JAMA Oncology | Original Investigation

Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With *IDH1* Mutation
The Phase 3 Randomized Clinical ClarIDHy Trial

Andrew X. Zhu, MD, PhD; Teresa Macarulla, MD; Milind M. Javle, MD; R. Kate Kelley, MD; Sam J. Lubner, MD; Jorge Adeva, MD; James M. Cleary, MD; Daniel V. T. Catenacci, MD; Mitesh J. Borad, MD; John A. Bridgewater, PhD; William P. Harris, MD; Adrian G. Murphy, MD; Do-Youn Oh, MD; Jonathan R. Whisenant, MD; Maeve A. Lowery, MD; Lipika Goyal, MD; Rachna T. Shroff, MD; Anthony B. El-Khoueiry, MD; Christina X. Chamberlain, PhD; Elia Aguado-Fraile, PhD; Sung Choe, PhD; Bin Wu, PhD; Hua Liu, PhD; Camelia Gliser, BS; Shuchi S. Pandya, MD; Juan W. Valle, MD; Ghassan K. Abou-Alfa, MD

IMPORTANCE Isocitrate dehydrogenase 1 (*IDH1*) variations occur in up to approximately 20% of patients with intrahepatic cholangiocarcinoma. In the ClarIDHy trial, progression-free survival as determined by central review was significantly improved with ivosidenib vs placebo.

OBJECTIVE To report the final overall survival (OS) results from the ClarIDHy trial, which aimed to demonstrate the efficacy of ivosidenib (AG-120)—a first-in-class, oral, small-molecule inhibitor of mutant IDH1—vs placebo for patients with unresectable or metastatic cholangiocarcinoma with *IDH1* mutation.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, randomized, double-blind, placebo-controlled, clinical phase 3 trial was conducted from February 20, 2017, to May 31, 2020, at 49 hospitals across 6 countries among patients aged 18 years or older with cholangiocarcinoma with *IDH1* mutation whose disease progressed with prior therapy.

INTERVENTIONS Patients were randomized 2:1 to receive ivosidenib, 500 mg, once daily or matched placebo. Crossover from placebo to ivosidenib was permitted if patients had disease progression as determined by radiographic findings.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival as determined by blinded independent radiology center (reported previously). Overall survival was a key secondary end point. The primary analysis of OS followed the intent-to-treat principle. Other secondary end points included objective response rate, safety and tolerability, and quality of life.

RESULTS Overall, 187 patients (median age, 62 years [range, 33-83 years]) were randomly assigned to receive ivosidenib (n = 126; 82 women [65%]; median age, 61 years [range, 33-80 years]) or placebo (n = 61; 37 women [61%]; median age, 63 years [range, 40-83 years]); 43 patients crossed over from placebo to ivosidenib. The primary end point of progression-free survival was reported elsewhere. Median OS was 10.3 months (95% CI, 7.8-12.4 months) with ivosidenib vs 7.5 months (95% CI, 4.8-11.1 months) with placebo (hazard ratio, 0.79 [95% CI, 0.56-1.12]; 1-sided $P = .09$). When adjusted for crossover, median OS with placebo was 5.1 months (95% CI, 3.8-7.6 months; hazard ratio, 0.49 [95% CI, 0.34-0.70]; 1-sided $P < .001$). The most common grade 3 or higher treatment-emergent adverse event (≥5%) reported in both groups was ascites (11 patients [9%] receiving ivosidenib and 4 patients [7%] receiving placebo). Serious treatment-emergent adverse events considered ivosidenib related were reported in 3 patients (2%). There were no treatment-related deaths. Patients receiving ivosidenib reported no apparent decline in quality of life compared with placebo.

CONCLUSIONS AND RELEVANCE This randomized clinical trial found that ivosidenib was well tolerated and resulted in a favorable OS benefit vs placebo, despite a high rate of crossover. These data, coupled with supportive quality of life data and a tolerable safety profile, demonstrate the clinical benefit of ivosidenib for patients with advanced cholangiocarcinoma with *IDH1* mutation.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02989857

JAMA Oncol. 2021;7(11):1669-1677. doi:10.1001/jamaoncol.2021.3836
Published online September 23, 2021.

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Ghassan K. Abou-Alfa, MD, Department of Medicine, Memorial Sloan Kettering Cancer Center, 300 E 66th St, New York, NY 10022 (abou-alg@mskcc.org); Andrew X. Zhu, MD, PhD, Department of Medicine, Massachusetts General Hospital Cancer Center, Harvard Medical School, 55 Fruit St, Boston, MA 02114 (andrew.zhu@jiahui.com).

Downloaded from jamanetwork.com by guest on 12/17/2025

Cholangiocarcinomas are rare, aggressive tumors, with an increasing incidence (mainly of the intrahepatic subgroup) and poor prognosis.[1,2] The median survival among patients with advanced disease is approximately less than 12 months,[3-5] with 5-year survival rates of 10% or less.[4] Most patients with unresectable or metastatic disease undergo palliative systemic therapy.[2] Chemotherapy remains the primary treatment option for cholangiocarcinoma management, with a combination of gemcitabine and cisplatin as the current first-line standard of care,[3] and FOLFOX (folinic acid, fluorouracil, and oxaliplatin) recommended as the second-line standard of care.[2] However, survival outcomes with first- or second-line chemotherapy are modest.[3,6,7] Some agents are approved for specific molecularly defined subsets of cholangiocarcinoma (eg, cholangiocarcinoma with fibroblast growth factor receptor [FGFR] fusions, with neurotrophic tyrosine receptor kinase fusions, or microsatellite instability-high cancer); however, isocitrate dehydrogenase 1 (*IDH1*; OMIM 147700) mutations rarely occur in these subgroups.[8-11] There is only 1 currently approved targeted treatment for patients with unresectable and metastatic cholangiocarcinoma.[12,13] These factors highlight the need for new treatment paradigms in this disease.[2,4]

Mutations in the metabolic enzyme IDH1 are detected in approximately 13% of intrahepatic cholangiocarcinomas and 1% of extrahepatic cholangiocarcinomas.[14] Mutations of *IDH1* play a central role in cholangiocarcinoma pathogenesis but are not associated with prognosis.[14,15] Ivosidenib (AG-120) is an oral, potent, targeted inhibitor of the *IDH1* variant, approved for the treatment of acute myeloid leukemia in subsets of patients with a susceptible *IDH1* variant.[16,17] In a phase 1, dose-escalation and expansion study (NCT02073994), ivosidenib treatment resulted in a median progression-free survival (PFS) of 3.8 months and median overall survival (OS) of 13.8 months, along with a well-tolerated safety profile, among 72 patients with heavily treated advanced cholangiocarcinoma with *IDH1* mutation.[18] These data supported further evaluation of ivosidenib in the randomized, double-blind, placebo-controlled phase 3 clinical ClarIDHy trial, which enrolled patients with previously treated cholangiocarcinoma with *IDH1* mutation. As of the January 31, 2019, data cutoff, the primary objective of the ClarIDHy trial was met, with a statistically significant improvement in PFS with ivosidenib compared with placebo (hazard ratio [HR], 0.37 [95% CI, 0.25-0.54]; 1-sided $P < .001$ by independent radiology center; HR, 0.47 [95% CI, 0.33-0.68]; 1-sided $P < .001$ by investigator).[19] The disease control rate observed with ivosidenib was due mostly to the stable disease rate (an objective response rate of 2% [3 partial responses] and a stable disease rate of 51% with ivosidenib vs an objective response rate of 0% and a stable disease rate of 28% with placebo). Final analyses of OS data from the ClarIDHy trial (final data cutoff: May 31, 2020), along with updated safety, additional baseline comutation data, and quality of life (QOL) data, are reported herein.

