Supplementary Online Content

Zhu AX, Macarulla T, Javle MM, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with *IDH1* mutation: the phase 3 randomized clinical ClarIDHy trial. *JAMA Oncol.* Published online September 23, 2021. doi:10.1001/jamaoncol.2021.3836

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

Isocitrate Dehydrogenase 1 Mutation Testing and Baseline Comutation Analyses

Isocitrate dehydrogenase 1 (*IDH1*) mutation testing methodology was previously reported.[1] Briefly, *IDH1* mutation status was centrally and prospectively confirmed by next-generation sequencing (NGS) testing using Oncomine Focus Assay (Thermo Fisher Scientific, Waltham, Massachusetts)[2,3] in archival formalin-fixed paraffin-embedded tumor samples.

Baseline comutation analyses were performed using the Oncomine Focus Assay panel. A targeted multibiomarker NGS assay designed for clinical research and molecular diagnostic development, the Oncomine Focus Assay detects more than 1000 biomarkers across 52 genes relevant for solid tumors. Different molecular variants (eg, hotspot, single-nucleotide variants and indels, copy number variation, and gene fusions) are detected simultaneously through concurrent DNA and RNA analysis. The key 52 genes included in the Oncomine Focus Assay are listed below.[3]

DNA			RNA
Hotspot genes		Copy number variants	Fusion drivers
AKT1	*JAK1*	*ALK*	*ABL1*
ALK	*JAK2*	*AR*	*ALK*
AR	*JAK3*	*BRAF*	*AKT3*
BRAF	*KIT*	*CCND1*	*AXL*
CDK4	*KRAS*	*CDK4*	*BRAF*
CTNNB1	*MAP2K1*	*CDK6*	*EGFR*
DDR2	*MAP2K2*	*EGFR*	*ERBB2*
EGFR	*MET*	*ERBB2*	*ERG*
ERBB2	*MTOR*	*FGFR1*	*ETV1*
ERBB3	*NRAS*	*FGFR2*	*ETV4*
ERBB4	*PDGFRA*	*FGFR3*	*ETV5*
ESR1	*PIK3CA*	*FGFR4*	*FGFR1*
FGFR2	*RAF1*	*KIT*	*FGFR2*
FGFR3	*RET*	*KRAS*	*FGFR3*
GNA11	*ROS1*	*MET*	*MET*
GNAQ	*SMO*	*MYC*	*NTRK1*
HRAS		*MYCN*	*NTRK2*
IDH1		*PDGFRA*	*NTRK3*
IDH2		*PIK3CA*	*PDGFRA*
			PPARG
			RAF1
			RET
			ROS1

Statistical Analyses

Details on the progression-free survival (PFS) analyses performed for this study population were reported previously.[1] Briefly, the primary end point of PFS was assessed by the independent radiology center based on the Response Evaluation Criteria in Solid Tumors version 1.1 assessment, and was defined as the time from the date of randomization to the date of first documentation of disease progression or death due to any cause, whichever occurred first. A total of 131 PFS events were required to provide 96% power at a 1-sided alpha of .025, assuming a hazard ratio (HR) of 0.5. Assuming an HR of 0.67 for overall survival (OS), a total of 150 OS events were required to provide 64% power at a 1-sided alpha of .025.

Subgroup Analyses

Subgroup analyses were performed on OS and HRs were estimated using Cox regression models. Subgroup analyses on PFS were reported previously.[1]

Allowance of Placebo-to-Ivosidenib Crossover

Patients receiving placebo who had documented radiographic disease progression as assessed by the local investigator and met the eligibility criteria were allowed to crossover to receive open-label ivosidenib.[1] Prior to unblinding and allowance of crossover, the sponsor confirmed that radiographic disease progression had been properly documented by the investigator, that the patient met the eligibility criteria for crossover, and that the investigator had provided an eligibility packet for medical monitor review and approval prior to crossover.

Supportive OS Analyses

As noted in the main text, the RPSFT method was used to reconstruct the survival curve for patients receiving placebo, as if the switch to the ivosidenib arm never occurred. RPSFT models are specialized tools developed in the 1990s that have been used for decades to adjust for the effect of treatment switching in clinical trials.[4-6]

Pharmacodynamic Sampling

Blood samples were collected before and after dosing to establish the circulating plasma concentration of D-2-hydroxyglutarate (2-HG). Plasma 2-HG levels were determined at baseline (cycle 1 day 1) and on treatment (cycle 2 day1) for all patients randomized to receive ivosidenib and patients initially randomized to receive placebo but that crossed over to open-label ivosidenib upon radiographic disease progression. The association between plasma 2-HG levels and treatment duration was examined.

Quality of Life Analyses

A mixed-effect model with repeated measurements was used on the change score from baseline for each subscale of the European Organisation for Research and Treatment of Cancer instruments as of the May 31, 2020, final OS analysis data cutoff date, with baseline score, treatment, visit, and treatment-by-visit as fixed effects, and patient as random effect. Visit was treated as a categorical variable. Compound symmetry covariance matrix was used. The focus was on cycle 2 day 1 and cycle 3 day 1, considering the availability of quality of life (QOL) data. *P* values were not adjusted for multiplicity.

eResults.

OS Subgroup Analyses

Subgroup analyses performed on OS are presented in eFigure 1 and were consistent with the overall OS analysis. The interpretability of these results, however, is affected by the high crossover rate (70.5%) and the relatively small sample size in some of the subgroups.

Quality of Life

Supplementary QOL results are presented in eFigures 3 and 4, and eTables 3-5. QOL analyses were limited by small sample sizes as patients tended to have short treatment duration. As of January 31 2019, data cutoff date for the primary PFS analysis, at least 1 QOL assessment was missing for a total of 98 patients (60 randomized to ivosidenib and 38 randomized to placebo). These patients were missing at least 1 QOL assessment for the following reasons: site error (ivosidenib, n = 38; placebo, n = 20), patient refusal (ivosidenib, n = 8; placebo, n = 5), patient deteriorated or hospitalized (ivosidenib, n = 3; placebo, n = 5), patient error (ivosidenib, n = 2; placebo, n = 3), tablet malfunction or technical issue (ivosidenib, n = 11; placebo, n = 9), instrument(s) not available in patient's language (ivosidenib, n = 2), and unknown (ivosidenib, n = 7; placebo, n = 5).

