Randomised phase 3 study of ivosidenib in *IDH1*-mutant chemotherapy-refractory cholangiocarcinoma

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Summary

Background

Isocitrate dehydrogenase 1 (*IDH1*) mutations occur globally in approximately 13% of patients with intrahepatic cholangiocarcinoma, a relatively uncommon cancer with a poor clinical outcome. This global phase 3 study was conducted to assess the efficacy and safety of ivosidenib (AG-120)—a small-molecule targeted inhibitor of mutated IDH1 (mIDH1)—in previously treated m*IDH1* cholangiocarcinoma.

Methods

In this double-blind study, patients aged ≥18 years with histologically confirmed m*IDH1* advanced cholangiocarcinoma who progressed on prior therapy were randomised 2:1 to ivosidenib 500 mg once daily or matched placebo, using an interactive web-based response system. These patients constituted the intent-to-treat analysis set (ITT) used for the primary efficacy analyses. Additional key eligibility criteria included ≤2 prior treatment regimens for advanced disease; an Eastern Cooperative Oncology Group Performance Status score of 0 or 1; and a measurable lesion as defined by Response Evaluation Criteria in Solid Tumors version 1·1. Placebo-to-ivosidenib crossover was permitted upon radiographic progression per investigator assessment. Patients were enrolled and treated at participating study centres on an outpatient basis. Safety was assessed in all patients who received ≥1 dose of ivosidenib. The primary endpoint was progression-free survival (PFS) by independent central review. Enrolment is complete; this study is registered with ClinicalTrials.gov, NCT02989857.

Findings

Recruitment occurred between Feb 20, 2017 and Mar 1, 2019. As of the Jan 31, 2019, data cut, 185 patients were randomised to ivosidenib (n=124) or placebo (n=61). Ivosidenib significantly improved median PFS compared with placebo (2·7 *vs* 1·4 months; hazard ratio [HR] 0·37; 95% CI 0·25–0·54; one-

sided p<0·0001). Six- and 12-month PFS rates for ivosidenib were 32% (95% CI 23–42) and 22% (13–32), respectively. No placebo-treated patients had a PFS ≥6 months. Median overall survival (OS) was 10·8 months (95% CI 7·7–17·6) for ivosidenib and 9·7 months (4·8–12·1) for placebo (HR 0·69 [0·44–1·10]; one-sided p=0·06). The median follow-up was 6·9 months (IQR 2·8–10·9) for PFS by independent central review and 8·8 months (4·5–13·6) for OS. The most common grade ≥3 adverse event in both treatment groups was ascites (4 [7%] of 59 placebo patients and 9 [7%] of 121 ivosidenib patients). Serious adverse events were reported in 36 ivosidenib patients and 13 placebo patients. There were no treatment-related deaths.

Interpretation

Ivosidenib improved PFS compared with placebo, and was well tolerated. This study demonstrates the clinical benefit of targeting mIDH1 in advanced m*IDH1* cholangiocarcinoma.

Funding

Agios Pharmaceuticals, Inc.

Research in context

Evidence before this study

The prognosis for intrahepatic cholangiocarcinoma is poor, with 5-year survival rates below 10%, and global incidence of the disease increasing in recent years. Surgery is the only curative option for localised cholangiocarcinoma, although rates of recurrence are high. For unresectable or metastatic disease, chemotherapy remains the primary treatment strategy, with gemcitabine plus cisplatin being the current standard of care. We searched PubMed from Jun 20, 2006 and Feb 1, 2016, with no language restrictions, using the terms “metastatic cholangiocarcinoma AND treatment,” and “IDH1 AND cholangiocarcinoma.” We identified several reports describing mutations in the metabolic enzyme isocitrate dehydrogenase 1 (IDH1) in approximately 20% of patients with intrahepatic cholangiocarcinoma. Moreover, we evaluated preclinical and clinical work published between Jun 20, 2006 and Feb 1, 2016, including those presented at scientific congresses, to understand the biological impact of the disease, as well as the outcomes among previously treated patients with advanced biliary tract cancers receiving chemotherapy. Ivosidenib is a potent, oral inhibitor of mutated IDH1 (mIDH1). In a phase 1 dose escalation and expansion study (NCT02073994), ivosidenib showed promising progression-free and overall survival outcomes, combined with a favourable safety and tolerability profile, in previously treated patients with m*IDH1* advanced cholangiocarcinoma.

Added value of this study

This global, randomised, double-blind study establishes the efficacy and safety of ivosidenib in patients with m*IDH1* cholangiocarcinoma who had progressed on prior standard chemotherapy. Ivosidenib treatment resulted in significant improvement in progression-free survival, with a favourable safety and tolerability profile.

Implications of all the available evidence

With no approved targeted therapies, and modest survival outcomes with chemotherapy in patients with unresectable or metastatic cholangiocarcinoma, there is an urgent need for new therapies. While cholangiocarcinoma-associated genetic alterations are now better defined, there are still no approved targeted therapies in this disease. This pivotal study of ivosidenib demonstrates a benefit in targeting mIDH1 in patients with advanced m*IDH1* cholangiocarcinoma, and highlights the clinical relevance of tumour mutation profiling in the management of this rare cancer with poor outcomes. Results from this study and the follow-up mature overall survival data will be used to support a potential application for regulatory approval of the drug to the FDA and other agencies in the future.

Introduction

Isocitrate dehydrogenase 1 (*IDH1*) mutations are detected in approximately 13% (8·5–20%) of intrahepatic cholangiocarcinomas globally,[1] with varying frequency.[2-4] Preclinical data demonstrate the role of *IDH* mutations in cholangiocarcinoma pathogenesis through their effect on liver progenitor cell differentiation and proliferation.[5] Ivosidenib (AG-120) is an oral, potent, targeted inhibitor of mutated IDH1 (mIDH1) approved for newly diagnosed acute myeloid leukaemia that is ineligible for intensive chemotherapy, and for relapsed/refractory acute myeloid leukaemia.[6-8] In a phase 1 dose escalation and expansion study, ivosidenib demonstrated a progression-free survival (PFS) of 3·8 months; 6- and 12-month PFS rates of 40·1% and 21·8%; a median overall survival (OS) of 13·8 months; and a favourable safety profile in patients with previously treated m*IDH1* advanced cholangiocarcinoma.[9] We report herein the results of a randomised phase 3 study investigating the efficacy and safety of ivosidenib in this population after failure of standard chemotherapy.

Methods

Study design and participants

This phase 3, multicentre, randomised, double-blind, placebo-controlled study assessed the efficacy and safety of ivosidenib in previously treated patients with m*IDH1* advanced cholangiocarcinoma. This study is registered with ClinicalTrials.gov, NCT02989857, and was conducted according to the International Conference on Harmonisation of Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.[10,11] Approval from the institutional review board/international ethics committee was obtained at each study site. An independent data and safety monitoring board regularly reviewed the data to ensure treatment safety and proper study conduct.

Eligible patients were 18 years of age or older with histologically confirmed advanced m*IDH1* cholangiocarcinoma. Up to two prior treatment regimens for advanced disease (unresectable or metastatic), with one gemcitabine- or 5-fluorouracil-based chemotherapy and no prior mIDH inhibitor therapy, were required. Progression at inclusion was determined and confirmed by the

investigator based on available medical history and/or imaging report. Additional key eligibility criteria included a life expectancy of ≥3 months; an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1;[12] a measurable lesion as defined by Response Evaluation Criteria in Solid Tumors version 1·1 (RECIST v1·1);[13] and adequate haematologic, hepatic, and renal function (appendix p 16). Before randomisation, *IDH1* mutation status was confirmed centrally by next-generation sequencing on formalin-fixed, paraffin-embedded tumour tissue using the Oncomine™ Focus Assay (Thermo Fisher Scientific) in a Clinical Laboratory Improvement Amendments–certified laboratory (see appendix p 5). Patients provided written informed consent before participating in the study.

Patients who have received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) were eligible provided measurable disease fell outside of the treatment field or within the field, and has shown ≥20% growth in tumour size since the post-treatment assessment. Patients were excluded if they received systemic anticancer therapy or an investigational agent <2 weeks prior to day 1 (washout from prior immune-based anticancer therapy being 4 weeks); received radiotherapy to metastatic sites of disease <2 weeks prior to day 1; underwent hepatic radiation, chemoembolization, and radiofrequency ablation <4 weeks prior to day 1. Patients with the following comorbidities were not permitted: active cardiac disease within 6 months prior to the start of study treatment; myocardial infarction; unstable angina and/or stroke; active hepatitis B or C (HBV/HBC) infections; known positive HIV antibody results, or AIDS-related illness. The complete study protocol is available in the appendix (pp 27–104).

