2. SYNOPSIS

Name of Sponsor: Institut de Recherches Internationales Servier (I.R.I.S.)	***(For National Authority Use only)***
Name of Finished Product: Ivosidenib Nivolumab Ipilimumab	
Name of Active Ingredient: Ivosidenib (S095031; formerly known as AG-120)	
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 **Protocol No.:** CL1-95031-006 **CT.gov No.:** NCT05921760	
Principal Investigator /Coordinating Investigator: Robin K. ("Katie") Kelley, MD Professor of Clinical Medicine Helen Diller Family Comprehensive Cancer Center Division of Hematology/Oncology University of California, San Francisco Phone: (415) 353-9888 Email: katie.kelley@ucsf.edu	
Number of Study Centers and Countries: 2 countries participated in this study and enrolled participants: United Kingdom (1 site), and United States (3 sites).	
Study Period: Initiation date: 23 Oct 2023 (date of first participant first visit) Completion date: 21 Nov 2024 (date of last participant last visit) This is an abbreviated CSR (aCSR), as the study was prematurely terminated on 09 Aug 2024 due to all participants developing an immune-mediated rash. This decision was based on an unfavorable benefit/risk balance for this combination, at these doses and for this indication.	
Phase of Development of the Study: Phase 1/2	
Publication (Reference): Not applicable.	
Background and Rationale for the Study: This was a Phase 1/2, non-comparative, multicenter, 2-phase, open-label clinical study to evaluate the clinical activity, safety/tolerability, efficacy, pharmacokinetics (PK), pharmacodynamics, and immunogenicity of ivosidenib (S095031 [formerly known as AG-120], an oral mutant isocitrate dehydrogenase 1 [IDH1] inhibitor) administered in combination with nivolumab and ipilimumab in participants with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation who had received ≤ 2 previous treatments for advanced disease. Cholangiocarcinoma (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 patient population to improve clinical outcomes. Emerging science suggests that a combination of an IDH1 inhibitor with immunotherapy (i.e., anti-CTLA4 and anti- programmed death 1 [PD-1] monoclonal antibodies [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 was the first study that tested a triple combination. This study intended to first test the safety of the combination in a small number of participants during a Safety Lead-in Phase in order to evaluate for dose-limiting toxicities (DLTs) and identify the recommended dose for the Expansion Phase.	

Objectives, Endpoints, and Estimands for the Study's Safety Lead-In Phase:

NOTE: Study CL1-95031-006 was terminated by the Sponsor during its Safety Lead-in Phase. As a result, disease response evaluation via Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was also provided for participants enrolled in the Safety Lead-in Phase.

Objectives	**Endpoints**
Primary Objective	Primary Endpoints
To evaluate the safety and tolerability of ivosidenib in combination with nivolumab and ipilimumab and determine the RCD of ivosidenib, nivolumab, and ipilimumab	DLTs associated with ivosidenib in combination with nivolumab and ipilimumab during the first 2 cycles of treatment AEs, AESIs, and SAEs
Estimand Attributes: Not applicable	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; DLT = dose-limiting toxicity; RCD = recommended combination dose; SAE = serious adverse event.

Objectives, Endpoints, and Estimands for the Study's Expansion Phase:

NOTE: Study CL1-95031-006 was terminated by the Sponsor during its Safety Lead-in Phase. As a result, the study's Expansion Phase was not conducted, and no Expansion Phase data are available.

Objectives	**Endpoints**
Primary Objective	Primary Endpoint
To assess the clinical activity of ivosidenib in combination with nivolumab and ipilimumab using RECIST v1.1	Objective response (confirmed CR or confirmed PR) of anti-tumor activity (using RECIST v1.1)
Estimand Attributes: 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* *Summary measure: objective response (Yes, No)* *Intercurrent events:* *Early treatment discontinuation* *Administration of further anti-cancer therapy*	

Abbreviations: CR = complete response; ORR = objective response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

Study Design:

This was a Phase 1/2, non-comparative, multicenter, 2-phase, open-label clinical study to evaluate ivosidenib administered in combination with nivolumab and ipilimumab in participants with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation who had received ≤ 2 previous treatments for advanced disease.

