemotherapy.

CCI [redacted]

In the ClarIDHy study, the incidence of Grade ≥ 3 treatment-emergent adverse events (TEAEs) were higher in the ivosidenib arm when compared with the placebo arm (51.2% *vs* 37.3%). The incidence of serious adverse events (SAEs) was also higher in the ivosidenib arm when compared with placebo (35.0% and 23.7%, respectively). There was similar incidence of Grade ≥ 3 TEAEs between ivosidenib treatment and placebo treatment in the first 2 months of treatments, before crossover from placebo to ivosidenib is allowed. Frequencies of treatment discontinuations due to TEAEs were similar in the ivosidenib arm compared with placebo (7.3% and 8.5%, respectively).

No events of Guillain-Barré syndrome or differentiation syndrome were reported in subjects with CCA. QT prolongation observed with ivosidenib was mostly of low grade, was manageable, and did not lead to life-threatening ventricular arrhythmias, and did not result in sudden cardiac death. The overall incidence of Grade 3 adverse reactions was low, the majority of which were consistent with the signs and symptoms of the underlying disease, which can be managed with routine monitoring that is part of standard of care.

Overall, the clinical benefit of ivosidenib has been demonstrated as a 2L/3L treatment option for subjects with locally advanced or metastatic mIDH1 CCA and the benefit of ivosidenib largely outweighs the potential risks related to the treatment in this population.

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 maximum tolerated dose reached at any dose tested up to 10 mg/kg. Most adverse events (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. A pattern of immune-related adverse events (irAEs) has been defined, for which management algorithms have been developed; these are provided in Appendix 9. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. Additional details on the safety profile of nivolumab or in combination with ipilimumab, including results from other clinical studies, are also available in the nivolumab IB.

Two Investigator-initiated studies tested the combination of nivolumab and ipilimumab in advanced biliary cancers. Among the 39 subjects included in a Phase 2 clinical trial investigating ipilimumab 1 mg/kg and nivolumab 3 mg/kg once every 3 weeks (Q3W) for a maximum of 4 cycles followed by nivolumab 3 mg/kg once every 2 weeks and continued for up to 96 weeks, the ORR was 23% (n = 9) with a disease control rate of 44% (n = 17); all responders had received prior chemotherapy, and none had a microsatellite unstable tumor. Immune-related toxic events were reported in 49% of subjects (n = 19), with 15% (n = 6) experiencing Grade 3 or 4 events. The most common irAE was rash/pruritis (33%), Grade 3 or higher irAE is rare, thyroiditis 3%, hypophysitis 5%, hepatitis 3%, enterocolitis/diarrhea 3%, and gastritis 3%. A separate trial investigated combination of 240 mg nivolumab once every 2 weeks and ipilimumab 1 mg/kg once every 6 weeks in advanced biliary cancer without prior systemic therapy (Sahai *et al*, 2022). Among 33 evaluable subjects, the 6-month PFS rate was 21.1% (95% CI, 9.4%-36.3%) and median OS was 8.2 months (95% CI, 5.8-16.9 months), while the ORR was 3.0% (95% CI, 0.1%-15.8%). The incidence of SAEs was 36.4%, with Grade ≥ 3 treatment-related AEs of fatigue (6.1%), aspartate aminotransferase (AST) increased, or alanine aminotransferase (ALT) increased (9.1% each), diarrhea (6.1%), and colitis (6.1%). There was no Grade 3 or higher hematologic AEs.

In summary, CCA with an IDH1 mutation is a rare, aggressive, and life-threatening malignancy. Ivosidenib is the only approved therapy targeting IDH1-mutated CCA. However, novel scientifically rational combination approaches are needed for this subject population to improve clinical outcomes and emerging science suggests that combination of an IDH1 inhibitor with immunotherapy, *i.e.*, anti-CTLA4 and anti-PD-1 mAbs, may work synergistically to enhance anti-tumor response in previously treated CCA. Although previous or ongoing studies have tested one or more of these drugs in combination, this is the first study that will test a triple combination. Therefore, the study will first test the safety of the combination in a small number of subjects during a Safety Lead-in phase in order to evaluate for DLTs and identify the RCD (For more details, see Section 4.1.4).

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

3. STUDY OBJECTIVES, ENDPOINTS AND ESTIMANDS

The study objectives and corresponding endpoints are summarized in Table (3) 1 and Table (3) 2 for the Safety Lead-in phase and Expansion phase, respectively.

Table (3) 1 - Study Objectives and Endpoints of the Safety Lead-in Phase

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of ivosidenib in combination with nivolumab and ipilimumab and determine the recommended combination dose (RCD) of ivosidenib, nivolumab, and ipilimumab	• Dose limiting toxicities (DLTs) associated with ivosidenib in combination with nivolumab and ipilimumab during the first 2 cycles of treatment • Adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)
Secondary	
To evaluate the pharmacokinetics (PK) of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma concentrations and PK parameters including, but not limited to, area under the concentration-*vs*-time curve (AUC) from 0 to time of last measurable concentration (AUC_{0-t}), AUC over 1 dosing interval at steady state ($AUC_{tau,ss}$), time to maximum concentration (T_{max}), maximum concentration (C_{max}), trough concentration (C_{trough}), apparent volume of distribution (Vd/F), and apparent clearance (CL/F)
To evaluate the pharmacodynamic (PD) effects of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma 2-hydroxygluturate (2-HG) concentration
Exploratory	
To evaluate ivosidenib exposure in tumor tissue	Tumor tissue concentrations of ivosidenib
To evaluate the PK of nivolumab and ipilimumab when given in combination with ivosidenib	Serum concentrations of nivolumab and ipilimumab
To evaluate immunogenicity of nivolumab and ipilimumab when given in combination with ivosidenib	Measurement of anti-drug antibody (ADA) to nivolumab and ipilimumab
To evaluate the PD effects of ivosidenib in tumor tissue when given in combination with nivolumab and ipilimumab	Tumor tissue 2-HG concentration
To identify molecular and cellular biomarkers that may be indicative of clinical response/resistance, PD activity, and the mechanism of action	Associations of pre-treatment molecular and cellular markers with patient outcome Differences in molecular and cellular markers between on-treatment and/or pre-treatment samples

Table (3) 2 - Study Objectives, Endpoints and Estimands of the Expansion Phase

Objectives	Endpoints	Other Estimand Attributes
Primary		
To assess the clinical activity of ivosidenib in combination with nivolumab and ipilimumab using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	Objective response (confirmed complete response [CR] or confirmed partial response [PR]) of anti-tumor activity (using RECIST v1.1)	The primary estimand of interest is the objective response rate (ORR). The attributes of the primary estimand are defined as follows: • Treatment: ivosidenib plus nivolumab and ipilimumab • Population: Safety Analysis Set • Summary measure: objective response (Yes, No) • Intercurrent events (IE): 1. Early treatment discontinuation 2. Administration of further anti-cancer therapy
Secondary		
To confirm the safety and tolerability of the recommended combination dose (RCD) of ivosidenib, nivolumab. and ipilimumab	Adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)	Not applicable
To evaluate additional efficacy parameters to assess anti-tumor activity of ivosidenib in combination with nivolumab and ipilimumab	• Duration of response (DOR), progression-free survival (PFS) and disease control (CR, PR, or SD maintained for at least 5 months), time to response (TTR) according to RECIST v1.1 • Overall survival (OS)	Not applicable
To evaluate the pharmacokinetics (PK) of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma concentrations and PK parameters including, but not limited to, area under the concentration-*vs*-time curve (AUC) from 0 to time of last measurable concentration (AUC_{0-t}), AUC over 1 dosing interval at steady state ($AUC_{tau,ss}$), time to maximum concentration (T_{max}), maximum concentration (C_{max}), trough concentration (C_{trough}), apparent volume of distribution (Vd/F), and apparent clearance (CL/F)	Not applicable
To evaluate the pharmacodynamic (PD) effects of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma 2-hydroxyglutarate (2-HG) concentration	Not applicable

Objectives	Endpoints	Other Estimand Attributes
Exploratory		
To evaluate ivosidenib exposure in tumor tissue	Tumor tissue concentrations of ivosidenib	Not applicable
To evaluate the PK of nivolumab and ipilimumab when given in combination with ivosidenib	Serum concentrations of nivolumab and ipilimumab	Not applicable
To evaluate immunogenicity of nivolumab and ipilimumab when given in combination with ivosidenib	Measurement of anti-drug antibody (ADA) to nivolumab and ipilimumab	Not applicable
To evaluate the PD effects of ivosidenib in tumor tissue when given in combination with nivolumab and ipilimumab	Tumor tissue 2-HG concentrations	Not applicable
To identify molecular and cellular biomarkers that may be indicative of clinical response/resistance, PD activity, and the mechanism of action	Associations of pre-treatment molecular and cellular markers with patient outcome Differences in molecular and cellular markers between on-treatment and/or pre-treatment samples	Not applicable

4. STUDY DESIGN

4.1. Investigational Plan

4.1.1. Study Plan

This is a Phase 1/2, non-comparative, multicenter, open-label study of ivosidenib, an oral mutant IDH1 inhibitor, administered in combination with nivolumab and ipilimumab. Subjects are required to have a histologically confirmed diagnosis of cholangiocarcinoma (CCA), a local molecular IDH1 gene-mutation CCA and not eligible for curative resection, transplantation, or ablative therapies. The study will be conducted in adult subjects with nonresectable or metastatic CCA. Subjects must have progression of disease or treatment intolerance and have received at least 1 but not more than 2 prior treatment regimens for advanced disease (nonresectable or metastatic). All subjects must have received either a gemcitabine- or a 5-fluorouracil (5-FU)–based chemotherapy regimen.

This study consists of a Safety Lead-in phase and an Expansion phase as shown in Figure (4.1.1) 1 and Figure (4.1.1) 2, respectively.

The first phase will be the Safety Lead-in to evaluate the safety and tolerability of ivosidenib in combination with nivolumab and ipilimumab in order to determine the recommended combination dose (RCD). This phase will enroll up to approximately 6-12 DLT-evaluable subjects with nonresectable or metastatic CCA with an IDH1 mutation.

The first 6 subjects enrolled will receive a dose of 500 mg QD of ivosidenib in combination with nivolumab [redacted] mg/kg and ipilimumab [redacted] mg/kg CCI [redacted] followed by nivolumab CCI [redacted] mg CCI [redacted] until progression (up to a maximum of 24 months of nivolumab). Based on the DLT evaluation of 500 mg QD, an additional 6 subjects may be enrolled to test an alternative dose of 250 mg QD. DLTs will be evaluated through Cycle 2 (*i.e.*, during the first 42 days, 21 days/cycle). DLT evaluability is determined by subjects who have received the combination therapy and experienced a DLT through Cycle 2 or who have received CCI [redacted] doses of nivolumab and ipilimumab, respectively, and at least 75% of ivosidenib at the assigned dose through Cycle 2 without experiencing a DLT through Cycle 2. CCI [redacted]

A minimum of 6 DLT-evaluable subjects will be required to evaluate the safety and tolerability of the combination. Subjects who are not DLT evaluable will be replaced. A DRT composed of Sponsor medical, safety, and statistical representatives, together with Principal Investigator(s), will review the available safety data when at least 6 subjects have completed at least 2 cycles of treatment or experienced a DLT within the first 2 cycles.

If at least 6 DLT-evaluable subjects have been treated at a dose level in the Safety Lead-in phase and the RCD has been reached, the DRT will meet to review the data from all subjects before declaring the RCD and initiating the Expansion phase.

The second phase will be an Expansion phase, which will evaluate the clinical activity of ivosidenib in combination with nivolumab and ipilimumab in subjects with nonresectable or metastatic CCA with an IDH1 mutation. Safety and tolerability data of ivosidenib in combination with nivolumab and ipilimumab will be reviewed on an ongoing basis during the study.

This part will be conducted in 2 IDH1-mutated CCA subpopulations:

- Cohort 1: anti-PD1/L1–naïve subpopulation: This subpopulation will include up to approximately 40 participants with nonresectable or metastatic CCA who have not received any anti-PD1/L1 therapy.
- Cohort 2: anti-PD1/L1 previously treated subpopulation: This subpopulation will include up to approximately 40 participants with nonresectable or metastatic CCA who have received anti-PD1/L1 therapy.

Subjects enrolled in this phase will receive the RCD of ivosidenib in combination with nivolumab [redacted] mg/kg and ipilimumab [redacted] mg/kg CCI [redacted] followed by nivolumab at CCI [redacted] mg CCI [redacted] until progression (up to a maximum of 24 total months of nivolumab).

CCI [redacted]

Subjects may continue to receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met. Subjects may continue to receive up to a maximum of 24 months of nivolumab. Subjects who are still deriving clinical benefit after 24 months may continue to receive ivosidenib monotherapy until disease progression, unacceptable toxicity, or other discontinuation criteria are met.

The study design for the Safety Lead-in is shown in Figure (4.1.1) 1 and for the Expansion phase in Figure (4.1.1) 2.

Figure (4.1.1) 1 - Safety Lead-in Phase

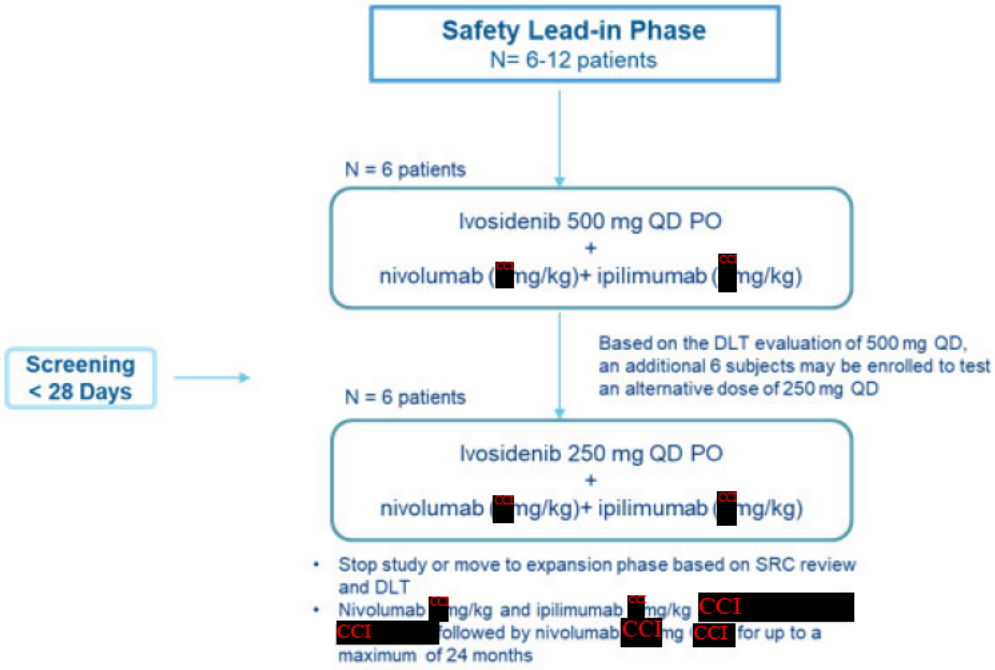
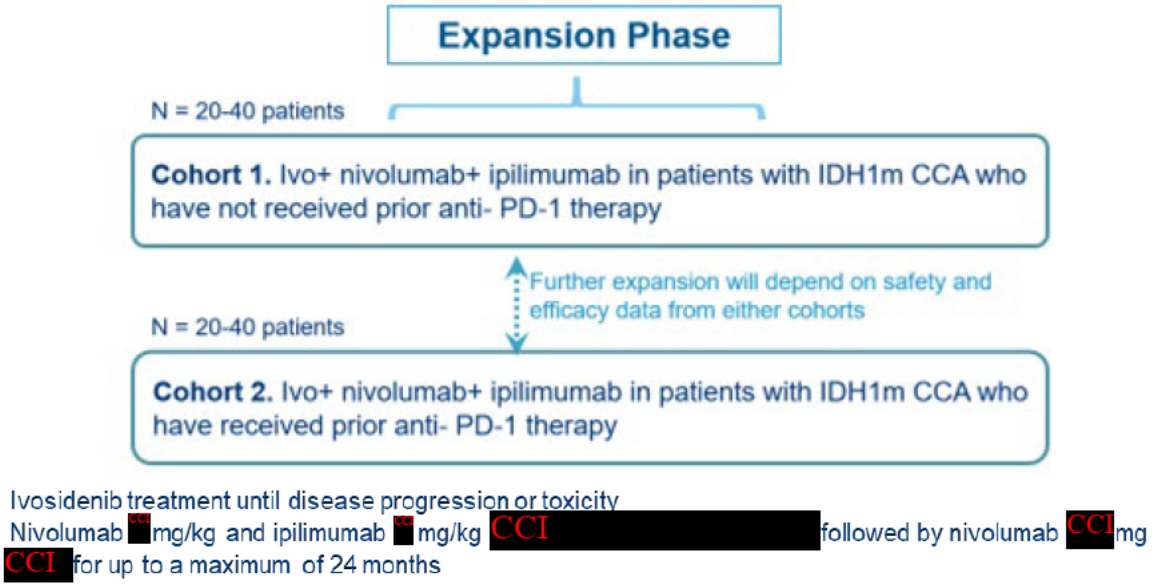


Figure (4.1.1) 2 - Expansion Phase



4.1.1.1. Study Periods

The study will be divided into the following periods for each subject.

4.1.1.2. Screening Period/Inclusion

Following subject signature of the informed consent form (ICF) (the signing of the ICF indicates the start of the study), subject eligibility will be confirmed during a Screening period that will occur within 28 days prior to the first dose of investigational medicinal product (IMP) for subjects in the Safety Lead-in phase and Expansion phase. Subjects will be enrolled based on local IDH1 mutation results. All subjects will have a radiographic evaluation (computed tomography [CT] or magnetic resonance imaging [MRI]) at Screening to confirm the presence of measurable disease (at least one measurable lesion, as defined by RECIST v1.1) according to the site radiologist/Investigator. Additional screening procedures for all subjects include medical, surgical, and medication history; complete physical examination, height, and weight; vital signs; Eastern Cooperative Oncology Group (ECOG) performance status; 12-lead ECG; evaluation of left ventricular ejection fraction (LVEF) (echocardiogram [ECHO], multiple gated acquisition [MUGA] scan, or by other method according to institutional practice); and clinical laboratory assessments (hematology, chemistry, thyroid function tests, coagulation, and pregnancy test). A buccal swab for germ-line mutation analysis will also be obtained at Screening.

In case of non-inclusion of a subject, it is the Investigator's responsibility to ensure, in accordance with the local standards of care and medical practices, that:

- The reason of non-inclusion is explained to the subject.
- Any event associated with any procedure/condition required by the study protocol (*e.g.*, an event occurring following the discontinuation of a forbidden treatment) is collected.
- Adequate alternative medical care is proposed to the subject.

A non-inclusion visit is not mandatorily carried out, provided these requirements are met and documented in the medical file of the subject.

4.1.1.3. Treatment Period

The study will include 2 separate phases, the Safety Lead-in phase and the Expansion phase. Eligible subjects can participate in one of the 2 phases only. Subjects enrolled in Safety Lead-in phase will not participate in the Expansion phase.

Safety Lead-In Phase

Following the Screening period, the first 6 subjects enrolled will receive a dose of 500 mg QD of ivosidenib in combination with nivolumab [redacted] mg/kg and ipilimumab [redacted] mg/kg CCI [redacted] followed by nivolumab CCI mg CCI (up to 24 total doses of nivolumab). Based on the DLT evaluation of 500 mg QD, an additional 6 subjects could be enrolled to test an alternative dose of 250 mg QD. DLTs will be evaluated through Cycle 2 (*i.e.*, during the first 42 days, 21 days/cycle). Subjects may receive up to a maximum of 24 months of nivolumab. Subjects who are still deriving clinical benefit after 24 months may continue to receive ivosidenib monotherapy until disease progression, unacceptable toxicity, or other discontinuation criteria are met (see Section 4.3).

Starting from Cycle 5, subjects in the Safety Lead-in phase who discontinue one IMP for a reason other than disease progression may continue to receive the other IMP with Sponsor

approval until disease progression or other discontinuation criteria (including the criterion of having received a maximum of 24 months of nivolumab) are met.

Expansion Phase

Following the Screening period, subjects enrolled into the Expansion phase will receive ivosidenib at the RCD as determined by the Safety Lead-in phase in combination with nivolumab [redacted] mg/kg and ipilimumab[redacted] mg/kg [redacted] followed by nivolumab at[redacted] mg[redacted]. Subjects may receive up to a maximum of 24 months of nivolumab. Subjects who are still deriving clinical benefit after 24 months may continue to receive ivosidenib monotherapy until disease progression, unacceptable toxicity, or other discontinuation criteria are met (see Section 4.3).

Starting from Cycle 5, subjects in the Expansion phase who discontinue one IMP for a reason other than disease progression may continue to receive the other IMP with Sponsor approval until disease progression or other discontinuation criteria (including the criterion of having received up to a maximum of 24 months of nivolumab) are met.

All subjects will undergo safety assessments throughout the Safety Lead-in and Expansion phase treatment periods, which will include limited physical examination, vital signs including weight, ECOG performance status, ECG, and clinical laboratory assessments (hematology, chemistry, thyroid function tests, coagulation, and pregnancy testing). Serial blood samples will be drawn at specified time points from all subjects receiving ivosidenib in combination with nivolumab and ipilimumab to determine ivosidenib plasma concentration–time profiles and PK parameters, PD, nivolumab and ipilimumab serum concentrations, and anti-drug antibody (ADA) parameters. Archival tumor (collected on Cycle 1 Day 1 [C1D1] only), and buccal swab samples (collected at Screening) and blood samples will be collected for exploratory biomarker analysis. All subjects will undergo radiographic evaluations (MRI or CT) to assess the extent of their disease at Screening and at regular intervals while on-treatment and/or at any time when progression of disease is suspected.

4.1.1.4. End of Treatment/Withdrawal Visit

All subjects will undergo an End of Treatment (EOT) assessment within 7 days after the last dose of IMP (for combination, this is to occur after all 3 IMPs have been discontinued). However, when this is not possible (*e.g.*, dose delay more than 7 days), EOT assessment can be performed at the 30-day safety follow-up visit. Every effort must be made to perform protocol-specified evaluations unless consent to participate in the study is withdrawn.

4.1.1.5. Post-Withdrawal Follow-up and End of Study

Safety Follow-up: Following discontinuation of study treatment, a post-treatment Safety Follow-up visit is to occur 30 (+5) days after the last dose of ivosidenib and immunotherapy. Subjects will be followed for an additional 100 (+5) days after the last dose of immunotherapy, unless they have started another anti-cancer therapy, whichever occurs earlier. Every effort must be made to perform protocol-specified evaluations unless consent to participate in the study is withdrawn.

PFS and Overall Survival Follow-up: Subjects who discontinue study treatment for reasons other than disease progression or withdrawal of consent from treatment and are alive by EOT will enter PFS follow-up with the same schedule of assessments as before study treatment discontinuation, until documented disease progression, death, the start of subsequent anti-cancer therapy, withdrawal of consent, or the end of study/study termination. Following discontinuation of study treatment, all subjects will be followed for survival. Subjects will be contacted every 12 weeks (± 2 weeks) after the subject experiences documented disease progression or begins subsequent anti-cancer therapy. This contact will continue for up to 2 years after the last subject has been enrolled, or until end of study, withdrawn consent, or are lost to follow-up, or the Sponsor has terminated the study, whichever occurs first.

Each subject will have an End of Study visit defined as the time at which the subject has permanently discontinued treatment and has completed the Safety Follow-up visit and survival follow-up period, or has died, been lost to follow-up, or withdrawn consent from the study or the Sponsor has terminated the study, whichever occurs first.

4.1.1.6. End of Trial

End of trial is defined as the date of the last visit/follow-up of the last subject (including visit or remote contact), or the date of the last contact attempt if the last subject is declared lost to follow-up.

4.1.2. Investigation Schedule

Assessments for subjects in the Safety Lead-in and Expansion phases are in Table (4.1.2) 1. PK and PD blood sampling are described in Table (4.1.2) 2 and Table (4.1.2) 3 for the Safety Lead-in phase and Expansion phase, respectively.

Table (4.1.2) 1 - Schedule of Assessments for Subjects in the Safety Lead-in Phase and Expansion Phase

Visit/Cycle	**Screening[1]**	**Cycle 1 (21 Days)**			**Cycle 2 (21 Days)**		**Cycles 3 and 4 (21 Days)**	**Cycle 5 and Beyond (28 Days Each Cycle)**	**End of Treatment [2]**	**Safety Follow-up[2]**		**PFS Follow -up[3]**	**Survival Follow-up**
Study Day	**D-28 to D-1**	**D1**	**D8**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**	**Within 7 Days After Last Dose**	**30 (+5) Days After Last Dose**	**100 (+5) Days After Last Nivolumab Dose**		**Every 12 weeks (± 2 weeks)**
Allocation to IMP[4]		X			X		X	X					
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics	X												
Disease History	X												
Medical and Surgical History	X												
Complete Physical Exam	X												
Limited Physical Exam		X		X	X	X	X	X	X				
Height and Weight[5]	X	X			X		X	X					
ECOG Performance Status	X	X			X		X	X	X	X			
Vital Signs[6]	X	X		X	X	X	X	X	X				
12-lead ECG[7,8]	X	X	X	X	X		X	X	X	X			
LVEF (ECHO, MUGA scan, or by other method according to institutional practice)	X												
Hematology[9]	X	X		X	X	X	X	X	X				
Serum Chemistry[10]	X	X		X	X	X	X	X	X				
Coagulation Studies[11]	X												
Pregnancy Test[12]	X[12]	X[12]			X[12]		X[12]	X[12]	X[12]				
Thyroid Function Tests[13]	X	X					X (only at C3D1)	X (every other cycle)	X				
Radiographic Evaluation of Disease[14]	X (D-21 to D-1)						X (only C3D1)[15]	X[15] (every other cycle)	X[15,16]			X	
Ivosidenib Administration[17]			X										

Visit/Cycle	**Screening[1]**	**Cycle 1 (21 Days)**			**Cycle 2 (21 Days)**		**Cycles 3 and 4 (21 Days)**	**Cycle 5 and Beyond (28 Days Each Cycle)**	**End of Treatment [2]**	**Safety Follow-up[2]**		**PFS Follow -up[3]**	**Survival Follow-up**
Study Day	**D-28 to D-1**	**D1**	**D8**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**	**Within 7 Days After Last Dose**	**30 (+5) Days After Last Dose**	**100 (+5) Days After Last Nivolumab Dose**		**Every 12 weeks (± 2 weeks)**
Nivolumab Administration[18]		X			X		X	X (every cycle)					
Ipilimumab Administration[19]		X			X		X						
IMP Compliance[20]					X		X	X	X				
Tumor Biopsy[21]	X						X (± 7 days for biopsy collection)		X				
Buccal Swab for Germ-line Mutation Analyses[22]	X												
Blood Sampling for Exploratory Biomarkers[23]	X				X		X	X	X				
Adverse Events[24]	X	X		X	X	X	X	X	X	X	X		
Prior and Concomitant Medications/Procedures[25]	X	X		X	X	X	X	X	X	X	X		
Subsequent Anti-cancer Therapy									X	X	X	X	X
Survival Status[26]													X

Abbreviations AE = adverse event; C = Cycle; CFR = Code of Federal Regulations; CT = computed tomography; D = Day; ECG = electrocardiogram; ECHO = echocardiography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = End of Treatment; FFPE = formalin-fixed paraffin-embedded; GDPR = General Data Protection Regulation; HIPAA = Health Insurance Portability and Accountability Act; ICF = informed consent form; IDH1 = Isocitrate dehydrogenase-1; IMP = investigational medicinal product; IV = intravenous; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; PFS = progression-free survival; Q3W = once every 3 weeks; Q4W = once every 4 weeks; QTcF = heart rate-corrected QT interval by Fridericia's method; RTSM = Randomisation and Trial Supply Management; SAE = serious adverse event.

