Updates in Immunotherapy & Targeted Therapy in Gastrointestinal Cancers

May Cho, MD.

UCDAVIS

Conflicts of Interest

Consultant:

Incyte, Eisai, Amgen, Ipsen, Astellas, Taiho, Exelixis, AstraZeneca

Updates in 2019

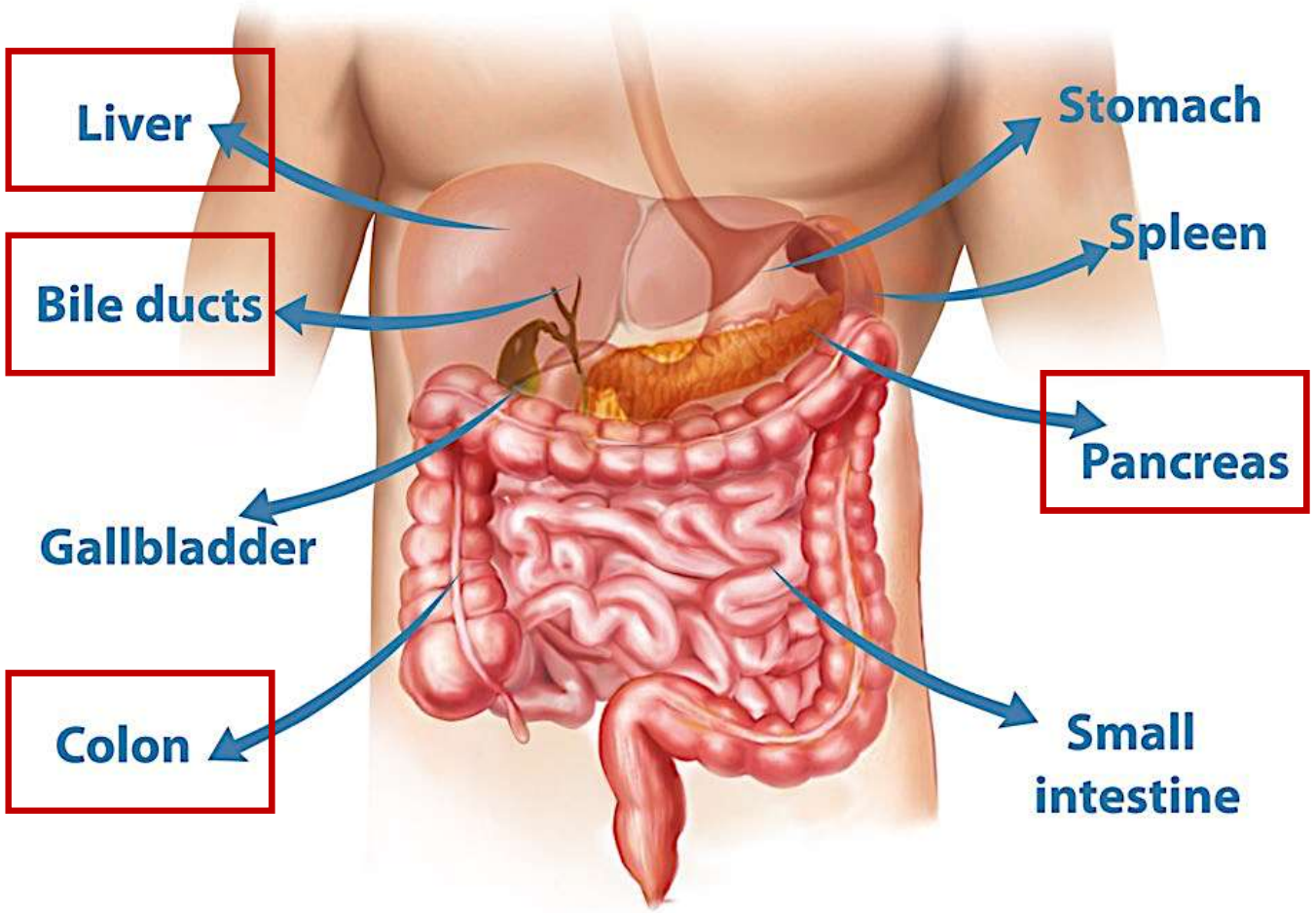


Figure 1. Colon Anatomy. Adapted from The Surgeons Collective. 2019, Retrieved from https://www.thesurgeonscollective.com.au/treatments/cancer-surgery-perth

Updates in 2019

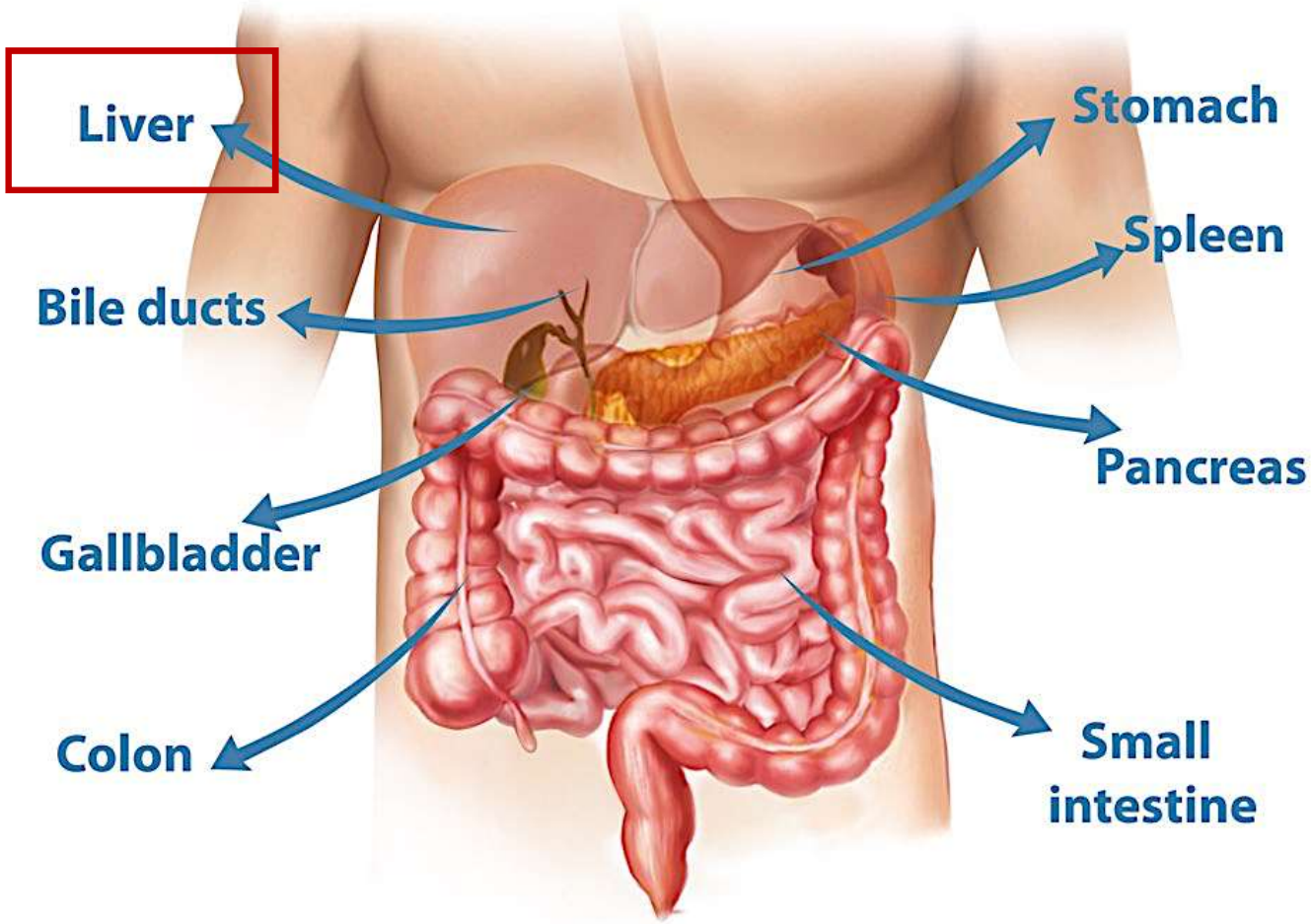
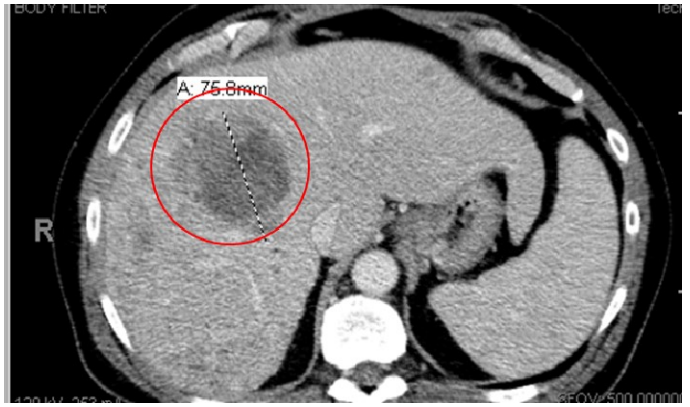
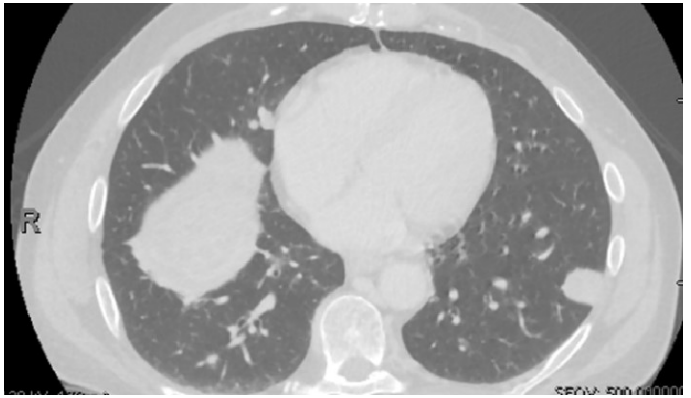


