Available Data with and Patient Selection for Anti-angiogenic Therapy for Progressive Metastatic HCC

Andrew X Zhu, MD, PhD
Director, Jiahui International Cancer Center
Shanghai, China
Director Emeritus, Liver Cancer Research
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

Regulatory and reimbursement issues aside, what would be your second-line therapy for a 65 yo with HCC, a Child-Pugh A score and a PS of 0 who received first-line sorafenib, had stable disease for 14 months and experienced disease progression (AFP = 2,500)?

Lenvatinib (1), Cabozantinib (1), Pembrolizumab (1)

Regulatory and reimbursement issues aside, what would be your second-line therapy for a 65 yo with HCC, a Child-Pugh A score and a PS of 0 who received first-line sorafenib, had stable disease for 14 months and experienced disease progression (AFP = 250)?

Lenvatinib (1), Pembrolizumab (1)

Regulatory and reimbursement issues aside, what would be your second-line therapy for a 65 yo with HCC, a Child-Pugh A score and a PS of 0 who received first-line lenvatinib, had stable disease for 14 months and experienced disease progression (AFP = 2,500)?

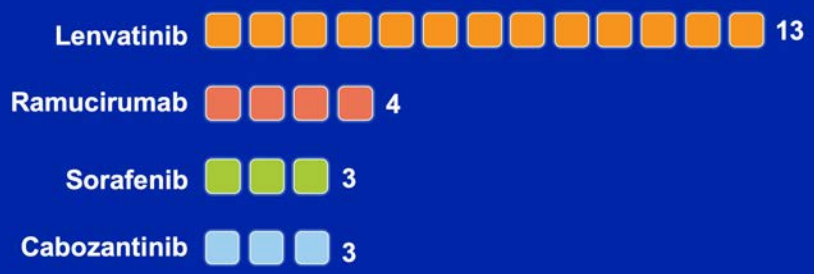
Regorafenib (2)

Sequencing of Agents in HCC

Current role of anti-angiogenic agents (sorafenib, lenvatinib, cabozantinib, ramucirumab)

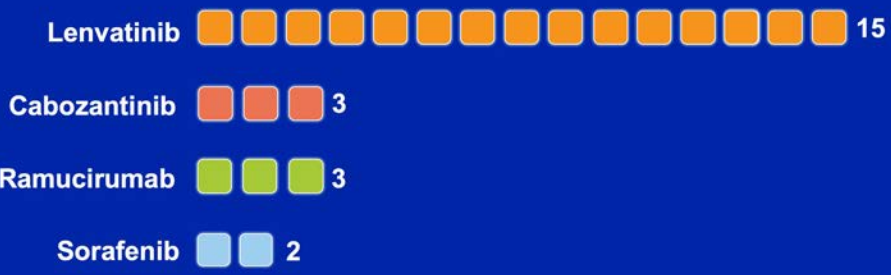
- After first-line sorafenib or lenvatinib
- After first-line atezolizumab/bevacizumab

Regulatory and reimbursement issues aside, what would be your second-line therapy for a 65 yo with HCC, a Child-Pugh A score and a PS of 0 who received first-line atezolizumab/bevacizumab and experienced disease progression after 6 months (AFP = 2,500)?



Regorafenib (2)

Regulatory and reimbursement issues aside, what would be your second-line therapy for a 65 yo with HCC, a Child-Pugh A score and a PS of 0 who received first-line atezolizumab/bevacizumab and experienced disease progression after 18 months (AFP = 2,500)?



Regorafenib (1), Nivolumab (1)

Second- and third-line therapies for a 65 yo with HCC, a Child-Pugh A score (PS 0) who received first-line atezolizumab/bevacizumab and experienced disease progression after 18 months (AFP = 2,500)

- Lenvatinib → Cabozantinib (8)
- Lenvatinib → Ramucirumab (4)
- Ramucirumab → Cabozantinib (3)
- Lenvatinib → Regorafenib (3)
- Cabozantinib → Ramucirumab (1)
- Regorafenib → Cabozantinib (1)
- Nivolumab → Regorafenib (1)
- Cabozantinib → Lenvatinib (1)
- Cabozantinib → Regorafenib (1)
- Sorafenib → Ramucirumab (1)
- Sorafenib → Cabozantinib (1)

Sequencing of Agents in HCC

Current role of anti-angiogenic agents (sorafenib, lenvatinib, cabozantinib, ramucirumab)

- After first-line sorafenib or lenvatinib
- After first-line atezolizumab/bevacizumab

Available Data with and Patient Selection for Anti-angiogenic Therapy for Progressive Metastatic HCC

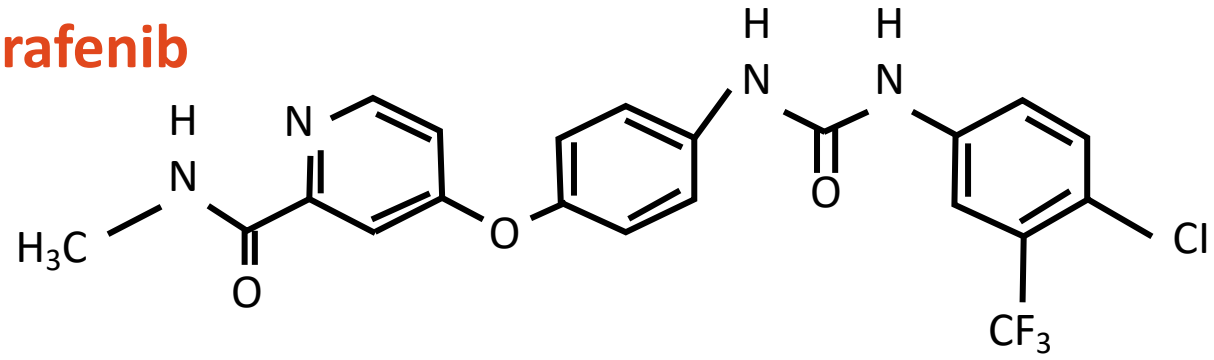
Andrew X Zhu, MD, PhD
Director, Jiahui International Cancer Center
Shanghai, China
Director Emeritus, Liver Cancer Research
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