Note One, or two if required by local regulation, original information and consent form(s) must be completed, dated, and signed personally by the participant and by the person responsible for collecting the informed consent. According to each study participant's own preference, the ICF could be made available both printed on paper or/and electronically through a HIPAA, 21 CFR Part 11, and GDPR compliant web-based platform. Local regulations permitting, the electronic signature for the ICF could be made available to interested study participants. Interested study participants will be offered the possibility to replace certain in-person visits to the research site by televisits. This means that some study visits could be conducted using a HIPAA, 21 CFR Part 11, and GDPR compliant web-based platform, as per each study participant's own preference. Follow-up (for survival status until the end of the study) can be done remotely by using various telecommunication technologies including but not limited to phone, web-based remote video-calling, and shared electronic medical records.

1. Day -28 is relative to first dose of IMP.
2. All subjects will undergo an EOT assessment within 7 days after the last dose of IMP (for combination, this is to occur after all 3 IMPs have been discontinued). However, when this is not possible (*e.g.,* dose delay more than 7 days), EOT assessment can be performed at the 30-day safety follow-up visit. A second Safety Follow-up will occur 100 (+5) days after last nivolumab dose or ipilimumab if no other anti-cancer therapy is initiated.
3. Subjects who discontinue study treatment for reasons other than disease progression or withdrawal of consent and are alive by EOT will enter PFS follow-up with the same schedule of assessments as before study treatment discontinuation, until documented disease progression, death, start of subsequent anti-cancer therapy, withdrawal of consent, or the end of study/study termination.
4. Allocation of IMP will occur via RTSM.
5. Height is to be obtained only at Screening assessment.
6. Systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Assessments should be conducted while the subject is seated or supine.
7. Subjects with a QTcF of ≥ 450 msec at baseline will not be allowed to enroll in the study. Up to three 12 lead ECG tests under stable condition can be performed at each visit during screening and throughout treatment and study follow-up.
8. ECG can be performed at any time during the study visit (on-site or at local clinic); however, it is required once weekly for the first 3 weeks of treatment, and then once every cycle for the duration of therapy.
9. Hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, and platelet count. Hemoglobin criteria of ≥ 9.0 g/dL or ≥ 5.6 mmol/L at Screening must be met without packed red blood cell transfusion within the prior 2 weeks. Subjects can be on stable dose of erythropoietin (≥ approximately 3 months). On C1D1, assessments should be conducted prior to IMP administration.
10. Sodium, potassium, chloride, calcium, magnesium, phosphorus, carbon dioxide, albumin, glucose, blood urea nitrogen (BUN)/UREA, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, total bilirubin, direct bilirubin, and indirect bilirubin. On C1D1, assessments should be conducted prior to IMP administration.
11. Activated partial thromboplastin time and either prothrombin time or international normalized ratio.
12. For women of childbearing potential, a serum pregnancy test will be performed at Screening, and a urine pregnancy test will be conducted on the day of IMP administration and is to be confirmed negative prior to dosing. If the urine pregnancy test is positive and cannot be confirmed negative, a serum pregnancy test must be performed and shown to be negative within 24 hours prior to the first day of IMP administration. An extension up to 72 hours prior to the start of study treatment is permissible in situations where the results cannot be obtained within the standard 24-hour window.
13. Thyroid function test includes triiodothyronine (T3) or free T3, free thyroxine, and thyroid stimulating hormone. Thyroid function tests are to be performed every 6 weeks for the first 4 cycles and then every 8 weeks starting from Cycle 5 and to be performed at EOT. On C1D1, assessments should be conducted prior to IMP administration. Thyroid function test results obtained after the visit are acceptable so long as the value at screening was normal or considered not clinically significant per investigator assessment.
14. Tumor assessments will include all known or suspected disease sites. CT imaging of the chest, abdomen, and pelvis (torso) with triphasic IV contrast should be performed at baseline and on study. For subjects with allergy to IV iodine contrast, CT chest without IV contrast and MRI abdomen with IV contrast should be performed at baseline and on study. Brain scans with CT or MRI should be performed at baseline in subjects with known treated brain metastases and on study at the same imaging time points as torso imaging. Additional anatomy should be imaged based on the signs and symptoms of individual subjects at baseline and follow-up. Radiographic assessment (CT or MRI or other imaging modalities as appropriate per RECIST v1 1 Appendix 4) for evaluation of disease response to be conducted at Screening (Day -21 to Day -1), every 6 weeks (±7 days) for the first 2 assessments (*i.e.*, through Week 12), and then every 8 weeks (± 7 days) thereafter independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. Tumor assessment frequency can be reduced to every 12 weeks after 2 years of treatment initiation.
15. Response to treatment is to be assessed at this visit if the subject discontinues treatment for reasons other than disease progression or start of another anticancer therapy.
16. If a subject goes off treatment for reasons other than disease progression or withdrawal of consent from treatment, response assessments will be conducted at the EOT visit
17. Ivosidenib is to be taken daily. Subjects should be instructed to take their daily dose at approximately the same time each day. Each daily dose should be taken with or without food. Subjects taking ivosidenib with food should be advised to avoid grapefruit or grapefruit products and avoid consuming a high-fat meal. If the subject forgets to take the daily dose, then they should take ivosidenib within 12 hours after the missed dose. If more than 12 hours have elapsed, then that dose should be omitted, and the subject should resume treatment with the next scheduled dose. The dose on C1D1, C1D15, and Day 1 of each cycle thereafter is to occur in-clinic to allow for pre-treatment assessments and to accommodate PK sampling. In subjects receiving the combination, on days when nivolumab and ipilimumab are administered, ivosidenib should be administered approximately 30 minutes before the start of the nivolumab infusion.
18. Nivolumab is to be administered over an approximately 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 30 minutes (-5 minutes/+10 minutes). When study treatments nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed, and subject has been observed to ensure that no infusion reaction has occurred.
19. Ipilimumab is to be administered over an approximately 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 30 minutes (-5 minutes/+10 minutes). When study treatments nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed, and subject has been observed to ensure that no infusion reaction has occurred. The time in between nivolumab and ipilimumab infusions is expected to be within approximately 30-minutes.
20. Treatment compliance for ivosidenib is to be assessed based on the drug diary and/or return of unused drug.
21. Tumor tissue for retrospective central laboratory confirmation of IDH1 gene mutation status and exploratory biomarker analysis at Screening is requested. Subjects will have locally documented presence of the IDH1 gene mutation for inclusion. If a subject cannot undergo a biopsy at Screening, collection of archival tumor tissue from the most recent biopsy/resection of at least 20 freshly cut, unstained FFPE slides (4-

5 µm each) plus 1 H&E slide will be submitted at a later time together with the pathology report upon sponsor's request. Tumor biopsies are to be collected at baseline, C3D1, and EOT from similar anatomical locations for exploratory biomarker analyses including PK/PD. In case of limited tissue amounts, biopsy samples will be formalin fixed and paraffin embedded. Please refer to the laboratory manual for priorities in tissue processing. If a required tumor biopsy (any time point) cannot be performed due to concerns around subject safety, a discussion with the Sponsor is required and biopsy can be omitted. Further details on screening and on-treatment biopsy collections are provided in the laboratory manual. Additional unscheduled tumor biopsy collected as standard of care, if any, will be used for the optional analysis of biomarkers (including genomic biomarkers).

22. A buccal swab for germ-line mutation analysis will be obtained at Screening.
23. Blood samples for exploratory biomarker assessments, including plasma circulating tumor DNA, will be collected at Screening and Day 1 of every cycle through Cycle 6, followed by every 6 months thereafter, and at EOT.
24. From the time of informed consent signing through the first dose of IMP, SAEs resulting from a study-related procedure and assessed as related to that procedure, as well as all fatal AEs whether or not related to research procedures, must be recorded. All AEs will be recorded from all subjects from the date of first dose through 30 days following the last dose of ivosidenib and/or nivolumab or ipilimumab, whichever occurs later. Following the 30-day Safety Follow-up period, any SAEs that occur within 100 days after last dose of immunotherapy are to be reported, or until the subject initiates another anti-cancer therapy, whichever is earlier. Only SAEs that are considered as related to either IMP by the Investigator are to be reported after the respective Safety Follow-up periods. Fatal events, related or not to the research, occurring after ICF signature and before first IMP administration, must be reported on an AE form.
25. All concomitant medications/procedures within 21 days of the first dose of IMP through 30 days (+ 5 days) after the last dose of ivosidenib and/or immunotherapy and through 100 days after the last dose of immunotherapy (whichever is later) are to be reported on the eCRF.
26. Subjects will be contacted every 12 weeks (± 2 weeks) after the subject experiences documented disease progression or begins subsequent anti-cancer therapy for up to 2 years after the last subject has been enrolled, or until death, lost to follow-up, withdrawal of consent from overall study participation, or Sponsor ending study, whichever occurs first.

Table (4.1.2) 2 - Pharmacokinetic and Pharmacodynamic Sampling for Subjects in the Safety Lead-in Phase: Ivosidenib in Combination with Nivolumab and Ipilimumab

Visit/Cycle:	**Screening**	**Cycle 1 (21 Days)**		**Cycle 2 (21 Days)**	**Cycle 3 (21 Days)**	**Cycle 4 (21 Days Each Cycle)**	**Cycle 5 and Beyond (28 Days Each Cycle)**
Study Day:	**D-28 to D-1**	**D1**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**
Blood Sample for Ivosidenib PK Pre-dose[1,2,3]		X	X	X	X	X	X[3]
Blood Sample for PD (2-HG) Pre-dose[1,2,3]		X	X	X	X	X	X[3]
Blood Sample for Nivolumab PK and Nivolumab ADA Pre-dose[1,2,4]		X		X	X	X	X[4]
Blood Sample for Ipilimumab PK and Ipilimumab ADA Pre-dose[1,2,5]		X		X	X	X	
Tumor Biopsy for Ivosidenib PK Pre-dose[6,7]	X						
Tumor Biopsy for Ivosidenib PK Post-dose[6]					X (± 7 days for biopsy collection)		
Tumor Biopsy for PD (2-HG) Pre-dose[6,7]	X						
Tumor Biopsy for PD (2-HG) Post-dose[6]					X (± 7 days for biopsy collection)		
Blood Sample for Nivolumab and Ipilimumab PK Post-dose[8]		X (EOI)					
Blood Sample for Ivosidenib PK Post-dose[8]							
2 Hours post-dose				X			
3 Hours post-dose				X			
4 Hours post-dose				X			
6 Hours post-dose				X			

Abbreviations: 2-HG = 2-hydroxyglutarate; ADA = anti-drug antibody; D = Day; EOI = End of Infusion; PD = pharmacodynamic; PK = pharmacokinetic.

1. On the days when pre-dose samples are to be collected, subjects should be instructed to not take that day's dose of ivosidenib, nivolumab or ipilimumab dose until PK/PD samples have been collected (ivosidenib dose is to be administered in the clinic).
2. Pre-dose blood samples for ivosidenib, nivolumab, and ipilimumab PK, ADA, and 2-HG are to be collected from all subjects within 30 minutes before ivosidenib, nivolumab, and ipilimumab dosing. All pre-dose samples may be collected in one blood draw.
3. Pre-dose blood samples for ivosidenib PK and 2-HG are to be collected on C1D1, C1D15, C2D1, C3D1, C4D1, C5D1, and Day 1 of every cycle through Cycle 13, and Day 1 of every other cycle thereafter (*e.g.*, Cycles 15, 17, etc.).
4. Pre-dose blood samples for nivolumab PK and nivolumab ADA are to be collected on C1D1, C2D1, C3D1, C4D1, and Day 1 of every 4 cycles up to 2 years (*e.g.*, C8D1, C12D1, etc.)
5. Pre-dose blood samples for ipilimumab PK and ipilimumab ADA are to be collected on C1D1, C2D1, C3D1, and C4D1.
6. Refer to the lab manual for details on tumor biopsy collection.
7. If a subject cannot undergo a biopsy at Screening, archived fresh-frozen tumor biopsy, if available, can be used for the measurement of baseline 2-HG.
8. Post-dose blood samples to be collected within ± 10 minutes of the specified time.

Table (4.1.2) 3 - Pharmacokinetic and Pharmacodynamic Sampling for Subjects in the Expansion Phase: Ivosidenib in Combination with Nivolumab and Ipilimumab

Visit/Cycle:	**Screening**	**Cycle 1 (21 Days)**		**Cycle 2 (21 Days)**	**Cycle 3 (21 Days)**	**Cycle 4 (21 Days)**	**Cycle 5 and beyond (28 Days Each Cycle)**
Study Day:	**D-28 to D-1**	**D1**	**D15 (± 2 Days)**	**D1 (± 3 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**
Blood Sample for Ivosidenib PK **Pre-dose**[1,2,3]		X	X	X	X	X	X[3]
Blood Sample for PD (2-HG) **Pre-dose**[1,2,3]		X	X	X	X	X	X[3]
Blood Sample for Nivolumab PK and Nivolumab ADA Pre-dose[1,2,4]		X		X	X	X	X[4]
Blood Sample for Ipilimumab PK and Ipilimumab ADA Pre-dose[1,2,5]		X		X	X	X	
Tissue Biopsy for Ivosidenib PK **Pre-dose**[6,7]	X						
Tissue Biopsy for Ivosidenib PK **Post-dose**[6]					X (± 7 days for tissue sample only)		
Tissue Biopsy for PD (2-HG) **Pre-dose**[6,7]	X						
Tissue Biopsy for PD (2-HG) **Post-dose**[6]					X (± 7 days for tissue sample only)		
Blood Sample for Nivolumab and Ipilimumab PK **Post-dose**[8]		X (EOI)					
Blood Sample for Ivosidenib PK **Post-dose**[8]							
2 hr post-dose						X	
3 hr post-dose						X	
4 hr post-dose						X	
6 hr post-dose						X	

Abbreviations: 2-HG = 2-hydroxyglutarate; ADA = anti-drug antibody; D = Day; EOI = End of Infusion; PD = pharmacodynamic; PK = pharmacokinetic.

1. On the days when pre-dose samples are to be collected, subjects should be instructed to not take that day's dose of ivosidenib, nivolumab or ipilimumab dose, until PK/PD samples have been collected (ivosidenib dose is to be administered in the clinic). If it is known that a dose is going to be delayed, then collect the pre-dose samples just prior to the delayed dose. However, if a pre-dose sample is collected, but the dose is subsequently delayed, do not collect an additional pre-dose sample.
2. Pre-dose blood samples for ivosidenib, nivolumab, and ipilimumab PK, ADA, and 2-HG are to be collected from all subjects within 30 minutes before ivosidenib, nivolumab, and ipilimumab dose. All pre-dose samples may be collected in one blood draw.
3. Pre-dose blood samples for ivosidenib PK and 2-HG are to be collected on C1D1, C1D15, C2D1, C3D1, C4D1, C5D1, and Day 1 of every cycle through Cycle 13, and Day 1 of every other cycle thereafter (e.g., Cycles 15, 17, etc.).
4. Pre-dose blood samples for nivolumab PK and nivolumab ADA are to be collected on C1D1, C2D1, C3D1, C4D1, and Day 1 of every 4 cycles up to 2 years (e.g., C8D1, C12D1, etc.)
5. Pre-dose blood samples for ipilimumab PK and ipilimumab ADA are to be collected on C1D1, C2D1, C3D1, and C4D1.
6. Refer to the lab manual for details on tumor biopsy collection.
7. If a subject cannot undergo a biopsy at Screening, archived fresh-frozen tumor biopsy, if available, can be used for the measurement of baseline 2-HG.

8. Post-dose blood samples to be collected within ±10 minutes of the specified time.

A mean volume of blood collected for all type of analyses is shown in Table (4.1.2) 4.

Table (4.1.2) 4 - Mean Blood Volume for CL1-95031-006

Visit/Cycle	Total volume/visit (mL)	Total volume/cycle (mL)
Screening	39.7	39.7
C1D1	53	67
C1D15	**14**	
C2D1	60	79
C2D15	19	
Cycle 3	48	48
Cycle 4	48	48
Cycle 5	41	41
Cycle 6	30	30
ODD cycles (C7, C9, C1, etc.)	9	
Even cycles (C8, C10, C12, etc.)	from 3 to 27 mL depending on assessments, except for cycles Cycle 14 and Cycle 22 where no blood draws are planned	
EOT	32	32

4.1.3. Dose Justification

4.1.3.1. Dose Justification for Ivosidenib

The selection of the 500 mg QD clinical dose of ivosidenib was based on PD (2-HG suppression), PK, safety, and efficacy data from the Phase 1 (AG120-C-002) and Phase 3 (AG120-C-005) studies. The 500-mg dose level is also the approved dose for the US Marketing Authorization of ivosidenib for the CCA indication (TIBSOVO®, 2021).

Plasma ivosidenib exposure increases in a less than dose-proportional manner from 200 mg to 1,200 mg QD, with exposure plateauing at daily doses above 500 mg QD. Mean plasma 2-HG concentrations for subjects with CCA were elevated at baseline (ranging from 222 to 5,220 ng/mL). After multiple doses of ivosidenib, plasma 2-HG levels were substantially reduced to concentrations similar to healthy subjects (CCI ng/mL). No additional 2-HG suppression was observed at doses > 500 mg QD compared with 500 mg QD, while doses < 500 mg QD were associated with lower levels of suppression. In tumor biopsies of subjects with CCA, near maximal mean reduction in 2-HG concentrations of 82.2% (coefficient of variation, 32.4%) was observed at the 500 mg QD dose. Analysis of the relationship between ivosidenib exposure and QT interval prolongation demonstrated that the risk of QT interval prolongation increases with increases in plasma C_{max} and suggests that doses higher than 500 mg QD may be associated with longer QT intervals.

In Study AG120-C-002, there have been minimal dose interruptions, and no apparent dose relationship for any commonly reported TEAEs or Grade ≥ 3 TEAEs. No DLTs were reported in the study. The Phase 3 study, AG120-C-005, demonstrated that as a single agent in subjects with advanced CCA, ivosidenib was generally well tolerated with a manageable safety profile.

The efficacy of ivosidenib at the recommended 500 mg QD dose was supported by the efficacy results from Study AG120-C-002. As of the 16 January 2019 cutoff date, the median OS was CCI at the 500 mg QD level.

The efficacy of ivosidenib at the recommended dose of 500 mg QD in subjects with CCA was established based upon the efficacy results of ivosidenib from Study AG120-C-005. Improvement in PFS by Independent Review Committee assessment was demonstrated for subjects randomized to treatment with ivosidenib compared with placebo (1-sided p-value < 0.0001; HR = 0.37; 95% CI: 0.25, 0.54). A benefit in OS was also observed in favor of ivosidenib.

In summary, the PK and PD profiles along with the safety and efficacy results of ivosidenib in subjects with CCA support selection of the 500 mg QD dose.

4.1.3.2. Dose Justification for Nivolumab and Ipilimumab Combination

The nivolumab and ipilimumab combination is currently approved in the US and EU in multiple tumor types, including melanoma, NSCLC, RCC, and CRC using a regimen of either nivolumab [redacted] mg/kg and ipilimumab [redacted] mg/kg or nivolumab [redacted] mg/kg and ipilimumab [redacted] mg/kg.

NIVO has a wide therapeutic index with no maximum tolerated dose identified at doses up to 10 mg/kg Q2W. Nivolumab PK was assessed using a population PK approach for both single-agent nivolumab and nivolumab with ipilimumab. When nivolumab [redacted] mg/kg was administered in combination with ipilimumab [redacted] mg/kg, the clearance (CL) of nivolumab was increased by 29%, and the CL of ipilimumab was unchanged compared with nivolumab administered alone. When nivolumab [redacted] mg/kg was administered in combination with ipilimumab [redacted] mg/kg, the CL of nivolumab and ipilimumab were unchanged. Additionally, the presence of anti-nivolumab antibodies increased the CL of nivolumab.

Subjects enrolled in this study will receive ivosidenib 500 mg QD in combination with nivolumab [redacted] mg/kg and ipilimumab [redacted] mg/kg concurrently [redacted]. The dosing regimen for nivolumab [redacted] mg/kg and ipilimumab [redacted] mg/kg was selected based on the encouraging clinical activity observed in previously treated BTC (Klein *et al*, 2020) and the current approval for this dosing regimen in advanced RCC and metastatic CRC. Additionally, the lower dose of ipilimumab ([redacted] mg/kg) provides a more manageable safety profile for this subject population.

4.1.3.3. Dose Justification for Nivolumab Flat Dose

After initiation of treatment and completion of the first [redacted] doses of nivolumab and ipilimumab combination, subjects will receive a flat dose of nivolumab [redacted] mg [redacted] for up to a maximum of 24 months. Relatively flat Exposure-Response (E–R) relationships were observed for safety across tumor types as monotherapy and in combination with ipilimumab which suggests that no additional washout is warranted before starting the NIVO 480 mg Q4W maintenance dose (Zhao *et al*, 2020).

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg once every 2 weeks (Q2W). Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications (OPDIVO, 2020). The less frequent 480 mg Q4W dosing regimen can reduce the burden to subjects of frequent, lengthy intravenous (IV) treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

4.1.4. Safety Lead-in Phase

4.1.4.1. Dose Administration Schedule

The Safety Lead-in phase will evaluate the safety and tolerability of ivosidenib in combination with nivolumab and ipilimumab in order to determine the RCD. This phase will enroll approximately 6-12 subjects with nonresectable or metastatic CCA with an IDH1 mutation.

The first 6 subjects enrolled in the Safety Lead-in phase will receive a dose of 500 mg QD of ivosidenib in combination with nivolumab [redacted] mg/kg and ipilimumab [redacted] mg/kg [redacted] followed by nivolumab at [redacted] mg [redacted] until progression (up to a maximum of 24 months). Depending on the DLT evaluation by the DRT, an alternative dose of 250 mg QD of ivosidenib, with the same doses of nivolumab and ipilimumab may be evaluated. A total of 12 DLT-evaluable subjects could be enrolled.

DLTs will be evaluated through Cycle 2 (*i.e.*, during the first 42 days, 21 days/cycle). DLT evaluability is determined by subjects who have received the combination therapy and experienced a DLT through Cycle 2 or who have received at least 2 doses of nivolumab and ipilimumab, respectively, and at least 75% of ivosidenib at the assigned dose through Cycle 2 without experiencing a DLT through Cycle 2. A minimum of 6 DLT-evaluable subjects will be required to evaluate the safety and tolerability of the combination.

Subjects who are not DLT evaluable will be replaced. A DRT composed of Sponsor medical, safety, and statistical representatives, together with Principal Investigator(s), will review the available safety data when at least 6 DLT-evaluable subjects have completed at least 2 cycles of treatment or experienced a DLT within the first 2 cycles.

On days when nivolumab and ipilimumab are administered, the ivosidenib dose will be administered in the clinic.

4.1.4.2. DLT Definition

All toxicities will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 based on the Investigator assessment. The DLT window of observation will be the first 42 days of dosing (*i.e.*, Cycles 1 and 2) of the Safety Lead-In phase. The occurrence of any of the following toxicities during the first 42 days of dosing (*i.e.*, through Cycle 2) will be considered a DLT if assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and considered to be related to study treatment by the Investigator.

In order to be evaluable for DLT, a subject must have had a DLT during Cycle 1 or 2, or have received 75% or more of the planned doses of ivosidenib and 2 full doses of nivolumab and ipilimumab through Cycle 2 and have not experienced a DLT. The subject must also be considered by the Investigator and Sponsor to have sufficient safety data available to conclude that a DLT did not occur.

Any of the following will be considered as DLTs that may be applicable for immuno-oncology (IO) therapy and ivosidenib:

- Any Grade ≥ 4 irAE.
- Any Grade 3 irAE (excluding colitis, pneumonitis, or carditis) that does not improve to Grade 2 within 7 days after onset of the event despite optimal medical management including systemic corticosteroids or does not improve to Grade ≤ 1 or baseline within 14 days.
- Any Grade ≥ 3 colitis.
- Any Grade 3 non-infectious pneumonitis irrespective of duration.
- Any Grade ≥ 2 pneumonitis that does not resolve to Grade ≤ 1 within 7 days of the initiation of maximal supportive care.
- Any Grade ≥ 2 myocarditis.
- Any Grade ≥ 2 neurological toxicity including Guillain-Barre syndrome, myasthenia gravis, encephalitis, and myelitis.
- AST or ALT > 3 × the upper limit of normal (ULN) with concurrent increase in total bilirubin > 2 × ULN without evidence of cholestasis or alternative explanations, *e.g.*, viral hepatitis, disease progression in the liver (Hy's law).
- Any Grade ≥ 3 non-irAE, except for those listed below.
- Any death unless related to disease progression, intercurrent illness, concomitant medications, or extraneous causes.

The DLT definition excludes the following conditions:

- Grade 3 QTc prolongation resolving to Grade 1 within 7 days.
- Grade 3 fatigue lasting ≤ 7 days.
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic.
- Grade 3 inflammatory reaction attributed to a local anti-tumor response (*e.g.*, inflammatory reaction at sites of metastatic disease, lymph nodes).
- Concurrent vitiligo or alopecia of any CTCAE grade.
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 7 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility.
- Grade 3 or 4 lymphopenia.
- Isolated Grade 3 thrombocytopenia that is not associated with clinically significant bleeding and does not require medical intervention.
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.
- Isolated Grade 3 amylase or lipase abnormalities that are not associated with clinical signs/symptoms or findings on imaging consistent with pancreatitis.

