ClarIDHy: A global, phase 3, randomized, double-blind study of ivosidenib vs placebo in patients with advanced cholangiocarcinoma with an isocitrate dehydrogenase 1 (IDH1) mutation

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Disclosures

- Ghassan Abou-Alfa declares the following potential conflicts of interest:
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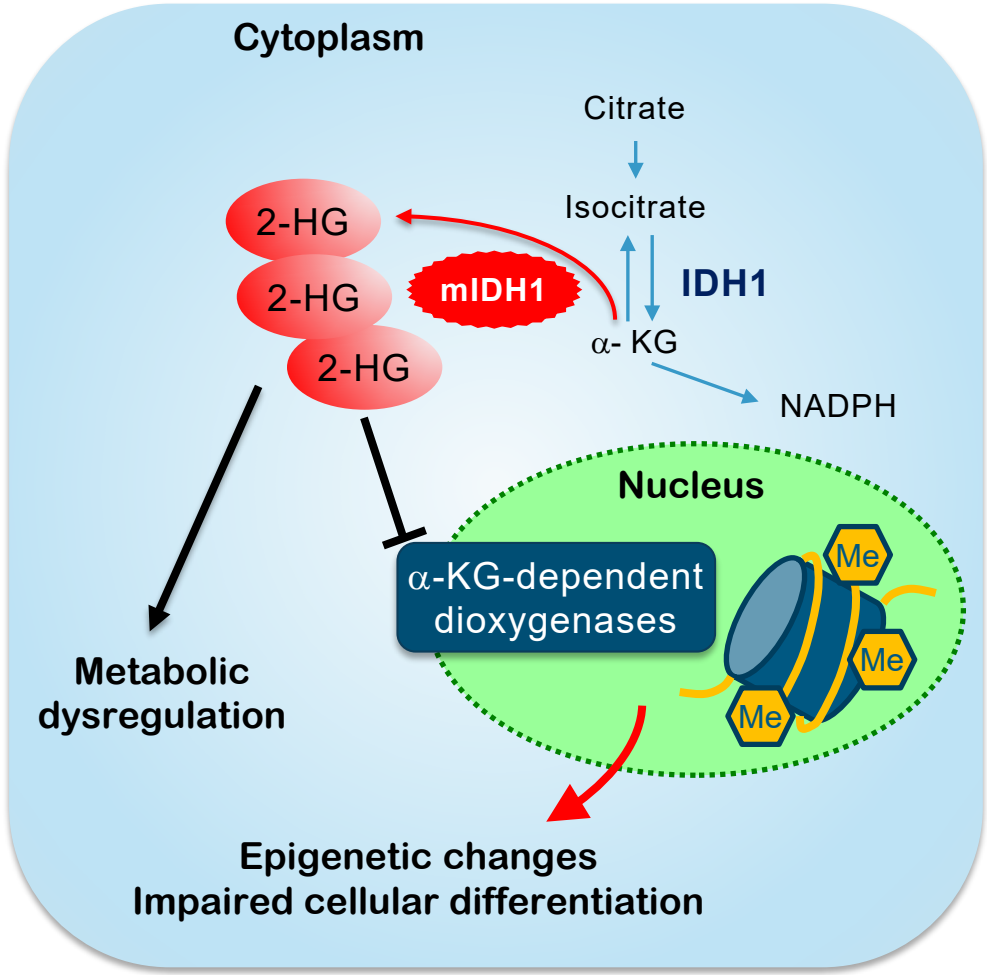
IDH1 mutations in advanced cholangiocarcinoma

- Advanced cholangiocarcinoma is an aggressive rare cancer with treatment options limited primarily to chemotherapy[1]
- IDH1 mutations occur in up to 20% of cholangiocarcinoma and do not confer a favorable prognosis[1]
- Ivosidenib (AG-120) is a first-in-class, oral, targeted, small-molecule inhibitor of the mutant IDH1 (mIDH1) protein,[2] and is FDA-approved for mIDH1 R/R AML and ND AML not eligible for intensive chemotherapy[3]
- A phase 1 study of ivosidenib included 73 previously treated mIDH1 cholangiocarcinoma patients and was associated with: median PFS, 3.8 months; 6- and 12-month PFS rates, 40.1% and 21.8%, respectively; and median OS 13.8 months[4]



2-HG=D-2-hydroxyglutarate; α-KG=alpha-ketoglutarate; AML=acute myeloid leukemia; FDA=Food and Drug Administration; Me=methyl groups; ND=newly-diagnosed; OS=overall survival; PFS=progression-free survival; R/R=relapsed/refractory.