Randomisation and masking

Patients were enrolled and treated by the investigators at participating study centres on an outpatient basis. They were randomly assigned 2:1 to ivosidenib or matched placebo, with block size of 6, and stratified by number of prior systemic treatment regimens for advanced disease (1 or 2). Randomisation into the two treatment arms was implemented by an interactive web-based

response system and generated by an independent statistical group. Ivosidenib and placebo were packaged and labelled identically to ensure that study personnel remained blinded to treatment assignment. Patients, investigators and their teams, and designated individuals from the sponsor were blinded to study treatment until disease progression, as assessed by the investigator (appendix pp 4–5).

Procedures

Ivosidenib 500 mg or placebo was given orally once daily in continuous 28-day cycles (±2 days), starting on cycle 1 day 1. Study visits were conducted every other week during cycles 1–3 (days 1 and 15) and on day 1 of subsequent cycles. Treatment was to continue until disease progression as determined by investigator, development of other unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, loss to follow-up, or study unblinding or ending. Continuation of treatment after radiographic disease progression was permitted, provided that the investigator deemed clinical benefit. Crossover from placebo to ivosidenib was permitted at radiologic progression by investigator-assessed RECIST v1·1 after unblinding if eligibility criteria were met. A post-treatment follow-up visit for safety occurred 28 days (no more than 33 days) after the last dose of study drug. Dose modifications of ivosidenib/placebo from 500 mg to 250 mg were permitted on study for management of adverse events (AEs). If more than one AE occurred that required a dose modification, upon resolution of all AEs to baseline or Grade 1, ivosidenib/placebo dose was reduced to 250 mg. Re-escalation may have been allowed with approval from the medical monitor. Radiographic assessment (CT or MRI) for evaluation of disease response was conducted from cycle 1 day 1 every 6 weeks (±5 days) through week 48, and every 8 weeks (±5 days) thereafter. Quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Cholangiocarcinoma and Gallbladder Cancer module (EORTC QLQ-BIL21); Patient Global Impression (PGI) questions adapted from the National Institute of Mental Health PGI of change (PGI-C) for three prespecified domains of interest

(physical functioning, pain, and appetite loss); and the 5-level EuroQol 5-Dimension (EQ-5D-5L) for future health economic modelling.[14-17]

Blood samples were drawn before and after dosing to determine circulating plasma concentrations of ivosidenib and D-2-hydroxyglutarate (2-HG), an oncometabolite that accumulates as a result of IDH mutations.[18]

Outcomes

The primary endpoint was PFS by central independent radiology centre (IRC) RECIST v1·1 assessment. PFS was defined as the time from the date of randomisation to the date of first documentation of disease progression or death owing to any cause, whichever occurred first. IRC did not perform real-time confirmation of locally determined radiographic progression.

Secondary efficacy endpoints included OS; objective response rate (ORR) by RECIST v1·1; duration of response and time to response (assessed by the investigator and IRC); PFS (by investigator review); pharmacokinetics/pharmacodynamics; and QoL assessed using EORTC QLQ-C30, EORTC QLQ-BIL21, PGI-C anchor questions; and EQ-5D-5L for health economic modelling. EQ-5D-5L findings based on final data will be reported elsewhere. Patients who discontinued treatment for reasons other than disease progression or withdrawal of consent entered PFS follow-up (every 6 weeks through week 48, and every 8 weeks thereafter), until documented disease progression or the start of new cancer treatment. Based on investigator confirmed radiographic progression, unblinding was permitted and eligible placebo subjects were permitted to received open label ivosidenib. There were no major deviations or protocol amendments that were considered likely to affect the primary endpoint of PFS or the study conclusions. OS follow-up evaluations occurred every 12 weeks after the end of treatment unless the patient was in PFS follow-up. OS follow-up continues after the primary endpoint has been reached.

Safety and tolerability were assessed from the first dose of study treatment by the incidence of treatment-emergent adverse events (TEAEs); by severity and type of AEs (per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4·03); and by evaluation of vital

signs, ECOG PS, clinical laboratory test results, and electrocardiograms (because ivosidenib-treated patients can develop QT prolongation).[6] AEs reported herein for ivosidenib are before crossover.

Statistical analysis

The intent-to-treat (ITT) population, comprising all randomised patients within the designated treatment group, was used for primary efficacy analyses and other analyses unless otherwise specified. The safety analysis population included all patients who received at least one dose of study treatment, with the actual treatment received as the treatment group unless otherwise specified.

A log-rank test stratified by the randomisation stratification factor was used to assess statistical significance. 95% CI for the survival rate estimates were calculated via the log-log transformation. A Cox regression model stratified by the randomisation stratification factor was used to estimate the hazard ratio (HR) and the 95% CI for the PFS comparison of the ivosidenib and placebo arms. Assuming an HR of 0·5 for PFS, a total of 131 PFS events would be required to provide 96% power at a one-sided alpha level of significance of 0·025 to reject the null hypothesis. OS analyses were conducted once at the time of the final analysis for PFS and will be conducted again at the occurrence of 150 OS events, approximately 24 months after the last patient has been randomised. Assuming an HR of 0·67 for OS, a total of 150 PS events will provide 64% power at a one-sided alpha level of significance of 0·025. Statistical analyses were done using the SAS software (version 9·4). The rank-preserving structural failure time (RPSFT) method was used to reconstruct the survival curve (pre-specified exploratory analysis) for placebo patients as if crossover had never occurred (see appendix p 5 for additional details).[19] RPSFT assumes that the treatment effect is the same for all patients, regardless of when the treatment is given. Subgroup analyses by prior line of therapy, sex, extent of disease, cholangiocarcinoma type, ECOG PS score, and region were performed on PFS per IRC and OS, and included Kaplan-Meier summaries, unstratified log-rank test, p values, and HRs

from Cox regression models. The proportional hazard assumption was met on the basis of graphic check.

Mixed-effect models with repeated measurements were conducted on change scores from baseline for subscales of the EORTC QLQ-C30 and QLQ-BIL21 corresponding to the three domains of interest included in the trial protocol and statistical analysis plan (see appendix pp 5–6).[14,15] Clinically meaningful changes on these subscales were estimated using the respective PGI-C ratings as anchors. The focus was on cycle 2 day 1, considering the availability of QoL data. QoL analyses were exploratory in nature; therefore, type 1 error control for multiplicity was not considered.

All time-to-event endpoints were estimated using Kaplan-Meier methods. Descriptive statistics were used to summarise safety data, response rates, QoL data, and pharmacokinetic/pharmacodynamic data. All reported p values are one-sided unless otherwise specified.

Role of the funding source

The first and last authors, in collaboration with the sponsor, designed the trial. The authors and the sponsor conducted data collection and analysis. The first and last authors wrote the first draft of the manuscript in collaboration with the sponsor. Further medical writing support was provided by the sponsor. The paper was revised in collaboration with all authors. The first and last author had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were recruited between February 20, 2017 and March 1, 2019. As of January 31, 2019 (the analysis cut-off date based on investigator-assessed PFS), 185 patients had been randomised to ivosidenib (n=124) or placebo (n=61) across 49 sites in six countries (figure 1). Two remaining patients in screening were randomised after the cut-off date. Baseline demographic and disease characteristics were similar in the ivosidenib and placebo arms; among all 185 patients, R132C was the most prevalent IDH1 mutation (129 [70%]), 171 (92%) had metastatic disease, and 86 (46%) had received two prior lines of therapy (table 1). The majority of eligible patients (173 [94%] of 185

patients) received a prior platinum-based therapy (118 ivosidenib and 55 placebo patients); 57 patients were considered ineligible, mainly due to not having documented *IDH*-mutated disease or ECOG PS >2. At the data cut, 35 (57%) of 61 placebo patients had crossed over to receive open-label ivosidenib. Of the remaining 26 placebo patients, 13 (50%) had died, eight (31%) were still receiving placebo, two were never dosed, two withdrew consent, and one received another treatment. Among the 121 ivosidenib-treated patients, 14 (12%) were permitted to continue beyond radiographic progression, as determined by the local investigator.