4.1.4.3. DLT Management

Ivosidenib, nivolumab, and ipilimumab must be immediately interrupted for any subject who experiences a DLT. If a DLT occurs, the subject should be withdrawn from all 3 drugs unless in the opinions of the Investigator, the subject is deriving clinical benefit and the AE can be managed without recurrence, and with Sponsor approval. If ivosidenib is resumed following a DLT, it should be resumed at a reduced dose (250 mg) after the AE has resolved to Grade 1 or

baseline, with approval from the Sponsor. If nivolumab and/or ipilimumab is resumed, it will be at the original starting dose and frequency without modification.

4.1.4.4. Reporting of DLT

All DLTs will be reported to I.R.I.S. within 24 hours after the Investigator becomes aware via the DLT form in the electronic case report form (eCRF). After completing the DLT form, the Investigator must also complete the Adverse Event page of the eCRF without waiting for the results of the clinical outcome or of additional investigations. When the DLT form is submitted, an email will be immediately and automatically sent to the Sponsor.

If the eCRF is unavailable when the Investigator is informed of the DLT, the Investigator should:

- Report the DLT on a paper DLT form.
- Send the form by email immediately to I.R.I.S. at the following address: *CL1-95031-006@servier.com*.

As soon as the eCRF becomes available, the site must enter the data in the eCRF.

4.1.4.5. Decision Process and Decision Rules

Subjects will receive a dose of 500 mg QD of ivosidenib in combination with nivolumab [redacted] mg/kg and ipilimumab [redacted] mg/kg CCI [redacted] followed by nivolumab at CCI mg CCI until progression (up to a maximum of 24 months).

At the end of Cycle 2, if ≥ 33% of DLT-evaluable subjects have experienced a DLT, further dosing in that cohort will be halted and the dose of ivosidenib will be reduced to 250 mg for all subjects in that cohort. The DRT may recommend enrolling up to an additional 6 subjects to receive ivosidenib at a 250 mg QD dose level, and the same dose stopping rules will be applied after review of the safety data through Day 42 (through Cycle 2). The DRT may decide to cease enrollment in a dosing cohort if fewer than 2 subjects experience DLTs but the nature of the event(s) is deemed a significant risk to subjects at that dose level. Because the immune-modulating regimen of nivolumab and ipilimumab itself may give rise to Grade 3 or 4 toxicity, the DRT will also consider the aggregate treatment-emergent data in relation to the known toxicity profile of nivolumab and ipilimumab and determine the acceptability of the safety profile of the combination. If 0 or 1 of the 6 evaluable subjects experiences a DLT during the first 2 cycles at the 500 mg or the 250 mg QD dose level, the study may proceed to the Expansion phase.

4.1.4.6. Replacement of Subjects in the Safety Lead-in Phase

Subjects who do not meet criteria to be DLT evaluable (see Section 4.1.4.2) will be replaced.

4.1.5. Expansion Phase

4.1.5.1. Dose Administration Schedule

Once the RCD of ivosidenib in combination with nivolumab and ipilimumab has been determined, the Expansion phase of the study will begin. Participants enrolled in this phase will receive ivosidenib at the RCD in combination with nivolumab at [redacted] mg/kg and ipilimumab at [redacted] mg/kg CCI [redacted] followed by nivolumab at CCI mg CCI until progression (up to a maximum of 24 months).

This part will be conducted in 2 IDH1-mutated CCA subpopulations:

- Cohort 1: anti-PD1/L1 naïve subpopulation: This subpopulation will include up to approximately 40 participants with nonresectable or metastatic CCA who have not received any anti-PD1/L1 therapy.
- Cohort 2: anti-PD1/L1 previously treated subpopulation: This subpopulation will include up to approximately 40 participants with nonresectable or metastatic CCA who have received anti-PD1/L1 therapy.

In both cohorts, subjects will receive ivosidenib at the assigned dose on Days 1 through 21 in 21-day cycles for first 4 cycles followed by 28-day cycles starting with Cycle 5. Dosing is continuous, and there are no planned rest periods. On days when subjects are receiving nivolumab and ipilimumab, ivosidenib should be administered approximately 30 minutes before the start of the infusion.

4.2. Measures to Minimize Bias

This is an open-label study. No blinding to study medication is required.

Products administered in this study (the IMPs) are ivosidenib, nivolumab, and ipilimumab. Ivosidenib will be supplied by the Sponsor, and nivolumab and ipilimumab will be supplied by Bristol-Myers Squibb.

All products will be labeled as investigational product for this study as required by local regulations.

Table (4.2) 1 provides a description of the IMP(s).

Table (4.2) 1 - Description of the IMPs

	Ivosidenib	**Nivolumab**	**Ipilimumab**
Pharmaceutical form	Tablet	Liquid	Liquid
Unit dosage	250 mg/tablet	[redacted] mg/mL ([redacted] mL)	[redacted] mg/mL ([redacted] mL)
Appearance, color	Blue oval-shaped film-coated tablet debossed "IVO" on one side and "250" on the other side	Clear to opalescent, colorless to pale-yellow liquid that may contain few light particles	Clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particulates
Composition	Lactose monohydrate	Sodium	Sodium

The labeling of packages complies with the regulatory requirements of each country involved in the study.

Ivosidenib will be provided as 60-count bottles of 250 mg tablets. On Day 1 of each cycle, subjects will receive one small box containing one bottle.

Nivolumab and ipilimumab will be provided as vial of solution for infusion.

4.2.1. IMP Management

For further details regarding IMP temperature management, returns, destructions, complaints, and handling, please refer to the pharmacy manual. IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to Section 6.2), accountability, and collection are the responsibility of the Investigator and/or pharmacist of the medical institution. All of these actions have to be done in the Randomization and Trial Supply Management (RTSM) system as explained in the training video embedded in RSTM, the user manual, and the pharmacy manual.

The IMP should be stored in a secure area with restricted access. Specific storage conditions are mentioned on IMP labeling. IMP management will be verified on a regular basis by the study monitor.

In case of temperature deviation, the Investigator/pharmacist should immediately:
- Block in RTSM the concerned boxes and place them in quarantine.
- Alert the monitor and forward all needed information and implement the instructions received.

Furthermore, the Investigator/pharmacist must put in place an adequate corrective/preventive action once the first temperature deviation occurs in order to avoid recurrence.

The Investigator and/or the pharmacist of the medical institution should only use the IMP provided for the participants involved in the study.

The Investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must enter and complete in real time the RTSM and all the documents provided by the Sponsor concerning IMP management (refer to the pharmacy manual). Destruction of the IMP is the responsibility of the Sponsor and/or the Investigator and/or the pharmacist of the medical institution.

Remaining treatments (used and unused IMPs) will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMP management. Used IMPs will be collected by the center at the time of preparation/administration along with the other wastes to be destroyed according to local routines.

A certificated destruction or equivalent will be performed according to standard modalities for that class of product and the attestation must be sent to the Sponsor. The practical procedures for destruction of unused IMP will be defined by the Sponsor and adapted to the center.

Recovery and destruction will be tracked in RTSM before the shipment of IMP to destruction. Destruction of IMP may be possible (after drug accountability and Sponsor authorization) when the product has been used, has expired or after at least the last visit of the last treated subject.

All defects or deterioration of IMPs or their packaging are to be reported to the study monitor. The Investigator will notify the monitor of all complaints set out by a subject/pharmacist (change of appearance, etc.).

In the event of anticipated return of IMPs to the Sponsor (batch recall), the Sponsor will prepare an information letter intended for the Investigator and/or pharmacist of the medical institution. This letter will be sent by the person locally responsible for the study to each study center. On receipt of the letter, the Investigator and/or the pharmacist will identify the participants in possession of the IMP at the moment the incident becomes known, by using RTMS or an equivalent document and will contact them immediately.

4.2.2. Management of Blinding Systems

Not applicable.

4.3. Discontinuation of the Study or Temporary Halt

4.3.1. Premature Discontinuation of the Study or Temporary Halt

After having informed the Investigator(s), this study may be temporarily halted or prematurely discontinued at any time for any sufficient reasonable cause by the Sponsor (or by the Sponsor further a request from a DRT or by the Institutional Review Board [IRB])/Independent Ethics Committee [IEC] or by the Competent Authorities).

Two copies of the written confirmation will be dated and signed by the Investigator(s). The IRB/IECs and Competent Authorities will be informed according to local regulations. If the study is prematurely discontinued due to safety concerns, subjects on treatment should be discontinued from treatment and seen as soon as possible and the same assessments as described in Section 4.1.1.3 should be performed.

If the study is prematurely discontinued for reasons other than safety, subjects who are receiving treatment at the time the study is discontinued may remain on IMP if they are clinically benefiting. Subjects may receive nivolumab up to a maximum of 24 months. Ivosidenib may be continued for as long as the subject is receiving clinical benefit. Under some circumstances, the Investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the subject's interests.

In case of study temporary halt, the study may resume after concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, following approval from the IRB/IEC and/or Competent Authorities, according to local regulations.

4.3.2. Premature Discontinuation of the Study in an Investigator Site (Early Site Closure)

The Sponsor reserves the right to close a study site at any time for any sufficient reasonable cause at the sole discretion of the Sponsor.

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

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

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

The IRB/IEC(s) and Competent Authorities will be informed according to local regulations.

4.3.3. Discontinuation of the Study in the Event of Objective Reached

Not applicable.

4.4. Source Data

Source data and source documents of the center should be clearly identified in a specific, detailed, and signed document before the beginning of the study. Subject's medical file (*e.g.*, information regarding the subject's medical history, ECG reports, clinical laboratory examination reports, imaging reports and all other subjects' examination results, requisition forms and registration forms) and drug diary will be considered as source documents.

5. STUDY POPULATION AND WITHDRAWAL OF PARTICIPANTS

5.1. Inclusion Criteria

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

Demographic Characteristics

1. Male or female participant age ≥ 18 years old.

General Criteria

2. Estimated life expectancy ≥ 12 weeks.
3. ECOG performance status ≤ 1.

Sex and Contraceptive/Barrier Requirements

4. Women of childbearing potential (WOCBP) must agree to abstain from sexual intercourse or to use 2 highly effective (Appendix 7) forms of contraception, at least one of which must be a barrier method, from the time of giving informed consent throughout the study, and for 5 months after the last dose of study treatment. Ivosidenib, nivolumab, and ipilimumab may have adverse effects on a fetus in utero. Furthermore, it is not known if nivolumab and ipilimumab have transient adverse effects on the composition of sperm. Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. Egg donation (ova, oocytes), for the purpose of reproduction, will not be allowed during the study and for 5 months after the last dose of study treatment.

- Male subjects with WOCBP partners must use a condom during the study and until at least 3 months after the last dose of study treatment. In addition, contraception should be considered for their female partners. Contraceptive measures do not apply if the subject is sterile, vasectomized, or sexually abstinent. Sperm donation from male subjects will not be allowed during the study and for 3 months after the last dose of study treatment.
  Note: Please refer to Appendix 7 for further contraception considerations.

Informed Consent

5. Obtained prior to any study-specific procedure as described in Section 13.3 of the protocol.

Medical and Therapeutic Criteria

6. Have a histopathological diagnosis consistent with nonresectable or metastatic cholangiocarcinoma and are not eligible for curative resection, transplantation or ablative therapies.
7. Have documented IDH1 gene-mutated disease based on local testing procedure (R132C/L/G/H/S mutations variants tested). Preferably using a tumor biopsy sample collected within the last 3 years.

8a Have disease progression or treatment intolerance following at least 1 and no more than 2 prior systemic regimens for advanced disease (nonresectable or metastatic) including the following:

i. For Cohort 1: subjects who have not received any prior immune checkpoint inhibitor therapy but received at least 1 gemcitabine- or 5-FU-containg regimen for advanced cholangiocarcinoma.

ii. For Cohort 2: subjects must have received at least two doses of anti-PD1/L1 therapy in first or second line, which may include combination with chemotherapy which should include at least 1 gemcitabine- or 5-FU-containg regimen for advanced cholangiocarcinoma. Combination therapy with other checkpoint inhibitors or investigational agents must be excluded.

iii. Safety Lead-in phase: subjects eligible for either Cohort 1 or Cohort 2.

Prior capecitabine or gemcitabine containing adjuvant chemotherapy will be considered a line of treatment if there is documented disease progression during or within 12 months of completing the therapy.

9. Participants must have at least one measurable lesion, as defined by RECIST v1.1. Subjects who have received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) are eligible provided measurable disease falls outside of the treatment field or if within the field but has shown ≥ 20% growth in size post-treatment assessment.
10. Adequate hematological function, defined as:
    i. WBC ≥ 2 x 10^9/L.
    ii. Absolute neutrophil count ≥ 1.5 x 10^9/L.
    iii. Hemoglobin ≥ 9 g/dL. In case of blood transfusion, the hemoglobin assessment must be performed 2 weeks or more after the transfusion.
    iv. Platelet count ≥ 100 x 10^9/L.
11. Adequate coagulation function as defined by International Normalization Ratio (INR), or Prothrombin Time (PT) or Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 ULN; Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study. Subjects receiving a factor Xa inhibitor who have abnormal PT/ partial thromboplastin time (PTT) may be eligible after discussion with the Sponsor.
12. Adequate renal function defined as: calculated creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault formula:
    1. (140 − Age) × (weight in kg) × (0.85 if female)/72 × serum creatinine.
13. Adequate hepatic function, defined as:
    i. Total serum bilirubin and direct bilirubin ≤ 1.5 x ULN (total serum bilirubin ≤ 3.0 x ULN for confirmed Gilbert disease).

ii(a) Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN, exception to this range will need to be discussed and approved by the study medical monitor.

iii. Serum albumin ≥ 2.8 g/dL.

5.2. Exclusion Criteria

Subjects meeting any of the following criteria may not be enrolled in the study:

General Criteria

14. Inability to swallow oral medication.
15. Pregnant and lactating women.
16. WOCBP who tested positive in a serum pregnancy test within 24 hours prior to the first day of IMP administration. An extension up to 72 hours prior to the start of study treatment is permissible in situations where the results cannot be obtained within the standard 24-hour window.
17. Unlikely to cooperate in the study.
18. Participation in another interventional study at the same time or within 2 weeks prior to the first IMP administration. Participation in non-interventional registries or epidemiological studies is allowed. In addition, the first dose of ivosidenib should not occur before a period greater than or equal to 5 half-lives or 28 days, whichever is shorter, of the last dose of the investigational molecule.

Medical and Therapeutic Criteria

19. Subjects who received prior treatment with an IDH inhibitor or prior treatment with an immune checkpoint inhibitor other than anti-PD1/L1.
20. Have a history of another primary cancer, with the exception of: a) curatively resected nonmelanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid or liquid tumor within 2 years prior (i.e., participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before and the subject has no evidence of disease), with no known active disease present that, in the opinion of the Investigator, will not affect subject outcome in the setting of current cholangiocarcinoma diagnosis.
21. Subjects with prior Grade ≥ 3 immune-related AE (irAE) resulting from ICI therapy or have history of life-threatening toxicity related to prior immune therapy (ICI or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g., hypothyroidism).
22. Subjects with active autoimmune disease or any condition requiring systemic treatment with either corticosteroids (> 10 mg daily of prednisone equivalents) or other immune-suppressive medications within 14 days of study treatment. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
23. Known prior severe hypersensitivity to investigational products or any component in their formulations.
24. Participants who have not recovered from toxicity of previous anti-cancer therapy, including Grade ≥ 1 non-hematologic toxicity, according to the NCI CTCAE v5.0, prior to the first IMP administration. Residual Grade ≤ 2 toxicity from chemotherapy (e.g., alopecia, neuropathy) may be allowed.
25. Major surgery within 4 weeks prior to the first IMP administration or participants who have not recovered from side effects of the surgery.

26. Have LVEF (ECHO, MUGA scan, or by other method according to institutional practice) < 40% by ECHO scan (or by other methods according to institutional practice) obtained within 28 days prior to the start of study treatment.
27. Subjects who have heart rate-corrected QT interval using Fridericia's formula (QTcF) of ≥ 450 msec or with other factors that increase the risk of QT prolongation or arrhythmic events (*e.g.*, heart failure, hypokalemia, family history of long QT interval syndrome). Subjects with bundle branch block and prolonged QTcF should be reviewed by the Sponsor for potential inclusion.
28. History of motor neuropathy considered to be of autoimmune origin (*e.g.*, Guillain-Barre syndrome, myasthenia gravis).
29. Known immunodeficiency or HIV, hepatitis B, or hepatitis C infection. Antibody to hepatitis B or C without evidence of active infection may be allowed. Subjects with chronic hepatitis B virus that is adequately controlled per institutional guideline will be permitted.
30. Severe or uncontrolled active acute or chronic infection.
31. Have known symptomatic brain metastases requiring steroids. Subjects with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and have radiographically stable disease for at least 3 months prior to study entry. Note: Up to 10 mg per day of prednisone equivalent will be allowed.
32. Subjects who have received systemic anti-cancer treatment or palliative radiotherapy to bone metastases or other non-liver lesions less than 2 weeks before the first dose of ivosidenib. Arterial therapies and radiation to liver lesions less than 4 weeks before the first dose of ivosidenib.
33. Treatment with a live/attenuated vaccine withing 30 days of first study treatment.
34. History of non-infectious pneumonitis that required steroids, current pneumonitis, or history of interstitial lung disease.
35. Subjects who discontinued prior treatment with ICIs for toxicity, irrespective of the Grade of the event that triggered discontinuation.
36. Any clinically significant medical condition (e.g., organ dysfunction) or laboratory abnormality likely to jeopardize the participant's safety or to interfere with the conduct of the study, in the Investigator's opinion.
37. Any contraindication to the use of nivolumab or ipilimumab as per standard labelling and local guidance.
38. Are taking known strong cytochrome P450 (CYP) 3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing.
    Note: Please refer to Appendix 10, Table 2 and Table 5, for further drug-drug interaction considerations.

Prior/Concomitant Therapy
For prior and forbidden concomitant medication, refer to Section 6.3.

5.3. Retest Management During Screening Period

A participant who has (a) laboratory result(s) that does not satisfy the entrance criteria may have the test(s) repeated providing that the Investigator judges it relevant according to the participant previous results, or medical history and if s/he considers laboratory abnormalities are likely to be transient. Results of the test(s) repeated should be obtained within the allowed

screening period. In this case the participant will not be required to sign another informed consent, and the original participant ID number assigned by the Investigator will be used.

For ECGs, up to three 12 lead ECG tests under stable condition can be performed at each visit during screening and throughout treatment and study follow-up.

In any case, the last result available for each parameter must be considered for the participant inclusion.

5.4. Participant Withdrawal

5.4.1. Withdrawal Criteria

Premature discontinuation of IMP does not mean that the subject prematurely stops the participation in the study.

Subjects discontinuing study treatment for reasons other than withdrawal of consent from overall study participation will be expected to continue in the study including Safety Follow-up visits and be contacted for survival follow-up. Information to be collected during the last visit for these subjects is given in Section 5.4.3.

The reasons for premature discontinuation of IMP are:

- AEs, according to the judgment of the Investigator, including no recovery in safety parameters.
- Disease progression as assessed by the Investigator/site radiologist according to RECIST v1.1 (Appendix 12). Clinically stable subjects may continue beyond confirmed disease progression if benefits are expected to outweigh risks in the opinion of the Investigator and in consultation with the Sponsor.
- Clinical disease progression manifested by symptomatic deterioration.
- Completion of a maximum of 24 months of nivolumab (note that subjects receiving combination may continue to receive ivosidenib monotherapy).
- Pregnancy (for reporting, see Section 8.10.2.3).
- Major protocol deviation if it interferes with the study evaluations and/or if it jeopardizes subject's safety, *e.g.*, any medical event requiring administration of an unauthorized concomitant treatment (see Section 6.3).
- Withdrawal of consent (only for IMP discontinuation): Subjects will be asked if they are willing to continue the safety and disease/survival follow-up.
- Physician decision (for reasons that cannot be included in any of the criteria listed above, for example, availability of a better therapeutic alternative for the subject).
- Study terminated by Sponsor.

5.4.2. Criteria for Premature Study Discontinuation

- Withdrawal of consent: Subjects may leave the study at any time for any reason if they wish to do so, without consequence. If a subject withdraws consent from overall study participation (and not just study treatment), no further evaluations should be performed, and no attempts should be made to collect additional data.
- Death.
- Lost to follow-up.

- Study terminated by Sponsor.

5.4.3. Procedure

Upon discontinuation of study treatment, the Investigator must:
- Notify the Sponsor immediately.
- Record this information in the eCRF, specifying the reason for the subject's withdrawal. If there are several reasons, the Investigator must indicate the main reason. The Investigator should document the discontinuation in the corresponding medical file.

An EOT visit should always be suggested to the subject and should take place within 7 days after the last IMP administration or at the 30-day safety follow-up visit if this is not possible, and prior to the start of a new anti-cancer therapy.

In the case of premature study treatment discontinuation due to an AE, the Investigator must make every effort to collect the information relating to the outcome of the event. If necessary, the information will be collected afterward. This information is recorded in that part of the eCRF that concerns AEs. If the Investigator cannot collect the information from a visit, the Investigator must collect it from the doctor ensuring the follow-up of the participant.

The dispositions to be taken after the IMP discontinuation are described in Section 6.5.

5.4.4. Lost to Follow-up

When the Investigator has no news of the participant, the Investigator must make every effort to contact the participant or a person around the participant (phone calls, letters including registered ones, etc.) to establish the reason for the discontinuation of IMP and to suggest that the participant attends a withdrawal visit. If after the Investigator has completed all due diligence and all attempts to contact the participant fail, the Investigator can then declare the participant "lost to follow-up". The Investigator should document all contact attempts in the corresponding medical file.

6. TREATMENT OF PARTICIPANTS

IMP treatment of study subjects is outlined in the sections below. Complete details are provided in the pharmacy manual.

6.1. IMPs Administered

Product Description and Dosage Form	Concentration	Primary Packaging	Secondary Packaging
Ivosidenib / tablet	Tablets of 250 mg	One pillbox = 60 tablets of 250 mg	One box containing one pillbox of 60 tablets
Nivolumab / solution for injection	CCI mg/mL	One vial = CCI mL CCI mg/mL	One box containing one vial
Ipilimumab / solution for injection	CCI mg/mL	One vial = CCI mL vial at CCI mg/mL	One box containing one vial

It is recommended that each dose should be taken with or without food. Subjects taking ivosidenib with food should be advised to avoid grapefruit or grapefruit products and avoid

consuming a high-fat meal (Please refer to examples of low-fat and high-fat meals in Appendix 12).

For treatment dose modifications due to toxicities, please refer to Section 8.12. All the IMP tracking is managed in RTSM in real time. The procedures to be followed by the Investigator or authorized person are detailed in the training video embedded in RSTM or user manual.

6.2. IMP Dispensing

After completion of IRT, IMPs will be allocated, dispensed, and tracked via RTSM by the pharmacist/responsible individual of the healthcare establishment upon prescription of the Investigator only. The Investigator may only use the IMPs provided for the subjects involved in the study and treated under the Investigator's responsibility. All dosages of nivolumab and ipilimumab are prescribed to the subject and all dose changes during the study must be done via RTSM and recorded in the eCRF. For doses of ivosidenib, should a subject be unable to receive or return to the site for dose administration, delivery of the dose to the subject's home is permitted.

One drug kit of ivosidenib will be dispensed to the subject at Day 1 of each cycle. Nivolumab will be infused to the subject at Day 1 of each cycle. The number of vials of nivolumab allocated and the volume to infuse will be calculated in RTSM based on subject weight (from Cycle 1 to Cycle 4) and will be the same (48 mL) beginning at Cycle 5. At Day 1 of the first 4 cycles (Cycle 1 to Cycle 4), ipilimumab will be infused to the subject. The number of vials of ipilimumab allocated and the volume to infuse will be calculated based on subject weight.

The pharmacist/responsible individual of the healthcare establishment prepares the treatment in accordance with the Pharmacy Manual and documents it in the drug kit tracking file or equivalent validated tracking system. The individual then either sticks the drug kit label to the paper label collection form or assigns a drug kit number in the validated electronic tool based on site procedures, or scans the QR code in the validated electronic tool at the site level to log the dispensation.

The drug kit will be identified by a 6-digit number for identification, tracking, and stock management purposes.

6.3. Previous and Concomitant Treatments

6.3.1. Prior Medications and Procedures

All medications administered and procedures conducted within 4 weeks (28 days) prior to the first day of study drug administration (C1D1) are to be recorded in the eCRF.

As available, transfusion history, including red blood cell and platelet transfusion, for 56 days prior to C1D1 should be recorded at the Screening visit. This documentation should include dates of each transfusion and units administered.

6.3.2. Concomitant Medications and Procedures

All medications (other than IMPs) and significant non-drug therapies (including physical therapy, IV medications and fluids, herbal/natural medications, over-the-counter medications, and blood transfusions) administered during the study must be listed in the eCRF. If changes

occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF. The Investigator should instruct the subject not to take any additional medications (including over-the-counter products) during the study without prior consultation with the Investigator. In general, the use of any concomitant medication deemed necessary for the care of the subject is permitted in this study, except as specifically prohibited in Section 6.3.2.1. Information on prior anti-neoplastic treatment received for the primary diagnosis including prior radiation therapy will be collected.

A list of prohibited and unauthorized treatments by drug class can be consulted in the eCRF.

6.3.2.1. Prohibited Concomitant Therapies

The following concomitant therapies are prohibited for participants receiving treatment with ivosidenib in combination with nivolumab and ipilimumab.

- Strong inducers of CYP3A4 (Table 2, Appendix 10): Ivosidenib is mainly metabolized by CYP3A4; therefore, subjects should not use strong CYP3A4 inducers during treatment with ivosidenib.
- Sensitive CYP3A4 substrates with a narrow therapeutic window: Ivosidenib is an inducer of human CYP3A4/5; therefore, medications of sensitive CYP3A4 substrates with a narrow therapeutic window (Table 2, Appendix 10) should be avoided unless the subject can be transferred to other medications prior to enrolling.
- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids. Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (*e.g.*, contrast dye allergy) or for treatment of non-autoimmune conditions (*e.g.*, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Any live/attenuated vaccine (*e.g.*, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella) during treatment and until 100 days post last dose.
- Any COVID-19 vaccine that cannot be rescheduled within 14 days prior to first dose of study drug or cannot be rescheduled during the DLT period.
- Any complementary medications (*e.g.*, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any concurrent systemic anti-neoplastic therapy (*i.e.*, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of CCA). If alternative therapy is required for treatment of the subject's disease, the subject should be discontinued from the study treatment.
- Any non-palliative radiation therapy. Localize radiation therapy administered with palliative intent is permitted for subjects who continue to receive ivosidenib following documented disease progression and must be documented on the CRF.