Disclosures

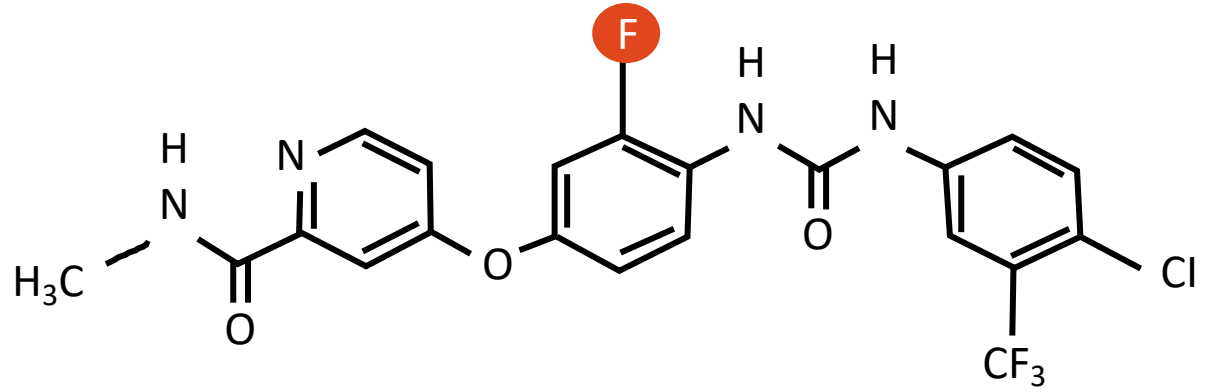
Advisory Committee	Bayer HealthCare Pharmaceuticals, Eisai Inc, Exelixis Inc, Lilly, Merck, Roche Laboratories Inc, Sanofi Genzyme

Sorafenib vs Regorafenib: Key Molecular Difference

Sorafenib



Regorafenib



- The addition of a fluorine atom in the central phenyl ring may lead to broader and more potent target profile than sorafenib: VEGFR1-3, c-KIT, TIE-2, PDGFR-β, FGFR-1, RET, c-RAF, BRAF, and p38 MAP kinase
- Regorafenib metabolites (M-2 and M-5) have continued antineoplastic effect during 1-wk washout period

Trojan. J Hepatocell Carcinoma. 2016;3:31. Kline. Pharmaceuticals. 2013;6:988.

Regorafenib vs Placebo in the Second Line (RESORCE)

HCC patients with documented radiologic progression during sorafenib treatment

Stratified by
- Geographic region (Asia vs rest of the world)
- Macrovascular invasion
- Extrahepatic disease
- ECOG PS (0 vs 1)
- AFP (< or ≥ 400 ng/mL)

N = 573

R

2:1

Regorafenib
160 mg orally;
3 wk on, 1 wk off (4 wk cycle)
n = 379

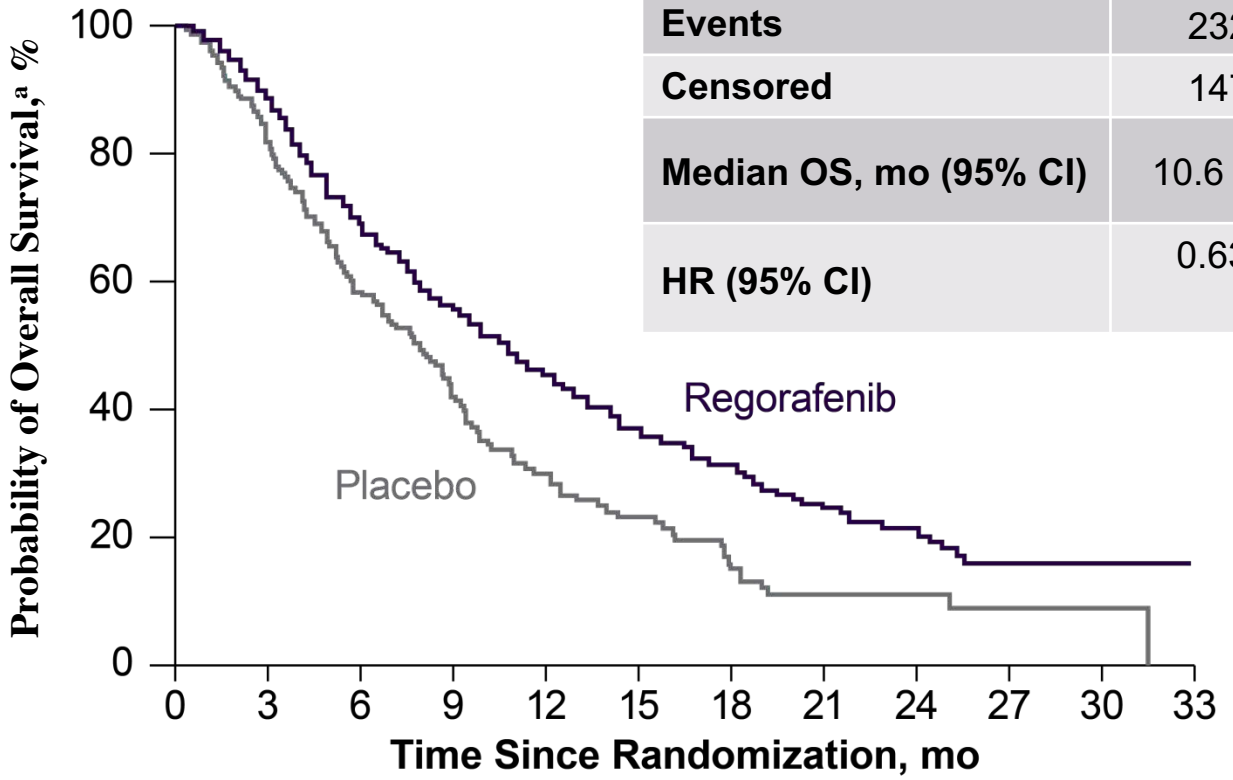
Placebo
n = 194

- All patients received best supportive care
- Patients were treated until disease progression, death, or unacceptable toxicity
- Primary endpoint: OS in ITT population
- Secondary endpoints: PFS, TTP, RR, DCR

Bruix J et al. *Lancet*. 2017;389:56-66.