The study originally consisted of a Safety Lead-in Phase and an Expansion Phase.

The Safety Lead-in Phase was performed to evaluate the safety and tolerability of ivosidenib in combination with nivolumab and ipilimumab in order to determine the recommended combination dose (RCD). A data review team (DRT)—composed of medical, safety, and statistical representatives from the Sponsor and the study's Principal Investigator (PI)—reviewed the available safety data after at least 6 participants completed at least 2 cycles of treatment or had a DLT within the first 2 cycles. Based on their review of the results from the Safety Lead-in Phase, the DRT would declare the RCD and authorize the beginning of the Expansion Phase of the study.

The objective of the Expansion Phase was to evaluate the clinical activity—including efficacy, safety/tolerability, PK, PD, and immunogenicity—of ivosidenib in combination with nivolumab and ipilimumab.

NOTE: Study CL1-95031-006 was terminated by the Sponsor during its Safety Lead-in Phase. As a result, the study's Expansion Phase was not conducted.

Participant eligibility was determined by the presence of measurable disease (at least one measurable lesion [as defined by RECIST v1.1] according to the site radiologist/Investigator following completion of radiographic evaluation (computed tomography [CT] or magnetic resonance imaging [MRI]) performed at screening. Additionally, participants were enrolled based on local confirmation of IDH1 mutation. After confirmation of measurable disease and IDH mutation status, participants underwent a 28-day screening period before initiation of ivosidenib/nivolumab/ipilimumab combination therapy. Eligible participants participated in only 1 of the study's 2 phases.

For the Safety Lead-in Phase, participants received ivosidenib once daily (QD; dosing began with 500 mg QD and was adjusted based on DLT evaluation) in combination with nivolumab 3 mg/kg and ipilimumab 1 mg/kg concurrently once every 3 weeks (Q3W) for 4 doses followed by nivolumab 480 mg once every 4 weeks (Q4W) (up to 24 total doses of nivolumab). DLTs were evaluated through Cycle 2 (i.e., during the first 42 days, 21 days/cycle). Participants could receive up to a maximum of 24 months of nivolumab. Participants who were still deriving clinical benefit after 24 months were permitted to continue receiving ivosidenib monotherapy until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

All participants underwent safety assessments (including physical examinations, vital sign measurements, electrocardiograms [ECGs], determination of European Cooperative Oncology Group [ECOG] performance status [PS], and clinical laboratory assessments), serial blood draws for assessment of PK, PD, immunological, and biomarker parameters, and radiographic evaluations (MRI or CT) to assess the extent of their disease.

This study was performed in strict accordance with Good Clinical Practice.

This is an aCSR, as the study was prematurely terminated. Based on the observance of the frequency, onset, and the outcome of events of immune-mediated rash observed in all participants treated with investigational medicinal product (IMP), and in the absence of documented radiographic responses, the Sponsor made the decision to stop further recruitment in the dosing cohort of 250 mg of ivosidenib in the Safety Lead-in Phase and not to proceed to the Expansion Phase.

Number of Participants (Planned and Analyzed):

Planned:

Safety Lead-in Phase: approximately 6 to 12 DLT-evaluable participants

Expansion Phase: approximately 80 participants

Analyzed:

Safety Lead-in Phase: 7 participants

Expansion Phase: Not applicable, as the study was terminated before the Expansion Phase commenced.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Participants were at least 18 years old, had an estimated life expectancy ≥ 12 weeks and an ECOG PS ≤ 1, had a histopathological diagnosis consistent with nonresectable or metastatic cholangiocarcinoma that were not eligible for curative resection, transplantation, or ablative therapies, and had documented IDH1 gene-mutated disease based on local confirmation (preferably via tumor biopsy analysis). Participants must have had disease progression or treatment intolerance following no more than 2 prior systemic therapeutic regimens for advanced disease (characterized as either nonresectable or metastatic). Participants must have had at least 1 measurable lesion as defined by RECIST v1.1, but must have had adequate hematological, coagulation, hepatic, and renal function. All participants must have received either a gemcitabine- or a 5-fluorouracil–based chemotherapy regimen. Female participants could not be pregnant or lactating and must have had a negative serum pregnancy test within 24 hours of study treatment initiation; additionally, both male and female participants were required to use contraception throughout the study and for at least 3 months (male participants) or 5 months (female participants) after their last dose of study treatment. Study candidates who had received prior treatment with an IDH inhibitor, had a history of primary cancer other than cholangiocarcinoma, or had any active autoimmune disease were prohibited from participating in the study.