1. Boscoe AN, et al. *J Gastrointest Oncol*. 2019;10:751-765. **2.** Popovici-Muller J, et al. *ACS Med Chem Lett*. 2018;9:300-305. **3.** TIBSOVO highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211192s001lbl.pdf. Accessed August 5, 2019. **4.** Lowery MA, et al. *Lancet Gastroenterol Hepatol*. 2019;4:711-720.

ClarIDHy: Study design and endpoints

Key eligibility criteria

- ≥18 years of age
- Histologically confirmed diagnosis of cholangiocarcinoma
- Centrally confirmed mIDH1* status by NGS
- ECOG PS score 0 or 1
- 1-2 prior therapies (at least 1 gemcitabine- or 5-FU-containing regimen)
- Measurable lesion as defined by RECIST v1.1
- Adequate hematologic, hepatic, and renal function

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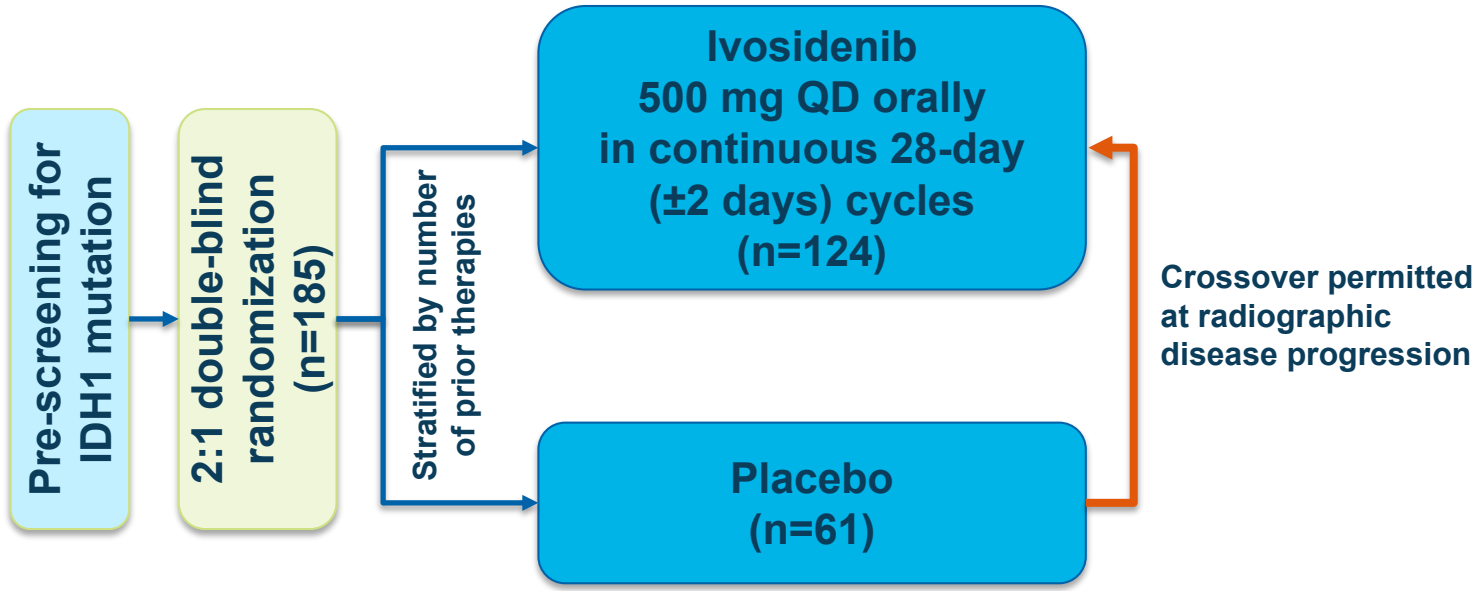