Key Points

Question Does ivosidenib treatment improve overall survival outcomes vs placebo among patients with chemotherapy-refractory cholangiocarcinoma with *IDH1* mutation?

Findings In this phase 3 randomized clinical trial including 187 previously treated patients with advanced cholangiocarcinoma with *IDH1* mutation, ivosidenib treatment resulted in numerically improved overall survival benefits vs placebo, despite a high rate of crossover. Ivosidenib preserved certain quality of life subscales and was well tolerated.

Meaning The combined efficacy data and tolerable safety profile, as well as corroborating quality of life data, support the clinical benefit of ivosidenib relative to placebo in cholangiocarcinoma with *IDH1* mutation, which has an unmet need for new treatments.

Methods

Study Design and Participants

The phase 3 ClarIDHy trial design has been reported previously.[19] This study was conducted from February 20, 2017, to May 31, 2020, at 49 hospitals across 6 countries (France, Italy, South Korea, Spain, the United Kingdom, and the United States),[19] among patients aged 18 years or older with histologically confirmed cholangiocarcinoma with *IDH1* mutation. Patients must have had documented disease progression after at least 1 but no more than 2 prior treatment regimens for advanced disease (nonresectable or metastatic), including gemcitabine or a fluorouracil-based chemotherapy regimen, and received no prior *IDH*-variant inhibitor therapy. Additional key eligibility criteria included an Eastern Cooperative Oncology Group performance status score of 0 or 1; an expected survival of at least 3 months; and adequate bone marrow, hepatic, and kidney function. Patient *IDH1*-variant status was confirmed centrally and prospectively by next-generation sequencing on formalin-fixed paraffin-embedded tumor tissue specimens using the Oncomine Focus Assay (Thermo Fisher Scientific) in a Clinical Laboratory Improvement Amendments–certified laboratory. Patients were evaluated for eligibility and enrolled by the participating investigators at the trial centers. This trial was conducted according to the International Conference on Harmonization of Good Clinical Practice guidelines and principles of the Declaration of Helsinki.[20] Approval from the institutional review board and independent ethics committee was obtained at each study site. All patients provided written informed consent before participating in the trial. Information on racial and ethnic categories reported by patients to the study team or from medical records was captured as part of the clinical database for this study according to applicable local regulation. An independent data and safety monitoring board regularly reviewed the safety data to ensure the safety of treatment and proper trial conduct. This trial is registered with ClinicalTrials.gov (NCT02989857). The complete study protocol is available in Supplement 1.

Downloaded from jamanetwork.com by guest on 12/17/2025

Randomization and Masking

Randomization and masking details have been described previously.[19] In brief, patients were randomly assigned 2:1 to receive ivosidenib or matched placebo, with a block size of 6, and stratified by number of previous systemic treatment regimens for advanced disease (1 vs 2).

Procedures

Procedures followed in the ClarIDHy trial were described previously.[19] Ivosidenib, 500 mg, or matched placebo were given orally once daily in continuous 28-day cycles. Treatment continued until disease progression as determined by the investigator, development of other unacceptable toxic effects, confirmed pregnancy, death, withdrawal of consent, loss to follow-up, or trial unblinding or ending. Crossover from the placebo group to the ivosidenib group was allowed for patients with disease progression as confirmed by radiography, per investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[21] Once the primary end point of PFS was met, any patients still receiving placebo were permitted to cross over to the ivosidenib group if they continued to meet eligibility criteria. Radiographic assessment (computed tomography or magnetic resonance imaging) for evaluation of disease response was conducted from day 1 of cycle 1 every 6 weeks (±5 days) through week 48, and every 8 weeks (±5 days) thereafter. Adverse events are reported for patients before crossover, unless otherwise specified.

Outcomes

The primary end point was PFS as determined by blinded independent radiology center per RECIST, version 1.1, and was reported elsewhere.[19] Overall survival, defined as the time from date of randomization to the date of death due to any cause, was a key secondary end point. Patients alive at the analysis cutoff date were censored at the date of last contact. Other secondary end points included objective response rate, PFS per investigator assessment, safety and tolerability, and QOL assessed using change from baseline on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the cholangiocarcinoma and gallbladder cancer module (EORTC QLQ-BIL21) scores and the Patient Global Impression of Change (PGI-C) and Patient Global Impression of Severity (PGI-S) anchor questions; health economic outcomes were assessed using the 5-level EuroQoL 5-dimension (EQ-5D-5L).[22-25] Three QOL domains of interest were prespecified in the statistical analysis plan: physical functioning, pain, and appetite loss. Safety was evaluated by the incidence, severity, and type of treatment-emergent adverse events (TEAEs) (per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03),[26] as described previously.[19]

Statistical Analysis

Overall survival was the first key secondary end point specified in the fixed-sequence testing strategy. It was tested only after statistical significance for PFS, as assessed by the independent radiology center, was achieved, to control the overall type I error in the trial at the 1-sided significance level of .025. Overall survival was planned to be analyzed twice: at the time of the primary PFS analysis and after 150 OS events had been reached (final OS analysis) (eMethods in Supplement 2). Overall survival was compared between the 2 groups by using the 1-sided log-rank test. The HR was estimated from the Cox proportional hazards regression model. The primary analysis of OS followed the intent-to-treat principle, which does not account for the effect of crossover. Consequently, the prespecified rank-preserving structural failure time (RPSFT) model was used to adjust for crossover.[27-29] The RPSFT method is based on a common treatment assumption: the treatment effect of ivosidenib is the same for all individuals, regardless of when treatment is received.[27-29]

Descriptive statistics were used to summarize safety and comutation data. Details on QOL analysis are provided in the eMethods in Supplement 2.