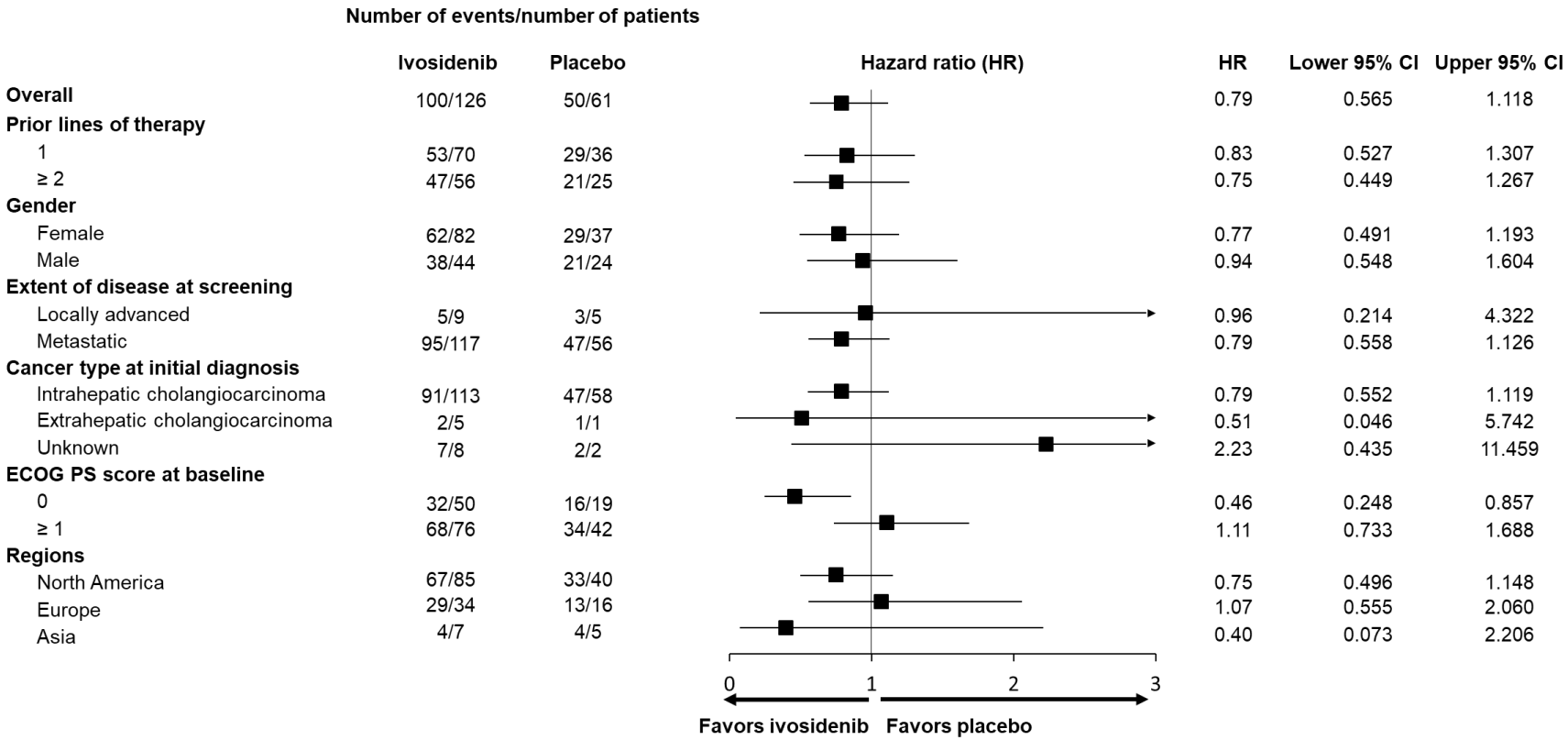
During the period ranging from January 31, 2019 to May 31, 2020, data cutoff date for the final OS analysis, at least 1 QOL assessment was missing for a total of 41 patients (29 randomized to ivosidenib and 12 randomized to placebo). These patients were missing at least 1 QOL assessment for the following reasons: COVID-19 (ivosidenib, n = 6; placebo, n = 5), site error (ivosidenib, n = 14; placebo, n = 5), patient deteriorated or unwell (ivosidenib, n = 3; placebo, n = 3), dose hold (placebo, n = 1), patient refusal (ivosidenib, n = 3), patient error (placebo, n = 1), tablet malfunction or technical issue (ivosidenib, n = 6; placebo, n = 2), instrument(s) not available in patient's language (ivosidenib, n = 2), visit occurred via phone (placebo, n = 1), not in contact with patient (placebo, n = 1), and unknown (ivosidenib, n = 2).

The schedule of assessments in the original study protocol was changed in an amendment to increase the frequency of the QOL questionnaire completion.

eReferences.

1. 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.
2. Williams HL, Walsh K, Diamond A, Oniscu A, Deans ZC. Validation of the Oncomine™ focus panel for next-generation sequencing of clinical tumour samples. *Virchows Arch.* 2018;473(4):489-503.
3. ThermoFisher Scientific. White paper: an approach for establishing Oncomine Focus Assay performance. https://tools.thermofisher.com/content/sfs/brochures/oncomine-focus-assay-performance-white-paper.pdf. Accessed March 4, 2021.
4. 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.
5. 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.
6. 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.

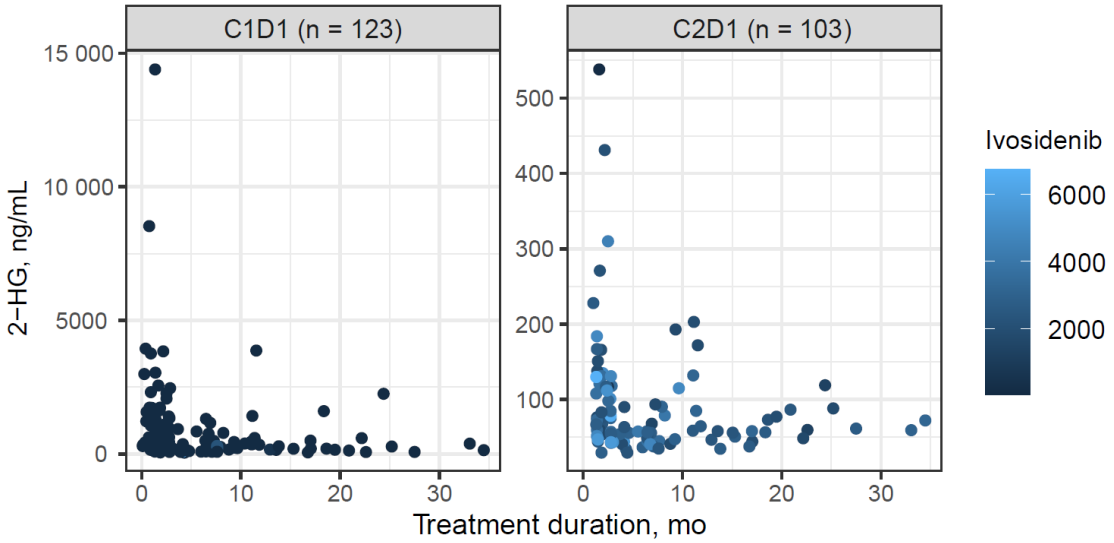
eFigure 1. Overall Survival in the Intent-to-Treat Population: Forest Plot by Subgroup



