2 SYNOPSIS

Name of Sponsor: I.R.I.S., 22, route 128, 91190 Gif-sur-Yvette - France	*(For National Authority Use only)*
Name of Finished Product: Ivosidenib **Name of Active Ingredient:** Ivosidenib (S95031; formerly known as AG-120)	
Title of study: A Phase 1, Multicenter, Open-label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Solid Tumors, Including Glioma, with an IDH1 Mutation. Protocol No.: AG120-C-002 CT.gov No.: NCT02073994 The description of the study protocol given hereafter includes the modifications of the 8 substantial amendments to the protocol.	
Principal Investigator: Ingo Mellinghoff, MD Memorial Sloan Kettering Cancer Center, New York, NY 10022.	
Study countries: A total of 13 study sites participated in this study, with 12 sites in the United States and 1 site in France. Overall, 174 patients were enrolled in the study and of these, 168 were dosed. Of the 168 patients who were dosed, 153 were from the sites in the USA and 15 were from the site in France.	
Publication (reference): Tap WD, Cote GM, Burris HA, et al. Phase I Study of the Mutant IDH1 Inhibitor Ivosidenib: Long-term Safety and Clinical Activity in Patients with Conventional Chondrosarcoma. *J Clin Oncol*. 2023. [PE0173924] Mellinghoff IK, Ellingson BM, Touat M, et al. Ivosidenib in Isocitrate Dehydrogenase 1-Mutated Advanced Glioma. J Clin Oncol. 2020;38(29):3398-3406. doi:10.1200/JCO.19.03327 [PMID: 32530764]	
Studied period: Initiation date: 14 March 2014 (date of first patient first visit) Completion date: 04 January 2024 (date of last patient last visit)	**Phase of development of the study:** Phase 1

Methodology:

This was a Phase 1, multicenter, open-label, dose-escalation and expansion, safety, pharmacokinetic (PK)/pharmacodynamic, and clinical activity study of orally administered ivosidenib in patients with advanced solid tumors, including glioma, with an isocitrate dehydrogenase 1 (IDH1) mutation.

The primary objectives of this study were to assess the safety and tolerability of treatment with ivosidenib administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle in patients with advanced solid tumors, including glioma; and to determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of ivosidenib in patients with advanced solid tumors, including glioma.

The primary clinical study report (CSR) presented results from the study as of a data cutoff date of 12 May 2017. As prespecified in the protocol and statistical analysis plan (SAP), the study data were analyzed and reported in the primary CSR based on 168 patients who received at least 1 dose of study treatment. The primary efficacy analysis for the study was based on all patients who were enrolled and received at least 1 dose of study treatment (168 patients). As of 12 May 2017 (data cutoff date for the primary CSR), 41 patients remained on treatment and 127 patients had discontinued study treatment.

Following the primary CSR, an interim CSR addendum was developed to provide updated information on the efficacy and safety outcomes of the study. This addendum was based on an extended dataset with a data cutoff date of 16 January 2019. As of 16 January 2019, 22 (13.1%) patients remained on treatment and 146 (86.9%) patients had discontinued treatment.

The purpose of this CSR final addendum is to summarize updated efficacy and safety results from Study AG120-C-002 based on the final dataset (database lock: 18 March 2024).

Number of patients:

Planned:
It was estimated that approximately 170 patients were to be enrolled in the study. Assuming that identification of the MTD and/or RP2D in the solid tumor, non-glioma dose escalation required the evaluation of 6 dose levels of ivosidenib with approximately 3 to 5 patients per dose level and approximately 5 dose levels of ivosidenib with 3 patients each in the glioma dose escalation cohorts, then approximately 45 patients were to be enrolled during the dose escalation phase of the study. Four cohorts of patients with cholangiocarcinoma (approximately 50 patients), chondrosarcoma, non-enhancing glioma, and other solid tumors not otherwise eligible for the other tumor-specific cohorts (each approximately 25 patients) with the IDH1 mutation that have recurred or progressed following standard therapy (total 125 patients) were to be enrolled in the expansion part of the study. Additional patients might have been enrolled during dose escalation, for the replacement of patients who were not evaluable for the dose escalation, for evaluation of alternative dosing regimens, or for further exploring safety, PK/pharmacodynamic, or preliminary clinical activity used to guide selection of the RP2D.