PFS by IRC assessment (primary endpoint) was evaluated in 76 (61%) of 124 ivosidenib patients and 50 (82%) of 61 placebo patients. Longer PFS by IRC was observed for patients receiving ivosidenib (n=76) than for those receiving placebo (n=50; HR 0·37; 95% CI 0·25–0·54; p<0·0001), with a median PFS of 2·7 months (95% CI 1·6–4·2) for ivosidenib versus 1·4 months (1·4–1·6) for placebo (figure 2A). PFS rates at 6 and 12 months were 32% (95% CI 23–42) and 22% (13–32) for ivosidenib; no placebo-treated patients were progression free for ≥6 months. The PFS benefit was observed across all subgroups (figure 2B). The median follow-up was 6·9 months (IQR 2·8–10·9) for PFS by IRC. PFS by investigator review was similar to that observed by IRC assessment (HR 0·47; 95% CI 0·33–0·68; p<0·0001), with an overall concordance of 77% for PFS status between investigator and IRC. Median investigator-assessed PFS was 2·7 months (95% CI 1·6–3·6) for ivosidenib versus 1·4 months (1·4–2·5) for placebo (appendix p 9; see appendix p 10 for crossover patients).

Median OS (ITT) was 10·8 months (95% CI 7·7–17·6) for ivosidenib versus 9·7 months (4·8–12·1) for placebo (HR 0·69 [0·44–1·10]; p=0·06) based on 78 OS events and 57% crossover from placebo (35 of 61 patients; figure 3). The 6-month and 12-month OS rates for ivosidenib were 67% % (95% CI 56–75) and 48% (36–59), respectively, versus 59% (44–71) and 38% (22–54) for placebo. OS by subgroup is reported in the appendix (p 11). The RPSFT-adjusted median OS was 6 months (95% CI 3·6–6·3 for placebo (HR 0·46 [0·28–0·75]; p=0·0008).

The ORR per IRC for ivosidenib was 2% (3 of 124 patients), comprising three partial responses. Sixty-three ivosidenib patients (51%) of 124 patients experienced stable disease (SD; appendix p 17). In

comparison, the ORR was 0% for placebo and 17 (28%) of 61 placebo patients had SD (appendix pp 17–18). Characteristics of ivosidenib patients achieving a confirmed partial response per IRC before unblinding are described in the appendix (p 19). The median (range) duration of treatment was 2·6 months (IQR 1·4–6·0) for ivosidenib and 1·6 months (1·1–2·7) for placebo (figure 4; see appendix p 13 for investigator-assessed data).

The most common TEAEs (in ≥10% [all grades] of patients who started treatment with ivosidenib) included, among all 121 ivosidenib patients, nausea (43 [36%]), diarrhoea (37 [31%]), and fatigue (32 [26%]; table 2; see appendix p 20 for expanded list, including TEAEs reported in the ivosidenib population after crossover). Grade ≥3 TEAEs were reported in 55 (45%) ivosidenib patients versus 21 (36%) of 59 placebo patients. The most common grade ≥3 adverse event in both treatment groups was ascites (4 [7%] of placebo patients and 9 [7%] of ivosidenib patients; table 2). AEs in ≥5% of patients assessed as treatment related by investigators were reported in 76 ivosidenib patients (63%) versus 22 on placebo (37%; appendix p 21). The most common treatment-related AEs in ivosidenib patients were diarrhoea (25 [21%]), nausea (25 [21%]), and fatigue (19 [16%]); most were grade 1/2 in severity (two patients reported grade 3 fatigue). Serious AEs (SAEs) were reported for 36 (30%) ivosidenib patients, of which 3 (3%) had an SAE assessed as related to ivosidenib (grade 4 hyperbilirubinaemia, grade 3 jaundice cholestatic, grade 2 electrocardiogram QT prolonged, and grade 3 pleural effusion). SAEs were reported in 13 (22%) placebo patients, none related to placebo. Overall, 14 (12%) ivosidenib patients and 10 (17%) placebo patients died within 30 days of receiving the last dose. Four ivosidenib patients (<4% of all ivosidenib patients) experienced an AE leading to death (pneumonia, sepsis, intestinal obstruction, and pulmonary embolism), none of which were assessed by the investigator as treatment related (appendix p 22), and 10 died due to progressive disease. No TEAE leading to death was reported in the placebo arm, with all 10 deaths due to progressive disease.

TEAEs requiring a dose reduction occurred in four patients (3%) on ivosidenib versus none on placebo. TEAEs leading to treatment discontinuation occurred in seven patients (6%) on ivosidenib

versus five (8%) on placebo. Treatment-related AEs leading to treatment discontinuation occurred in two ivosidenib patients (2%; grade 2 generalised oedema and grade 4 hyperbilirubinaemia).

At baseline, 113 ivosidenib and 52 placebo patients completed the EORTC QLQ-C30 assessment, and 107 ivosidenib and 51 placebo patients completed the QLQ-BIL21 assessment. By mixed-effect models with repeated measurements analysis, the decline from baseline at cycle 2 day 1 on the EORTC QLQ-C30 Physical Functioning subscale (higher score denoting better functioning) was significantly less for ivosidenib patients (n=62; least squares mean [standard error]: –3·4 [1·81]; p=0·006; appendix p 14 and p 23) than for placebo patients (n=20; –13·1 [3·04]). Furthermore, the decline was clinically meaningful in the placebo arm only, according to PGI-C anchor-based analyses suggesting that a 12- to 13-point score decrease represents clinically meaningful worsening of physical functioning (appendix p 7 and p 24). Differences in pain and appetite loss subscales were not statistically significant between arms, and clinically meaningful changes could not be determined owing to data availability.

Pharmacokinetic/pharmacodynamic parameters observed in this study were consistent with previous findings.[20] After one cycle of ivosidenib, mean trough plasma 2-HG decreased by up to 97% from baseline to cycle 2 day 1 (first treatment cycle), to levels similar to those observed in healthy individuals, versus a 47% increase with placebo (two-sided p<0·0001, at cycle 2 day 1). This decrease was maintained throughout continued ivosidenib dosing (up to 19 cycles), whereas plasma 2-HG remained elevated on placebo during the observation period (appendix p 15).

Discussion

This randomised phase 3 study demonstrates the clinical benefit of targeting mIDH1 in patients with advanced m*IDH1* cholangiocarcinoma. The PFS HR of 0·37 and PFS rates at 6 and 12 months of 32% and 22%, respectively, following ivosidenib are clinically meaningful. Although the absolute improvement in median PFS seems modest, the statistical strength of the HR reflects a 63% reduction in risk of progression, along with a substantial improvement in progression-free

proportion at 6 and 12 months. The benefit is independent of number of prior therapies and is consistent across subgroups. This improvement in PFS is important in the context of a favourable safety and tolerability profile in the chemotherapy-refractory setting. The disease control rate associated with ivosidenib (53%) was primarily driven by SD, reflecting the mechanism of action of ivosidenib, which is specific to epigenetic modifications promoting cellular differentiation rather than a direct cytotoxic mechanism.

Although the crossover design enabled 35 (57%) of 59 placebo patients to receive ivosidenib at disease progression, there was still a favourable OS trend for ivosidenib versus placebo in the ITT population. Using RPSFT modelling to adjust for the impact of placebo-to-ivosidenib crossover resulted in a statistically significant improvement in OS, with a difference of 4·8 months in median OS between ivosidenib and placebo (HR 0·46; p<0·0001). The RPSFT-adjusted OS results from the placebo arm are consistent with survival outcomes from historical and recent data for patients managed with best supportive care, active symptom control, or second-line chemotherapy.[21-24] ORR per IRC was 2% for ivosidenib vs 0% for placebo. Despite small post-baseline sample sizes, the clinical benefit of ivosidenib was further supported by EORTC QLQ-C30 Physical Functioning subscale scores, indicating that placebo patients experienced a significantly greater decline in physical functioning than ivosidenib patients at cycle 2 day 1. Moreover, a favourable pharmacokinetic/pharmacodynamic profile was observed in patients with advanced m*IDH1* cholangiocarcinoma who received once-daily 500 mg ivosidenib. Detailed pharmacokinetic/pharmacodynamic data for this patient population will be published elsewhere.