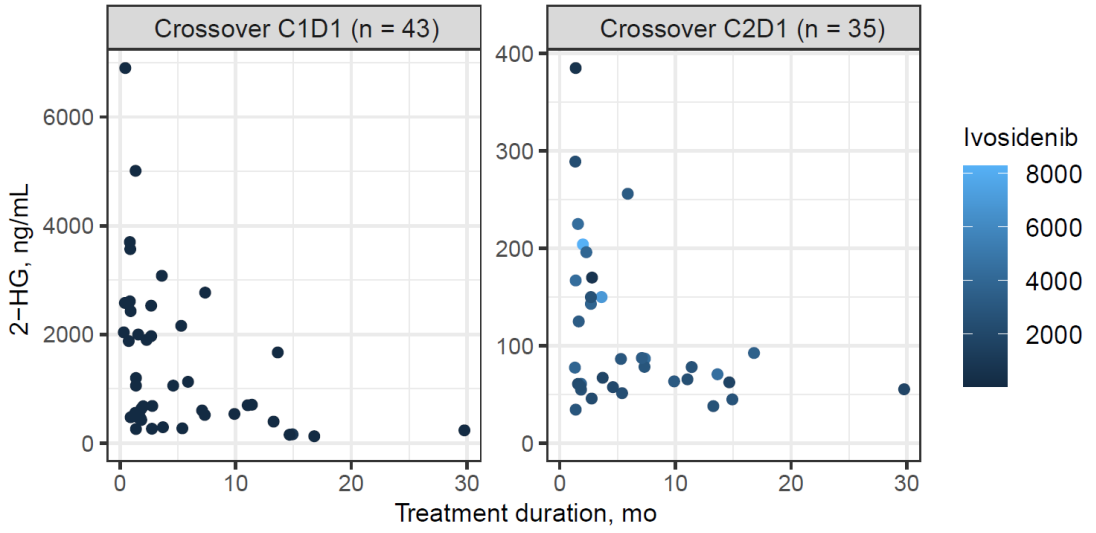
A stratified Cox regression model with placebo as the comparator was used to calculate the HR for the "Overall" subgroup. The HR for each subgroup was calculated from an unstratified Cox regression model. The number of prior lines of therapy was based on the actual prior lines received by the patients per eligibility, reviewed by the sponsor's medical monitor. Disease was considered metastatic in any patient with both local and metastatic status. Extrahepatic disease also included perihilar disease. The baseline assessment was defined as the most recent measurement before the first dose of study drug. If patients were not dosed, the latest assessment was taken as the baseline assessment. Two-sided 95% CIs are displayed.

eFigure 2. Plasma D-2-Hydroxyglutarate (2-HG) Levels Following Ivosidenib Treatment

A. Plasma 2-HG levels at baseline (C1D1) and on treatment (C2D1) for patients randomized to ivosidenib, plotted against ivosidenib treatment duration

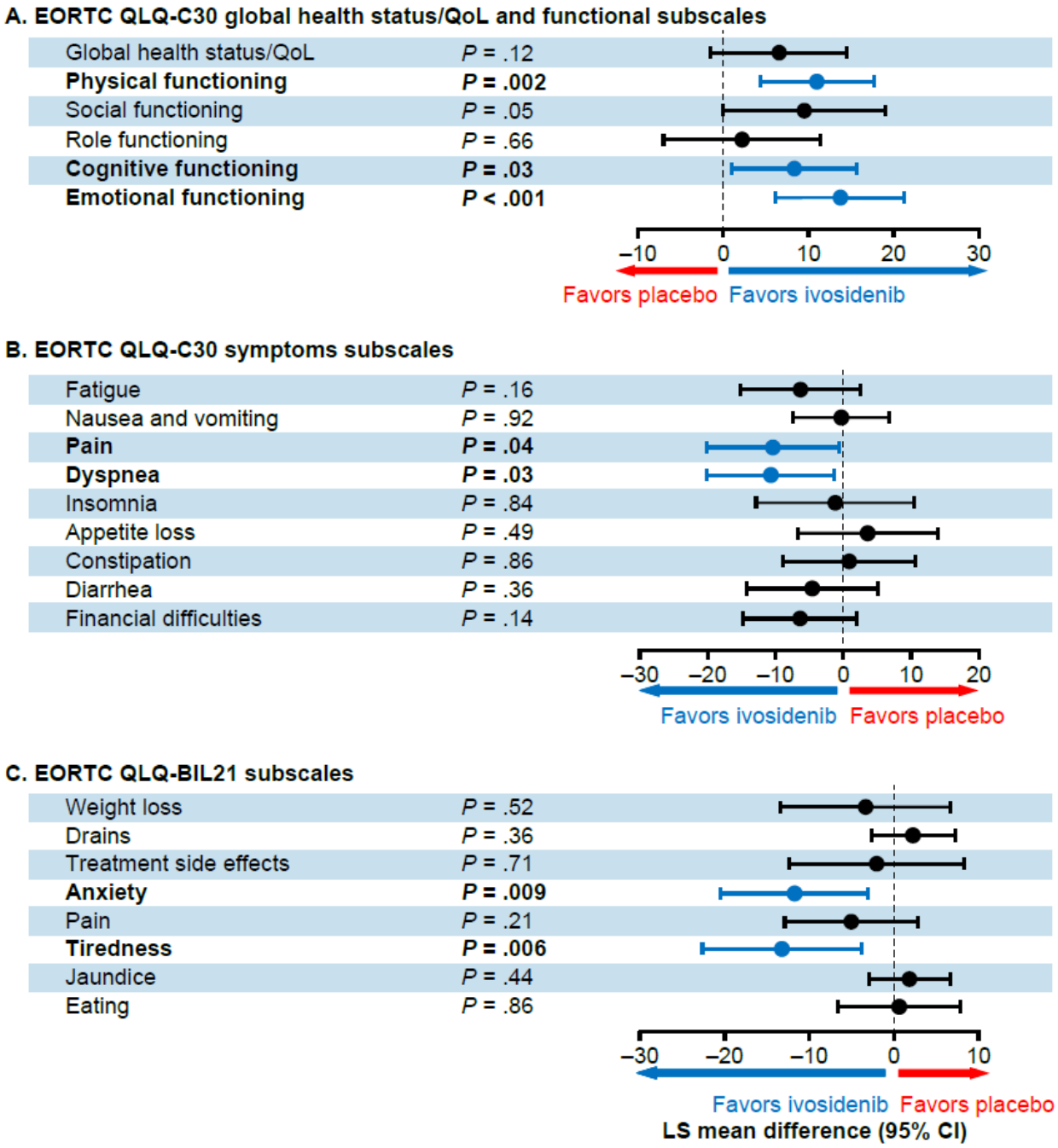


B. Plasma 2-HG levels pre (C1D1) and post (C2D1) crossover for patients who were initially randomized to placebo and crossed over to ivosidenib treatment, plotted against duration of ivosidenib treatment