Figure 1. Colon Anatomy. Adapted from The Surgeons Collective. 2019, Retrieved from https://www.thesurgeonscollective.com.au/treatments/cancer-surgery-perth

Case

- A 58 yo man with hepatitis C cirrhosis presents with abdominal pain, vomitting, and 25# weight loss
- Imaging reveals multiple liver lesions that enhance in arterial phase and washout in the portal-venous phase
  - Multiple lung metastases seen
- Based on his labs and exam, his Child-Pugh score is A6





Case – Question

- What is your next step?

1. Liver biopsy
2. Transplant
3. Sorafenib
4. Lenvatinib
5. Atezolizumab/Bevacizumab

Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

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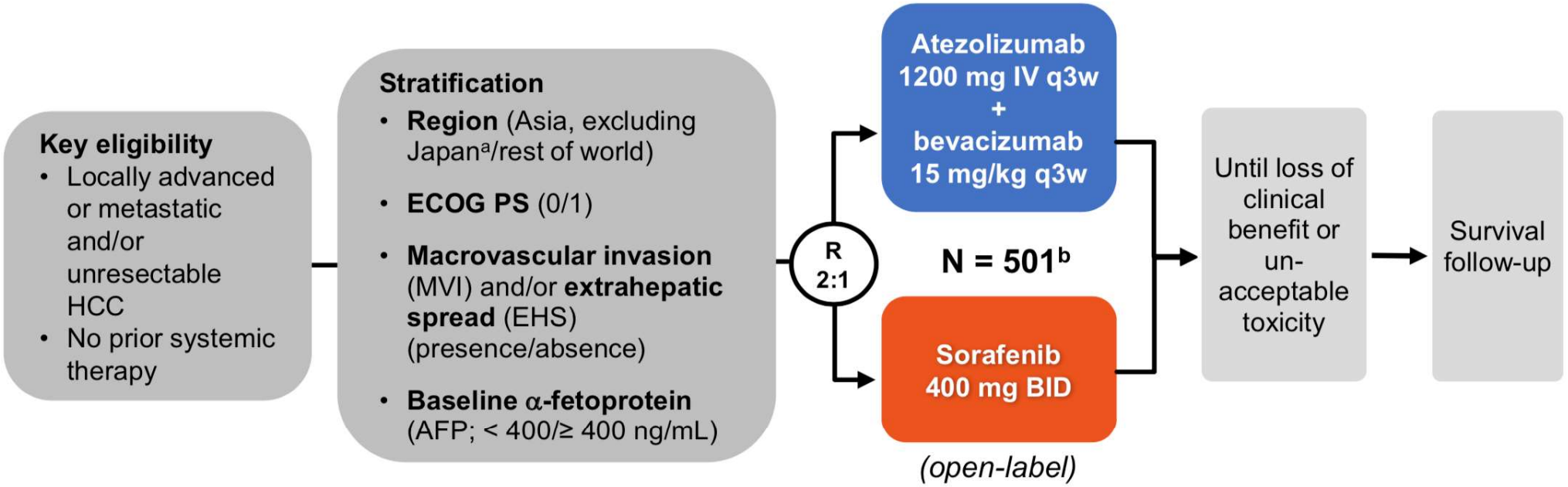
ESMO Asia 2019

Background

- Multikinase inhibitors sorafenib and lenvatinib are the preferred first-line systemic treatments for unresectable hepatocellular carcinoma (HCC)[1-7]
  - While these agents have had modest effects on overall survival, they are both associated with considerable side effects
  - With sorafenib, the median overall survival ranges from ≈ 12 to 14 months; however, no treatment has demonstrated a statistically significant and clinical meaningful improvement in overall survival beyond sorafenib in over a decade
- A Phase 1b study (NCT02715531) of atezolizumab (anti–PD-L1) + bevacizumab (anti-VEGF) in patients with advanced HCC demonstrated a tolerable safety profile and promising antitumour activity, with an objective response rate of 36% and a median progression-free survival of 7.3 months[8-9]
- Here we report the results of IMbrave150, a global, open-label, Phase 3, randomised study of atezolizumab + bevacizumab vs sorafenib in patients with unresectable HCC who have not received prior systemic therapy

1. NCCN Clinical Practice Guidelines. V2.2019; 2. Vogel A, et al. *Ann Onc* 2019; 3. Cheng AL, et al. *Lancet Oncol* 2009; 4. Kudo M, et al. *Lancet* 2018; 5. Llovet JM, et al. *N Engl J Med* 2008; 6. Boige V, et al. *Oncologist* 2012; 7. Finn RS, et al. *Expert Rev Anticancer* 2009; 8. Lee MS, et al. ESMO 2019; 9. Hsu C-H, et al. ESMO Asia 2019.

