Wake Forest®
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Update Hepatobiliary/Pancreas

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Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Consultant: Celgene, Ipsen, Taiho, Merck

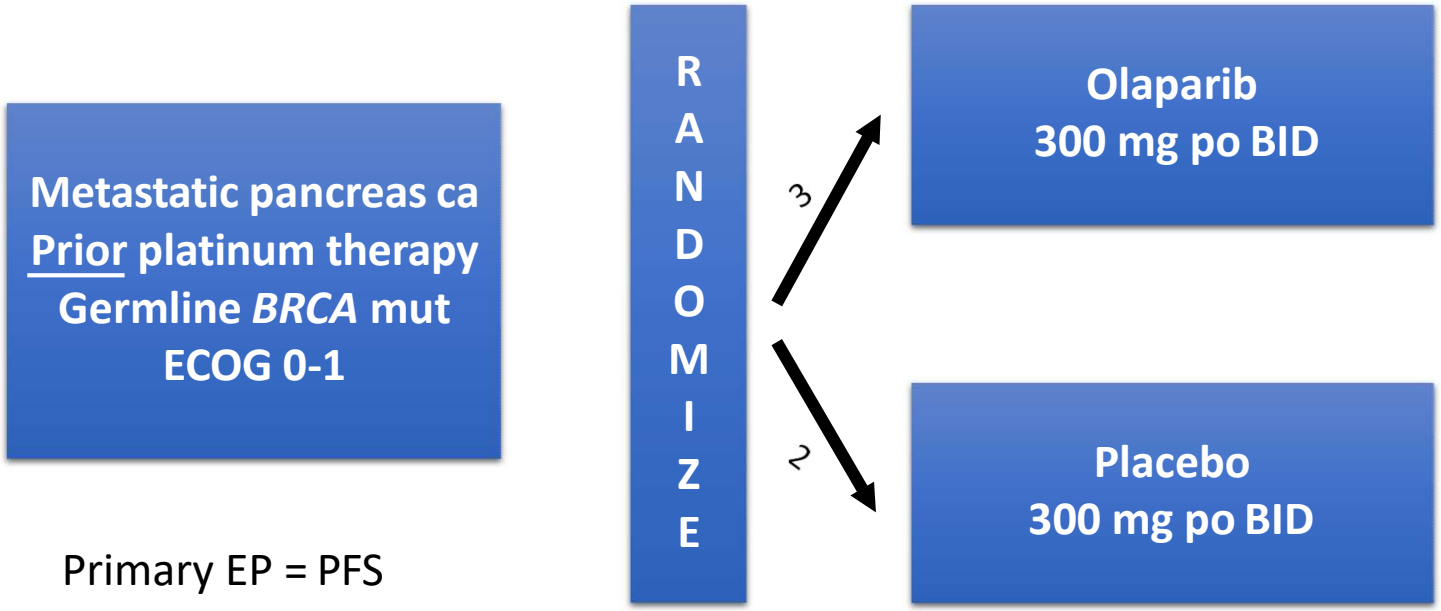
Pancreas Cancer

We Have Made Progress in the 1st-Line Metastatic Setting

Trial[1]	Date	Patients (n)	Treatment	Median survival (mo)	P value
Burris et al[2]	1997	126 (unresectable, LA or metastatic pancreatic cancer)	5-FU vs. gemcitabine	4.41 5.65*	Log-Rank Test 0.0025
NCIC[3]	2007	569 (unresectable, LA or metastatic pancreatic cancer)	gemcitabine vs. gemcitabine + erlotinib	5.91 6.24	0.038 (HR = 0.82 [95% CI, 0.69–0.99])
PRODIGE[4]	2011	342 (metastatic)	gemcitabine vs. FOLFIRINOX	6.8 11.1	<0.001 (HR = 0.57 [95% CI, 0.45–0.73])
Ueno, et al[5]	2013	834 (LA, or metastatic pancreatic cancer)	gemcitabine vs. S-1 vs. gemcitabine + S-1	8.8 9.7 10.1	gemcitabine vs. S-1: <0.001 (non-inferiority; HR = 0.96 [97.5% CI, 0.78–1.18]) gemcitabine vs. gemcitabine + S-1: 0.15 (superiority; HR = 0.88 [97.5% CI, 0.71–1.08])
MPACT[6]	2013	861 (metastatic)	gemcitabine vs. gemcitabine + nab-paclitaxel	6.7 8.5	<0.001 (HR = 0.72 [95% CI, 0.62–0.83])

1. Ryan DP, et al. N Engl J Med 2014;371:1039;
2. Burris HA, et al. J Clin Oncol 1997;15:2403;
3. Moore MJ, et al. J Clin Oncol 2007;25:1960; 4.Conroy T, et al. N Engl J Med 2011;364:1817;
5. Ueno H, et al. J Clin Oncol 2013;31:1640;
6. Von Hoff DD, et al. N Engl J Med 2013;369:1691.

POLO: Phase 3 international PARPi maintenance study in gBRCA mutated patients



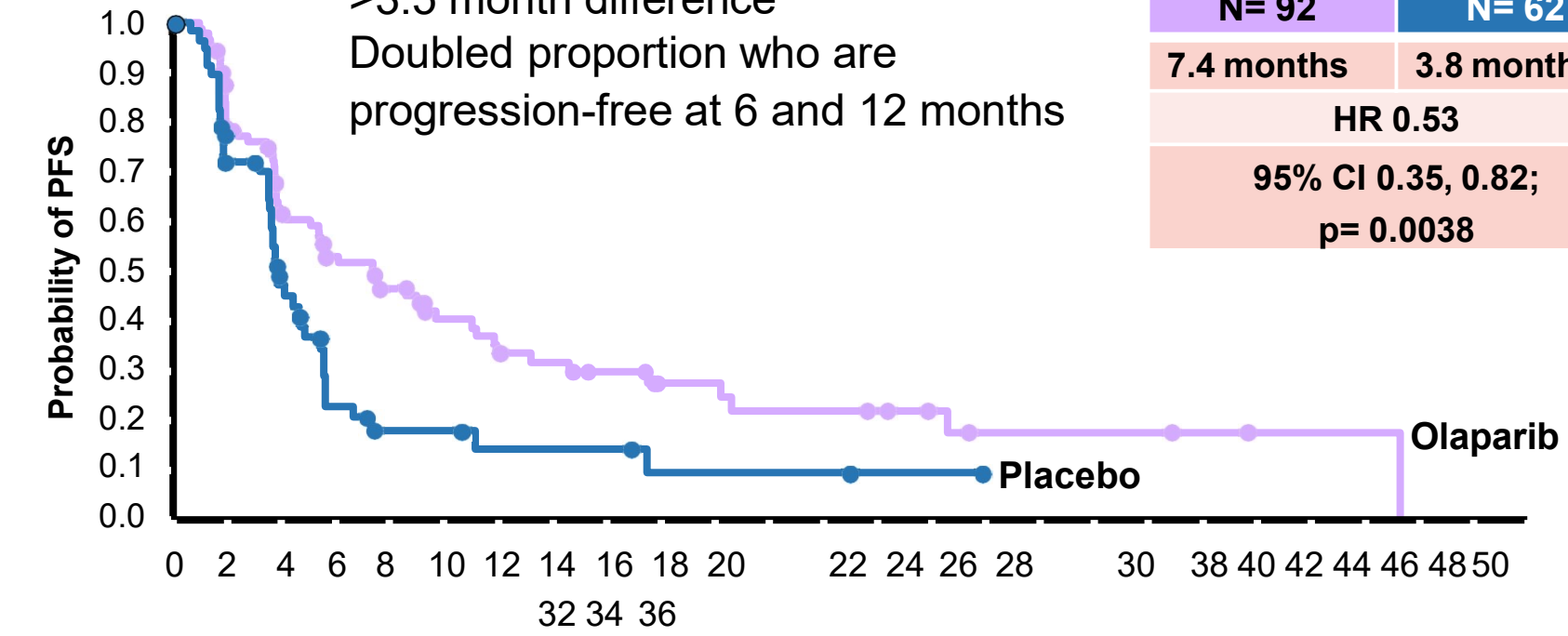
Primary EP = PFS
N = 145

NCT02184195

Primary Endpoint: Blinded Central Review

>3.5 month difference
Doubled proportion who are progression-free at 6 and 12 months

Olaparib N= 92	Placebo N= 62
7.4 months	3.8 months
HR 0.53	
95% CI 0.35, 0.82; p= 0.0038	

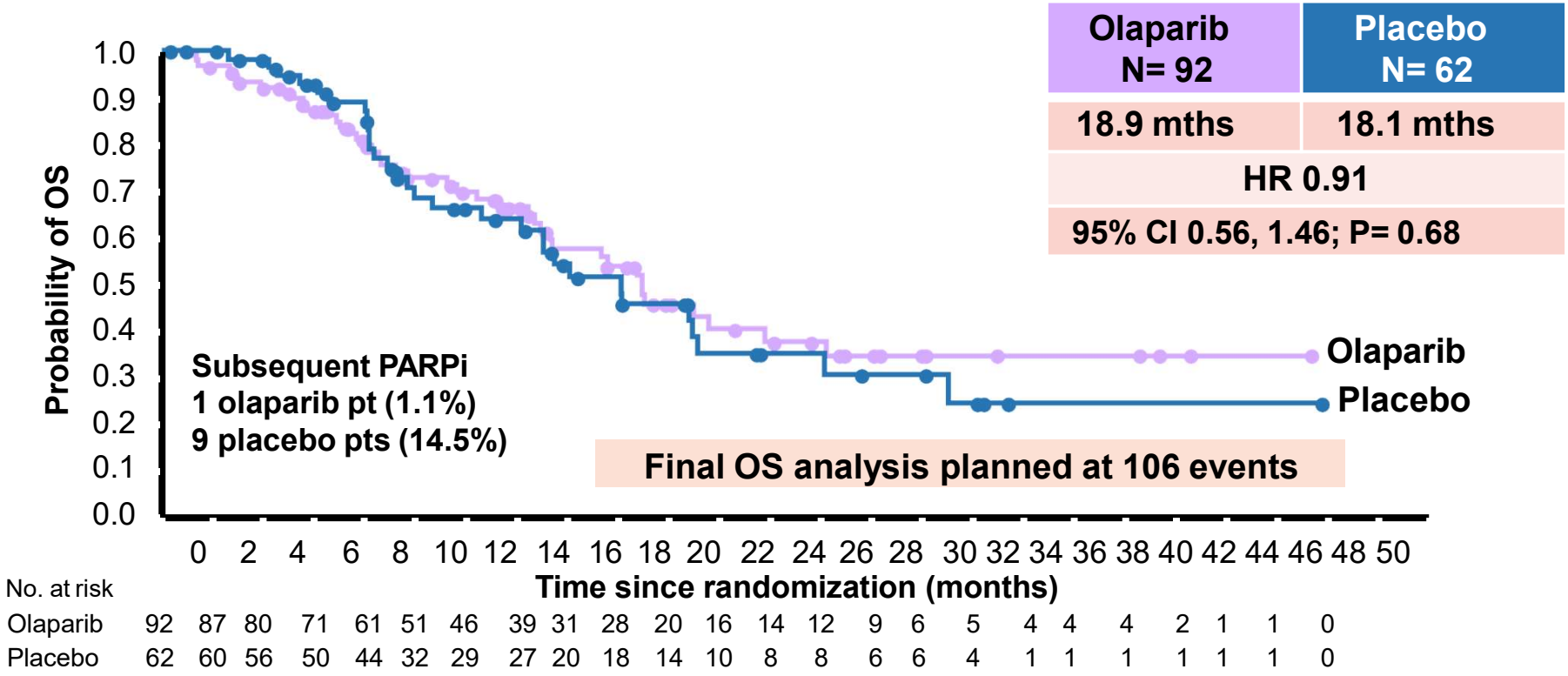


No. at risk

	92	69	50	41	34	24	18	17	14	10	10	8	8	7	5	3	3	3	3	2	1	1	1	0
Placebo	62	39	23	10	6	6	4	4	4	2	2	2	2	1	1	0								

Golan, T. New Engl J Med, 2019

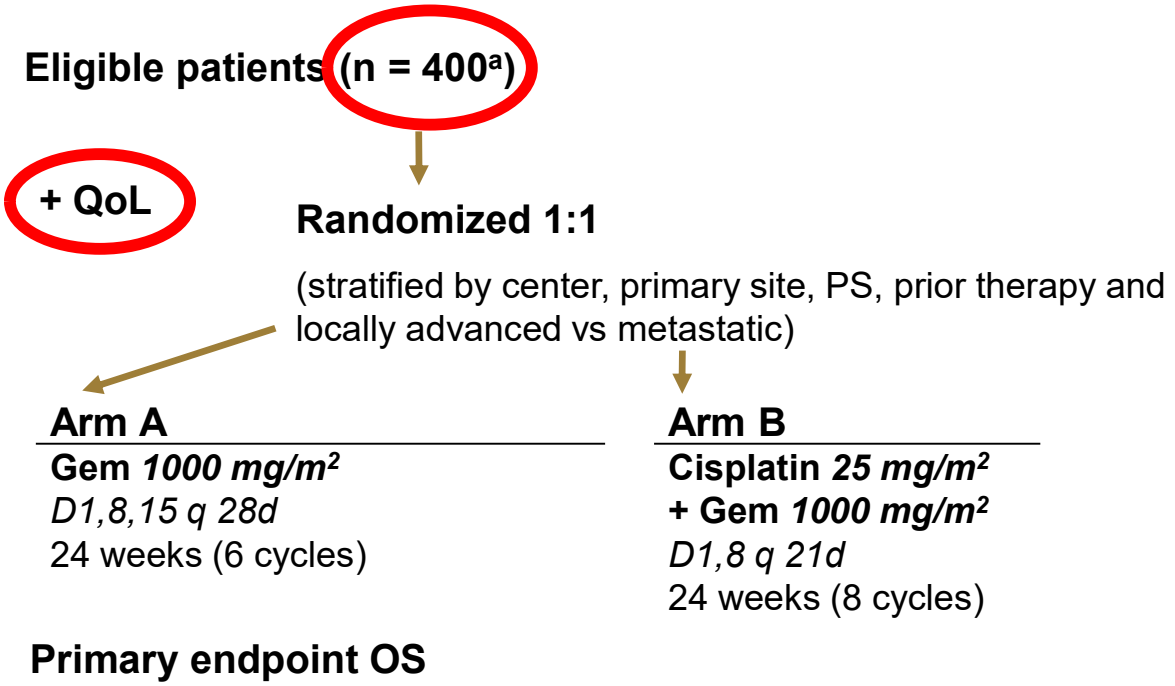
Overall Survival (46% Maturity)