RESORCE Trial: Overall Survival[1]

	Regorafenib (n = 379)	Placebo (n = 194)
Events	232 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS, mo (95% CI)	10.6 (9.1-12.1)	7.8 (6.3-8.8)
HR (95% CI)	0.63 (0.50-0.79); *P* < .0001 (2-sided)	



No. at Risk

Regorafenib	379	316	224	170	122	78	54	34	21	10	4	0
Placebo	194	149	95	62	37	26	16	8	5	3	1	0

[a] Based on mRECIST.

1. Bruix J et al. *Lancet*. 2017;389:56-66.

RESORCE Trial: Efficacy[1]

Endpoint[a]	Regorafenib (n = 379)	Placebo (n = 194)	Statistic
Median OS, mo	10.6	7.8	HR = 0.63 *P* < .0001
Median PFS, mo	3.1	1.5	HR = 0.46 *P* < .001
Median TTP, mo	3.2	1.5	HR = 0.44 *P* < .001
ORR, %	10.6	4.1	*P* = .005
DCR, %	65.2	36.1	*P* < .001

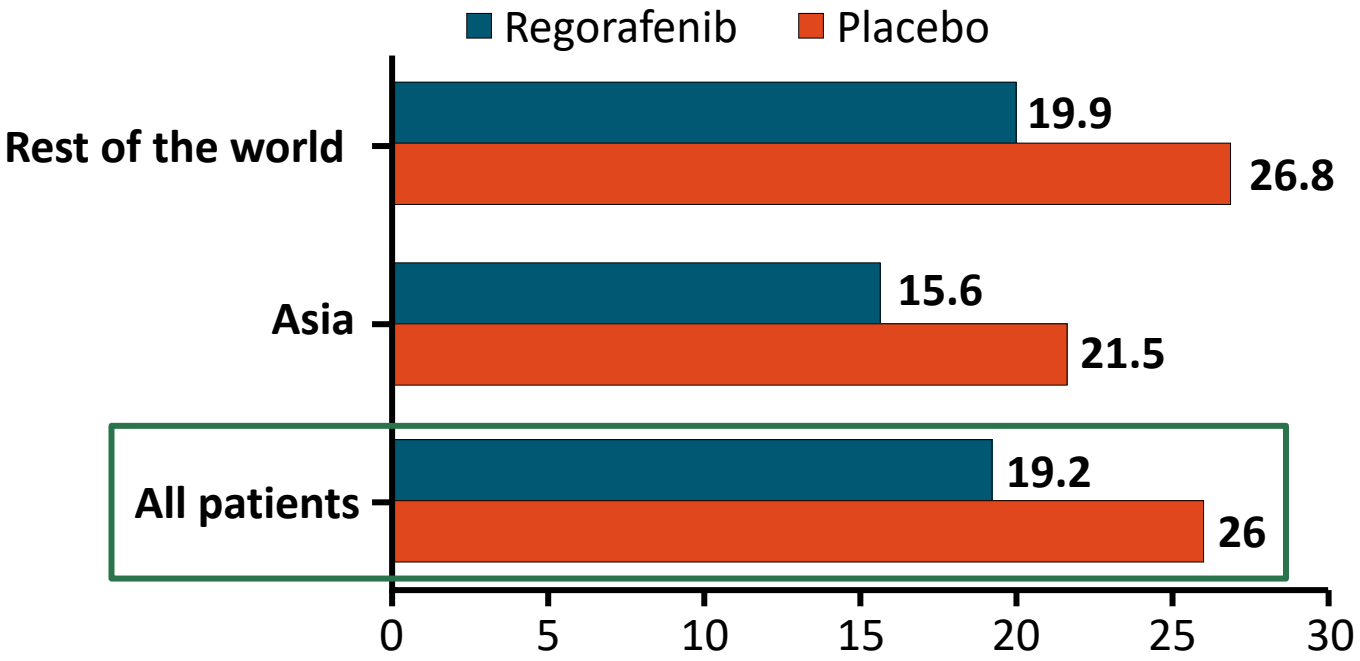
[a] Based on mRECIST.

1. Bruix J et al. *Lancet*. 2017;389:56-66.

Median OS of 26 Months From First Sorafenib Dose to Death in RESORCE study

Exploratory analysis of time from start of prior sorafenib treatment to death on RESORCE study drug

	n	(CI)
Rest of the world	120	(17.5-25.9)
	231	(23.3-28.9)
Asia	73	(12.2-24.9)
	143	(19.6-27.8)
All patients	193	(16.3-22.8)
	374	(22.6-28.1)