IMbrave150 study design



Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

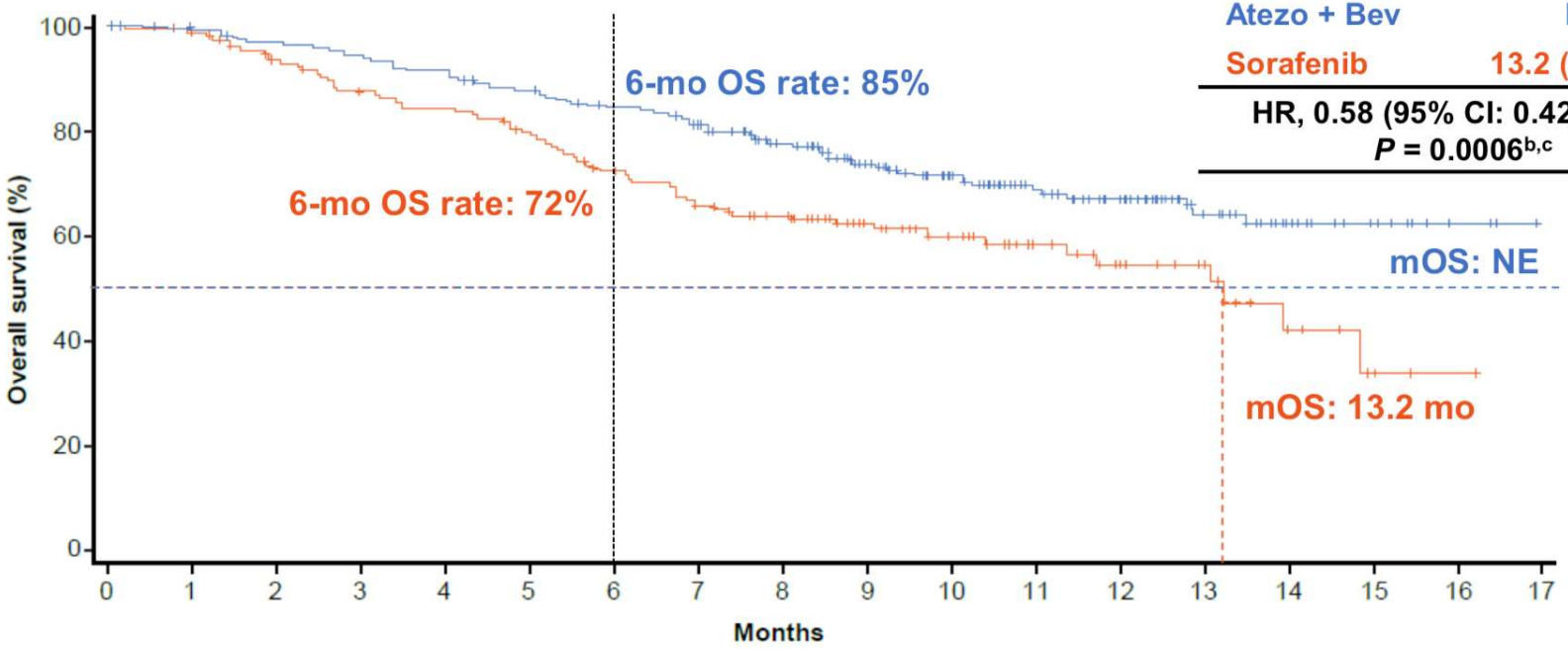
IMbrave150 baseline characteristics (ITT)

Characteristic	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median age (range), years	64 (26-88)	66 (33-87)
Sex, male, n (%)	277 (82)	137 (83)
Region, n (%)		
Asia (excluding Japan[a])	133 (40)	68 (41)
Rest of world	203 (60)	97 (59)
ECOG PS 1, n (%)	127 (38)	62 (38)
Child-Pugh class, n (%)		
A | B	333 (99) | 1 (< 1)	165 (100) | 0
BCLC staging at study entry, n (%)		
A | B | C	8 (2) | 52 (15) | 276 (82)	6 (4) | 26 (16) | 133 (81)
Aetiology of HCC, n (%)		
HBV | HCV | Non-viral	164 (49) | 72 (21) | 100 (30)	76 (46) | 36 (22) | 53 (32)
AFP ≥ 400 ng/mL, n (%)	126 (38)	61 (37)
EHS, n (%)	212 (63)	93 (56)
MVI, n (%)	129 (38)	71 (43)
EHS and/or MVI, n (%)	258 (77)	120 (73)
Prior TACE, n (%)	130 (39)	70 (42)
Prior radiotherapy, n (%)	34 (10)	17 (10)

[a] Japan is included in rest of world.

OS: co-primary endpoint

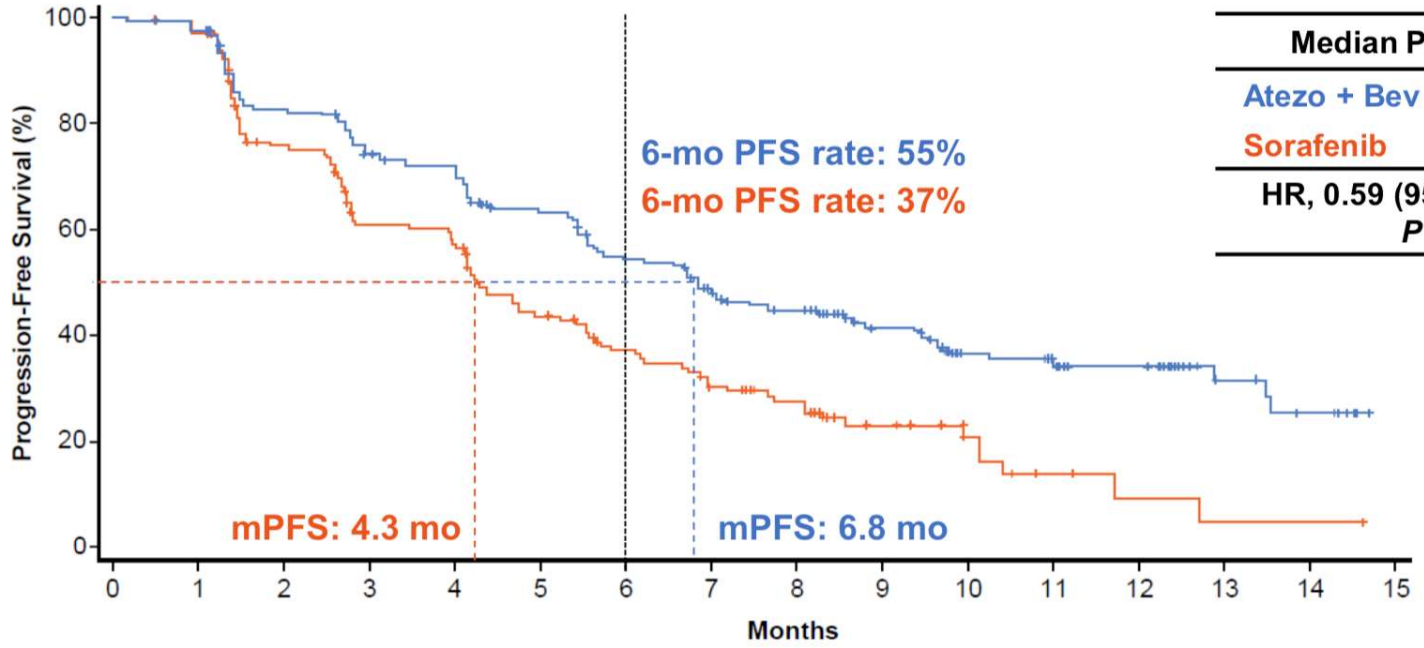
Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b]	
P = 0.0006[b,c]	



No. at risk																		
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Confirmed PFS[a]: co-primary endpoint