Golan, T. New Engl J Med, 2019

Biliary Cancer

Prospective, National, Multicenter Phase 3 Study: ABC-02 Schema



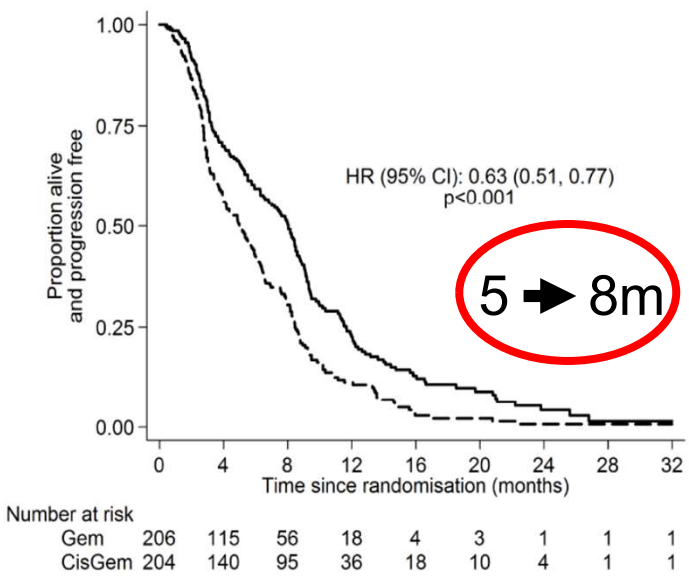
Inclusion criteria:

- Histologically / cytologically verified, non-resectable or recurrent/metastatic CCC, GB, or ampullary carcinoma
- Adequate biliary drainage, no uncontrolled infection
- ECOG PS 0-2
- LFTs: bilirubin ≤ 1.5 x ULN, ALT/ AST/ alk phos ≤ 3 x ULN (≤ 5 if liver metastases)
- No prior systemic treatment[b]
- Consenting informed-patients

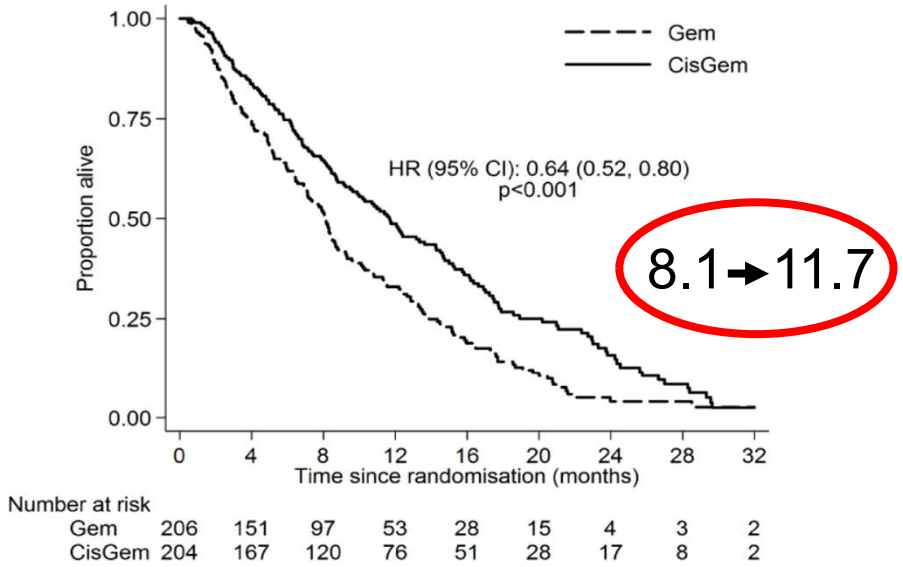
[a] Including 86 patients in ABC-01.
[b] Allowed: palliative surgery, relapse following curative surgery, PDT, radiotherapy with documented progression.
Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

ABC-02 Results

Progression-free Survival (ITT)



Overall Survival (ITT)



Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

ABC-02: Duration of Treatment and Second Line Treatment

Duration of Treatment

Median duration of treatment (P = 0.003)

Gemcitabine	14 weeks
Cisplatin/gemcitabine	21 weeks

Reason for discontinuation, n	Gem	Cis/Gem
Completed	54	79
Disease progression	40	20
Death	24	17
Co-morbidity	14	5
Toxicity	11	5
Withdrew consent	7	8
SAE	1	3
Clinician's decision	3	1
Adverse events	1	0
Unknown	8	2

Second Line Treatment

Treatment, %	Gem	CisGem
Any treatment	36 (17.5%)	36 (17.7%)
Platinum-based	13 (6.3%)	10 (4.9%)

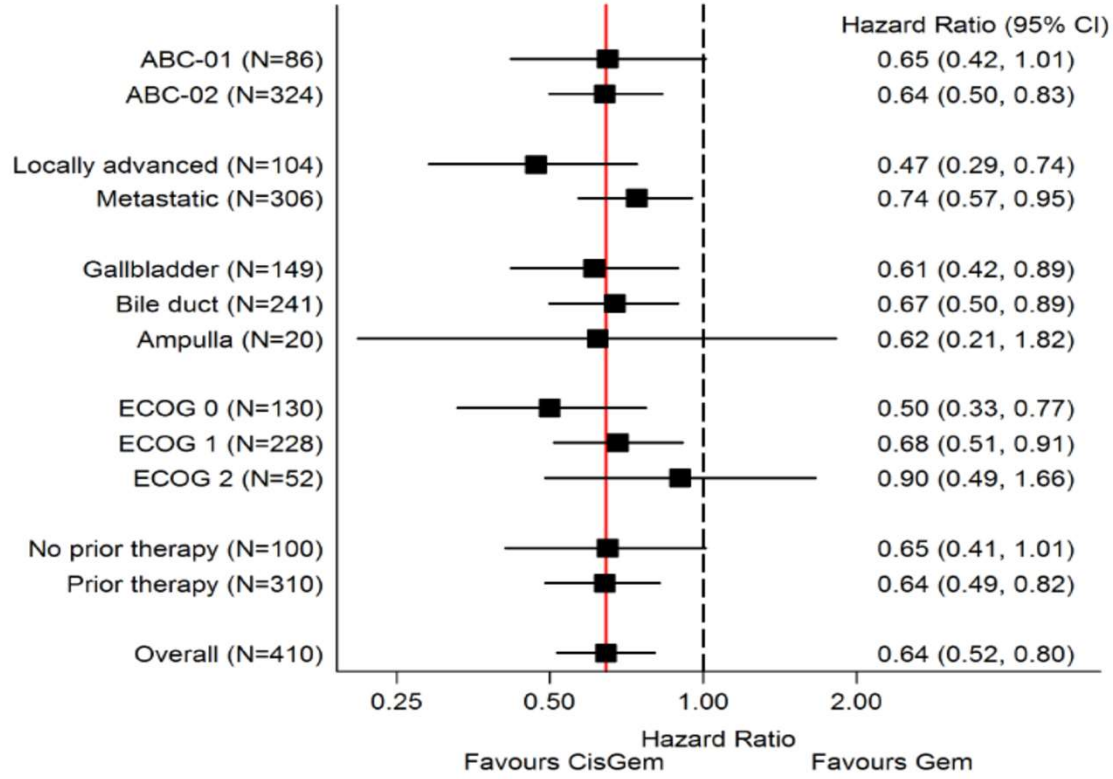
Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

ABC-02: Toxicity Profile

Toxicity, n (%)	Gem	CisGem	*P* value
Hematologic toxicity			
Platelets	13 (6.5)	17 (8.6)	0.439
Hemoglobin	6 (3.0)	15 (7.6)	0.042
Neutrophils	33 (16.6)	50 (25.3)	0.034
Infection without neutropenia	23 (11.6)	12 (6.1)	0.053
Infection with neutropenia	14 (7.0)	20 (10.1)	0.275
Nonhematologic toxicity			
ALT	34 (17.1)	19 (9.6)	0.028
Other liver function	39 (19.6)	26 (13.1)	0.082
Any liver function	54 (27.1)	33 (16.7)	0.012
Lethargy	33 (16.6)	37 (18.7)	0.582
Renal function	2 (1.0)	3 (1.5)	0.649
DVT/Thromboembolic disease	4 (2.0)	11 (5.6)	0.064

Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

ABC-02 Overall Survival Stratified Sub-



Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

ABC-02 Conclusions

- Cisplatin and gemcitabine for advanced biliary cancer significantly improved overall survival (by 3.6 m)
- Reduced risk of death by 36% (HR 0.64, *P* <0.001)
- Significantly improved progression-free survival and tumour control
- Benefit gained with no clinically significant added toxicity or decrease in QoL
- CisGem is recommended as a standard of care and the backbone for future studies

Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

Gemcitabine/DDP/Nab-paclitaxel

GCN regimen

Gem/Cis/nab-paclitaxel[1]
[NCT02392637]
USA (MDA and Mayo)
Single-arm, phase 2
N =61

Schedule | gemcitabine 800mg/m^2 + cisplatin 25 mg/m^2 + nab-paclitaxel 100 mg/m^2; D1,8 q21d

8 (63%) ICC, 9 (15%) ECC, 13 (22%) GBC, 47 (78%) had metastatic disease, and 13 (22%) had locally advanced disease

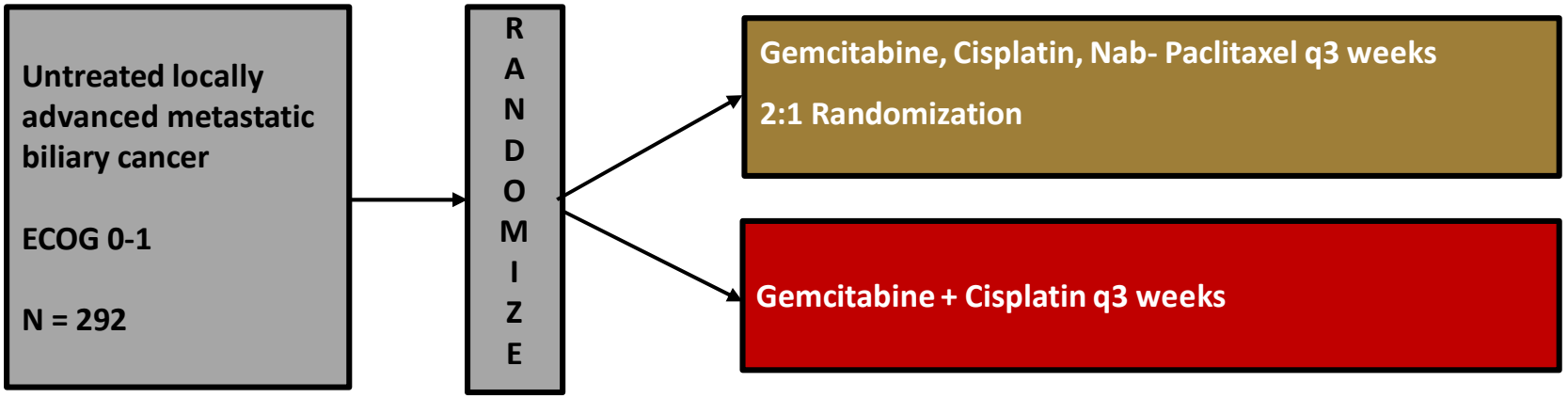
PFS: 11.8 months

PR: 45%

OS: 19.2 months

Rachna T et al *JAMA Oncol.* 2019;5(6):824

Phase 3 SWOG 1815



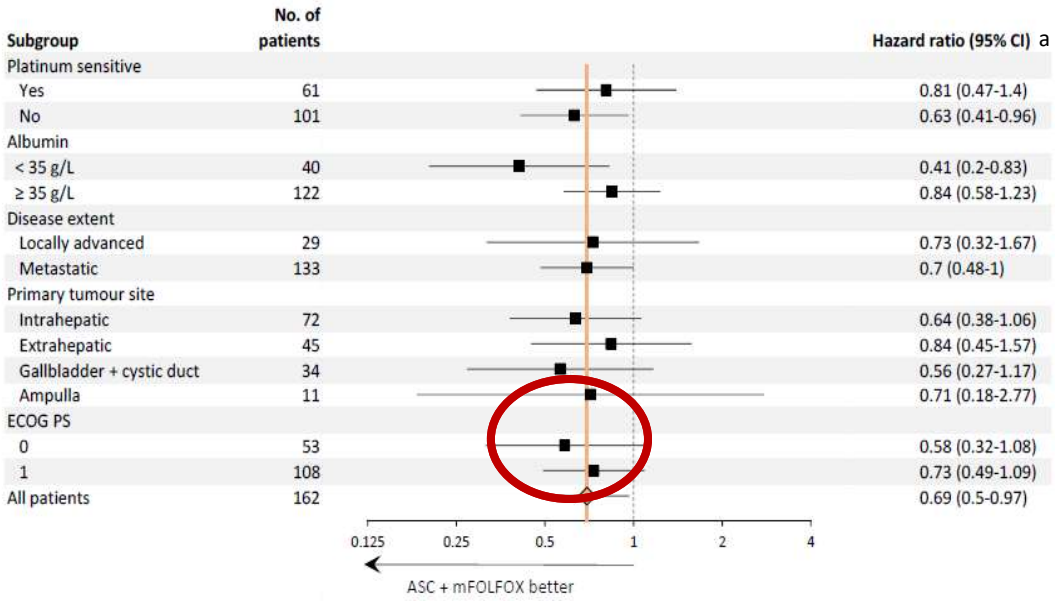
Primary endpoint: overall survival
Secondary: ORR, PFS, DCR, Safety, Ca 19-9 response

https://www.clinicaltrials.gov/ct2/show/NCT03768414. Accessed October 7, 2019.