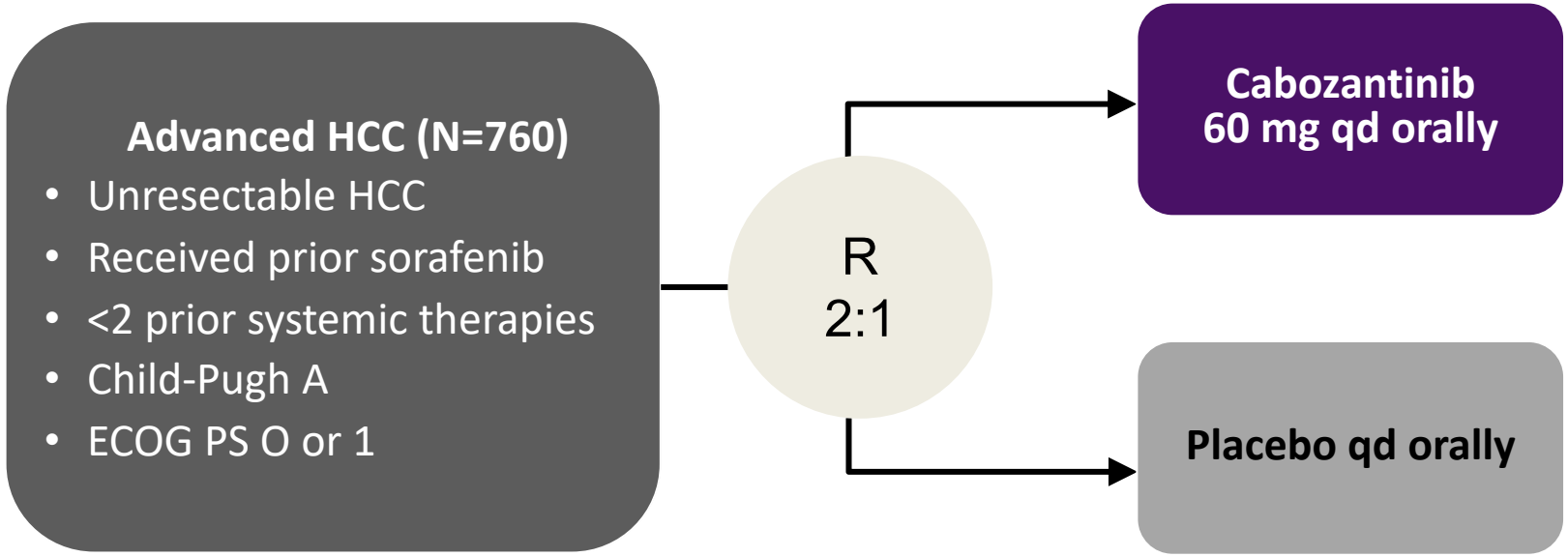
Finn RS et al J Hepatol 2018

RESORCE: Select Treatment-Emergent AEs

AEs, %	Regorafenib (n = 379)			Placebo (n = 194)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
HFSR	**53**	**13**	**N/A**	**8**	**1**	**N/A**
Diarrhea	41	3	0	15	0	0
Fatigue	40	9	N/A	32	5	N/A
Hypertension	**31**	**15**	**< 1**	**6**	**5**	**0**
Anorexia	31	3	0	15	2	0
Bilirubin increased	29	10	1	18	8	3
Abdominal pain	28	3	0	22	4	0
AST increased	25	10	1	20	10	2
Ascites	16	4	0	16	6	0
Anemia	16	4	1	11	5	1
Hypophosphatemia	**10**	**8**	**1**	**2**	**2**	**0**

Bruix. Lancet. 2017;389:56.

CELESTIAL: A Phase III Study of Cabozantinib vs Placebo in Patients With HCC Who Have Received Prior Sorafenib



