Final results from ClarIDHy, a global, phase 3, randomized, double-blind study of ivosidenib vs placebo in patients with previously treated cholangiocarcinoma and an isocitrate dehydrogenase 1 (*IDH1*) mutation

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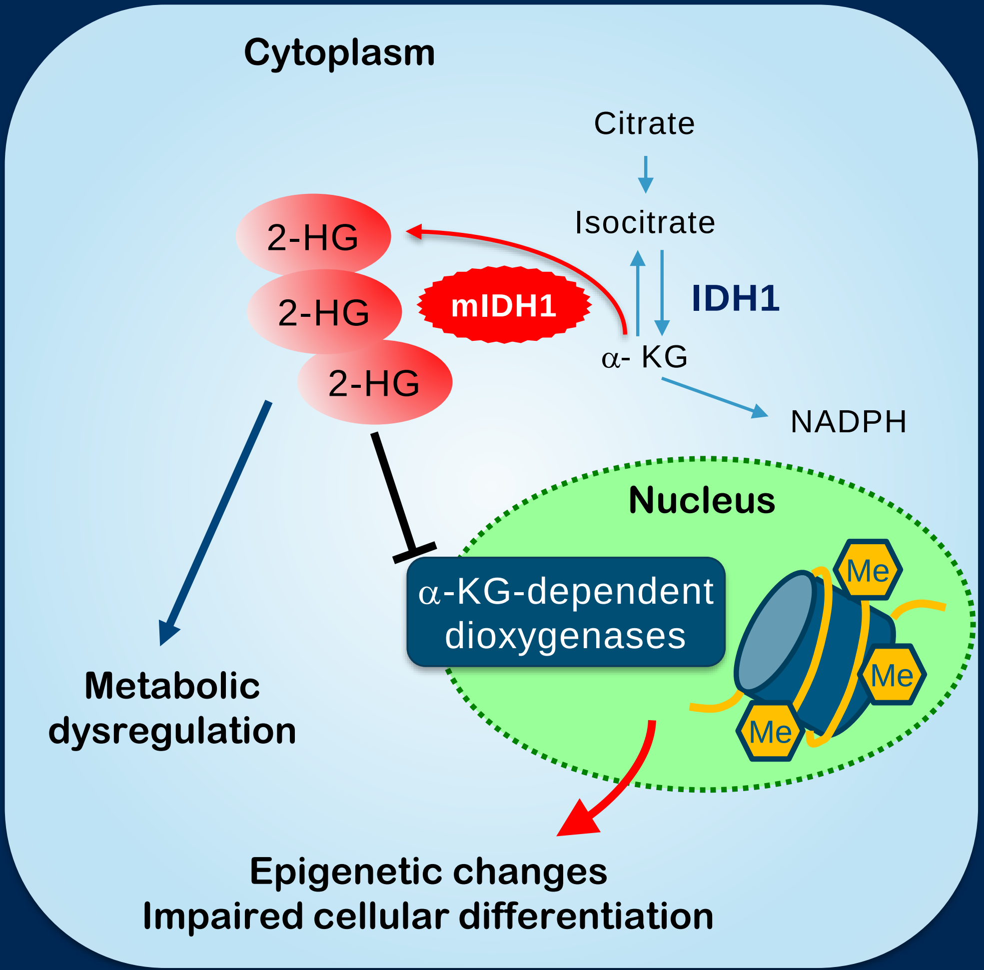
IDH1 mutations in advanced cholangiocarcinoma (CCA)

- CCA is a rare cancer for which there are limited effective therapies
- *IDH1* mutations occur in up to 20% of intrahepatic CCAs,[1] resulting in production of the oncometabolite D-2-hydroxyglutarate (2-HG), which promotes oncogenesis
    - *IDH1* mutations in CCA are not associated with prognosis[1]
- Ivosidenib (AG-120) is a first-in-class, oral, small-molecule inhibitor of mutant IDH1 (mIDH1)[2]
- The phase 3 ClarIDHy study aimed to demonstrate the efficacy of ivosidenib vs placebo in patients with unresectable or metastatic m*IDH1* CCA[3]