Results

Patients

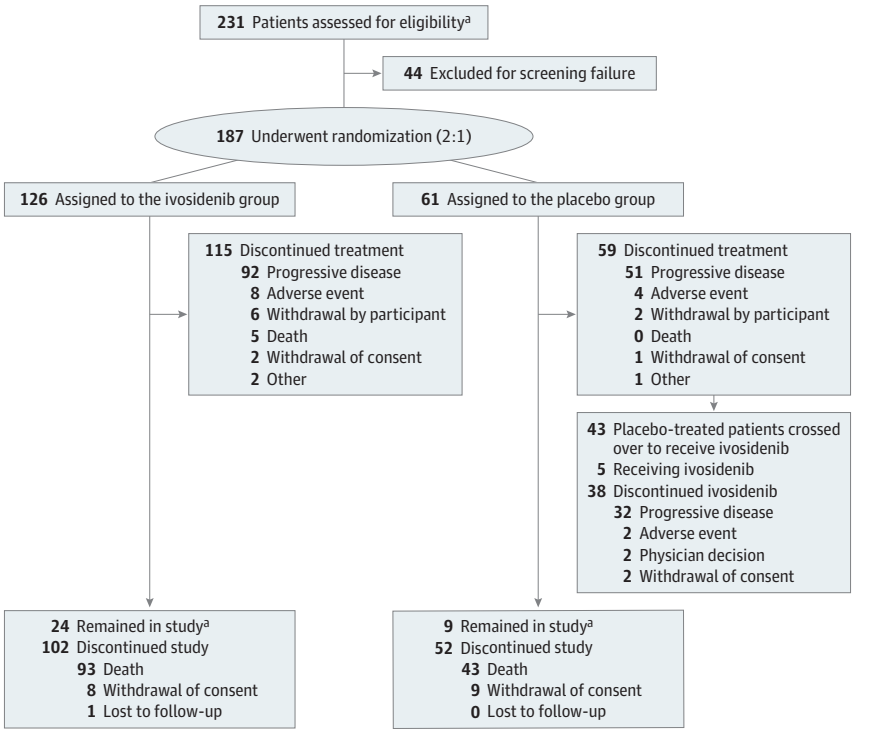
Overall, 231 patients were assessed for eligibility between February 20, 2017, and March 1, 2019. As of May 31, 2020 (data cutoff date for the final OS analysis), 187 patients (median age, 62 years [range, 33-83 years]; American Indian or Alaska Native patients, 1 [0.5%], Asian patients, 23 [12%], Black or African American patients, 2 [1%], Native Hawaiian or other Pacific Islander patients, 1 [0.5%], White patients, 106 [57%], other race, 1 [0.5%], race not reported, 1 [0.5%], missing race, 52 [28%], Hispanic or Latino patients, 9 [5%], not Hispanic or Latino patients, 124 [66%], ethnicity not reported, 2 [1%], missing ethnicity, 52 [28%]) had been randomly assigned to receive ivosidenib (n = 126; 82 women [65%]; median age, 61 years [range, 33-80 years]) or placebo (n = 61; 37 women [61%]; median age, 63 years [range, 40-83 years]). The patient flow diagram is shown in **Figure 1**. Baseline demographic and disease characteristics were similar in the ivosidenib group and the placebo group (**Table**). Among all 187 patients, 173 (93%) had metastatic disease, and 88 (47%) had received 2 prior lines of therapy; R132C was the most prevalent *IDH1* variant (131 patients [70%]) (Table). As of the data cutoff date, 43 patients (70%) originally randomly assigned to receive placebo had crossed over to receive open-label ivosidenib.

Efficacy

Based on 150 OS events (100 for ivosidenib [79%] and 50 for placebo [82%]), the median OS was 10.3 months (95% CI, 7.8-12.4 months) with ivosidenib and 7.5 months (95% CI, 4.8-11.1 months) with placebo (HR, 0.79 [95% CI, 0.56-1.12]; 1-sided $P = .09$) (**Figure 2**A).[30] The RPSFT-adjusted median OS was 5.1 months (95% CI, 3.8-7.6 months) with placebo (HR, 0.49 [95% CI, 0.34-0.70]; 1-sided $P < .001$). The 12-month survival rate was 43% (95% CI, 34%-51%) for the ivosidenib group vs 36% (95% CI, 24%-48%) for the placebo group. Overall survival benefit by subgroup is reported in the eResults and eFigure 1 in Supplement 2. The OS data were mature; 37 patients were censored (26 of 126 patients [21%] in the ivosidenib group and 11 of 61 patients [18%] in the placebo group). The maxi-

Downloaded from jamanetwork.com by guest on 12/17/2025

Figure 1. CONSORT Diagram



[a] As of the data cutoff date (May 31, 2020).

mum treatment duration with ivosidenib was 34.4 months (range, 0.1-34.4 months) vs 6.9 months (range, 0-6.9 months) with placebo. The median treatment duration was 2.8 months (range, 0.1-34.4 months) for the ivosidenib group (n = 123) and 1.6 months (range, 0-6.9 months) for the placebo group (n = 59) (Figure 2B and C). The median treatment duration for the ivosidenib group after 43 patients crossed over from the placebo group was 2.7 months (range, 0.3-29.8 months) (Figure 2C). Treatment duration appeared to be longer for patients with plasma D-2-hydroxyglutarate levels below 100 ng/mL after 1 cycle of ivosidenib treatment (eMethods and eFigure 2 in Supplement 2). A total of 25 of 166 patients (15%), including 6 patients who crossed over from the placebo group, remained in the ivosidenib group for at least 1 year.

Safety

The most common all-grade TEAE in both treatment groups before crossover was nausea (51 of 123 patients [42%] who received ivosidenib and 17 of 59 patients [29%] who received placebo) (eTable 1 in Supplement 2). The most common grade 3 or higher TEAE reported in both treatment groups was ascites (11 patients [9%] who received ivosidenib and 4 patients [7%] who received placebo) (eTable 2 in Supplement 2). Other most common grade 3 or higher TEAEs (≥5%) with ivosidenib vs placebo were anemia (8 patients [7%] vs 0 patients), increased blood bilirubin level (7 patients [6%] vs 1 patient [2%]), and hyponatremia (7 patients [6%] vs 6 patients [10%]).

Six patients (5%) receiving ivosidenib experienced a TEAE leading to death, none of which were assessed by the investigator as being associated with treatment, and were considered to be complications associated with the underlying disease or comorbid conditions. Serious TEAEs were reported for 42 patients (34%) receiving ivosidenib and were considered associated with treatment for 3 patients (2%) (grade 4 hyperbilirubinemia, grade 3 cholestatic jaundice, grade 2 prolonged QT interval on electrocardiogram, and grade 3 pleural effusion; hyperbilirubinemia and cholestatic jaundice were observed in the same patient). These patients were the same 3 reported previously.[19] Serious TEAEs were reported for 14 patients (24%) receiving placebo; none were associated with treatment.

Prolonged QT interval on electrocardiogram, a TEAE of special interest, was reported for 12 patients (10%) receiving ivosidenib and 2 patients (3%) receiving placebo. Treatment-emergent adverse events requiring a dose reduction and interruption were uncommon, with 5 patients (4%) in the ivosidenib group requiring a dose reduction vs none in the placebo group. Treatment-emergent adverse events leading to study drug discontinuation occurred for 9 patients (7%) in the ivosidenib group vs 5 patients (8%) in the placebo group.