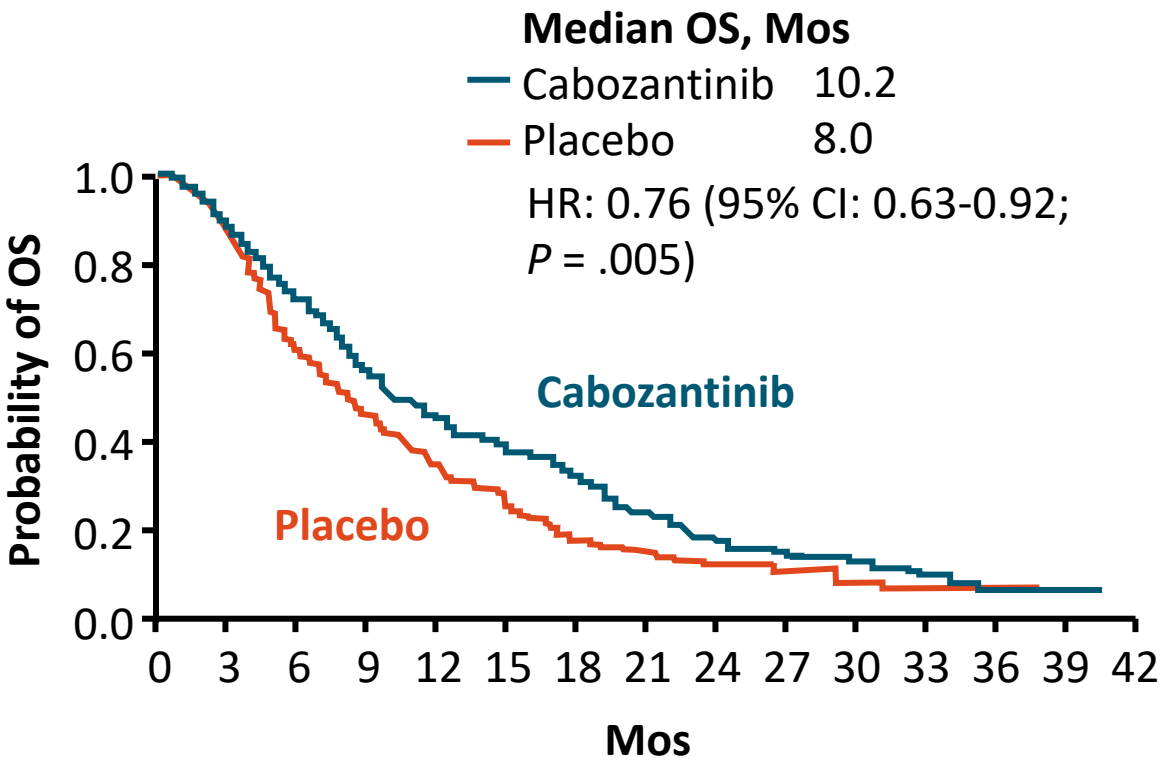
Primary endpoint
- OS

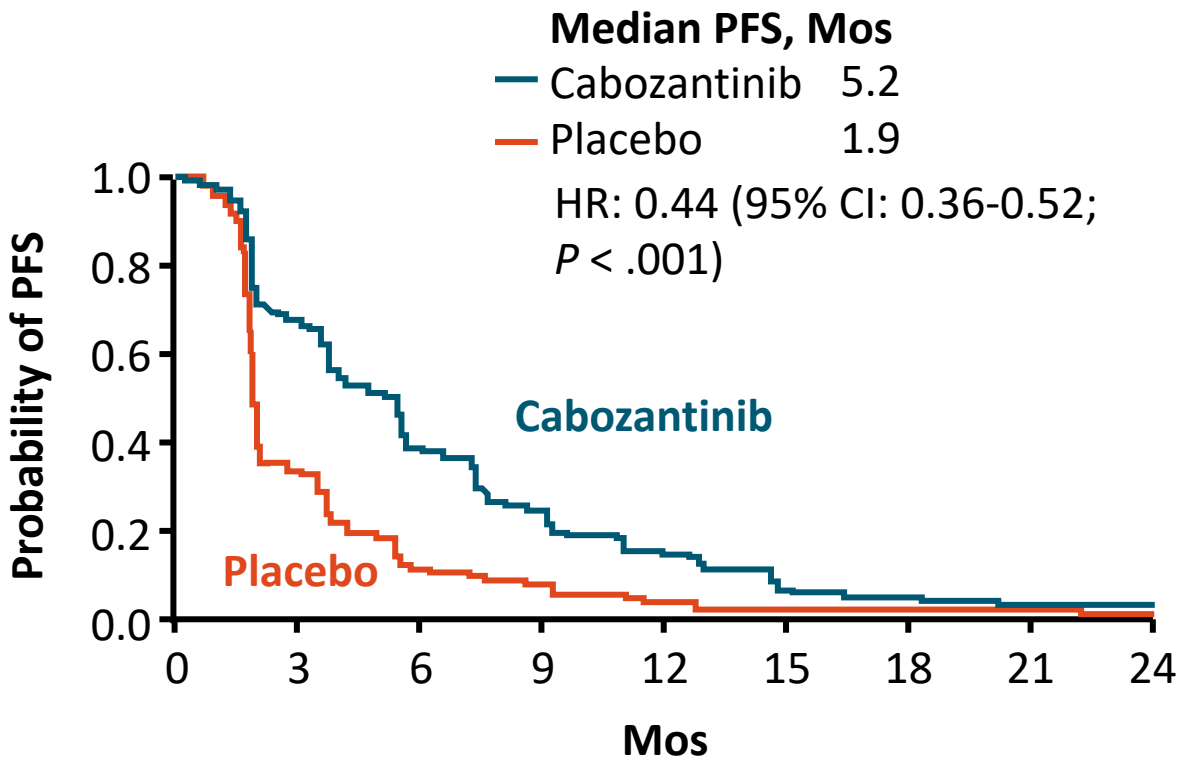
Secondary endpoints
- PFS, ORR

Other endpoints
- Safety/tolerability, PK, biomarkers, HRQOL

Abou Alfa et al NEJM 2018;379:54-63

CELESTIAL: Survival





Abou-Alfa. NEJM. 2018;379:54.

CELESTIAL: Select Treatment-Related AEs

AEs, %*	Cabozantinib (n = 467)			Placebo (n = 237)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Diarrhea	54	10	< 1	19	2	0
Decreased appetite	48	6	0	18	< 1	0
Palmar–plantar erythrodysesthesia	46	17	0	5	0	0
Fatigue	45	10	0	30	4	0
Nausea	31	2	0	18	2	0
Hypertension	29	16	< 1	6	2	0
Vomiting	26	< 1	0	12	3	0
Increase in aspirate aminotransferase level	22	11	1	11	6	< 1
Asthenia	22	7	<1	8	2	0

*Occurring in ≥ 20% of patients in one treatment group.

Abou-Alfa. NEJM. 2018;379:54.

OS and PFS benefit based on baseline AFP level in CELESTIAL trial

Magnitude of Benefit Observed for OS and PFS by Baseline AFP Level in the Phase III CELESTIAL Trial

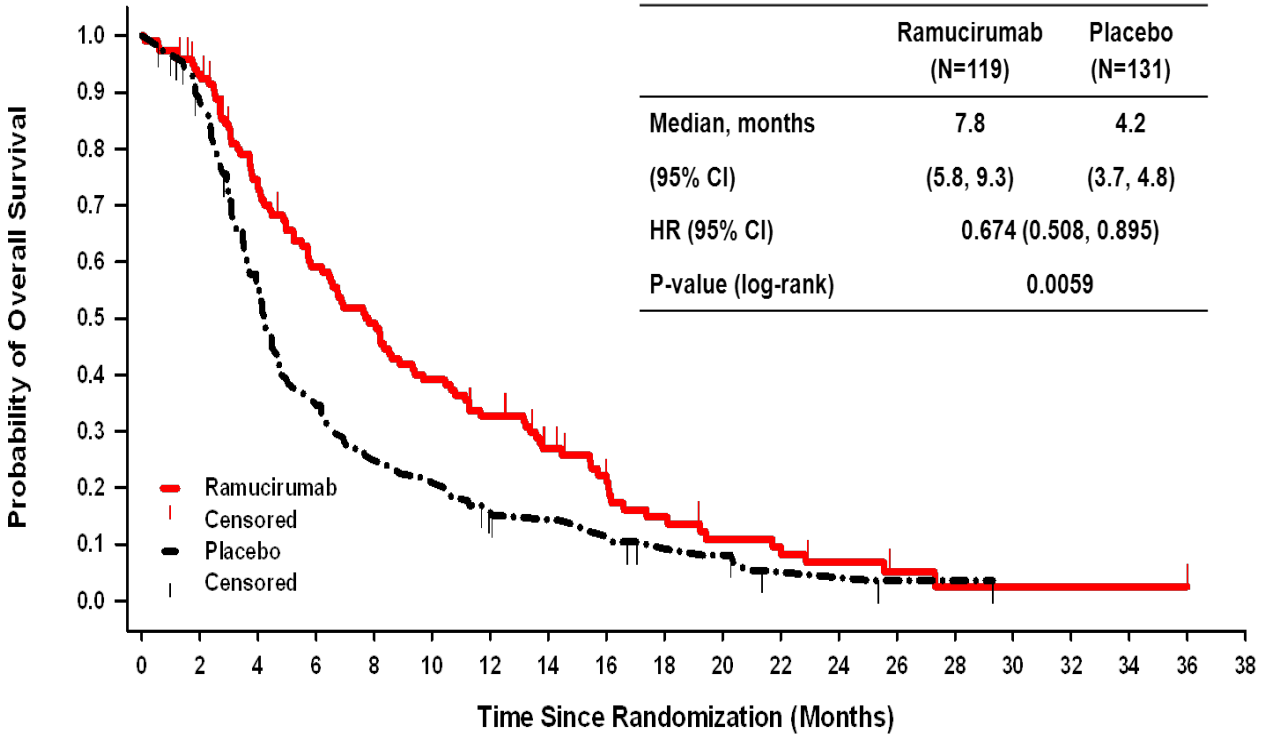
Patients by baseline AFP	Median OS			Median PFS		
	Cabozantinib	Placebo	HR (95% CI)	Cabozantinib	Placebo	HR (95% CI)
All	10.2	8.0	0.76 (0.63-0.92	5.2	1.9	0.44 (0.36-0.52)
AFP <20 ng/mL	14.4	13.7	0.97 (0.67-1.40)	5.6	2.0	0.57 (0.41-0.78)
AFP ≥20 ng/mL	9.5	5.8	0.67 (0.54-0.84	4.3	1.9	0.41 (0.33-0.51)
AFP <200 ng/mL	13.9	10.9	0.83 (0.63-1.10)	5.5	1.9	0.52 (0.40-0.67)
AFP ≥200 ng/mL	8.8	5.3	0.70 (0.54-0.91)	4.0	1.9	0.39 (0.30-0.50)
AFP <400 ng/mL	13.9	10.3	0.81 (0.62-1.04)	5.5	1.9	0.47 (0.37-0.60)
AFP ≥400 ng/mL	8.5	5.2	0.71 (0.54-0.94)	3.9	1.9	0.42 (0.32-0.55)