Analyzed:
As of the final database lock date of 18 March 2024, a total of 168 patients received at least 1 dose of ivosidenib across 8 dose cohorts. All 168 patients who received at least 1 dose of ivosidenib were included in the FAS and SAS datasets. Sixty (35.7%) patients were included in the DDS and 158 (94.0%) patients were included in the PP set.

Statistical methods:

Statistical analysis was primarily descriptive in nature since the primary objective of the study was to determine the MTD(s) and/or RP2D(s) of ivosidenib. Tabulations were produced for disposition, demographic and baseline characteristics, safety, and clinical activity parameters. Patients treated during the dose escalation portion were pooled with those receiving the same dose and schedule during the expansion portion, unless otherwise specified. Data were pooled across sites.
All parameters were summarized according to assigned dose level, malignancy type, and overall. Efficacy parameters were summarized by dose level and malignancy type.
Categorical variables were summarized by frequency distributions (number and percentages of patients) and continuous variables were summarized by descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum). Time-to-event endpoints were estimated using Kaplan-Meyer (KM) methods, point estimates and 95% confidence intervals (CIs) were provided where appropriate, estimates of the median and other quantiles, as well as individual time points (e.g., 3-month, 6-month, 9-month, 12-month, 18-month and 24-month rates) were produced.
All data were provided in by-patient listings.
The study data were analyzed and reported based on all patients' data by the cutoff date.

Safety measures and endpoints
Safety was evaluated by:
- Monitoring of AEs, including determination of DLTs, SAEs, and AEs leading to treatment discontinuation. The severity of AEs was assessed by the NCI CTCAE (version 4.03).
- Monitoring of safety laboratory parameters, physical examination findings, vital signs, 12 lead ECGs, evaluation of LVEF, and ECOG PS.

Pharmacokinetics and Pharmacodynamics
- Serial blood sampling for determination of concentration-time profiles of ivosidenib.
- Blood, urine, and CSF (in glioma subjects) sampling for determination of 2-HG levels.
- Tumor biopsies for evaluation of 2-HG and ivosidenib.

Clinical activity measures and endpoints
Clinical activity of ivosidenib was evaluated by:
- Serial radiographic evaluations (CT or MRI) to determine response to treatment based on RECIST v1.1 for patients without glioma or by RANO or RANO LGG (expansion portion patients only) criteria for patients with glioma.
- Endpoints of clinical activity included overall response rate, duration of response (DOR), PFS, OS (for cholangiocarcinoma patients only), and time to response.

Exploratory endpoints
- Tumor samples to assess Ki67 levels.

- Blood, urine, and tumor samples, as well as imaging (1H-MRS) in patients with glioma, to explore early clinical activity and the prognostic relationship of pharmacodynamic markers.
- Tumor samples for evaluation of morphology and for cellular differentiation via hematoxylin and eosin staining and IHC for specific cell-type markers.
- Plasma samples for cholesterol and 4β-OHC levels as a potential CYP3A4 induction marker for patients enrolled in the dose escalation portion.
- Plasma, urine, and tumor tissue for metabolic profiling.
- FLAIR tumor volume measurements to evaluate tumor growth rate in patients with non-enhancing glioma.

Analysis populations
The following patient populations (i.e., analysis sets) were evaluated and used for presentation of the clinical data:

- **Dose Determining Set (DDS)**: All patients who either had a DLT during Cycle 1, or who completed at least 75% of their planned Cycle 1 doses (21 out of 28 days) and were considered by the CST to have had sufficient safety data available to conclude that a DLT did not occur during Cycle 1.
- **Safety Analysis Set (SAS)**: All patients who were enrolled and received at least 1 dose of study treatment. Patients were classified according to the actual treatment received. The SAS was used for safety analyses.
- **Full Analysis Set (FAS)**: All patients who were enrolled and received at least 1 dose of study treatment. Patients were classified according to the assigned dose level, schedule, or arm. The FAS was used for all analyses except for safety analyses (e.g., baseline, demographic, efficacy).
- **Per Protocol (PP) Analysis Set**: A subset of patients for whom the baseline scan and at least 1 post-baseline scan are available and evaluable, and who were compliant with the requirements of the study protocol and had no major protocol deviations, which include the following:
  - Patient did not have solid tumor malignancy.
  - Patient did not have documented IDH1 gene-mutated disease (by site test result).
  - Patient received alternative anticancer therapy for their malignancy while on ivosidenib.
- **Pharmacokinetic Analysis Set (PAS)**: All patients who had at least 1 blood sample provided for evaluable PK data for ivosidenib.

Study patients (disposition, demographics and baseline characteristics)
A summary of patient disposition was produced, including the number in each analysis population (DDS, SAS, FAS, PP), the treatment status, the reasons for treatment discontinuation. Summaries were presented by phases, disease types, and dose groups. Study completion status was summarized. The number of cholangiocarcinoma patients who entered survival follow-up and the deaths during the survival follow-up were summarized. The disposition table for glioma presented enhancing glioma, non-enhancing glioma, and all glioma patients separately.
A by-patient listing for disposition was provided. A listing of patients who failed screening was provided. A separate listing was provided for patients who were enrolled into the study but did not receive study drug and the reason for not receiving study drug. Screen failures and enrolled but not dosed patients were excluded from all analyses.
Demographics and baseline disease characteristics summaries were presented by overall phase, disease types, and dose groups based on FAS.
Individual patient listings were provided to support the summary tables.

Of note, there was no impact of the COVID-19 pandemic on the analysis of the results for this study.

Efficacy analysis

The primary efficacy analysis was based on Investigator review. The following response criteria were used in the study:

- Cholangiocarcinoma and chondrosarcoma: RECIST v1.1.
- Enhancing glioma: RANO Criteria.
- Non-enhancing glioma in dose escalation portion: RANO criteria.
- Non-enhancing glioma in expansion portion: RANO LGG criteria.

Efficacy data were summarized as follows:

- Overall phase for cholangiocarcinoma and chondrosarcoma and enhancing glioma.
- Dose escalation portion for non-enhancing glioma.
- Expansion portion for non-enhancing glioma.
- Overall phase for non-enhancing glioma.

Dose groups were: <500 mg, 500 mg, and >500 mg.

All efficacy data were listed by disease type and patient, and were summarized accordingly.

The number and proportion of patients with each category of best overall response were provided. The objective response rate was summarized and it's 2-sided exact binomial 95% confidence interval was calculated.

Safety analysis

Unless specified otherwise, the safety data were summarized based on the SAS.
Safety analyses were presented by disease type and dose groups. Data were pooled for each dose group across the dose escalation and expansion portions.
The following disease types were considered in the safety analyses: cholangiocarcinoma, chondrosarcoma, enhancing glioma, non-enhancing glioma, all glioma, other IDH1 mutant solid tumor, and all disease types.
The following dose groups were displayed in the analyses: 100 mg BID, 300 mg QD, 400 mg QD, 500 mg QD, 600 mg QD, 800 mg QD, 900 mg QD, and 1,200 mg QD. All the data listings were provided by phase, disease types, and dose groups.

Exploratory analysis

Local IDH1 mutation result (Yes or No) were summarized by disease types. Number of patients and the percentage of patients who are in each IDH1 category were displayed in the disease history table.
A data listing with local IDH1 data were to be provided.
The analysis methods and results for the tumor volumetric analyses for non-enhancing glioma in expansion portion will be provided in a subsequent stand-alone report.
An interim analysis of the study was conducted. This analysis was based on the data available up to the cutoff date of 12 May 2017. Following this interim analysis, an addendum was developed to provide updated information on the efficacy and safety outcomes of the study. This addendum was based on an extended dataset with a data cutoff date of 16 January 2019.

SUMMARY OF RESULTS AND CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 168 patients received at least 1 dose of ivosidenib across 8 dose cohorts.