Quality of Life

The numbers of patients with available EORTC QLQ-C30 and EORTC QLQ-BIL21 assessments at baseline, day 1 of cycle 2, and day 1 of cycle 3 are provided in eTable 3 in Supplement 2 and missing data are described in the eResults in Supplement 2. Ivosidenib preserved QLQ-C30 physical functioning (where a higher score denotes better functioning), whereas patients receiving placebo experienced declines from baseline at day 1 of cycle 2 and day 1 of cycle 3 (eFigures 3 and 4 in Supplement 2). At day 1 of cycle 2, the least-squares mean (SE) change

Downloaded from jamanetwork.com by guest on 12/17/2025

from baseline was -2.4 (1.8) for ivosidenib vs -13.3 (3.0) for placebo, with a least-squares mean difference in change from baseline for ivosidenib vs placebo of 11.0 (95% CI, 4.2-17.7; 2-sided $P = .002$) (eTable 4 in Supplement 2). The decline in physical functioning at day 1 of cycle 2 was clinically meaningful only in the placebo group, based on the threshold estimated using anchor-based methods described previously.[19] At day 1 of cycle 3, the least-squares mean (SE) change from baseline was -0.2 (1.9) for ivosidenib vs -12.6 (3.9) for placebo, with a least-squares mean difference in change from baseline for ivosidenib vs placebo of 12.3 (95% CI, 3.9-20.8; 2-sided $P = .004$) (eTable 5 in Supplement 2). Ivosidenib was favored on the QLQ-C30 pain subscale (where a higher score denotes worse symptoms) at day 1 of cycle 2 (least-squares mean difference in change from baseline for ivosidenib vs placebo, -10.4 [95% CI, -20.2 to -0.5]; 2-sided $P = .04$). Neither group was favored on other prespecified subscales (QLQ-C30 appetite loss and QLQ-BIL21 pain and eating). For the exploratory QOL analyses, $P \leq .05$ was considered to indicate a difference between groups. At day 1 of cycle 2, ivosidenib was favored for all other subscales in which differences were observed, including QLQ-C30 emotional functioning, cognitive functioning, and dyspnea and QLQ-BIL21 anxiety and tiredness (eFigure 3 in Supplement 2). At day 1 of cycle 3, the difference in the QLQ-C30 emotional functioning subscale persisted, favoring ivosidenib (eFigure 4 in Supplement 2). Findings for the PGI-C and EQ-5D-5L assessments were reported previously.[19,31]

Baseline Covariant Analyses

All screened patients underwent a determination of variant *IDH1* status and identification of covariants in archival formalin-fixed paraffin-embedded samples using a 52-gene next-generation sequencing panel (Oncomine Focus Assay). Tumor tissue specimens were collected from 0.3 months up to 7.5 years before randomization (median, 3.7 months). The covariants identified among the 187 enrolled patients are shown in eTable 6 in Supplement 2. The most frequent oncogenic covariants found in this data set were *PI3KCA* (n = 20 [11%]), *KRAS* (n = 14 [8%]), *BRAF* (n = 8 [4%]), and *FGFR2* (n = 8 [4%]). These findings are consistent with covariant analyses reported previously in a phase 1 study of ivosidenib.[18] All detected *FGFR2* covariants were short variants; the common intrahepatic cholangiocarcinoma *FGFR2* fusion partner genes (*BICC1*, *MGEA5*, and *TACC3*) are not specifically targeted in the Oncomine Focus Assay panel. No significant association was observed between baseline covariants in any single gene and OS, PFS, or treatment duration (eFigure 5 in Supplement 2).

Discussion

To our knowledge, this is the first randomized phase 3 trial demonstrating the clinical benefit of targeting the *IDH1* variant for patients with advanced cholangiocarcinoma with *IDH1* mutation or any other solid tumor with *IDH1* mutation. Ivosidenib demonstrated a 63% reduction in the risk of progression or death (HR, 0.37 [95% CI, 0.25-0.54]; 1-sided $P < .001$) compared with placebo among patients previously treated with

Table. Demographic and Baseline Characteristics

Characteristic	Patients, No. (%)	
	Ivosidenib (n = 126)	Placebo (n = 61)
Sex		
Female	82 (65)	37 (61)
Male	44 (35)	24 (39)
Age, median (range), y	61 (33-80)	63 (40-83)
Race		
American Indian or Alaska Native	1 (1)	0
Asian	15 (12)	8 (13)
Black or African American	1 (1)	1 (2)
Native Hawaiian or other Pacific Islander	1 (1)	0
White	71 (56)	35 (57)
Other	1 (1)	0
Not reported	1 (1)	0
Missing	35 (28)	17 (28)
Ethnicity		
Hispanic or Latino	7 (6)	2 (3)
Not Hispanic or Latino	84 (67)	40 (66)
Not reported	0	2 (3)
Missing	35 (28)	17 (28)
Randomization strata, prior line of therapy		
1	66 (52)	33 (54)
2	60 (48)	28 (46)
IDH1 mutation		
R132C	86 (68)	45 (74)
R132L	21 (17)	7 (11)
R132G	17 (13)	6 (10)
R132S	2 (2)	1 (2)
R132H	0	2 (3)
ECOG PS score at baseline		
0	50 (40)	19 (31)
1	75 (60)	41 (67)
2	0	1 (2)
3	1 (1)	0
Cholangiocarcinoma type at diagnosis		
Intrahepatic	113 (90)	58 (95)
Extrahepatic or perihilar	5 (4)	1 (2)
Unknown	8 (6)	2 (3)
Extent of disease at screening		
Local or regional	9 (7)	5 (8)
Metastatic	117 (93)	56 (92)
Presence at screening		
Ascites	34 (27)	13 (21)
Biliary stent	13 (10)	7 (11)
CA19-9 levels at baseline, median (range), U/mL[a]	41.5 (0-61 200)[b]	39 (0.1-11 529)[b]

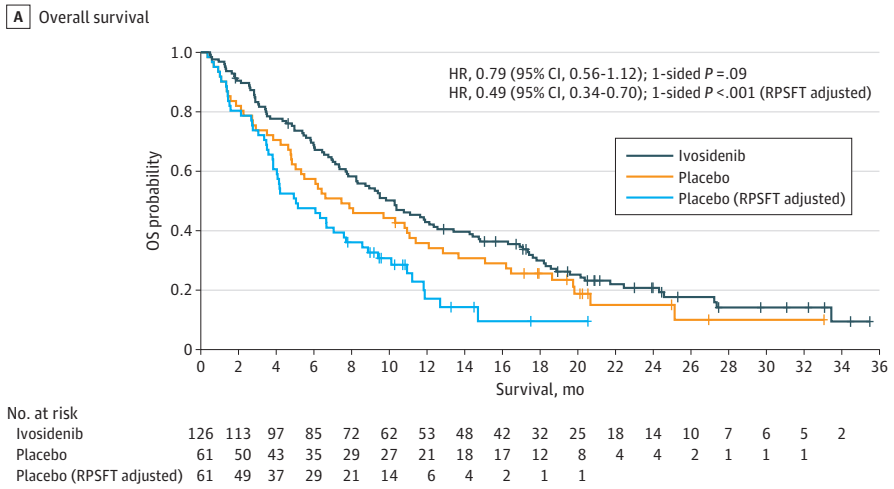
Abbreviations: CA19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; *IDH1*, isocitrate dehydrogenase 1.