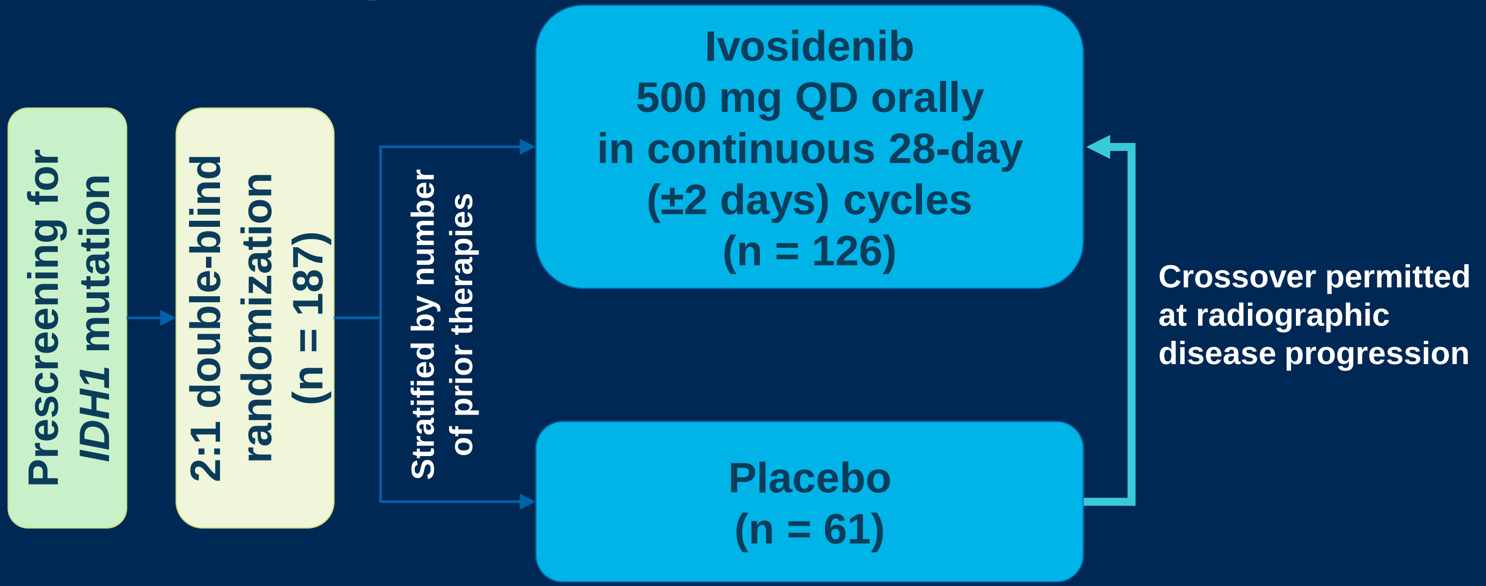


α-KG = alpha-ketoglutarate; Me = methyl groups; NADPH = nicotinamide adenine dinucleotide phosphate hydrogen

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. Abou-Alfa GK et al. *Lancet Oncol*. 2020;21:796-807.

ClarIDHy: Study design and endpoints

Key eligibility criteria
- ≥ 18 years of age
- Histologically confirmed diagnosis of CCA
- Centrally confirmed m*IDH1*[a] 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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Reprinted from The Lancet Oncology, 21, Abou-Alfa et al, Ivosidenib in *IDH1*-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study, 796-807, Copyright 2020, with permission from Elsevier.

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

- **Primary endpoint:** progression-free survival (PFS) by blinded independent radiology center (IRC)
- **Key secondary endpoints:** overall survival (OS); objective response rate; PFS by local review; pharmacokinetics/pharmacodynamics; health-related quality of life (HRQOL)[b]; safety and tolerability

[a]*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.

[b]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

Abou-Alfa GK et al. *Lancet Oncol*. 2020;21:796-807.

Baseline characteristics

Characteristic	Ivosidenib n = 126	Placebo n = 61
Randomization strata, n (%)		
1 prior line of therapy	66 (52.4)	33 (54.1)
2 prior lines of therapy	60 (47.6)	28 (45.9)
IDH1 mutation, n (%)		
R132C	86 (68.3)	45 (73.8)
R132L/G/S/H	21 (16.7); 17 (13.5); 2 (1.6); 0	7 (11.5); 6 (9.8); 1 (1.6); 2 (3.3)
ECOG PS score at baseline,[a] n (%)		
0	50 (39.7)	19 (31.1)
1	75 (59.5)	41 (67.2)
CCA type at diagnosis, n (%)		
Intrahepatic	113 (89.7)	58 (95.1)
Extrahepatic/perihilar	5 (4.0)	1 (1.6)
Unknown	8 (6.3)	2 (3.3)
Extent of disease at screening, n (%)		
Local/regional	9 (7.1)	5 (8.2)
Metastatic	117 (92.9)	56 (91.8)

[a]Two patients had an ECOG PS worsen to 2 (placebo) and 3 (ivosidenib) at baseline assessment upon study start

