systemic therapy beyond 1st line in advanced HCC

Shereef Elsamany

Consultant of Medical Oncology

Oncology Center/KAMC

Systemic Therapy for HCC

- Systemic therapy is standard of care for patients with:
  - BCLC stage C
    - Extrahepatic metastases
    - Portal vein invasion
    - ECOG PS 1-2
  - BCLC stage B
    - Extensive multifocal or infiltrative disease
    - Patients who progress on or are not candidates for liver-directed therapy

Reig M et al, J of Hepatol 2021

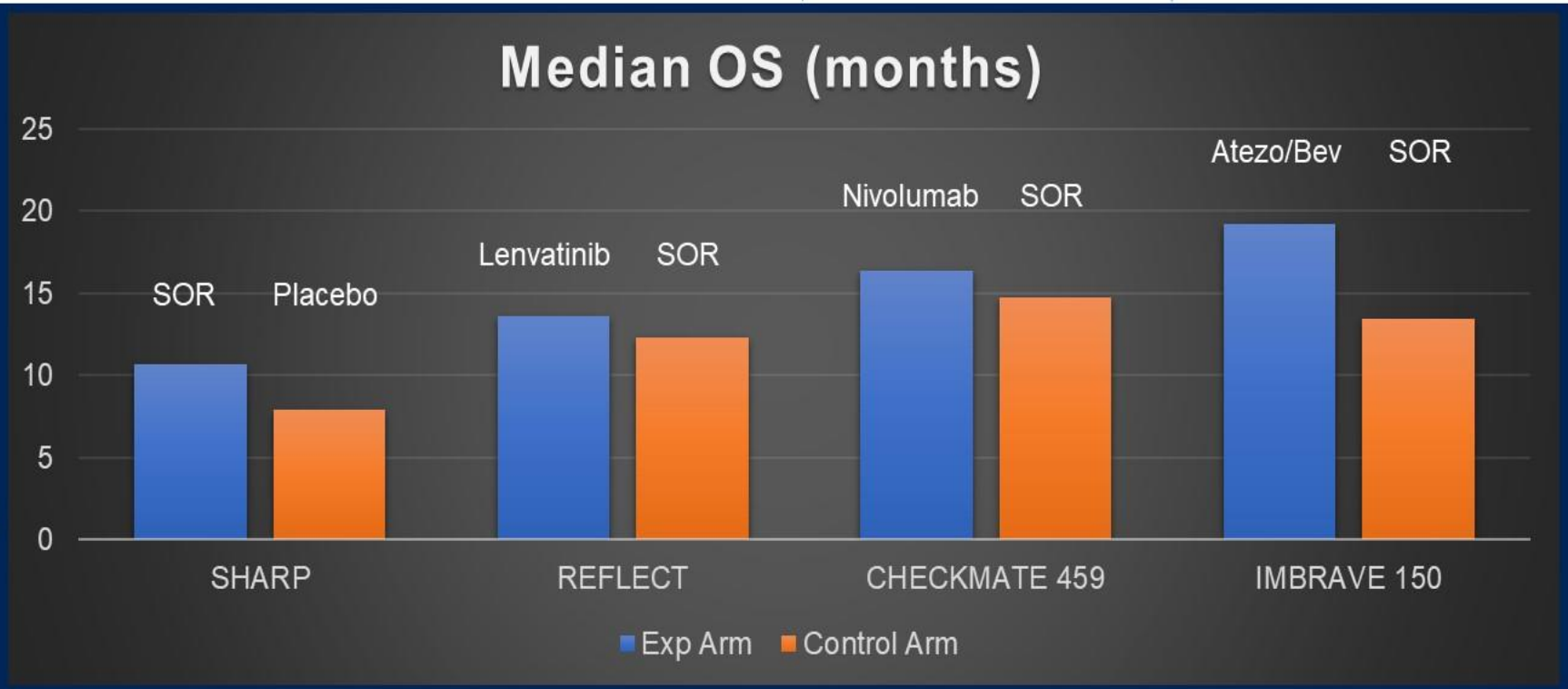
The Evolution of First Line Systemic Therapy for Hepatocellular Carcinoma

SHARP
Sorafenib
vs Placebo

REFLECT
Lenvatinib vs
Sorafenib

CHECKMATE
459
Nivolumab vs
Sorafenib

IMBRAVE 150
Atezo/Bev vs
Sorafenib

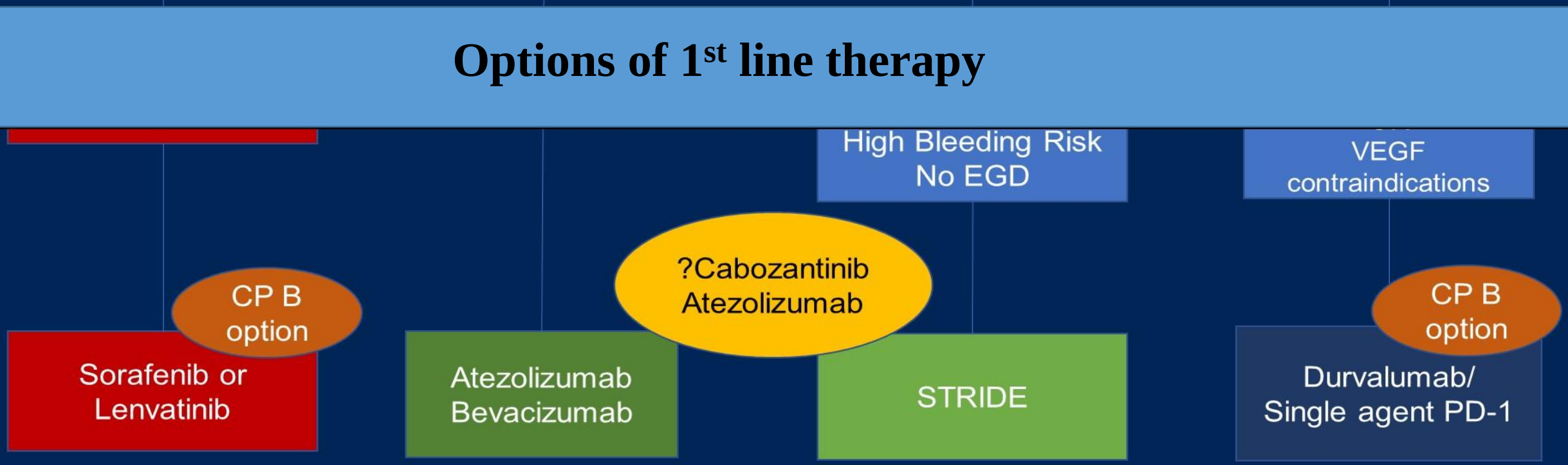


Met primary endpoint

Primary endpoint not met

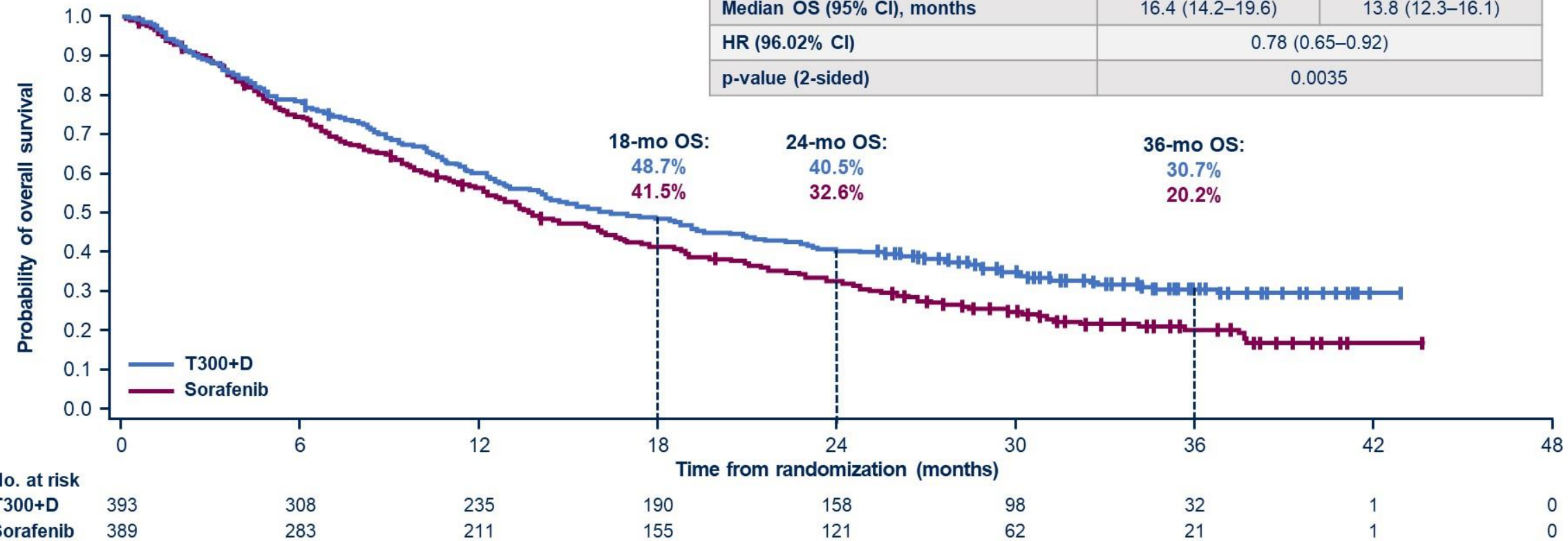
Llovet JM et al. N Engl J Med. 2008; Kudo M et al, Lancet 2018; El-Khoueiry, A et al, Lancet 2017; Yau T et al, Lancet Oncol. 2022; Finn RS et al, J. Clin. Oncol. 39, (2021)

Options of 1st line therapy



Primary objective: overall survival for T300+D vs sorafenib

	T300+D (n=393)	Sorafenib (n=389)
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65–0.92)	
p-value (2-sided)	0.0035	



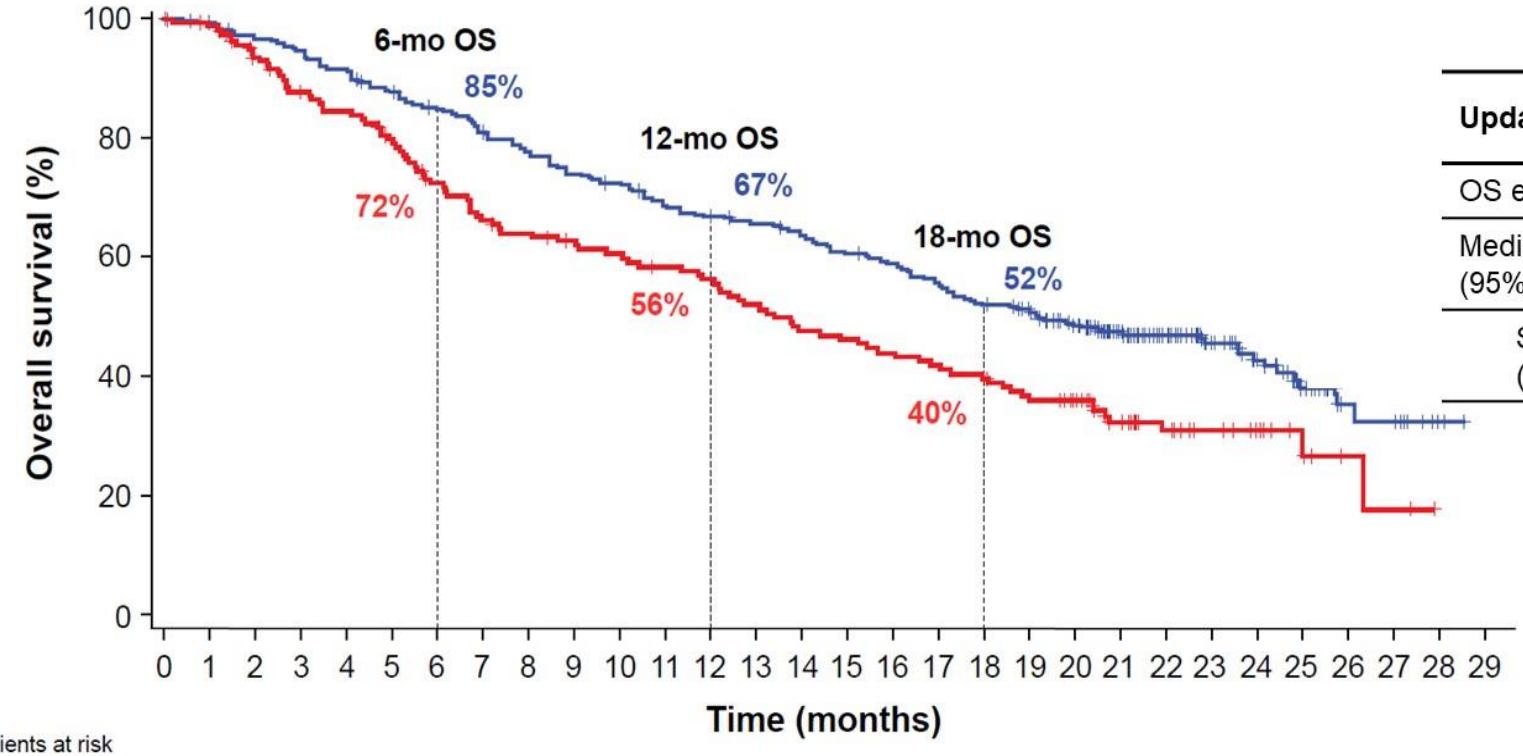
No. at risk									
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