[a] Patients included in the safety analysis set, before crossover.

[b] Placebo, n = 59; ivosidenib, n = 123.

Downloaded from jamanetwork.com by guest on 12/17/2025

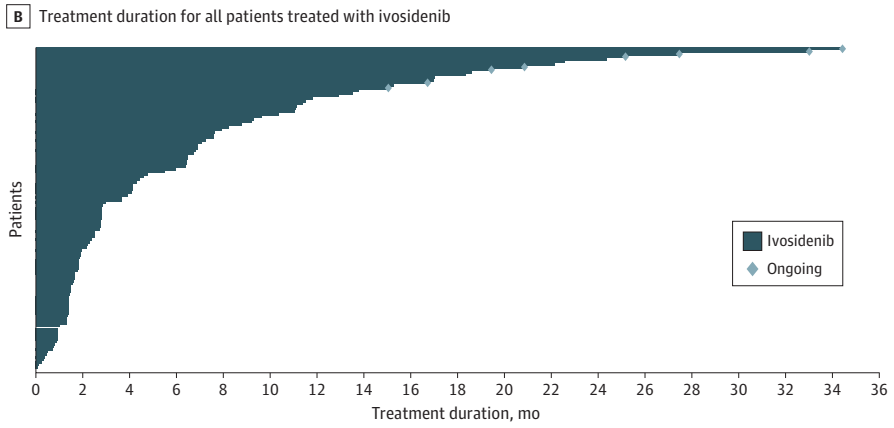
Figure 2. Overall Survival and Treatment Duration in the Intent-to-Treat Population

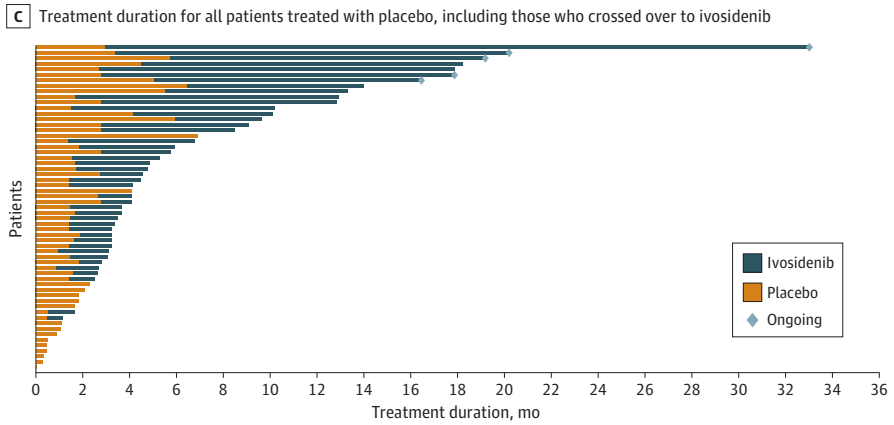


No. at risk

Ivosidenib	126	113	97	85	72	62	53	48	42	32	25	18	14	10	7	6	5	2
Placebo	61	50	43	35	29	27	21	18	17	12	8	4	4	2	1	1	1	
Placebo (RPSFT adjusted)	61	49	37	29	21	14	6	4	2	1	1							

Treatment group	Events/patients, No.	OS, median (95% CI), mo
Ivosidenib	100/126	10.3 (7.8-12.4)
Placebo	50/61	7.5 (4.8-11.1)
Placebo adjusted by RPSFT	49/61	5.1 (3.8-7.6)





A, Overall survival in the intent-to-treat population. Reproduced from Zhu.[30] B, Median treatment duration with ivosidenib (n = 123), 2.8 months (range, 0.1-34.4 months). C, All patients treated with placebo are shown in orange (n = 59); those who crossed over to ivosidenib are shown in dark blue (n = 43). Median treatment duration with placebo, 1.6 months (range, 0-6.9 months); median treatment duration with ivosidenib after crossover, 2.7 months (range, 0.3-29.8 months). HR indicates hazard ratio; OS, overall survival; and RPSFT, rank-preserving structural failure time. Crosses indicate censoring.

[a] Patients without documentation of death at the data cutoff date were censored at the date the patient was last known to be alive or the data cutoff date, whichever was earlier.

chemotherapy.[19] In a previous report, the *IDH1*-variant allele fraction from plasma circulating tumor DNA and the plasma D-2-hydroxyglutarate levels were suppressed by ivosidenib,[32] further supporting the antitumor and pharmacodynamic effect of the drug. The robust improvement in PFS led to the addition of ivosidenib to contemporary treatment guidelines as a subsequent-line treatment option for patients with cholangiocarcinoma with *IDH1* mutation after disease progres-

Downloaded from jamanetwork.com by guest on 12/17/2025

sion: the NCCN Clinical Practice Guidelines in Oncology (see Additional Information in the end matter),[33] the *Thésaurus National de Cancérologie Digestive* guidelines (France),[34] and the *Associazione Italiana de Oncologia Medica* guidelines (Italy).[35]

To some extent, the population in this trial represents a real-world population in that patients receiving second-line and third-line treatment were included and there were no exclusions for comorbid conditions, such as ascites, pleural effusions, or biliary stents. In fact, more than 90% of patients had metastatic disease at baseline, and approximately 25% had baseline ascites. Progression-free survival among patients with advanced biliary cancer receiving second-line chemotherapy is approximately 2 to 3 months,[11,36,37] and chemotherapy may lead to cumulative toxic effects. Ivosidenib provides an alternative therapeutic option for patients in need of new noncytotoxic treatments that can target tumors, delay progression, preserve QOL, and potentially extend survival.

In this final analysis, ivosidenib numerically improved OS, despite a high rate of crossover from the placebo group (70%), and this improvement was further supported by the difference in OS vs placebo when adjusted for crossover (HR, 0.49 [95% CI, 0.34-0.70]; 1-sided $P < .001$). The median OS of 10.3 months compares favorably with the published literature on chemotherapy and other targeted agents for patients with advanced biliary tract cancer, for whom the median OS is approximately 6 months.[5,36,38,39] The 12-month survival rate was 43% for the ivosidenib group. In addition, QOL results tended to favor ivosidenib, with preservation of domains including physical and emotional functioning relative to worsening for patients in the placebo group through day 1 of cycle 3. The presence of comutations at baseline has been investigated in this data set to identify potential genes or biological pathways that may be associated with overall response with ivosidenib. The most common oncogenic comutations identified in this study were *PI3KCA*, *KRAS*, *BRAF*, and *FGFR2*, consistent with a previous report on ivosidenib.[18] No significant association was found between comutations in any single gene and OS, PFS, or treatment duration in this large data set—an important factor for this type of analysis—of patients with cholangiocarcinoma with *IDH1* mutation. These findings suggest that rational treatment combinations for this patient population may include *PI3K*-targeting agents but not agents targeting neurotrophic tyrosine receptor kinase fusions.