Ivosidenib was well tolerated; the most common TEAEs in ivosidenib patients were low-grade diarrhoea, nausea, and fatigue. Similarly, the rates of treatment discontinuation or dose reduction were low. Although the findings reported here are specific to patients with m*IDH1* advanced cholangiocarcinoma, representing a relatively small subset of the disease population,[1] the incidence of intrahepatic cholangiocarcinoma is increasing internationally[25,26] and represents an area of growing unmet need.[1,9,27]

The study has some limitations. Although median OS in ivosidenib patients was longer than in those receiving placebo, statistical difference between the two treatment groups was not reached, partly owing to the impact of placebo-to-ivosidenib crossover and the data not being mature at the time of primary analysis (42% of events). Despite this, there was a significant improvement in OS for ivosidenib versus RPSFT-adjusted OS for placebo (median 10·8 *vs* 6 months; HR 0·46; 95% CI 0·28–0·75; p<0·0001). Without established efficacious alternatives, there was no justification for withholding ivosidenib from placebo patients with m*IDH1* cholangiocarcinoma. Additionally, the limited patient-reported outcome data collection prevented a thorough evaluation of relevant QoL parameters in this specific population.

In conclusion, ivosidenib therapy significantly improved PFS and OS after adjusting for crossover, with a favourable safety profile, in patients with advanced m*IDH1* cholangiocarcinoma who had progressed on standard chemotherapy. This study demonstrates the feasibility and clinical benefit of targeting a molecularly defined subgroup of cholangiocarcinoma and warrants tumour mutation profiling as a new standard of care in this heterogeneous disease.[28-30]

Contributors

GKA-A, CG, SSP, and AXZ designed the trial and developed the protocol. LJ developed the statistical analysis plan. GKA-A, TM, MMJ, RKK, SJL, JA, JMC, DVC, MJB, JB, WPH, AGM, D-YO, JW, MAL, LG, RTS, ABE-K, JWV, and AXZ participated in the recruitment of patients and collection and analysis of data, in collaboration with the sponsor. LJ, CG, and SSP participated in the analysis of clinical data. BF, LJ, and SSP participated in the analysis of pharmacokinetic and pharmacodynamic data. BW and SSP developed the strategy for prospective and central testing of IDH1 status for enrolment and BW led the efforts in IDH1 CTA validation and implementation in the trial. CXC, LJ, and SSP participated in the analysis of patient-reported outcome data. Statistical analyses were done by a contract research organisation, overseen by qualified statisticians employed by the sponsor, including LJ. All authors interpreted the data. GKA-A and AXZ wrote the first draft of the manuscript. All authors contributed

to the review and revision of the manuscript for important intellectual content and approved the final version for submission.

Declaration of interests

GKA-A is a consultant for 3DMedcare, Agios, Alignmed, Amgen, Antengene, Aptus, ASLAN, Astellas, Astra Zeneca, Bayer, Beigene, Bioline, BMS, Boston Scientific, Bridgebio, Carsgen, Celgene, Casi, Cipla, CytomX, Daiichi, Debio, Delcath, Eisai, Exelixis, Flatiron, Genoscience, Halozyme, Hengrui, Incyte, Inovio, Ipsen, Jazz, Jansen, Klus, Kyowa Kirin, LAM, Lilly, Loxo, Merck, Mina, Novella, Onxeo, PCI Biotech, Pfizer, Pieris, QED, Redhill, Sanofi, Servier, Silenseed, SillaJen, Sobi, Targovax, Tekmira, Twoxar, Vicus, Yakult, and Yiviva; has received research grant/funding from ActaBiologica, Agios, Array, AstraZeneca, Bayer, Beigene, BMS, Casi, Celgene, Exelixis, Genentech, Halozyme, Incyte, Lilly, Mabvax, Novartis, OncoQuest, Polaris Puma, QED, and Roche. TM is on advisory boards for Baxalta, Celgene, H3B, QED, and Shire; has received honoraria from Genzyme, Roche, Sanofi, Shire, and Tesaro; has participated in speaker bureaus for Celgene, Sanofi, and Shire; has received research grant/funding (to institution) from Agios, ASLAN, AstraZeneca, Baxalta, Bayer, Genentech, Halozyme, Immunomedics, Lilly, Merrimack, Millennium, Novartis, Novocure, Pfizer, Pharmacyclics, and Roche; has received travel/accommodation funding from Bayer, H3B, Merck, and Sanofi. MMJ is on advisory boards for EDO, More Health, and OrigiMed; has received honoraria from Merck, Seattle Genetics, and Taiho; has received research grant/funding from ArQule (to institution), Lilly (to institution), Meclun (to individual), Novartis (to individual), and QED (to individual). RKK is on advisory boards for Agios (funding to institution), AstraZeneca (funding to institution), BMS (funding to institution), Genentech/Roche (IDMC; advisory board and funding to individual), and Ipsen (funding to individual); has received travel/accommodation funding from Ipsen; has received research grant/funding (to institution) from Agios, AstraZeneca, Bayer, BMS, Exelixis, Lilly, MedImmune, Merck, Merck Serono, Novartis, Partner Therapeutics, QED, and Taiho. SJL is a consultant for Farcast Biosciences. JMC is on advisory boards for Agios, and BMS; has received honoraria from Agios; has received travel/accommodation funding from Agios, BMS, and Roche; has received research

grant/funding from Merck and Tesaro. DVC has received honoraria from Astellas, BMS, Daiichi Sankyo, Five Prime, Foundation Medicine, Genentech/Roche, Guardant, Lilly, Merck, Taiho, and Tempus. MJB holds stock in AVEO, Intercept, and OncBioMune; has received honoraria from ADC, Exelixis, G1, Immunovative, Inspyr, Lynx Group, Western Oncolytics; has received travel/accommodation funding from AstraZeneca; has received research grant/funding (to institution) from Adaptimmune, Agios, ARIAD, Basilea, Bioline, Boston Biomedical, Celgene, Dicerna, Halozyme, Incyte, Isis, MedImmune, Merck Serono, Mirna, Novartis, Pieris, PUMA, QED, Redhill, Senhwa, SillaJen, Sun, Taiho, and Toray. JB is on advisory boards for AstraZeneca, Basilea, Bayer, Incyte, Merck Serono, Roche, and Servier; has received honoraria from Merck Serono and Servier; has received travel/accommodation funding from Bristol-Myers Squibb, Bristol-Myers Squib/Medarex, MDS, Merck Serono, and Servier; has participated in speaker bureaus for Amgen and Celgene; has received research grant/funding from Amgen. WPH is on advisory boards for Bayer, Bristol-Myers Squibb, Eisai, Exelixis, Neo Therma, QED, and Zymeworks; has received research grant/funding from Agios, ArQule, Bayer, Bristol-Myers Squibb, BTG, Eisai, Exelixis, Halozyme, MedImmune, and Merck. AGM has received research grant/funding from Bristol-Myers Squibb. D-YO is on advisory boards from ASLAN, AstraZeneca, Bayer, Celgene, Genentech/Roche, Halozyme, Merck Serono, Novartis, Taiho, and Zymeworks; has research grant/funding (to institution) from Array, AstraZeneca, Lilly, and Novartis. MAL is on advisory boards for Agios, and Roche; has participated in speaker bureaus for Novartis; has received travel funding from Ipsen. LG is on advisory boards for Agios, Alentis, Debiopharm, Klus, Pieris, QED, Sirtex, and Taiho; is a consultant for Alentis, H3B, Incyte; has received travel funding from Taiho; is a IDMC member for AstraZeneca. RTS is on advisory boards for Agios, Clovis, Debiopharm, Exelixis, Incyte, Merck, QED, and Seattle Genetics; has received research grant/funding from Agios, Exelixis, Halozyme, Merck, Pieris, and Taiho. ABE-K is on advisory boards for Agenus, Agios, Bayer, BMS, CytomX, Eisai, Exelixis, Gilead, Merck, Merck Serono, Pieris, and Roche/Genentech (consultant and advisory board); has received research grant/funding from Astex (to institution), AstraZeneca (to institution), and Merck (to

institution). BF, CXC, LJ, CG, and SSP are employees of and hold stock in Agios Pharmaceuticals, Inc. BW is an employee of, holds stock in, and holds patents, royalties, and other intellectual property with Agios Pharmaceuticals, Inc. JWV is on advisory boards for Agios, AstraZeneca, Debiopharm, Delcath, Genoscience, Imaging Equipment Limited, Incyte, Ipsen, Keocyt, Merck, Mundipharma, Novartis, NuCana, PCI, Pieris, Pfizer, QED, Servier, and Wren Laboratories; has received travel/accommodation funding from Ipsen, Novartis, and NuCana; has participated in speaker bureaus for Ipsen, Novartis, and Pfizer. AXZ is on advisory boards for Bayer, Eisai, Exelixis, Lilly, Merck, Roche/Genentech, and Sanofi. All remaining/other authors declare no competing interests.