PRESENTED BY: Ghassan K Abou-Alfa, MD, MBA

Updated OS



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

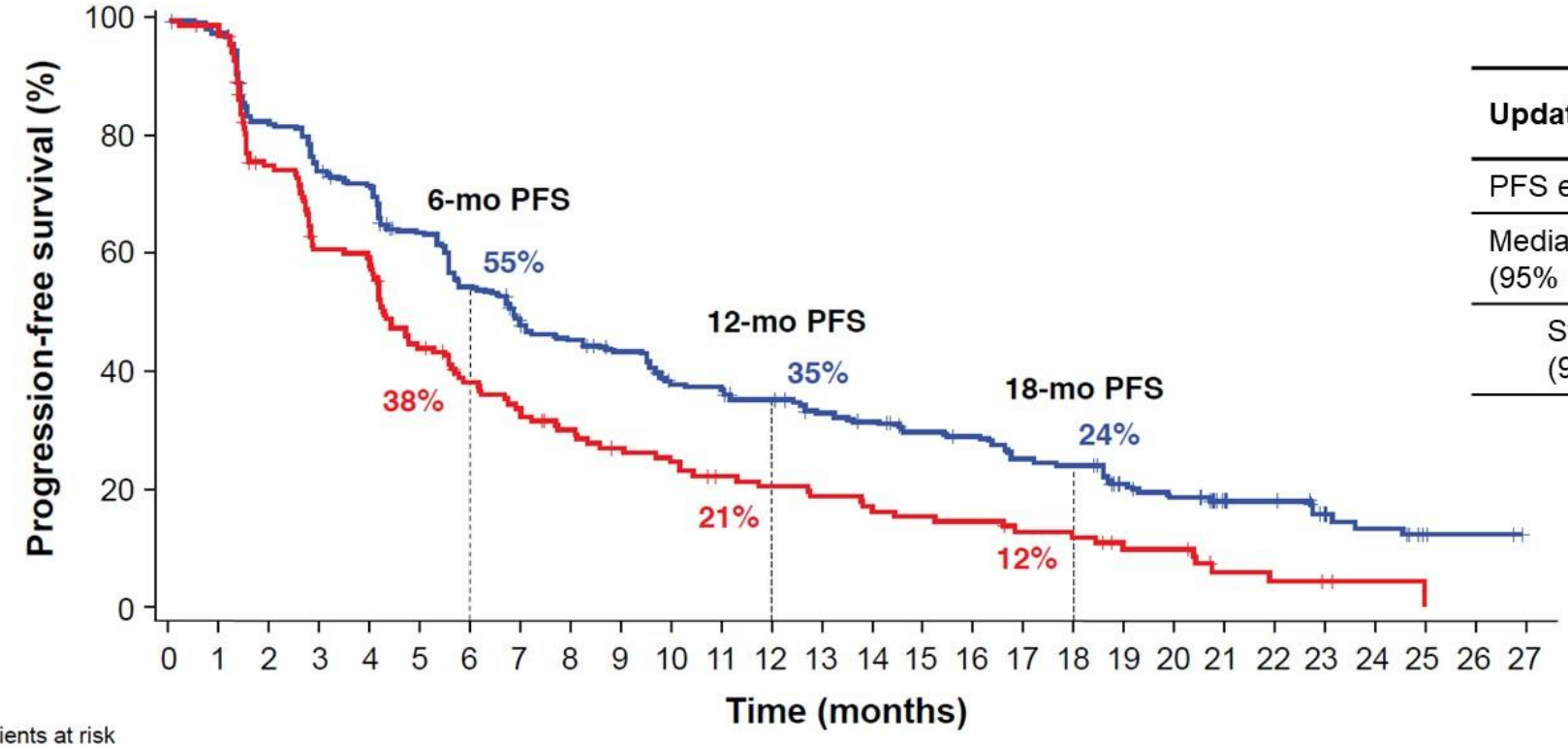
No. of patients at risk

Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

Updated PFS by IRF RECIST 1.1



No. of patients at risk

Atezo + Bev	336	323	271	245	234	204	174	149	141	132	113	111	102	93	88	80	77	67	64	47	41	27	25	17	12	4	3	NE
Sorafenib	165	150	110	88	84	63	52	44	39	34	31	26	24	22	19	18	17	14	13	9	9	4	3	2	1	1	NE	NE

Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) *P* = 0.0001[b]	

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

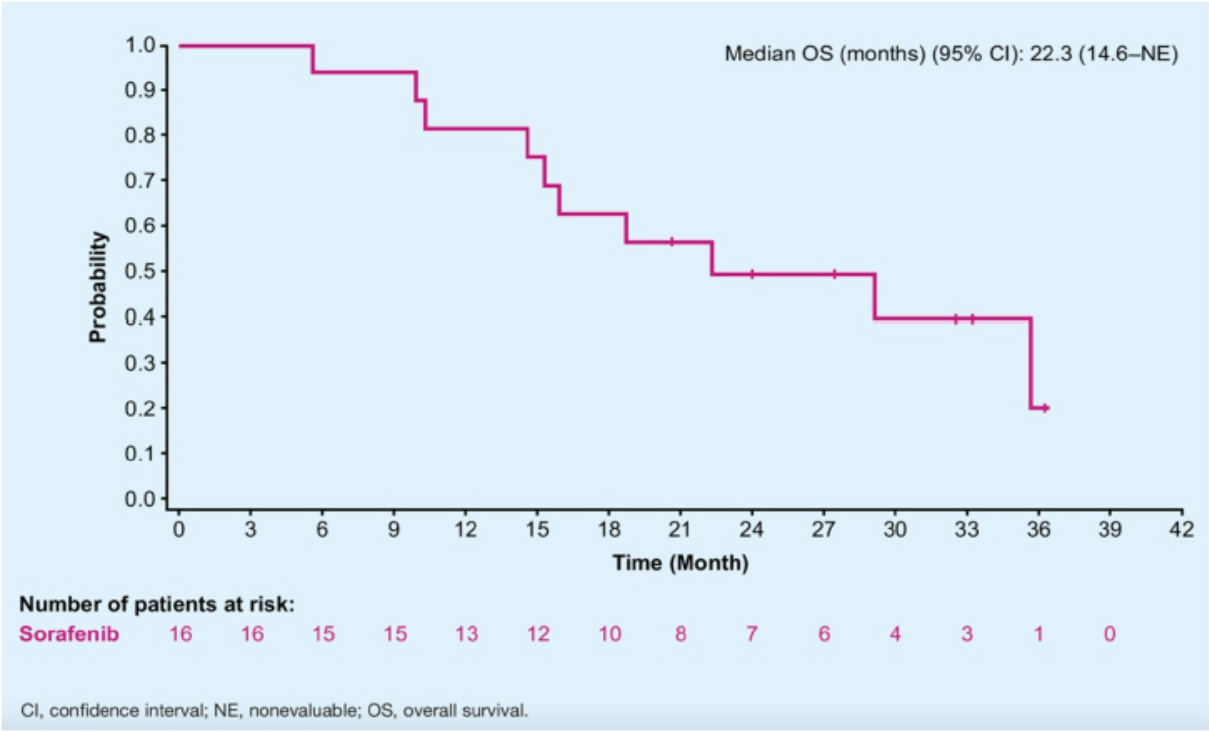
[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

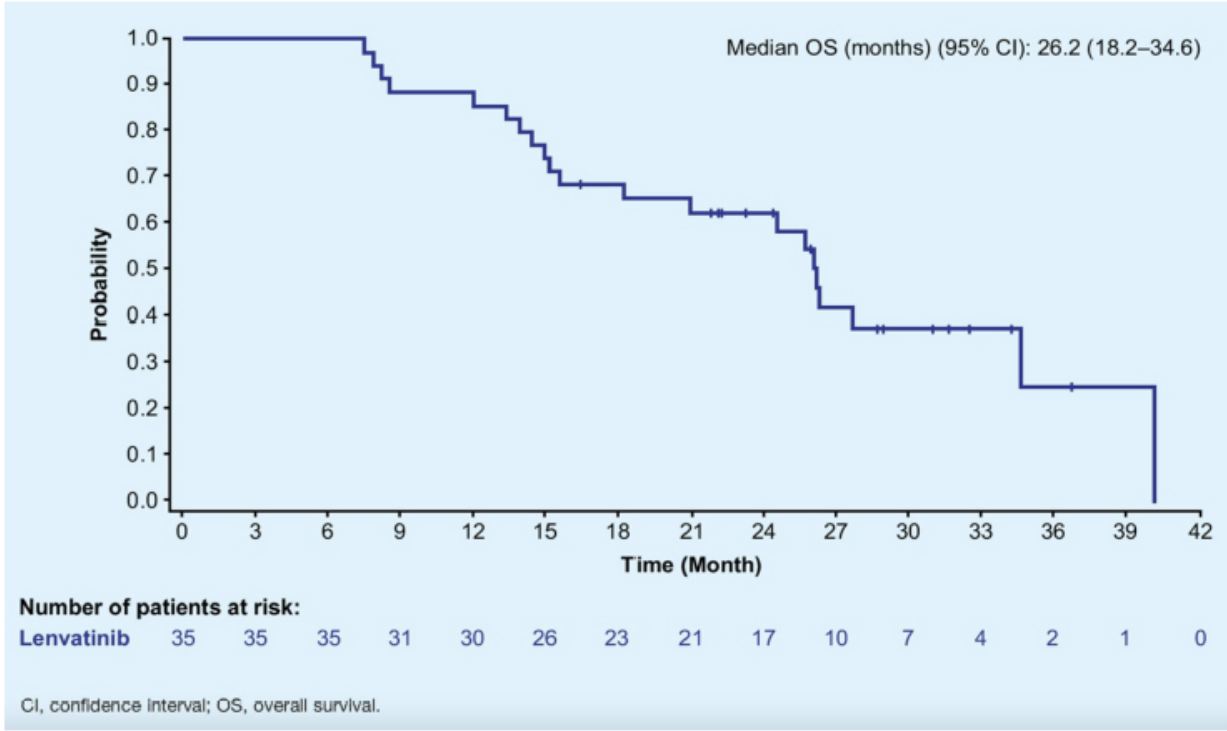
Table S1. Follow-up systemic treatment for hepatocellular carcinoma

	Atezolizumab plus bevacizumab (n=336)	Sorafenib (n=165)
≥1 systemic treatment*	120 (36)	86 (52)
Second-line therapy	102 (30)	81 (49)
Third-line therapy	33 (10)	39 (24)
Type of therapy		
Tyrosine kinase inhibitors	108 (32)	54 (33)
Immunotherapy	11 (3)	43 (26)
Chemotherapy	11 (3)	15 (9)
Angiogenesis inhibitors†	6 (2)	10 (6)
Others	6 (2)	6 (4)

Data are n (%). *Fourth-line or later therapies are not included. †Monoclonal antibodies.

Posthoc Analysis: Sorafenib versus Lenvatinib followed by Other Therapies



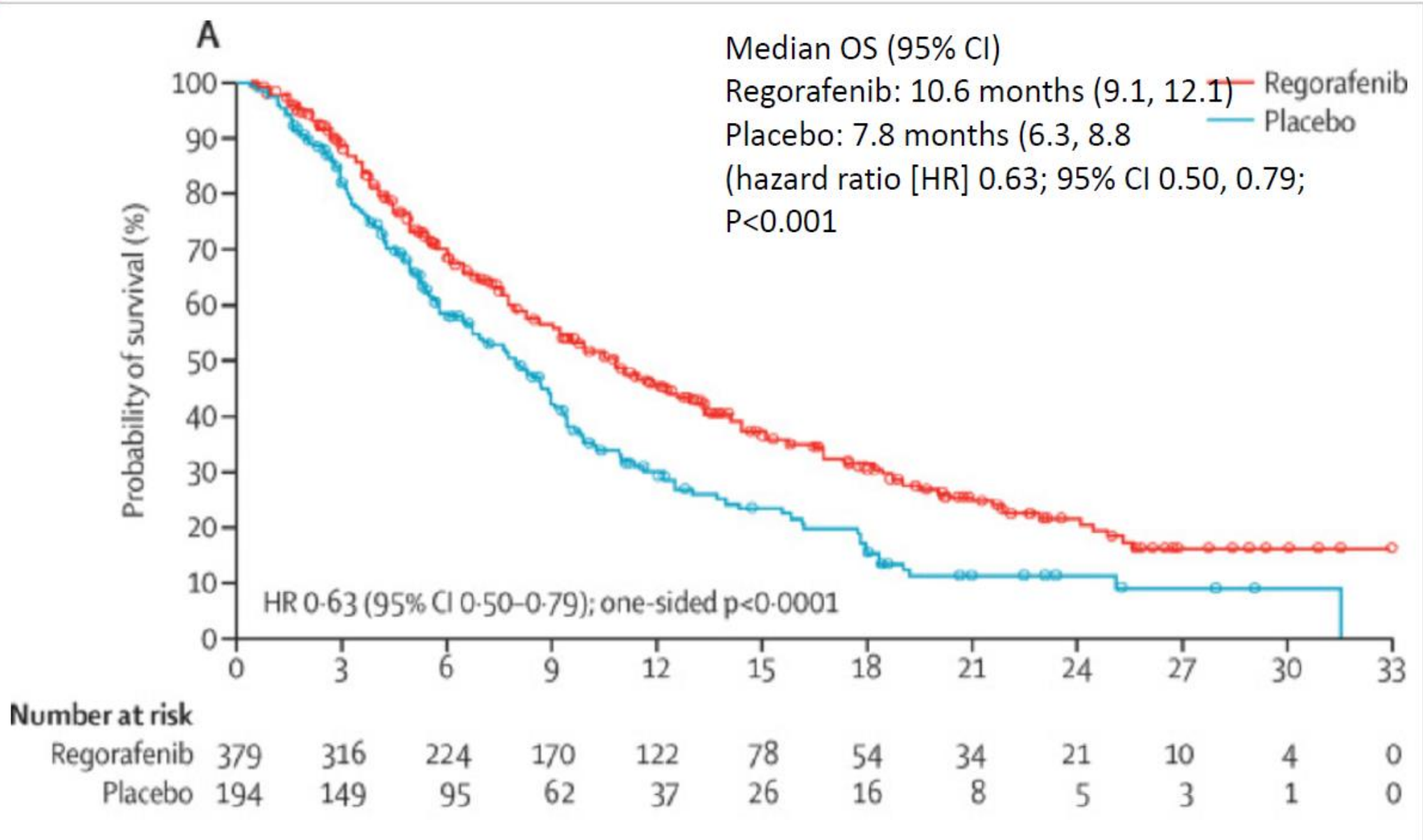


Alsina A, et al. *J Clin Oncol.* 2019; 37 (suppl 4; abstr 371)