6.3.2.2. Concomitant Therapies Requiring Careful Monitoring (Use with Caution)

Based on the results of in vitro and in vivo studies, the following therapies should be avoided and replaced with alternative treatments. If this is not possible, participants receiving these drugs should be carefully monitored.

- Concomitant use of drugs with a potential for QT prolongation should be avoided and replaced with alternative treatments. If this is not possible, subjects receiving these drugs

should be adequately monitored by ECG controls, drug concentration (where applicable), and serum electrolytes (*i.e.*, potassium and magnesium).
These medications include but are not limited to:
  - Fluoroquinolones such as, ciprofloxacin and moxifloxacin.
  - Azole antifungals such as fluconazole and posaconazole.
  - Serotonin (5-HT3) antagonists such as granisetron and ondansetron. See Appendix 10, Table 4 for a complete list of medications known to prolong the QT interval.
- Moderate or strong inhibitors of CYP3A4: Ivosidenib clinical trials and physiologically based pharmacokinetic simulations have shown that ivosidenib plasma concentrations increase with co-administration of a strong or moderate CYP3A4 inhibitor, and increased ivosidenib plasma concentrations may increase the risk of QTc prolongation. Therefore, alternative therapies that are not moderate or strong CYP3A4 inhibitors should be considered during treatment with ivosidenib. If concomitant use of moderate CYP3A4 inhibitors is unavoidable, subjects should be monitored for increased risk of QTc prolongation. If a strong CYP3A4 inhibitor must be co-administered, reduce the ivosidenib dose to 250 mg QD. If the strong inhibitor is discontinued, increase the ivosidenib dose (after at least 5 half-lives of the strong CYP3A4 inhibitor) to the recommended dose of 500 mg QD (see Table 5 in Appendix 10).
- Sensitive substrates of CYP2C9: Ivosidenib may also induce CYP2B6, CYP2C8, and CYP2C9. Consider alternative therapies that are not sensitive substrates of CYP2C9 (*e.g.*, phenytoin, warfarin). Monitor INR levels more frequently in subjects receiving warfarin (a CYP2C9 substrate) during initiation or discontinuation of ivosidenib.
- Coadministration of ivosidenib may decrease the concentrations of hormonal contraceptives. Consider alternative methods of contraception in subjects receiving ivosidenib as described Appendix 7.

6.4. IMP Compliance

For ivosidenib, subjects will be dispensed the appropriate number of Sponsor-packaged and labeled bottles to allow for 21 ± 2 days of dosing for the first 4 cycles then for 28 ± 2 days of dosing from the Cycle 5. Alternatively, they may be dispensed appropriate bottle(s) until the next scheduled visit. The number of pill bottles dispensed and the number of tablets returned by the subject are to be counted by the Investigator or delegate and recorded. For the infusion therapies, the number of vials dispensed will be counted by the Investigator or designee and recorded in the eCRF and RTSM or an equivalent document.

Subjects will receive instructions for home administration of IMP along with a diary to record the date and time of each dose, as well as the number and strength (mg) of tablets taken.

Treatment compliance will be assessed using the drug diary and/or return of unused drug. Accountability for the IMP at the study site is the responsibility of the Investigator. The Investigator will ensure that the IMP is used only in accordance with this protocol.

Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and return to Sponsor or its designee (or disposal of the drug, if approved by Sponsor). These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all IMP received from Sponsor.

Accountability records will include dates, quantities, batch/serial numbers, expiration dates, and subject numbers. The Sponsor or designee will review drug accountability at the site on an ongoing basis during monitoring visits. IMP must not be used for any purpose other than the present study. IMP that has been dispensed to a subject and returned unused must not be redispensed to a different subject. All unused and used IMP should be retained at the site until inventoried by the study monitor. All used, unused, or expired IMP, disposed of at the study site per the site's standard operating procedures and documented via a destruction certificate, or drug kits can be recovered from the site and, after Sponsor approval, sent to a destruction body who will destroy and provide a destruction certificate for documentation.

6.5. Discontinuation of the IMP

After the discontinuation of the IMP, the participant's treatment is left to the physician's discretion.

7. ASSESSMENT OF EFFICACY

7.1. Efficacy Measurements

Efficacy measurements performed during the study are indicated in Table (4.1.2) 1.

Standard response criteria will be applied for disease assessments and response evaluations (RECIST v1.1 [Table (4.1.2) 1]). Assessments should be performed at the intervals specified in the investigation schedules and in the event of suspected disease progression.

The same method(s) of disease evaluation and the same techniques should be used throughout the study as the baseline.

7.2. Methods and Measurement Times

Response will be assessed by the Investigator or qualified designee and will be noted at each evaluation point as complete response (CR), partial response (PR), SD, progressive disease, or not evaluable (NE) (Table (7.2) 1).

Radiographic assessments (CT or MRI) for evaluation of disease response are to be conducted at Screening (Day -21 to to Day -1), every 6 weeks (± 7 days) for the first 2 assessments (*i.e.*, through Week 12), and then every 8 weeks (± 7 days) thereafter, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. Tumor assessment frequency may be reduced to every 12 weeks 2 years after treatment initiation.

Per RECIST v1.1, response should be confirmed by repeat imaging assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of the response may be performed at the earliest 4 weeks after the first documentation of response or at the next scheduled scan (approximately 6 to 8-week interval from last scan), whichever is clinically indicated.

The Investigator should consider all lesions (target and non-target) in assessing the tumor burden at repeat imaging prior to making a decision for continuation of treatment.

Table (7.2) 1 - Imaging After First Radiological Evidence of Disease Progression

Scenario	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiological evidence of disease progression	Repeat imaging at ≥ 4 weeks to confirm disease status	May continue study treatment per Investigator discretion while waiting confirmation scan	Repeat imaging at ≥ 4 weeks to confirm disease progression per Investigator discretion only	Discontinue treatment
Repeat scan confirms disease progression	No additional imaging required	Discontinue treatment (exception upon consultation with the Sponsor)	No additional imaging required	NA
Repeat scan shows SD, PR, or CR	Continue tumor imaging assessment at scheduled intervals	Continue study treatment per Investigator discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or is clinically stable as per Investigator discretion

Abbreviations CR = complete response; NA = not applicable; PR = partial response; SD = stable disease.

Note: if a subject has confirmed radiological disease progression but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered after consultation with the Sponsor. In this case, the subject must have absence of symptoms and signs of progression of disease, absence of decline in ECOG performance status, and absence of tumor progression at critical anatomic sites. In such cases, subject should be followed for tumor assessment and safety per protocol required schedule of assessment.

7.3. Central Imaging Facility

During the Expansion phase, a central imaging facility may evaluate imaging studies and supportive clinical data in a central and independent fashion, from subjects enrolled in Safety Lead-In phase and the Expansion phase. The facility will not perform independent clinical evaluations. The central imaging facility may be chartered to establish radiographic progression and may consider selected clinical data solely to aid in the interpretation of radiographic images. A detailed site-specific Imaging Core Manual will be made available regarding scan acquisition requirements. All radiological scans acquired at all scheduled time points and any additional (unscheduled) radiological images acquired to evaluate for potential metastatic disease also may be sent to the central imaging facility. In addition, the most recent pre-treatment scans (*i.e.*, prior to screening) may also be requested, if available, from subjects in the dose escalation phase of the study. These scans will be collected and sent to a central imaging facility as detailed in the site-specific Imaging Core Manual.

The site is expected to maintain a copy of digital data for the retention period applicable to the protocol, GCP, and federal, international and/or state legal and medical requirements. The Sponsor and/or designee may retain the media until or beyond study completion.

7.4. Continuation of Treatment Beyond Radiographic Progression

In the event of radiographic progression per RECIST v1.1 but in the absence of clinical deterioration, worsening ECOG performance status, or disease progression that may compromise organ function, the subject may continue to receive study treatment with ivosidenib, nivolumab, and/or ipilimumab at the discretion of the treating physician in consultation with the Sponsor. Nivolumab will be permitted for up to a maximum of 24 months from date of first dose. If there is clinical deterioration or continued radiographic progression documented on subsequent imaging, treatment with either ivosidenib, nivolumab, or both will be discontinued, and the subject will complete the EOT and Safety Follow-up visits and enter Survival Follow-up.

All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options, will still apply. Treatment beyond progression may be administered during or after localized interventions (surgery/radiation therapy).

8. ASSESSMENT OF SAFETY

All AEs and other situations relevant to the safety of the participants must be followed up and fully and precisely documented to ensure that the Sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

8.1. Specification of Safety Parameters

Safety measurements, including a limited physical examination and vital signs including weight, performed during the study are indicated in Table (4.1.2) 1.

8.2. Methods and Measurement Times

Safety measurements will include ECOG performance status, ECG, and clinical laboratory assessments (hematology, chemistry, thyroid function tests, coagulation, and pregnancy testing) and be performed locally per the schedule outlined in Table (4.1.2) 1.

Clinical laboratory assessment details for assessments performed centrally are described in the study lab manual.

8.3. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a subject participating in a clinical study, whether or not there is a causal relationship with the IMP and/or experimental procedures, occurring or detected from the date the participant signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (*e.g.*, run-in period) are also concerned).

An AE can therefore be:

- Any unfavorable and unintended sign (including an abnormal finding from an additional examination such as lab tests, X-rays, and ECG) that is deemed clinically relevant by the Investigator.
- Any symptom or disease.
- Any worsening during the study of a symptom or a disease already present when the participant entered the study (increase in frequency and/or intensity).

Fatal studied disease progression, detected during a study visit or at an additional examination or occurred since the previous study visit. An AE can arise from any use of the drug (*e.g.*, off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Of note:

- Any hospitalization for administration of anti-tumoral treatment and/or associated protocol (during or after the study) or other care measures for cancer (*e.g.*, overnight hospital stay to receive a blood or platelets transfusion), for social reasons, educational purpose (*e.g.*, learning of diabetes management by the participant) or routine check-up should not be considered as an AE and should not be reported in the eCRF.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the studied disease should not be considered as an AE unless judged by the Investigator to be more severe than expected for the participant's condition.
- Non-fatal studied disease progression should not be considered as an AE.
- The following procedures, whether planned before the study or not, whether leading to a hospitalization or not, **should not be reported in the eCRF and should be kept in the source data (or participant file):**
  - therapeutic procedures related to a non-aggravated medical history (*e.g.*, cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study),
  - prophylactic procedures (*e.g.*, sterilization, wisdom teeth removal),
  - comfort procedures (*e.g.*, cosmetic surgery),
  - control procedures of a pre-existing condition without aggravation (*e.g.*, colonoscopy to control the remission of colon cancer).

8.4. Definition of Serious Adverse Events

An SAE is any AE that, at any dose:

- results in death,
- is life-threatening(1),
- requires insubject hospitalization or prolongation of existing hospitalization,
- is medically significant(2),
- results in persistent or significant disability/incapacity(3),
- is a congenital anomaly/birth defect(4).

(1) Life-threatening in this context refers to 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.

(2) Any event that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the participant or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalization, or development of drug dependence or drug abuse). The Investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to Sponsor.

(3) Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

(4) Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

It is under Investigator's responsibility to evaluate the AE seriousness according to international guidance (see ICH Topic E2A and EU DIRECTIVE 2001/20/EC of 4 April 2001 or further regulation (EU) No 536/2014). The Sponsor will review the AE seriousness. The seriousness may be upgraded (but never downgraded).

8.5. Definition of Overdose

This refers to any intake of a quantity of IMP that is above the maximum dose recommended in the study protocol, independent of the occurrence of any AE.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol.

8.5.1. Overdose or Incorrect Administration

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects. Any study treatment overdose or incorrect administration of study treatment should be noted on the Study Drug Administration eCRF.

All AEs associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor by the Investigator within 24 hours after learning of the event.

8.6. Definition of Adverse Event of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest or concern regarding the IMP for which recording rules, special documentation such as hospital records and/or adjudication committee could be appropriate. It may be a serious or non-serious AE that may require further investigation in order to be characterized and understood.

8.6.1. QT Prolongation

Any QT prolongation event assessed as Grade ≥ 2 (*i.e.*, QTcF interval longer than 480 msec or ≥ 60 msec change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia), irrespective of the seriousness, should be reported as an AESI to the Sponsor within 24 hours. See Section 8.6.1.1 for further details on managing subjects with QT prolongation. Heart rate-corrected QT interval will be calculated using Fridericia's formula (QTcF = QT/RR1/3).

8.6.1.1. Management of QT Prolongation

Events of QT prolongation (*i.e.*, QTcF Grade ≥ 3) should be reported as AESIs to the Sponsor within 24 hours, according to expedited reporting procedures (see Section 8.3).

Subjects may be at increased risk for the development of QT prolongation when treated with ivosidenib in combination with fluoroquinolones, azole antifungal agents, or serotonin (5-HT3) antagonists. Investigators must be vigilant; refrain from administering concomitant medications associated with QT prolongation and if no other therapeutic options are available, monitor subjects receiving study treatment with the combination of these drugs and evaluate ECG and electrolytes (including potassium, magnesium, and calcium), particularly in subjects presenting with nausea, vomiting, or diarrhea. Systemic administration of a moderate or strong CYP3A4 inhibitor requires careful monitoring of QTcF.

Subjects who experience QT prolongation (*i.e.*, QTcF > 480 msec; NCI CTCAE Grade ≥ 2) while receiving study treatment should be promptly evaluated for causality of the QT prolongation and managed according to the following guidelines.

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked, and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects.
- If no other cause is identified and the Investigator believes it is appropriate, particularly if QTcF remains elevated (after the above measures have been implemented, or as determined by the Investigator), study treatment may be interrupted, and an ECG should be rechecked in approximately 1 week after the QT prolongation event was first observed or more frequently as clinically indicated.
  Please refer to Table (8.12.1) 1 for the management of QT prolongation by NCI CTACE grade.

8.7. Immune-Related Adverse Events

Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (*e.g.*, infection or 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 case report form.

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

AEs associated with nivolumab and ipilimumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of nivolumab and/or ipilimumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of nivolumab and/or ipilimumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue nivolumab and/or ipilimumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with nivolumab and/or ipilimumab are provided in Appendix 8 and Appendix 10.

8.8. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens in intensity or grade.

When an AE becomes serious (regardless of changes in grade or severity), the eCRF should be updated to reflect this. As such, a new AE (serious event with onset date for when AE became serious) should be added to the eCRF.

However, the same does not hold true for AEs that change from serious to non-serious events. When an AE does not resolve but is downgraded from a serious to a non-serious event, a new AE is not required to be captured on the eCRF. A resolution date is required to be entered on the SAE form once an AE changes from a serious to non-serious event since this would result in the SAE resolving.

A recurrent AE is 1 that resolves between subject evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

8.8.1. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if it meets any of the following criteria:

a. Accompanied by clinical symptoms.
b. Results in a change in study treatment (*e.g.*, dosage modification, treatment interruption, or treatment discontinuation).
c. Results in a medical intervention (*e.g.*, potassium supplementation for hypokalemia) or a change in concomitant therapy.
d. Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (*e.g.*, alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (*i.e.*, cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range. Where possible, please enter a condition (*e.g.*, neutropenia) rather than the lab finding (*e.g.*, decreased neutrophils).

8.9. Classification of an Adverse Event (Seriousness, Severity, Causality, Expectedness)

It is important that the Investigator gives their own opinion regarding the **seriousness**, the **intensity** of the event, as well as the **cause-effect relationship** between an AE and the research or disease progression. This evaluation must be assessed by the Investigator and reported in the AE form. In addition, the Sponsor will be responsible for the evaluation of the **expectedness** of the event (see Section 8.10.3).

The seriousness should be evaluated according to international guidance (see definition Section 8.4, It is under Investigator's responsibility to evaluate the AE seriousness according to international guidance (see ICH Topic E2A and EU DIRECTIVE 2001/20/EC of 4 April 2001 or further regulation (EU) No 536/2014). The Sponsor will review the AE seriousness. The seriousness may be upgraded (but never downgraded).

The severity of all AEs will be graded according to the NCI CTCAE version 5.0 on a 5-point scale (Grade 1 to 5):

- Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[1].
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
- Grade 4: life-threatening consequences; urgent intervention indicated.
- Grade 5: death related to AE.

The cause-effect relationship: The Investigator must make an assessment in the AE form whether the AE is related or not to the research, meaning:

- a procedure scheduled in the study protocol (*e.g.*, exercise test, MRI), or
- a change or withdrawal of previous/concomitant treatment related to the conditions of the protocol.

Moreover, the Investigator has to assess if the AE is related to disease progression. Cases ticked "related" by the Investigator or judged by the Sponsor as having a reasonable suspected causal relationship to the IMP (AE linked to the mechanism of action of the IMP), will be considered as suspected adverse drug reactions. In general, if a relationship between AE and IMP is at least reasonably possible (*i.e.*, the relationship cannot be ruled out) it is to be considered as "related".

[1] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden".

8.10. Reporting Procedures

8.10.1. Time Frame for AE Reporting

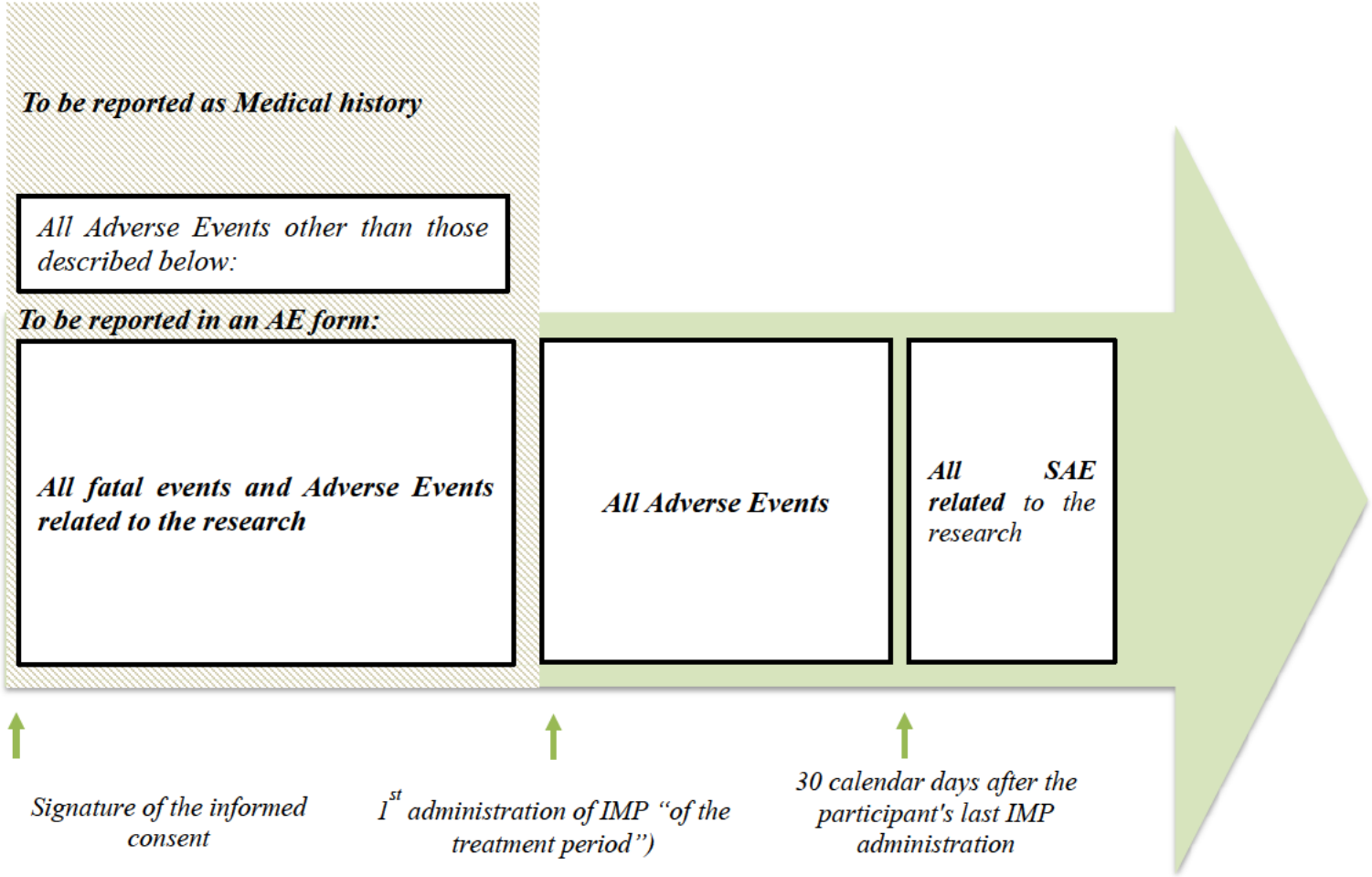
Any event meeting the above-mentioned definitions (see Section 8.3; Figure (8.10.1) 1) must be reported to the Sponsor on an AE form if it occurs:

- Before the first administration of IMP, for fatal events and events related to the research.
- At any time after the first administration of IMP.
- Up to 30 calendar days after the subject's last administration for all AEs and AESIs (including overdose).
- Up to 90 calendar days after the subject's last administration for all SAEs, or until the subject initiates new anti-cancer therapy, whichever is earlier.
- Up to 180 calendar days after the subject's last administration for all pregnancies and exposures during breastfeeding, or until the subject initiates new anti-cancer therapy, whichever is earlier.
- Irrespective of the time of onset in case of SAEs assessed as related to the research.

Of note, non-fatal events occurring between the signature of the ICF and the first administration of the IMP for which the Investigator does not consider an association with the research must be reported as medical history or as signs or symptoms related to the studied disease in the dedicated form of the eCRF.

Fatal events, related or not to the research, occurring after ICF signature and before first IMP administration, must be reported on the AE form.

Figure (8.10.1) 1 - Rules for Adverse Event Reporting



8.10.2. Responsibilities of the Investigator

For any AE or special situation mentioned above, the Investigator must:

- **Note in the participant's medical file** the date on which the Investigator learned of the event (at a follow-up visit or a telephone contact with the participant or a third person, etc.) and any other relevant information that the Investigator has learned of the event.
- **Assess** the event in terms of seriousness, severity, and causality.
- **Report the event to the Sponsor** using the AE form.
- **Document** the event with additional useful information.
- Ensure the **follow-up** of the event.
- **Fulfil Investigator regulatory obligations** to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.
- **Demonstrate oversight of data reported** and ensure the whole content's accuracy, completeness, and legibility in accordance with the GCP (see Section 14.1).

Moreover, the Investigator must report to the Sponsor and/or to the IRB/IEC and/or to the Competent Authorities in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the test drug or that would be sufficient to consider changes in the test drug administration or in the overall conduct of the clinical investigation.

8.10.2.1. Documentation of the Event

The Investigator must ensure that all events are well documented and provide the Sponsor, on request, with anonymized copies of relevant documents (*e.g.*, autopsy report and terminal medical reports [ICH E6 (R2)]).

8.10.2.2. Follow-up of Adverse Events

The Investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, severity (improvement), seriousness, measures taken, causality, or outcome regarding an AE already reported must be written up in a new complete evaluation of the event documented on the Adverse Event form previously created for the event.

In case of worsening of severity, a new complete evaluation of the event must be documented on a new Adverse Event form. If the AE has not resolved at the participant's final visit in the study, the participant must be followed up suitably and any information on the outcome of the event noted on the Adverse Event form previously created for the event.

If the follow-up of the participant is not done by the Investigator (*e.g.*, hospitalization, followed by a specialist or the participant's general practitioner), the Investigator will do everything possible to establish/maintain contact with the person/department in charge of follow-up of the participant.

8.10.2.3. Special Situations (Pregnancy, Overdoses, Intake of IMPby a Person Around the Participant)

Pregnancy

If a female participant in the study becomes pregnant, the Investigator must:

- Stop immediately the test drug (if the pregnancy is a non-inclusion/exclusion criterion).
- Report it on the specific eCRF Pregnancy form and notify the Sponsor immediately (*i.e.*, without delay and within 24 hours of awareness at the latest).
- Pregnancy should not be reported as an AE except in the following circumstances:
  - If it is associated with an AE. This consequence itself should be reported as an AE.
  - While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE. Abnormal pregnancy outcomes (*e.g.,* spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Contribute to the follow-up of this pregnancy and provide the Sponsor with information concerning this follow-up (notably using the second page of the specific paper Pregnancy form).

If the partner of a participant becomes pregnant during the study, the pregnancy should not be reported in the eCRF. The Investigator should **immediately** contact the Sponsor (contact details provided in the Investigator's study file) who will determine the procedure to be followed.

Overdose of IMP

- In case of overdose, the Investigator should report it on the IMP administration page. Overdose should not be reported as an AE except in the following circumstances:
  - The overdose is associated with an AE. This consequence itself should be reported as an AE.
  - The overdose is intentional with possible suicidal/self-harming intent should be reported as an AE regardless of sequelae.
- Overdose should be followed up to ensure that the information is as complete as possible with regard to:
  - Dose details (number of units, duration, etc.) and, if multiple overdoses, details regarding other medicinal products or substance, context of occurrence (*i.e.*, intentional [suicide attempt, other reason] or accidental [error in prescription, administration, dispensing, dosage]), related signs and symptoms ("No related adverse events" to be reported otherwise), and outcome.
- Insofar as possible, a blood sample should be collected for assay of the IMP taken.

Intake of IMP or Occupational Exposure by a Person Around the Participant

This event should not be reported in the eCRF. The Investigator should **immediately** (*i.e.*, without delay and within 24 hours of awareness at the latest) contact the Sponsor (contact details provided in the Investigator's study file) who will determine the procedure to be followed.

8.10.2.4. Recording Methods in the eCRF

Adverse events must be documented on the Adverse Event form of the eCRF.

In case of chronic disease:
- If the disease is known when the participant enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks), this will be documented as an AE.
- If a disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the Adverse Event form previously created for the event, which will clearly describe the diagnosis.