Patient disposition

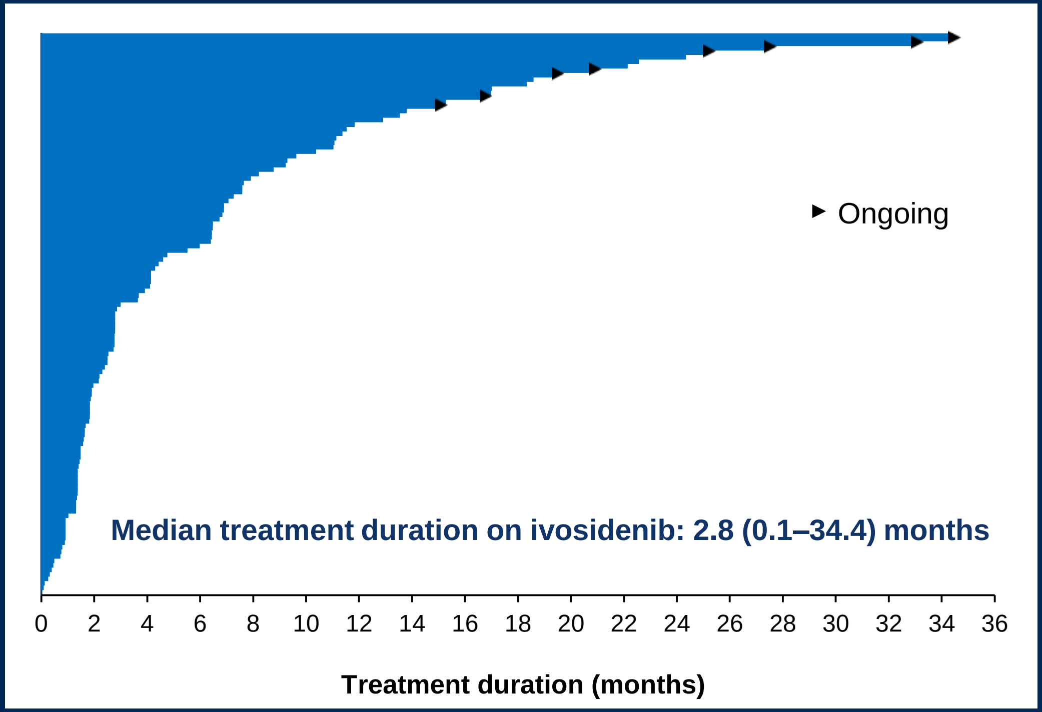
	Ivosidenib n = 126	Placebo n = 61
Treated, n (%)	123 (97.6)	59 (96.7)
On treatment	8 (6.5)	0
Discontinued treatment	115 (93.5)	59 (100)
Progressive disease	92 (74.8)	51 (86.4)
Adverse events	8 (6.5)	4 (6.8)
Withdrawal by patient	6 (4.9)	2 (3.4)
Death	5 (4.1)	0
Withdrawal of consent	2 (1.6)	1 (1.7)
Other	2 (1.6)	1 (1.7)
Not treated, n (%)	3 (2.4)	2 (3.3)
On study, n (%)	24 (19.0)	9 (14.8)

- As of May 31, 2020, **43 placebo-treated patients (70.5%) crossed over to open-label ivosidenib upon radiographic disease progression and unblinding as permitted by study protocol**
  - 18 placebo patients (29.5%) did not cross over: death (n = 12)[a], withdrawal of consent (n = 2)[a], randomized to placebo but never dosed (n = 2), took the wrong drug (n = 1), received another treatment (n = 1)