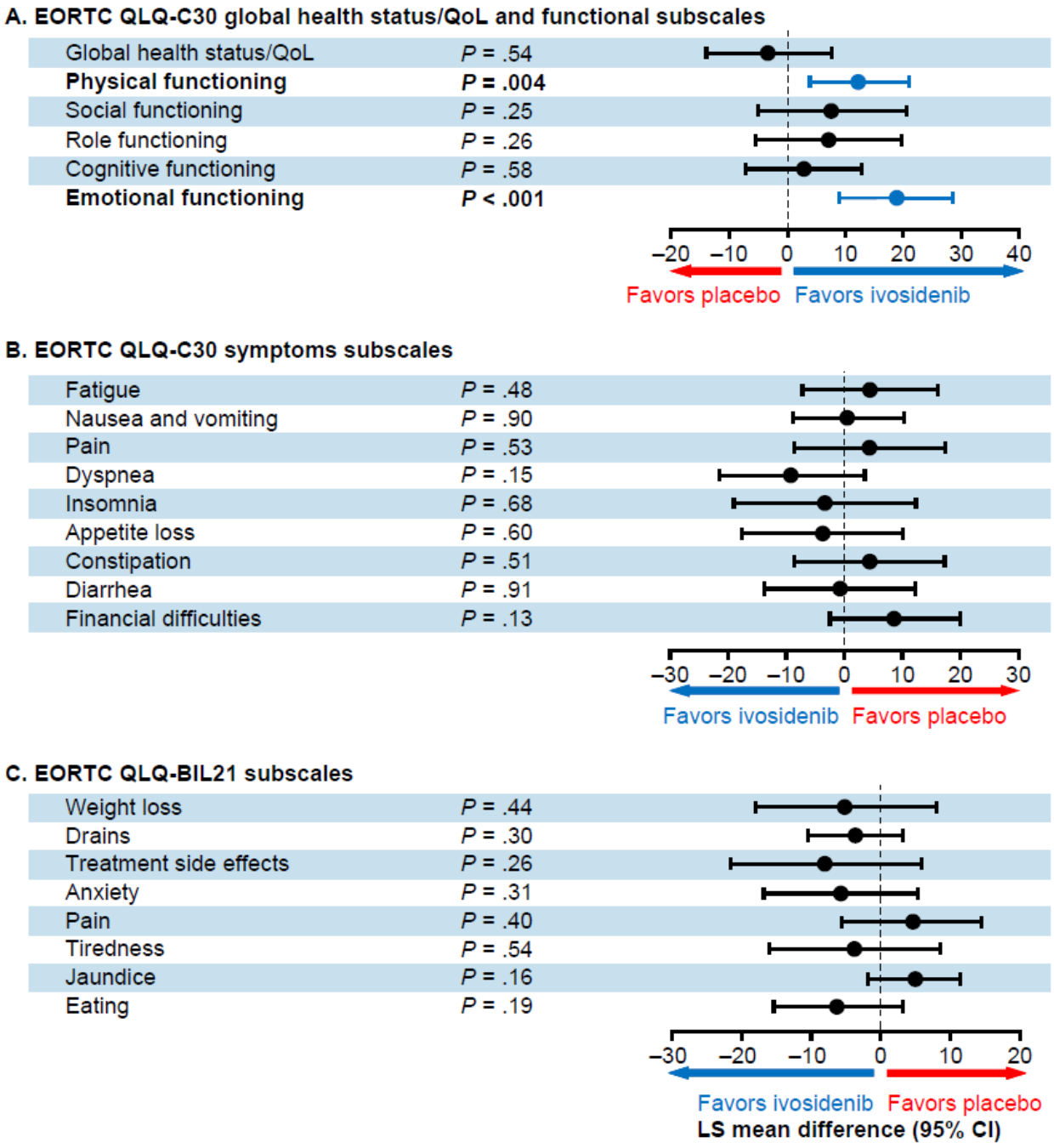
C1D1 indicates cycle 1 day 1; C2D1, cycle 2 day 1.

eFigure 3. Mixed-Effect Model With Repeated Measurements Least Squares Mean Differences of Ivosidenib vs Placebo Before Crossover for EORTC QLQ-C30 and EORTC QLQ-BIL21 Change Scores Between Arms at Cycle 2 Day 1



At cycle 2 day 1, n = 21 for placebo and n = 67 for ivosidenib for QLQ-C30 assessment; n = 20 for placebo and n = 65 for ivosidenib for QLQ-BIL21 assessment. Bolded subscales and corresponding data points in blue indicate differences of $P \leq .05$. Two-sided P values are shown. EORTC QLQ-BIL21 indicates European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cholangiocarcinoma and gallbladder cancer module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoL, quality of life.