ABC-06: Active Symptom Control ± mFOLFOX

- ASC ± mFOLFOX in ABC after prior gemcitabine/cisplatin therapy
- 162 patients were randomized (1:1)
  - 44% intrahepatic, 28% extrahepatic, 21% gallbladder, and 7% ampullary
- Median OS: 5.3 mo ASC vs. 6.2 mo combo (adjusted HR 0.69 [95% CI 0.50-0.97]; *P* = 0.031)
  - 6-month survival rate: 35.5% vs 50.6%
  - 12-month survival rate: 11.4% vs 25.9%
- Grade 3/4 toxicities were reported in 32 (39%) and 48 (59%) patients in the ASC alone and combination groups, respectively

Supgroup Analyses All Favor the Combination Over ASC Alone



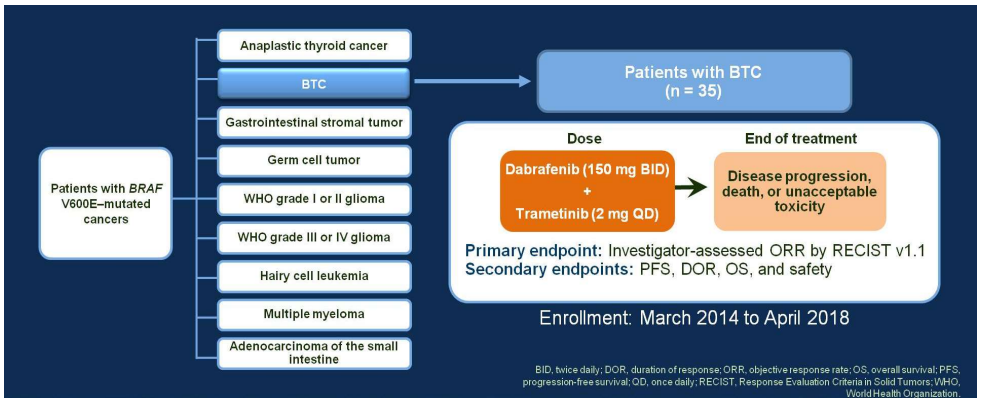
[a] HRs are adjusted for platinum sensitivity, albumin and stage.

ASC, active symptom control.

Lamarca A, et al. *J Clin Oncol* 2019;37,(suppl; abstr 4003).

The Phase 2 ROAR Study Evaluated Combined BRAF and MEK Inhibition in *BRAF*-Mutated Cancers, Including BTC

- *BRAF* mutations have been reported in approximately 5%-7% of iCCAs; these mutations may be enriched in iCCA vs other types of biliary cancers



ROAR Study Design (NCT02034110)

Baseline Demographics – BTC Cohort (n = 35)

Parameter	BTC Cohort (n = 35)
Age, median (range), years	57.0 (26-77)
Male, n (%)	15 (43)
ECOG PS, n (%)	
0	14 (40)
1	20 (57)
2	1 (3)
Histology, n (%)	
Adenocarcinoma	26 (74)
Hepatocholangiocarcinoma	6 (17)
Cholangiocarcinoma	3 (9)
Measurable disease present at screening, n (%)	35 (100)
Stage at enrollment[a]	
Stage II	1 (3)
Stage IV	26 (74)
Stage IVA	1 (3)
Stage IVB	6 (17)
Time since diagnosis, median (range), years	1.1 (0.1-8.8)

Presented By Zev Wainberg at 2019 Gastrointestinal Cancer Symposium

The Phase 2 ROAR Study Results of the BTC Cohort

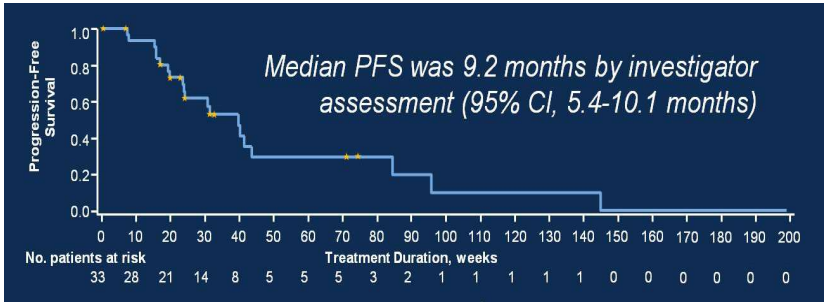
Best Overall Response

Response	Investigator-Assessed Response ITT/Evaluable Population (n = 33)	Response by Independent Review ITT/Evaluable Population (n = 33)
Best overall response, n (%)		
CR	0	0
PR	14 (42)	12 (36)
SD	15 (45)	13 (39)
PD	4 (12)	4 (12)
Not evaluable[a]	0	2 (6)
Missing	0	2 (6)
ORR (CR + PR), n (%)	14 (42)	12 (36)
95% CI	25.5-60.8	20.4-54.9

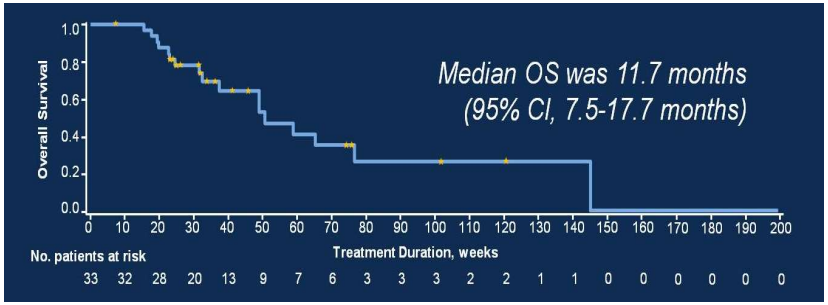
- DOR at 6 months was 66% (95% CI, 32%-86%)
- The most common AEs were pyrexia (40%), rash (29%), nausea, diarrhea, fatigue (23% each), chills (20%)
  - 57% of patients had at least Grade 3/4

Presented By Zev Wainberg at 2019 Gastrointestinal Cancer Symposium

Progression-Free Survival



Overall Survival



Ivosidenib Phase 1 and Phase 3 Studies

Phase 1 Study

CCA, chondrosarcoma, glioma, others [NCT02073994]

CCA cohort[1]: n = 73 [dose escalation (n = 24); dose-expansion 500 mg QD (n = 49)]

No DLTs; drug-related AEs: fatigue, nausea, diarrhea, vomiting

Activity:

Median PFS 3.8 months

6-month PFS: 40.1%

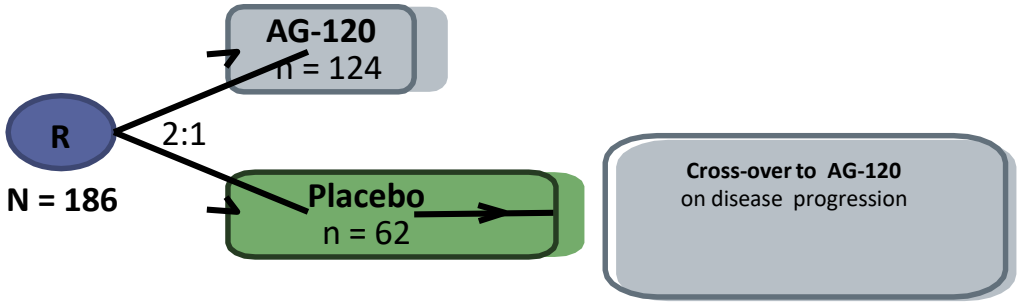
12-month PFS: 21.8%

RR 5% (4 PRs)

OS: 13.8 m

Phase 3 Study (ClarIDHy)

Second-line, placebo- controlled
[NCT02989857][2]



AG-120 is a first-in-class, potent, oral inhibitor of the mutant IDH1 enzyme

1. Lowery MA, et al. *Lancet Gastroenterol Hepatol*. 2019;4:711-720. 2. Abou-Alfa GK, et al. ESMO 2019:abstract LBA10_PR.

ClarIDHy: End Points, Sample Size, and Key Eligibility Criteria

Endpoints

- 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

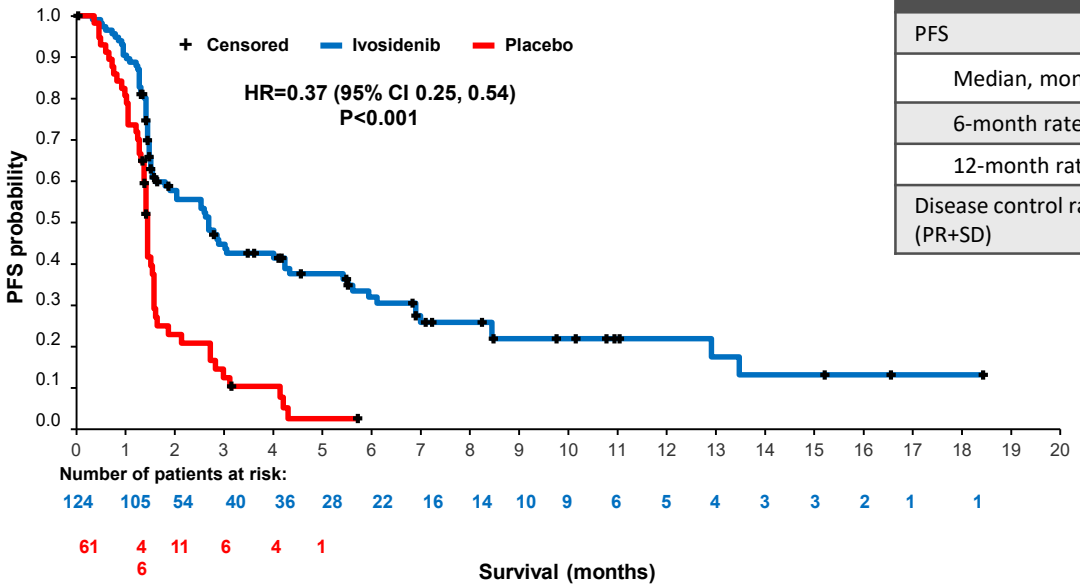
- ~186 patients based on HR 0.5, 96% power, 1-sided alpha = 0.025
- 780 patients were screened for IDH1 mutations across 49 sites and 6 countries

Eligibility

- ≥18 years of age
- Histologically confirmed diagnosis of CCC
- 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

Abou-Alfa GK, et al. ESMO 2019:abstract LBA10_PR.

ClarIDHy: PFS by IRC

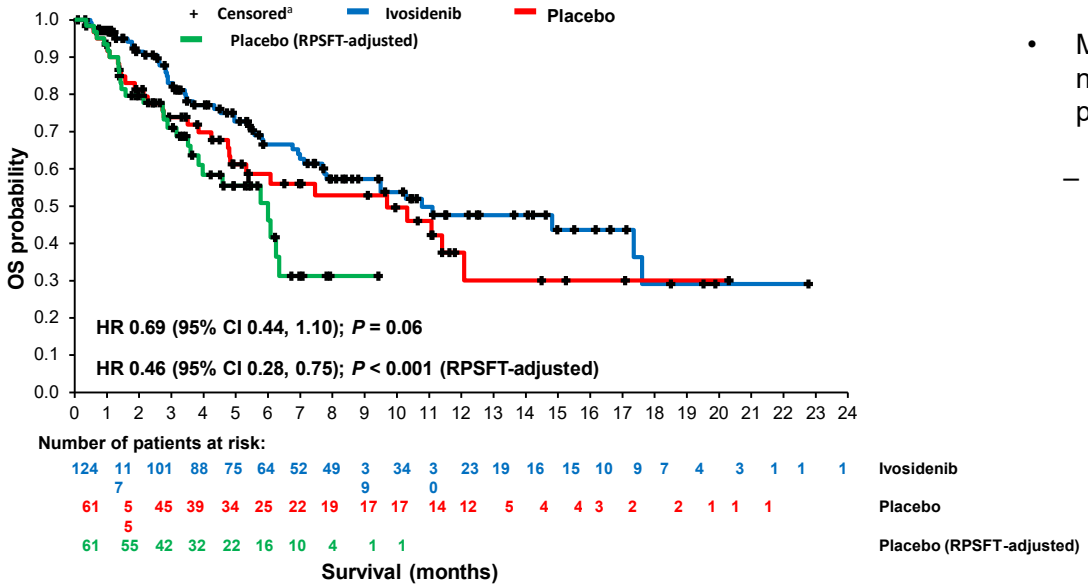


	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

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

Abou-Alfa GK, et al. ESMO 2019:abstract LBA10_PR.