AFP indicates alpha-fetoprotein; OS, overall survival; PFS, progression-free survival.

Kelley RK et al, ILCA 2019

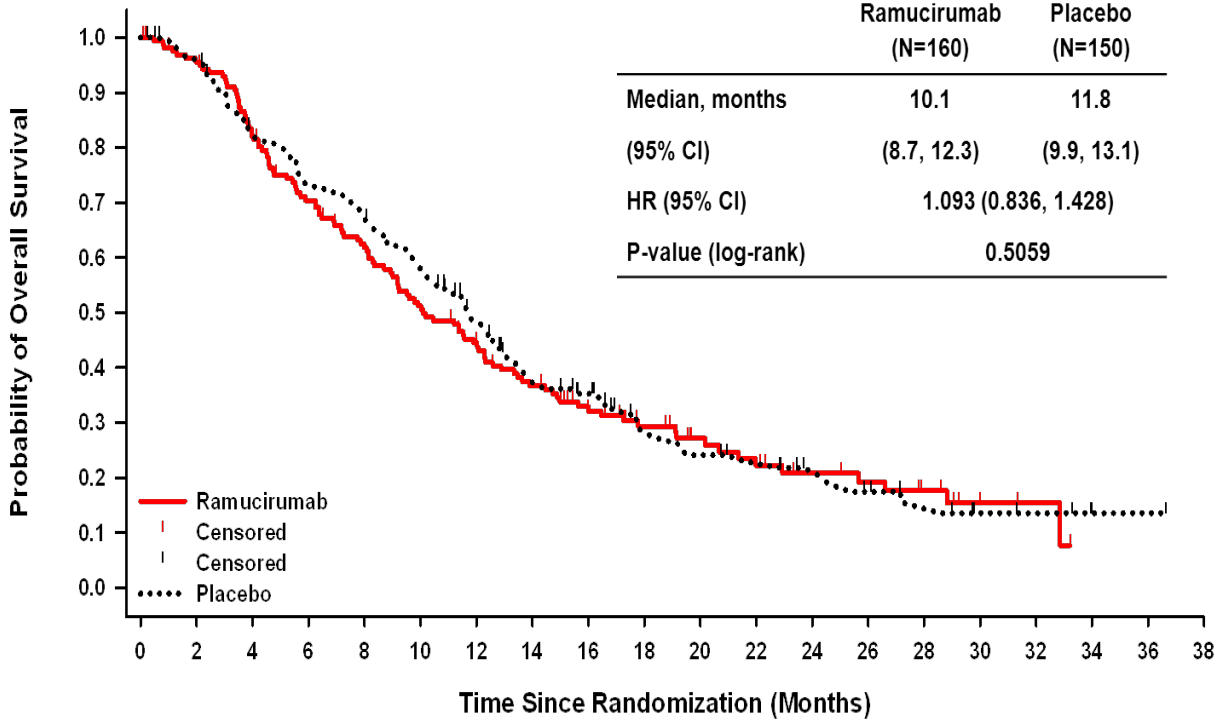
REACH Study: Overall Survival in Patients With Baseline alpha-fetoprotein ≥ or < 400 ng/mL

AFP≥400 ng/mL



	Ramucirumab (N=119)	Placebo (N=131)
Median, months	7.8	4.2
(95% CI)	(5.8, 9.3)	(3.7, 4.8)
HR (95% CI)	0.674 (0.508, 0.895)	
P-value (log-rank)	0.0059	

AFP <400 ng/mL

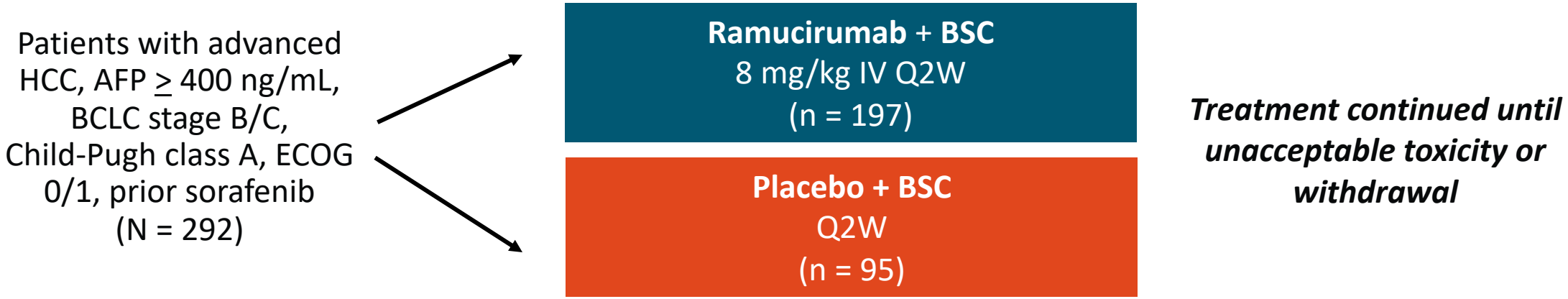


	Ramucirumab (N=160)	Placebo (N=150)
Median, months	10.1	11.8
(95% CI)	(8.7, 12.3)	(9.9, 13.1)
HR (95% CI)	1.093 (0.836, 1.428)	
P-value (log-rank)	0.5059	

Zhu AX et al, Lancet Oncol. 2015;16:859.