More exposure to TTT, Better survival

Line -1	Atezolizumab + Bevacizumab	**Vs**	Durvalumab + Tremelimumab			
First Line	Sorafenib	Lenvatinib				
Second Line	Regorafenib	Cabozantinib	Ramucirumab	Pembrolizumab	Nivolumab	Nivolumab plus Ipilimumab
Third Line	Cabozantinib					

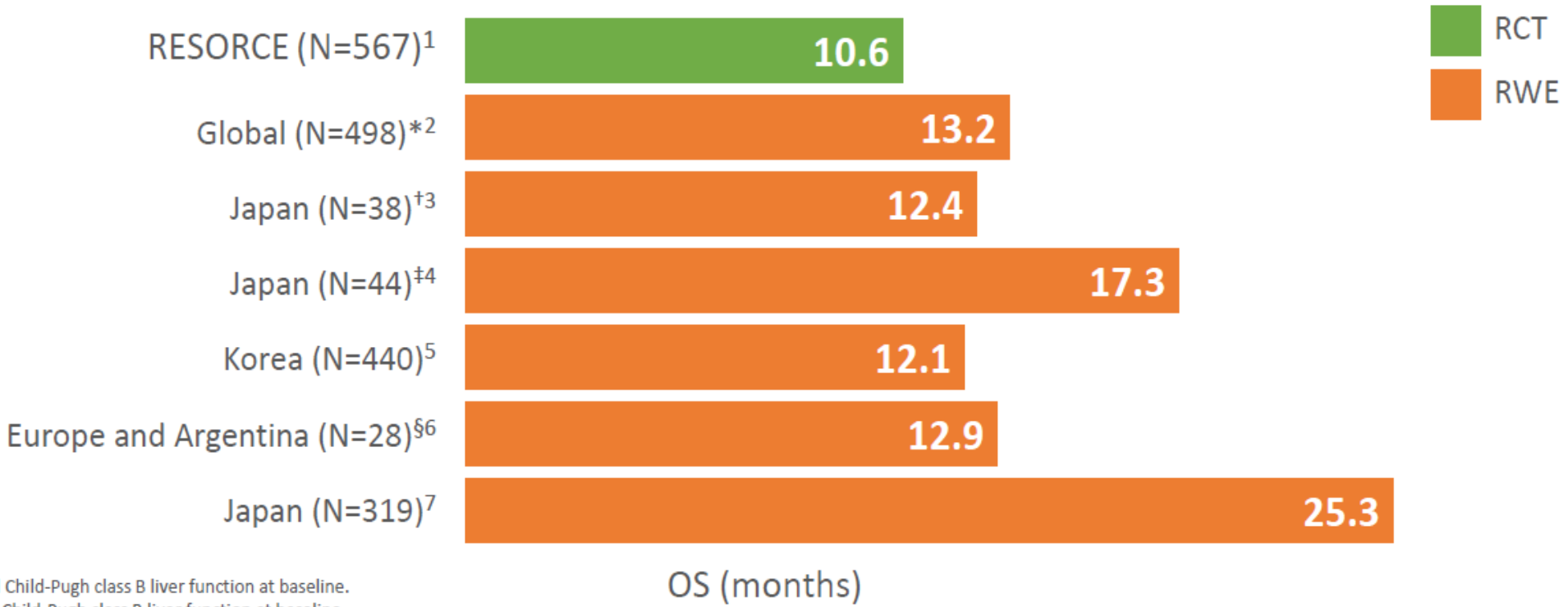
Regorafenib vs. Placebo Overall Survival



Bruix, J. et al. Lancet. Volume 389, No. 10064, p56–66, 7 January 2017

Real-world studies show a consistent OS benefit with regorafenib in clinical practice

Median OS of patients with HCC treated with regorafenib in the RESORCE trial and in real-world clinical practice



*11% of patients had Child-Pugh class B liver function at baseline.
†13% of patients had Child-Pugh class B liver function at baseline.
‡9.1% of patients had Child-Pugh class B liver function at baseline.
§Post-transplantation patients.

References: 1. Bruix J, et al. *Lancet*. 2017;389(10064):56-66. **2.** Lim HY, et al. Poster presented at: American Society of Clinical Oncology; January 23-25, 2020; San Francisco, CA. **3**. Wang W, et al. *Cancers*. 2019; 11:1517. **4.** Ogasawara S, et al. *Invest New Drugs*. 2020;38:172-180. **5.** Yoo C, et al. *Liver Int*. 2020;40(9):2263-2271. **6.** Iavarone M, et al. *Am J Transplant*. 2019; 19(11):3176-3184. **7.** Yumita S, et al. *J Hepatol*. 2019;70:e90-e91.

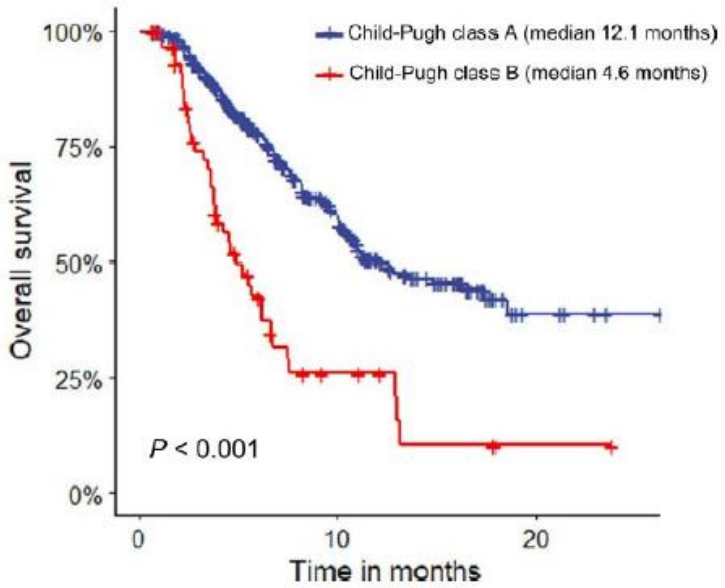
Regorafenib in the Real World: Korean Multicenter Study