ClarIDHy: OS by 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

[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.

Abou-Alfa GK, et al. ESMO 2019:abstract LBA10_PR.

ClarIDHy: Treatment-emergent Adverse Events (TEAEs)

	Placebo (n = 59)	Ivosidenib (n = 121)	Total ivosidenib (n = 156)[a]
Any TEAE, n (%)	57 (96.6)	115 (95.0)	146 (93.6)
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

[a] 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

Abou-Alfa GK, et al. ESMO 2019:abstract LBA10_PR.

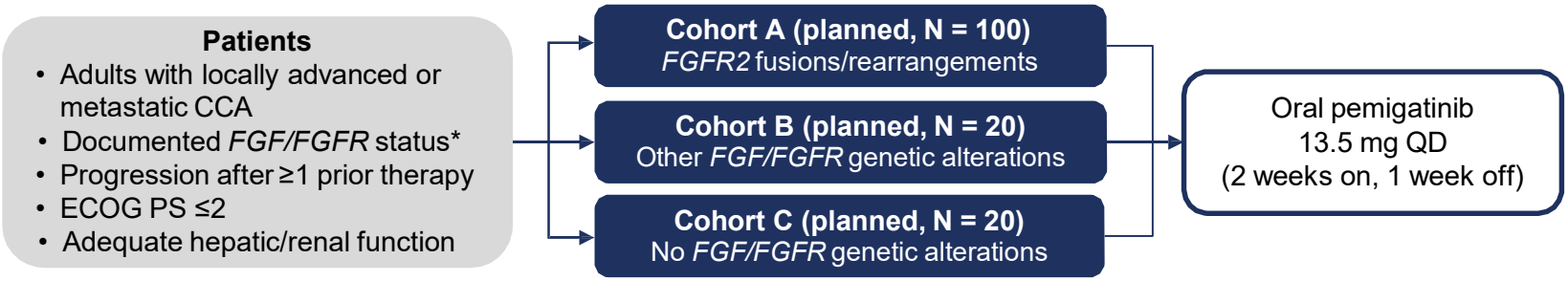
ClarIDHy: Authors' Conclusions

- 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

Abou-Alfa GK, et al. ESMO 2019:abstract LBA10_PR.

FIGHT-202 STUDY DESIGN

- Phase 2 open-label, single-arm study evaluating the efficacy and safety of pemigatinib in patients with previously treated locally advanced or metastatic CCA (NCT02924376)
  - Sites opened in the United States, Europe, Middle East, and Asia



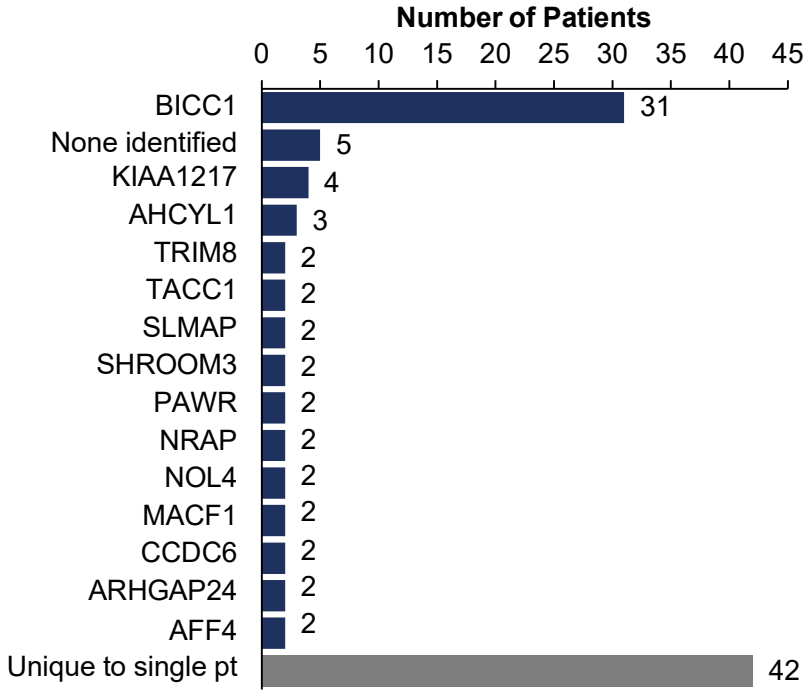
Vogel A ESMO 2019

CLINICAL CHARACTERISTICS

Characteristics	Cohort A (n = 107) *FGFR2* Fusions/ Rearrangements	Cohort B (n = 20) Other *FGF/FGFR* Genetic Alterations	Cohort C (n = 18) No *FGF/FGFR* Genetic Alterations	Total (N = 146)*
ECOG PS, n (%)	45 (42)	7 (35)	7 (39)	59 (40)
0	57 (53)	10 (50)	8 (44)	76 (52)
1	5 (5)	3 (15)	3 (17)	11 (8)
2				
Number of prior regimens,† n (%)	65 (61)	12 (60)	12 (67)	89 (61)
1	29 (27)	7 (35)	2 (11)	38 (26)
2	13 (12)	1 (5)	4 (22)	19 (13)
≥3				
Prior cancer surgery, n (%)	38 (36)	6 (30)	4 (22)	48 (33)
Prior radiation, n (%)	28 (26)	3 (15)	5 (28)	36 (25)
CCA location, n (%)	105 (98)	13 (65)	11 (61)	130 (89)
Intrahepatic	1 (1)	4 (20)	7 (39)	12 (8)
Extrahepatic	1 (1)	3 (15)‡	0	4 (3)
Other/Missing				

* The total includes 1 patient who received pemigatinib but had undetermined *FGF/FGFR* status; analyzed for safety but not efficacy, and was not assigned to a cohort.
† Maximum number of 5 therapies in cohort A and 3 in cohort B/C.
‡ Other includes gallbladder (n = 2) and ampulla of vater (n = 1) cancer.

FGFR2 FUSIONS/REARRANGEMENTS (COHORT A)



- Fusions are a product of chromosomal rearrangement
  - Consistent with Foundation Medicine terminology, rearrangements are classified as fusions if the partner gene is previously described or in-frame
- Among 107 patients in cohort A:
  - 92 fusions; 15 rearrangements
  - 56 different partner genes
  - 42 partners unique to single patients
  - Most common:
    - *BICC1* (29%)
    - No partner identified (5%)

For further information on genomic analyses in FIGHT-202, see ESMO Poster #720P presented Sunday, September 29, 2019.

RESPONSE

Variable	Cohort A (n = 107) *FGFR2* Fusions/ Rearrangements	Cohort B (n = 20) Other *FGF/FGFR* Genetic Alterations	Cohort C (n = 18) No *FGF/FGFR* Genetic Alterations
ORR (95% CI), %	**35.5 (26.50–45.35)**	0	0
Best OR,* n (%)	3 (2.8)	0	0
CR	35 (32.7)	0	0
PR	50 (46.7)	8 (40.0)	4 (22.2)
SD	16 (15.0)	7 (35.0)	11 (61.1)
PD	3 (2.8)	5 (25.0)	3 (16.7)
Not evaluable†			
Median DOR (95% CI), mo	7.5 (5.7–14.5)	—	—
DCR (CR + PR + SD) (95% CI), %	82 (74–89)	40 (19–64)	22 (6–48)

* Assessed and confirmed by independent central review.
† Postbaseline tumor assessment was not performed owing to study discontinuation (2 participants in cohort A, 4 participants in cohort B, 3 participants in cohort C) or was performed prior to the minimum interval of 39 days for an assessment of SD (1 participant in cohort A, 1 participant in cohort B).

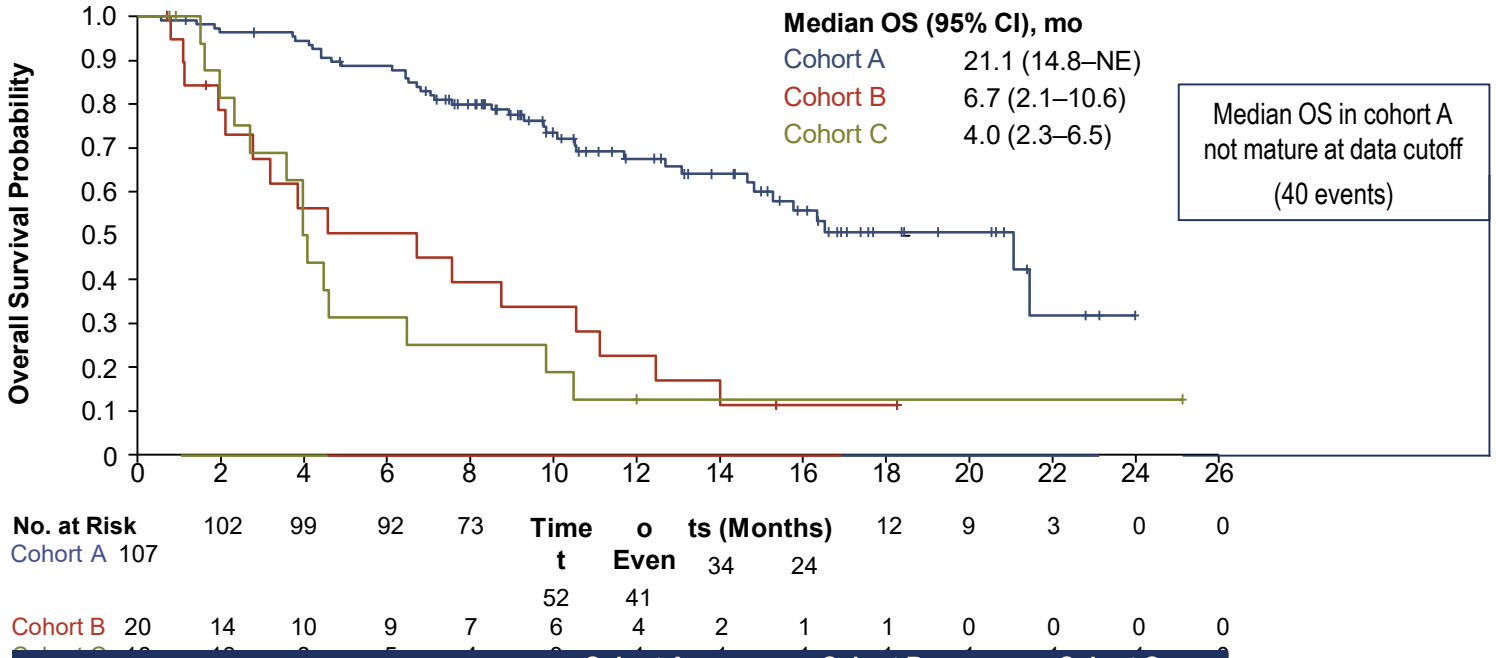
ADVERSE EVENTS OCCURRING IN ≥25% OF PATIENTS

	Any AEs (N = 146)*	
Hyperphosphatemia†	**88 (60)**	**0**
Alopecia	72 (49)	0
Diarrhea	68 (47)	4 (3)
Fatigue	**62 (42)**	**7 (5)**
Nail toxicities†	62 (42)	3 (2)
Dysgeusia	59 (40)	0
Nausea	58 (40)	3 (2)
Constipation	51 (35)	1 (1)
Stomatitis	**51 (35)**	**8 (5)**
Dry mouth	49 (34)	0
Decreased appetite	48 (33)	2 (1)
Vomiting	40 (27)	2 (1)
Dry eye	37 (25)	1 (1)
Arthralgia	36 (25)	9 (6)

- **Hyperphosphatemia**† managed with a low phosphate diet, phosphate binders, and diuretics, or dose reduction/interruption
  - All grade 1 or 2
  - Few (n = 3) required dose reductions/interruptions
- **Hypophosphatemia**† occurred in 23% of patients
  - Most common grade ≥3 AE (12%)
  - None clinically significant/serious; none led to discontinuation/dose reduction
- **Serous retinal detachment**† occurred in 4% of patients
  - Mostly grade 1/2 (grade ≥3, 1%)
  - None resulted in clinical sequelae

* Safety analysis includes 1 patient who did not have confirmed *FGF/FGFR* status by central laboratory and was not assigned to any cohort.
† Combined MedDRA Preferred Terms.

OVERALL SURVIVAL



	Cohort A	Cohort B	Cohort C
Median (range) duration of follow-up, mo	15.4 (7.0–24.7)	19.9 (16.2–23.5)	24.2 (22.0–26.1)
Median (range) duration of treatment, mo	7.2 (0.2–24.0)	1.4 (0.2–12.9)	1.3 (0.2–4.7)

The study was not designed to compare cohorts.