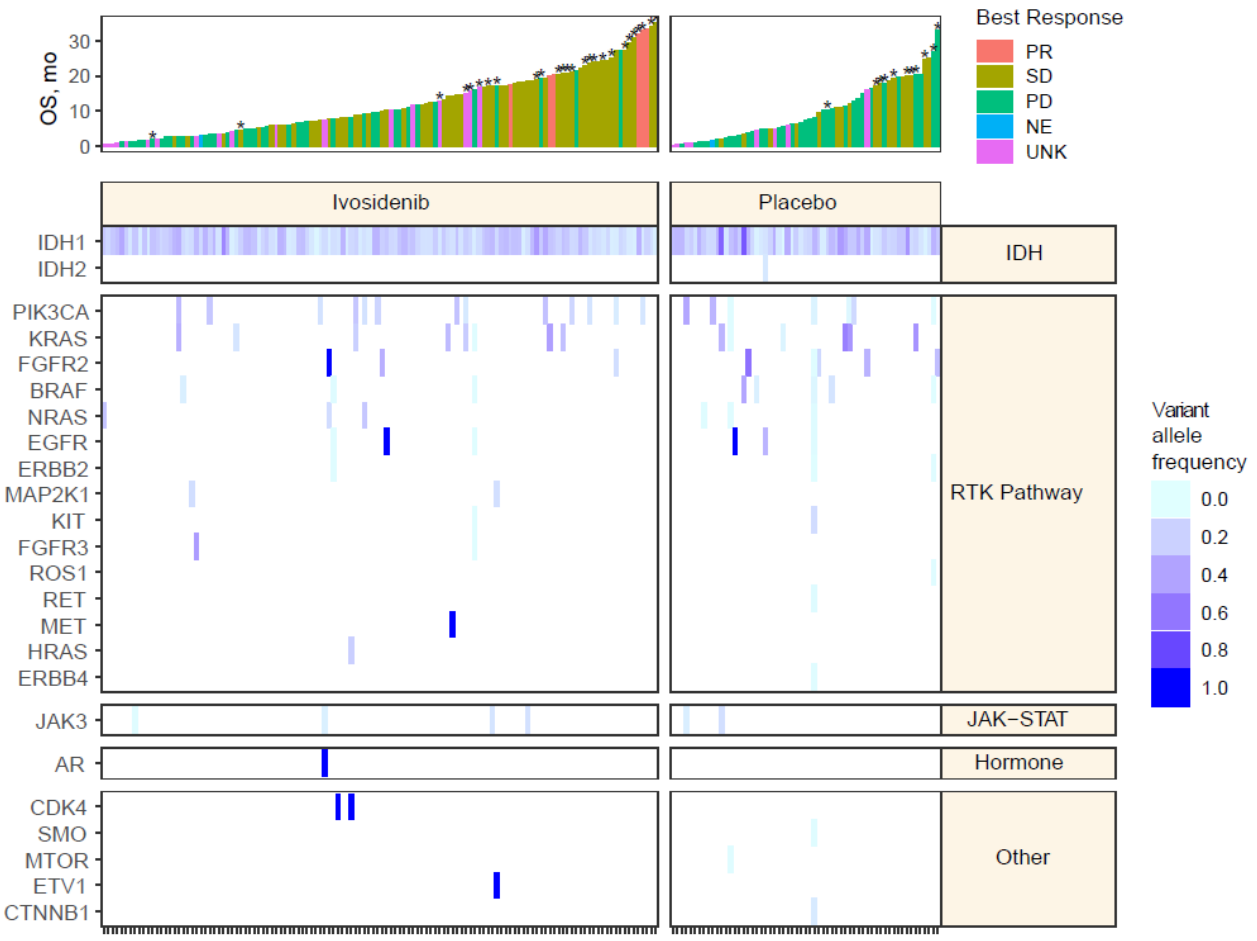
eFigure 4. Mixed-Effect Model With Repeated Measurements Least Squares Mean Differences of Ivosidenib vs Placebo Before Crossover for EORTC QLQ-C30 and EORTC QLQ-BIL21 Change Scores Between Arms at Cycle 3 Day 1



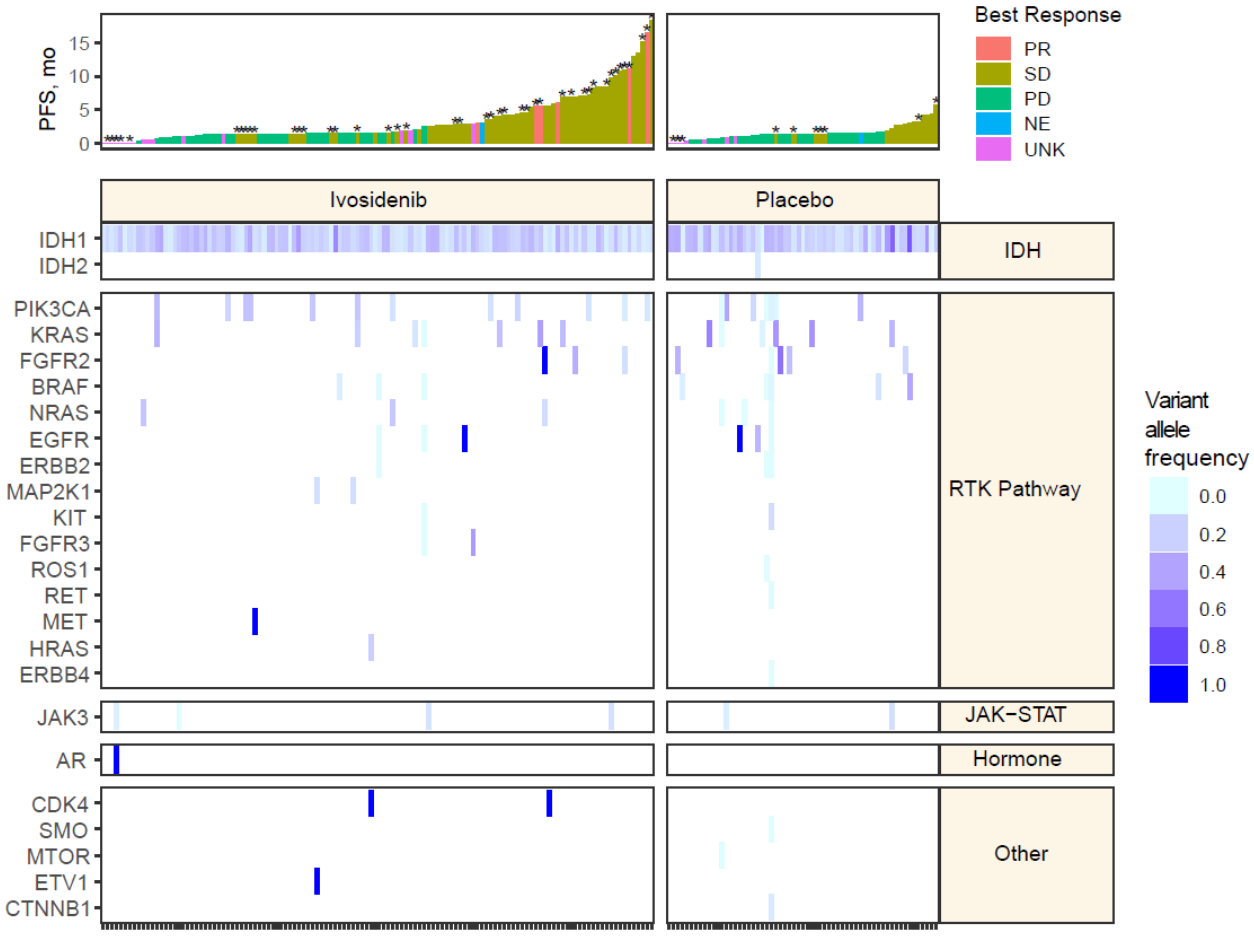
At cycle 3 day 1, n = 9 for placebo and n = 50 for ivosidenib (QLQ-C30); n = 9 for placebo and n = 48 for ivosidenib (QLQ-BIL21). Bolded subscales and corresponding data points in blue indicate differences of $P \leq .05$. Two-sided *P* values are shown. EORTC QLQ-BIL21 indicates European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cholangiocarcinoma and gallbladder cancer module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoL, quality of life.