Limitations

Although the findings reported here herald a paradigm shift in the treatment of cholangiocarcinoma, the study has some limitations. It is very likely that the treatment effect estimate on the primary analysis of OS was confounded by the allowance of crossover. The option for crossover was included in the study design based on feedback from patient advocacy groups and clinicians. This study design feature supported the accrual of this rare biomarker-selected patient population. Moreover, analyses of the QOL data were limited by small sample sizes at day 1 of cycle 2 and day 1 of cycle 3 owing, in part, to rapid progression and subsequent withdrawal from the study, which is typical of this disease. Last, a limitation of the comutation analysis was the lack of on-study biopsies to understand mechanisms of resistance. Additional translational studies are under way to assess the relapse mechanisms using circulating tumor DNA sequencing.

Conclusions

Taken together, the efficacy data and tolerable safety profile, as well as supportive QOL data, demonstrate the clinical benefit of ivosidenib compared with placebo for patients with this aggressive disease in which there is an unmet need for new therapies.

ARTICLE INFORMATION

Accepted for Publication: June 7, 2021.

Published Online: September 23, 2021. doi:10.1001/jamaoncol.2021.3836

Open Access: This is an open access article distributed under the terms of the CC-BY-NC-ND License. © 2021 Zhu AX et al. *JAMA Oncology*.

Author Affiliations: Department of Medicine, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston (Zhu, Lowery, Goyal); Jiahui International Cancer Center, Jiahui Health, Shanghai, China (Zhu); Hospital Universitario Vall d'Hebron, Barcelona, Spain (Macarulla); Department of Gastrointestinal Medical Oncology, MD Anderson Cancer Center, Houston, Texas (Javle); Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco (Kelley); Department of Medicine, University of Wisconsin Carbone Cancer Center, Madison (Lubner); Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain (Adeva); Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (Cleary); Department of Medicine, University of Chicago Medical Center, Chicago, Illinois (Catenacci); Department of Hematology-Oncology, Mayo Clinic, Scottsdale, Arizona (Borad); Department of Medical Oncology, University College London Cancer Institute, London, United Kingdom (Bridgewater); Department of Medicine, University of Washington, Seattle (Harris); Department of Oncology–Gastrointestinal Cancer, Johns Hopkins University, Baltimore, Maryland (Murphy); Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Integrated Major in Innovative Medical Science, Seoul National University Graduate School, Seoul, South Korea (Oh); Medical Oncology and Hematology, Utah Cancer Specialists, Salt Lake City (Whisenant); Trinity St James Cancer Institute, Trinity College Dublin, Dublin, Ireland (Lowery); Department of Medicine, University of Arizona Cancer Center, Tucson (Shroff); Department of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles (El-Khoueiry); Agios Pharmaceuticals Inc, Cambridge, Massachusetts (Chamberlain, Aguado-Fraile, Choe, Wu, Liu, Gliser, Pandya); Now with Servier Pharmaceuticals, LLC, Boston, Massachusetts (Chamberlain, Choe, Liu, Gliser, Pandya); Repare Therapeutics, Cambridge, Massachusetts (Aguado-Fraile); Bristol Myers Squibb, Cambridge, Massachusetts (Wu); Division of Cancer Sciences, University of Manchester, Department of Medical Oncology, The Christie National Health Service Foundation Trust, Manchester, United Kingdom (Valle); Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York (Abou-Alfa); Department of Medicine, Weill Medical College at Cornell University, New York, New York (Abou-Alfa).

Author Contributions: Drs Zhu and Abou-Alfa had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Zhu and Abou-Alfa contributed equally to this study.
Concept and design: Zhu, Javle, Kelley, Cleary, Lowery, Goyal, Shroff, Wu, Liu, Gliser, Pandya, Valle, Abou-Alfa.
Acquisition, analysis, or interpretation of data: Zhu, Macarulla, Javle, Kelley, Lubner, Adeva, Cleary, Catenacci, Borad, Bridgewater, Harris, Murphy, Oh, Whisenant, Goyal, Shroff, El-Khoueiry, Chamberlain, Aguado-Fraile, Choe, Wu, Liu, Gliser, Pandya, Valle, Abou-Alfa.
Drafting of the manuscript: Zhu, Javle, Borad, Oh, Shroff, Pandya, Abou-Alfa.

Downloaded from jamanetwork.com by guest on 12/17/2025

Critical revision of the manuscript for important intellectual content: Zhu, Macarulla, Javle, Kelley, Lubner, Adeva, Cleary, Catenacci, Borad, Bridgewater, Harris, Murphy, Oh, Whisenant, Lowery, Goyal, El-Khoueiry, Chamberlain, Aguado-Fraile, Choe, Wu, Liu, Gliser, Pandya, Valle, Abou-Alfa.
Statistical analysis: Oh, Liu, Abou-Alfa.
Administrative, technical, or material support: Zhu, Kelley, Lubner, Cleary, Borad, Harris, Lowery, Goyal, Wu, Pandya, Abou-Alfa.
Supervision: Zhu, Macarulla, Javle, Kelley, Lubner, Harris, Oh, El-Khoueiry, Wu, Pandya, Valle, Abou-Alfa.