All 168 patients discontinued treatment. Median treatment duration for these 168 patients was 3.70 months (range: 0.4, 103.2 months).

Overall, the most common reasons for discontinuation of study treatment across the 168 treated patients were progressive disease in 132 (78.6%) patients, followed by “other reason” in 12 (7.1%) patients, and clinical progression (defined as clinical deterioration, without evidence of radiographic progressive disease) in 11 (6.5%) patients.

All 168 patients who received at least 1 dose of ivosidenib were included in the FAS and SAS datasets. A total of 60 (35.7%) patients were included in the DDS.

Ten patients were excluded from the PP population: 8 patients who did not have a baseline scan plus at least 1 post-baseline scan available and evaluable, and 2 patients who did not have documented IDH1 gene-mutated disease (by site test result).

BASELINE CHARACTERISTICS

- **Cholangiocarcinoma**

Of the overall 73 patients with cholangiocarcinoma (dose escalation and expansion combined) in the FAS, the median age was 60.0 years (range: 32, 81 years). The majority of patients were female (49 patients, 67.1%).

- **Chondrosarcoma**

Of the overall 21 patients with chondrosarcoma (dose escalation and expansion combined) in the FAS, the median age was 55.0 years (range: 30, 88). The majority of patients were male (13 patients, 61.9%).

- **Glioma**

Of the overall 66 patients with glioma (non-enhancing and enhancing), in the FAS (dose escalation and expansion combined), the median age was 41.0 years (range: 21, 71 years), with the majority of patients being <60 years (62 patients, 93.9%). The majority of patients were male (41 patients, 62.1%).

CLINICAL ACTIVITY RESULTS

- **Cholangiocarcinoma**

All 73 patients with cholangiocarcinoma discontinued treatment with ivosidenib. The primary reason for treatment discontinuation was progression of disease (58 [79.5%] patients). The median treatment duration for patients with cholangiocarcinoma was 3.68 months (range: 0.6, 80.4 months). Twenty-eight (38.4%) patients received ivosidenib for ≥6 months and 16 (21.9%) patients received ivosidenib for ≥12 months. Overall, of the 73 patients with cholangiocarcinoma, 41 (56.2%) patients experienced a BOR of SD. The ORR (CR or PR) was 5.5%, with 4 patients who achieved a PR (1 patient who received 300 mg QD ivosidenib and 3 patients who received 500 mg QD ivosidenib). The median PFS was 3.8 months (95% CI: 3.6, 7.3). The 12-month and 24-month PFS rates were 20.8% and 2.0%, respectively; however, data were censored for 9 (12.3%) patients. The median OS was 12.2 months (95% CI: 9.2, 20.0). The 12- month and the 24-month OS rates were 50.6% and 30.5%, respectively; however, data were censored for 17 (23.3%) patients. Responses were similar between patients in the overall dose group and in the 500 mg QD dose group.

The TTRs for the 4 patients who achieved a PR were 3.9, 7.4, 3.7, and 5.6 months, respectively, and the DOR for each of these patients was 5.6, 7.3, 12.9, and 47.3 months, respectively. Duration of response and TTR data for these 4 patients with cholangiocarcinoma who achieved a PR suggest a more durable response with ivosidenib treatment when compared with the duration of the most recent prior systemic therapy (9.4-80.4 months vs 1.1-2.7 months).

- **Chondrosarcoma**

All 21 patients with chondrosarcoma discontinued treatment with ivosidenib. The primary reason for treatment discontinuation was progression of disease (12 [57.1%] patients). The median treatment duration for patients with chondrosarcoma was 2.89 months (range: 0.4, 102.2 months). Six (28.6%) patients received ivosidenib for ≥ 12 months. Overall, of the 21 patients with chondrosarcoma (dose escalation and expansion combined) in the FAS, 8 (38.1%) patients experienced a BOR of SD. One (4.8%) patient achieved a CR and 2 (9.5%) patients achieved a PR.