CONCLUSIONS

- 56 unique *FGFR2* fusion genes were observed in cohort A (*FGFR2* fusions or rearrangements), supporting the use of fusion partner–agnostic testing
- Adverse events were manageable and consistent with the mechanism of action of pemigatinib
- In cohort A, pemigatinib treatment resulted in
  - ORR of 35.5% with durable responses
  - Median PFS of 6.9 months
- These results demonstrate the potential therapeutic benefit of pemigatinib for patients with previously treated locally advanced or metastatic CCA and *FGFR2* fusions or rearrangements
- A phase 3 study is ongoing in the first-line setting to evaluate pemigatinib versus gemcitabine plus cisplatin in patients with CCA and *FGFR2* fusions or rearrangements (NCT03656536)

Summary

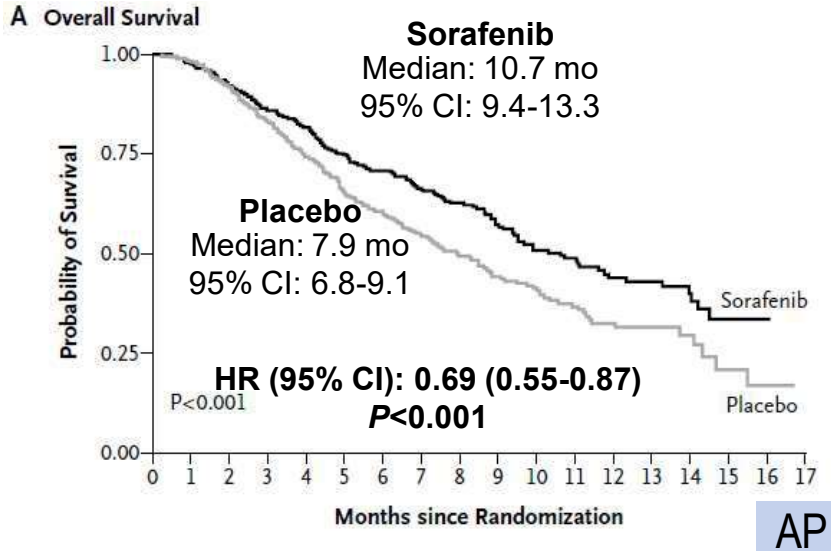
- Advanced or metastatic Biliary Cancers
  - Clinical trials are paramount
  - Tissue is the issue:
    - MSI testing and NGS routine to direct therapy
      - IDH mutation, FGF fusions/re-arrengements, BRAF, HER-2. MSI-H, TMB, PD-LI(+)
  - Gem/DDP (a first-line standard)
    - Gem/DDP+Nabpaclitaxel in selected pts?
  - FOLFOX (is it a second line standard in pt with no targetable mutations?)
- Regional therapy for selected patients

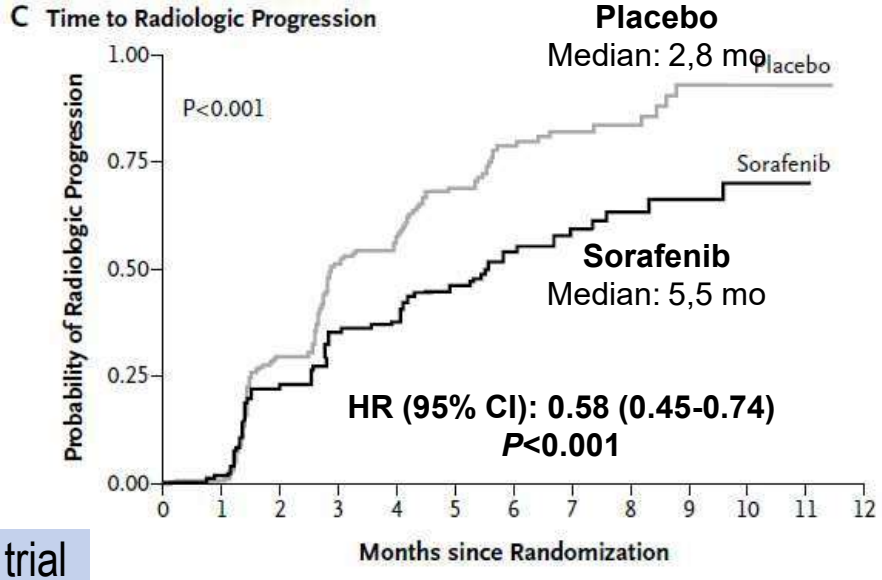
HCC

Advanced stage: Systemic treatments:

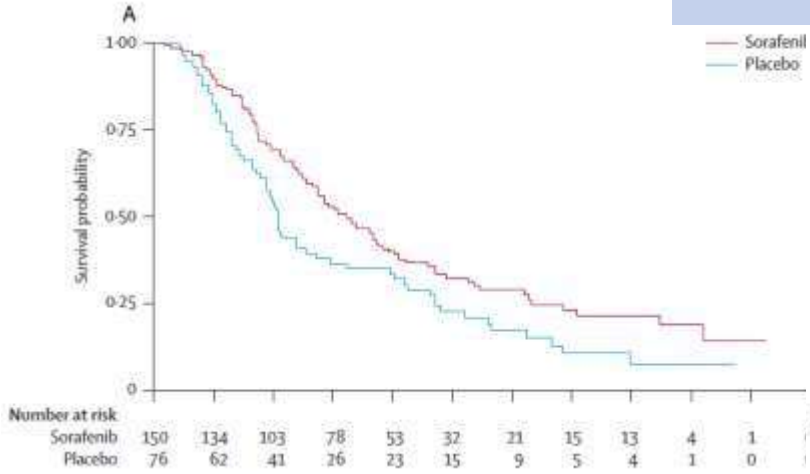
Sorafenib

SHARP trial

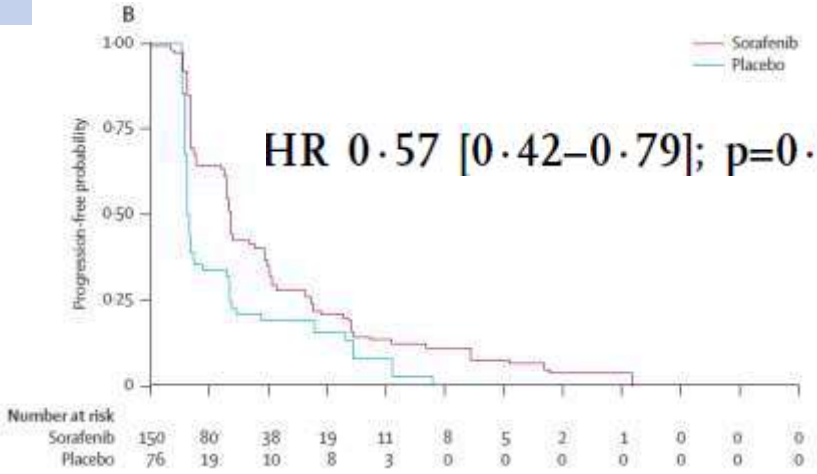




AP trial



[HR] 0·68 [95% CI 0·50–0·93]; p=0·014)



HR 0·57 [0·42–0·79]; p=0·0005)

Llovet JM, et al N Engl J Med 2008; Bruix J, et al J Hepatol 2012; Chen AL, et al Lancet Oncol 2009.

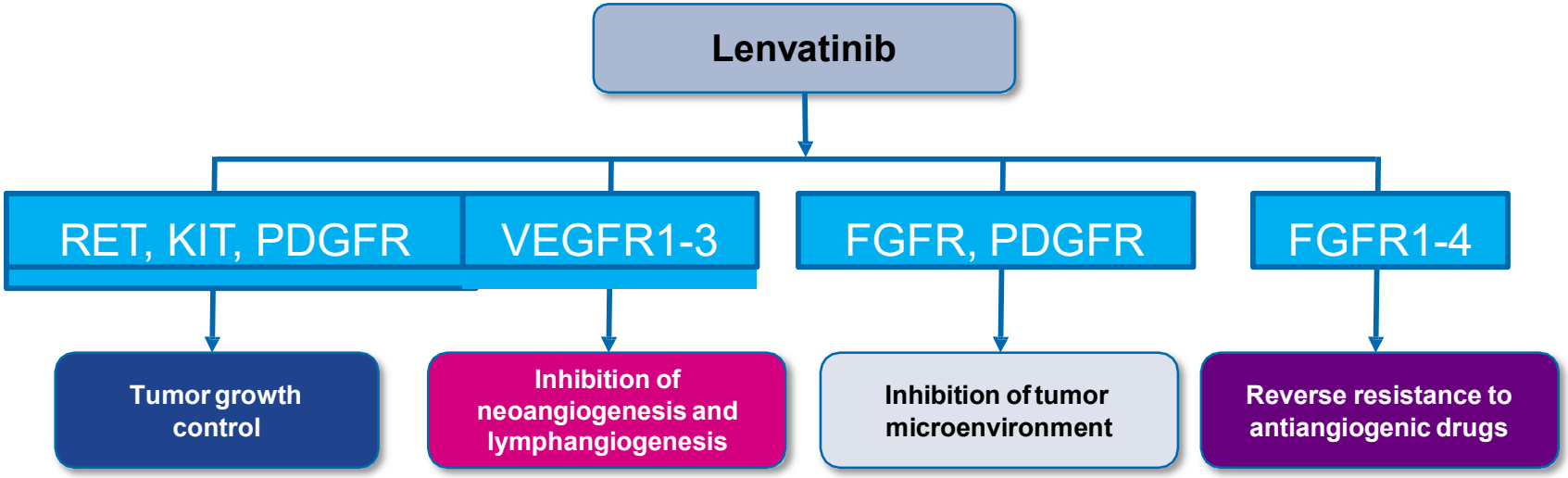
Systemic treatments:

Sorafenib: indications

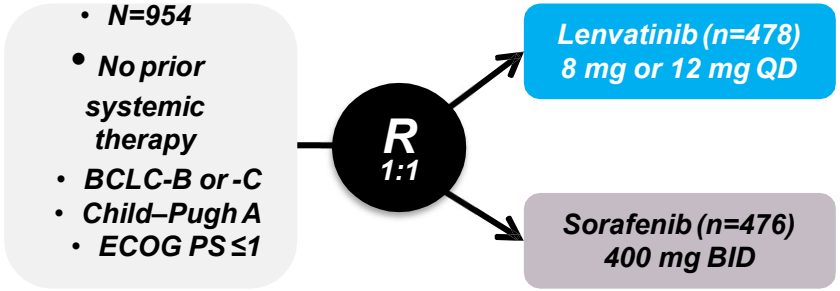
- Advanced stage:
  - Portal vein invasion,
  - Extra-hepatic metastases,
  - Child-Pugh A, B
  - PS: 0 – 2
- SHARP and AP trials: inclusions limited to
  - Advanced stages BCLC or progression after TACE
  - PS 0, 1, 2
  - Child-Pugh A
  - Biology « correct »
- No molecular biomarker available.

Llovet JM, et al N Engl J Med 2008

Lenvatinib

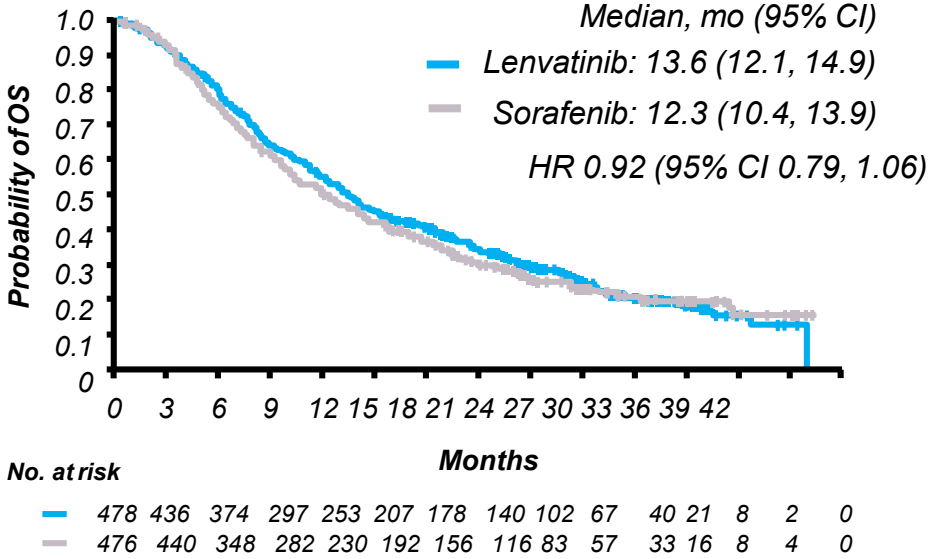

Lenvatinib
RET, KIT, PDGFR
VEGFR1-3
FGFR, PDGFR
FGFR1-4
Tumor growth control
Inhibition of neoangiogenesis and lymphangiogenesis
Inhibition of tumor microenvironment
Reverse resistance to antiangiogenic drugs

REFLECT: STUDY DESIGN AND PRIMARY ENDPOINT



BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; R, randomized; TTP, time to progression.
Kudo M, et al. *Lancet* 2018;391:1163–1173.