An independent data monitoring committee monitored the safety data throughout the study

- **Primary endpoint:** PFS by blinded independent radiology center (IRC)
- **Secondary endpoints included:** safety and tolerability; PFS by local review; OS; objective response rate; quality of life (QoL)†; pharmacokinetics/pharmacodynamics
- Sample size of ~186 patients based on hazard ratio (HR)=0.5, 96% power, 1-sided alpha=0.025
- 780 patients were screened for IDH1 mutations across 49 sites and 6 countries

*IDH1 mutation status prospectively confirmed by NGS-based Oncomine™ Focus Assay on formalin-fixed, paraffin-embedded tumor tissue in a Clinical Laboratory Improvement Amendments-certified laboratory.

†Assessed using EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BIL21, and PGI questions.

ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=5-level EuroQoL-5 Dimension questionnaire; FU=fluorouracil; NGS=next-generation sequencing; PGI=Patient Global Impression; QD=once daily; QLQ-BIL21=Cholangiocarcinoma and Gallbladder Cancer module; QLQ-C30=Quality of Life Questionnaire Core 30; RECIST=Response Evaluation Criteria in Solid Tumors.

ClarIDHy: Patient disposition

	Ivosidenib (n=124)	Placebo (n=61)
Treated, n (%)	121 (97.6)	59 (96.7)
On treatment	38 (31.4)	8 (13.6)
Discontinued treatment	83 (68.6)	51 (86.4)
Progressive disease	65 (53.7)	44 (74.6)
Adverse events	6 (5.0)	4 (6.8)
Death	4 (3.3)	0
Withdrawal by patient	6 (5.0)	2 (3.4)
Withdrawal of consent	1 (0.8)	1 (1.7)
Other	1 (0.8)	0
Not treated, n (%)	3 (2.4)	2 (3.3)
On study, n (%)	71 (57.3)	27 (44.3)