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

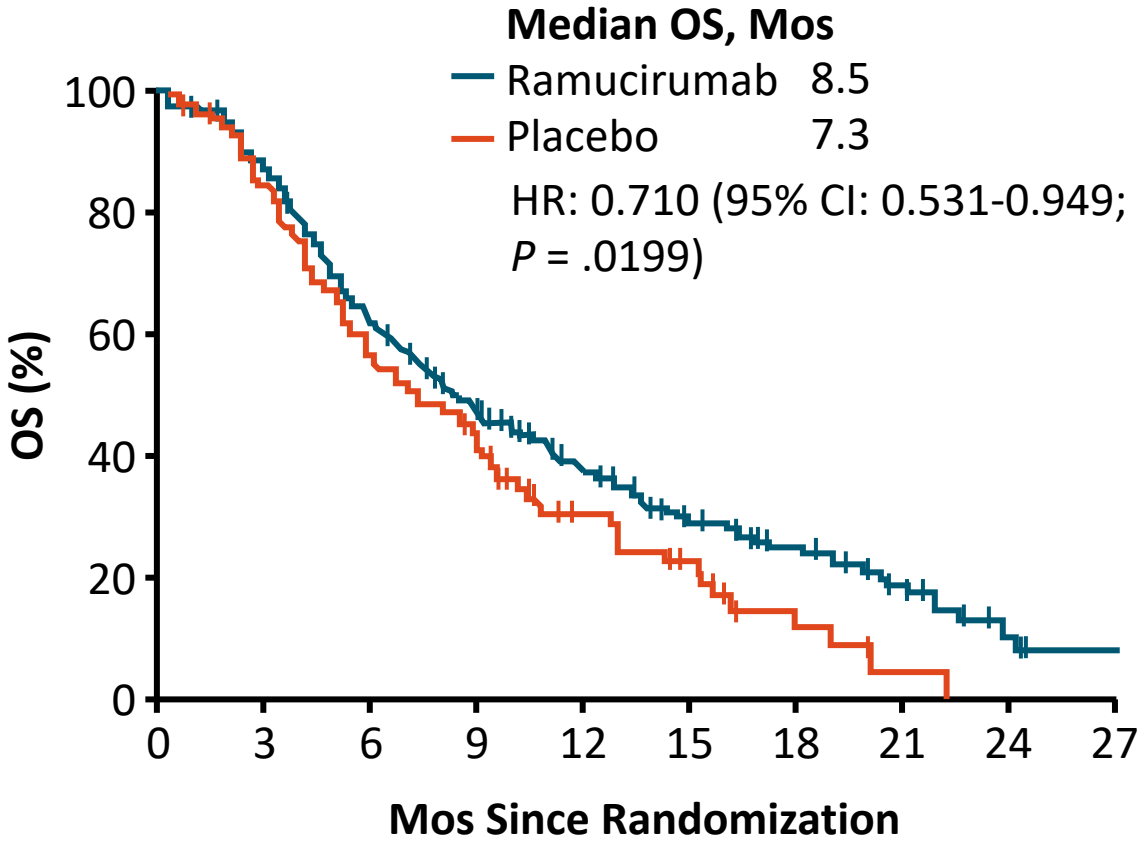
- Randomized, double-blind, multicenter phase III trial[1]
  - **Ramucirumab**: **anti-VEGFR2 monoclonal antibody**
  - REACH trial: patients with PD on sorafenib were randomly assigned to ramucirumab vs placebo; although the primary endpoint of OS was not met, a prespecified population of patients with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

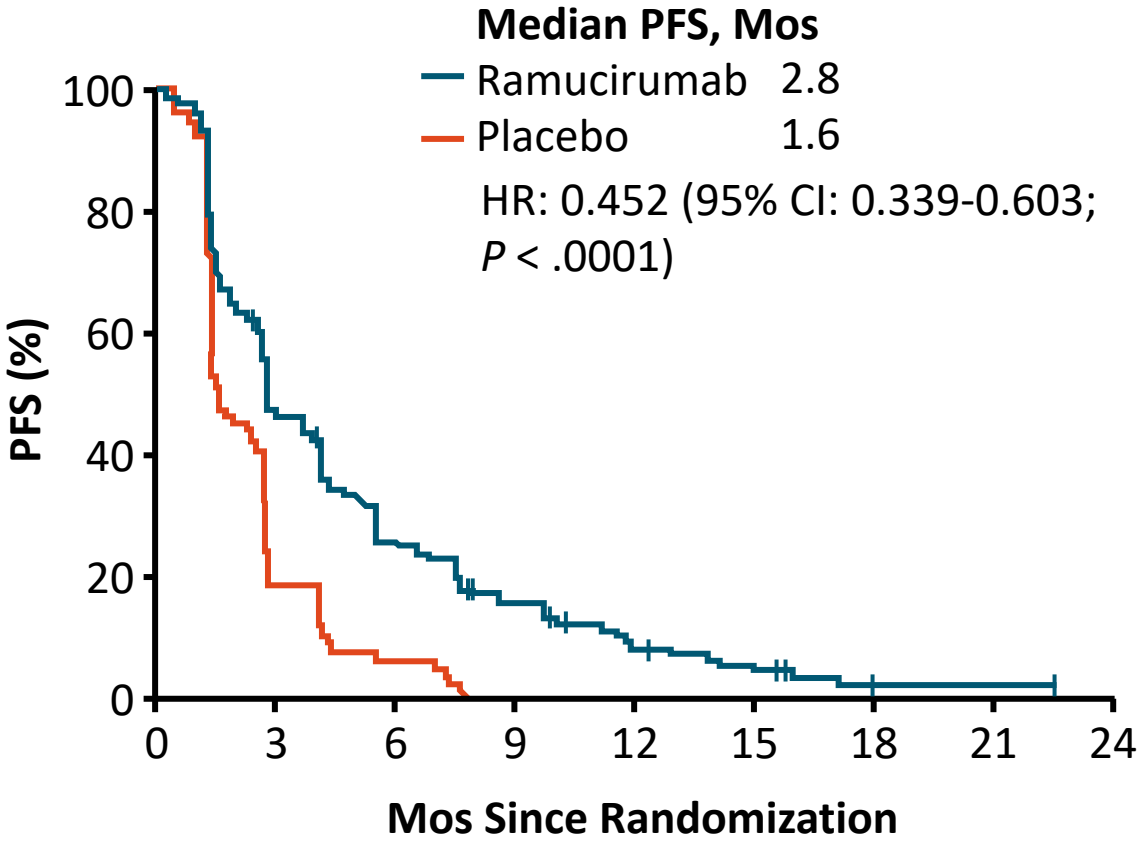


- Primary endpoint: OS; secondary endpoints: PFS, ORR, time to radiographic progression, time to FHSI-8 score decline, time to ECOG PS decline