eFigure 5. Baseline Comutation Data in Tumor Tissue

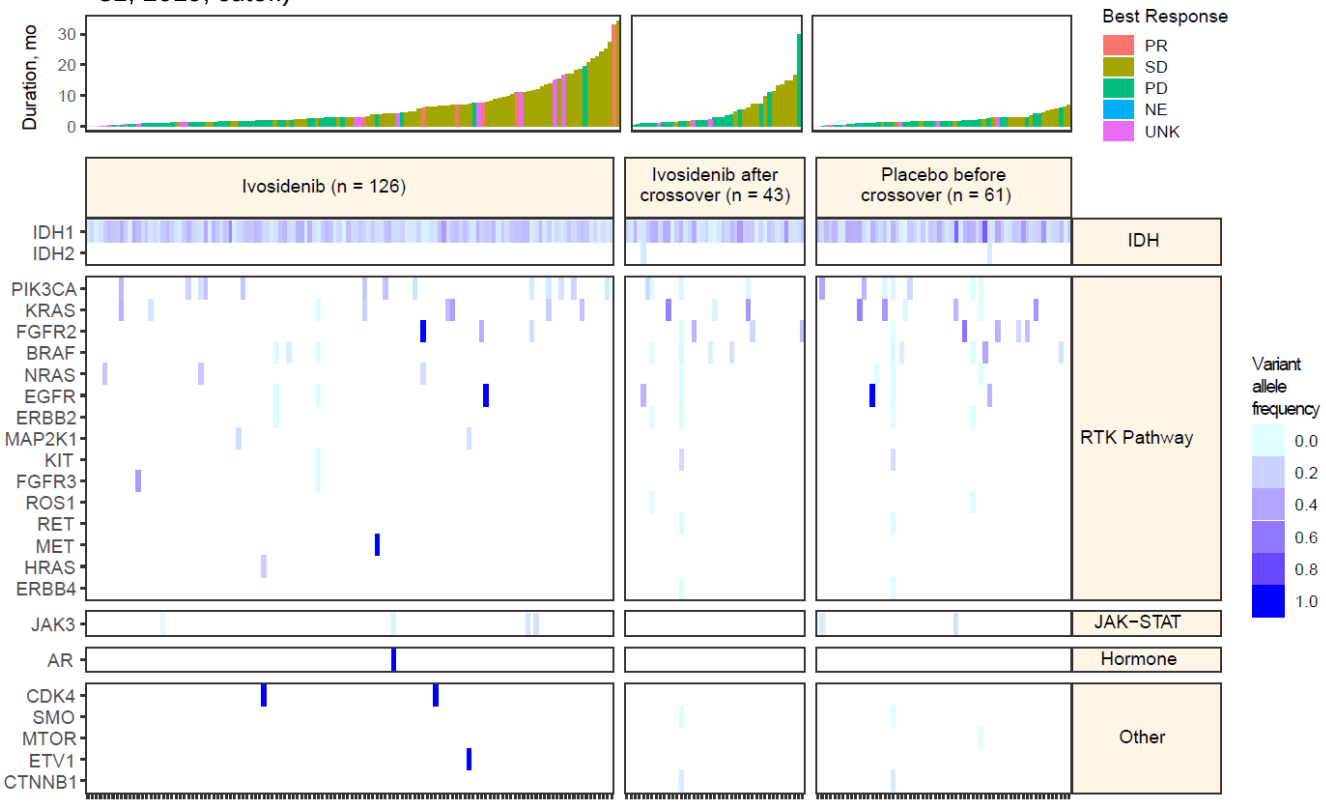
A. Patients sorted by OS (May 31, 2020, cutoff) and best overall response (January 31, 2019, cutoff)



B. Patients sorted by PFS (January 31, 2019, cutoff) and best overall response (January 31, 2019, cutoff)



C. Patients sorted by treatment duration (May 31, 2020, cutoff) and best overall response (January 31, 2019, cutoff)



NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; UNK, unknown.

eTable 1. Treatment-Emergent Adverse Events by Grade, Including Crossover Patients

	No. (%)														
	Placebo (n = 59)					Ivosidenib (n = 123)					Total ivosidenib (n = 166)[a]				
Adverse event[b]	Grade 1-2	Grade 3	Grade 4	Grade 5	All grades	Grade 1-2	Grade 3	Grade 4	Grade 5	All grades	Grade 1-2	Grade 3	Grade 4	Grade 5	All grades
Nausea	16 (27)	1 (2)	0	0	17 (29)	48 (39)	3 (2)	0	0	51 (41)	59 (36)	4 (2)	0	0	63 (38)
Diarrhea	10 (17)	0	0	0	10 (17)	43 (35)	0	0	0	43 (35)	54 (33)	1 (1)	0	0	55 (33)
Fatigue	9 (15)	1 (2)	0	0	10 (17)	34 (28)	4 (3)	0	0	38 (31)	43 (26)	5 (3)	0	0	48 (29)
Abdominal pain	8 (14)	1 (2)	0	0	9 (15)	27 (22)	3 (2)	0	0	30 (24)	33 (20)	4 (2)	0	0	37 (22)
Cough	5 (8)	0	0	0	5 (8)	31 (25)	0	0	0	31 (25)	36 (22)	0	0	0	36 (22)
Decreased appetite	11 (19)	0	0	0	11 (19)	28 (23)	2 (2)	0	0	30 (24)	34 (20)	2 (1)	0	0	36 (22)
Ascites	5 (8)	4 (7)	0	0	9 (15)	17 (14)	11 (9)	0	0	28 (23)	18 (11)	15 (9)	0	0	33 (20)
Vomiting	11 (19)	0	0	0	11 (19)	25 (20)	3 (2)	0	0	28 (23)	29 (17)	4 (2)	0	0	33 (20)
Anemia	3 (5)	0	0	0	3 (5)	14 (11)	8 (7)	0	0	22 (18)	18 (11)	12 (7)	0	0	30 (18)
Edema peripheral	6 (10)	0	0	0	6 (10)	16 (13)	1 (1)	0	0	17 (14)	24 (14)	1 (1)	0	0	25 (15)
Constipation	11 (19)	0	0	0	11 (19)	19 (15)	0	0	0	19 (15)	24 (14)	0	0	0	24 (14)
Asthenia	6 (10)	2 (3)	0	0	8 (14)	16 (13)	0	0	0	16 (13)	18 (11)	2 (1)	0	0	20 (12)
Back pain	5 (8)	2 (3)	0	0	7 (12)	16 (13)	0	0	0	16 (13)	18 (11)	1 (1)	0	0	19 (11)
Pyrexia	6 (10)	0	0	0	6 (10)	16 (13)	1 (1)	0	0	17 (14)	17 (10)	2 (1)	0	0	19 (11)
Headache	4 (7)	0	0	0	4 (7)	16 (13)	0	0	0	16 (13)	18 (11)	0	0	0	18 (11)
Aspartate aminotransferase increased	2 (3)	1 (2)	0	0	3 (5)	8 (7)	6 (5)	0	0	14 (11)	9 (5)	8 (5)	0	0	17 (10)