Data sharing statement

The data collected for the study will not be made available to others. We encourage investigators interested in data sharing and collaboration to contact the corresponding author.

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References

1. Boscoe AN, Rolland C, Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. *J Gastrointest Oncol* 2019; **10**: 751–65.
2. Borger DR, Tanabe KK, Fan KC, et al. Frequent mutation of isocitrate dehydrogenase (IDH)1 and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping. *Oncologist* 2012; **17**: 72-9.
3. Kipp BR, Voss JS, Kerr SE, et al. Isocitrate dehydrogenase 1 and 2 mutations in cholangiocarcinoma. *Hum Pathol* 2012; **43**: 1552–8.

4. Wang P, Dong Q, Zhang C, et al. Mutations in isocitrate dehydrogenase 1 and 2 occur frequently in intrahepatic cholangiocarcinomas and share hypermethylation targets with glioblastomas. *Oncogene* 2013; **32**: 3091–100.

5. Saha SK, Parachoniak CA, Ghanta KS, et al. Mutant IDH inhibits HNF-4α to block hepatocyte differentiation and promote biliary cancer. *Nature* 2014; **513**: 110–4.

6. Agios Pharmaceuticals Inc. TIBSOVO (ivosidenib). Highlights of prescribing information. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211192s001lbl.pdf (accessed Aug 5, 2019).

7. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med* 2018; **378**: 2386–98.

8. Popovici-Muller J, Lemieux RM, Artin E, et al. Discovery of AG-120 (ivosidenib): a first-in-class mutant IDH1 inhibitor for the treatment of IDH1 mutant cancers. *ACS Med Chem Lett* 2018; **9**: 300–5.

9. Lowery MA, Burris HA III, Janku F, et al. Safety and activity of ivosidenib in patients with IDH1-mutant advanced cholangiocarcinoma: a phase 1 study. *Lancet Gastroenterol Hepatol* 2019; **4**: 711–20.

10. Baber N. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). *Br J Clin Pharmacol* 1994; **37**: 401–4.

11. World Medical Association 64th General Assembly. Declaration of Helsinki. Ethical principles for medical research involving human subjects. 2013. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed Aug 5, 2019).

12. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55.

13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.

14. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365–76.

15. Friend E, Yadegarfar G, Byrne C, et al. Development of a questionnaire (EORTC module) to measure quality of life in patients with cholangiocarcinoma and gallbladder cancer, the EORTC QLQ-BIL21. *Br J Cancer* 2011; **104**: 587–92.

16. Guy W. ECDEU assessment manual for psychopharmacology. Rockville, MD, USA: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, 1976.

17. Szende A, Janssen B, Cabases J, eds. Self-reported population health: an international perspective based on EQ-5D. Dordrecht, The Netherlands: Springer, 2014.

18. Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* 2009; **462**: 739–44.

19. Morden JP, Lambert PC, Latimer N, Abrams KR, Wailoo AJ. Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study. *BMC Med Res Methodol* 2011; **11**: 4.

20. Lowery MA, Burris HA, III, Janku F, et al. Safety and activity of ivosidenib in patients with IDH1-mutant advanced cholangiocarcinoma: a phase 1 study. *Lancet Gastroenterol Hepatol* 2019; **4**: 711-20.

21. Moik F, Riedl JM, Winder T, et al. Benefit of second-line systemic chemotherapy for advanced biliary tract cancer: a propensity score analysis. *Sci Rep* 2019; **9**: 5548.

22. Lamarca A, Palmer DH, Wasan HS, et al. ABC-06 | A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced/metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. *J Clin Oncol* 2019; **37**: 4003.

23. Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. *Ann Oncol* 2014; **25**: 2328–38.

24. Ying J, Chen J. Combination versus mono-therapy as salvage treatment for advanced biliary tract cancer: a comprehensive meta-analysis of published data. *Crit Rev Oncol Hematol* 2019; **139**: 134–42.

25. Patel N, Benipal B. Incidence of cholangiocarcinoma in the USA from 2001 to 2015: a US cancer statistics analysis of 50 states. *Cureus* 2019; **11**: e3962.

26. Blechacz B. Cholangiocarcinoma: current knowledge and new developments. *Gut Liver* 2017; **11**: 13–26.

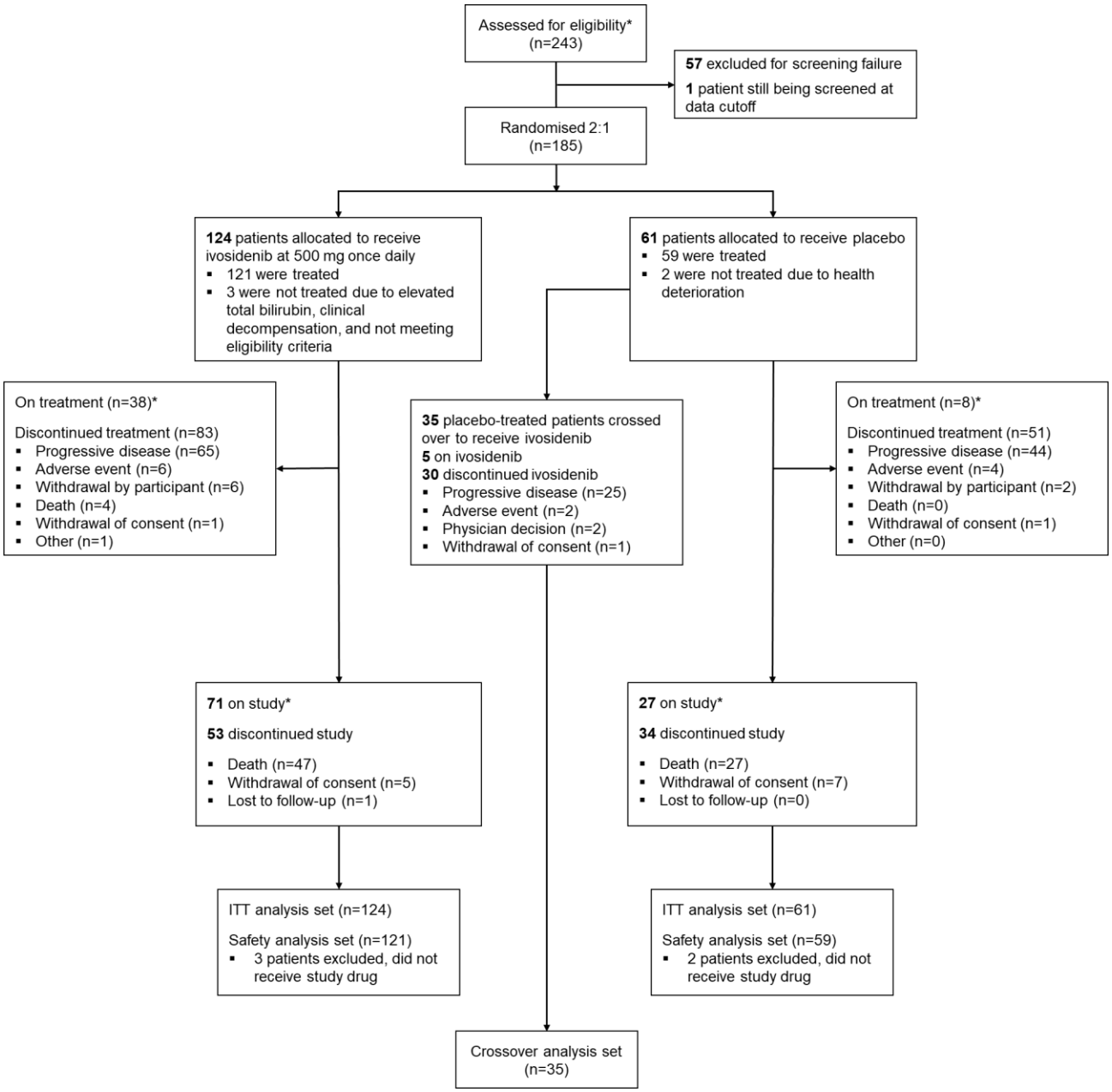
27. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol* 2018; **15**: 95–111.

28. Javle M, Bekaii-Saab T, Jain A, et al. Biliary cancer: utility of next-generation sequencing for clinical management. *Cancer* 2016; **122**: 3838–47.

29. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409–13.

30. Javle M, Lowery M, Shroff RT, et al. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. *J Clin Oncol* 2018; **36**: 276–82.