Conflict of Interest Disclosures: Dr Zhu reported serving as a consultant for or is on scientific advisory boards for AstraZeneca, Bayer, Eisai, Exelixis, Gilead, Lilly, Merck, Roche/Genentech, and Sanofi-Aventis; and receiving research funding from Bayer, Bristol Myers Squibb, Lilly, Merck, and Novartis outside the submitted work. Dr Macarulla reported being on advisory boards for AstraZeneca, Baxalta, Celgene, Eisai, Genzyme, Incyte, Ipsen, Lab, Lilly, Menarini, Merck Sharp & Dohme, Polaris, Prime Oncology, QED, Roche, Sanofi-Aventis, Servier, Shire, and Surface Oncology Inc; receiving travel/accommodation funding from Celgene, H3 Biomedicine, Merck, Sanofi, and Servier; and receiving research grant/funding (to institution) from Agios, ASLAN, AstraZeneca, Baxalta, Bayer, Celgene, Genentech, Halozyme, Immunomedics, Lilly, Merrimack, Millennium, Novartis, Novocure, Pfizer, Pharmacyclics, and Roche outside the submitted work. Dr Javle reported being on advisory boards for AstraZeneca, EMD Serono, Incyte, Merck, Mundipharma, OncoSil, and QED; and receiving honoraria or research support from Bayer, Beigene, Incyte, Merck, Merck Serono, Novartis, Pieris, QED, Rafael, and Seattle Genetics outside the submitted work. Dr Kelley reported being on advisory boards for Agios (funding to institution), AstraZeneca (funding to institution), Bristol Myers Squibb (funding to institution), Exact Sciences (funding to individual), Genentech/Roche (funding to individual), Gilead (funding to individual), and Merck (funding to institution); receiving travel/accommodation funding from Ipsen; and receiving research grant/funding (to institution) from Adaptimmune, Agios, AstraZeneca, Bayer, Bristol Myers Squibb, EMD Serono, Exelixis, Genentech/Roche, Lilly, MedImmune, Merck Sharp & Dohme, Novartis, Partner, QED, and Taiho outside the submitted work. Dr Cleary reported being on advisory boards for Bristol Myers Squibb; receiving travel/accommodation funding from Agios, Bristol Myers Squibb, and Roche; and receiving research grant/funding from AbbVie (funding to individual), AstraZeneca (funding to individual), Bristol Myers Squibb (funding to institution), Esperas (funding to individual), Genentech/Roche (funding to institution), Merck (funding to individual), Merus (funding to institution), and Tesaro (funding to individual) outside the submitted work. Dr Catenacci reported being on advisory boards for Amgen, Astellas, Bristol Myers Squibb, Daiichi Sankyo/UCB Japan, Genentech/Roche, Guardant Health, Lilly, Merck, Seattle Genetics, Taiho, and Zymeworks; participating in speakers' bureaus for Foundation Medicine, Genentech, Guardant Health, Lilly, Merck, and Tempus; and receiving honoraria from Amgen, Archer, Astellas, Bristol Myers Squibb, Daiichi Sankyo/UCB Japan, Five Prime, Foundation Medicine, Genentech/Roche, Gristone Oncology, Guardant Health, Lilly, Merck, Natera, Pieris, QED, Seattle Genetics, Taiho, Tempus, and Zymeworks outside the submitted work. Dr Borad reported being on advisory boards for Agios (funding to institution), ArQule (funding to institution), Celgene (funding to institution), De Novo (funding to individual), Exelixis (funding to individual), G1 (funding to individual), Genentech (funding to individual), Halozyme (funding to institution), Immunovative Therapies (funding to individual), Imvax (funding to individual), Inspyr (funding to individual), Insys (funding to institution), KLUS (funding to individual), Lynx Group (funding to individual), Merck (funding to individual), Novartis (funding to institution), Pieris (funding to institution), Taiho (funding to institution), and Western Oncolytics (funding to individual); holding stock in AVEO, Gilead, Intercept, and Spectrum; receiving travel/accommodation funding from ArQule, AstraZeneca, and Celgene; and receiving research grant/funding (to institution) from Adaptimmune, Agios, ARIAD, Basilea, BioLineRx, Boston Biomedical, Celgene, Dicerna, Eisai, EMD Serono, Halozyme, ImClone Systems, Incyte, Ionis Pharmaceuticals, MedImmune, Merck Serono, miRNA, Novartis, Pieris, Puma Biotechnology, QED, Redhill Biopharma, Senhwa Biosciences, SillaJen, Sun Biopharma, Taiho, Threshold, and Toray Industries outside the submitted work. Dr Bridgewater reported being on advisory boards for AstraZeneca, Basilea, Bayer, Incyte, Merck Serono, Roche, and Servier; receiving honoraria from Merck Serono and Servier; receiving travel/accommodation funding from Bristol Myers Squibb, Bristol Myers Squibb/Medarex, Merck Serono, Merck Sharp & Dohme, and Servier; participating in speakers' bureaus for Amgen, Bristol Myers Squibb, and Celgene; and receiving research grant/funding from Amgen outside the submitted work. Dr Harris reported being on advisory boards for Bristol Myers Squibb, Eisai, Exelixis, NeoTherma, QED, and Zymeworks; receiving travel/accommodation funding from Eisai; and receiving research grant/funding (to institution) from Agios, ArQule, Bayer, Bristol Myers Squibb, BTG, Exelixis, Halozyme, MedImmune, and Merck outside the submitted work. Dr Murphy reported being on advisory boards for AbbVie; and receiving research grant/funding from Bristol Myers Squibb outside the submitted work. Dr Oh reported being on advisory boards for ASLAN, AstraZeneca, Basilea, Bayer, Beigene, Celgene, Genentech/Roche, Halozyme, Merck Serono, Novartis, Taiho, and Zymeworks; and receiving research grant/funding from Array BioPharma, AstraZeneca, Beigene, Lilly, Merck Sharp & Dohme, Novartis, and Servier outside the submitted work. Dr Lowery reported being on advisory boards for Agios, Celgene, Pfizer, and Roche outside the submitted work. Dr Goyal reported being on advisory boards for Agios, Alentis, AstraZeneca, H3 Biomedicine, Incyte, QED, Sirtex Medical, and Taiho Oncology; being a consultant for Agios, Alentis, Exelixis, Genentech, Incyte, QED, Sirtex Medical, and Taiho Oncology; and receiving research grant/funding (to institution) from Adaptimmune, Bayer, Bristol Myers Squibb, Eisai, Genentech, Leap, Loxo Oncology, MacroGenics, Merck, Novartis, NuCana, and Relay outside the submitted work. Dr Shroff reported being on advisory boards for Agios, Clovis, Debiopharm, Exelixis, Merck, QED, and Seattle Genetics; and receiving research grant/funding from Agios, Halozyme, Lilly, Merck, and Pieris outside the submitted work. Dr El-Khoueiry reported being on advisory boards for ABL Bio, Agenus, Agios, Bayer, Bristol Myers Squibb, CytomX, Eisai, Exelixis, Gilead, Merck, Merck Serono, Pieris, QED, Roche/Genentech, and Target PharmaSolutions (consultant and advisory board); and receiving research grant/funding from Astex (to institution), AstraZeneca (to institution), and Merck (to institution) outside the submitted work. Drs Chamberlain, Choe, Liu, and Pandya and Ms Gliser were employees of and held stock in Agios at the time of this study; they are now employees of Servier. Dr Aguado-Fraile was an employee of and held stock in Agios, at the time of this study. Dr Wu was an employee of, held stock in, and held patents, royalties, and other intellectual property with Agios at the time of this study. Dr Valle reported being on advisory boards for Agios, AstraZeneca, Debiopharm, Genoscience, Hutchison MediPharma, Imaging Equipment Ltd, Incyte, Ipsen, Keocyt, Merck, Mundipharma, Novartis, NuCana, PCI Biotech, Pfizer, Pieris, Servier, QED, and Wren Laboratories; receiving travel/accommodation funding from Lilly, NuCana, and Pfizer; participating in speakers' bureaus for Imaging Equipment Ltd, Ipsen, Novartis, and NuCana; and receiving honoraria from Ipsen outside the submitted work. Dr Abou-Alfa reported serving as a consultant for or being on scientific advisory boards for Agios, AstraZeneca, Autem Medical, Bayer, Beigene, Berry Genomics, Celgene, Eisai, Flatiron Health, Genoscience, Gilead, Incyte, Ipsen, LAM, Lilly, Merck Serono, Minapharm, QED, RedHill Biopharma, Roche/Genentech, SillaJen, TheraBionic, twoXAR, and Vector Health; receiving travel/accommodation funding from Polaris; and receiving research funding (to institution) from Agios, AstraZeneca, Bayer, Bristol Myers Squibb, CASI, Exelixis, Incyte, Polaris, Puma Biotechnology, and QED outside the submitted work. Drs Zhu, Chamberlain, Aguado-Fraile, Choe, Wu, Liu, and Pandya and Ms Gliser were employees at Agios Pharmaceuticals Inc, when the study was conducted and completed. No other disclosures were reported.