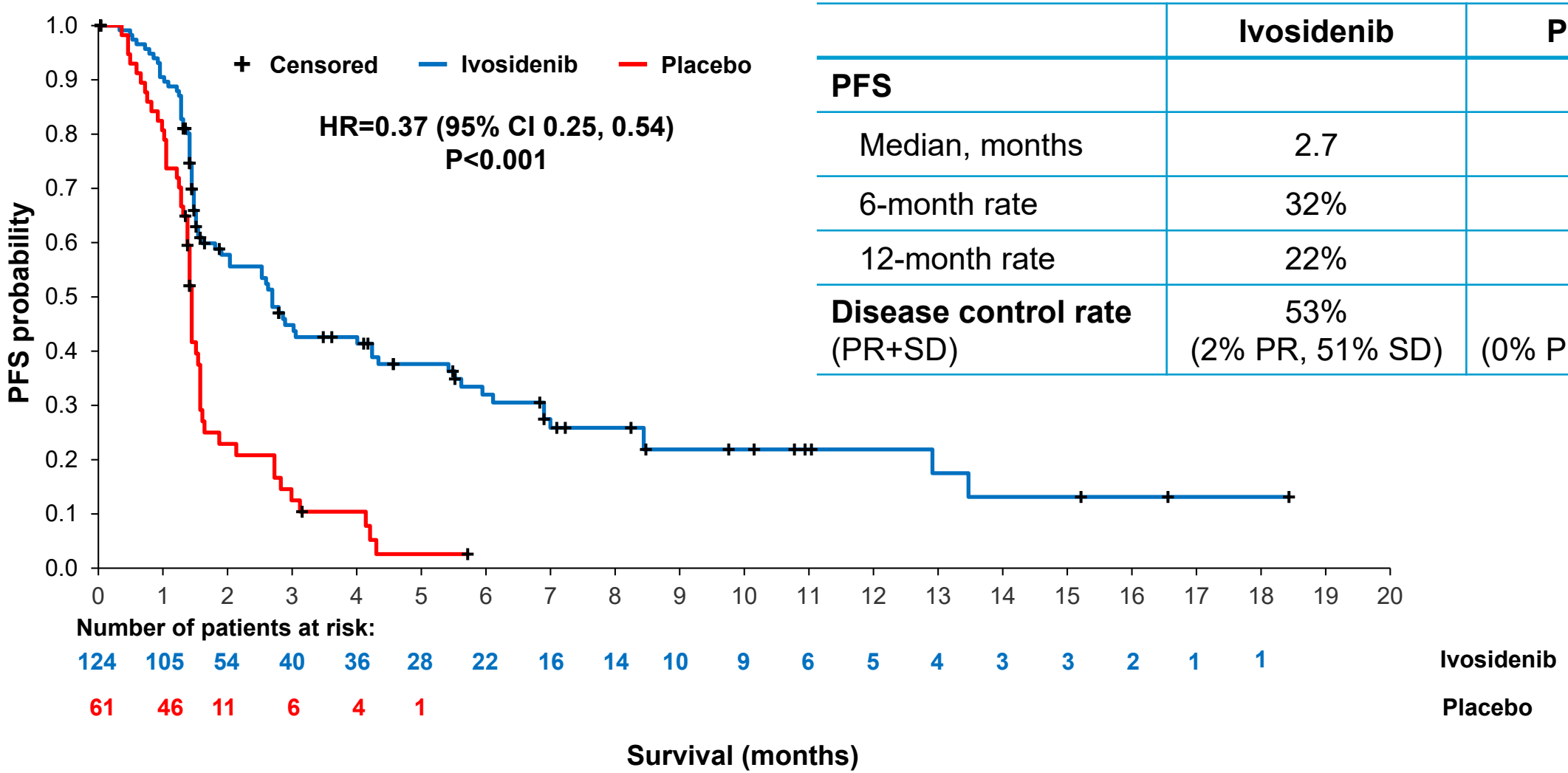
- As of the January 31, 2019 data cut, 35 placebo-treated patients (57.4%) crossed over to open-label ivosidenib upon radiographic disease progression and unblinding
- 26 placebo-treated patients (42.6%) did not cross over due to the following reasons: death (n=13), still on placebo treatment (n=8), never dosed (n=2), withdrawal of consent (n=2), received another treatment (n=1)

ClarIDHy: Baseline characteristics

Characteristic	Ivosidenib (n=124)	Placebo (n=61)
Randomization strata, n (%)		
1 prior line of therapy	66 (53.2)	33 (54.1)
2 prior lines of therapy	58 (46.8)	28 (45.9)
IDH1 mutation, n (%)		
R132C	84 (67.7)	45 (73.8)
R132L/G/S/H	21 (16.9); 17 (13.7); 2 (1.6); 0	7 (11.5); 6 (9.8); 1 (1.6); 2 (3.3)
ECOG PS score at baseline,* n (%)		
0	49 (39.5)	19 (31.1)
1	74 (59.7)	41 (67.2)
Cholangiocarcinoma type at diagnosis, n (%)		
Intrahepatic	111 (89.5)	58 (95.1)
Extrahepatic/Perihilar	5 (4.0)	1 (1.6)
Unknown	8 (6.5)	2 (3.3)
Extent of disease at screening		
Local/regional	9 (7.3)	5 (8.2)
Metastatic	115 (92.7)	56 (91.8)

*Two (2) patients had an ECOG worsen to 2 (placebo) and 3 (ivosidenib) at baseline assessment upon study start.