Dyspnea	8 (14)	2 (3)	0	0	10 (17)	12 (10)	1 (1)	0	0	13 (11)	15 (9)	2 (1)	0	0	17 (10)
Abdominal distension	5 (8)	0	0	0	5 (8)	13 (11)	1 (1)	0	0	14 (11)	15 (9)	1 (1)	0	0	16 (10)
Blood alkaline phosphatase increased	3 (5)	3 (5)	0	0	6 (10)	8 (7)	3 (2)	0	0	11 (9)	12 (7)	3 (2)	0	0	15 (9)
Blood bilirubin increased	3 (5)	1 (2)	0	0	4 (7)	6 (5)	7 (6)	0	0	13 (11)	6 (4)	8 (5)	1 (1)	0	15 (9)
Hypertension	1 (2)	1 (2)	0	0	2 (3)	9 (7)	2 (2)	0	0	11 (9)	10 (6)	5 (3)	0	0	15 (9)
Hyponatremia	1 (2)	5 (8)	1 (2)	0	7 (12)	7 (6)	5 (4)	2 (2)	0	14 (11)	7 (4)	6 (4)	2 (1)	0	15 (9)
Weight decreased	2 (3)	1 (2)	0	0	3 (5)	8 (7)	1 (1)	0	0	9 (7)	14 (8)	1 (1)	0	0	15 (9)
Abdominal pain upper	2 (3)	0	0	0	2 (3)	10 (8)	0	0	0	10 (8)	14 (8)	0	0	0	14 (8)
Alanine aminotransferase increased	1 (2)	0	0	0	1 (2)	9 (7)	2 (2)	0	0	11 (9)	11 (7)	3 (2)	0	0	14 (8)
Insomnia	3 (5)	0	0	0	3 (5)	10 (8)	1 (1)	0	0	11 (9)	13 (8)	1 (1)	0	0	14 (8)
Electrocardiogram QT prolonged	2 (3)	0	0	0	2 (3)	10 (8)	2 (2)	0	0	12 (10)	11 (7)	2 (1)	0	0	13 (8)
Arthralgia	5 (8)	0	0	0	5 (8)	8 (7)	1 (1)	0	0	9 (7)	11 (7)	1 (1)	0	0	12 (7)
Hypokalemia	3 (5)	0	1 (2)	0	4 (7)	9 (7)	1 (1)	0	0	10 (8)	10 (6)	2 (1)	0	0	12 (7)
Rash	0	0	0	0	0	10 (8)	0	0	0	10 (8)	12 (7)	0	0	0	12 (7)
Dizziness	1 (2)	0	0	0	1 (2)	7 (6)	0	0	0	7 (6)	11 (7)	0	0	0	11 (7)
Hypoalbuminemia	3 (5)	1 (2)	0	0	4 (7)	6 (5)	2 (2)	0	0	8 (7)	9 (5)	2 (1)	0	0	11 (7)
White blood cell count decreased	1 (2)	0	0	0	1 (2)	7 (6)	2 (2)	0	0	9 (7)	9 (5)	2 (1)	0	0	11 (7)
Gastroesophageal reflux disease	2 (3)	0	0	0	2 (3)	9 (7)	0	0	0	9 (7)	10 (6)	0	0	0	10 (6)
Hyperbilirubinemia	0	0	0	0	0	4 (3)	2 (2)	2 (2)	0	8 (7)	6 (4)	2 (1)	2 (1)	0	10 (6)
Hyperglycemia	1 (2)	0	0	0	1 (2)	8 (7)	0	0	0	8 (7)	10 (6)	0	0	0	10 (6)
Hypomagnesemia	3 (5)	0	0	0	3 (5)	9 (7)	0	0	0	9 (7)	10 (6)	0	0	0	10 (6)
Muscle spasms	1 (2)	0	0	0	1 (2)	6 (5)	0	0	0	6 (5)	10 (6)	0	0	0	10 (6)
Pruritus	3 (5)	0	0	0	3 (5)	6 (5)	1 (1)	0	0	7 (6)	9 (5)	1 (1)	0	0	10 (6)
Chills	3 (5)	0	0	0	3 (5)	8 (7)	0	0	0	8 (7)	9 (5)	0	0	0	9 (5)
Hypophosphatemia	0	3 (5)	0	0	3 (5)	2 (2)	4 (3)	0	0	6 (5)	3 (2)	6 (4)	0	0	9 (5)
Platelet count decreased	3 (5)	0	0	0	3 (5)	4 (3)	3 (2)	0	0	7 (6)	5 (3)	4 (2)	0	0	9 (5)

[a] Total ivosidenib includes 43 patients initially assigned to placebo who had crossed over to ivosidenib upon radiographic disease progression and unblinding.
[b] Cutoff of at least 5% used for all-grade treatment-emergent adverse events based on the total ivosidenib arm.

eTable 2. Summary of Grade 3 or Higher TEAEs, Including Crossover Patients

	No. (%)		
	Placebo (n = 59)	**Ivosidenib (n = 123)**	**Total ivosidenib (n = 166)[a]**
Any grade ≥3 TEAE	22 (37)	62 (50)	88 (53)
Any related grade ≥3 TEAE	0	8 (7)	11 (7)
Most common grade ≥3 TEAEs[b]			
Ascites	4 (7)	11 (9)	15 (9)
Anemia	0	8 (7)	12 (7)
Blood bilirubin increased	1 (2)	7 (6)	9 (5)
Hyponatremia	6 (10)	7 (6)	8 (5)
Hypophosphatemia	3 (5)	4 (3)	6 (4)
Hypertension	1 (2)	2 (2)	5 (3)
Blood alkaline phosphatase increased	3 (5)	3 (2)	3 (2)

Abbreviation: TEAE, treatment-emergent adverse event.