Kim *et al.*, Liver Int 2020; 40: 2544

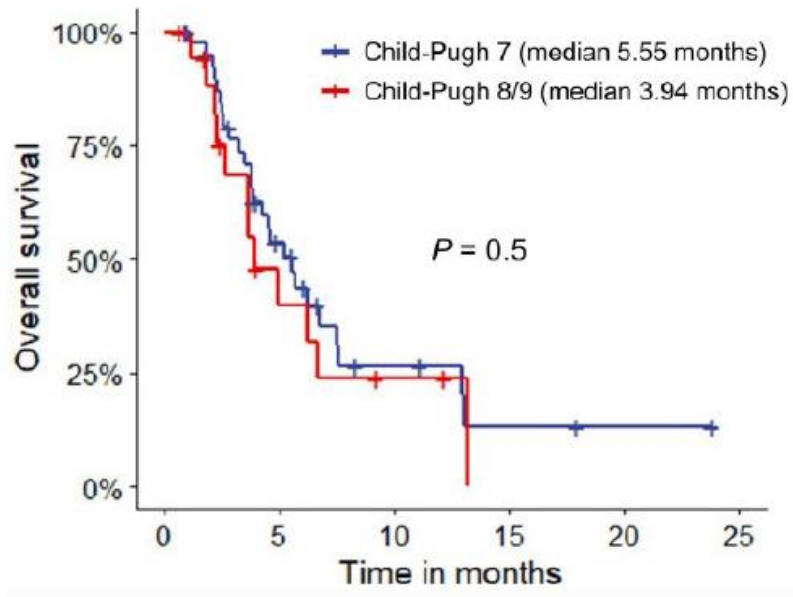
HCC, BCLC Stage B / C

CP A (n=440) *vs.* CP B (n=59) patients

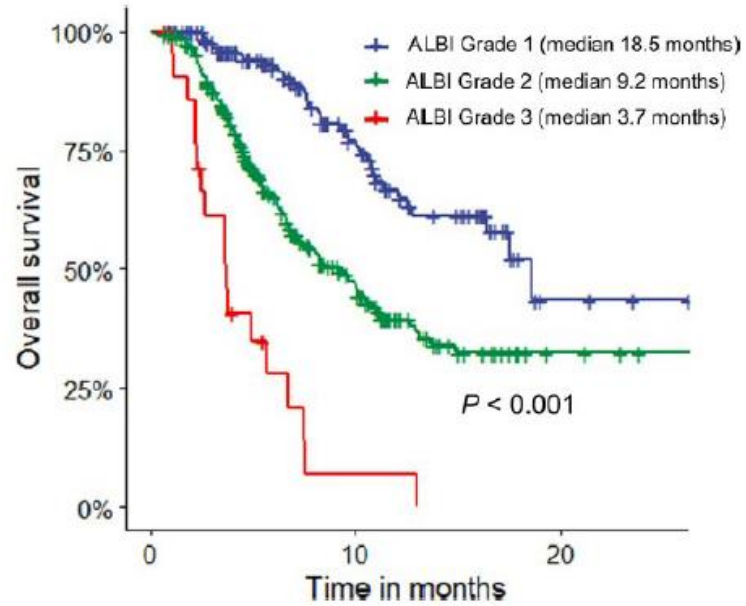
OS: CP A vs. CP B



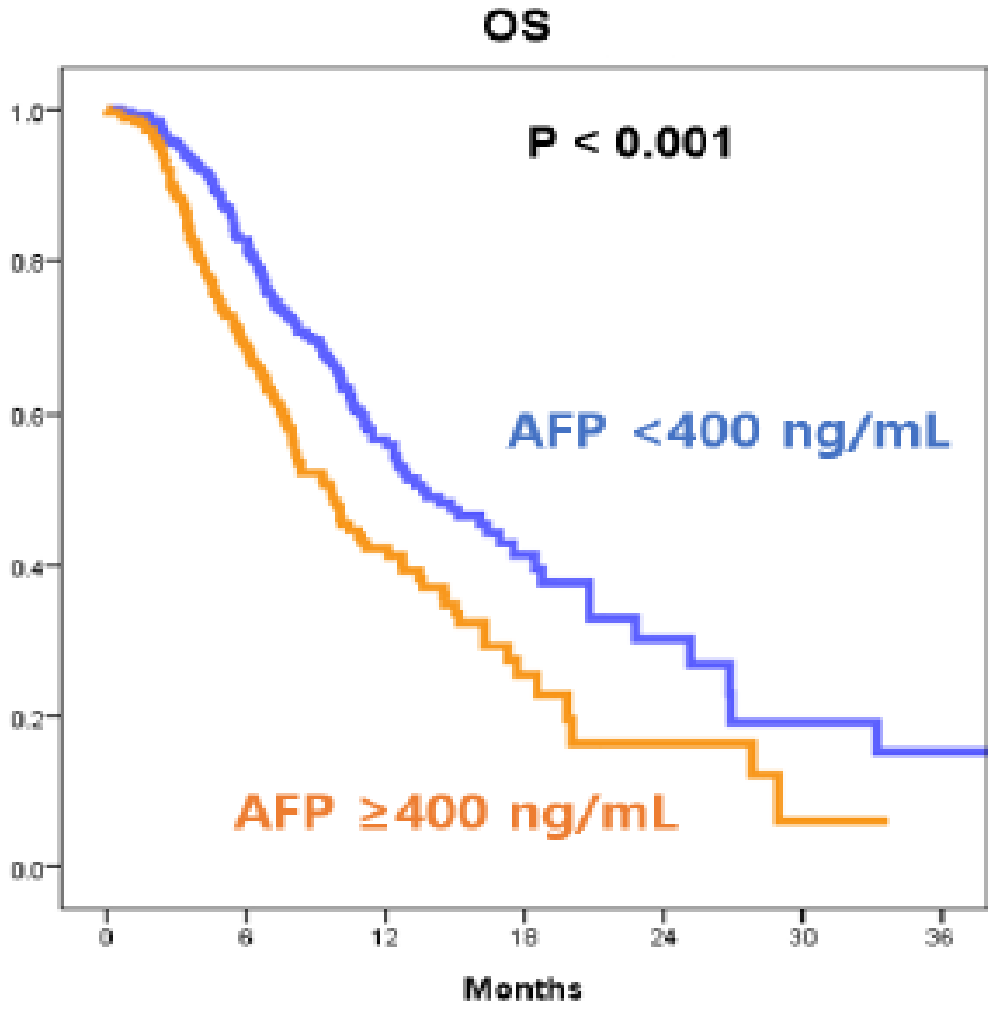
CP B-Subgroups



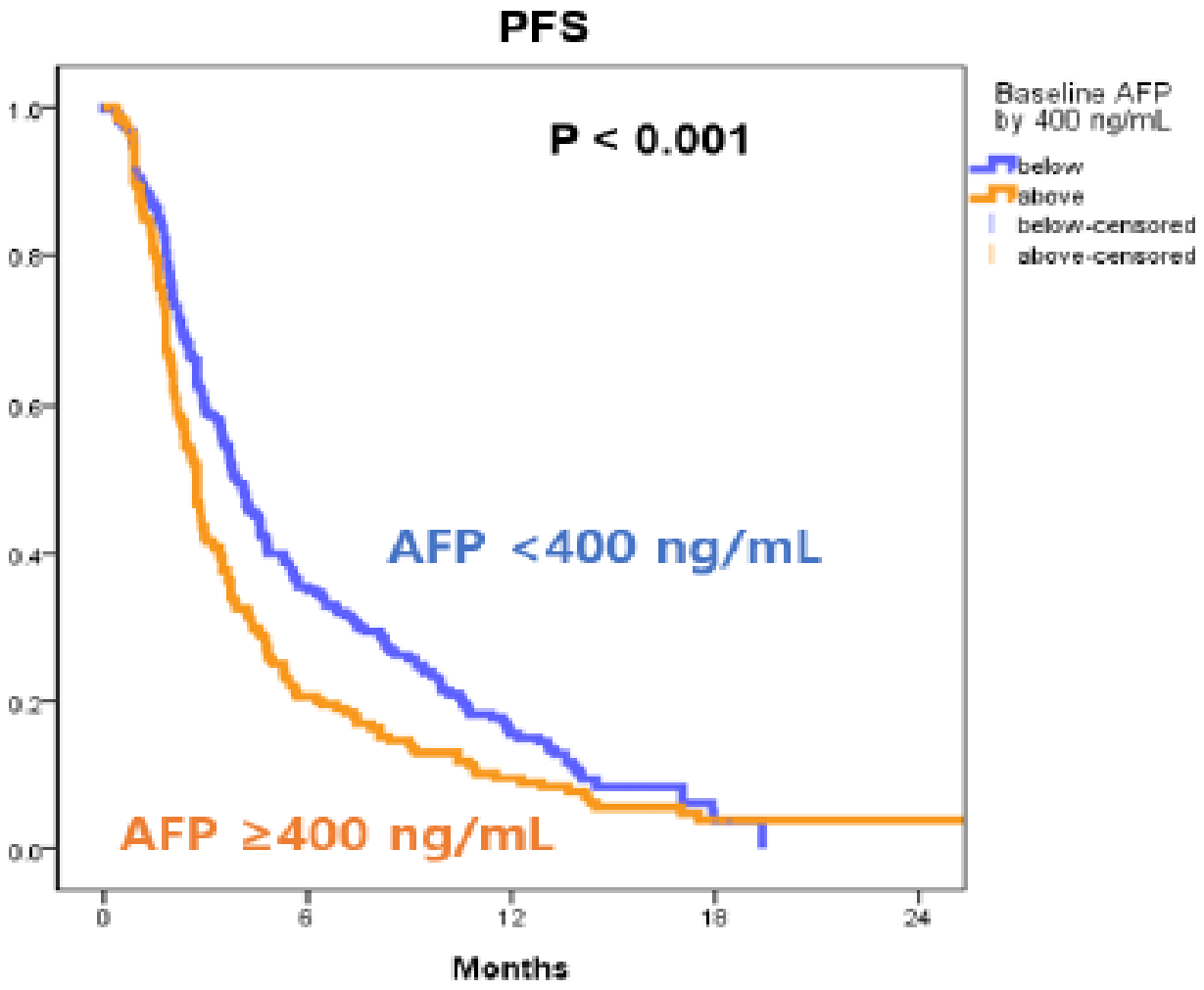
ALBI-Grade



PFS and OS by baseline AFP

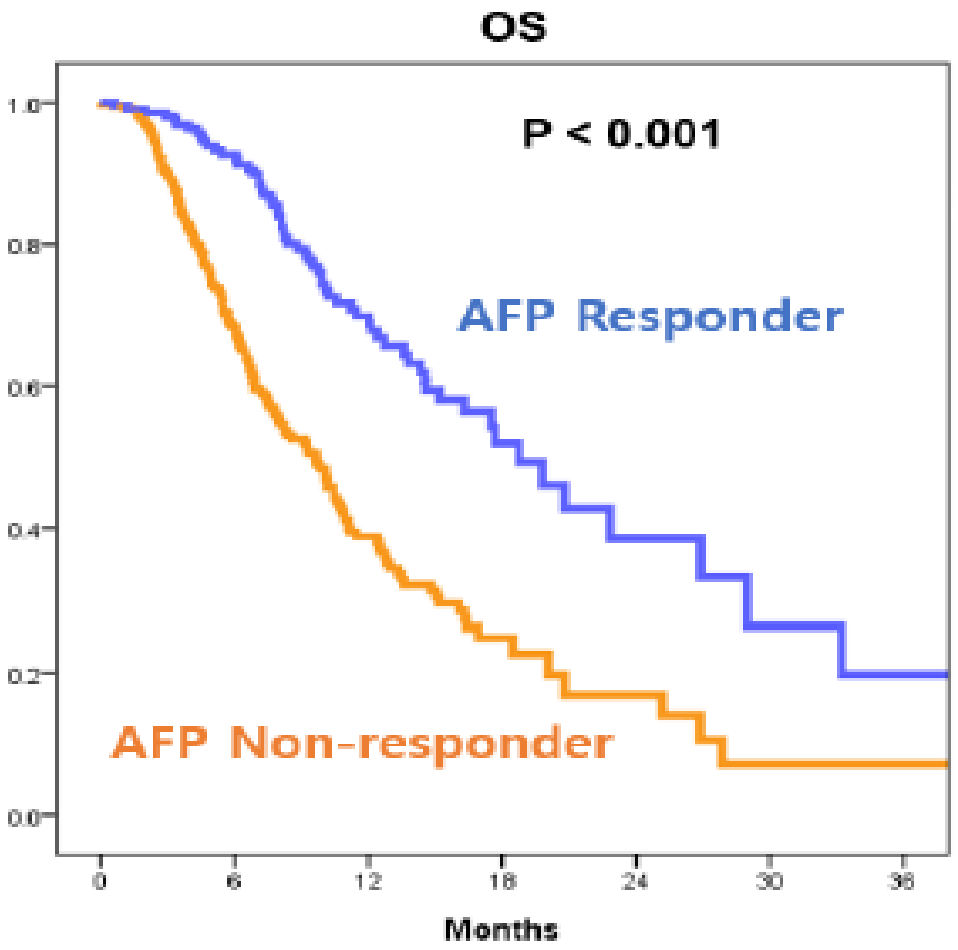


13.6 vs 9.6

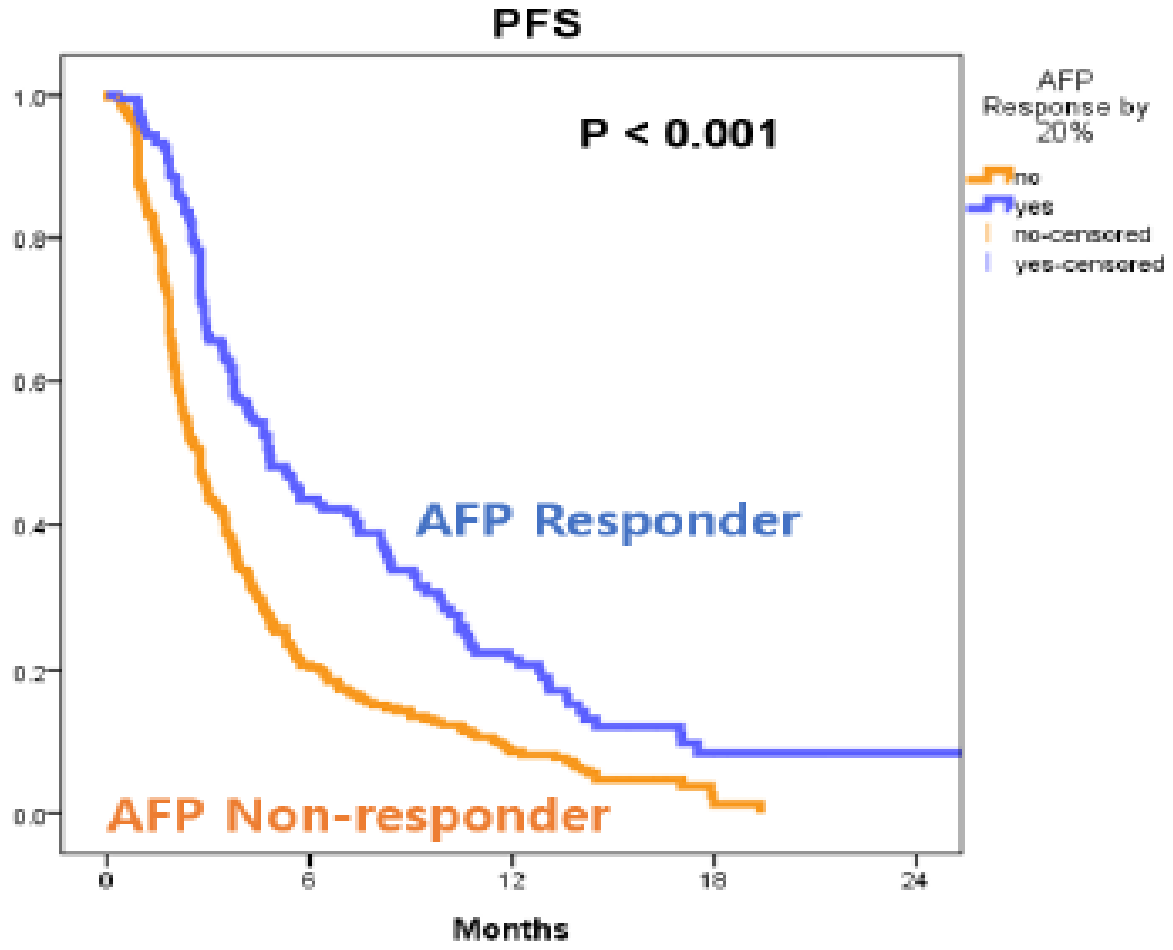


3.9 vs 2.8

PFS and OS by AFP response



18.7 vs 9.7



4.8 vs 2.8

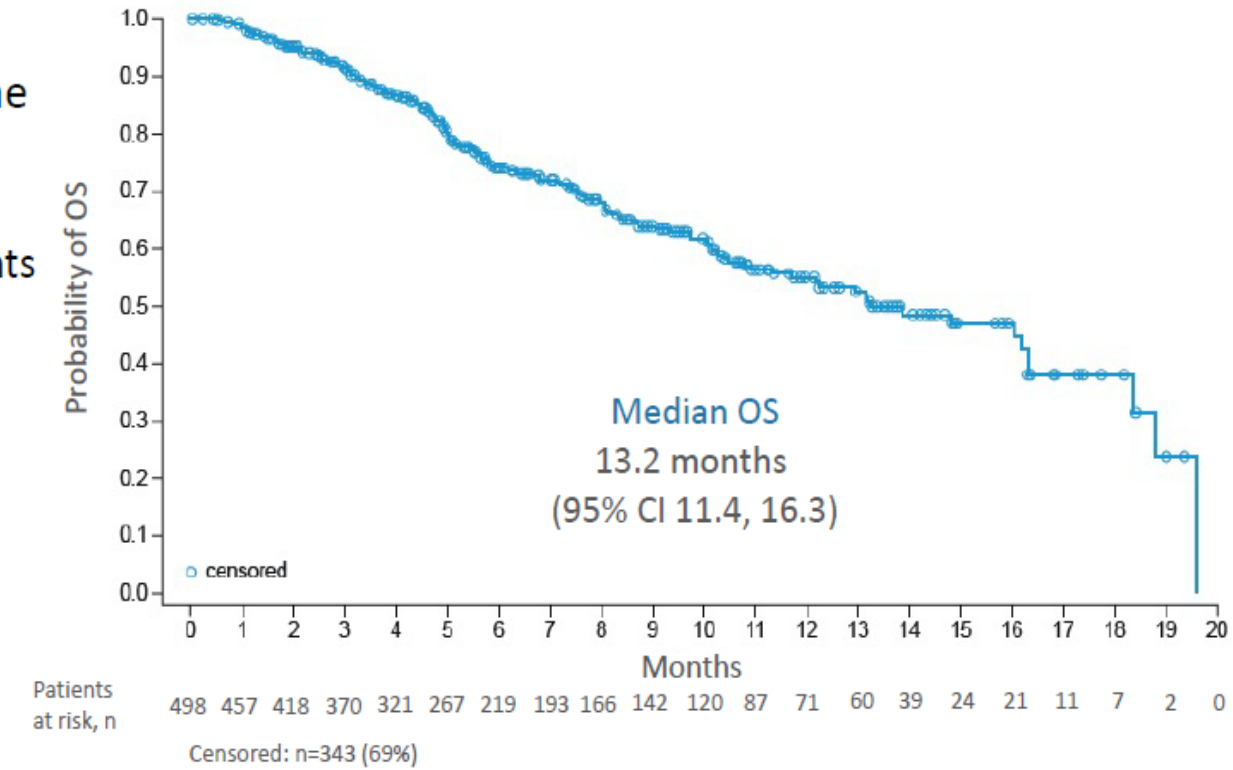
REFINE study

- 1,008 were evaluable for interim analysis.
- 62% stage C, 62% Child–Pugh A , 83% ECOG PS 0 or 1.
- 96% prior sorafenib
- 9% had ≥1 prior immunotherapy (most common: nivolumab [50%] and pembrolizumab [21%]),
- 6% multikinase inhibitor other than sorafenib (lenvatinib [62%])
- 17% two or more prior therapies

Interim analyses from REFINE have shown a consistent treatment benefit with regorafenib in patients with HCC

- The REFINE study is an ongoing, observational study of regorafenib in HCC[1]
  - The patient population is more varied than the population of the RESORCE trial[1,2]:
    - More patients had an ECOG PS ≥1 and Child-Pugh B liver function, and 17% of patients had received ≥2 lines of prior therapy[1]
- Median OS was longer than that reported in the RESORCE trial (10.6 months), but the number of censored patients was high (69%)[1,2]

OS in the REFINE study[1]



Despite a more varied patient population in real-world clinical practice, median OS of regorafenib remains consistent

References: 1. Lim HY, et al. Poster presented at: American Society of Clinical Oncology; January 23-25, 2020; San Francisco, CA. **2.** Bruix J, et al. *Lancet*. 2017;389(10064):56-66.