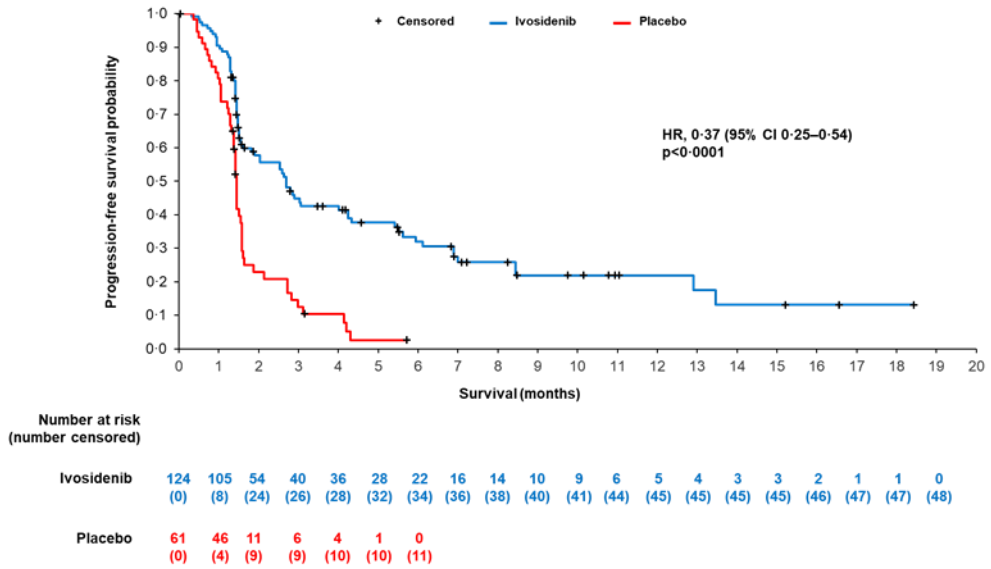
Figure 1: **Patient flow diagram**



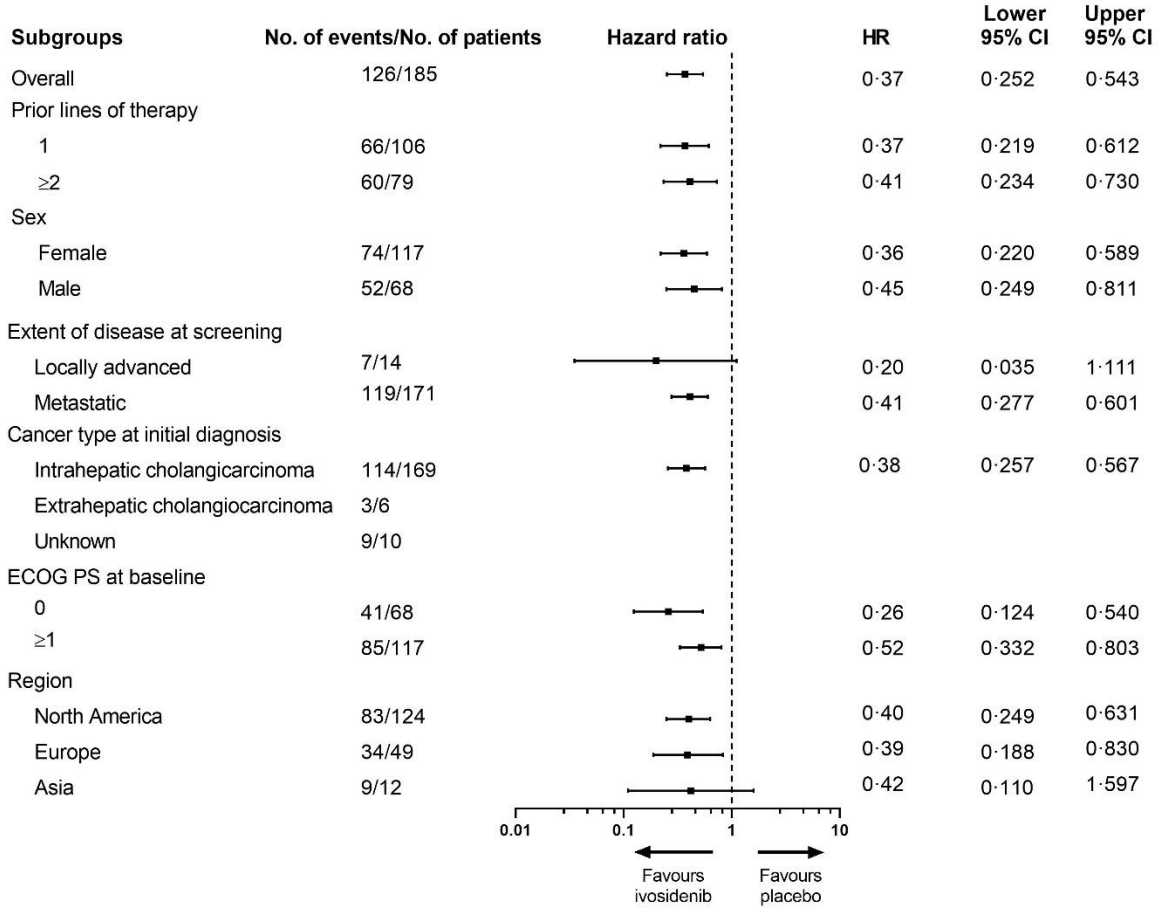
Crossover analysis set: a subset of placebo-treated patients who crossed over and received ivosidenib upon radiographic progressive disease. ITT analysis set: all patients who were randomised, with the treatment group designated according to the randomisation. Safety analysis set: all patients who received any amount of study drug (ivosidenib or placebo), with treatment group designated according to the actual study treatment received. ITT=intention-to-treat. *As of data cut-off, Jan 31, 2019.

Figure 2: **Progression-free survival assessed by the independent radiology centre before crossover in the intent-to-treat population**

A

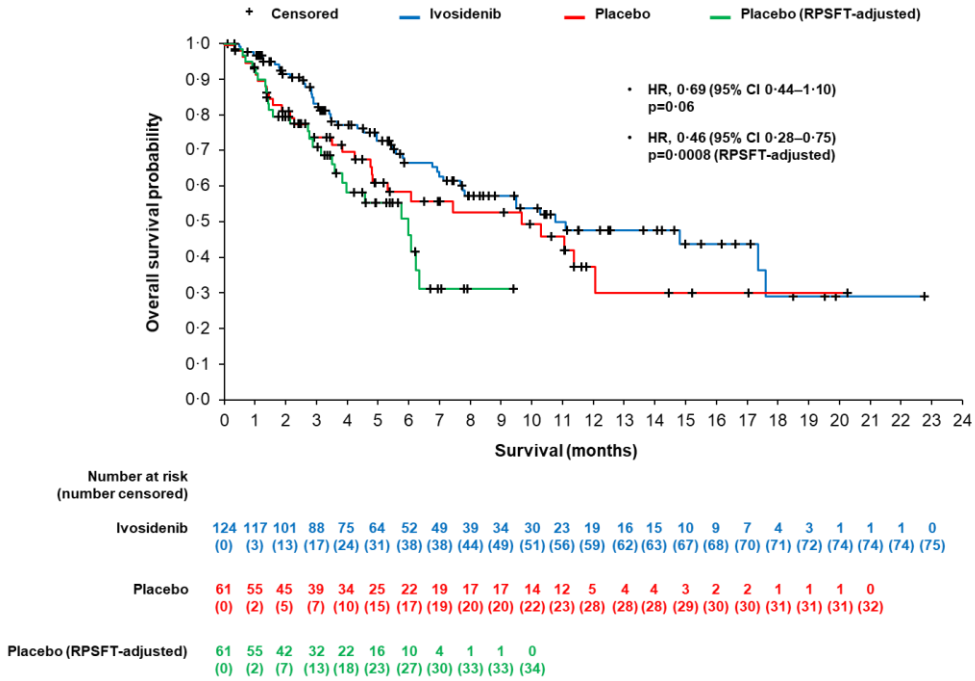


B



(A) The Kaplan-Meier plot of the probability of progression-free survival among patients receiving ivosidenib compared with those receiving placebo. Scans after local disease progression per investigator assessment were excluded from this analysis. Patients starting treatment with a new anticancer therapy before IRC-assessed progression or death were censored at the last adequate assessment prior to the new anticancer therapy. Patients without a post-baseline assessment and no death were censored at the randomisation date. Patients without progression/death by the data cut-off date were censored at the last adequate assessment date. Patients with progression/death following a long gap (≥2 consecutive scheduled assessments missing) were censored at the date of the last adequate assessment prior to the gap. (B) Forest plot of progression-free survival hazard ratios for key subgroups. Scans after local disease progression per investigator assessment were excluded from this analysis. The hazard ratio for the "Overall" subgroup was calculated from the stratified Cox regression model with placebo as the denominator. The hazard ratio for each subgroup was calculated from the unstratified Cox regression model. Subgroups with event numbers ≤5 or number of patients ≤10 were not plotted because the small sample size would not support any robust interpretation. The number of prior lines of therapy was based on the actual prior lines that patients received per eligibility, reviewed by the sponsor's medical monitor. If patients had both local and metastatic status, disease was considered to be metastatic. Perihilar disease was considered to be extrahepatic disease. The baseline measurement was defined as the most recent measurement prior to the first dose of study drug. If patients were not dosed, the latest assessment was considered to be the baseline assessment. Error bars indicate two-sided 95% CIs. ECOG PS=Eastern Cooperative Oncology Group Performance Status. HR=hazard ratio.