8.10.2.5. Procedure for an Event Requiring an Immediate Notification

In case of an event requiring an immediate notification, the Investigator must:
- **Immediately** after being informed of this event, **fill in** the **participant's medical file** as well as the **Adverse Event form** of the eCRF (for SAEs and AESIs if applicable) according to the general instructions available in the eCRF, without waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into the eCRF an email will be immediately and automatically sent to the Sponsor. However, for special situations requiring an immediate notification (as defined in Section 8.10.2.3) the completion of the Adverse Event form should not be performed systematically.
- If requested by the Sponsor (person designated in the contact details provided in the Investigator's study file), provide anonymized copies of the documents that provide additional useful information.
- Fulfil Investigator regulatory obligations to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.
- In case of an SAE occurring in a first-in-human study, if the Investigator establishes or even suspects a relationship with the study protocol, they must immediately suspend the administration of IMP (and AxMP if applicable) in all participants. In this case, the written consent of the enrolled participants must be obtained again before the study is resumed.

Moreover, on request, the Investigator should provide the Sponsor with the documents required in Section 8.10.2.1.

If an AE that is initially non-serious worsens and becomes an SAE, this must be reported **immediately** on an "Adverse Event" form of the eCRF.

In case the eCRF is unavailable when the Investigator was informed of an AE to be reported immediately, the Investigator should:
- **Immediately** fill in a paper Adverse Event page:
  - For serious event, on a paper Adverse Event – Initial Information page.
  - For event initially non-serious, on a paper Adverse Event – Initial Information page, and the worsening leading to seriousness on a paper Adverse Event – Additional Information page.
- Immediately send the page(s) by email to the person(s) designated in the contact details provided in the Investigator's study file or outside working hours, the 24-hour phone number.
- As soon as the eCRF becomes available, the Investigator should enter these data in the Adverse Event form of the eCRF.

8.10.3. Responsibilities of the Sponsor

In accordance with international guidance, the assessment of the seriousness and the causality of AEs is usually made by the Investigator but falls also under Sponsor's duties, who is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Competent Authorities and Ethics Committees.

The Sponsor will review the seriousness of the AEs and the causality of (at least) the SAEs, whether reported by the Investigator or upgraded by the Sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of documents providing useful information such as reports of further consultations, laboratory test reports, and reports of other examinations aiding diagnosis may be requested for the event assessment. If the assessments of the Investigator and the Sponsor are different, both will be reported in the clinical study report (CSR).

In addition, the Sponsor is responsible for determining whether an AE is **expected or unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IMP.

Independently of the regulatory obligations of the Investigator, the Sponsor must report the pharmacovigilance data and any new safety finding likely to affect the benefit/risk balance of the product, required in ICH GCP guidelines and local regulations, to the appropriate Authorities, to all the Investigators involved, and to the trial participants involved (through the Investigators) as described in Section 13.4. **Responsibilities of Data Review Committee**

During the Safety Lead-in phase, the DRT, composed of Investigator(s) and the Sponsor's medical, safety, and statistical representative(s), will meet to evaluate clinical and laboratory safety data in order to make decisions regarding determination of the RCD. The DRT will meet at minimum:

- Before deciding that a dose is the RCD and the Expansion phase can be opened.
- If the rate of DLTs indicates that the dose should be de-escalated, the DRT will meet to determine if the 250 mg QD dose should be tested.
- If either the 500 mg and/or the 250 mg dose is determined to have unacceptable toxicity.

8.12. Dose Modification and Management for Adverse Events

8.12.1. Study Treatment Dose Modification and Management Associated with Ivosidenib

For any AE, including AEs not specifically mentioned in Table (8.12.1) 1, the Investigator may decide to delay dosing or modify the dose of ivosidenib based on clinical judgment. These decisions should be discussed with the Sponsor prior to implementation. Dose modifications of ivosidenib from 500 mg to 250 mg will be permitted on study for management of AEs (Table (8.12.1) 1). If more than one AE occurs that would require a dose modification, upon resolution of all AEs to baseline or Grade 1, ivosidenib should be dose reduced to 250 mg. Re-escalation may be allowed with approval from the Sponsor.

Dose delays are discouraged, except as needed for management of AEs. Dose delays up to 28 days will be permitted at the discretion of the Investigator in consultation with the Sponsor for reasons including management of AEs and for mitigating circumstances (*e.g.*, planned procedures). Palliative biliary decompression procedures will be permitted on study and will not require interruption of ivosidenib (see Section 8.12.5).

If the subject cannot resume ivosidenib within 28 days, the subject should be discontinued from ivosidenib. Other reasons for treatment termination are provided in Section 5.4.1. If ivosidenib is discontinued, the subject may continue receiving nivolumab and ipilimumab or nivolumab alone. If subject permanently discontinues treatment from all three drugs, the EOT and Safety Follow-up visits will be completed as well as the PFS follow-up (if disease has not progressed) and Survival Follow-up visits. Exemptions may be considered for those subjects who are determined by the Investigator to have received clinical benefit from treatment. If a dose is delayed for the management of an AE, the subject should resume the study at the next planned visit within a dosing cycle.

If a strong CYP3A4 inhibitor must be co-administered, reduce the ivosidenib dose to 250 mg QD. If the strong inhibitor is discontinued, increase the ivosidenib dose (after at least 5 half-lives of the strong CYP3A4 inhibitor) to the recommended dose of 500 mg QD.

Table (8.12.1) 1 - Management of Ivosidenib related QT Prolongation and Adverse Events by NCI CTCAE Grade

NCI CTCAE Grade	**Management**
Grade 2: Average QTc interval greater than 480 msec up to 500 msec	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTc interval-prolonging effects. • Interrupt ivosidenib. • Restart ivosidenib at 500 mg once daily after the QTc interval returns to less than or equal to 480 msec. • Monitor ECGs should be conducted at least weekly for 2 weeks following resolution of QTc prolongation.
Grade 2 nausea or vomiting (related or unrelated)	• Consider holding dose of ivosidenib until resolution of adverse event (AE) to Grade ≤ 1 within 28 days of supportive therapy. • Manage with supportive therapy according to the institutional standard of care. • May resume ivosidenib at same dose.
Grade 3: Average QTc interval greater than 500 msec	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTc interval-prolonging effects. • Interrupt ivosidenib. • Resume ivosidenib at a reduced dose of 250 mg once daily when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. • Consider re-escalating the dose of ivosidenib to 500 mg daily if an alternative etiology for QTc prolongation can be identified.

NCI CTCAE Grade	**Management**
Grade 3 AEs (related, first event)	• Interrupt ivosidenib until toxicity resolves to Grade 1or lower, or baseline, then resume at 250 mg, or re-escalation to 500 mg with Sponsor approval. • If Grade 3 toxicity recurs (a second time), interrupt ivosidenib dose until the toxicity resolves, then resume 250 mg daily. • If Grade 3 toxicity recurs (a third time), discontinue ivosidenib.
Grade 4 AEs (related) including QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	• Discontinue ivosidenib permanently.

Abbreviations ECG = electrocardiogram; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QTc = heart rate-corrected QT interval; QTcF = heart rate-corrected QT interval using Fridericia's method.
Note Per NCI CTCAE, version 4.03.

8.12.2. Dose Modifications and Management Associated with Nivolumab and/or Ipilimumab

Dose delay criteria apply for all drug-related adverse events (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 are met. Delay nivolumab and ipilimumab dosing for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

For subjects who require the delay of nivolumab and ipilimumab, re-evaluate weekly, or more frequently, if clinically indicated and resume dosing when criteria to resume treatment are met. Continue tumor assessments per protocol even if dosing is delayed.

If discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue; if nivolumab is discontinued, however, ipilimumab will not continue as monotherapy.

If a subject meets criteria for discontinuation of nivolumab/ipilimumab and Investigator is unable to determine whether the event is related to both or one study drug, the participant must discontinue both nivolumab and ipilimumab. Subjects may continue receiving ivosidenib. If subject permanently discontinues treatment from all three drugs, EOT and Safety Follow-up Visits will be completed, as well as PFS follow-up (if disease has not progressed) and survival follow-up visits.

Subjects may resume treatment with nivolumab/ipilimumab if they have completed AE management (*i.e.* corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Appendix 8 and Appendix 9.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks for Q3 week treatment and 10 weeks for Q4 week treatment, the Medical Monitor (or designee) must be consulted.

8.12.3. Dose Modification for Ivosidenib, Nivolumab and Ipilimumab

When study interventions are administered in combination, attribution of an AE to a single component is likely to be difficult. When an AE cannot be clearly attributed to any one or combination of drugs, the most stringent criteria for dose modification (based on Dose modification for ivosidenib and ipilimumab/nivolumab - Table (8.12.1) 1 and Appendix 8) must be used for all three drugs.

Dose delay: When study interventions are administered in combination, if the AE is considered immune-related, both nivolumab and ipilimumab interventions should be held according to recommended dose modifications (Appendix 8). QTc prolongation and other Grade3 or higher adverse events that are possibly related to ivosidenib should be managed according to dose modification recommendations in Table (8.12.1) 1.

Re-starting Study Interventions: Subjects may not have any dose modifications (no change in dose or schedule) of nivolumab and/or ipilimumab in this study. At the 250 mg QD dose level, no dose re-escalation is allowed for ivosidenib. If the toxicity does not resolve or the criteria for resuming treatment are not met, the subject must be discontinued from all study interventions. If the toxicities do resolve and conditions are aligned with what is defined in Appendix 8 and Table (8.12.1) 1 ivosidenib, nivolumab and/or ipilimumab may be restarted at the discretion of the Investigator.

8.12.4. Treatment of Related Infusion Reactions Associated with Nivolumab and Ipilimumab

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

Treatment recommendations are provided below based on NCI CTCAE v5.0 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 1,000 mg at least 30 minutes before additional nivolumab administrations.

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

- Stop the study drug 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 1,000 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 1,000 mg administered at least 30 minutes before nivolumab and/or ipilimumab 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 [*e.g.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: life-threatening consequences; urgent intervention indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 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. Monitor participant until the Investigator judges that the symptoms will not recur. Study drug will be permanently discontinued. Follow 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 (*e.g.*, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine or corticosteroids).

8.12.5. Biliary Tract Obstruction During Treatment

In the event of the development of obstructive jaundice due to biliary tract obstruction, the appropriate measures will be taken to diagnose and relieve the obstruction. Study treatment interruption is not required but will be permitted at the discretion of the Investigator.

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Assessments Related to Inclusion Criteria

All Screening procedures must be performed within 28 days prior to first dose for subjects in the Safety Lead-in or the Expansion phase. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent if acceptable to and approved by the site's IRB/IEC.

Inclusion and Exclusion Criteria
Inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively) will be reviewed for each potential subject and documented in the subject medical record and eCRF.

Demographic Data, and Medical, Surgical, and Disease History
Subject demographic data, including sex, year of birth, age, race, and ethnicity, will be obtained during Screening and according to applicable local regulations.

A complete medical, surgical, and disease history, and the date of initial diagnosis of the underlying CCA, will be obtained during Screening. The medical history is to include all relevant prior medical history as well as all current medical conditions.

All medications administered and procedures conducted within 28 days before the first dose of IMP through 30 days after last dose of IMP should be reported in the eCRF.

9.2. Measurement of Drug Concentration

9.2.1. Sample Collection Time Points

Serial or sparse blood samples will be drawn before and after dosing of study treatment in order to determine circulating plasma and tissue concentrations of ivosidenib. The blood samples will also be used for the determination of 2-HG concentrations (see Section 9.3).

Blood samples will be drawn on Day 1 of Cycle 2 (for Safety Lead-in phase) or Day 1 of Cycle 4 (for Expansion phase) at the following time points: pre-dose (within 30 minutes before ivosidenib dose), 2, 3, 4, and 6 hours (± 10 minutes) post-dose. Additional blood samples for ivosidenib PK and 2-HG PD assessments will be drawn pre-dose (within 30 minutes before ivosidenib dose) on C1D1, C1D15, C2D1, C3D1, C4D1, C5D1, and Day 1 of every cycle through Cycle 13, and Day 1 of every other cycle thereafter.

Sparse blood samples will also be drawn before and after dosing of study treatment in order to determine circulating serum concentrations of nivolumab and ipilimumab. Specifically, for nivolumab serum concentration assessment, blood samples will be drawn at pre-dose (within 30 minutes before the ivosidenib dose) on C1D1, C2D1, C3D1, and C4D1, followed by pre-dose collection on Day 1 of every 4 cycles up to 2 years, and at end of infusion after first dose of nivolumab on C1D1. For ipilimumab serum concentration assessment, blood samples will be drawn at pre-dose (within 30 minutes before the ivosidenib dose) on C1D1, C2D1, C3D1, and C4D1, and at end of infusion after first dose of ipilimumab on C1D1. Predose samples for all three IMPs may be collected in one blood draw.

If enough material is available, tumor tissue (fresh-frozen) may be used to determine tumor drug concentration of ivosidenib in order to evaluate tumor exposure of ivosidenib on C1D1 and C3D1. Tumor sample collection is detailed in Section 9.3.

9.2.2. Sampling Methods

Blood for assessment of PK parameters of ivosidenib and 2-HG concentrations will be collected and processed according to the laboratory manual. Every effort will be made to collect PK samples at the time points specified. No additional samples will be collected without formal amendment to this protocol. Analysis will be performed at a central laboratory (Specialty Laboratory) using validated bioanalytical methods. A detailed laboratory manual specifying

sample collection, processing, handling, storage, and shipment will be provided to the study sites; retention time for specimens will be specified therein. If a collected plasma sample is inadequate or insufficient for PK analysis, the analysis of PK can be done using samples for biomarker studies.

9.3. Pharmacodynamics Measurements

Samples of blood for measuring the plasma concentrations of 2-HG will be obtained before the first dose of ivosidenib given on C1D1 (within 30 minutes before the ivosidenib dose). Additional PD samples include single pre-dose blood samples that will be collected prior to dosing ivosidenib (within 30 minutes before the ivosidenib dose) on C1D15, C2D1, C3D1, C4D1, C5D1, and Day 1 of every cycle through Cycle 13, and Day 1 of every other cycle thereafter (*e.g.*, Cycles 15, 17, etc.).
Subjects will be requested to have tumor tissue newly collected at Screening for baseline tumor 2-HG measurement and other exploratory biomarker assessment. A post-dose tumor sample will be collected on C3D1 for 2-HG measurement and other exploratory biomarker assessments.
All time points are described in the investigational schedule.
Biopsies can be collected at Screening and on C3D1 from a similar site as screening. At each time point, tumor biopsies must include at a minimum 3 core needle samples (3 to 4 core samples if feasible). If a subject cannot undergo a biopsy at Screening, archived fresh-frozen tumor biopsy, if available, can be used for the measurement of baseline 2-HG.
If a required tumor biopsy (any time point) cannot be performed due to concerns around subject safety, a discussion with the Sponsor is required and biopsy can be omitted.
The tissue obtained by core needle biopsy will be:

- Fixed in 10% normal buffered formalin and later embedded in paraffin to produce slides for biomarker assessments (detailed in Section 9.5).
- Processed as fresh-frozen tissue for assessment of concentrations of 2-HG (using liquid chromatography with tandem mass spectrometry).
- If there is enough material, samples may also be used for determining tumor drug concentrations of ivosidenib or for assessment of other exploratory biomarkers.

Detailed instructions for the collection, handling, processing, storage, and shipment conditions will be outlined in the laboratory manual (or equivalent) for the study and provided to the study sites.

9.4. Anti-Drug Antibody Measurements

Sparse blood samples will be drawn before and after dosing of study treatment in order to determine circulating serum concentrations ADA to nivolumab and/or ipilimumab that may arise during treatment. Specifically, for nivolumab serum ADA concentration assessment, blood samples will be drawn at pre-dose (within 30 minutes before the ivosidenib dose) on C1D1, C2D1, C3D1, C4D1, followed by pre-dose collection on Day 1 of every 4 cycles up to 2 years.

For ipilimumab serum ADA concentration assessment, blood samples will be drawn at pre-dose (within 30 minutes before the ivosidenib dose) on C1D1, C2D1, C3D1, and C4D1.

9.5. Assessment of Biomarkers

The purpose of the exploratory biomarker assessments of pre-treatment samples is to identify and validate cells, proteins, and/or expression/mutation of genes that may predict which subjects are likely to respond to the study treatment. Comparison of pre- and post-treatment samples aims to identify the mechanism of action and/or mechanism of resistance of the study drug(s).

Tumor biopsies or archival tissue sections will be collected at Screening. If a subject cannot undergo a biopsy at Screening, collection of archival tumor tissue from the most recent biopsy/resection of at least 20 freshly cut, unstained formalin-fixed paraffin-embedded slides (4-5 µm each) plus 1 H&E slide will be submitted at a later time, for future exploratory biomarker analyses, together with the pathology report upon sponsor's request. Detailed instructions for tumor tissue collection and shipping for central testing will be provided in a separate laboratory manual. Tumor biopsies will also be collected at post-treatment (at Cycle 3), and at EOT from similar anatomical locations. Additional unscheduled tumor biopsy(ies) collected as standard of care, if any, will be used for the optional analysis of biomarkers. Biomarkers, which will be analyzed from the tumor biopsies, include but are not limited to the analysis of immune checkpoint proteins and other proteins, tumor microenvironment, presence and/or frequencies of IDH1 and other oncogenic gene alterations.

Liquid biopsies such as peripheral blood mononuclear cells (PBMCs) and circulating tumor DNA (ctDNA) will be derived from blood and will be collected longitudinally at each cycle until C6D1, followed by every 6 months thereafter, and at EOT. Biomarkers that will be analyzed from PBMCs and ctDNA will include but are not limited to gene alteration, immune cell, and protein (cytokine) assessments at baseline and/or longitudinally.

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a sampling collection, or not perform or discontinue an analysis due to either practical or strategic reasons (*e.g.*, inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of the Sponsor.

9.5.1. Mandatory Assessment

Participation in the study implies a systematic participation in the mandatory investigation. All participants will have to consent to this investigation by signing the main information and consent form for participation in the study. In addition, in case of consent withdrawal, related samples will be destroyed after mandatory assessment is completed and in any case before the CSR final version is made available.

9.5.2. Sampling, Processing, and Storage

Detailed instructions for the collection, handling, processing and storage conditions are outlined in the laboratory manual (or equivalent) for the study. All samples (except the ones dedicated to retrospective analysis and ADA) have to be destroyed at the latest when the CSR final version is made available. If they are optional assessments and participant withdrawn consent, please refer to Section 9.5.5.

Structures in charge of collecting, processing, storing, and assaying samples are described in Section 1. **Labelling and Transfer to Analytical Center**

Samples will be single coded with a unique number and thus will not carry any personal identifiers. Sample collection information must be entered as required on the appropriate sample collection eCRF page(s) and requisition form(s). Detailed instructions for the sample labelling and shipments are outlined in the laboratory manual (or equivalent) for the study.

9.5.4. Transfer of Analytical Results

Final analytical results will be transferred to Data Management according to section Data Management (Section 14.2).

9.5.5. Optional Assessment

Participation in the study does not imply a mandatory or systematic participation in the optional analysis of biomarkers on tumor biopsy(ies) that may be collected as standard of care. Biomarkers, which will be analyzed from the tumor biopsies, include but are not limited to the analysis of immune checkpoint proteins and other proteins, tumor microenvironment, presence and/or frequencies of IDH1 and other oncogenic gene alterations. Participants who agree to participate in the optional analysis of the biomarkers must provide consent for this analysis in the ICF, which can be withdrawn at any time without compromising the participation in the overall clinical study investigations. In addition, in case of consent withdrawal, related samples will be destroyed before any further optional assessment is completed.

The goal of the optional analysis of biomarkers on unscheduled biopsy(ies) collected as per standard of care is to provide supportive data for the clinical study. Depending on the results obtained during the study and at the discretion of the Sponsor, analysis may be omitted, or discontinued for practical or strategic reasons (e.g. inadequate number of samples, issues related to the quality of the sample or the assay that preclude analysis, impossibility to perform correlative analyses, etc.).Overall results of the genomic biomarkers assessment may be transmitted to the participant upon request at the end of the study.

There will be no communication of individual results to the Investigator or to the participant unless these results are proven to impact the therapeutic strategy.

9.5.5.1. Retrospective Analyses

Retrospectives analyses involving human biological samples are considered as optional assessments and are performed after the end of the study (planned or not in the clinical study protocol).

Participation in these retrospective analyses is optional and is not mandatory for the inclusion of a given participant in the study (please refer to Section 9.5.5).

If the participant agrees, some additional samples/remaining biomarker samples may be stored after the end of the study.

They could be further analyzed to address scientific questions related to the product or disease including research related to improvements or enhancements in the development of bioanalytical methods.

A decision to perform such exploratory biomarker research studies will be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

Samples will be kept in suitable conditions in a central bio-repository specialized in storage of biological samples until further notification from the Sponsor and may be stored up to 25 years after study closure completion.

10. STATISTICS

This section is a general outline of the statistical methods that will be implemented in this trial. More details will be specified in the statistical analysis plan (SAP).

10.1. Statistical Analysis

10.1.1. General Methods

Study data will be summarized for disposition, demographic and baseline characteristics, safety, PK, PD, and clinical anti-tumor activity.

Categorical data will be summarized by frequency distributions (number and percentages of participants) and continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). In each cohort of the Expansion phase, participants treated during the Safety Lead-in phase will be pooled with those receiving the same dose of ivosidenib during the Expansion phase, unless otherwise specified. All summaries, listings, figures, and analyses will be performed by dose level and total in the Safety Lead-in phase, and by cohort and total in the Expansion phase, unless specified otherwise.

The study data will be analyzed and reported in the CSR based on all participants' data from both the Safety Lead-in and Expansion phases.

10.1.2. Analysis Sets

The following analysis sets will be evaluated and used for presentation of the data:

- DLT-Evaluable Set: All participants enrolled during the Safety Lead-in phase who have received any dose of the combination therapy and experienced a DLT through Cycle 2, or who have received at least 2 doses of nivolumab and ipilimumab, respectively, and at least 75% of ivosidenib at the planned dose through Cycle 2 without experiencing a DLT through Cycle 2 will be considered evaluable for DLT assessment. This analysis set will be the primary set to determine the RCD, which will be further investigated at the Expansion phase.
- Safety Analysis Set: All participants enrolled who have received any amount of study treatment (ivosidenib in combination with nivolumab and ipilimumab). The Safety Analysis Set will be the primary analysis set for clinical anti-tumor activity, safety, and other analyses, unless otherwise specified.
- Response-Evaluable Set: All participants in the Safety Analysis Set for whom a baseline disease assessment and at least one post-baseline response assessment are available and evaluable. The Response-Evaluable Set will be used for the supportive analysis for the primary endpoint of objective response.

- Pharmacokinetic Analysis Set: All participants who have had at least one blood sample providing evaluable PK data for ivosidenib in combination with nivolumab and ipilimumab.
- Pharmacodynamic Analysis Set: All participants who have had at least one blood sample providing evaluable plasma 2-HG data for ivosidenib in combination with nivolumab and ipilimumab.
- ADA Analysis Set: All participants with a baseline ADA assessment and at least one post-treatment ADA assessment.

10.1.3. Disposition and Baseline Characteristics

The participants' disposition and baseline characteristics will be described in the Safety Analysis Set. The number of participants and the reasons for exclusion will be listed as well as the disposition of participants, including reasons for treatment discontinuation and study withdrawal. Major protocol deviations will be summarized. Protocol deviations will be listed. Characteristics of participants including demography, characteristics of the disease at diagnosis and study entry, medical history, and prior therapy will be summarized.

10.1.4. Exposure

Study drug exposure, including number of doses administered, total dose, duration of treatment, the proportion of participants with dose modifications, the dose intensity (computed as the ratio of actual dose received and actual duration), and relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration) will be listed and summarized using descriptive statistics for each drug separately.

The Safety Analysis Set will be the primary analysis set.

10.1.5. Analysis of Primary Endpoints

10.1.5.1. Safety Lead-in Phase: Estimation of the RCD - Ivosidenib in Combination with Nivolumab and Ipilimumab

One of the primary endpoints during the Safety Lead-in phase is DLT through Cycle 2. The criteria of DLT rate < 33% will be used to determine the RCD for ivosidenib in combination with nivolumab and ipilimumab. DLT rate will be calculated based on the DLT-Evaluable Set by dose level. The DRT will review the aggregate treatment-emergent safety data in addition to DLTs to determine the RCD.

10.1.5.2. Expansion Phase: Objective Response per Investigator Assessment of Anti-tumor Activity (Using RECIST v1.1)

The primary endpoint during the Expansion phase is the objective response per RECIST v1.1 for solid tumors [Appendix 5]) (Eisenhauer *et al*, 2009).

The primary estimand of interest is the ORR. The attributes of the primary estimand are defined as follows:

- Treatment: ivosidenib plus nivolumab and ipilimumab.
- Population: Safety Analysis Set.
- Variable: ORR (for the primary efficacy endpoint).
- Summary measure: objective response (Yes, No).
- Intercurrent events (IE):

1. Early treatment discontinuation
2. Administration of further anti-cancer therapy

Primary analysis
The primary analysis for the primary endpoint of objective response will be based on the Safety Analysis Set.

The ORR will be calculated as the proportion of participants who achieve confirmed CR or PR with the 2-sided exact binomial 95% CI by cohort. Participants treated at the RCD and enrolled during the Safety Lead-in phase will be pooled with those receiving the same dose of ivosidenib during the Expansion phase for each cohort as appropriate.

Supportive Analysis
A supportive analysis for the primary endpoint of objective response will be based on the Response-Evaluable Set.

Additional sensitivity analysis may be conducted based on retrospective central review if available.

Other estimands of interest for the primary endpoint of objective response may be analyzed as appropriate.

10.1.6. Analysis of Secondary Endpoints

10.1.6.1. Analysis of Secondary Efficacy Endpoints

The primary analysis for response-related secondary efficacy endpoints will be based on Investigator assessment. Additional sensitivity analysis may be conducted based on retrospective central review if available. Two-sided 95% CIs for the response rates will be calculated where appropriate. Duration of response (DOR) and PFS determined by Investigator per RECIST v1.1 will be assessed using Kaplan-Meier methods for each cohort to estimate the median and quantiles of the relevant endpoint where appropriate.