Posthoc Phase III
Sorafenib followed by Regorafenib

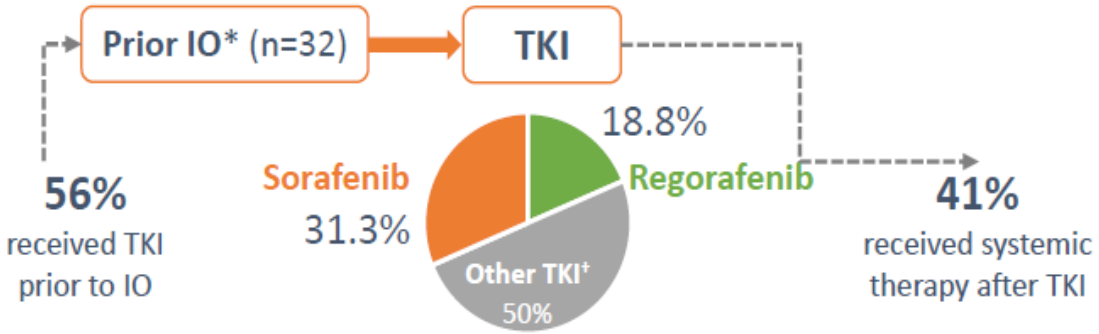
Time from start of sorafenib treatment to death in RESOURCE

	Regorafenib (n= 374)	Placebo (n=193)
Median, months (95% CI)	26.0 (22.6-28.1)	19.2 (16.3-22.8)

Finn RS, et al. *J Hepatol*. 2018 Aug;69(2):353-358

More exposure to TTT, Better survival

Regorafenib has been used after IO therapies in real-world clinical practice*[1-3]

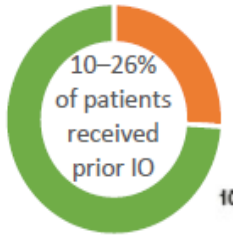


Median OS

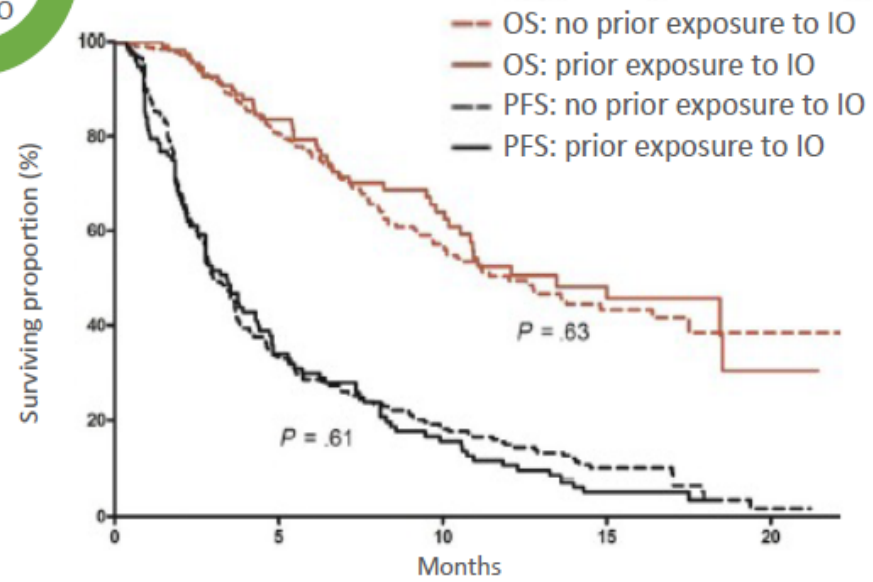
From start of **IO-TKI** sequence: **21.3 months**
(95% CI 10.5, 28.2)

From start of **TKI: 14.3 months**
(95% CI 6.6, 23.6)

*Pembrolizumab (18.8%), nivolumab (56.3%), nivolumab + ipilimumab (12.5%), or pembrolizumab + ipilimumab (12.5%).
†Lenvatinib (40.6%) and axitinib (9.4%).



Survival with regorafenib according to prior IO exposure (n=440)[2]



*Including nivolumab, pembrolizumab, durvalumab, atezolizumab + bevacizumab, tremelimumab, and other investigational agents.

- **Regorafenib has demonstrated activity with acceptable tolerability following IO therapy in patients with advanced HCC**
- **Regorafenib has shown OS benefit in the ≥2L setting following IO therapies, with no new safety signals identified**

References: 1. Yau T, et al. Poster presented at: American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2019; Chicago IL. **2.** Yoo C, et al. *Liver Int*. 2020;40(9):2263-2271. **3.** Merle P, et al. Poster presented at: International Liver Cancer Association Conference; September 11-13, 2020. **4.** Merle P, et al. Poster presented at: European Society for Medical Oncology Virtual Congress; September 19-21, 2020.

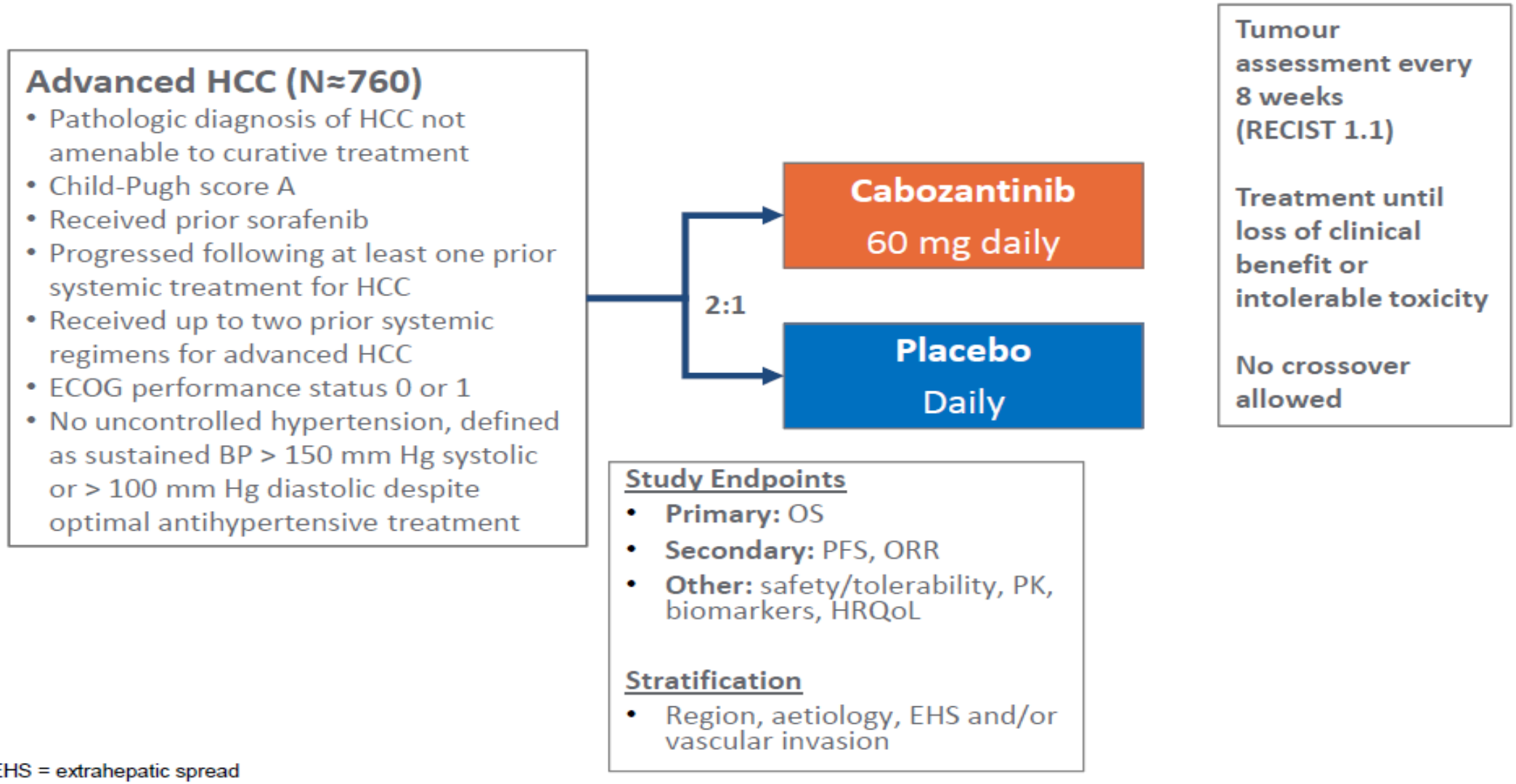
Line -1	Atezolizumab + Bevacizumab	**Vs**	Durvalumab + Tremelimumab			
First Line	Sorafenib	Lenvatinib				
Second Line	Regorafenib	Cabozantinib	Ramucirumab	Pembrolizumab	Nivolumab	Nivolumab plus Ipilimumab
Third Line	Cabozantinib					

Cabozantinib versus placebo in patients with advanced hepatocellular carcinoma who have received prior sorafenib: results from the randomised Phase III CELESTIAL trial

- Ghassan K. Abou-Alfa, Tim Meyer, Ann-Lii Cheng, Anthony El-Khoueiry, Lorenza Rimassa, Baek-Yeol Ryoo, Irfan Cicin, Philippe Merle, YenHsun Chen, Joong-Won Park, Jean-Frederic Blanc, Luigi Bolondi, Heinz-Josef Klümpen, Stephen L. Chan, Vincenzo Dadduzio, Colin Hessel, Anne Borgman-Hagey, Gisela Schwab,
Robin Kate Kelley on behalf of the CELESTIAL investigators

Presented at ASCO GI, San Francisco February 2018 and
ASCO, Chicago 2018 (encore)

CELESTIAL: cabozantinib vs placebo in advanced HCC (Phase III randomised study)



EHS = extrahepatic spread

Abou-Alfa GK *et al.*, ASCO 2018. Abstract 4019.

CELESTIAL: Baseline characteristics

	Cabozantinib (N=470)	Placebo (N=237)
Median age, years (range)	64 (22–86)	64 (24–86)
Male, %	81	85
ECOG Performance Status 0 / 1, %	52 / 48	55 / 45
AFP ≥ 400 ng/mL, %	41	43
Enrollment Region, %		
Asia / Europe / North America / Pacific	25 / 49 / 23 / 3	25 / 46 / 25 / 5
Aetiology of HCC, %		
HBV	38	38
HCV	22	22
Other	40	41
Extrahepatic spread of disease, %	79	77
Macrovascular invasion, %	27	34
Extrahepatic spread and/or macrovascular invasion, %	85	84

Asia: Hong Kong, South Korea, Singapore, Taiwan; **Pacific**: Australia and New Zealand

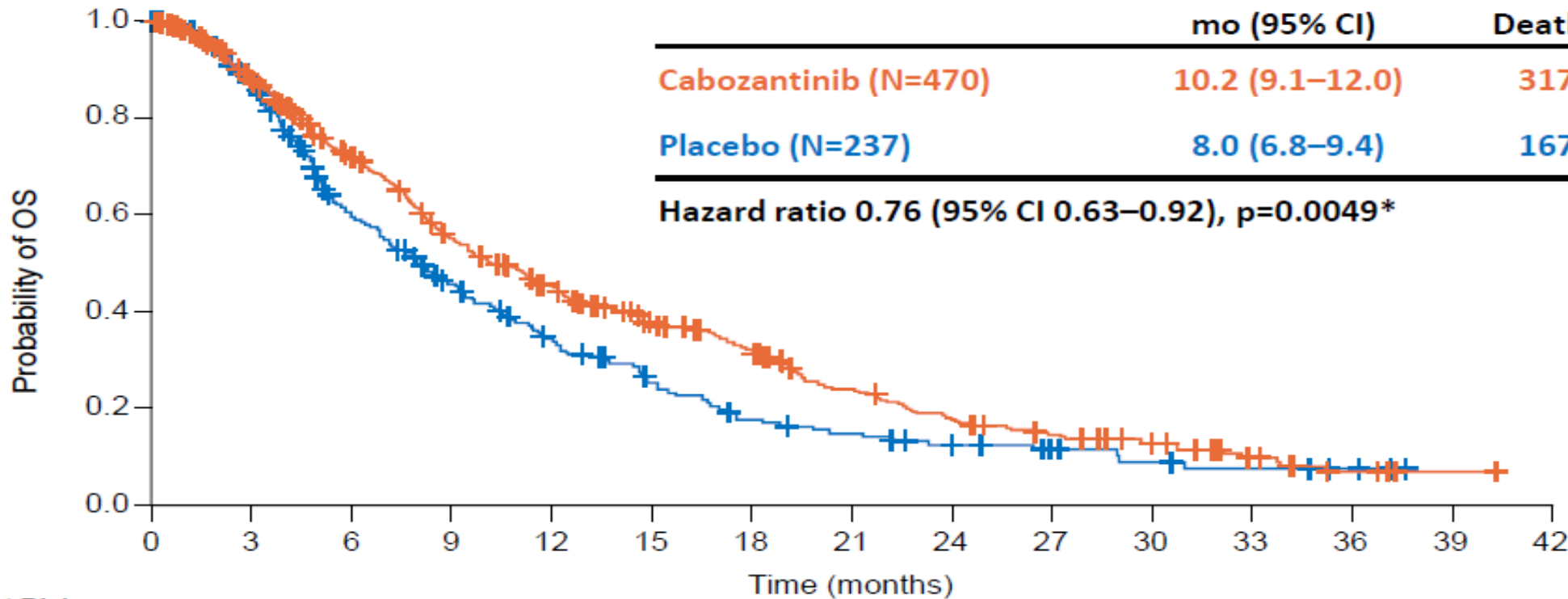
Abou-Alfa GK *et al.*, ASCO 2018. Abstract 4019.

CELESTIAL: Prior therapy

	Cabozantinib (N=470)	Placebo (N=237)
Prior systemic anticancer regimens for advanced HCC, %		
One prior regimen	71	73
Two prior regimens	28	26
Prior systemic therapy, %		
Sorafenib	100	100
Regorafenib	1	1
Lenvatinib	0	<1
Tivantinib	<1	1
Anti-PD-1/PD-L1	3	1
Chemotherapy	9	13
Investigational agents	13	8
Local liver-directed non-radiation anticancer therapy, %	44	48
Median total duration of prior sorafenib, months	5.3	4.8
Median time from disease progression to randomisation, months	1.6	1.7

Abou-Alfa GK *et al.*, ASCO 2018. Abstract 4019.