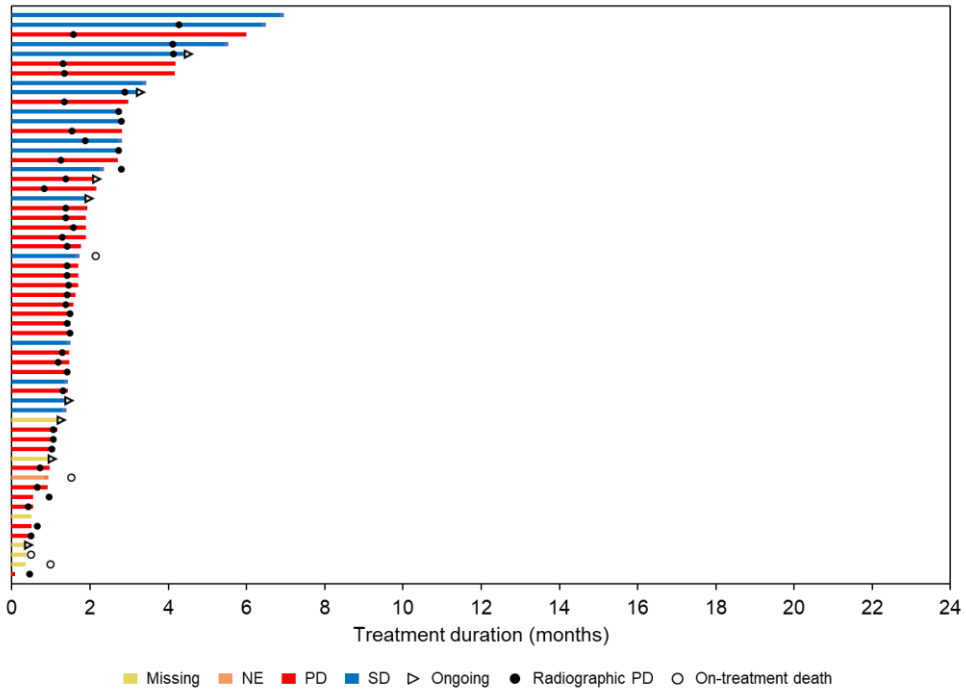
Figure 3: **Overall survival in the intent-to-treat population**



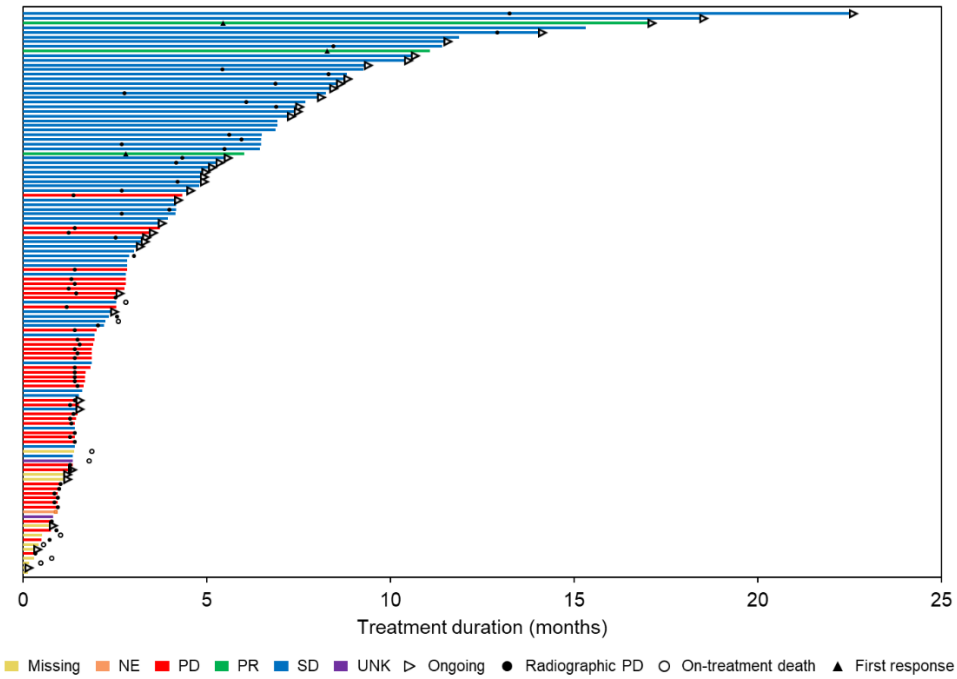
Patients without documentation of death at the time of the data cut-off date were censored at the date the patient was last known to be alive or the data cut-off date, whichever was earlier. The intent-to-treat population comprises all randomised patients, with the treatment group designated according to the randomisation. HR=hazard ratio. RPSFT=rank-preserving structural failure time.

Figure 4: **Treatment duration and response assessed by the independent radiology centre before crossover in the intent-to-treat population**

A Placebo



B Ivosidenib



(A) The swim lane plot of treatment duration and response assessed by the independent radiology centre for patients receiving placebo and (B) the swim lane plot of treatment duration and response assessed by the independent radiology centre for patients receiving ivosidenib. The median treatment duration was 2·6 months (IQR 1·4–6·0) for ivosidenib and 1·6 months (1·1–2·7) for placebo. Coloured bars represent the best overall response as determined by the independent radiology centre. PR required confirmation per Response Evaluation Criteria in Solid Tumors version 1·1. SD occurring <38 days from the randomisation date was considered to be unknown. Filled circles indicate the progression date if the patient had radiographic progression. Patients who did not have disease progression determined by the independent radiology centre are indicated with an open circle at the date of death while receiving treatment. NE=not evaluable. PD=progressive disease. PR=partial response. SD=stable disease. UNK=unknown.

***Table 1*: Demographic and baseline characteristics**

	Ivosidenib (n=124)	Placebo (n=61)	Total (n=185)
Characteristic			
Female/male	80/44	37/24	117/68
Age, years	61 (33–80)	63 (40–83)	62 (33–83)
Randomisation stratum			
One prior line of therapy	66 (53%)	33 (54%)	99 (54%)
Two prior lines of therapy	58 (47%)	28 (46%)	86 (46%)
ECOG PS			
0	49 (40%)	19 (31%)	68 (37%)
1	74 (60%)	41 (67%)	115 (62%)
2	0	1 (2%)	1 (1%)
3	1 (1%)	0	1 (1%)
Cholangiocarcinoma type at diagnosis			
Intrahepatic	111 (90%)	58 (95%)	169 (91%)
Extrahepatic	1 (1%)	1 (2%)	2 (1%)
Perihilar	4 (3%)	0	4 (2%)
Unknown	8 (6%)	2 (3%)	10 (5%)
Extent of disease at screening			
Local/regional	9 (7%)	5 (8%)	14 (8%)
Metastatic	115 (93%)	56 (92%)	171 (92%)
Liver cirrhosis at screening			
Yes	6 (5%)	3 (5%)	9 (5%)
Hepatitis B	1 (1%)	0	1 (1%)
Hepatitis C	0	1 (2%)	1 (1%)
Alcohol	1 (1%)	0	1 (1%)
Other	4 (3%)	2 (3%)	6 (3%)
No	118 (95%)	58 (95%)	176 (95%)
IDH1 mutation			
R132C	84 (68%)	45 (74%)	129 (70%)
R132L	21 (17%)	7 (11%)	28 (15%)
R132G	17 (14%)	6 (10%)	23 (12%)
R132S	2 (2%)	1 (2%)	3 (2%)
R132H	0	2 (3%)	2 (1%)
CA19-9 levels at baseline*, units/mL	42·0 (0–18 560)[†]	39·0 (0·1–11 529)[†]	..