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

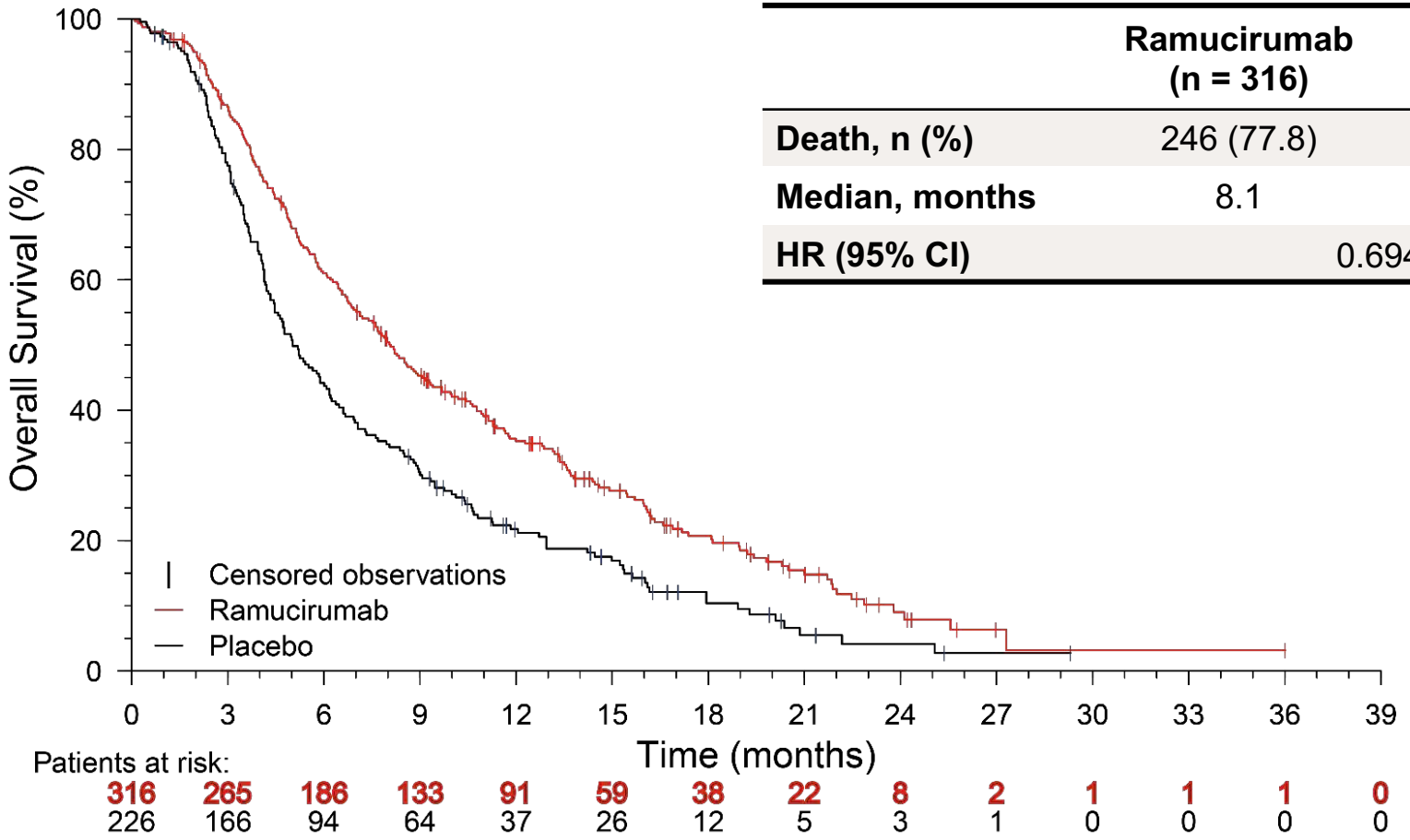
REACH-2: Survival





Zhu. Lancet Oncol. 2019;20:282.

Pooled Overall Survival: REACH-2/REACH (AFP ≥400 ng/mL)



	Ramucirumab (n = 316)	Placebo (n = 226)	Difference	P-value
Death, n (%)	246 (77.8)	190 (84.1)		
Median, months	8.1	5.0	3.1	
HR (95% CI)		0.694 (0.571, 0.842)		0.0002

No heterogeneity in treatment effect observed across both studies.

A random effect frailty model after adjusting for study (as random effect) produced a similar treatment result (HR=0.689; p=0.0002)

Zhu AX, et al. *Lancet Oncology 2019*

REACH-2: Select Treatment-Related AEs

AE, %*	Ramucirumab (n = 197)		Placebo (n = 95)	
	Grades 1/2	Grades 3-5	Grades 1/2	Grades 3-5
Fatigue	24	4	14	3
Peripheral edema	24	2	14	0
Decreased appetite	22	2	19	1
Abdominal pain	18	2	11	2
Nausea	19	0	12	0
Diarrhea	16	0	14	1
Headache	14	0	4	1
Constipation	13	1	19	1
Insomnia	11	0	5	1
Pyrexia	10	0	3	0
Vomiting	10	0	7	0

AE, %*	Ramucirumab (n = 197)		Placebo (n = 95)	
	Grades 1/2	Grades 3-5	Grades 1/2	Grades 3-5
Bleeding/ hemorrhage	19	6	9	3
Epistaxis	13	1	3	0
Hypertension	12	13	7	5
Proteinuria	18	2	4	0
Liver injury/ failure	21	18	14	16
Ascites	14	5	5	2

*Occurring in ≥ 10% of patients in one treatment group.

Zhu. Lancet Oncol. 2019;20:282.