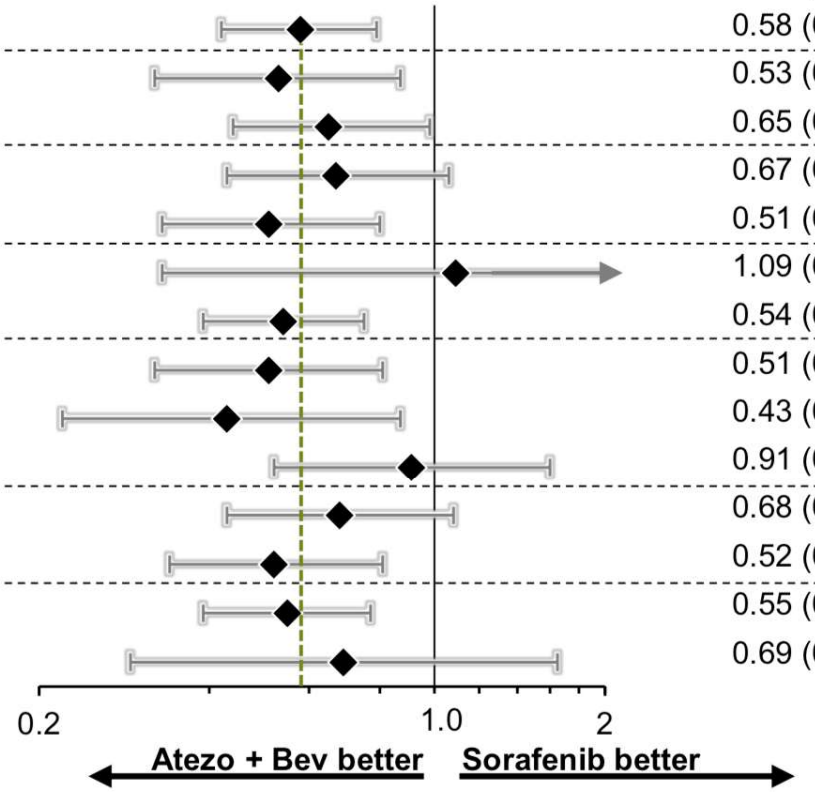
Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d] *P* < 0.0001[d]	

No. at risk																
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

[a] Assessed by IRF per RECIST 1.1. [b] 197 patients (59%) in the Atezo + Bev arm vs 109 (66%) in the sorafenib arm had an event. [c] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [d] The 2-sided *P* value boundary is 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

OS subgroups

Characteristic (n)	Atezo + Bev mOS, mo (n = 336)	Sorafenib mOS, mo (n = 165)	HR (95% CI)[a]
All patients (501)	NE	13.2	0.58 (0.42, 0.79)
Asia (excluding Japan[b]) (201)	NE	13.1	0.53 (0.32, 0.87)
Rest of world (300)	NE	13.2	0.65 (0.44, 0.98)
ECOG PS 0 (312)	NE	13.9	0.67 (0.43, 1.06)
ECOG PS 1 (189)	NE	7.4	0.51 (0.33, 0.80)
BCLC stage B[c] (78)	NE	14.9	1.09 (0.33, 3.53)
BCLC stage C[c] (409)	NE	11.4	0.54 (0.39, 0.75)
HBV HCC (240)	NE	13.9	0.51 (0.32, 0.81)
HCV HCC (108)	NE	13.1	0.43 (0.22, 0.87)
Non-viral HCC (153)	NE	14.9	0.91 (0.52, 1.60)
AFP ≥ 400 ng/mL (187)	12.8	9.1	0.68 (0.43, 1.08)
AFP < 400 ng/mL (314)	NE	13.9	0.52 (0.34, 0.81)
EHS and/or MVI (378)	NE	10.4	0.55 (0.39, 0.77)
No EHS and MVI (123)	NE	14.9	0.69 (0.29, 1.65)



NE, not estimable.
[a] Unstratified HR shown for all characteristics except for "All patients," where stratified HR is shown. [b] Japan is included in rest of world.
[c] BCLC stage A not shown, as there were only 14 patients; thus, estimation is not meaningful.
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

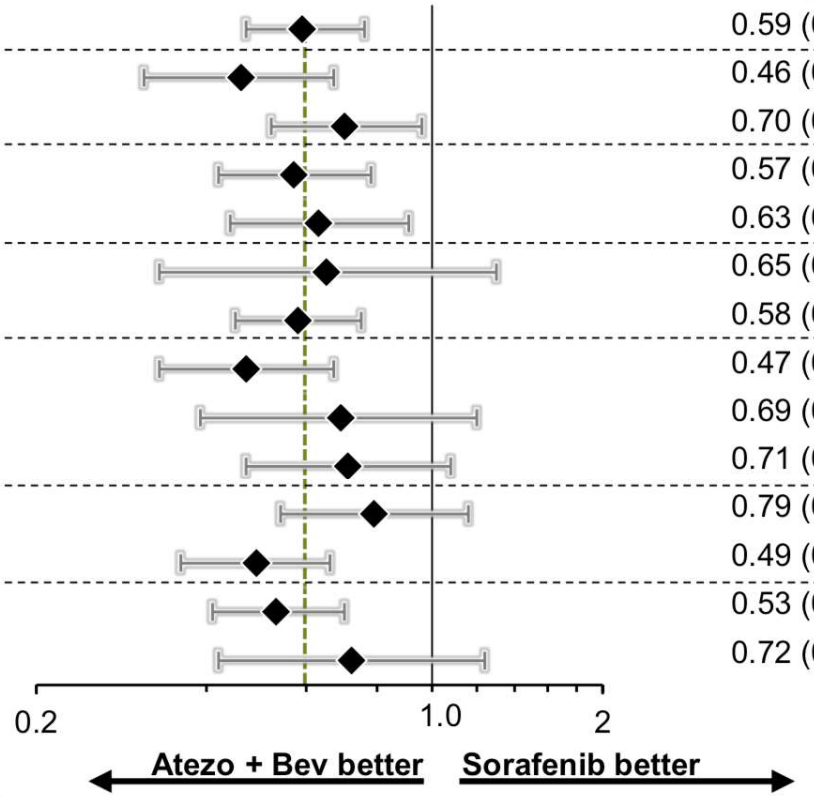
Response rate and duration of response

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n **(%)** (95% CI)	89 **(27)** (23, 33)	19 **(12)** (7, 18)	108 **(33)** (28, 39)	21 **(13)** (8, 20)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	**< 0.0001**		**< 0.0001**	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Ongoing response, n (%)[c]	77 (87)	13 (68)	84 (78)	13 (62)
Median DOR, months (95% CI)	NE	6.3 (4.7, NE)	NE	6.3 (4.9, NE)
Event-free rate at 6 months, n (%)	88	59	82	63

[a] IRF HCC mRECIST–evaluable population was based on patients who presented with measurable disease at baseline per HCC mRECIST criteria.
[b] Stratification factors included geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] Denominator is patients with confirmed CR/PR. Data cutoff: 29 Aug 2019; median survival follow-up, 8.6 mo.