[a] Total ivosidenib includes 43 patients initially assigned to placebo who had crossed over to ivosidenib upon radiographic disease progression and unblinding.

[b] Most common TEAEs is defined as the AE events reported by ≥5% in any column.

eTable 3. Summary of Quality of Life Assessment Completion

	Ivosidenib		**Placebo**	
	EORTC QLQ-C30	**EORTC QLQ-BIL21**	**EORTC QLQ-C30**	**EORTC QLQ-BIL21**
Baseline	N = 114	N = 108	N = 53	N = 52
Cycle 2 day 1, No. (%)	68 (60)	68 (63)	24 (45)	23 (44)
Cycle 3 day 1, No. (%)	52 (46)	52 (48)	12 (23)	12 (23)

At baseline, 114 of 126 (90.5%) randomized patients in the ivosidenib arm and 53 of 61 (87%) patients randomized in the placebo group completed the EORTC QLQ-C30 assessment and 108 (85.7%) and 52 (85%) completed the QLQ-BIL21 assessment.

Abbreviations: EORTC QLQ-BIL21, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cholangiocarcinoma and gallbladder cancer module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

eTable 4. EORTC QLQ-C30 and QLQ-BIL21 Prespecified Subscale Score Changes From Baseline at Cycle 2 Day 1 From Mixed-Effect Modelling for Ivosidenib vs Placebo Before Crossover

	EORTC QLQ-C30				EORTC QLQ-BIL21			
	Least squares mean (SE) change		Difference, ivosidenib vs placebo (95% CI)		Least squares mean (SE) change		Difference, ivosidenib vs placebo (95% CI)	
Subscale	**Ivosidenib (n = 67)**	**Placebo (n = 21)**		***P* value**	**Ivosidenib (n = 65)**	**Placebo (n = 20)**		***P* value**
Physical functioning (higher scores represent better functioning)	–2.4 (1.75)	–13.3 (2.95)	11.0 (4.23-17.73)	.002				
Pain (higher scores represent worse symptoms)	2.2 (2.48)	12.5 (4.35)	–10.4 (–20.18 to –0.52)	.04	5.1 (1.94)	10.1 (3.49)	–5.1 (–12.93 to 2.80)	.21
Appetite loss[a] (higher scores represent worse symptoms)	7.9 (2.60)	4.3 (4.55)	3.6 (–6.65 to 13.91)	.49	4.3 (1.84)	3.6 (3.19)	0.7 (–6.56 to 7.88)	.86

Two-sided *P* values are shown.

Abbreviations: EORTC QLQ-BIL21, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cholangiocarcinoma and gallbladder cancer module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

[a] For EORTC QLQ-BIL21, the eating subscale was assessed.

eTable 5. EORTC QLQ-C30 and QLQ-BIL21 Prespecified Subscale Score Changes From Baseline at Cycle 3 Day 1 From Mixed-Effect Modelling for Ivosidenib vs Placebo Before Crossover

	EORTC QLQ-C30				EORTC QLQ-BIL21			
	Least squares mean (SE) change		Difference, ivosidenib vs placebo (95% CI)	*P* value	Least squares mean (SE) change		Difference, ivosidenib vs placebo (95% CI)	*P* value
Subscale	**Ivosidenib (n = 50)**	**Placebo (n = 9)**			**Ivosidenib (n = 48)**	**Placebo (n = 9)**		
Physical functioning (higher scores represent better functioning)	–0.2 (1.89)	–12.6 (3.88)	12.3 (3.85-20.78)	.004				
Pain (higher scores represent worse symptoms)	–1.2 (2.73)	–5.3 (5.96)	4.1 (–8.74 to 17.04)	.53	2.3 (2.16)	–2.1 (4.70)	4.4 (–5.82 to 14.55)	.40
Appetite loss[a] (higher scores represent worse symptoms)	–0.5 (2.89)	3.2 (6.40)	–3.7 (–17.46 to 10.11)	.60	–2.0 (2.02)	4.1 (4.24)	–6.1 (–15.34 to 3.12)	.19

Two-sided *P* values are shown.

Abbreviations: EORTC QLQ-BIL21, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cholangiocarcinoma and gallbladder cancer module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

[a] For EORTC QLQ-BIL21, the eating subscale was assessed.

eTable 6. Gene Comutation Frequency at Baseline

	No. (%)		
Gene name	**Placebo (n = 61)**	**Ivosidenib (n = 126)**	**Total (N = 187)**
PIK3CA	7 (11)	13 (10)	20 (11)
KRAS	6 (10)	8 (6)	14 (7)
BRAF	5 (8)	3 (2)	8 (4)
FGFR2	5 (8)	3 (2)	8 (4)
EGFR	3 (5)	3 (2)	6 (3)
JAK3	2 (3)	4 (3)	6 (3)
NRAS	3 (5)	3 (2)	6 (3)
ERBB2	2 (3)	1 (1)	3 (2)
CDK4	0 (0)	2 (2)	2 (1)
FGFR3	0 (0)	2 (2)	2 (1)
KIT	1 (2)	1 (1)	2 (1)
MAP2K1	0 (0)	2 (2)	2 (1)
AR	0 (0)	1 (1)	1 (1)
CTNNB1	1 (2)	0 (0)	1 (1)
ERBB4	1 (2)	0 (0)	1 (1)
ETV1	0 (0)	1 (1)	1 (1)
HRAS	0 (0)	1 (1)	1 (1)
IDH2	1 (2)	0 (0)	1 (1)
MET	0 (0)	1 (1)	1 (1)

MTOR	1 (2)	0 (0)	1 (1)
RET	1 (2)	0 (0)	1 (1)
ROS1	1 (2)	0 (0)	1 (1)
SMO	1 (2)	0 (0)	1 (1)

The following genes were assayed in the Oncomine platform but no mutations in those genes (copy number variants, single-nucleotide variants, and/or fusions) were detected in the ClarIDHy dataset: *ABL1*, *AKT1*, *AKT3*, *ALK*, *AXL*, *CCND1*, *CDK6*, *DDR2*, *ERBB3*, *ERG*, *ESR1*, *ETV4*, *ETV5*, *FGFR1*, *FGFR4*, *GNA11*, *GNAQ*, *JAK1*, *JAK2*, *MAP2K2*, *MYC*, *MYCN*, *NTRK1*, *NTRK2*, *NTRK3*, *PDGFRA*, *PPARG*, *RAF1*.