Investigational Medicinal Products:

Ivosidenib – Ivosidenib was supplied as 250 mg strength tablets to be administered orally QD for each 21-day treatment cycle. Beginning with the fifth treatment cycle, the length of each cycle increased to 28 days.

In the study's Safety Lead-in Phase, ivosidenib was administered orally at a starting dose of 500 mg QD. Enrollment in this cohort was closed on 20 Mar 2024 and the ivosidenib 250 mg cohort was opened for enrollment.

Participants received 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 was continuous: there were no rest periods. On days when participants were also administered nivolumab, ivosidenib was administered approximately 30 minutes before the start of the nivolumab infusion.

Nivolumab – Nivolumab was administered as 30-minute (- 5/ +10 minutes) infusions at 3 mg/kg intravenous (IV) Q3W for the first four doses followed by 480 mg Q4W until progression and for up to a maximum of 24 months. Nivolumab infusion occurred prior to ipilimumab infusion. Following completion of each nivolumab infusion, participants were monitored for 30-60 minutes for adverse reactions; any adverse reactions were followed up within 24 hours of occurrence to ensure resolution of the event. Premedications were not recommended before the first infusion of nivolumab.

Ipilimumab – Ipilimumab was administered as 30-minute (- 5 / + 10 minutes) infusions at 1 mg/kg IV Q3W for 4 total doses. On days when both nivolumab and ipilimumab infusions were scheduled to occur, ipilimumab infusions were expected to begin within 30 minutes after completing nivolumab infusions. Following completion of each ipilimumab infusion, participants were monitored for 30-60 minutes for adverse reactions; any adverse reactions were followed up within 24 hours of occurrence to ensure resolution of the event.

Participants taking ivosidenib were advised to avoid grapefruit, grapefruit products, and consuming high-fat meals.

No premedication was required prior to participants receiving the first dose of ivosidenib.

Study Periods and Duration of Each:

Screening period: Following their signature of the informed consent form (ICF) (the signing of the ICF indicates the start of the study), each participant's eligibility was confirmed during a screening period that occurred during the 28-day duration before they received their first dose of IMP.

Active treatment period: Treatment occurred until disease progression was observed; additionally, participants were discontinued from treatment earlier if unacceptable toxicity or other discontinuation criteria occurred. End of Treatment (EOT) evaluations were performed as soon as possible after the decision was made to discontinue treatment. Participants could continue to receive up to a maximum of 24 months of nivolumab treatment. Participants who were still deriving clinical benefit after 24 months were permitted to continue receiving ivosidenib monotherapy until disease progression, unacceptable toxicity, or other discontinuation criteria occurred.

Safety follow-up period: Following treatment discontinuation, all participants had a 30-day (+ 5 days) safety follow-up visit. During the 30-day (+5 days) safety follow-up period, all adverse events (AEs) and new medications (including new anti-cancer therapy) were reported. After completing their 30-day (+ 5 days) safety follow-up visit, participants were followed for an additional 100 days (+5 days) after their last dose of immunotherapy or until they began any other anti-cancer therapy, whichever occurred earlier.

Overall survival (OS) follow-up period: Beginning after the EOT visit, participants were to be contacted every 12 ± 2 weeks to assess OS for up to 2 years after study enrollment had closed or until the participant had died, was lost to follow-up, or had withdrawn consent from overall study participation, or the Sponsor had terminated the study, whichever occurred first. As the study was prematurely terminated, OS assessment ended with the last participant last visit date of the study (21 Nov 2024).