The median PFS was 5.6 months (95% CI: 1.9, 7.4). The 12-month and 24-month PFS rates were 22.6% each. The TTR for patients with chondrosarcoma that achieved CR or PR was 29.2, 49.8, 35.0 months, respectively, and the DOR for each of these patients was 53.5, 25.8, and 67.9 months, respectively.

- **Glioma**

Non-enhancing glioma

All 35 patients with non-enhancing glioma discontinued the treatment with ivosidenib. The primary reason for treatment discontinuation was progressive disease (27 [77.1%] patients).

Patients with non-enhancing glioma had a median treatment duration of 18.37 months (range: 1.4, 103.2 months). Twenty-two (62.9%) patients received ivosidenib for ≥12 months.

Across the 35 patients with non-enhancing glioma (dose escalation and expansion combined) in the FAS, the ORR was 2.9%, 1 patient had a PR; and 30 (85.7%) patients had a BOR of SD. In the overall population of patients with non-enhancing glioma, the median PFS was 13.6 months (95% CI: 9.2, 33.2). The 12-month and 24-month PFS rates were 54.3% and 39.6%, respectively.

Enhancing glioma

All 31 patients with enhancing glioma discontinued treatment with ivosidenib. The primary reason for treatment discontinuation was progressive disease (29 [93.5%] patients).

Patients with enhancing glioma had a median treatment duration of 1.94 months (range: 0.4, 93.1 months). Five (16.1%) patients received ivosidenib for ≥12 months.

Across all 31 patients with enhancing glioma, there were no patients who achieved a CR or PR. A total of 14 (45.2%) patients had a BOR of SD; and 17 (54.8%) patients had a BOR of PD. In the overall population of patients with enhancing glioma, the median PFS was 1.4 months (95% CI: 1.0, 1.9). The 12-month and 24-month PFS rates were 9.7% and 6.5%, respectively.

SAFETY RESULTS

- **Extent of exposure**

The median treatment duration was 3.70 months (range: 0.4-103.2 months), with 70 (41.7%) patients receiving study drug for ≥6 months and 49 (29.2%) patients receiving study drug for ≥12 months. Among patients in the 500 mg dose group, the median treatment duration was 4.06 months (range: 0.4-94.8 months), with 56 (43.1%) patients receiving study drug for ≥6 months and 40 (30.8%) patients receiving study drug for ≥12 months.
Median relative dose intensity was 99.6% across all 168 patients. There were few occurrences of dose modifications. This indicates excellent overall compliance.

- **Action taken with study drug**

Overall, few dose reductions were reported during the study; 7 (4.2%) patients had at least 1 dose reduction and 2 (1.2%) patients had at least 2 dose reductions. Forty-seven (28.0%) patients overall had at least 1 occurrence of study drug being held, and 20 (11.9%) patients had at least 2 occurrences of study drug being held during the study. The most common AEs leading to study drug being held, reported in >1 patient, included nausea (5 [3.0%] patients), vomiting, anaemia and pyrexia (4 [2.4%] patients, each), and abdominal pain, COVID-19, arthralgia and headache (2 [1.2%] patients, each). Study drug doses were held for a median of 7 days overall, with 16 (9.5%) patients having consecutive days of doses held for <5 days and 31 (18.5%) patients having consecutive days of doses held for ≥5 days. In 31 (18.5%) patients, at least 1 adverse event led to study drug being held.