ClarIDHy: PFS by IRC



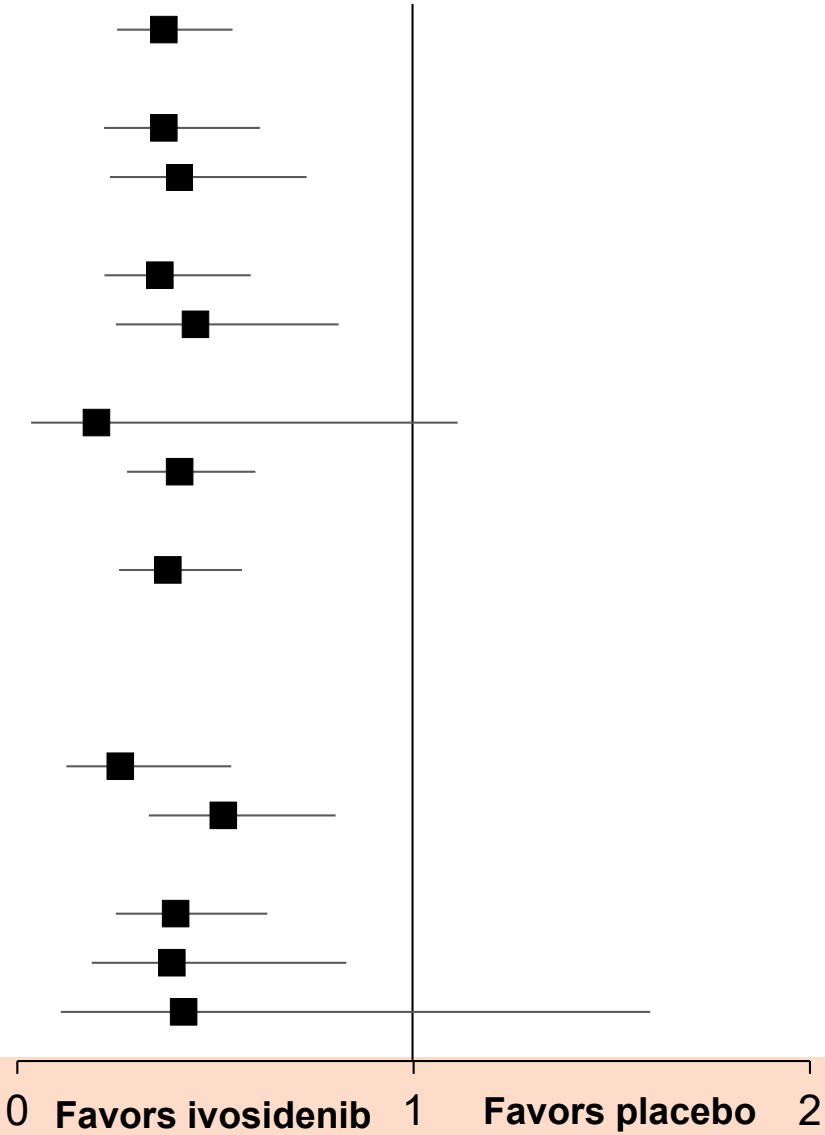
	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

NE=not estimable; PR=partial response; SD=stable disease.