CELESTIAL- Primary endpoint : OS



	Median OS mo (95% CI)	No. of Deaths
Cabozantinib (N=470)	10.2 (9.1–12.0)	317
Placebo (N=237)	8.0 (6.8–9.4)	167

Hazard ratio 0.76 (95% CI 0.63–0.92), p=0.0049*

No. at Risk

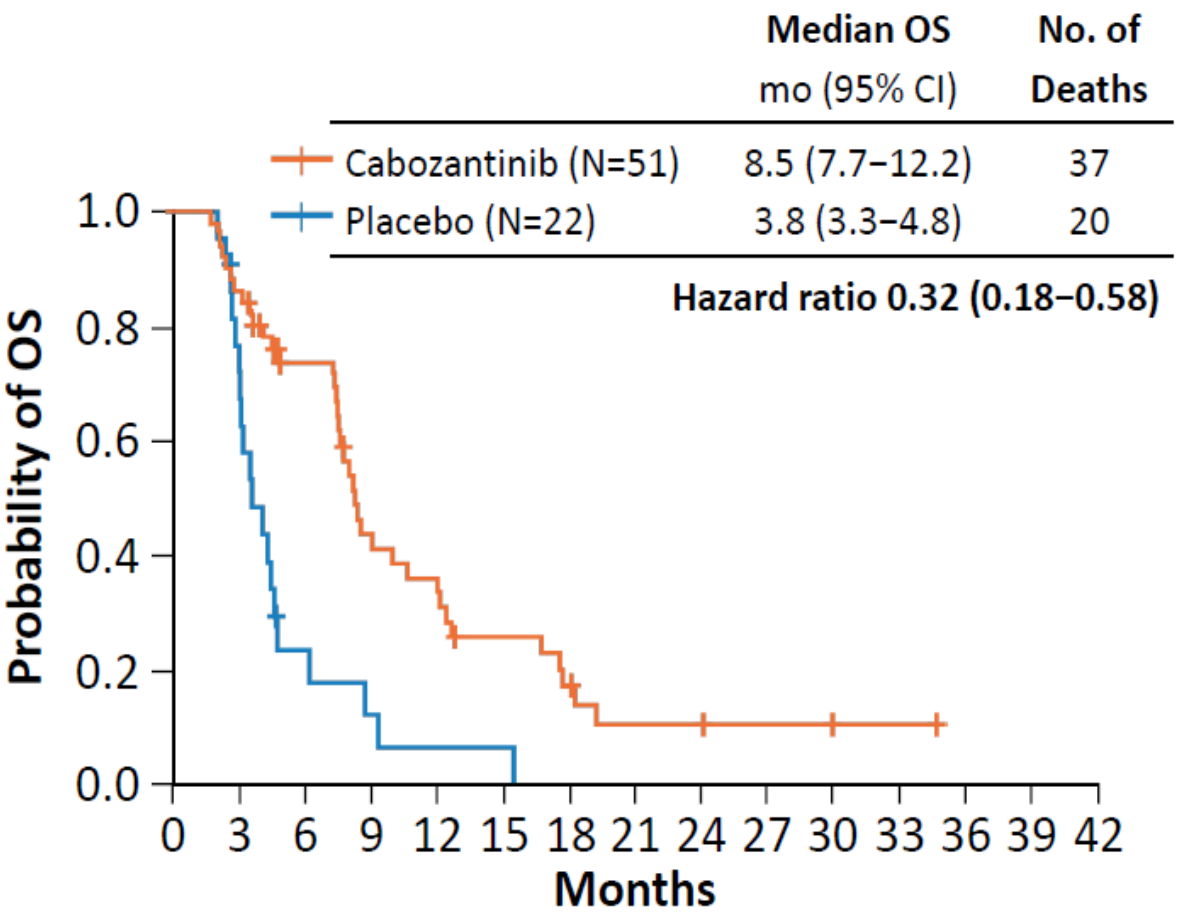
Cabozantinib	470	382	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

*Critical p-value ≤ 0.021 for second interim analysis

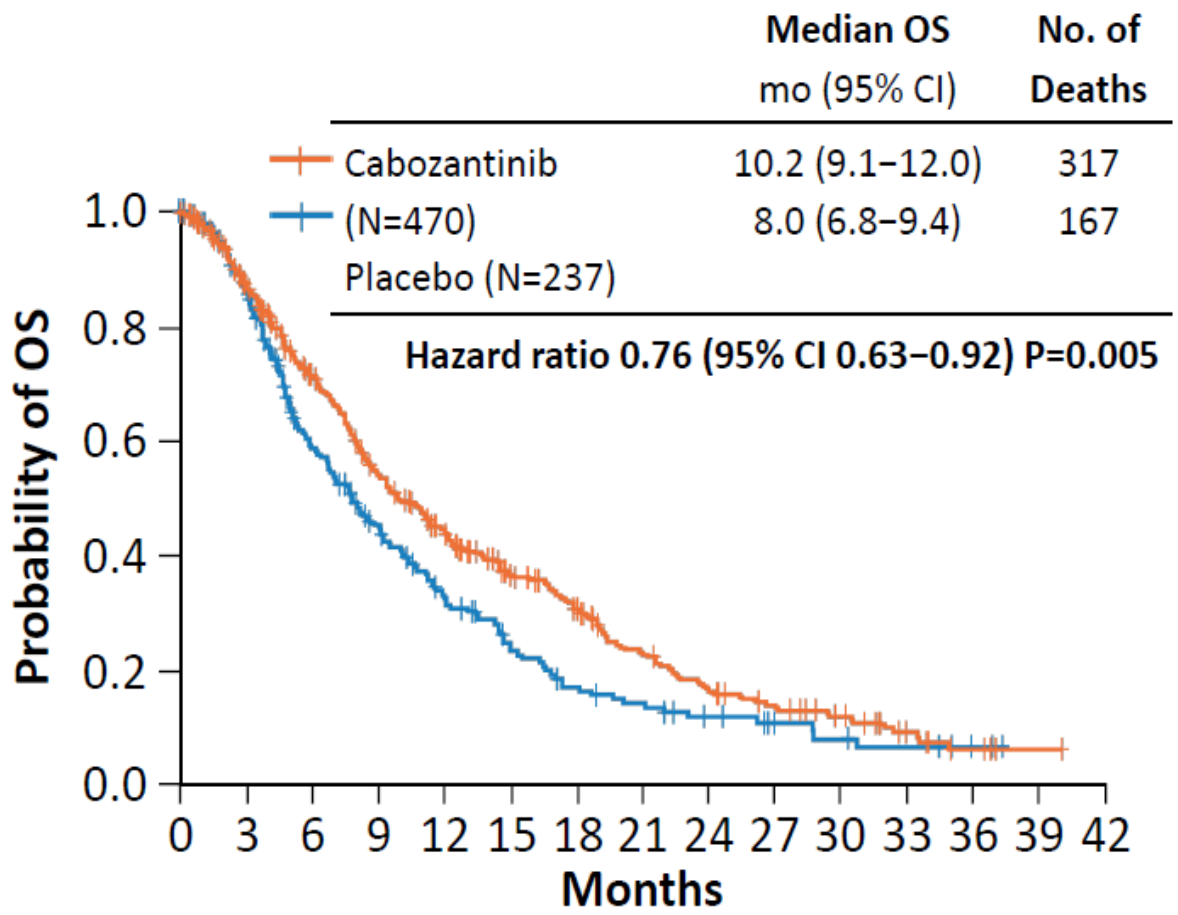
Abou-Alfa GK *et al.*, ASCO 2018. Abstract 4019.

Cabozantinib Child-Pugh B Overall Survival

Child-Pugh B Subgroup



Overall



El-Khoueiri A, et al. ESMO World GI 2020, Abstract SO-9

Line -1	Atezolizumab + Bevacizumab	**Vs**	Durvalumab + Tremelimumab			
First Line	Sorafenib	Lenvatinib				
Second Line	Regorafenib	Cabozantinib	Ramucirumab	Pembrolizumab	Nivolumab	Nivolumab plus Ipilimumab
Third Line	Cabozantinib					

REACH-2: Phase III Study Design

- Multicenter, double-blind, placebo-controlled, randomized phase III trial

Advanced HCC patients with baseline AFP ≥ 400 ng/mL, BCLC stage B/C, Child-Pugh A, ECOG PS 0/1 with prior sorafenib (N = 292)

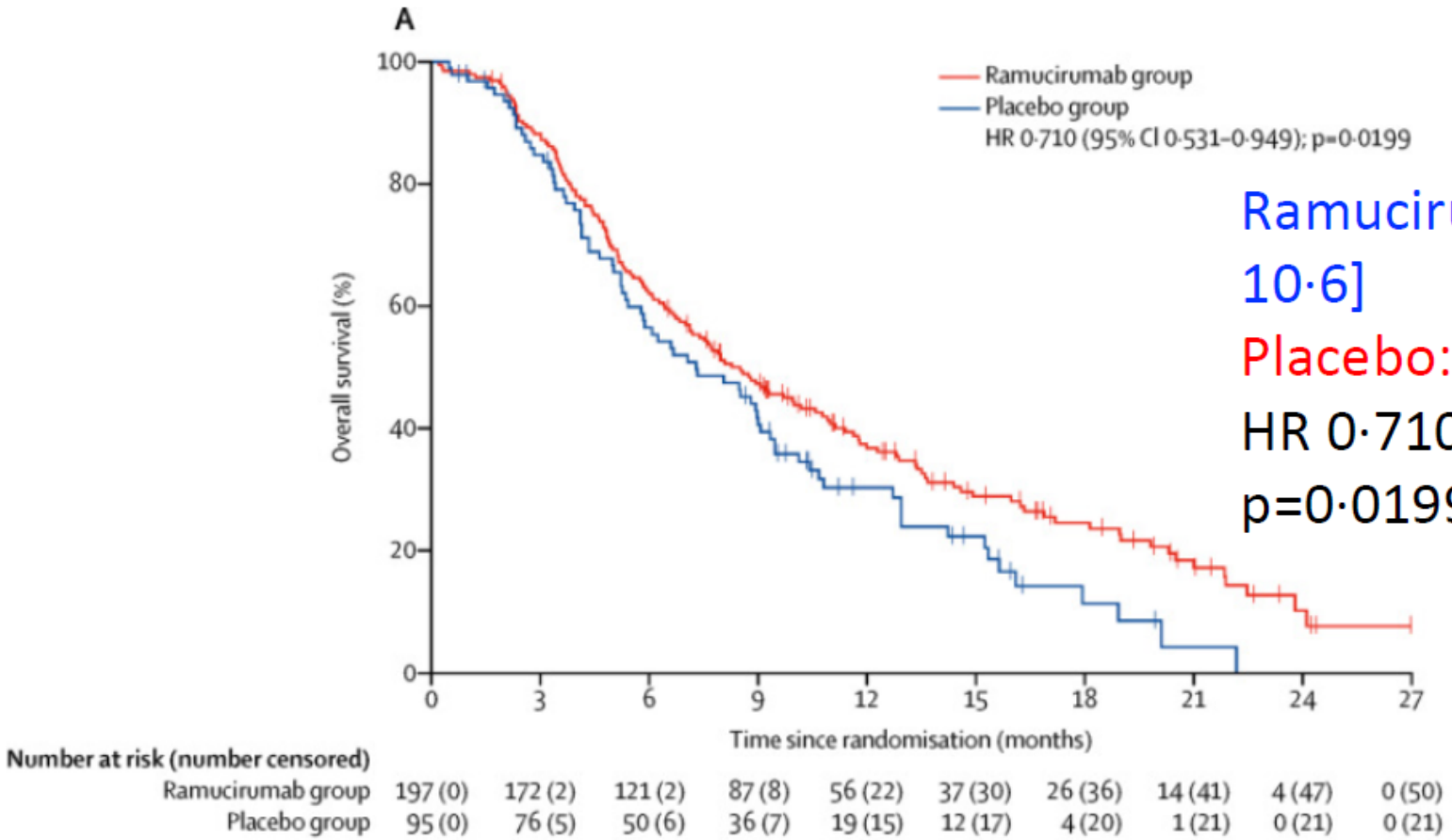
Ramucirumab 8 mg/kg IV Q2W + Best supportive care (n = 197)
Placebo Q2W + Best supportive care (n = 95)

- Primary: OS
- Secondary: PFS, TTP, ORR, time to deterioration,* safety, PK, immunogenicity

Zhu AX, et al. ASCO 2018. Abstract 4003.

Slide credit:

Ramucirumab vs Placebo in Patients with Baseline AFP ≥ 400ng/mL



Ramucirumab : 8·5 months [95% CI 7·0–10·6]

Placebo: 7·3 months [5·4–9·1]

HR 0·710 [95% CI 0·531–0·949]; p=0·0199

Zhu A et al. *The Lancet Oncology*, Vol. 20, No. 2, p282–296,
Abou-Alfa, GK, *The Lancet Oncology*, Vol. 20, No. 2, p177–179

REACH-2: Clinical Responses

Response Rate	Ramucirumab (n = 197)	Placebo (n = 95)	*P* Value
ORR, % (95% CI)	4.6 (1.7-7.5)	1.1 (0-3.1)	.1697
DCR, % (95% CI)	59.9 (53.1-66.7)	38.9 (29.1-48.8)	.0006
Best OR, %			
▪ CR	0	0	
▪ PR	4.6	1.1	
▪ SD	55.3	37.9	
▪ PD	33.5	50.5	
▪ NE	6.6	10.5	

Zhu AX, et al. ASCO 2018. Abstract 4003.