- **Adverse events**

Almost all patients (165 [98.2%]) treated with ivosidenib experienced an AE during the study. The most commonly reported adverse events by PT reported in ≥10% of overall patients were fatigue (34.5%), nausea (31.0%), diarrhoea (26.8%), vomiting (20.8%), headache and decreased appetite (19.6% each), arthralgia (17.3%), abdominal pain (16.1%), anaemia and oedema peripheral (13.1% each), cough (11.3%), constipation (10.7%), and back pain (10.1%).
Overall, the incidence of treatment-related AEs was 64.9% (109 patients); the most common treatment-related events reported in ≥5% of overall patients were fatigue (19.6%), nausea (17.9%), diarrhoea (14.9%), vomiting (8.9%), electrocardiogram QT prolonged, anaemia and decreased appetite (6.5% each), and aspartate aminotransferase increased (5.4%). Most AEs reported were nonserious and Grade 1 or Grade 2 in severity.
The incidence of AEs Grade ≥3 was 39.3%, with the most common AEs Grade ≥3 being hyponatraemia, reported in 6 (3.6%) patients; anaemia, hypophosphatemia and ascites, reported in 5 (3.0%) patients each; and abdominal pain, pulmonary embolism reported in 4 (2.4%) patients each.
Adverse events in the gastrointestinal disorders SOC were among the commonly reported AEs (112 patients, 66.7%) in patients treated with ivosidenib. Most were Grade 1 or 2 in severity and did not lead to treatment discontinuation. The protocol did not specify that anti-emetics should be used. Overall, 54 (32.1%) patients received serotonin (5HT3) antagonists, and 47 (28%) patients were treated with other anti-emetic medications. One (0.6%) patient with an SAE within gastrointestinal disorders SOC that was assessed as related to the study drug.
The incidence of SAEs (25.6%) was low. No SAE was reported in more than 4 patients; SAEs reported in >1 patient included pyrexia and seizure reported for 4 (2.4%) patients, each, headache reported for 3 (1.8%) patients; and ascites, biliary tract infection, *Clostridium difficile* infection, pleural effusion, partial seizures, confusional state, cholangitis infective, pneumonia reported for 2 (1.2%) patients each. Three (1.8%) patients experienced treatment-related SAEs of anaemia, supraventricular extrasystole, and colitis (0.6% each). Six (3.6%) patients experienced SAEs leading to on-treatment deaths including respiratory failure, fall, cardiac arrest, acute respiratory failure, *Clostridium difficile* infection, and procedural haemorrhage. None of these deaths were assessed as related to ivosidenib by the Investigator.
Study treatment modifications and discontinuations due to AEs were uncommon during the study. Overall, AEs leading to permanent study drug discontinuation and AEs leading to study drug reductions were reported for 3 (1.8%) patients each, and AEs leading to the study drug being held for 31 (18.5%) patients.
QT interval prolongation is an identified ADR associated with ivosidenib treatment and is closely monitored by the sponsor. Overall, 15 (8.9%) patients experienced an AE of electrocardiogram QT prolonged; there were no concurrent reports of syncope, dizziness, or light-headedness in any of these patients. AEs of Grade 3 or higher of QT prolongation and cardiac arrest were reported in 2 patients and 1 patient, respectively. The Grade 5 cardiac arrest was the only AE within the SMQ (broad) of torsade de pointes/QT prolongation that was reported as serious. A small number of patients had a QTcF value of >480 to ≤500 msec (3 patients, 1.8%) or >500 msec (2 patients, 1.2%) post-baseline. Ten (6%) patients had a post-baseline increase in QTcF of >60 msec. There did not appear to be a relationship between the use of concomitant medications with the potential for QT prolongation and the occurrence of QT interval prolongation events during treatment with ivosidenib.

- **Laboratory tests**

There were no clinically significant findings in post-baseline assessments for hematology parameters, coagulation parameters, vital signs, physical examination assessments, LVEF, or ECOG PS.

- **Other tolerance criteria (vital signs, ECG, etc)**

Overall, in this population of patients with advanced solid tumors and a high incidence of complications, and substantial comorbidities, ivosidenib was well tolerated.

CONCLUSION

Consistent with results presented in the primary CSR, ivosidenib was associated with a clinically meaningful stable disease signal and a few durable partial responses, primarily in patients with cholangiocarcinoma, chondrosarcoma, and in patients with non-enhancing glioma. Patients with other solid tumors and the majority of patients with enhancing glioma experienced disease progression. The median treatment durations and PFS rates among patients with cholangiocarcinoma, chondrosarcoma, and non-enhancing glioma provide preliminary evidence of clinical activity in these indications with high unmet medical need. Overall, administration of ivosidenib to patients with advanced solid tumors, including glioma, was found to be safe and well tolerated.

Date of the report: 12 September 2024