Statistical Methodology:

Analysis sets:

The following analysis sets were used for presentation of the data:

- DLT-Evaluable Set: All participants enrolled during the Safety Lead-in Phase who received any dose of the combination therapy and experienced a DLT through Cycle 2, or who 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 were considered evaluable for DLT assessment. This analysis set was the primary set to determine the RCD.
- Safety Analysis Set (SAS): All participants enrolled who received any amount of study treatment (ivosidenib in combination with nivolumab and ipilimumab). The SAS was the primary analysis set for clinical anti-tumor activity, safety, and other analyses, unless otherwise specified.
- PK Analysis Set: All participants who had at least one blood sample providing evaluable PK data for ivosidenib in combination with nivolumab and ipilimumab.

- Pharmacodynamic Analysis Set: All participants who had at least one blood sample providing evaluable plasma 2-hydroxygluturate (2-HG) data for ivosidenib in combination with nivolumab and ipilimumab.
- Anti-drug antibody (ADA) Analysis Set: All participants with a baseline ADA assessment and at least one post-treatment ADA assessment.

Since the study did not proceed to the Expansion Phase, the primary endpoint objective response (OR) for the Expansion Phase was not evaluated. Therefore, the Response-Evaluable Set was not evaluated.

Efficacy analysis:

Tumor response was to be evaluated as per RECIST v1.1. Since the study stopped enrollment for the Safety Lead-in Phase and did not proceed to the Expansion Phase, only listings were generated for efficacy analyses for the Safety Lead-in Phase. The listings were based on the SAS and included response assessments and best overall response (BOR).

BOR was based on all post-baseline disease assessments until the first documentation of progressive disease or end of treatment, and prior to the initiation of a subsequent anti-cancer therapy, whichever occurred first.

BOR included the following categories:

- Complete Response (CR): at least 2 CRs with at least 4 weeks apart.
- Partial Response (PR): at least 2 PRs or better (PR followed by PR or PR followed by CR) with at least 4 weeks apart, and not qualifying for a CR.
- Stable disease (SD): at least 1 SD assessment (or better) ≥ 36 days after the start of IMPs, and not qualifying for CR or PR.
- Progressive disease (PD): documentation of progressive disease after start of IMPs (and not qualifying for CR, PR, SD).
- Non-evaluable: all other cases.

PK analysis:

Individual concentrations of ivosidenib (in plasma and tumor tissue), nivolumab and ipilimumab (in serum) for each visit and timepoint of collection by participant, was presented as listings. Spaghetti plots of individual plasma concentration-time profiles for ivosidenib on Cycle 2 Day 1 was plotted on linear-linear scale and log linear scales using nominal time. Plots of concentrations of nivolumab and ipilimumab by visit were presented. The PK Analysis Set was used for listings of concentration data for ivosidenib, nivolumab and ipilimumab.

Pharmacodynamic analysis:

Individual plasma and tumor 2-HG concentrations, at each visit and collection timepoint by participant was listed. Spaghetti plots of individual 2-HG concentrations by visit were plotted. The Pharmacodynamic Analysis Set was the primary analysis set for listings and figures of 2-HG concentrations.

Safety analysis:

All safety analyses were performed in the SAS and summaries contained only data collected during the on-treatment period, unless otherwise specified.

Details of the observed DLTs were presented in a listing based on the DLT-Evaluable Set and only for the Safety Lead-in Phase.

Number of events, number and percentage of participants reporting at least one event were presented in a summary table for treatment-emergent adverse events (TEAEs) by system organ class (SOC), preferred term (PT) and severity.

Interim analysis:

Since the Sponsor terminated the study early while the Safety Lead-in Phase was still ongoing, the futility interim analysis described in the protocol was not conducted.

Data Review Team (DRT):

A DRT— composed of the study's Investigators and medical, safety, and statistical representatives from the Sponsor reviewed the available safety data in all participants enrolled in the ivosidenib 500 mg QD and 250 mg QD dose cohorts of the Safety Lead-in Phase to determine whether 500 mg QD or 250 mg QD was the ivosidenib RCD for the Expansion Phase.

Summary of Results and Conclusions

Study participation and baseline characteristics:

Seven participants were screened and enrolled in the study: 4 in the ivosidenib 500 mg cohort and 3 in the ivosidenib 250 mg cohort. Five participants were enrolled in sites in the US and 2 participants were enrolled in sites in Great Britain. All participants were female (100%) with a median age of 65 years (range: 32 to 81 years) in the ivosidenib 500 mg cohort and 42 years (range: 39 to 67 years) in the ivosidenib 250 mg cohort. Participants were either White (85.7%) or Asian (14.3%), and most (85.7%) were not of Hispanic or Latino ethnicity.