Slide credit: [illegible]

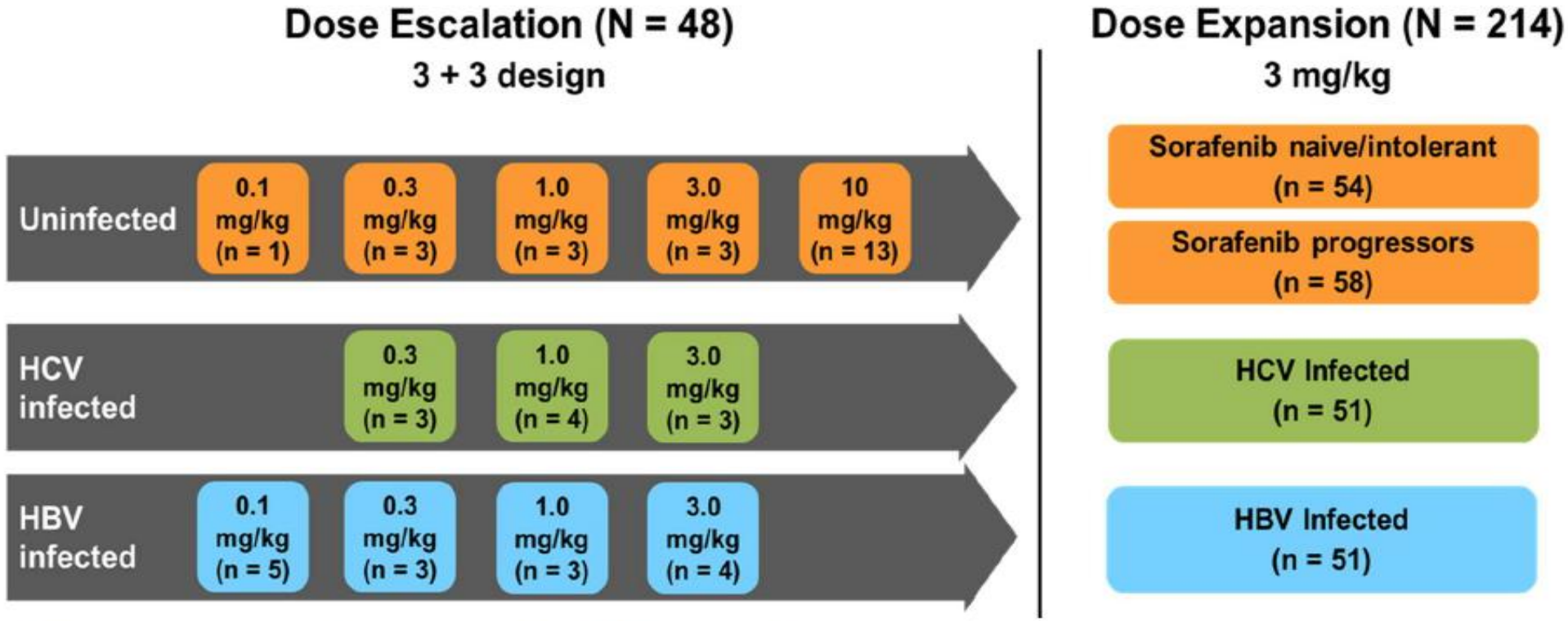
Line -1	Atezolizumab + Bevacizumab	**Vs**	Durvalumab + Tremelimumab			
First Line	Sorafenib	Lenvatinib				
Second Line	Regorafenib	Cabozantinib	Ramucirumab	Pembrolizumab	Nivolumab	Nivolumab plus Ipilimumab
Third Line	Cabozantinib					

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

*Anthony B El-Khoueiry, *Bruno Sangro, *Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero*

* Joint First Authors

CheckMate 040: Phase 1/2 Study of Nivolumab in Patients With Advanced HCC

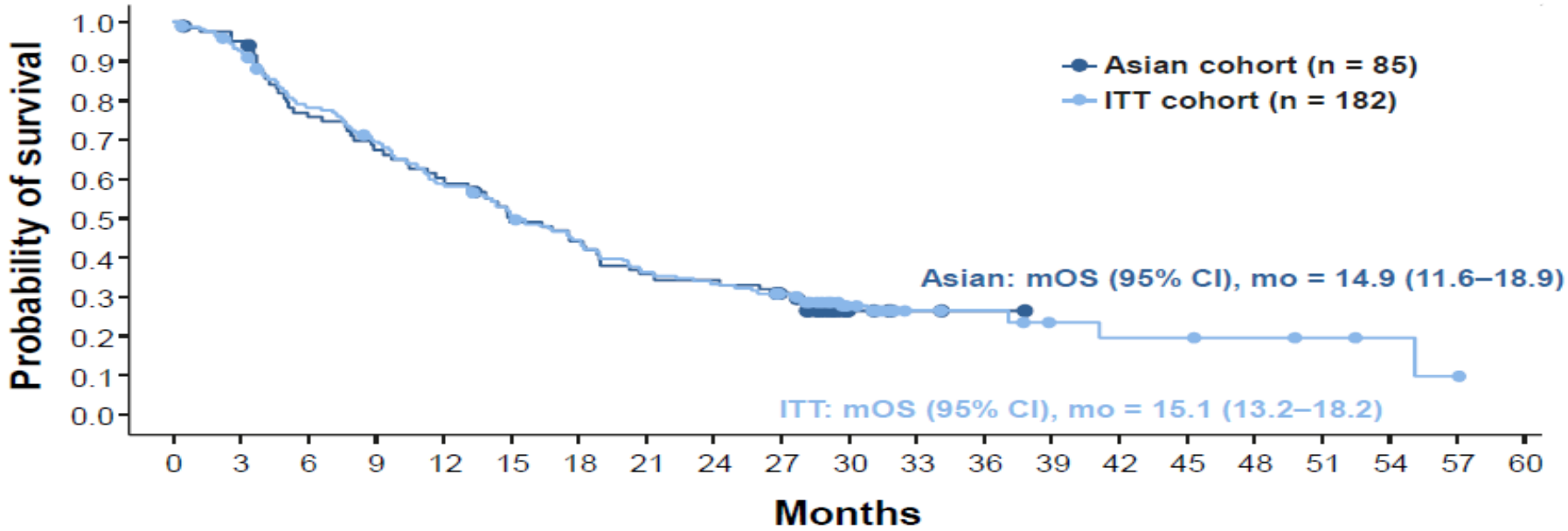


- Disease assessment imaging (CT or MRI) every 6 weeks
- Interim analysis data cutoff date: March 15, 2016

CT, computed tomography; MRI, magnetic resonance imaging; Q6W, every 6 weeks.

Overall Survival of Sorafenib-experienced patients treated with Nivolumab

Checkmate 040 (Cohort 1 & 2): ITT and Asian cohort analysis



	Median OS (95% CI), mo	12-mo OS rate (95% CI), %	18-mo OS rate (95% CI), %	24-mo OS rate (95% CI), %
ITT cohort	15.1 (13.2–18.2)	59.0 (51.4–65.8)	44.6 (37.2–51.8)	33.6 (26.7–40.6)
Asian cohort	14.9 (11.6–18.9)	60.3 (49.0–69.9)	44.4 (33.5–54.7)	34.5 (24.4–44.8)

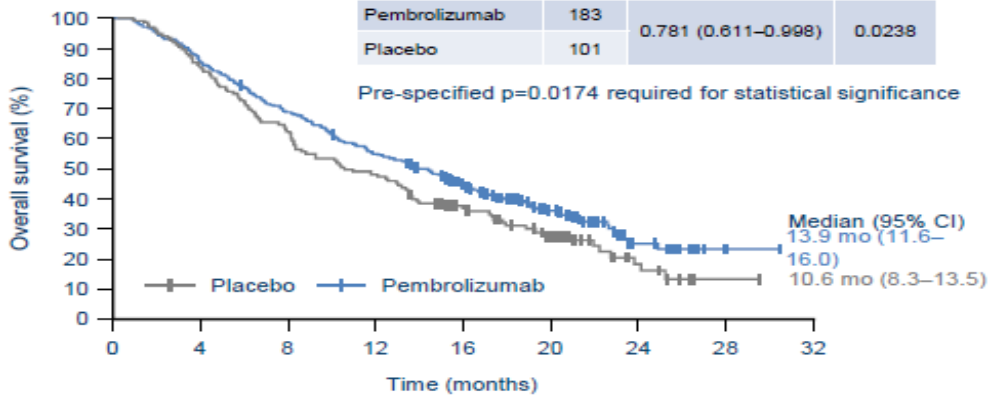
- Median follow-up of approximately 31 months in each cohort

KEYNOTE-240 – OS/PFS update from ASCO 2019

OS

	Events	HR (95% CI)	p-value
Pembrolizumab	183	0.781 (0.611–0.998)	0.0238
Placebo	101		

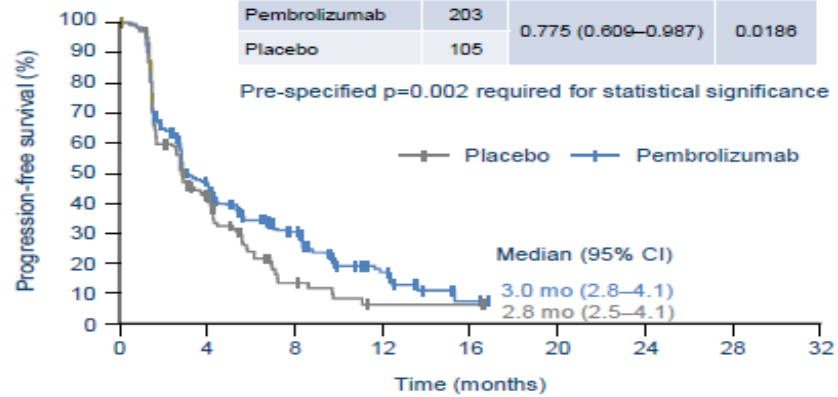
Pre-specified p=0.0174 required for statistical significance



PFS

	Events	HR (95% CI)	p-value
Pembrolizumab	203	0.775 (0.609–0.987)	0.0186
Placebo	105		

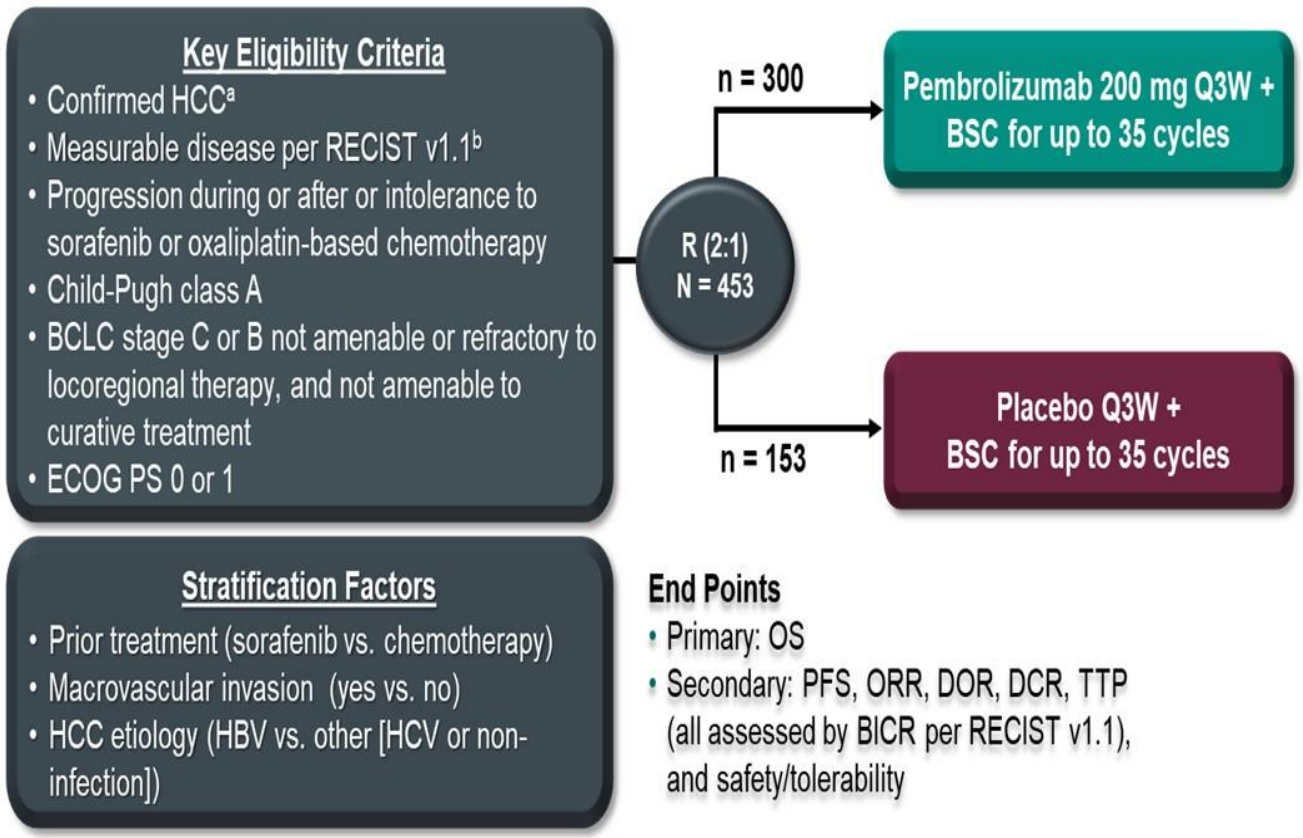
Pre-specified p=0.002 required for statistical significance



KEYNOTE-240 did not meet the statistical criteria for either of the dual primary endpoints

Finn R, *et al. J Clin Oncol* 2019;15_suppl: 4004.