Data are median (range) or n (%).*From patients included in the safety analysis set, before crossover. [†]Placebo, n=59; ivosidenib, n=121. ECOG PS=Eastern Cooperative Oncology Group Performance Status.

***Table 2*: Treatment-emergent adverse events**

	Ivosidenib (n=121)				**Placebo (n=59)**			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Nausea	40 (33)	3 (2)	0	0	14 (24)	1 (2)	0	0
Diarrhoea	37 (31)	0	0	0	9 (15)	0	0	0
Fatigue	28 (23)	4 (3)	0	0	9 (15)	1 (2)	0	0
Cough	25 (21)	0	0	0	5 (8)	0	0	0
Abdominal pain	23 (19)	3 (2)	0	0	7 (12)	1 (2)	0	0
Decreased appetite	21 (17)	2 (2)	0	0	11 (19)	0	0	0
Vomiting	20 (17)	3 (2)	0	0	10 (17)	0	0	0
Ascites	16 (13)	9 (7)	0	0	5 (8)	4 (7)	0	0
Asthenia	15 (12)	0	0	0	6 (10)	2 (3)	0	0
Constipation	15 (12)	0	0	0	10 (17)	0	0	0
Oedema peripheral	15 (12)	0	0	0	6 (10)	0	0	0
Pyrexia	15 (12)	0	0	0	6 (10)	0	0	0
Anaemia	14 (12)	4 (3)	0	0	3 (5)	0	0	0
Headache	13 (11)	0	0	0	4 (7)	0	0	0
Dyspnoea	12 (10)	1 (1)	0	0	7 (12)	2 (3)	0	0
Abdominal distension	10 (8)	1 (1)	0	0	5 (8)	0	0	0
Electrocardiogram QT prolonged	10 (8)	1 (1)	0	0	1 (2)	0	0	0
Back pain	10 (8)	0	0	0	4 (7)	1 (2)	0	0
Alanine aminotransferase increased	8 (7)	2 (2)	0	0	1 (2)	0	0	0
Hypokalaemia	8 (7)	1 (1)	0	0	2 (3)	0	1 (2)	0
Insomnia	8 (7)	1 (1)	0	0	3 (5)	0	0	0
Aspartate aminotransferase increased	7 (6)	6 (5)	0	0	2 (3)	1 (2)	0	0
Blood alkaline phosphatase increased	7 (6)	3 (2)	0	0	3 (5)	3 (5)	0	0

Hypoalbuminaemia	7 (6)	0	0	0	3 (5)	1 (2)	0	0
Hyponatraemia	6 (5)	4 (3)	2 (2)	0	1 (2)	5 (8)	1 (2)	0
White blood cell count decreased	6 (5)	2 (2)	0	0	1 (2)	0	0	0
Arthralgia	6 (5)	1 (1)	0	0	4 (7)	0	0	0
Weight decreased	6 (5)	1 (1)	0	0	1 (2)	1 (2)	0	0
Hypertension	6 (5)	0	0	0	1 (2)	1 (2)	0	0
Blood bilirubin increased	5 (4)	7 (6)	0	0	3 (5)	1 (2)	0	0
Pleural effusion	4 (3)	1 (1)	1 (1)	0	2 (3)	0	0	0
Confusional state	4 (3)	1 (1)	0	0	4 (7)	0	0	0
Pruritus	4 (3)	1 (1)	0	0	2 (3)	0	0	0
Urinary tract infection	4 (3)	1 (1)	0	0	1 (2)	0	0	0
Hyperkalaemia	3 (2)	3 (2)	0	0	3 (5)	2 (3)	0	0
Hyperbilirubinaemia	3 (2)	1 (1)	2 (2)	0	0	0	0	0
Platelet count decreased	2 (2)	3 (2)	0	0	3 (5)	0	0	0
Fall	2 (2)	2 (2)	0	0	1 (2)	0	0	0
Hypercalcaemia	2 (2)	1 (1)	0	0	5 (8)	1 (2)	0	0
Rash maculo-papular	2 (2)	1 (1)	0	0	3 (5)	0	0	0
Thrombocytopenia	2 (2)	1 (1)	0	0	2 (3)	0	0	0
Dysphagia	2 (2)	0	1 (1)	0	2 (3)	0	0	0
Lymphocyte count decreased	2 (2)	0	0	0	0	2 (3)	0	0
Dehydration	1 (1)	4 (3)	0	0	1 (2)	1 (2)	0	0
Hypophosphataemia	1 (1)	3 (2)	0	0	0	3 (5)	0	0
Pneumonia	1 (1)	2 (2)	0	1 (1)	0	1 (2)	0	0
Acute kidney injury	1 (1)	2 (2)	0	0	1 (2)	0	0	0
Jaundice	1 (1)	2 (2)	0	0	0	0	0	0
Pain	1 (1)	2 (2)	0	0	1 (2)	0	0	0
Hypotension	1 (1)	1 (1)	0	0	1 (2)	1 (2)	0	0
Rectal haemorrhage	1 (1)	1 (1)	0	0	0	0	0	0

Transaminases increased	1 (1)	1 (1)	0	0	0	0	0	0
Abdominal pain lower	1 (1)	0	0	0	0	1 (2)	0	0
Hepatic cirrhosis	1 (1)	0	0	0	0	1 (2)	0	0
Jaundice cholestatic	0	2 (2)	1 (1)	0	0	0	0	0
Cholangitis	0	2 (2)	0	0	0	0	0	0
Hepatic failure	0	2 (2)	0	0	0	1 (2)	0	0
Abdominal infection	0	1 (1)	1 (1)	0	0	0	0	0
Intestinal obstruction	0	1 (1)	0	1 (1)	0	0	0	0
Neutrophil count decreased	0	0	2 (2)	0	0	0	0	0
Bile duct obstruction	0	1 (1)	0	0	0	0	0	0
Bile duct stenosis	0	1 (1)	0	0	0	0	0	0
Biliary sepsis	0	1 (1)	0	0	0	0	0	0
Cachexia	0	1 (1)	0	0	0	0	0	0
Cholangitis acute	0	1 (1)	0	0	0	0	0	0
Cognitive disorder	0	1 (1)	0	0	0	0	0	0
Device-related infection	0	1 (1)	0	0	0	0	0	0
Encephalopathy	0	1 (1)	0	0	0	0	0	0
Escherichia bacteraemia	0	1 (1)	0	0	0	0	0	0
Failure to thrive	0	1 (1)	0	0	0	0	0	0
Gastroenteritis	0	1 (1)	0	0	0	0	0	0
Gastrointestinal haemorrhage	0	1 (1)	0	0	0	0	0	0
Hip fracture	0	1 (1)	0	0	0	0	0	0
Malnutrition	0	1 (1)	0	0	0	0	0	0
Mental status changes	0	1 (1)	0	0	0	0	0	0
Muscular weakness	0	1 (1)	0	0	2 (3)	0	0	0
Parainfluenzae virus infection	0	1 (1)	0	0	0	0	0	0
Portal vein thrombosis	0	1 (1)	0	0	0	0	0	0
Restlessness	0	1 (1)	0	0	1 (2)	0	0	0

Staphylococcal infection	0	1 (1)	0	0	0	0	0	0
Upper gastrointestinal haemorrhage	0	1 (1)	0	0	0	0	0	0
Vascular access complication	0	1 (1)	0	0	0	0	0	0
Arterial injury	0	0	1 (1)	0	0	0	0	0
Gamma-glutamyltransferase increased	0	0	1 (1)	0	0	0	1 (2)	0
Pulmonary embolism	0	0	0	1 (1)	0	0	0	0
Sepsis	0	0	0	1 (1)	0	0	2 (3)	0

Data are n (%), where n is the number of patients who experienced that TEAE and grade combination. TEAE is defined as any adverse event that occurred between the first dose of any study drug and 28 days following the last dose. All grade 3-5 TEAEs that occurred before crossover, along with their corresponding grade 1-2 TEAEs, are shown. TEAEs that occurred after crossover from the placebo group to the ivosidenib group are not listed here and are reported in the appendix (p 20). TEAEs are sorted in descending frequency based on the grade 1-2 column for ivosidenib. TEAE=treatment-emergent adverse event.