PFS subgroups

Characteristic (n)	Atezo + Bev mPFS, mo (n = 336)	Sorafenib mPFS, mo (n = 165)	HR (95% CI)[a]
All patients (501)	6.8	4.3	0.59 (0.47, 0.76)
Asia (excluding Japan[b]) (201)	7.7	2.8	0.46 (0.31, 0.67)
Rest of world (300)	6.7	4.9	0.70 (0.52, 0.96)
ECOG PS 0 (312)	7.9	4.8	0.57 (0.42, 0.78)
ECOG PS 1 (189)	5.6	4.0	0.63 (0.44, 0.91)
BCLC stage B[c] (78)	NE	8.6	0.65 (0.33, 1.30)
BCLC stage C[c] (409)	6.4	4.1	0.58 (0.45, 0.75)
HBV HCC (240)	6.7	2.8	0.47 (0.33, 0.67)
HCV HCC (108)	8.3	5.8	0.69 (0.39, 1.20)
Non-viral HCC (153)	7.1	5.6	0.71 (0.47, 1.08)
AFP ≥ 400 ng/mL (187)	5.2	4.1	0.79 (0.54, 1.16)
AFP < 400 ng/mL (314)	8.3	4.4	0.49 (0.36, 0.66)
EHS and/or MVI (378)	6.1	4.0	0.53 (0.41, 0.70)
No EHS and MVI (123)	9.9	8.6	0.72 (0.42, 1.24)



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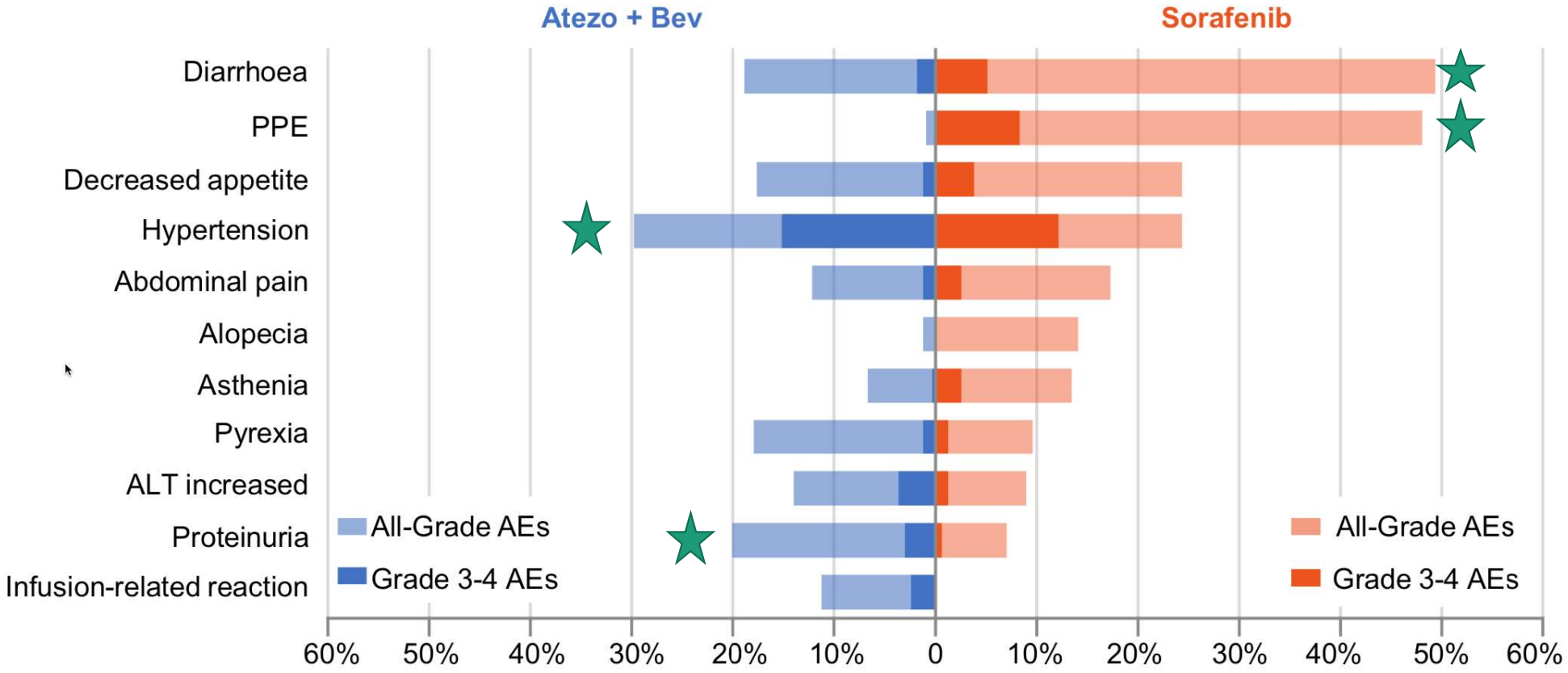
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Safety[a]

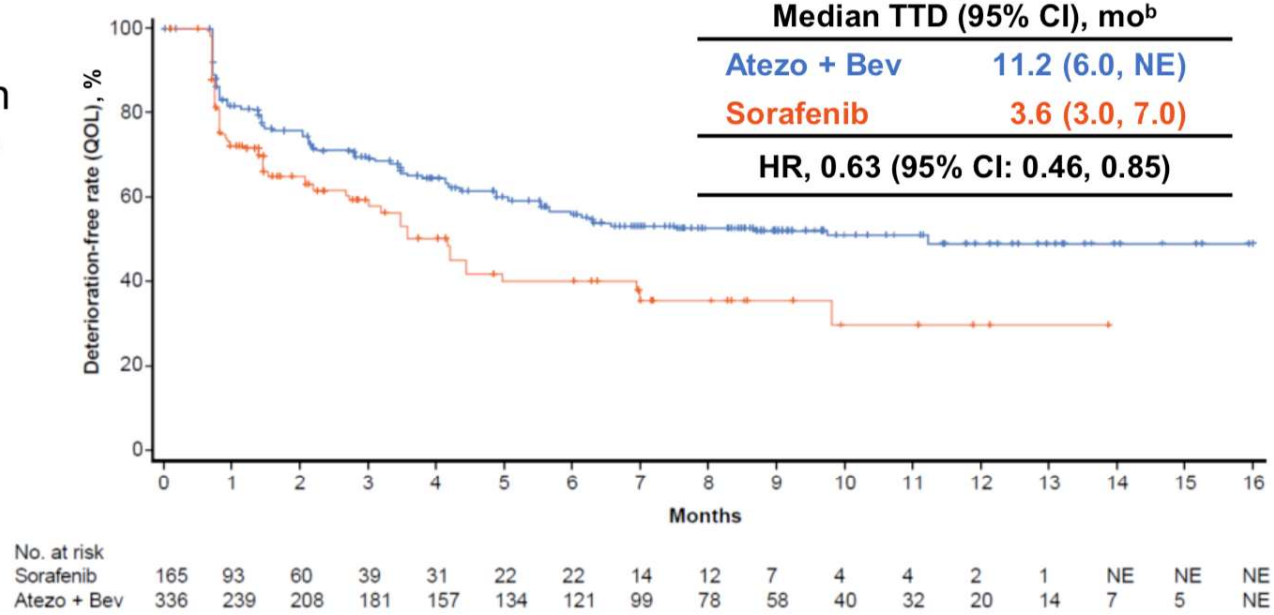
≥ 10% frequency of AEs in either arm and > 5% difference between arms



PPE, palmar-plantar erythrodysaesthesia.
[a] Safety-evaluable population.

Patient-reported outcomes[a]

- Atezolizumab + bevacizumab delayed the time to deterioration of patient-reported quality of life compared with sorafenib



EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire for Cancer; TTD, time to deterioration.
[a] Pre-specified secondary endpoint that was not formally tested; EORTC QLQ-C30 administered every 3 weeks on treatment and every 3 months after treatment discontinuation or progression. [b] Time to deterioration defined as first decrease from baseline of ≥ 10 points[1] in the patient-reported health-related global health status/quality of life (GHS/QoL) scale of the EORTC QLQ-C30 maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
1. Osoba D, et al. *J Clin Oncol.* 1998.
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

IMbrave150 conclusions

- IMbrave150 demonstrated statistically significant and clinically meaningful improvement with atezolizumab + bevacizumab over sorafenib for OS and IRF-assessed PFS per RECIST 1.1
  - OS HR, 0.58 (95% CI: 0.42, 0.79); *P* = 0.0006
  - IRF-PFS HR, 0.59 (95% CI: 0.47, 0.76); *P* < 0.0001

  Co-primary endpoints in ITT population
- PFS and OS benefits were generally consistent across subgroups
- Statistically significant and clinically meaningful improvements were seen in ORR and responses were durable with atezolizumab + bevacizumab
- The safety and tolerability profile of atezolizumab + bevacizumab was in line with the known safety profiles of each individual component and the underlying disease
- Treatment with atezolizumab + bevacizumab resulted in a clinically meaningful delay in deterioration of patient-reported quality of life vs sorafenib
- Atezolizumab + bevacizumab should be considered a practice-changing treatment for patients with unresectable HCC who have not received prior systemic therapy

Case – Question

- What is your next step?