All participants had intrahepatic CCA with a median disease duration of 7.03 months in the ivosidenib 500 mg cohort and 22.83 months in the ivosidenib 250 mg cohort. ECOG-PS at baseline was either 0 or 1 at baseline.

Of the 7 participants enrolled in the study, all participants discontinued treatment due to progressive disease (57.1%) or due to AEs (42.9%). All participants discontinued the study due to death (71.4%), voluntary withdrawal (14.3%), or due to termination of the study by the Sponsor (14.3%).

Efficacy results:

The primary objective of the Expansion Phase of this study was to assess the clinical activity of ivosidenib in combination with nivolumab and ipilimumab using RECIST v1.1. Since the study was terminated after enrolling 7 participants for the Safety Lead-in Phase and did not proceed to the Expansion Phase, only listings of disease response were generated for the Safety Lead-in Phase. Of the 7 participants in the study, SD was reported in 2 participants in the ivosidenib 500 mg cohort and in 1 participant in the ivosidenib 250 mg cohort. Progressive disease was reported in the remaining 4 participants.

PK, pharmacodynamic, and ADA results:

The study data including PK (ivosidenib, nivolumab and ipilimumab), pharmacodynamics (2-HG), and ADA were limited due to the study's premature termination and the results should be interpreted with caution. The observed plasma exposures of ivosidenib after multiple dose administration of ivosidenib at 500 mg QD or 250 mg QD were largely comparable to previously observed exposures in CCA participants from the AG-120-C 002 and AG120-C-005 studies. Plasma 2-HG levels decreased in 4 out of 7 participants from elevated values at baseline after 1 cycle of ivosidenib treatment. Immunogenicity assessments based on ADA measurements were evaluable for 6 out of 7 participants.

Safety results:

All participants experienced a TEAE, including ivosidenib-related TEAEs, Grade ≥ 3 TEAE, and treatment-related Grade ≥ 3 TEAE. The most frequently reported SOCs were gastrointestinal disorders, skin and subcutaneous tissue disorders, general disorders and administration site conditions, and respiratory, thoracic and mediastinal disorders. Immune-mediated dermatitis was the most frequently reported TEAE in either treatment group. Most TEAEs were Grade 1 or Grade 2.

All participants developed an immune-mediated rash which required dose modifications, and included 3 nonserious and 3 serious Grade 3 events during the first 2 cycles (42-day DLT evaluation period), one of which was reported a DLT (in the ivosidenib 250 mg cohort).

Most participants maintained stable physical activity levels. Only 1 participant had an ECOG-PS of 3 at 2 visits; all others had an ECOG-PS of 0, 1, or 2 at any visit.

Three participants in the ivosidenib 500 mg cohort and 2 participants in the ivosidenib 250 mg cohort died; only 1 participant in the ivosidenib 250 mg cohort had a TEAE leading to on-treatment death. Two participants in each group died due to progressive disease.

Conclusions:

No new safety signals for ivosidenib were identified in the course of this prematurely terminated study. The Sponsor made the decision to stop further recruitment in the dosing cohort of 250 mg of ivosidenib in the Safety Lead-in Phase and not to proceed to the Expansion Phase on consideration of the overall data from the participants enrolled. All participants at both enrolled dose levels developed an immune-mediated rash which required dose modifications, and included 3 nonserious and 3 serious Grade 3 events during the first 2 cycles (42-day DLT evaluation period), one of which was reported a DLT (in the ivosidenib 250 mg cohort). Rash is a listed event in the label information of each individual study treatment. Based on the observance of the frequency, onset, and the outcome of these events with this combination, and in the absence of documented radiographic responses, the Sponsor made the decision to stop further recruitment in this study. This decision was not a safety measure, but rather a decision based on an unfavorable benefit/risk balance for this

combination, at these doses and for this indication. No further conclusions on the efficacy of the combination could be determined due to limited data.
Date of the Report: 10 Sep 2025