Funding/Support: This study was supported by Agios Pharmaceuticals Inc. Servier Pharmaceuticals LLC has completed the acquisition of Agios' oncology business.

Role of the Funder/Sponsor: The study was designed and data analyzed by the sponsor in collaboration with the investigators. The manuscript was written and revised in collaboration with all coauthors and the sponsor. Further assistance with medical writing was provided by the sponsor.

Meeting Presentations: This study was presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 17, 2021; virtual; and the Annual Meeting of American Society of Clinical Oncology; June 4, 2021; virtual.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank the participating patients and their families, and the nurses, research coordinators, study management team, and the independent data monitoring committee. We thank biostatistician Liewen Jiang, PhD, who was an employee of Agios at the time of this study, for her contributions to this study. Medical writing support, which was in accordance with Good Publication Practice guidelines, was

Downloaded from jamanetwork.com by guest on 12/17/2025

provided by Vanessa Ducas, PhD, Excel Medical Affairs, and was funded by Agios Pharmaceuticals Inc and Servier Pharmaceuticals LLC.

Additional Information: NCCN Guidelines were referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines) for Hepatobiliary Cancers V.1.2021.[33] National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the 5 most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

REFERENCES

1. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist*. 2016;21(5):594-599. doi:10.1634/theoncologist.2015-0446

2. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol*. 2020;17(9):557-588. doi:10.1038/s41575-020-0310-z

3. Valle J, Wasan H, Palmer DH, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273-1281. doi:10.1056/NEJMoa0908721

4. Ramírez-Merino N, Aix SP, Cortés-Funes H. Chemotherapy for cholangiocarcinoma: an update. *World J Gastrointest Oncol*. 2013;5(7):171-176. doi:10.4251/wjgo.v5.i7.171

5. 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(15)(suppl):abstract 4003. doi:10.1200/JCO.2019.37.15_suppl.4003

6. Plentz RR, Malek NP. Systemic therapy of cholangiocarcinoma. *Visc Med*. 2016;32(6):427-430. doi:10.1159/000453084

7. Adeva J, Sangro B, Salati M, et al. Medical treatment for cholangiocarcinoma. *Liver Int*. 2019;39(suppl 1):123-142. doi:10.1111/liv.14100

8. Merck & Co Inc. Highlights of prescribing information: KEYTRUDA (pembrolizumab). Accessed February 10, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s084lbl.pdf

9. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in *TRK* fusion–positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731-739. doi:10.1056/NEJMoa1714448

10. Doebele RC, Drilon A, Paz-Ares L, et al; trial investigators. Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):271-282. doi:10.1016/S1470-2045(19)30691-6

11. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509-2520. doi:10.1056/NEJMoa1500596

12. Incyte Corporation. Highlights of prescribing information: pemazyre (pemigatinib). Accessed February 10, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213736s000lbl.pdf

13. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21(5):671-684. doi:10.1016/S1470-2045(20)30109-1

14. 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(4):751-765. doi:10.21037/jgo.2019.03.10

15. Saha SK, Parachoniak CA, Ghanta KS, et al. Mutant IDH inhibits HNF4α to block hepatocyte differentiation and promote biliary cancer. *Nature*. 2014;513(7516):110-114. doi:10.1038/nature13441

16. 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(4):300-305. doi:10.1021/acsmedchemlett.7b00421

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

18. 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(9):711-720. doi:10.1016/S2468-1253(19)30189-X

19. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in *IDH1*-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(6):796-807. doi:10.1016/S1470-2045(20)30157-1

20. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

21. 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(2):228-247. doi:10.1016/j.ejca.2008.10.026

22. 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(5):365-376. doi:10.1093/jnci/85.5.365

23. Friend E, Yadegarfar G, Byrne C, et al; EORTC Quality of Life Group. 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(4):587-592. doi:10.1038/sj.bjc.6606086

24. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.

25. Szende A, Janssen B, Cabases J, eds. *Self-Reported Population Health: An International Perspective Based on EQ-5D*. Springer; 2014. doi:10.1007/978-94-007-7596-1

26. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE): version 4.03. Accessed August 16, 2021. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

27. Watkins C, Huang X, Latimer N, Tang Y, Wright EJ. Adjusting overall survival for treatment switches: commonly used methods and practical application. *Pharm Stat*. 2013;12(6):348-357. doi:10.1002/pst.1602

28. 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. doi:10.1186/1471-2288-11-4

29. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Commun Stat Theory Methods*. 1991;20(8):2609-2631. doi:10.1080/03610929108830654

30. Zhu AX. Final results from ClarIDHy, a global, phase III, randomised, double-blind study of ivosidenib versus placebo in patients with previously treated cholangiocarcinoma and an isocitrate dehydrogenase 1 (*IDH1*) mutation. *EMJ Oncol*. 2021;9(suppl 2):2-5.

31. Chamberlain CX, Andrae DA, Jiang L, et al. Health-related quality of life in patients treated with ivosidenib for mutant-IDH1 cholangiocarcinoma: results from ClarIDHy. Presented at: Cholangiocarcinoma Foundation Annual Conference; July 22-24, 2020; Virtual.

32. Aguado-Fraile E, Tassinari A, Ishii Y, et al. Molecular and morphological changes induced by ivosidenib correlate with efficacy in mutant-*IDH1* cholangiocarcinoma. *Future Oncol*. 2021;17(16):2057-2074. doi:10.2217/fon-2020-1274

33. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Hepatobiliary Cancers V.1.2021. Accessed March 11, 2021. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1438

34. Malka D, Bernardini D, Boudjema K, et al. Cancer des voies biliaires. Thésaurus National de Cancérologie Digestive. Société Nationale Française de Gastro-Entérologie. Accessed March 10, 2021. http://www.tncd.org

35. Associazione Italiana de Oncologia Medica. Practice guidelines for biliary tract neoplasms. Accessed March 10, 2021. https://www.aiom.it/wp-content/uploads/2019/10/2019_LG_AIOM_Vie_biliari.pdf

36. Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. *Ann Oncol*. 2014;25(12):2328-2338. doi:10.1093/annonc/mdu162

37. Brieau B, Dahan L, De Rycke Y, et al. Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: a large multicenter study by the Association des Gastro-Entérologues Oncologues. *Cancer*. 2015;121(18):3290-3297. doi:10.1002/cncr.29471

38. 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(1):5548. doi:10.1038/s41598-019-42069-1

39. 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;139:134-142. doi:10.1016/j.critrevonc.2019.01.001

Downloaded from jamanetwork.com by guest on 12/17/2025