Overall survival



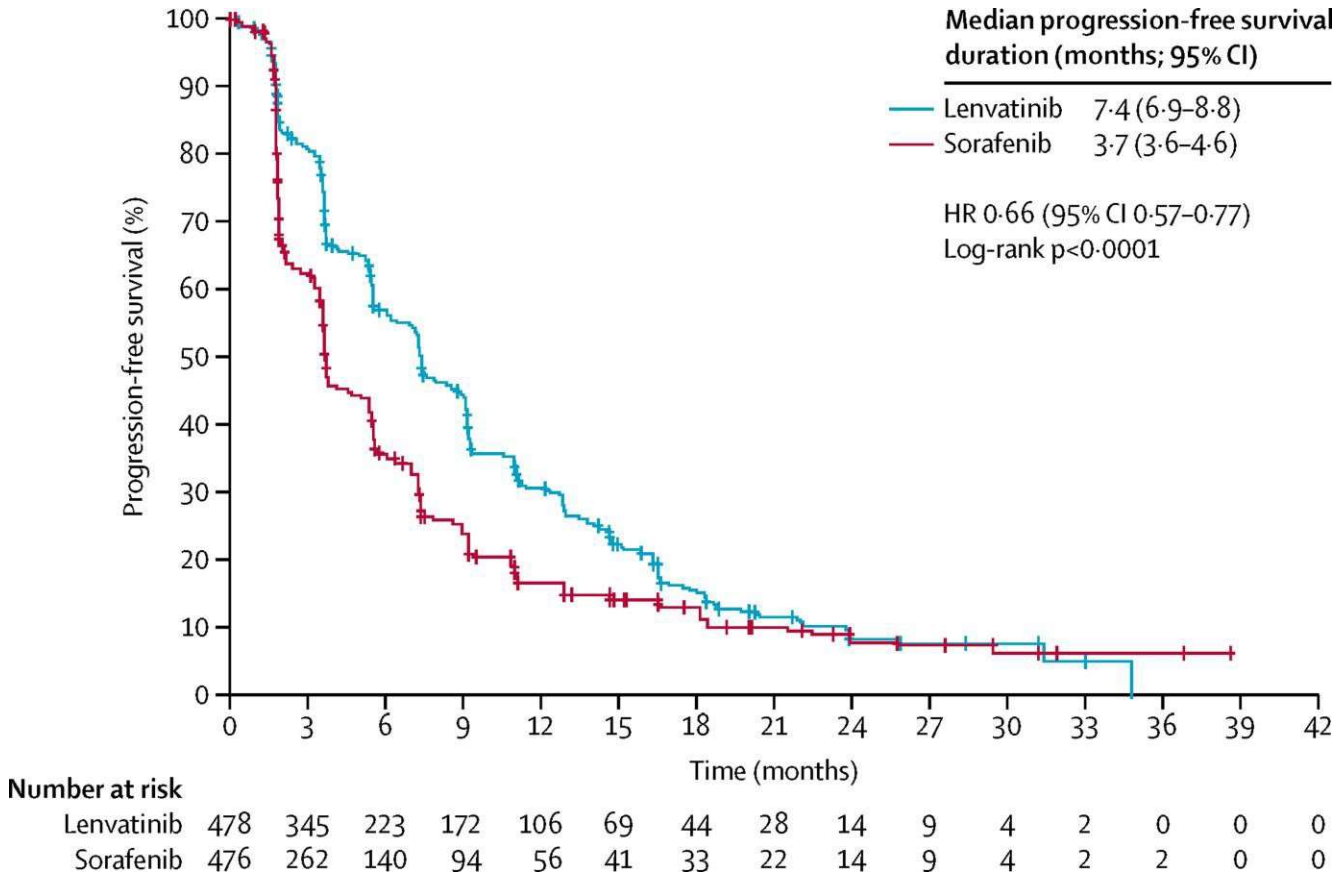
Non-inferiority, open-label study design

Patients with ≥50% liver occupation, clear bile duct invasion, or main portal vein invasion were excluded

Primary endpoint: OS

Secondary endpoints: PFS, TTP, ORR

Lenvatinib vs Sorafenib PFS



Lenvatinib mRECIST Response

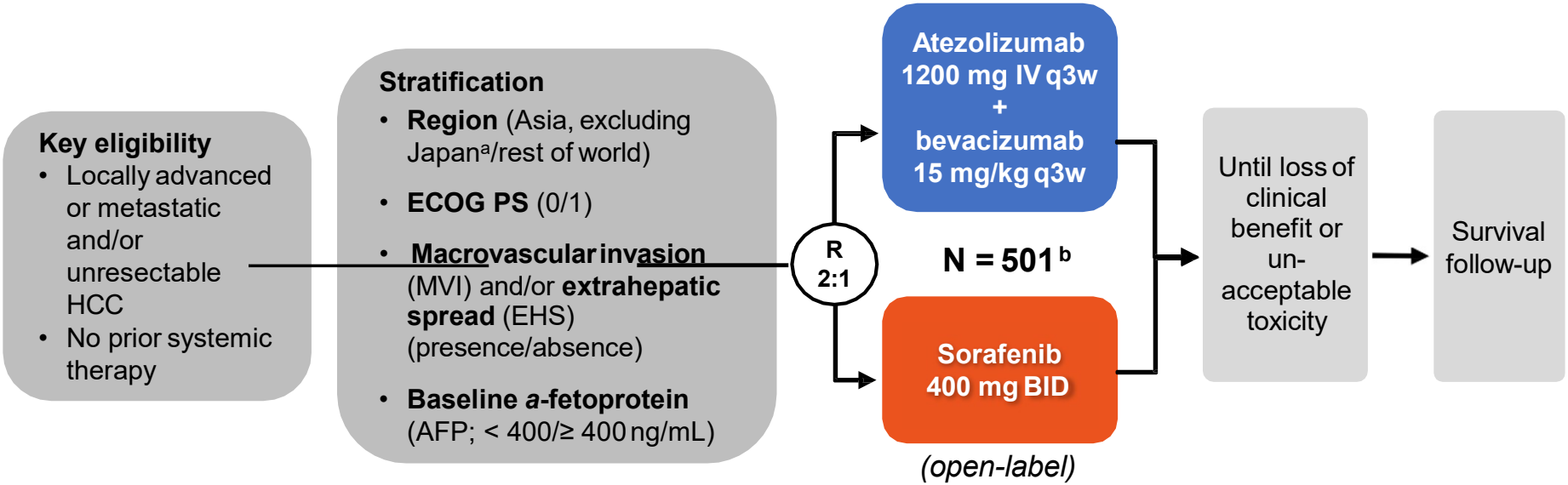
	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Objective response (%, 95% CI)	194 (40·6%, 36·2–45·0)	59 (12·4%, 9·4–15·4)	OR 5·01 (3·59–7·01)	<0·0001
Complete response	10 (2%)	4 (1%)	..	..
Partial response	184 (38%)	55 (12%)	..	..
Stable disease	159 (33%)	219 (46%)	..	..
Durable stable disease lasting ≥23 weeks	84 (18%)	90 (19%)	..	..
Progressive disease	79 (17%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	46 (10%)	..	..

REFLECT: TWO DIFFERENT TOXICITY PROFILES

TEAEs occurring in ≥20% of patients, n (%)	Lenvatinib (n=476)		Sorafenib (n=475)	
	Any	Grade 3/4	Any	Grade 3/4
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhea	184 (39)	20 (4)	220 (46)	20 (4)
Decreased appetite	162 (34)	22 (5)	127 (27)	6 (1)
Decreased weight	147 (31)	36 (8)	106 (22)	14 (3)
Fatigue	141 (30)	18 (4)	119 (25)	17 (4)
Hand-foot skin reaction	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (<1)	57 (12)	0
Alopecia	14 (3)	0	119 (25)	0
Nausea	93 (20)	4 (1)	68 (14)	4 (1)

Kudo M, et al. *Lancet* 2018;391:1163–1173.

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.

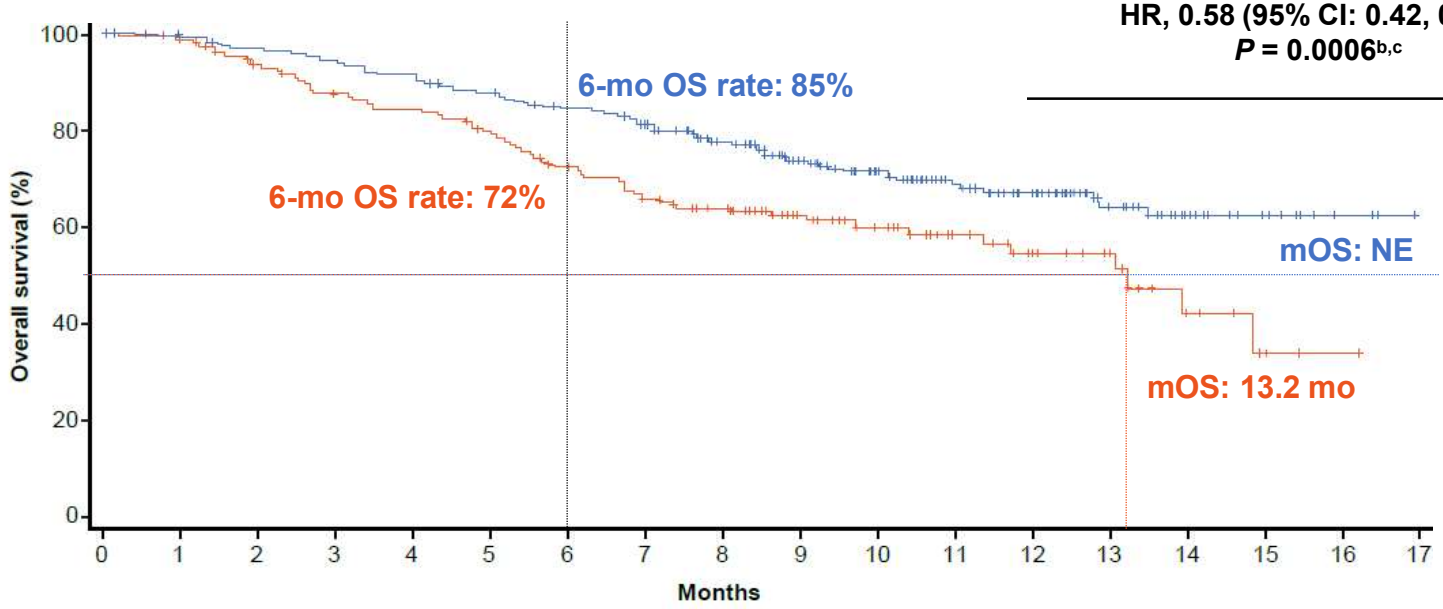
IMbrave150 baseline characteristics (ITT)

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]	

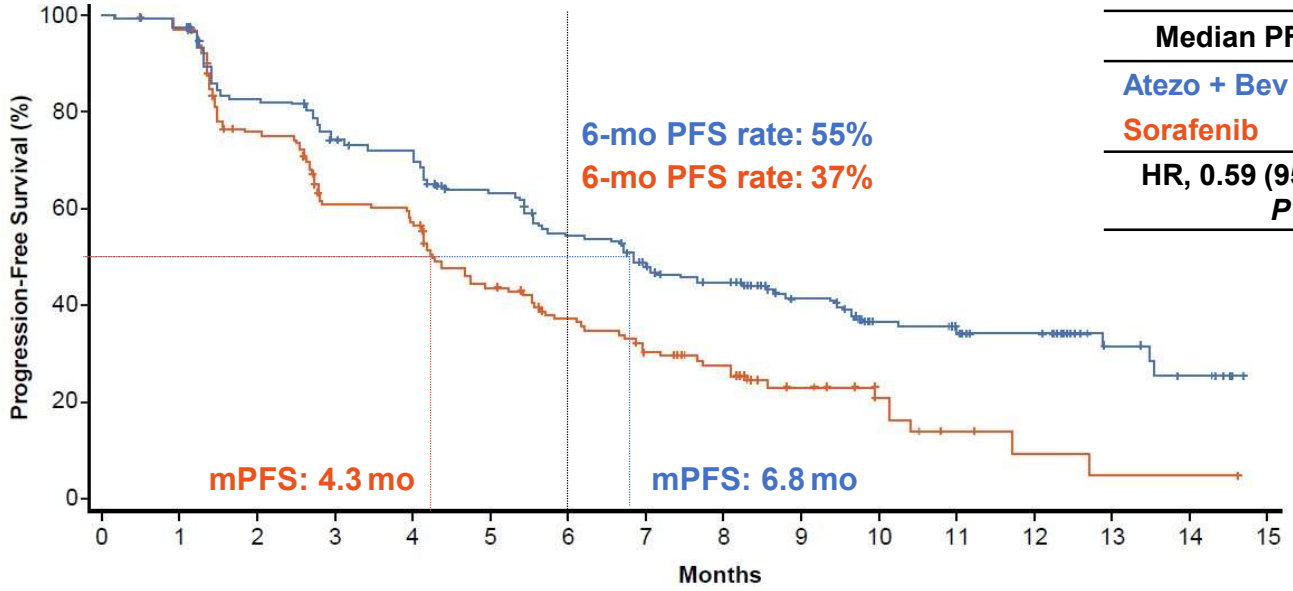


No. at risk																		
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

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.