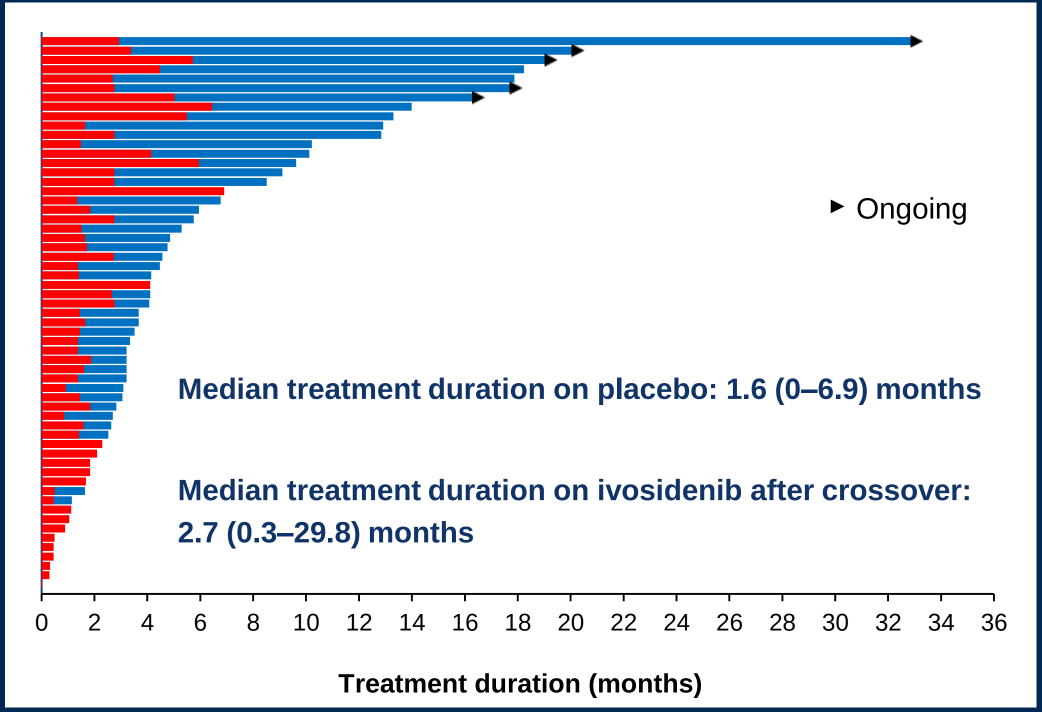
[a]Captured as end of study reason

Treatment duration

All patients treated with **ivosidenib** (n = 123)

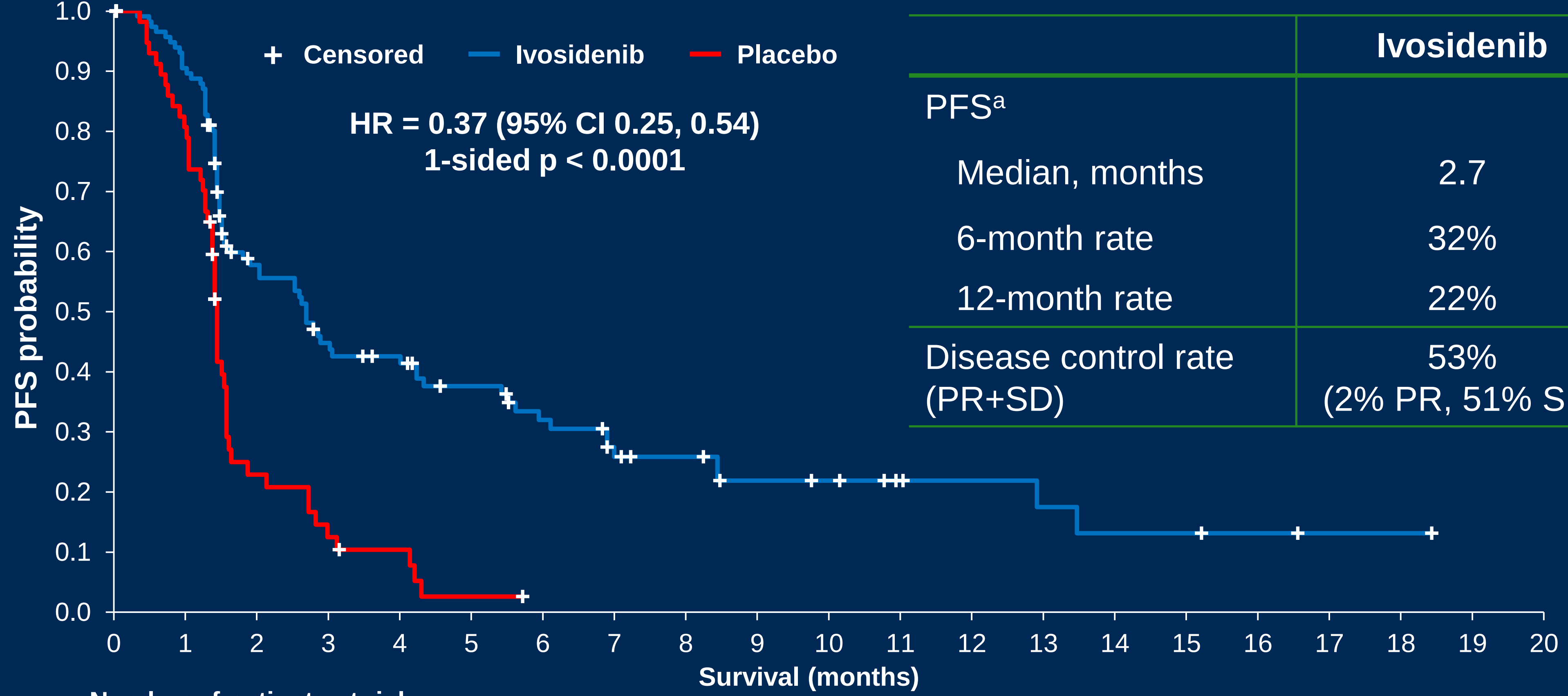


All patients treated with **placebo** (red, n = 59), including those who crossed over to ivosidenib (blue, n = 43)



- 25 patients (15.1%), including 6 patients who crossed over from placebo, remained on ivosidenib ≥ 1 year

Primary endpoint of PFS by IRC was met



Number of patients at risk:

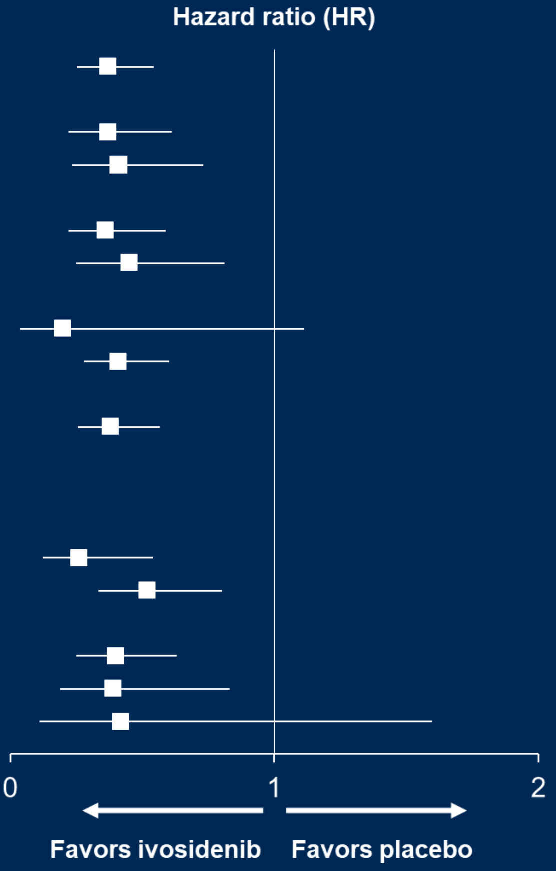
Ivosidenib	124	105	54	40	36	28	22	16	14	10	9	6	5	4	3	3	2	1	1
Placebo	61	46	11	6	4	1													

	Ivosidenib	Placebo
PFS[a]		
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)

[a]All randomized patients as of 31Jan2019
NE = not estimable; PR = partial response; SD = stable disease
Abou-Alfa GK et al. Lancet Oncol. 2020;21:796-807.

PFS by IRC: Ivosidenib efficacy consistent across subgroups[a]

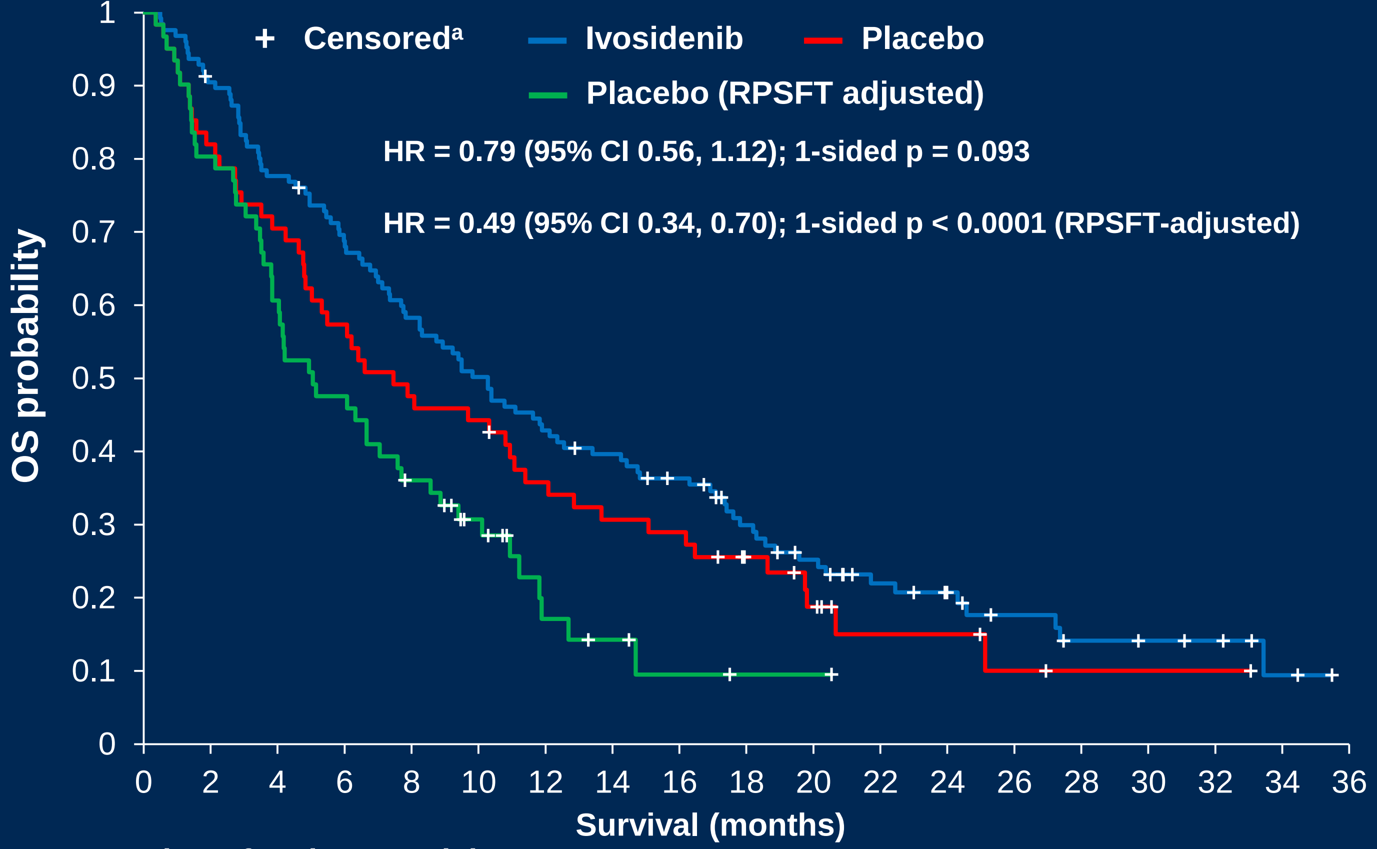
	Events/N	HR	Lower 95% CI	Upper 95% CI
Overall	126/185	0.37	0.252	0.543
Prior lines of therapy				
1	66/106	0.37	0.219	0.612
≥ 2	60/79	0.41	0.234	0.730
Sex				
Female	74/117	0.36	0.220	0.589
Male	52/68	0.45	0.249	0.811
Extent of disease at screening				
Locally advanced	7/14	0.20	0.035	1.111
Metastatic	119/171	0.41	0.277	0.601
Cancer type at initial diagnosis				
Intrahepatic CCA	114/169	0.38	0.257	0.567
Extrahepatic CCA	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