- Best overall response (BOR) will be determined per participant as the best response recorded (either CR, PR, SD or PD) from the start of the treatment until disease progression, end of treatment, or initiation of subsequent anti-cancer therapy, whichever occurs first.
- DOR: Among responders with confirmed CR or confirmed PR, DOR will be calculated as the date of the first occurrence of confirmed response to the date of documented disease progression or death, whichever occurs first. Participants without disease progression or death will be censored at the last evaluable response assessment date. Additional details of censoring rules will be defined in the SAP.
- Disease control rate (DCR): Disease control rate is defined as the rate of confirmed CR, confirmed PR, and SD maintained for at least 5 months.
- Time to response (TTR): TTR will be calculated as the date of the first dose to the date of the first occurrence of a confirmed CR or confirmed PR, whichever occurs first.
- PFS is defined as the time from the date of the first dose of the study medication to the date of first documentation of disease progression as determined by the Investigator or death due to any cause, whichever occurs first. Detailed censoring rules will be defined in the SAP.
- OS is defined as the time from the date of the first dose to the date of death due to any cause.

10.1.6.2. Analysis of Secondary Safety Endpoints

Safety summaries will contain only data collected during the on-treatment period, unless otherwise specified. Safety data will be summarized. In general, the on-treatment period is defined as the time from the date of the first dose of study drugs to 30 days from the last dose of study drugs. For immune-mediated adverse events, the on-treatment period is defined as the time from the date of the first dose of study drugs to 100 days from the last dose of nivolumab.

10.1.6.2.1. Adverse Events

Summary tables for AEs will include TEAEs, which are AEs that start or worsen during the on-treatment period. The incidence of TEAEs will be summarized according to Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class and/or Preferred Term, severity (based on NCI CTCAE grades), type of event, and relation to study treatment. The following summaries will be generated:

- All TEAEs.
- Most common TEAEs (*i.e.*, reported by ≥ 10% of participants for each cohort).
- Treatment-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher treatment-related TEAEs.
- SAEs.
- TEAEs leading to treatment discontinuation.
- TEAEs leading to dose reduction.
- AEs leading to on-treatment death.

By-participant listings will be provided for AEs leading to on-treatment death, and TEAEs, SAEs, and TEAEs leading to treatment discontinuation.

10.1.6.2.2. Laboratory Abnormality

For laboratory tests covered by the NCI CTCAE version 5.0 or later, grades will be assigned for these tests, and Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests not covered by the NCI CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology and chemistry laboratory tests:

- Descriptive statistics for the actual values (and/or change from baseline) or frequencies of clinical laboratory parameters over time.
- Shift tables using NCI CTCAE grades to compare baseline with the worst post-baseline value (for laboratory tests for which NCI CTCAE grades are not defined, shift tables using the low/normal/high/[low and high] classification to compare baseline with the worst post-baseline value may be generated).

In addition to the above-mentioned tables and listings, graphical displays of key safety parameters, such as scatter plots of actual or change in laboratory tests over time or box plots, may be specified in the SAP.

10.1.6.2.3. Other Safety Data

The actual values (and/or the changes from baseline) of physical examination over time and vital signs over time will be listed by participant.

Descriptive statistics of ECOG performance status scores over time will be summarized. Shift tables may be generated for ECOG performance status scores from baseline to worst value of post-baseline assessments.

Descriptive statistics for the actual values and changes from baseline in ECG data over time will be summarized. QTc will be calculated using Fridericia's correction. In addition, a categorical analysis of QTc may be performed for each time point. Maximum QTc and maximum changes from baseline may also be summarized similarly. ECG abnormalities, if collected, will be presented in a listing.

10.1.6.2.4. Prior and Concomitant Medications

Prior medications taken prior to the start of study drugs will be listed by participant and summarized.

Concomitant medications taken at the time of or after the start of study drugs and prior to the last dose plus 35 days will be listed by participant and summarized.

10.1.7. Analysis of Exploratory Endpoints

All participants with evaluable sample measurements will be included in the analysis. Actual values or changes/shifts from baseline of exploratory biomarkers will be summarized over time and may be displayed graphically.

There may be circumstances when a decision is made to stop collection, not perform, or discontinue the analysis of PD or biomarker samples due to either practical or strategic reasons (*e.g.*, inadequate sample numbers, issues related to the quality of samples, or issues related to the assay that precludes the analysis of samples). Under such circumstances, the sample size may be too small to perform any data analysis and the available data will only be listed as applicable.

Additional analyses may be planned and reported separately from this study.

10.1.8. Handling of Missing Values and Discontinuation

For continuing events (*e.g.*, AEs, concomitant medications), the status of the event continuing will be denoted in the listings. Other missing data will simply be noted as missing in appropriate tables/listings.

For the purposes of reporting, participants continuing to receive study drug will have time-to-event data (*e.g.*, DOR) censored at the date of last documented disease assessment prior to the data cutoff date.

Further details of censoring rules for efficacy analyses will be documented in the SAP.

Participants who have disease progression and continue to receive treatment after progression will be considered as having documented progressive disease at the time of first progression.

Participants with a best overall response of "Unknown" or "Not Evaluable" will be considered non-responders in estimating response rates for the primary estimand.

10.2. Determination of Sample Size

It is estimated that up to approximately 92 subjects will be enrolled in this Phase 1/2 study, with approximately 6 to 12 DLT-evaluable participants in the Safety Lead-in phase and up to approximately 40 participants in each Expansion phase cohort. The number of subjects in the Expansion phase cohorts include the subjects enrolled in the Safety Lead-in phase and treated at the RCD.

The rationale of choosing the planned sample sizes for the Safety Lead-in phase and the Expansion phase are described in Section 10.2.1 and Section 10.2.2, respectively. Due to the exploratory nature of this study, the planned sample sizes are not determined based on formal evaluation using statistical power and type I error, but to provide a reasonable precision of the estimation of ORR (Table (10.2.2) 1).

10.2.1. Safety Lead-in Phase

During the Safety Lead-in phase, one of the primary endpoints is DLT through Cycle 2. Approximately 6 to 12 DLT-evaluable subjects will be enrolled to be evaluated at up to 2 dose levels of ivosidenib in combination with nivolumab and ipilimumab:

- 500 mg QD: Initially approximately 6 DLT-evaluable subjects will be examined. If at least 2 DLTs from the 6 subjects are observed, a lower dose of 250 mg QD ivosidenib will be considered for assessment with consideration of the overall safety data from the 6 subjects.
- 250 mg QD: Another approximately 6 DLT-evaluable subjects will be examined.

10.2.2. Expansion Phase

During the Expansion phase, subjects will be enrolled into 2 cohorts and treated at the RCD:

- Cohort 1, anti-PD1/L1 naïve subpopulation: This cohort will include up to approximately 40 participants with nonresectable or metastatic CCA who have not received any anti-PD1/L1 therapy.
- Cohort 2, anti-PD1/L1 previously treated subpopulation: This cohort will include up to approximately 40 participants with nonresectable or metastatic CCA who have received anti-PD1/L1 therapy.

Each cohort will enroll up to approximately 40 subjects to provide reasonable certainty in estimating the primary estimand ORR for the primary endpoint of objective response. CCI [redacted]

CCI [redacted]

CCI [redacted]	[redacted]
[redacted]	[redacted]

CCI [redacted]	[redacted]
[redacted]	[redacted]

10.3. Pharmacokinetic Analyses and PK/PD Analysis

10.3.1. Pharmacokinetic Interpretation

Concentrations of ivosidenib, nivolumab and ipilimumab might be used alone or combined with data from other studies for modelling activities such as population PK modelling and physiological based pharmacokinetic modeling, in order to support the development of ivosidenib. Pharmacokinetic parameters will be estimated using noncompartmental analysis methods. Descriptive statistics (*i.e.*, number of subjects, mean, standard deviation, geometric mean and coefficient of variation, median, minimum, and maximum) will be used to summarize PK parameters of ivosidenib given in combination with nivolumab and ipilimumab for each dose and cohort; and where appropriate, for the entire population. Such parameters may include (but are not limited to) area under the concentration-*vs*-time curve (AUC) from 0 to time of last measurable concentration (AUC_{0-t}), AUC from 0 to infinity ($AUC_{0-\infty}$), AUC over 1 dosing interval at steady state ($AUC_{tau,ss}$), time to maximum concentration (T_{max}), maximum concentration (C_{max}), trough concentration (C_{trough}), $t_{½}$, apparent volume of distribution (Vd/F), and apparent clearance (CL/F).

The relationships between dose and both C_{max} and AUC will be explored graphically for dose proportionality where appropriate. Descriptive statistics (*i.e.*, number of subjects, mean, standard deviation, geometric mean and coefficient of variation, median, minimum, and maximum) will be summarized for the PK concentration data over planned time points.

The Pharmacokinetic Analysis Set will be used for summaries of PK data, as well as listings of derived parameters and concentration data for ivosidenib, nivolumab, and ipilimumab.

Descriptive statistics will be used to summarize PK concentrations at different nominal time points across participants by dose and cohort.

10.3.2. PK/PD Interpretation When Applicable

Descriptive statistics, including but not limited to number of subjects, mean, and standard deviation, will be used to summarize plasma and tissue 2-HG concentrations at different nominal time points across participants by dose and cohort. The potential relationship between plasma exposure of ivosidenib and plasma 2-HG levels will be explored with descriptive and graphical methods as appropriate. Similar evaluation will be performed using tissue exposure of ivosidenib and tissue 2-HG levels, if data permit.

The Pharmacodynamic Analysis Set will be the primary analysis set for summaries and listing of 2-HG concentrations and changes from baseline in circulating concentrations 2-HG.

Details of the PK and PD analyses will be described in an analysis plan.

10.4. Interim Analyses

A Bayesian 2-stage design with a futility interim analysis will be implemented for each expansion cohort. Futility analysis will be conducted for each cohort when approximately 20 response-evaluable subjects have completed at least 4 cycles of treatment or discontinued study treatment. The following futility rule will be considered for the futility analysis:

- Cohort 1, anti-PD1/L1–naïve subpopulation: If there are 2 or fewer responders (based on unconfirmed CR or unconfirmed PR) of 20 subjects, enrollment may stop; otherwise, enrollment will continue.
- Cohort 2, anti-PD1/L1 previously treated subpopulation: If there are 0 or 1 responders (based on unconfirmed CR or unconfirmed PR) of 20 subjects, enrollment may stop; otherwise, enrollment will continue.

Additional interim analyses may be conducted during the Expansion phase if necessary. The Sponsor may determine to terminate or further expand cohorts after the interim analyses.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will allow the monitors, the persons responsible for the audit, the representatives of the IRB/IEC, and of the Competent Authorities to have direct access to source data/documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the structure mentioned in Section 1.

If on-site monitoring cannot be accomplished, remote Source Data Verification may be performed in accordance with local regulations.

Details of clinical site monitoring are documented in a Monitoring Plan. The Monitoring Plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

12.1.1. Before the Study

The Investigator will allow the monitor to visit the site and facilities where the study will take place to ensure compliance with the protocol requirements.

Training sessions may be organized for the Investigators and/or instruction manuals may be given to the Investigators.

12.1.2. During the Study

The Investigator will allow the monitor to:
- review of the study site's processes and procedures,
- verify appropriate clinical Investigator supervision of study site staff and third-party vendors,
- inspect the site, the facilities, and the material used for the study,
- meet all members of the team involved in the study,
- consult the documents relevant to the study,
- have access to the eCRFs and service provider's database,
- check that the eCRFs have been filled out correctly,
- directly access source documents for comparison of data therein with the data in the eCRFs,
- verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study monitoring will be carried out at regular intervals, depending on the recruitment rate and/or the investigation schedule, and arranged between the Investigator and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerized Medical File

If computerized medical files are used, and if the computer system allows, no change made in the medical files by the Investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (*i.e.*, audit trail). The Investigator will save data at regular intervals.

The Investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorized access to the data and to the computer system.

If the computerized medical files are considered as not validated by the Sponsor, the Investigator undertakes:
- at the start of the study, to print the medical files of all participants allowing a reliable verification of the study criteria (*e.g.*, medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol),
- during the study, to print in real time each data entry and each data change.

The Investigator will personally sign, date, and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the Investigator will provide all the print-outs of the medical files of the participants. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the Investigator will supply the monitor, at each visit, with a print-out of the medical files of the participants and the records of the changes made. Each print-out will be personally dated and signed by the Investigator and the monitor on the first page. The number of pages will also be indicated by the Investigator and the monitor on the first page.

If the computerized medical files are considered as validated by the Sponsor, the Investigator undertakes to give access to the monitor to the computerized medical files of all participants. If the monitor cannot access to the tracking of the changes made to the medical files, the Investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the participants. Each print-out will be personally dated and signed by the Investigator and the monitor on the first page. The number of pages will also be indicated by the Investigator and the monitor on the first page.

The Investigator undertakes to keep:
- all medical file print-outs signed and dated by the Investigator and by the monitor when the computer system is considered as not validated by the Sponsor,
- if the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the Sponsor or when the monitor cannot access to the audit trail in the computer system,
- all original source documents (originals of specific examinations, informed consent forms, RTSM reports, or equivalent document).

12.3. Audit - Inspection

The Investigator should be informed that an audit by the Sponsor or its representative may be carried out before, during, or after the end of the study.

If on-site auditing cannot be accomplished and is required, remote audit may be performed in accordance with local regulations.

The Investigator should be informed that the Competent Authorities may also carry out an inspection in the facilities of the Sponsor and/or the study center(s). The Sponsor will inform the Investigators concerned immediately upon notification of a pending study center inspection in case the notification is not sent directly to the Investigator. Likewise, the Investigator will inform the Sponsor of any pending inspection notification received related to the study.

The Investigator must allow the representatives of the Competent Authorities and persons responsible for the audit:
- to inspect the site, facilities, and material used for the study,
- to meet all members of the team involved in the study,
- to have direct access to study data and source documents,
- to consult all the documents relevant to the study.

If the computerized medical file is considered as not validated, the Investigator undertakes to provide all the source documents and the print-outs of the medical files of the participants and, if the computer system used allows, the record of the changes made during the study.

If the computerized medical file is considered as validated, the Investigator undertakes to:
- give access to the representatives of the Competent Authorities and persons responsible for the audit to the computerized medical files of all participants,
- provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

12.4. Supervisory Committees

Not applicable.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the "Participant information and consent form" document, the "Legal representative information and consent form" document, the list of Investigators document, the insurance documents, and the SmPC or IB of administered IMPs will be submitted to (an) IRB(s)/IEC(s) by the Investigator(s) or the national coordinator(s) or the Sponsor in accordance with local regulations.

The study will not start in a center before written approval by corresponding IRB/IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study Conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964 (see Appendix 1), with GCP, and with the applicable regulatory requirements.

13.3. Participant Information and Informed Consent

In any case, the participant (and/or his/her legal representative, when required) must be informed that he/she is entitled to be informed about the outcome of the study by the Investigator.

The Investigator or a person designated by him/her is required to collect written consent from each participant before his/her participation in the study. Prior to this, the Investigator or his/her delegate must inform each participant of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs. If applicable, the Investigator may advise the participant about donation and cryopreservation of germ cells in line with recommendations on contraception provided. The participant must be informed that he/she has the possibility not to participate in the study and that he/she is free to reconsider his/her consent at any time.

The participant will be provided with an information and consent form in clear, simple language. He/she must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

One, or two if required by local regulation, original information and consent form(s) must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent.

According to each study participant own preference, ICF could be made available both printed on paper or/and electronically through a HIPAA, 21 CFR part 11 and GDPR compliant web-based platform. Local regulations permitting, the electronic signature for the ICF could be made available to interested study participants.

If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion. The participant must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form(s). The witness must then complete, sign and date the form(s) together with the person responsible for collecting the informed consent.

The participant will be given one signed copy (or original if required by local regulation) of the information and consent form. A signed original will be kept by the Investigator. A copy of the information and consent form in the language(s) of the country is given in the "Participant information and consent form" document attached to the protocol.

Interested study participants will be offered the possibility to replace certain in-person visits to the research site by televisits (where possible). This means that some study visits could be conducted using a HIPAA, 21 CFR part 11 and GDPR compliant web-based platform, as per each study participant own preference.

This follow-up (for survival status until the end of the study) can be done remotely by using various telecommunication technologies including but not limited to phone, web-based remote video-calling, and shared electronic medical records.

13.4. Modification of the Information and Consent Form

Any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the IRB/IEC(s), and if applicable to the Competent Authorities.

A copy of the new version(s) of the information and consent form(s) in the language(s) of the country will be given in the amendment to the "Participant Information and consent form".

Such amendments may only be implemented after written approval of the IRB/IEC has been obtained and compliance with the local regulatory requirements, except for an amendment required to eliminate an immediate risk to the study participants.

Each participant affected by the amendment must complete, date and co-sign one, or two if required by local regulation, original(s) of the new version of the information and consent form together with the person who collected the informed consent (and an independent witness, if applicable). They will receive one signed copy (or original, if required by local regulation) of the amendment to the information and consent form(s). The signed original(s) will be kept by the Investigator.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study Data

A 21 CFR Part 11-compliant electronic data capture system will be used in this study. An eCRF is designed to record the data required by the protocol and collected by the Investigator.

The eCRF will be produced by I.R.I.S. or Servier Full Service Provider (FSP) Data Management in compliance with its specifications. The Investigator or a designated person from his/her team will be trained for the use of the eCRF by the Sponsor, or Servier FSP Data Management.

Data entry at the Investigator's site will be performed by the Investigator or by the designated person from his/her team after completion of the participant's Medical File.

The Investigator or the designated person from his/her team agrees to complete the eCRF, at each participant visit, and all other documents provided by the Sponsor (*e.g.*, documents relating to the IMP management).

Data recorded directly on the eCRF and considered as source data (see Section 4.3) must be collected immediately in the eCRF. The other eCRF forms must be completed as soon as possible following each visit.

All corrections of data on the eCRF must be made by the Investigator or by the designated person from his/her team in electronic data capture (EDC) system according to the provided instructions. All data modification will be recorded using the audit trail feature of EDC system, including date, reason for modification, and identification of the person who has made the change.

To ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorized personnel only, whether resident within the Investigator's sites, the Sponsor, or third parties. Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction/ clarification from the Investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However, the Investigator has the possibility to modify a data if deemed necessary via a request to the Sponsor.

The Investigator or authorized member for sign-off must confirm the authenticity of the data recorded in the eCRF by signing-off the eCRF in a timely manner as defined in the eCRF guide.

14.2. Data Management

Data are collected via an eCRF and stored in a secured database.

In case of data exceptionally collected on paper form, the clinical Data Management of I.R.I.S. or the CRO is responsible for the data entry processing.

For data collected on the eCRF, Servier FSP Data Management is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. A query is submitted in the EDC system (Clinical One) for the Investigator/site to respond to and make any necessary changes to the data.

The Medical Review Department is responsible for data coding including:
- medical/surgical history, AEs, and procedures using MedDRA
- medications using World Health Organization, Drug Dictionary (WHO-Drug)

The coding process is described in a specification manual.
The Investigator ascertains he/she will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact the Sponsor or its representatives monitoring the study, if any, to request approval of a protocol deviation, as no deviations are permitted. If the Investigator feels a protocol deviation would improve the conduct of the study, this must be considered as a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC, it cannot be implemented. All-important protocol deviations will be recorded and reported in the CSR.

When data validation is achieved, a review of the data is performed according to the Sponsor standard operating procedure, as applicable. When the database has been declared to be complete and accurate, it will be locked and made available for data analysis.

14.3. Archiving

The Investigator will keep all information relevant to the study for at least 25 years after the end of the study, or more if specified by the local regulation.

At the end of the study, the Investigator or an authorized member of his/her team will download an electronic copy of each participant's data from the eCRF and should keep it in a reliable, secure, and durable location. The file includes all data and comments reported in the eCRF, the history of all queries and signatures, and the full audit trail reports.

The file must include appropriate restrictions (password protection) and adequate protection from loss, physical damage, or deterioration for the duration of the archiving period.

15. INSURANCE

I.R.I.S., or any affiliated company of SERVIER GROUP in charge of the management of clinical trials, is insured under the liability insurance program subscribed by LES LABORATOIRES SERVIER to cover its liability as Sponsor of clinical trials on a worldwide basis.

Where an indemnification system and/or a mandatory policy are in place, I.R.I.S. or any affiliated company of SERVIER GROUP will be insured under a local and specific policy in strict accordance with any applicable law.

All relevant insurance documentation is included in the file submitted to any authorities' approval of which is required.

16. OWNERSHIP OF THE RESULTS – DATA SHARING POLICY AND PUBLICATION POLICY

I.R.I.S., acting as the Study Sponsor, assumes full responsibilities relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

I.R.I.S. will ensure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end shall be submitted to the Sponsor in accordance with the guidelines set forth in the applicable publication policy or financial agreement.

The Investigator, who submitted the project, shall take the Sponsor's comments into due consideration.

Servier's Data Sharing Policy is available at https://clinicaltrials.servier.com/data-request-portal/. Researchers can ask for a study protocol, subject-level and/or study-level clinical trial data including CSRs.

They can ask for all interventional clinical studies:
- submitted for new medicines and new indications approved after 01 January 2014 in the European Economic Area (EEA) or the US
- where Servier or an affiliate is the Marketing Authorization Holder. The date of the first Marketing Authorization of the new medicine (or the new indication) in one of the EEA Member States will be considered within this scope.

In addition, Servier's Data Sharing Policy includes all interventional clinical studies in subjects:
- sponsored by Servier
- with a first subject enrolled as of 01 January 2004 onward
- for New Chemical Entity or New Biological Entity (new pharmaceutical form excluded) for which development has been terminated before any Marketing Authorization approval

The datasets generated and/or analyzed during the current study will be available upon request from www.clinicaltrials.servier.com after the Marketing Authorization has been granted.

Summary results and a lay summary will be published on www.clinicaltrials.servier.com within 12 months after the end of the study.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the Sponsor and the Investigator

17.1.1. Persons to Inform

In accordance with local regulations, the Investigator and/or the Sponsor will inform the Director of the medical institution, the pharmacist involved in the study, and the Director of the analysis laboratory.

17.1.2. Substantial Protocol Amendment and Amended Protocol

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by the Investigator and the Sponsor.

The substantial protocol amendment must be drafted in accordance with the Sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the Investigator(s) or the coordinator(s) or the Sponsor, in accordance with local regulations, to the IRB/IEC that examined the initial protocol. They can be implemented only after a favourable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, except for a measure required to eliminate an immediate risk to the study participants.

When the submission is performed by the Investigator or the coordinator, the latter must transmit a copy of IRB/IEC's new written opinion to the Sponsor, immediately upon receipt.

Furthermore, the substantial amendment and amended protocol are to be submitted to the Competent Authorities in accordance with local regulations.

17.1.3. Final Study Report

The study report will be drafted by the Sponsor in compliance with I.R.I.S. standard operating procedure.

The Sponsor's representative and the Investigator must mutually agree on the final version. One copy of the final report must be dated and signed by the Investigator and the Responsible Medical Officer of the concerned Therapeutic Area.
The CSR, the summary of the results of the clinical trial together with a summary that is understandable to a layperson will be submitted where applicable within 1 year after the end of the clinical trial worldwide.
If the clinical trial is still ongoing but ended in the European countries, the statistical analysis will not be relevant before the end of the study worldwide. Therefore, the timelines defined above still apply.**Concerning the Sponsor**

The Sponsor undertakes to:
- supply the Investigator with adequate and sufficient information concerning the IMP administered during the study to enable him/her to carry out the study,
- supply the Investigator with IB if the test drug is not marketed,
- supply the Investigator with SmPC, the one best suited to ensure participant safety, and any potential updated version during the study:
  - for the test drug if marketed, to be appended to the IB (Section 4 Guidance for the Investigator),
  - for all reference products used in the study.
- obtain any authorization to perform the study and/or import license for the IMP administered that may be required by the local authorities before the beginning of the study,
- provide the Investigator annually, or with another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/IEC(s),

- take all the necessary precautions to maintain the safety of the processed data, in particular their confidentiality, their integrity and their availability, by assessing risks identified concerning personal data protection. The following measures will be implemented (non-exhaustive):
  - Management of authorization to access to personal data (eCRF),
  - Identification and authentication measures before accessing personal data (eCRF),
  - Traceability measures for the access to and modification of personal data (eCRF),
  - Secured data transfer,
  - Time limit for storing personal data.
- handle any security breach by implementing an internal committee (including CISO, DPO, communication department) in order to qualify the security incident (information systems, nature and number of personal data impacted), to define an action plan for corrective actions and to notify to relevant person (authority and/or if needed individuals).

17.3. Concerning the Investigator

17.3.1. Confidentiality - Use of Information

All documents and information given to the Investigator by the Sponsor with respect to ivosidenib and Study CL1-95031-006 are strictly confidential.
The Investigator expressly agrees that data on his/her professional and clinical experience is collected by the Sponsor on paper and computer and stored for its sole use relating to its activities as the Sponsor of clinical trials, in accordance with GCP.

He/she has a right to access, modify, and delete his/her own personal data by applying to the Sponsor.
In case a participant wants to exercise his/her rights regarding personal data protection, he/she will contact the Investigator. The Investigator will forward the request to the Sponsor (see Appendix 6).

The Investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the Sponsor. The clinical study protocol given to the Investigator may be used by him/her or his/her colleagues to obtain the informed consent of study participants. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorization of the Sponsor.

The Investigator must not disclose any information without the prior written consent from I.R.I.S., except to the representatives of the Competent Authorities, and only at their request. In the latter case, the Investigator commits himself/herself to informing I.R.I.S. prior to disclosure of information to these authorities.

A participant screening log and a full identification and enrolment list of each participant will be completed and kept in a safe place by the Investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

The participant screening log must be completed from the moment the Investigator checks that a participant could potentially take part in the study (by assessment of participant medical history during a visit or by examination of the medical file).

17.3.2. Organization of the Center

Every person to whom the Investigator delegates under his/her responsibility a part of the follow-up of the study (co-Investigator, nurse) and any other person involved in the study for this center (cardiologist, pharmacist) must figure in the "Organization of centre" document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the center.

17.3.3. Documentation Supplied to the Sponsor

The Investigator undertakes before the study begins:

- to provide his/her dated and signed English curriculum vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the Sponsor and to send it to the Sponsor, together with that of his/her co-Investigator(s),
- to provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured,
- to provide any other document required by local regulation (*e.g.*, Food & Drug Administration 1572 form),
- to send, a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members.

The CVs of other members of the team involved in the study (if possible, in English) will be collected during the study (at least, members involved in the participants' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

17.3.4. Notification of a Serious Breach

A serious breach is defined as any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety, the rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial.

The Investigator should immediately report any events that might meet the definition of a serious breach to the contact point designated by the Sponsor. S/he should ensure that the study site is able to identify the occurrence of a (suspected) serious breach and that any suspected serious breach is promptly reported to the Sponsor or delegated party.