http://bit.ly/2PimCgu

Confirmed PFS[a]: co-primary endpoint



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

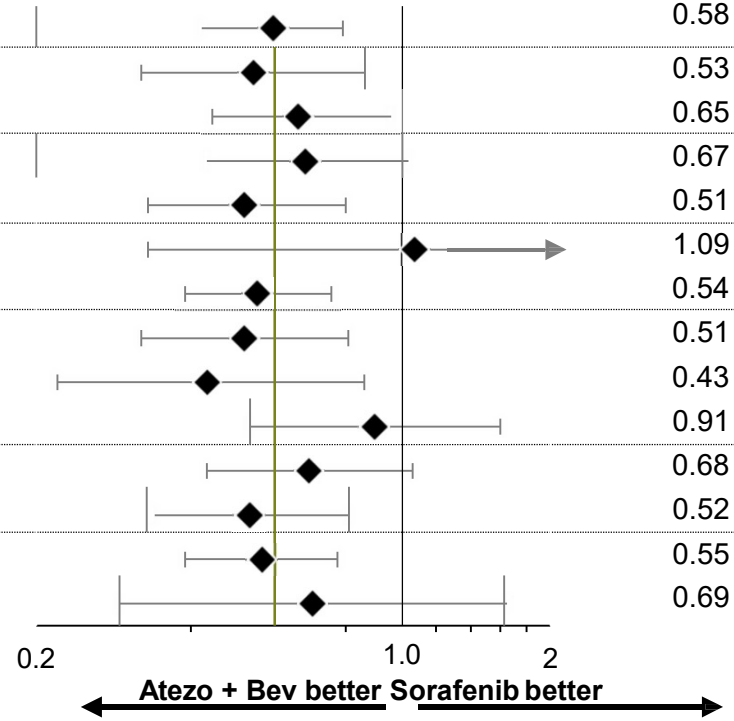
Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d]	
P < 0.0001[d]	

[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.

http://bit.ly/2PimCgu

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)

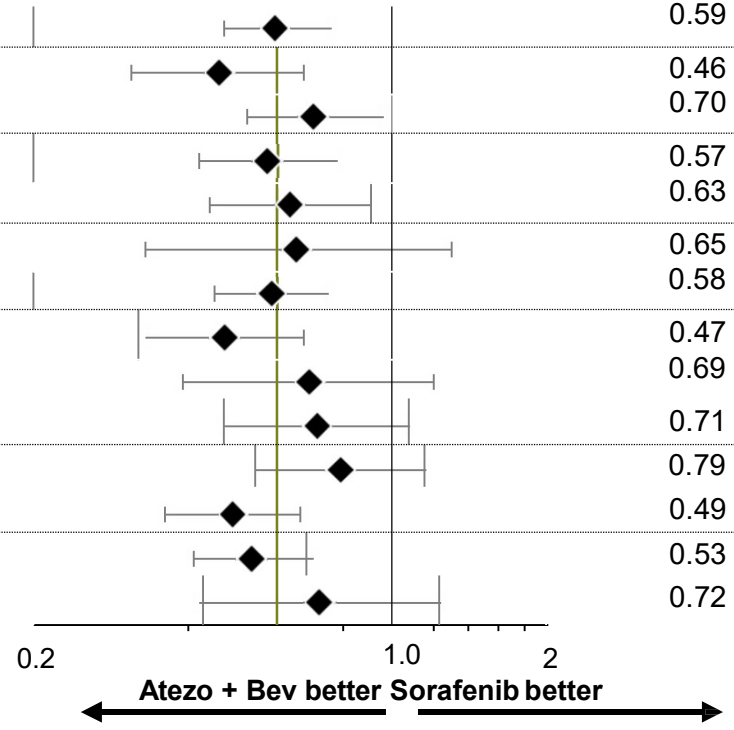


NE, not estimable.
[a] Unstratified HR shown for all characteristics except for "All patients," where stratified HR is shown. [b] Japan is included in rest of world.
[c] BCLC stage A not shown, as there were only 14 patients; thus, estimation is not meaningful.
Data cutoff, 29 Aug 2019; median survival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

http://bit.ly/2PimCgu

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)



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.

http://bit.ly/2PimCgu

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.

http://bit.ly/2PimCgu

Safety summary[a]

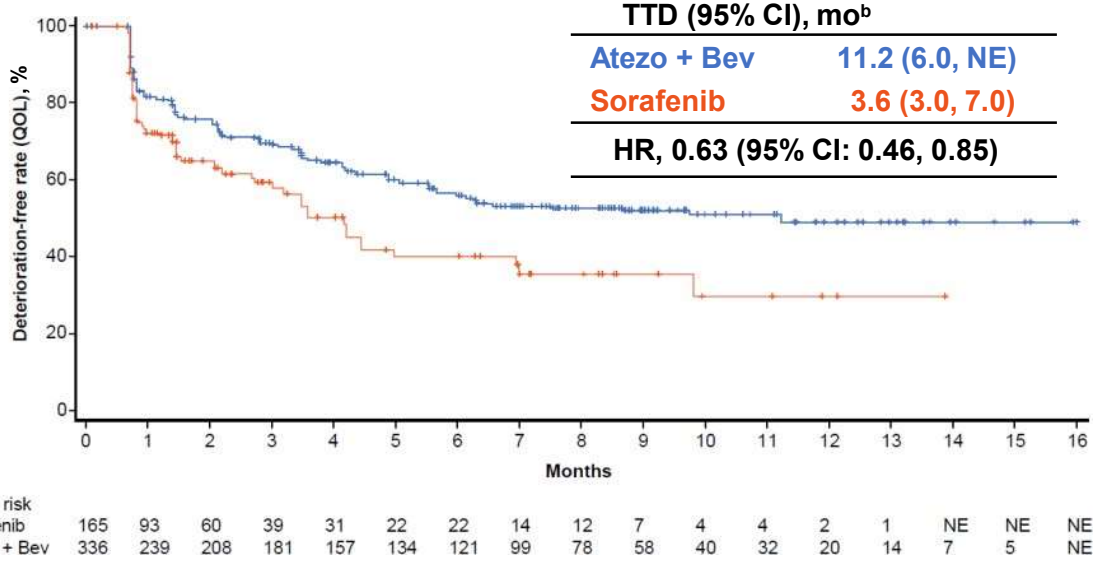
Characteristic	Atezo + Bev (n = 329)	Sorafenib (n = 156)
Treatment duration, median, mo	**Atezo = 7.4; Bev = 6.9**	**2.8**
All-Grade AEs, any cause, n (%)	323 (98)	154 (99)
Treatment-related all-Grade AEs	276 (84)	147 (94)
Grade 3-4 AE , n (%)[b]	186 (57)	86 (55)
Treatment-related Grade 3-4 AE[b]	117 (36)	71 (46)
Serious adverse event, n (%)	125 (38)	48 (31)
Treatment-related SAE	56 (17)	24 (15)
Grade 5 AE, n (%)	15 (5)	9 (6)
Treatment-related Grade 5 AE	6 (2)	1 (< 1)
AE leading to withdrawal from any component, n (%)	51 (16)	16 (10)
AE leading to withdrawal from both components	23 (7)	16 (10)
AE leading to dose interruption of any study treatment, n (%)	163 (50)	64 (41)
AE leading to dose modification of sorafenib, n (%)[c]	0	58 (37)

[a] Safety-evaluable population. [b] Highest grade experienced.
[c] No dose modification allowed for Atezo + Bev arm.

Patient-reported outcomes[a]

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

Quality of life	Median TTD (95% CI), mo[b]
Atezo + Bev	11.2 (6.0, NE)
Sorafenib	3.6 (3.0, 7.0)
HR, 0.63 (95% CI: 0.46, 0.85)	



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. ESMO Asia: IMbrave150 - presented by Dr Ann-Lii Cheng http://bit.ly/2PimCgu

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

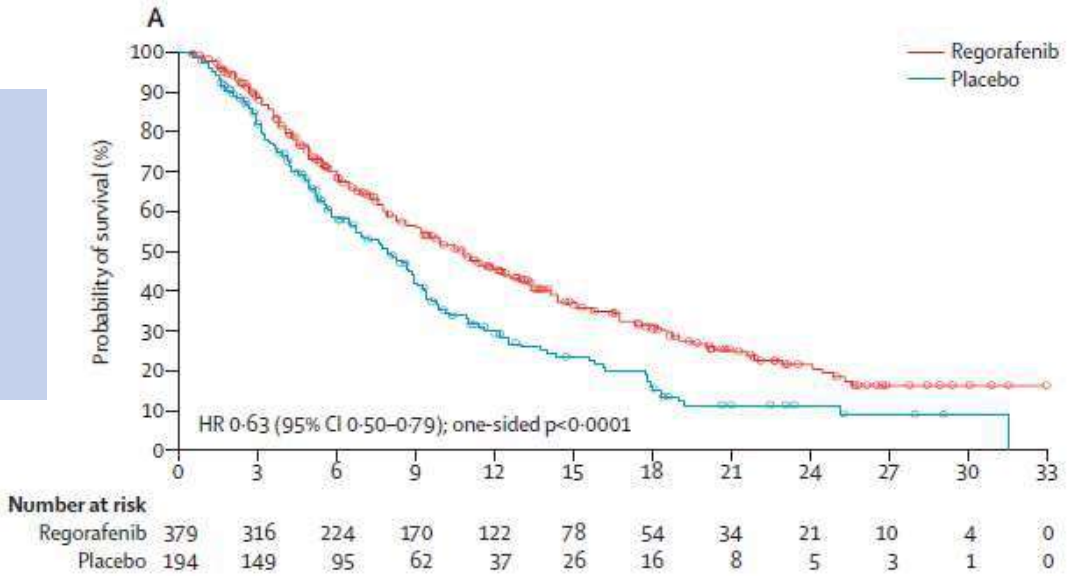
- PFS and OS benefits were generally consistent across subgroups
- Statistically significant and clinically meaningful improvements were seen in ORR and responses were durable with atezolizumab + bevacizumab
- The safety and tolerability profile of atezolizumab + bevacizumab was in line with the known 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

Second-Line

Second line after sorafenib: regorafenib: RESORCE trial

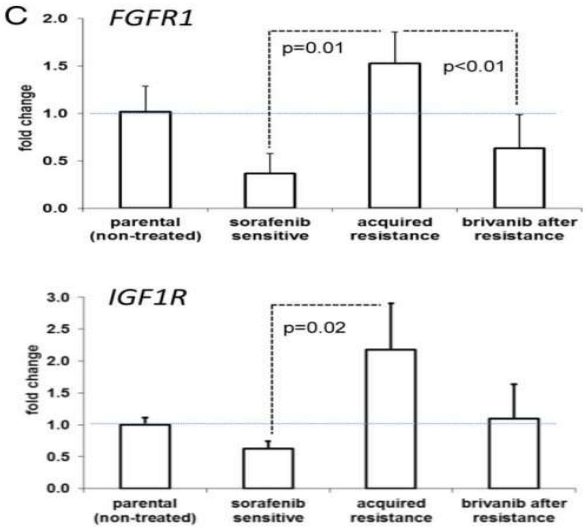
- RESORCE trial:
  - Progression during sorafenib
  - In patients who tolerated well sorafenib (> 400 mg/d , 20 d / month)
  - 160 mg/QD 3 weeks on 1 week off

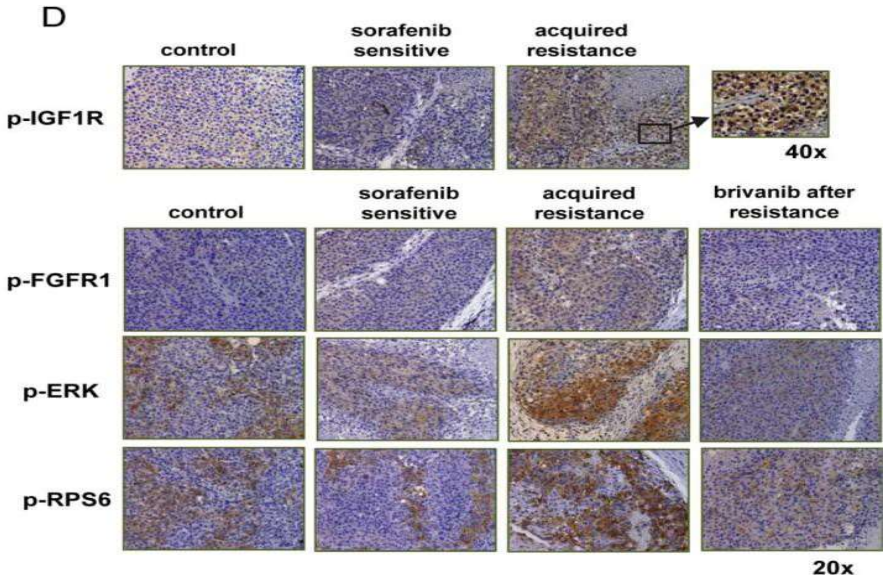
	Regorafenib	HR:	Placebo
mOS	10.6 m	0.63	7.8 m
mTTP	3.2 m	0.44	1.5 m
ORR	10.6%		4.1%
DCR	65.2%		36.1%



Bruix J, et al. Lancet 2016

Acquired Resistance to Sorafenib is Driven by Activation of IGF and FGF Signaling





Tovar V, et al. Gut 2017;66:530–540

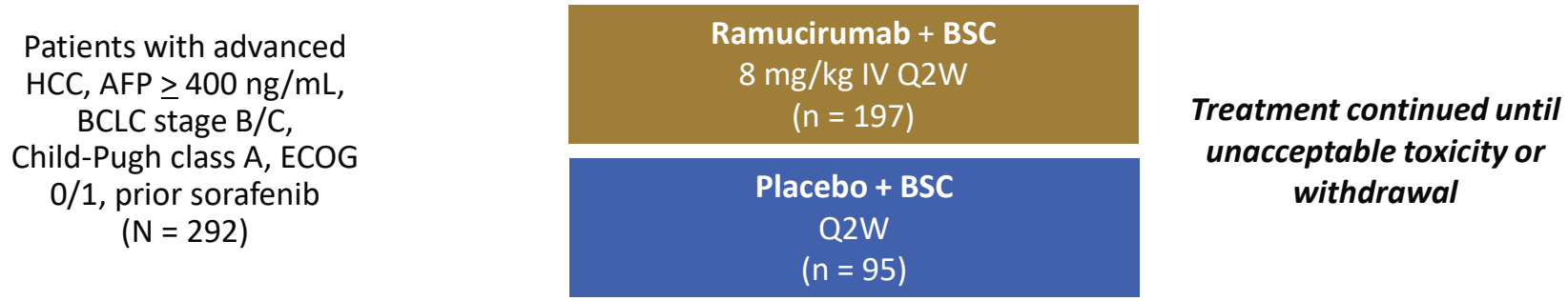
Exploratory Analysis of Survival With the Sequence of Sorafenib and Regorefanib