[a]Subgroups with number of events ≤ 5 or number of patients ≤ 10 were not plotted. All randomized patients as of 31Jan2019

Abou-Alfa GK et al. *Lancet Oncol*. 2020;21:796-807.

Overall survival (final analysis)



Number of patients 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	
RPSFT-adj.	61	49	37	29	21	14	6	4	2	1	1							

	Ivosidenib n = 126	Placebo n = 61
Number of events (%)	100 (79.4)	50 (82.0)
Median OS,[b] months	10.3	7.5
6-month rate, %	69	57
12-month rate, %	43	36

- The rank-preserving structural failure time (RPSFT)[1,2] model was implemented as a prespecified analysis to adjust for the effect of crossover from placebo to ivosidenib
- The median OS for placebo after adjustment for crossover was **5.1 months**

[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
[b]All randomized patients as of 31May2020

1. Watkins C et al. *Pharm Stat*. 2013;12:348-57. **2.** Robins JM, Tsiatis AA. *Commun Stat Theory Methods*.1991;20:2609-31.

TEAEs (> 15%[a])

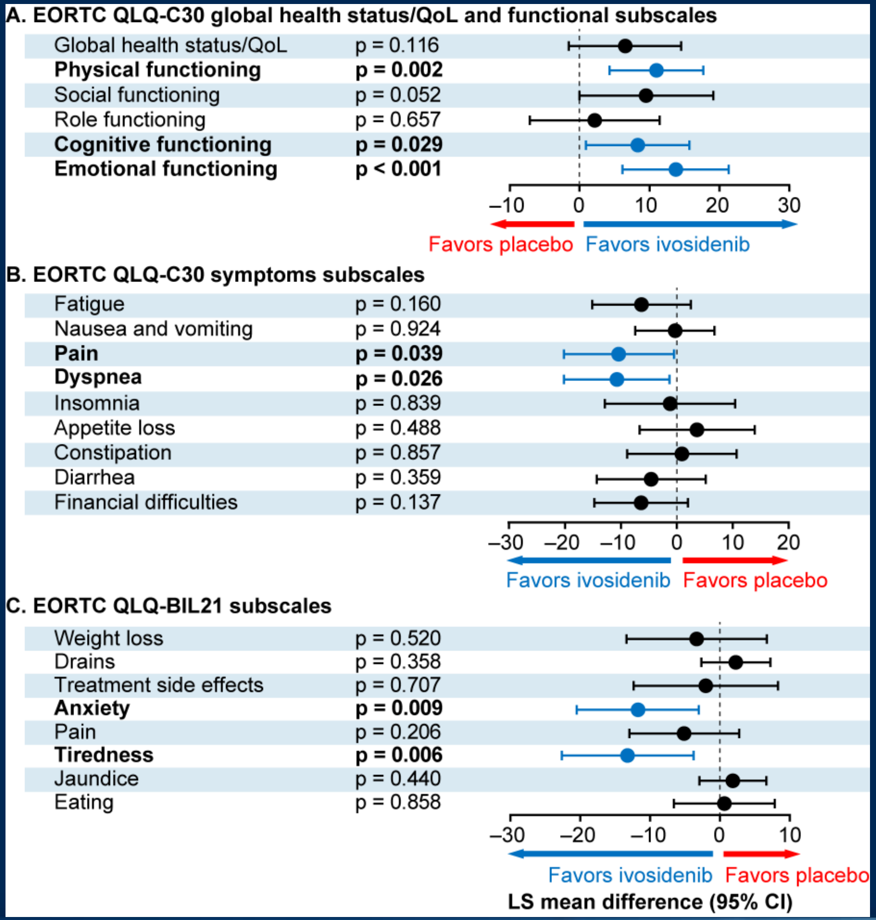
	Placebo n = 59	Ivosidenib n = 123	Total ivosidenib n = 166[b]
Any TEAE, n (%)	57 (96.6)	120 (97.6)	161 (97.0)
Most common TEAEs, n (%)			
Nausea	17 (28.8)	51 (41.5)	63 (38.0)
Diarrhea	10 (16.9)	43 (35.0)	55 (33.1)
Fatigue	10 (16.9)	38 (30.9)	48 (28.9)
Abdominal pain	9 (15.3)	30 (24.4)	37 (22.3)
Cough	5 (8.5)	31 (25.2)	36 (21.7)
Decreased appetite	11 (18.6)	30 (24.4)	36 (21.7)
Ascites	9 (15.3)	28 (22.8)	33 (19.9)
Vomiting	11 (18.6)	28 (22.8)	33 (19.9)
Anemia	3 (5.1)	22 (17.9)	30 (18.1)
Edema peripheral	6 (10.2)	17 (13.8)	25 (15.1)