1. Liver biopsy
2. Transplant
3. Sorafenib
4. Lenvatinib
5. Atezolizumab/Bevacizumab

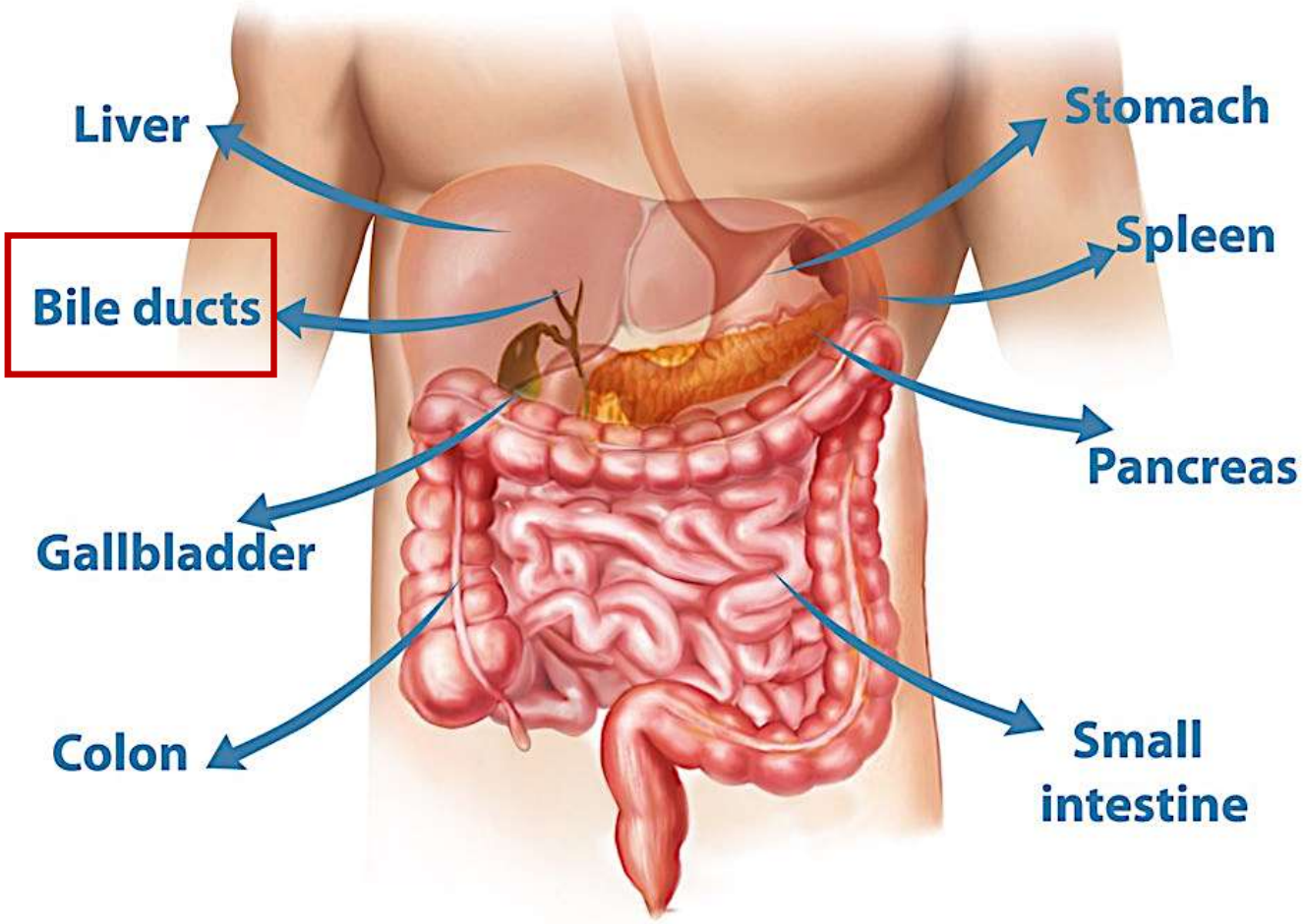
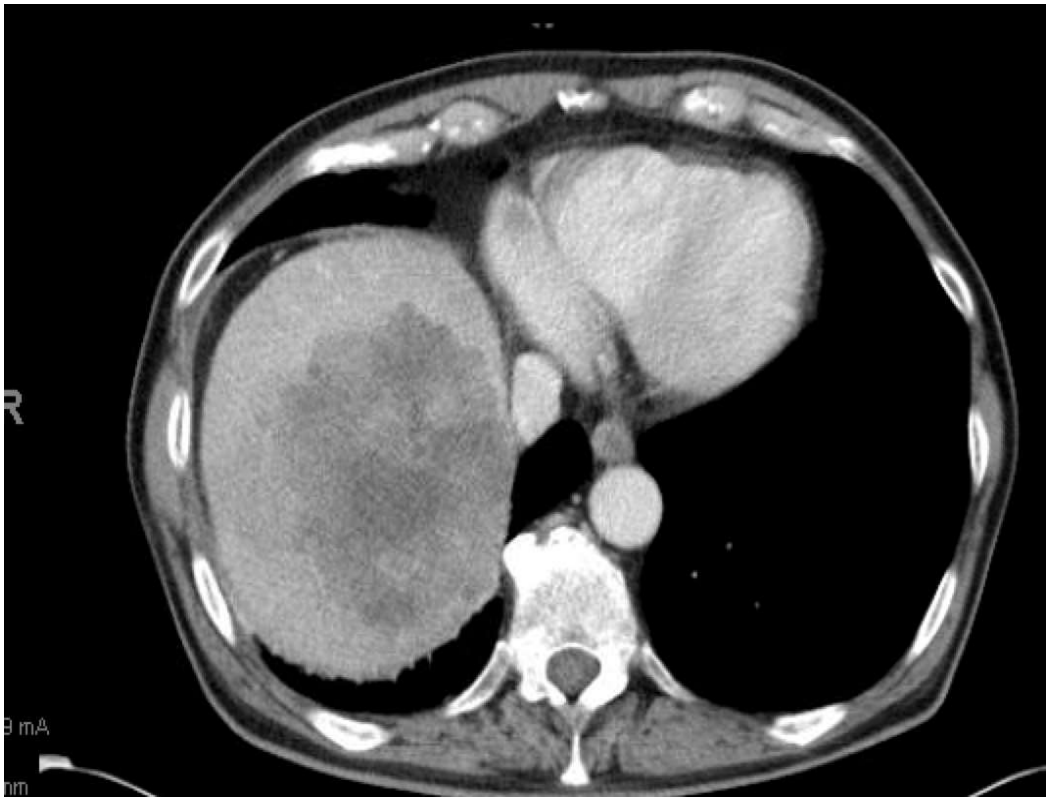


Figure 1. Colon Anatomy. Adapted from The Surgeons Collective. 2019, Retrieved from https://www.thesurgeonscollective.com.au/treatments/cancer-surgery-perth

Case

- A 77 yo man with diabetes, CKD presents with cough and CT shows 12.3 X 8.2 X 13.7 cm liver lesion, Porta hepatis adenopathy, portocaval adenopathy.
- Underwent palliative cisplatin and gemcitabine, cisplatin held due to AKI on CKD. Then found to have progression.
- Next Generation Sequencing shows IDH1 mutation.