	Regorafenib	Placebo
Time from start of prior sorafenib treatment to death on RESORCE study drug		
All patients		
n	374	193
Median, months (95% CI)	26.0 (22.6, 28.1)	19.2 (16.3, 22.8)
Asia		
n	143	73
Median, months (95% CI)	21.5 (19.6, 27.8)	15.6 (12.2, 24.9)
Rest of the world		
n	231	120
Median, months (95% CI)	26.8 (23.3, 28.9)	19.9 (17.5, 25.9)

Finn R et al. GI Cancers Symposium 2017

REACH-2: Ramucirumab for Patients With Previously Treated HCC and Higher AFP

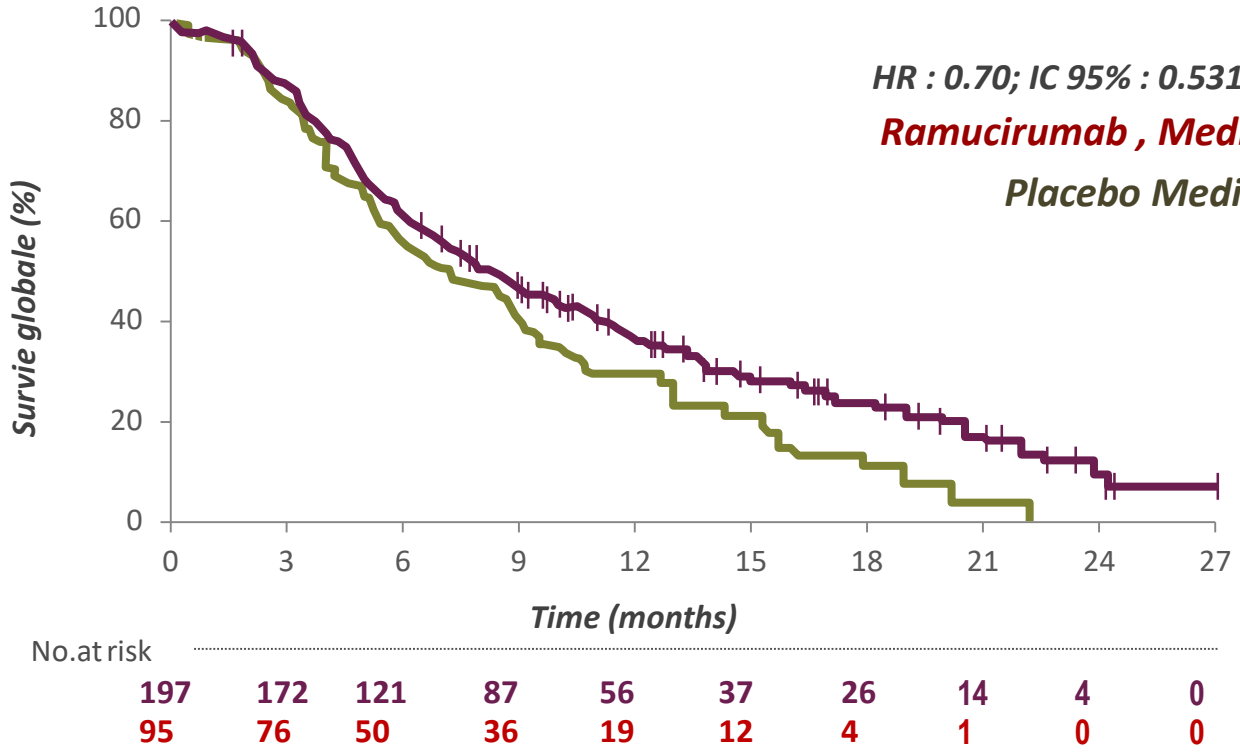
- Randomized, double-blind, multicenter phase III trial[1]
  - **Ramucirumab**: **anti-VEGFR2 monoclonal antibody**
  - REACH trial: patients with PD on sorafenib were randomly assigned to ramucirumab vs placebo;
    although the primary endpoint of OS was not met, a prespecified population of patients with baseline
    AFP ≥ 400 ng/mL and Child-Pugh class A demonstrated a significant OS advantage[2]



- Primary endpoint: OS; secondary endpoints: PFS, ORR, time to radiographic progression, time to FHSI-8 score decline, time to ECOG PS decline

1. Zhu. Lancet Oncol. 2019;20:282. 2. Zhu. Lancet Oncol. 2015;16:859.

REACH-2 : Overall survival, AFP level > 400 ng/mL



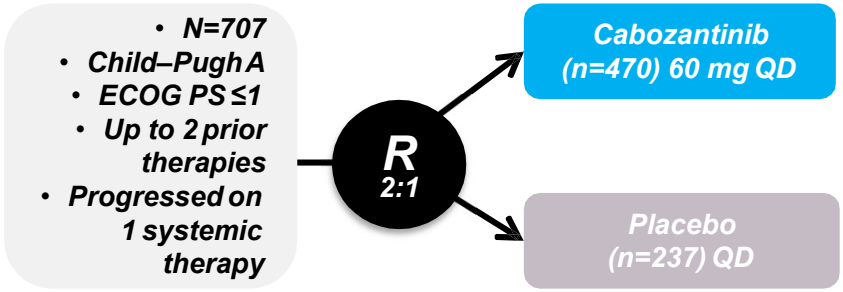
HR : 0.70; IC 95% : 0.531 – 0.949, p=0.0199

Ramucirumab , Median : 8.5 months

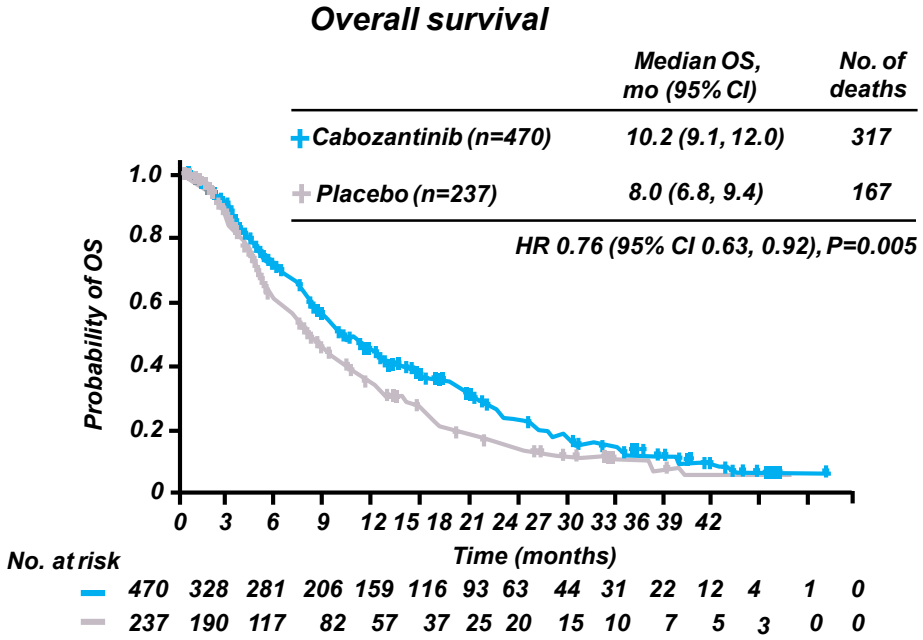
Placebo Median : 7.3 months

Zhu AX, et al., Lancet Oncol 2019;20:282-96

CELESTIAL: study design and primary endpoint



- Primary endpoint: OS
- Secondary endpoints: PFS, ORR
- 27% of patients had 2 prior regimens



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; R, randomized.
Abou-Alfa G, et al. N Engl J Med 2018;379:54–63.

Abou-Alfa G, et al. N Engl J Med 2018;379:54–63.

CELESTIAL: AE profile

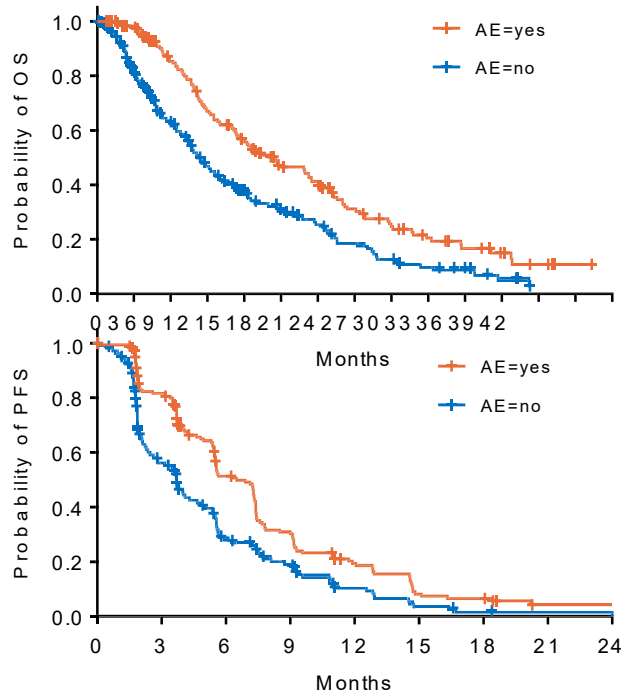
Preferred term, %	Cabozantinib (n=467)	Placebo (n=237)
Any grade 3 or 4 AE	68	37
PPE/HFSR	17	0
Hypertension	16	2
Increased AST	12	6
Fatigue	10	4
Diarrhea	10	2
Asthenia	7	2
Decreased appetite	6	<1
Anemia	4	5

Drug exposure	Cabozantinib (n=467)	Placebo (n=237)
Median duration of exposure (range), months	3.8	2.0
Median average daily dose	35.8 mg	58.9 mg
Any dose reduction	62%	13%
Discontinuation due to TEAE	16%	3%

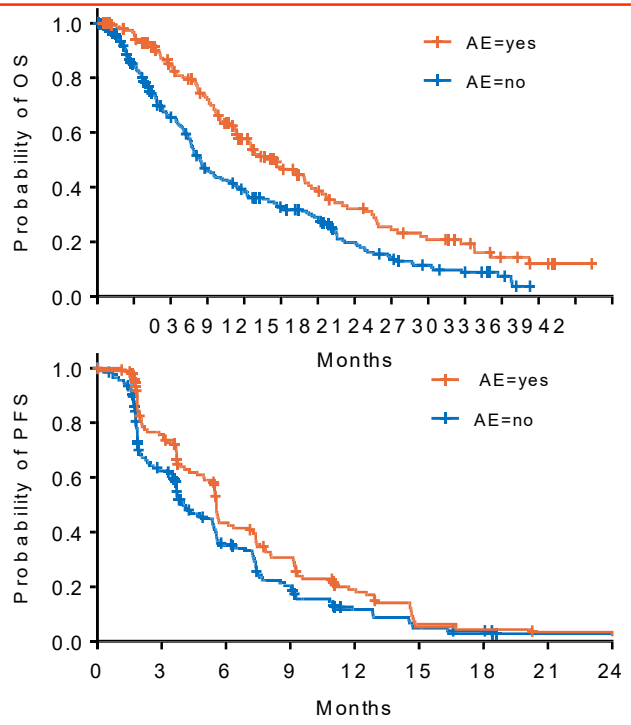
Abou-Alfa G, et al. N Engl J Med 2018;379:54–63.

Cabozantinib Outcome Correlation with Adverse Events

PPE (any grade, first 8 wks)



Hypertension (SBP ≥150, first 8 wks)



Abou-Alfa, GK, et al. J Clin Oncol 37, 2019 (suppl; abstr4088)

Conclusions Systemic treatment of HCC

- 1st line
  - Sorafenib
  - Lenvatinib
  - Atezolizumab/Bevacizumab
- 2nd line
  - Regorafenib
  - Nivolumab
  - Pembrolizumab
  - Cabozantinib
  - Ramucirumab

Which of the following treatment regimens improve survival compared to Sorafenib as first line therapy in HCC

- A- Levatinib
- B- Ramucirumab
- C- Cabozantinib
- D- Atezolizumab and Bevacizumab
- E- Levatinib and Pembrolizumab

Answer

- Atezolizumab and Bevacizumab: 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. PFS HR, 0.59 (95% CI: 0.47, 0.76); *P* < 0.0001. ESMO ASIA Plenary Session 2019.
- Levatinib improved PFS and RR compared to sorafenib but did not improve survival. Kudo M, et al. *Lancet* 2018;391:1163–1173.
- Cabozantinib improves survival compared to placebo as second-ine therapy in HCC . Abou-Alfa G, et al. N Engl J Med 2018;379:54–63
- Ramucirumab is a second-line choice for HCC with high alfa-fetoprotein
- Pembrolizumab + levatinib combination is undergoing first-line study.