KEYNOTE-394 Study Design (NCT03062358) and Statistical Considerations



- **Overall Type I error = 0.025 controlled across testing of OS, PFS, and ORR[1]**
  - **Initial allocation PFS = 0.002; OS = 0.023**
  - **Re-allocated per multiplicity strategy specified in the protocol among 3 endpoints above**
- **Per protocol, there were 2 interim and 1 final analysis for OS and 1 interim and 1 final analysis for PFS and ORR**
  - **Interim analysis for PFS and ORR at the time of OS 1st interim analysis**
  - **Final analysis at the time of OS 2nd interim analysis**
- **Efficacy boundaries**
  - ***P* = 0.0193 for OS (final analysis cutoff, June 30, 2021, based on 350 observed events)**
  - ***P* = 0.0134 for PFS and *P* = 0.0091 for ORR (at 2nd interim cutoff, June 30, 2020; only if OS criteria met)**

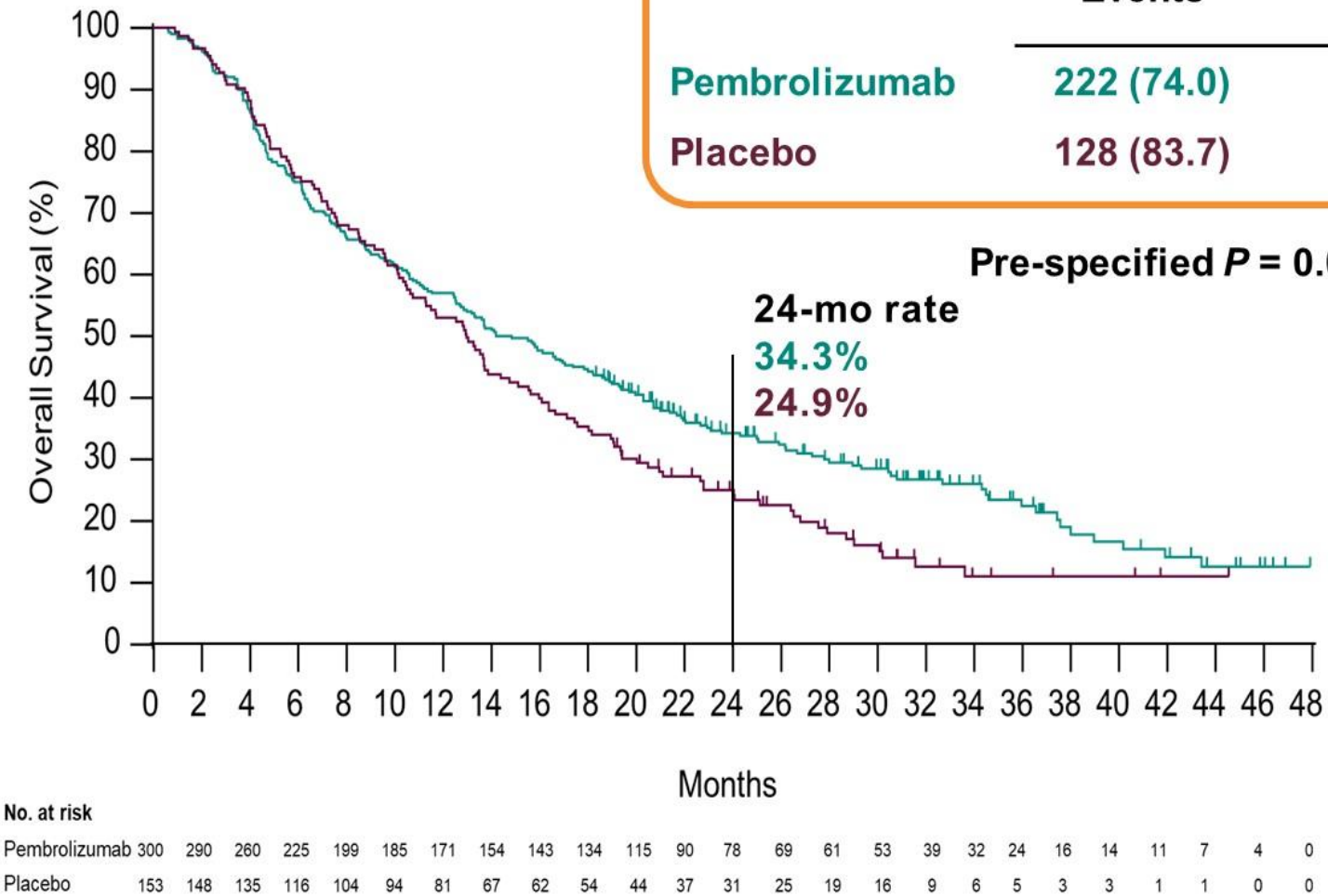
[a]Histologically, cytologically, or radiographically confirmed HCC. [b]Based on investigator assessment.

1. Maurer W, Bretz F. *Stat Biopharm Res.* 2013; 5(4): 311-20. 2. Finn RS et al. *J Clin Oncol.* 2020;38:193-202

Median time from randomization to data cutoff for the final analysis was 33.8 months (range 18.7-49.0) and 21.8 months (range 6.7-37.0) for the 2nd interim analysis.

Overall Survival

	Events	OS, median (95% CI), mo	HR (95% CI)	*P*[a]
Pembrolizumab	222 (74.0)	14.6 (12.6-18.0)	0.79 (0.63-0.99)	*0.0180*
Placebo	128 (83.7)	13.0 (10.5-15.1)		



Pre-specified *P* = 0.0193 required for statistical significance

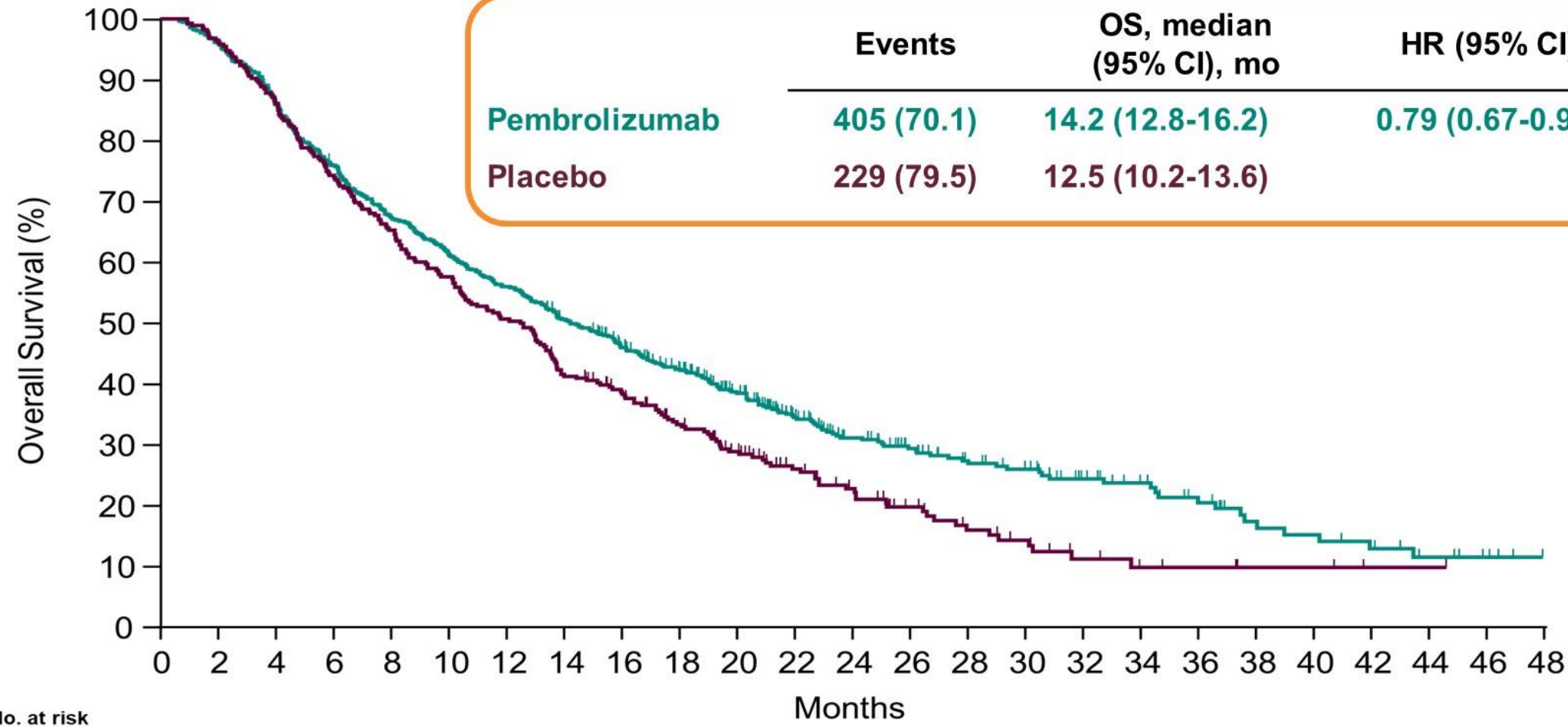
Post-Study Systemic Anticancer Therapy

	Pembrolizumab n = 300	Placebo n = 153
Any post-study systemic anticancer therapy	152 (50.7)	102 (66.7)
PD-1 inhibitor or PD-L1 inhibitor[b]	62 (20.7)	43 (28.1)

[a]One-sided *P* for testing difference. Data cutoff: June 30, 2021 (final analysis). [b]Includes both with/without prior exposure to other post-study systemic anticancer therapies.

Overall Survival Based on Meta-Analysis of KEYNOTE-394 and KEYNOTE-240

	Events	OS, median (95% CI), mo	HR (95% CI)
Pembrolizumab	405 (70.1)	14.2 (12.8-16.2)	0.79 (0.67-0.93)
Placebo	229 (79.5)	12.5 (10.2-13.6)	

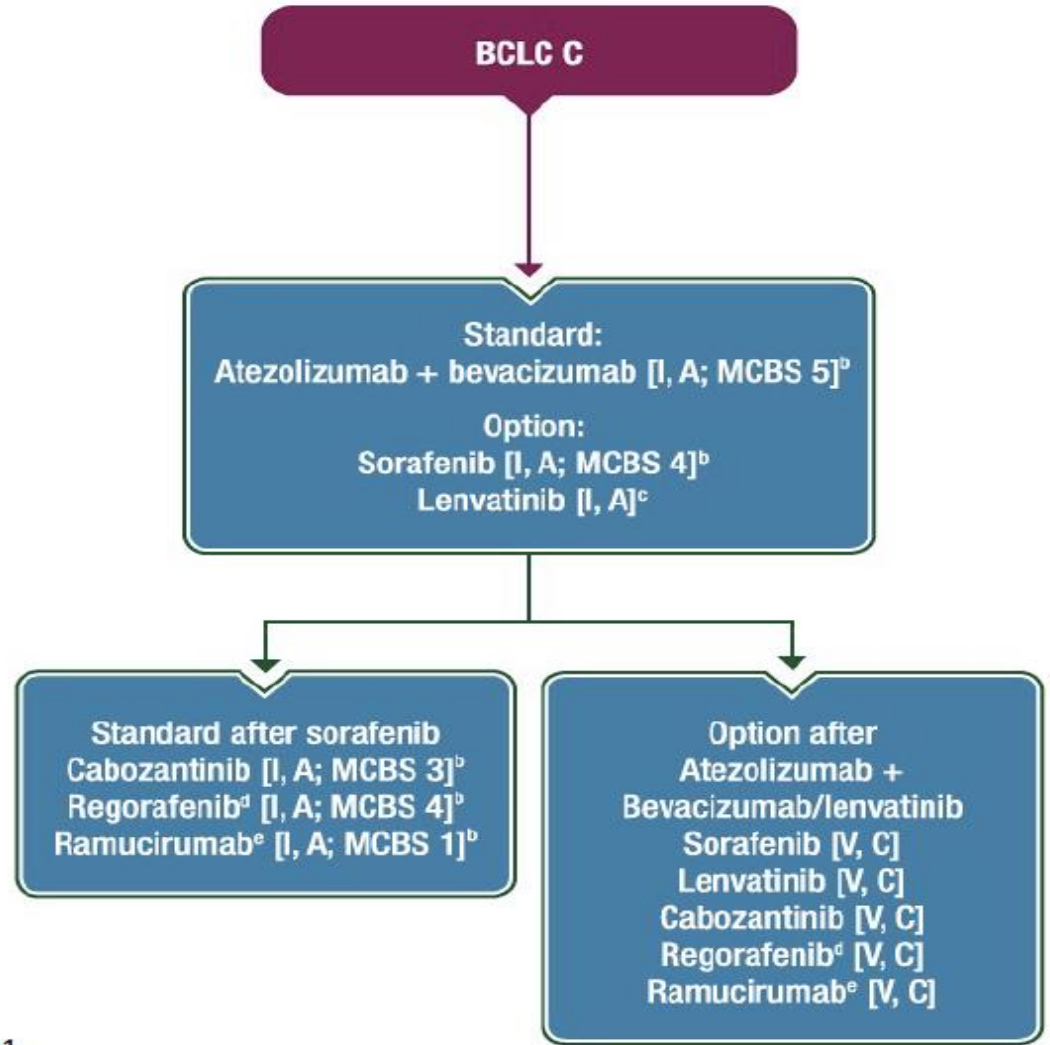


No. at risk

Pembrolizumab	578	555	497	438	389	354	323	289	253	220	172	123	94	76	62	54	39	32	24	16	14	11	7	4	0
Placebo	288	278	248	214	188	166	146	118	104	84	67	50	39	28	20	16	9	6	5	3	3	1	1	0	0

Meta-analysis of pooled OS data from KEYNOTE-240[2] and KEYNOTE-394 was performed using all patients receiving pembrolizumab or placebo in the intent-to-treat populations of each study. Data cutoff: KEYNOTE-240: January 2, 2019 (final analysis; Finn RS et al. *J Clin Oncol* 2020;38:193-202); KEYNOTE-394: June 30, 2021 (final analysis).

ESMO guidelines 2021



ESMO guidelines on HCC (eUpdate 2021) - Galle et al. Ann Oncol 2021

Thank you