Case – Question #1

- What is your next step?

1. FOLFOX
2. FOLFIRI
3. Abraxane
4. Ivosidenib

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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[1]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [2]Weill Medical College at Cornell University, New York, NY, USA; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]MD Anderson Cancer Center, Houston, TX, USA; [5]University of California San Francisco, San Francisco, CA, USA; [6]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; [7]Hospital Universitario 12 de Octubre, Madrid, Spain; [8]Dana-Faber Cancer Institute, Boston, MA, USA; [9]University of Chicago Medical Center, Chicago, IL, USA; [10]Mayo Clinic Cancer Center, Phoenix, AZ, USA; [11]UCL Cancer Institute, London, UK; [12]University of Washington, Seattle, WA, USA; [13]Johns Hopkins University, Baltimore, MD, USA; [14]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [15]Utah Cancer Specialists, Salt Lake City, UT, USA; [16]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [17]University of Manchester, The Christie NHS Foundation Trust, Manchester, UK; [18]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

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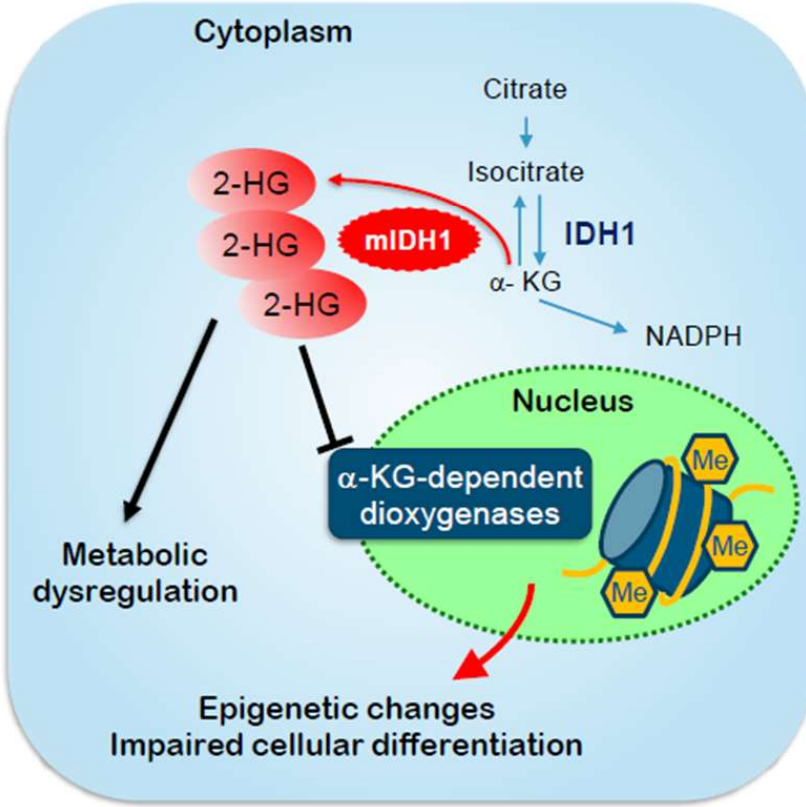
IDH1 mutations in advanced cholangiocarcinoma

- 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.

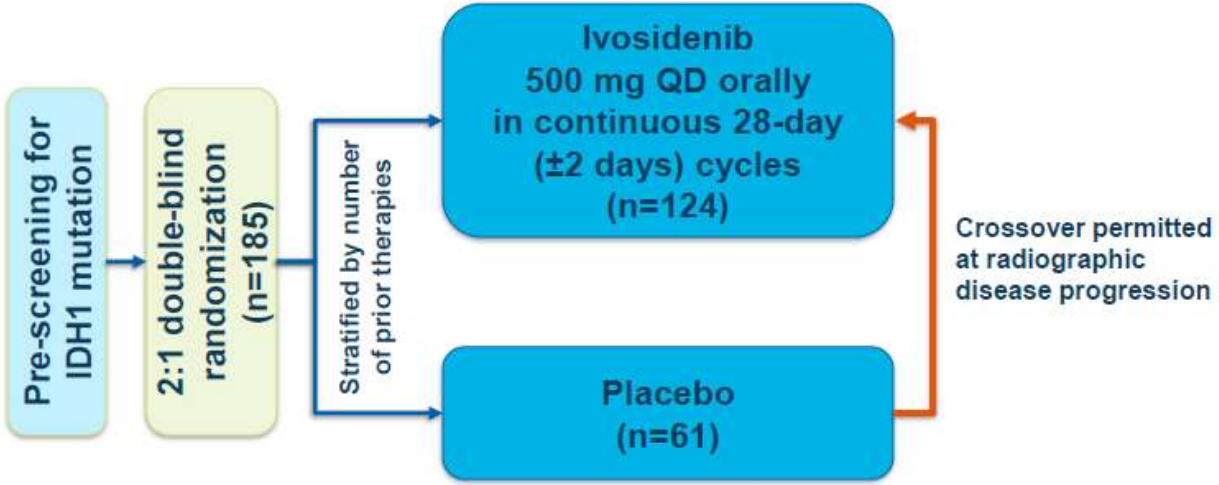
1. Boscoe AN, et al. *J Gastrointest Oncol*. 2019;10:751-765. **2.** Popovici-Muller J, et al. *ACS Med Chem Lett*. 2018;9:300-305. **3.** TIBSOVO highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211192s001lbl.pdf. Accessed August 5, 2019. **4.** Lowery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

NCT02989857



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.

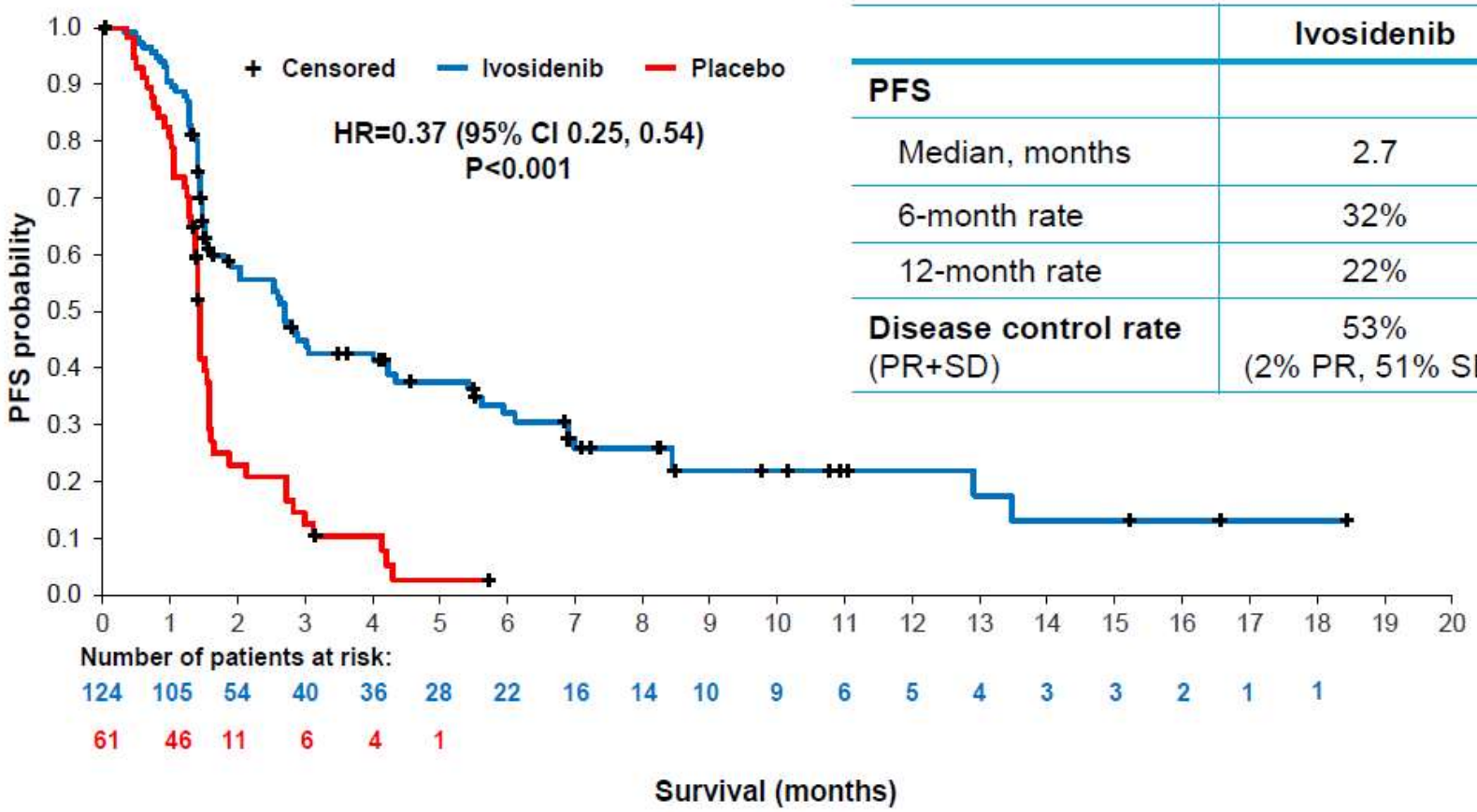
ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=5-level EuroQoL-5 Dimension questionnaire; FU=fluorouracil; NGS=next-generation sequencing; PGI=Patient Global Impression; QD=once daily; QLQ-BIL21=Cholangiocarcinoma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