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19. APPENDICES

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that "A physician shall act in the subject's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of subjects, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on subjects or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their subjects in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the subjects who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens, and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious subjects, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the subject which aspects of their care are related to the research. The refusal of a subject to participate in a study or the subject's decision to withdraw from the study must never adversely affect the subject-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the subjects who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, Sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual subject, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the subject or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Subject Registration Form
Dose allocation - Subject Registration Form

PARTICIPANT REGISTRATION FORM SAFETY LEAD IN / CL1-95031-006

Centre n° : |__|__|__|__| - Participant n°(= e-CRF n°): |__|__|__|__|__|

Please complete Section A and return to sponsor department

by e-mail to S95031-006@servier.com

Section A

To be completed once Informed Consent Form signed

Participant identification :

Year of birth (yyyy): |__|__|__|__| Gender: ☐ Male ☐ Female

Diagnosis of the primary tumor type :……

Participant Informed Consent Form signature date (dd/mm/yyyy): |__|__| / |__|__| / |__|__|__|__|

Expected baseline completion date (dd/mm/yyyy): |__|__| / |__|__| / |__|__|__|__|

Section A completed by:……

Please complete Section B and return to sponsor department

by e-mail to S95031-006@servier.com

Section B

To be completed after baseline period

Investigator name: ……

Does the Participant comply with all inclusion/exclusion criteria? ☐ Yes ☐ No

If yes, inclusion date (dd/mm/yyyy) : |__|__| / |__|__| / |__|__|__|__|

Section B completed by:……

Date: |__|__| / |__|__| / |__|__|__|__| Signature:……..……..

Section C

Sponsor or its designee

IVOSIDENIB dose: |__|__|__| mg

Section C completed by:……

Date and signature of the sponsor Medical Monitor:…….…….	

Filing in Sponsor TMF (if applicable) and Investigator TMF

Appendix 3: Subject Performance Status

Status Karnofsky	Grade	Status ECOG* - ZUBROD / WHO
Normal, no complaints; no evidence of disease.	100	
	0	Fully active, able to carry on all pre-disease performance without restriction.
Able to carry on normal activity; minor signs or symptoms of disease.	90	
Normal activity with efforts; some signs or symptoms of disease.	80	
	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light housework, office work.
Cares for self; unable to carry on normal activity or to do active work.	70	
Requires occasional assistance but is able to care for most of his personal needs.	60	
	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires considerable assistance and frequent medical care.	50	
Disabled; requires special care and assistance.	40	
	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Severely disabled; hospital admission is indicated although death not imminent.	30	
Very sick; hospital admission necessary; Active supportive treatment necessary.	20	
	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Moribund; fatal processes progressing rapidly.	10	
Dead	0 5	Dead

** As published in Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982,5 649-655.*

Appendix 4: New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version 1.1), Eisenhauer, 2009

Measurability of tumor at baseline

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

Measurable

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

- 10 mm by CT-scan (CT-scan slice thickness no greater than 5 mm)
- 10 mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT-scan (CT-scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable

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

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Tumor response evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.
Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether subjects having non-measurable disease only are also eligible.

Baseline Documentation of 'Target' and 'Non-target' Lesions
When more than one measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).
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.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. 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 2 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 that is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.
A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumor regression in the measurable dimension of the disease.

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

Response Criteria
This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions:
Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease: 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 progressive disease, taking as reference the smallest sum diameters while on study.

Special Notes on the Assessment of Target Lesions
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 CR criteria are met because 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 progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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 (*e.g.,* 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 eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: 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.

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'.

Evaluation of Non-target Lesions
This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.
Complete response (CR): Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive disease: Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special Notes on Assessment of Progression of Non-target Disease
The concept of progression of non-target disease requires additional explanation as follows:
When the subject 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 quality for unequivocal progression status. 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.
When the subject has only non-measurable disease. This circumstance arises in some Phase 3 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 subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: *i.e.*, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the subject should be considered to have had overall progressive disease 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.

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

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

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET (a 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image) at follow-up is a sign of progressive disease based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is progressive disease.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of progressive disease will be the date of the initial abnormal FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not progressive disease.

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the BOR.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table 1: Time Point Response: Subjects with Target (± Non-target) Disease

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

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

When subjects have non-measurable disease only (therefore non-target), Table 2 is to be used.

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

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	on-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations CR = complete response; PD = progressive disease; NE = not evaluable.

1 = Non-CR/non-PD' is preferred over stable disease' 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.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is NE at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of progressive disease. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved progressive disease status, regardless of the contribution of the missing lesion.

Best Overall Response: All Time Points

The BOR is determined once all the data for the subject is known.

Best response determination in trials where confirmation of CR or PR **is not** required: best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of

progressive disease. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of CR or PR **is** required: CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the BOR can be interpreted as in Table 3.

Table 3: Best Overall Response When 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[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

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

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

Special Notes 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 subjects with CR may not have a total sum of 'zero' on the eCRF.

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Tables 1 through 3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).
In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.
For equivocal findings of progression (*e.g.*, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of Tumor Re-evaluation
Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of Phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6 to 8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.
After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (*e.g.,* time to progression, disease-free survival, PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3-4 months after treatment) and should not be affected by delays in therapy, drug holidays, or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

Confirmatory Measurement/Duration of Response

Confirmation
In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, *i.e.*, in randomised trials (Phase 2 or 3) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

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

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of progressive disease).
The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of subjects achieving SD for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.
Note: The duration of response and SD as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Appendix 5: End of Cohort Meeting Minutes Template

End of cohort meeting minutes

Protocol : *CL1-95031-006*

Meeting decision on dose allocation at the End of Cohort No. ____: ____mg

Date of meeting / conference call: |__|__| / |__|__| / |__|__|__|__|

Attendees		
	Name(s):	**Role(s):**
Investigator trial site		
Innovation Therapeutic Pole		
Methodology Department		
Clinical pharmacokinetics		

Cumulative Summary of Subjects Treated

Subject No.	Treatment Start Date	Treatment Stop Date	Dose	DLT	Comment

Dose proposed by Methodology department

Dose proposed = ____ mg

Documents reviewed during the meeting:

- Interim safety report (*date*) - Preliminary PK results slideset (*plasma/urine*) *(date)*
- Core laboratory or clinical data *e.g.,* QT, echo data
- Others….

Details on safety issues (by subject No.)

1. **Subject No.**
2. **Subject No.**
3. **Subject No.**

Decision at the end of the cohort meeting:

❑ Dose allocation continued ❑ Dose allocation stopped	**Next cohort = ____ mg**

Comments:

E.g., Following review of the documents and data raised after the administration of x mg of IMP from *dd/mm/yyyy* to *dd/mm/yyyy*, it has been confirmed that the dose has been well tolerated and that the escalation to the next dose level (x mg of IMP) is appropriate.

Date: |__|__| / |__|__| / |__|__|__|__| Signature(s) of trial coordinator: ……

Appendix 6: Instructions to Investigator for Handling Data Rights Requests

DATA PROTECTION / GDPR (General Data Protection Regulation of 27 April 2016 n°2016/679)–

INSTRUCTIONS TO INVESTIGATOR FOR HANDLING DATA RIGHTS REQUESTS

In the framework of a research study/clinical trial, a participant to the study may exercise his/her rights, *i.e.*, may ask I.R.I.S. (as data controller) for:

- access to his/her data
- rectification of inaccurate/incomplete information
- restriction of processing of data
- objection to processing of data
- data portability (receiving his/her data in a readable format)

In accordance with the Informed Consent Form and information notice provided to participant, we requested participant to contact you first for exercising their rights.

Request for exercise of rights:

20. has to be a **written** one (either originating from mail or email from a participant or from request expressed orally to you and put in written)
21. has to be sent **by you** by email or by mail **to** I.R.I.S. (as data controller) to central address dataprivacy@servier.com or local Servier address as mentioned in ICF/information notice provided/available

DO **Instructions to be followed by you**	**DO NOT** **What you should not do**
Email title: Data protection rights	Do not forward participant email (if applicable)
Study name/number	
Participant number	**No information regarding participant identity**: No participant's name, email address, participant's signature
As soon as possible without exceeding a week	

I.R.I.S. and INVESTIGATOR responsibilities

GDPR requirement:
It is mandatory for I.R.I.S. as data controller to provide an answer to participant/volunteer within 1 month following the request (article 12 of GDPR)
Clinical trials requirements:
It is prohibited for I.R.I.S. as a Sponsor to know the identity of the participants/volunteer participating to studies

	I.R.I.S. responsibility	**Investigator responsibility**
Forward/inform I.R.I.S. of the request		YES
Timelines	Answer within 1 month once expressed by the participant	Request: transmitted to I.R.I.S. as soon as expressed by the participant Answer: transmitted by you to participant as soon as sent by I.R.I.S.
Answer the request	YES	

Appendix 7: Contraception Considerations

Definition of women of childbearing potential and contraception methods

Women of childbearing Potential

A woman is considered of childbearing potential (WOCBP), *i.e.*, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Contraception methods

Definition of highly effective contraception methods for the study:

Highly effective methods of birth control refer to those which result in a low failure rate (*i.e.* less than 1% per year), when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception when associated with inhibition of ovulation (oral, injectable, implantable), some intra-uterine devices, intrauterine hormone-releasing system, true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, male sterilization (vasectomy).

Definition of acceptable contraception methods for the study:

Acceptable contraception methods for the study are those considered as highly effective methods, male or female condom with or without spermicide, cap, diaphragm or sponge with spermicide.

Appendix 8: 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	Nivolumab monotherapy: Delay dose	Dosing may resume when AE resolves to baseline.
		When administered with ipilimumab: Permanently discontinue Ipilimumab	Nivolumab monotherapy may be resumed when AE resolves to baseline. If Grade 3 diarrhea or colitis recurs while on nivolumab monotherapy, 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 or ALT > 3 x and ≤ 5 x upper limit of normal (ULN) or T.bili > 1.5 x and ≤ 3 x ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 x ULN or T.bili > 3 x ULN, regardless of baseline value	Delay dose or permanently discontinue	In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the Investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy.
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	

Drug-Related Adverse Event (AE) per CTCAE V5	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
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 Medical Monitor 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 Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
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 Medical Monitor 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.

Drug-Related Adverse Event (AE) per CTCAE V5	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor 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
	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, (*i.e.*, 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, (*i.e.*, 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

Drug-Related Adverse Event (AE) per CTCAE V5	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
	Severe or life-threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	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 subject becomes asymptomatic.
	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 subject 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	

Drug-Related Adverse Event (AE) per CTCAE V5	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
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.
	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

Appendix 9: 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 (IO) 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 IO drug-related AEs. The oral equivalent of the recommended IV doses may be considered for ambulatory subjects 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 IO 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.

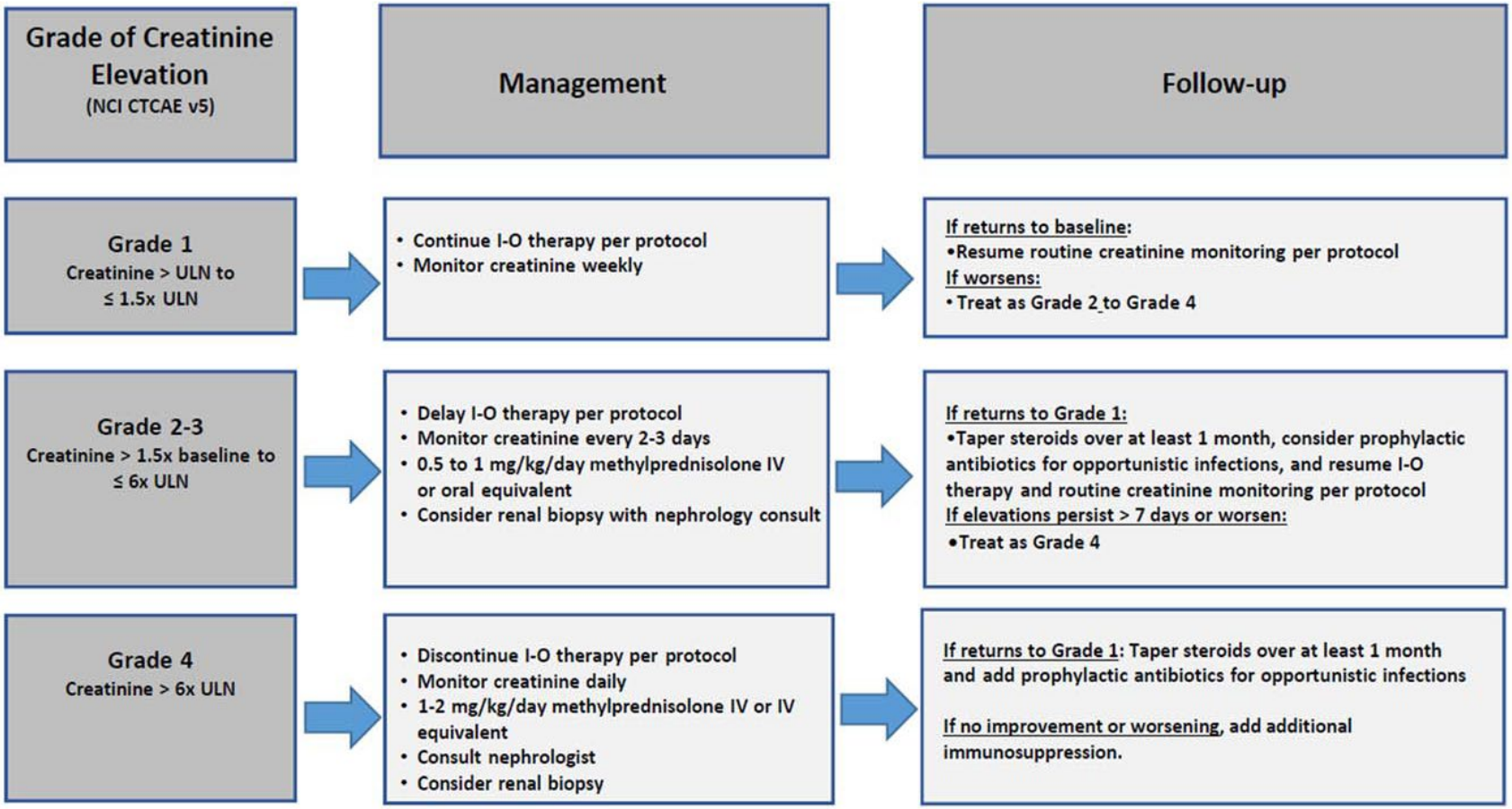
Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: 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.

Renal Adverse Event Management Algorithm

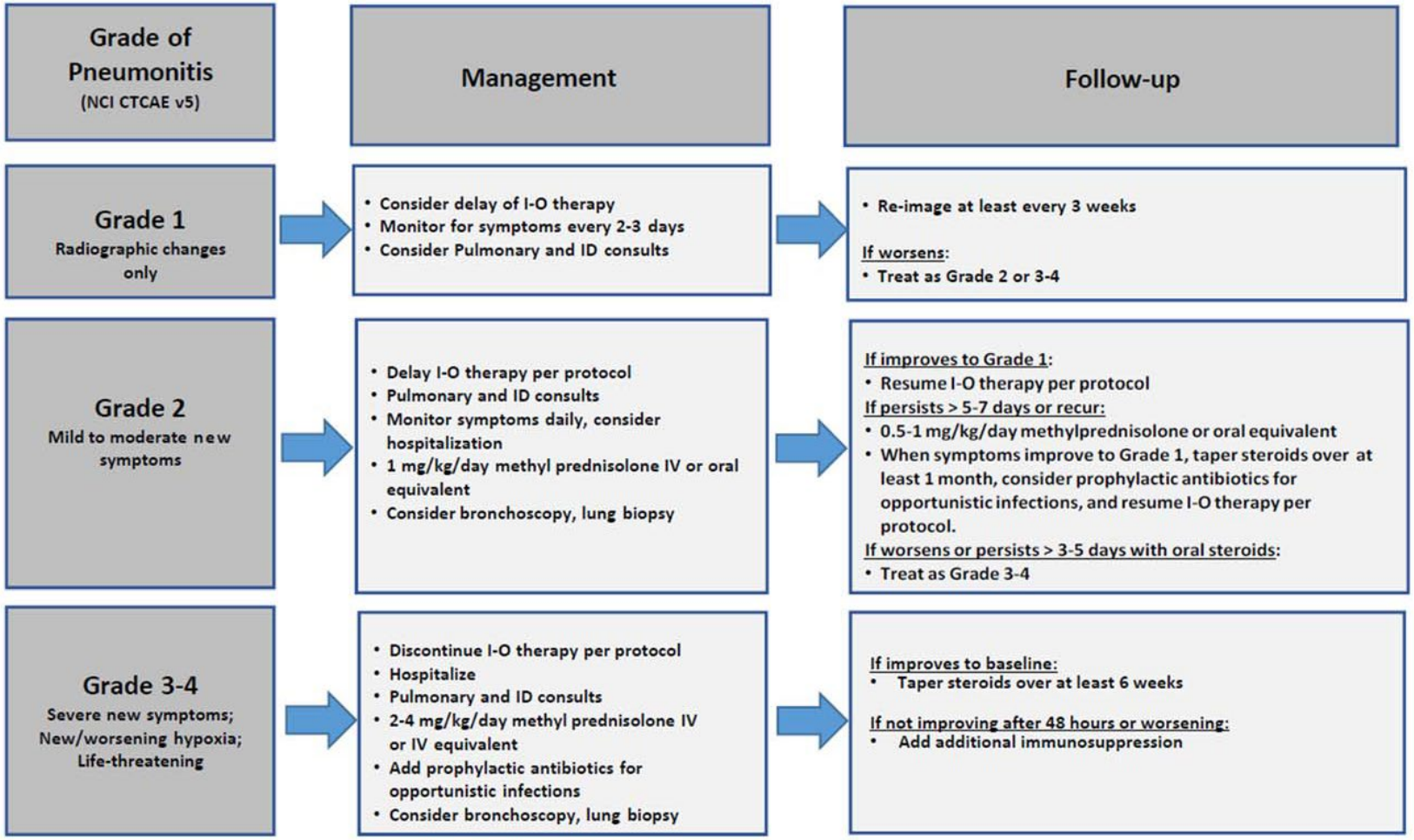
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Pulmonary Adverse Event Management Algorithm

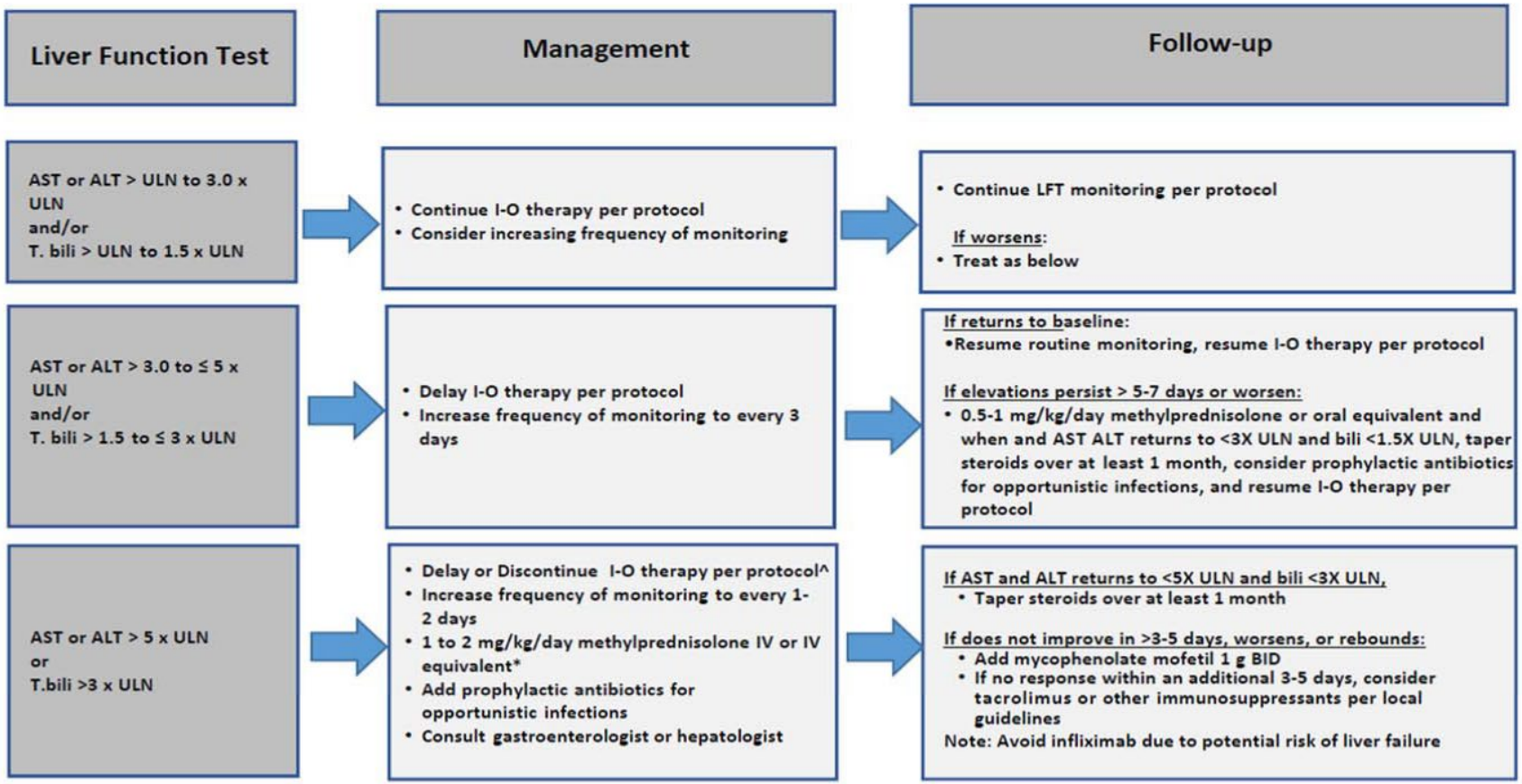
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



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.

Hepatic Adverse Event Management Algorithm

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



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.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

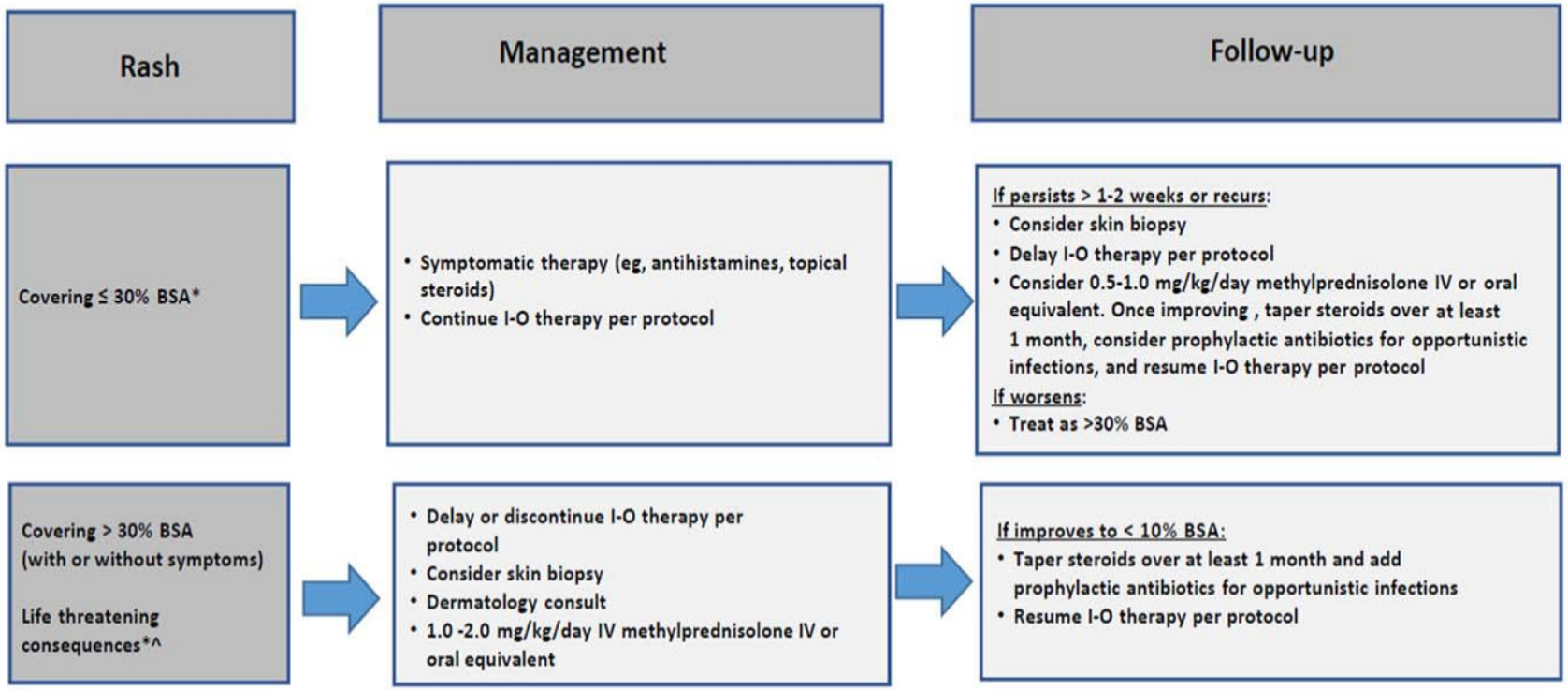
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

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.