ClarIDHy: Ivosidenib efficacy consistent across subgroups*

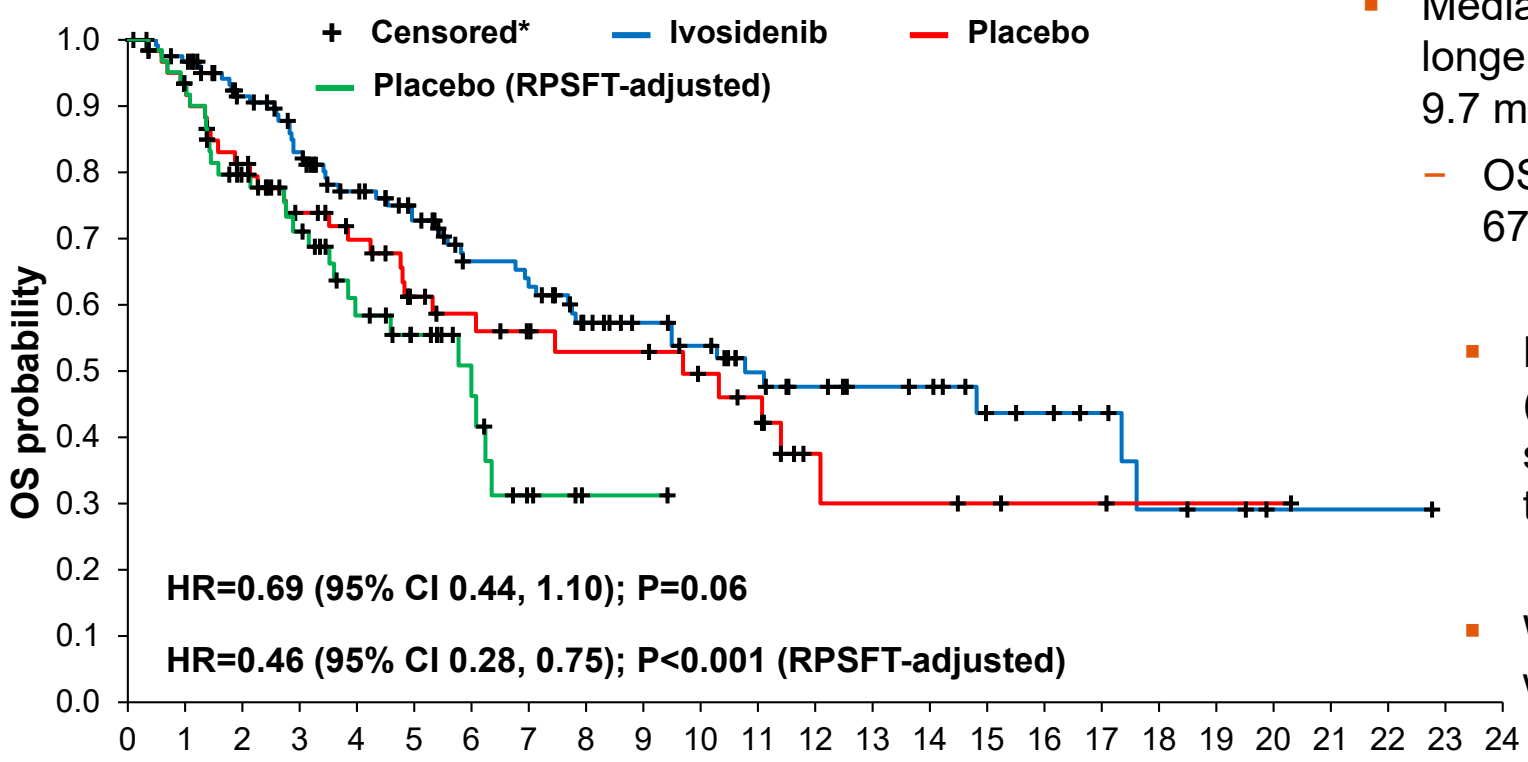
PFS by IRC

	Events/N	HR	Lower 95% CI	Upper 95% CI
Overall	126/185	0.37	0.252	0.543
Prior lines of therapy				
1	66/106	0.37	0.219	0.612
≥2	60/79	0.41	0.234	0.730
Gender				
Female	74/117	0.36	0.220	0.589
Male	52/68	0.45	0.249	0.811
Extent of disease at screening				
Locally advanced	7/14	0.20	0.035	1.111
Metastatic	119/171	0.41	0.277	0.601
Cancer type at initial diagnosis				
Intrahepatic cholangiocarcinoma	114/169	0.38	0.257	0.567
extrahepatic cholangiocarcinoma	3/6			
unknown	9/10			
ECOG PS score at baseline				
0	41/68	0.26	0.124	0.540
≥1	85/117	0.52	0.332	0.803
Regions				
North America	83/124	0.40	0.249	0.631
Europe	34/49	0.39	0.188	0.830
Asia	9/12	0.42	0.110	1.597



*Subgroups with events number ≤5 or number of patients ≤10 were not plotted.

ClarIDHy: OS by intent-to-treat (ITT)



- Median OS based on 78 events was numerically longer with ivosidenib than placebo (10.8 vs. 9.7 months)
  - OS rates at 6 and 12 months for ivosidenib: 67% and 48% vs. 59% and 38% for placebo
- Rank-preserving structural failure time (RPSFT)[1,2] method used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib
- With the RPSFT method, the median OS with placebo adjusts to 6 months

*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.