ClarIDHy: 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



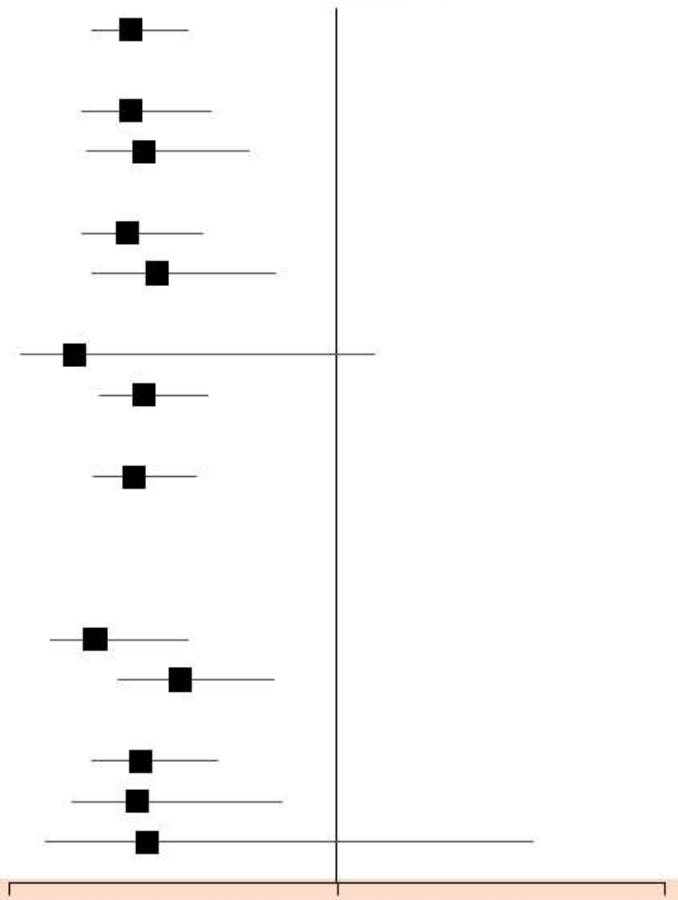
	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

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

ClarIDHy: Ivosidenib efficacy consistent across subgroups*

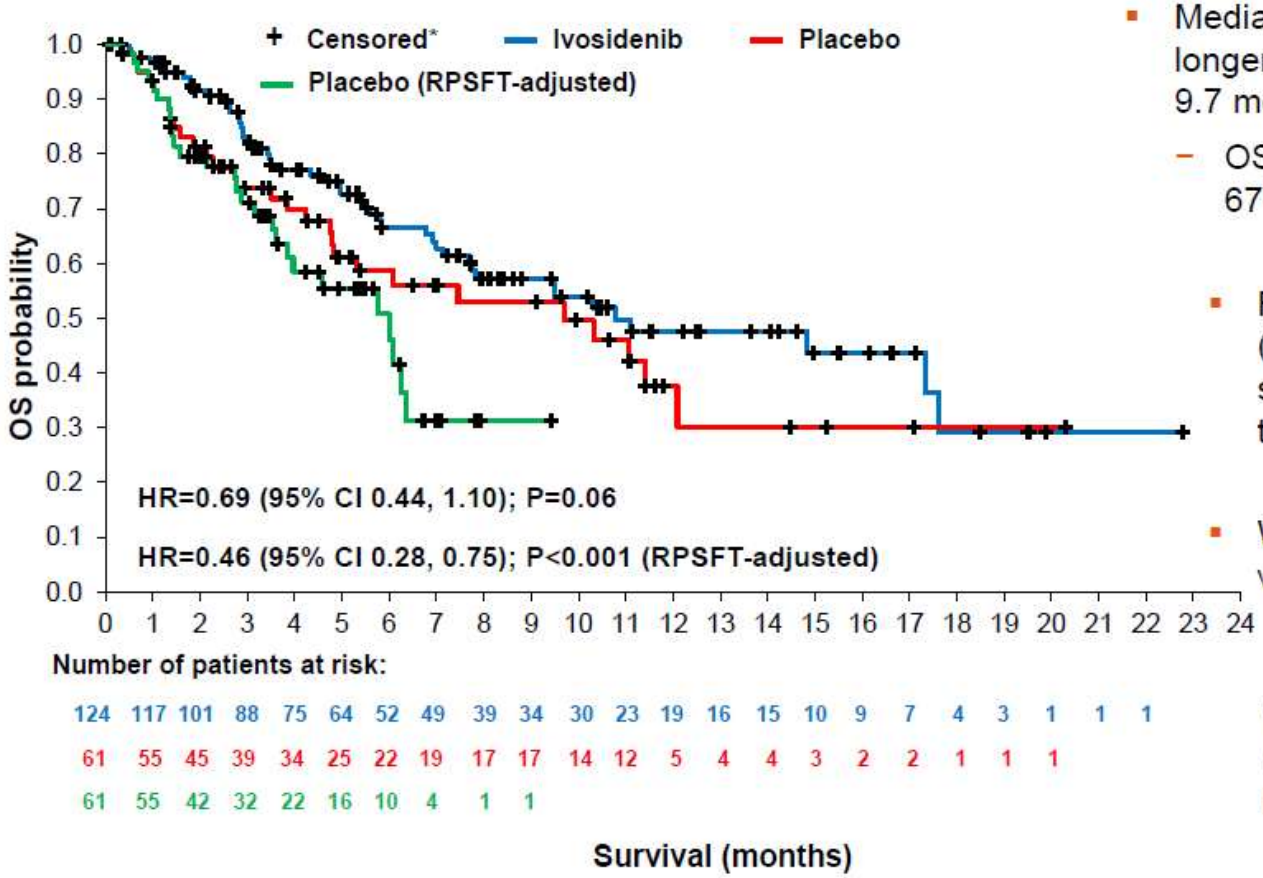
PFS by IRC

	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