Skin Adverse Event Management Algorithm

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



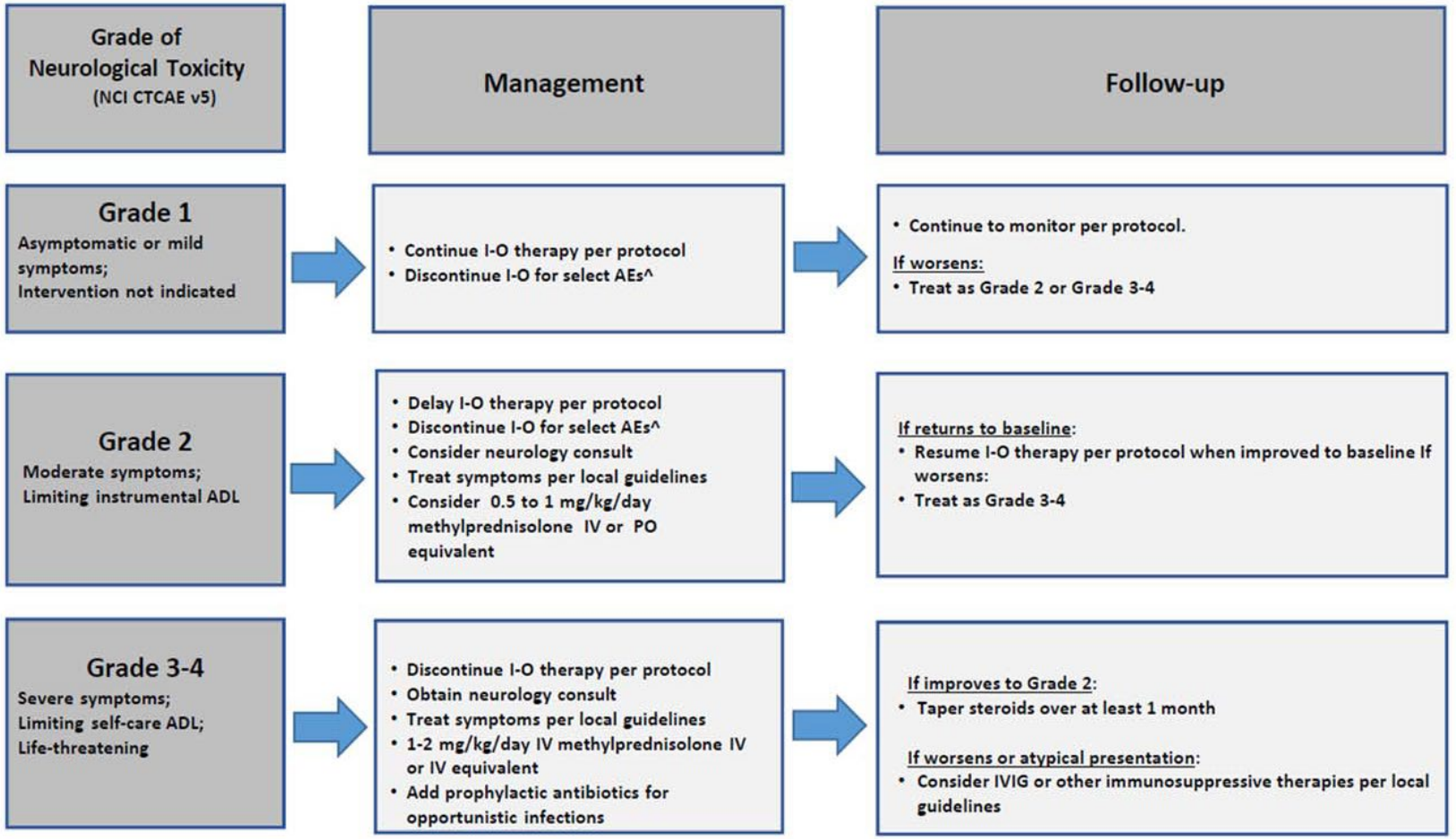
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Neurological Adverse Event Management Algorithm

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

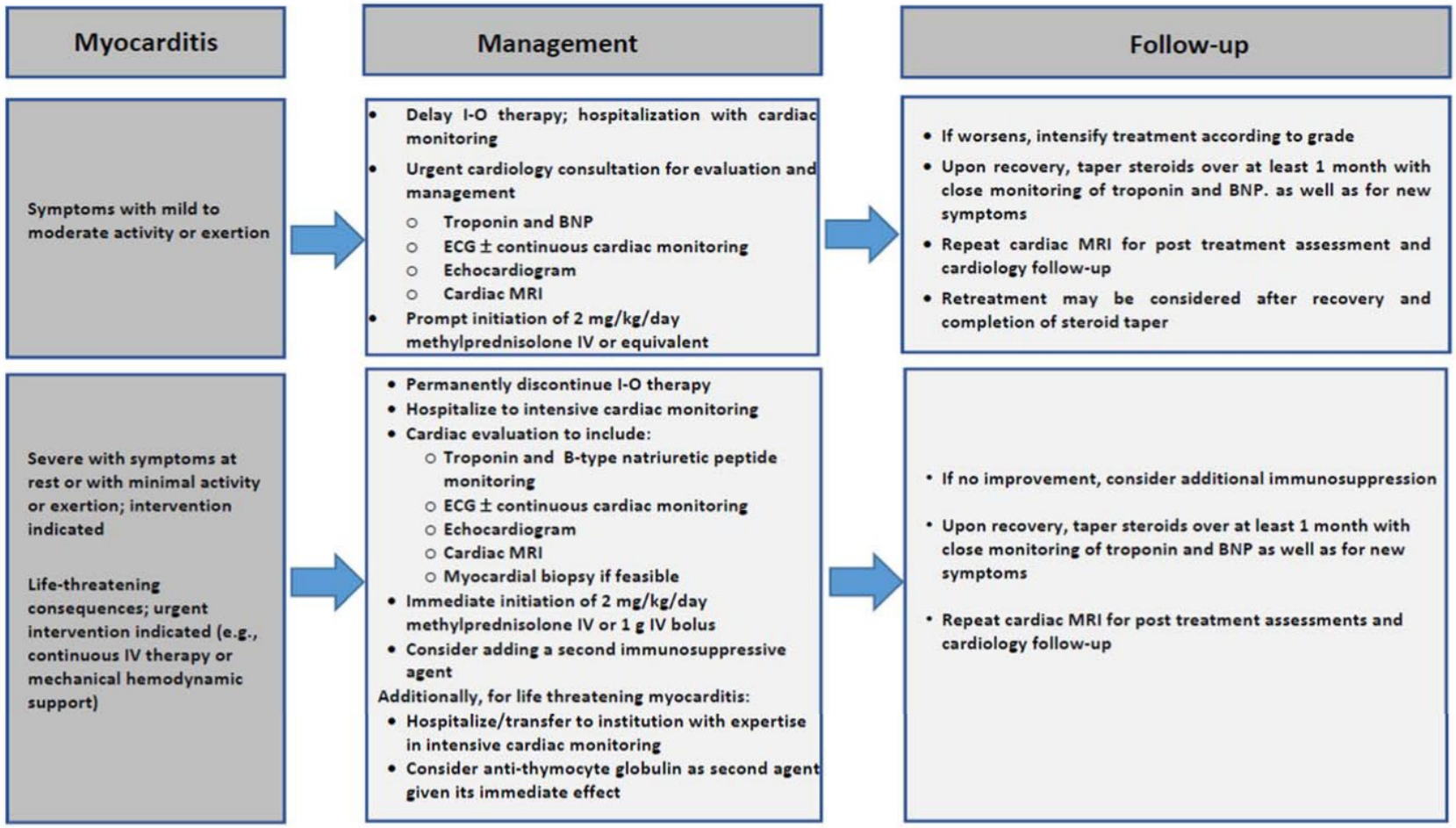


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

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.

Appendix 10: ECOG Performance Status and Prohibited Concomitant Medications

Table 1 Eastern Cooperative Oncology Group Performance Status Scoring

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

Source Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5 649-655.

Table 2 Prohibited Concomitant Medications

Prohibited medications and certain foods are not allowed in this study while subjects are receiving study drug.	
Strong CYP3A Inducers	**CYP3A Substrates with a Narrow Therapeutic Window**
Avasimibe, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, rifabutin, St. John's wort	Alfentanil, astemizole[1], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, everolimus, sirolimus, tacrolimus, terfenadine[1]

Note that this is not an exhaustive list. For an updated list, see the following link http //www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm08 0499.htm
"CYP substrates with a narrow therapeutic window" refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[1] Withdrawn from the United States market because of safety reasons.

Table 3 New York Heart Association Classification

Class	Symptomatology
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Source The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass Little, Brown & Co; 1994 253-256.

Fridericia's Formula

$QTcF = QT/RR^{1/3}$

Table 4 Medications Known to Prolong the QT Interval

amiodarone	dofetilide	grepafloxacin	moxifloxacin	quinidine
astemizole	dolasetron	halofantrine	norfloxacin	sevoflurane
azithromycin	domperidone	haloperidol	ofloxacin	sotalol
bepridil	droperidol	ibutilide	ondansetron	sparfloxacin
chloroquine	erythromycin	itraconazole	palonosetron	terfenadine
chlorpromazine	escitalopram	ketoconazole	pentamidine	thioridazine
ciprofloxacin	flecainide	levofloxacin	pimozide	voriconazole
citalopram	gatifloxacin	levomethadyl	posaconazole	
clarithromycin	gemifloxacin	mesoridazine	probucol	
disopyramide	granisetron	methadone	procainamide	

For a complete and updated (ongoing) list of medications, please use the following link https //crediblemeds.org/healthcare-providers/

Table 5 Examples of Strong and Moderate CYP3A4 Inhibitors

Moderate CYP3A4 Inhibitors
Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
Strong CYP3A4 Inhibitors
Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole
Ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole
Ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

Note Based on FDA guidelines; Investigators should follow local institutional guidelines, where appropriate.

Appendix 11: Examples of Low-Fat and High-Fat, High-Calorie Meals

Low-fat breakfast:

A) 2 slices of white bread toast, 1 tablespoon light fat margarine, 1 tablespoon of jelly, and 8 ounces of skim milk (319 calories and 8.2 grams of fat)

B) 1 cup of cereal, 1 slice of toast with jam, 8 ounces of skim milk, and 1 cup of decaffeinated coffee or tea (520 calories and 2 grams of fat)

A high-fat breakfast consists of the following and may be adapted to the local regional preference: 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk. This representative high-fat breakfast contains approximately 1000 calories and 58 grams of fat.

Appendix 12: National Cancer Institute Common Terminology Criteria for Adverse Events

The NCI CTCAE, version 5.0 can be accessed at the following location: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

RECIST v1.1

Tumor lesions are to be categorized as measurable *versus* non-measurable and target *versus* non- target based on RECIST v1.1 (Eisenhauer *et al*, 2009).

Measurable Lesions
Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm on the short axis when assessed by CT scan.

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

Target Lesions
When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and measured at baseline.

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

Pathological lymph nodes that are defined as measurable and identified as target lesions must have a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes contributes to the baseline sum.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions
All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as ‘present’, ‘absent’ or ‘unequivocal progression.’

The following criteria outlined in Table 6 and Table 7 will be used to assess response to treatment.

Table 6: Disease Response Criteria for Target and Non-target Lesions

Category	**Response Criteria**	
	Target Lesions	**Non-target Lesions/Tumor Markers**
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm	Disappearance of all non-target lesions, and normalization of tumor marker level All lymph nodes must be non-pathological in size (< 10 mm short axis).
Partial response (PR)	A ≥ 30% decrease in the sum of the diameter of target lesions, taking as reference the baseline sum diameter	Not applicable
Stable disease (SD) / incomplete response	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameter since the treatment started	Persistence of 1 or more non-target lesion(s) and/or Maintenance of tumor marker levels above the normal limits
Progressive disease	A ≥ 20% increase in the sum of the diameter of target lesions, taking as reference the smallest sum diameter recorded since the treatment started. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm, or The appearance of 1 or more new lesions	Appearance of 1 or more new lesions, and/or Unequivocal progression of existing non-target lesions

Table 7: Overall Disease Response Criteria

Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Incomplete response/Non-Progressive disease	No	PR
SD	Incomplete response/Non-Progressive disease	No	SD
Progressive disease	Any	Yes or no	Progressive disease
Any	Progressive disease	Yes or no	Progressive disease
Any	Any	Yes	Progressive disease

Abbreviations CR = complete response; PR = partial response; SD = stable disease.

Appendix 13: Local modification of the clinical study protocol (GBR)

FINAL VERSION DATE:	20 December 2023
COUNTRY CONCERNED:	United Kingdom
CENTRES CONCERNED:	All centres in United Kingdom

NATURE OF MODIFICATIONS

- Update of inclusion criteria 4 and Appendix 7 to clarify acceptable contraception methods.

- In line with CTFG guidance, an additional pregnancy test to be performed at the end of the relevant systemic exposure; at the 100-day safety follow up visit.

- Clarification added to section 8.4 that all SAEs must be reported to the sponsor immediately and within 24 hours of awareness at the latest.

Paragraph impacted 5.1 Inclusion Criterion- 4 - Sex and Contraceptive/Barrier requirements
Amended text:

Women of childbearing potential (WOCBP) must agree to abstain from sexual intercourse or to use 2 forms of contraception, one of which must be highly effective and one a barrier method (Appendix 7) ~~highly effective (Appendix 7) forms of contraception, at least one of which must be a barrier method~~, from the time of giving informed consent throughout the study, and for 5 months after the last dose of study treatment.

Paragraph impacted Appendix 7 - Contraception considerations
Amended text:

Definition of acceptable contraception methods for the study: ~~Acceptable contraception methods for the study are those considered as highly effective methods.~~ In addition to a highly effective method, the second form of contraception may include male or female condom with or without spermicide, cap, diaphragm or sponge with spermicide.

Paragraph impacted 4.1.2 Investigational Schedule
Amended text: a new cross (X) is present in the Table (4.1.2) 1 column safety follow-up 100 (+5) Days After Last Nivolumab Dose and line pregnancy test.

Table (19) 1 - Schedule of Assessments for Subjects in the Safety Lead-in Phase and Expansion Phase

Visit/Cycle	**Screening[1]**	**Cycle 1 (21 Days)**			**Cycle 2 (21 Days)**		**Cycles 3 and 4 (21 Days)**	**Cycle 5 and Beyond (28 Days Each Cycle)**	**End of Treatment[2]**	**Safety Follow-up[2]**		**PFS Follow-up[3]**	**Survival Follow-up**
Study Day	**D-28 to D-1**	**D1**	**D8**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**	**Within 7 Days After Last Dose**	**30 (+5) Days After Last Dose**	**100 (+5) Days After Last Nivolumab Dose**		**Every 12 weeks (± 2 weeks)**
Allocation to IMP[4]		X			X		X	X					
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics	X												
Disease History	X												
Medical and Surgical History	X												
Complete Physical Exam	X												
Limited Physical Exam		X		X	X	X	X	X	X				
Height and Weight[5]	X	X			X		X	X					
ECOG Performance Status	X	X			X		X	X	X	X			
Vital Signs[6]	X	X		X	X	X	X	X	X				
12-lead ECG[7,8]	X	X	X	X	X		X	X	X	X			
LVEF (ECHO, MUGA scan, or	X												

Visit/Cycle	**Screening[1]**	**Cycle 1 (21 Days)**			**Cycle 2 (21 Days)**		**Cycles 3 and 4 (21 Days)**	**Cycle 5 and Beyond (28 Days Each Cycle)**	**End of Treatment[2]**	**Safety Follow-up[2]**		**PFS Follow-up[3]**	**Survival Follow-up**
Study Day	**D-28 to D-1**	**D1**	**D8**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**	**Within 7 Days After Last Dose**	**30 (+5) Days After Last Dose**	**100 (+5) Days After Last Nivolumab Dose**		**Every 12 weeks (± 2 weeks)**
by other method according to institutional practice)													
Hematology[9]	X	X		X	X	X	X	X	X				
Serum Chemistry[10]	X	X		X	X	X	X	X	X				
Coagulation Studies[11]	X												
Pregnancy Test[12]	X[12]	X[12]			X[12]		X[12]	X[12]	X[12]		X		
Thyroid Function Tests[13]	X	X					X (only at C3D1)	X (every other cycle)	X				
Radiographic Evaluation of Disease[14]	X (D-21)						X (only C3D1)[15]	X[15] (every other cycle)	X[15,16]			X	
Ivosidenib Administration[17]			X										
Nivolumab Administration[18]		X			X		X	X (every cycle)					
Ipilimumab Administration[19]		X			X		X						
IMP Compliance[20]					X		X	X	X				
Tumor Biopsy[21]	X						X (± 7 days for biopsy collection)		X				

Visit/Cycle	**Screening[1]**	**Cycle 1 (21 Days)**			**Cycle 2 (21 Days)**		**Cycles 3 and 4 (21 Days)**	**Cycle 5 and Beyond (28 Days Each Cycle)**	**End of Treatment[2]**	**Safety Follow-up[2]**		**PFS Follow-up[3]**	**Survival Follow-up**
Study Day	**D-28 to D-1**	**D1**	**D8**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D15 (± 2 Days)**	**D1 (± 2 Days)**	**D1 (± 2 Days)**	**Within 7 Days After Last Dose**	**30 (+5) Days After Last Dose**	**100 (+5) Days After Last Nivolumab Dose**		**Every 12 weeks (± 2 weeks)**
Buccal Swab for Germ-line Mutation Analyses[22]	X												
Blood Sampling for Exploratory Biomarkers[23]	X				X		X	X	X				
Adverse Events[24]	X	X		X	X	X	X	X	X	X	X		
Prior and Concomitant Medications/Procedures[25]	X	X		X	X	X	X	X	X	X	X		
Subsequent Anti-cancer Therapy									X	X	X	X	X
Survival Status[26]													X

Abbreviations AE = adverse event; C = Cycle; CFR = Code of Federal Regulations; CT = computed tomography; D = Day; ECG = electrocardiogram; ECHO = echocardiography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = End of Treatment; FFPE = formalin-fixed paraffin-embedded; GDPR = General Data Protection Regulation; HIPAA = Health Insurance Portability and Accountability Act; ICF = informed consent form; IDH1 = Isocitrate dehydrogenase-1; IMP = investigational medicinal product; IV = intravenous; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; PFS = progression-free survival; Q3W = once every 3 weeks; Q4W = once every 4 weeks; QTcF = heart rate-corrected QT interval by Fridericia's method; RTSM = Randomisation and Trial Supply Management; SAE = serious adverse event.

Note One, or two if required by local regulation, original information and consent form(s) must be completed, dated, and signed personally by the participant and by the person responsible for collecting the informed consent. According to each study participant's own preference, the ICF could be made available both printed on paper or/and electronically through a HIPAA, 21 CFR Part 11, and GDPR compliant web-based platform. Local regulations permitting, the electronic signature for the ICF could be made available to interested study participants. Interested study participants will be offered the possibility to replace certain in-person visits to the research site by televisits. This means that some study visits could be conducted using a HIPAA, 21 CFR Part 11, and GDPR compliant web-based platform, as per each study participant's own preference. Follow-up (for survival status until the end of the study) can be done remotely by using various telecommunication technologies including but not limited to phone, web-based remote video-calling, and shared electronic medical records.

1. Day -28 is relative to first dose of IMP.
2. All subjects will undergo an EOT assessment within 7 days after the last dose of IMP (for combination, this is to occur after all 3 IMPs have been discontinued). However, when this is not possible (*e.g.,* dose delay more than 7 days), EOT assessment can be performed at the 30-day safety follow-up visit. A second Safety Follow-up will occur 100 (+5) days after last nivolumab dose or ipilimumab if no other anti-cancer therapy is initiated.
3. Subjects who discontinue study treatment for reasons other than disease progression or withdrawal of consent and are alive by EOT will enter PFS follow-up with the same schedule of assessments as before study treatment discontinuation, until documented disease progression, death, start of subsequent anti-cancer therapy, withdrawal of consent, or the end of study/study termination.
4. Allocation of IMP will occur via RTSM.
5. Height is to be obtained only at Screening assessment.
6. Systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Assessments should be conducted while the subject is seated or supine.
7. Subjects with a QTcF of ≥ 450 msec at baseline will not be allowed to enroll in the study. Up to three 12 lead ECG tests under stable condition can be performed at each visit during screening and throughout treatment and study follow-up.
8. ECG can be performed at any time during the study visit (on-site or at local clinic); however, it is required once weekly for the first 3 weeks of treatment, and then once every cycle for the duration of therapy.
9. Hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, and platelet count. Hemoglobin criteria of ≥ 9.0 g/dL or ≥ 5.6 mmol/L at Screening must be met without packed red blood cell transfusion within the prior 2 weeks. Subjects can be on stable dose of erythropoietin (≥ approximately 3 months). On C1D1, assessments should be conducted prior to IMP administration.
10. Sodium, potassium, chloride, calcium, magnesium, phosphorus, carbon dioxide, albumin, glucose, blood urea nitrogen (BUN)/UREA, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, total bilirubin, direct bilirubin, and indirect bilirubin. On C1D1, assessments should be conducted prior to IMP administration.
11. Activated partial thromboplastin time and either prothrombin time or international normalized ratio.
12. For women of childbearing potential, a serum pregnancy test will be performed at Screening, and a urine pregnancy test will be conducted on the day of IMP administration and is to be confirmed negative prior to dosing. If the urine pregnancy test is positive and cannot be confirmed negative, a serum pregnancy test must be performed and shown to be negative within 24 hours prior to the first day of IMP administration. An extension up to 72 hours prior to the start of study treatment is permissible in situations where the results cannot be obtained within the standard 24-hour window.
13. Thyroid function test includes triiodothyronine (T3) or free T3, free thyroxine, and thyroid stimulating hormone. Thyroid function tests are to be performed every 6 weeks for the first 4 cycles and then every 8 weeks starting from Cycle 5 and to be performed at EOT. On C1D1, assessments should be conducted prior to IMP administration. Thyroid function test results obtained after the visit are acceptable so long as the value at screening was normal or considered not clinically significant per investigator assessment.
14. Tumor assessments will include all known or suspected disease sites. CT imaging of the chest, abdomen, and pelvis (torso) with triphasic IV contrast should be performed at baseline and on study. For subjects with allergy to IV iodine contrast, CT chest without IV contrast and MRI abdomen with IV contrast should be performed at baseline and on study. Brain scans with CT or MRI should be performed at baseline in subjects with known treated brain metastases and on study at the same imaging time points as torso imaging. Additional anatomy should be imaged based on the signs and symptoms of individual subjects at baseline and follow-up. Radiographic assessment (CT or MRI or other imaging modalities as appropriate per RECIST v1.1 Appendix 4) for evaluation of disease response to be conducted at Screening (Day -21 to Day -1), every 6 weeks (±7 days) for the first 2 assessments (*i.e.*, through Week 12), and then every 8 weeks (± 7 days) thereafter independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. Tumor assessment frequency can be reduced to every 12 weeks after 2 years of treatment initiation.
15. Response to treatment is to be assessed at this visit if the subject discontinues treatment for reasons other than disease progression or start of another anticancer therapy.
16. If a subject goes off treatment for reasons other than disease progression or withdrawal of consent from treatment, response assessments will be conducted at the EOT visit
17. Ivosidenib is to be taken daily. Subjects should be instructed to take their daily dose at approximately the same time each day. Each daily dose should be taken with or without food. Subjects taking ivosidenib with food should be advised to avoid grapefruit or grapefruit products and avoid consuming a high-fat meal. If the subject forgets to take the daily dose, then they should take ivosidenib within 12 hours after the missed dose. If more than 12 hours have elapsed, then that dose should be omitted, and the subject should resume treatment with the next scheduled dose. The dose on C1D1, C1D15, and Day 1 of each cycle thereafter is to occur in-clinic to allow for pre-treatment assessments and to accommodate PK sampling. In subjects receiving the combination, on days when nivolumab and ipilimumab are administered, ivosidenib should be administered approximately 30 minutes before the start of the nivolumab infusion.
18. Nivolumab is to be administered over an approximately 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 30 minutes (-5 minutes/+10 minutes). When study treatments nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed, and subject has been observed to ensure that no infusion reaction has occurred.
19. Ipilimumab is to be administered over an approximately 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 30 minutes (-5 minutes/+10 minutes). When study treatments nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed, and subject has been observed to ensure that no infusion reaction has occurred. The time in between nivolumab and ipilimumab infusions is expected to be within approximately 30-minutes.
20. Treatment compliance for ivosidenib is to be assessed based on the drug diary and/or return of unused drug.
21. Tumor tissue for retrospective central laboratory confirmation of IDH1 gene mutation status and exploratory biomarker analysis at Screening is requested. Subjects will have locally documented presence of the IDH1 gene mutation for inclusion. If a subject cannot undergo a biopsy at Screening, collection of archival tumor tissue from the most recent biopsy/resection of at least 20 freshly cut, unstained FFPE slides (4-

5 µm each) plus 1 H&E slide will be submitted at a later time together with the pathology report upon sponsor's request. Tumor biopsies are to be collected at baseline, C3D1, and EOT from similar anatomical locations for exploratory biomarker analyses including PK/PD. In case of limited tissue amounts, biopsy samples will be formalin fixed and paraffin embedded. Please refer to the laboratory manual for priorities in tissue processing. If a required tumor biopsy (any time point) cannot be performed due to concerns around subject safety, a discussion with the Sponsor is required and biopsy can be omitted. Further details on screening and on-treatment biopsy collections are provided in the laboratory manual.

22. A buccal swab for germ-line mutation analysis will be obtained at Screening.
23. Blood samples for exploratory biomarker assessments, including plasma circulating tumor DNA, will be collected at Screening and Day 1 of every cycle through Cycle 6, followed by every 6 months thereafter, and at EOT.
24. From the time of informed consent signing through the first dose of IMP, SAEs resulting from a study-related procedure and assessed as related to that procedure, as well as all fatal AEs whether or not related to research procedures, must be recorded. All AEs will be recorded from all subjects from the date of first dose through 30 days following the last dose of ivosidenib and/or nivolumab or ipilimumab, whichever occurs later. Following the 30-day Safety Follow-up period, any SAEs that occur within 100 days after last dose of immunotherapy are to be reported, or until the subject initiates another anti-cancer therapy, whichever is earlier. Only SAEs that are considered as related to either IMP by the Investigator are to be reported after the respective Safety Follow-up periods. Fatal events, related or not to the research, occurring after ICF signature and before first IMP administration, must be reported on an AE form.
25. All concomitant medications/procedures within 21 days of the first dose of IMP through 30 days (+ 5 days) after the last dose of ivosidenib and/or immunotherapy and through 100 days after the last dose of immunotherapy (whichever is later) are to be reported on the eCRF.
26. Subjects will be contacted every 12 weeks (± 2 weeks) after the subject experiences documented disease progression or begins subsequent anti-cancer therapy for up to 2 years after the last subject has been enrolled, or until death, lost to follow-up, withdrawal of consent from overall study participation, or Sponsor ending study, whichever occurs first

Paragraph impacted 8.4 Definition of Serious Adverse Events
Amended text:

An SAE is any AE that, at any dose:
results in death,
is life-threatening(1),
requires insubject hospitalization or prolongation of existing hospitalization,
is medically significant(2),
results in persistent or significant disability/incapacity(3),
is a congenital anomaly/birth defect(4).
All SAEs must be reported to the sponsor immediately, i.e., without delay and within 24 hours of awareness at the latest.

(1) Life-threatening in this context refers to 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.

(2) Any event that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the participant or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalization, or development of drug dependence or drug abuse). The Investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to Sponsor.

(3) Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

(4) Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.