- Grade ≥ 3 TEAEs: 37.3% for placebo vs 53% for total ivosidenib
  - Most common grade ≥ 3 TEAEs[c] (placebo vs total ivosidenib): ascites (6.8% vs 9.0%), anemia (0% vs 7.2%), blood bilirubin increased (1.7% vs 5.4%)
- TEAEs leading to discontinuation were more common for placebo (8.5% vs 6.6%) than total ivosidenib
- TEAEs leading to dose reductions (0% vs 3.0%) and interruptions (18.6% vs 30.1%) were less common for placebo relative to total ivosidenib

[a]> 15% cutoff used for all grade TEAEs based on total ivosidenib
[b]Total ivosidenib includes 43 patients initially assigned to placebo who had crossed over to ivosidenib upon radiographic disease progression and unblinding. All randomized patients as of 31May2020
[c]> 5% cutoff used for grade ≥ 3 TEAEs based on total ivosidenib
TEAE = treatment-emergent adverse event

Ivosidenib preserved certain HRQOL subscales

MMRM LS mean differences of ivosidenib versus placebo for EORTC QLQ-C30 and EORTC QLQ-BIL21 change scores between arms at C2D1[a]



- Subscales corresponding to physical functioning, pain, and appetite loss were prespecified in the statistical analysis plan. P-values were not adjusted for multiplicity
  - Ivosidenib preserved QLQ-C30 **Physical Functioning**[b] whereas placebo patients experienced decline from baseline at C2D1 (2-sided $p = 0.002$) and C3D1 (2-sided $p = 0.004$)
  - Ivosidenib was favored on the QLQ-C30 **Pain**[c] subscale at C2D1 (2-sided $p = 0.039$); no difference at C3D1
  - Neither arm was favored on other prespecified subscales (QLQ-C30 **Appetite Loss**[c] and QLQ-BIL21 **Pain** and **Eating**[c], all 2-sided $p > 0.050$)

[a]At C2D1: n = 21 for placebo and n = 67 for ivosidenib (QLQ-C30); n = 20 for placebo and n = 65 for ivosidenib (QLQ-BIL21). At C3D1: n = 9 for placebo and n = 50 for ivosidenib (QLQ-C30); n = 9 for placebo and n = 48 for ivosidenib (QLQ-BIL21). All randomized patients as of 31May2020
[b]Higher scores denote better health status or function
[c]Higher scores denote worse symptoms
C2D1 = cycle 2 day 1; C3D1 = cycle 3 day 1; LS = least squares; MMRM = mixed-effect models with repeated measurements

Conclusions

- ClarIDHy is the first randomized phase 3 study of a targeted, oral therapeutic with a noncytotoxic mechanism of action in advanced m*IDH1* CCA
- Ivosidenib demonstrated a highly statistically significant improvement in PFS (HR = 0.37, 1-sided $p < 0.0001$) compared with placebo
- Ivosidenib resulted in a numeric improvement in OS despite a high rate of crossover from the placebo arm (~70%), and this improvement was further supported by the RPSFT adjustment for crossover (HR = 0.49, 1-sided $p < 0.0001$)
- The efficacy data coupled with a tolerable safety profile and supportive HRQOL data demonstrate the clinical benefit of ivosidenib in this aggressive disease in which there is an unmet need for new therapies