1. Watkins C, et al. *Pharm Stat*. 2013;12:348-357. **2.** Robins JM, Tsiatis AA. *Commun Stat Theory Methods*. 1991;20:2609-2631.

ClarIDHy: Treatment-emergent adverse events (TEAEs)

	Placebo (n=59)	Ivosidenib (n=121)	Total ivosidenib (n=156)*
Any TEAE, n (%)	57 (96.6)	115 (95.0)	146 (93.6)
Most common TEAEs, n (%)			
Nausea	15 (25.4)	43 (35.5)	50 (32.1)
Diarrhea	9 (15.3)	37 (30.6)	45 (28.8)
Fatigue	10 (16.9)	32 (26.4)	37 (23.7)
Cough	5 (8.5)	25 (20.7)	30 (19.2)
Abdominal pain	8 (13.6)	26 (21.5)	29 (18.6)
Ascites	9 (15.3)	25 (20.7)	29 (18.6)
Decreased appetite	11 (18.6)	23 (19.0)	27 (17.3)
Anemia	3 (5.1)	18 (14.9)	25 (16.0)
Vomiting	10 (16.9)	23 (19.0)	25 (16.0)

- Grade ≥3 TEAE: 35.6% for placebo vs. 46.2% for total ivosidenib. Most common (placebo vs. total ivosidenib): ascites (6.8% vs. 7.7%), bilirubin increase (1.7% vs. 5.8%), anemia (0% vs. 5.1%), AST increase (1.7% vs. 5.1%)
- TEAEs leading to discontinuation were more common for placebo (8.5% vs. 5.8%) than total ivosidenib
- TEAEs leading to dose reductions (2.6% vs. 0%) and interruptions (26.3% vs. 16.9%) were more common for total ivosidenib relative to placebo

*Total ivosidenib includes 35 patients initially assigned to placebo who had crossed over to ivosidenib upon radiographic disease progression and unblinding.
>15% TEAEs based on total ivosidenib

ClarIDHy: QoL results

EORTC QLQ-C30 Physical Function Score, change from baseline at C2D1	Ivosidenib (n=62)	Placebo* (n=20)
Least square mean (SE)†	−3.4 (1.8)	−13.1 (3.0)
Difference (95% CI) vs. placebo	9.8 (2.8, 16.7)	–

- Change from baseline on physical functioning at C2D1‡ favored ivosidenib where placebo patients had a significantly larger (P=0.006§) and clinically meaningful decline in EORTC QLQ-C30 Physical Functioning score compared with ivosidenib patients
- Change from baseline on emotional functioning at C2D1‡ favored ivosidenib where placebo patients had worsened emotional functioning than ivosidenib patients based on EORTC QLQ-C30 Emotional Functioning and QLQ-BIL21 Anxiety symptom scores
- Data limited by small sample size at post-baseline time points

*Analyses focused on data from patients randomized to placebo, before crossover.
†Higher score is better.
‡Analyses focused on C2D1 considering the availability of QoL data.
§MMRM analysis of the change from baseline subscale score was applied, 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. P-value was not adjusted for multiplicity.
‖12- to 13-point score decrease estimated from anchor-based analyses represents clinically meaningful worsening.
C2D1=Day 1 of Cycle 2; MMRM=mixed-effect models with repeated measurements; SE=standard error.

Conclusions

- Ivosidenib significantly improved PFS relative to placebo (HR=0.37 [95% CI 0.25, 0.54]; P<0.001) in previously treated patients with mIDH1 advanced cholangiocarcinoma
- Ivosidenib resulted in a numerical improvement in OS compared with placebo based on ITT, and a significant improvement in OS vs. placebo when adjusting for crossover using the RPSFT method (HR=0.46 [95% CI 0.28, 0.75]; P<0.001)
- Ivosidenib 500 mg QD demonstrated a favorable safety profile
- Ivosidenib was associated with better physical and emotional functioning compared with placebo based on EORTC QLQ-C30 and QLQ-BIL21 QoL scores
- These pivotal data demonstrate the clinical relevance and benefit of ivosidenib in mIDH1 cholangiocarcinoma, and establish the role for genomic testing in this rare cancer with a high unmet need

Acknowledgments

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