Acknowledgments

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- Editorial assistance was provided by Vanessa Ducas, PhD, Excel Scientific Solutions, Fairfield, CT, USA, and supported by Agios

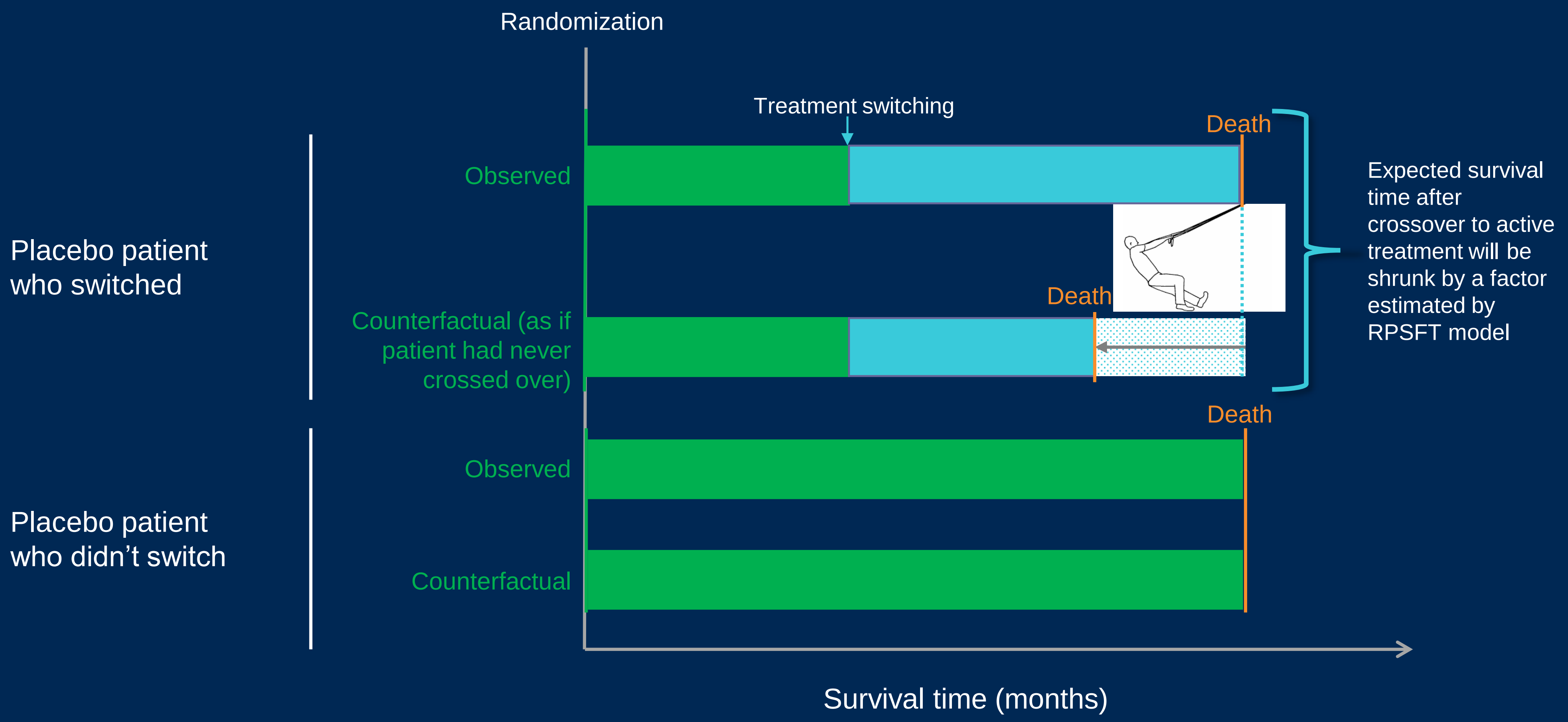
Backup

RPSFT method in clinical trials

- In ClarIDHy, placebo patients meeting crossover eligibility criteria upon radiographic disease progression were allowed to receive open-label ivosidenib,[1] causing the treatment effect estimate on OS to be confounded
- RPSFT models (developed in the 1990s) have been used for decades to adjust for the effect of treatment switching[2-4]

1. Abou-Alfa GK et al. *Lancet Oncol*. 2020;21:796-807. **2.** Watkins C et al. *Pharm Stat*. 2013;12:348-57. **3.** Morden JP et al. *BMC Med Res Methodol*. 2011;11: 4. **4.** Robins JM, Tsiatis AA. *Commun Stat Theory Methods*.1991;20:2609-31.

RPSFT model



Randomization
Treatment switching
Death
Observed
Placebo patient who switched
Death
Counterfactual (as if patient had never crossed over)
Expected survival time after crossover to active treatment will be shrunk by a factor estimated by RPSFT model
Death
Observed
Placebo patient who didn't switch
Counterfactual
Survival time (months)