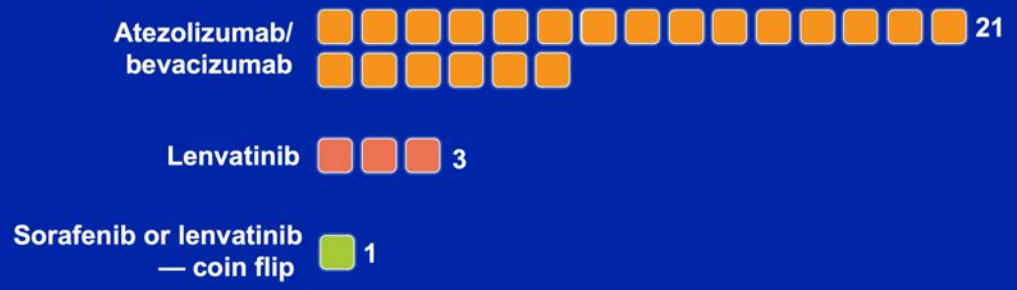
First-Line Systemic Therapy for Patients with Unresectable Hepatocellular Carcinoma (HCC)

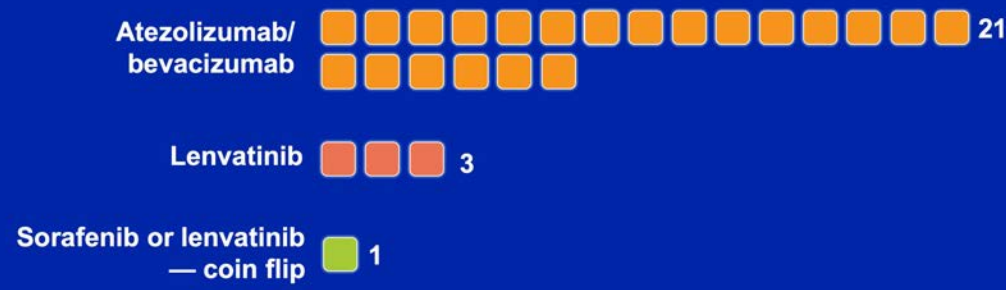
Richard S Finn, MD
Professor of Clinical Medicine
Division of Hematology/Oncology
David Geffen School of Medicine at UCLA
Director, Signal Transduction and Therapeutics Program
Jonsson Comprehensive Cancer Center at UCLA
Los Angeles, California

Is HCC the new RCC (checkpoint inhibitor/VEGF inhibitor)?

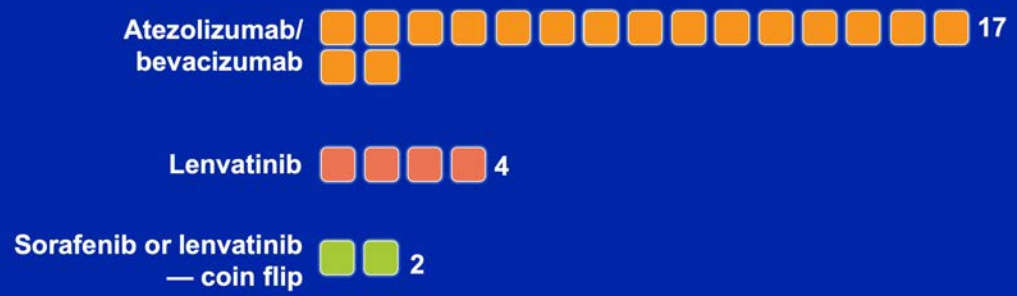
Regulatory and reimbursement issues aside, what would be your current preferred first-line systemic treatment for a 65-year-old patient with HCC, a Child-Pugh A score and a performance status (PS) of 0?



Regulatory and reimbursement issues aside, what would be your current preferred first-line systemic treatment for a 78-year-old patient with HCC, a Child-Pugh A score and a PS of 0?



Regulatory and reimbursement issues aside, what would be your current preferred first-line systemic treatment for a 65-year-old patient with HCC and painful bone metastases?



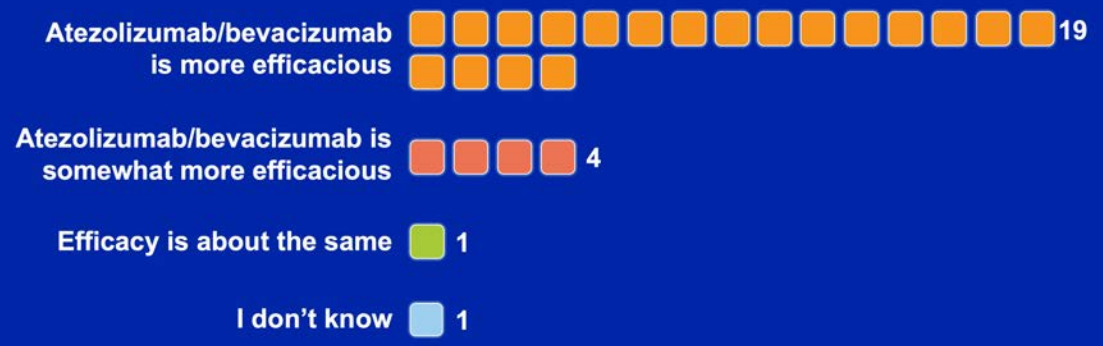
First-Line Systemic Therapy for HCC

IMbrave150: Atezolizumab/bevacizumab

- Antitumor activity
- Toxicity
- Patients with compromised liver function

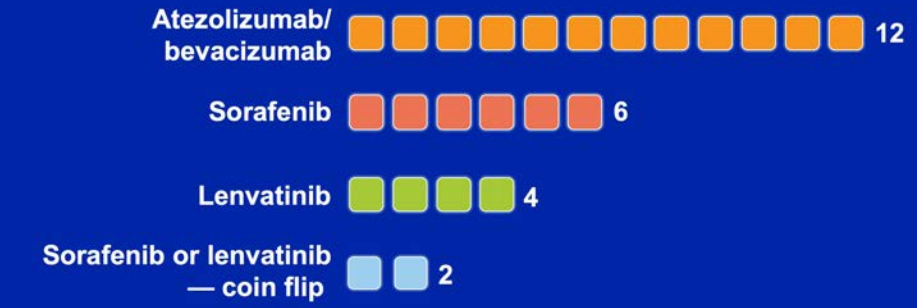
Current role of first-line lenvatinib and sorafenib

Based on clinical trial data and your experience, how would you compare the global antitumor efficacy of atezolizumab/bevacizumab and sorafenib or lenvatinib as first-line therapy for HCC?



Based on clinical trial data and your experience, how would you compare the global tolerability profiles of atezolizumab/bevacizumab and sorafenib or lenvatinib as first-line therapy for HCC?

Regulatory and reimbursement issues aside, what would be your current preferred first-line systemic treatment for a 78-year-old patient with HCC, a Child-Pugh B7 score and a PS of 1?



Palliative care (1)

First-Line Systemic Therapy for HCC

IMbrave150: Atezolizumab/bevacizumab

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Disclosures

- Consultant: AstraZeneca, C Stone, Bayer, Bristol Myers Squibb, Eisai, Eli-Lilly, Exelixis, Merck, Novartis, Pfizer, Roche/Genentech

LENVATINIB: REFLECT STUDY

- Lenvatinib is an oral multikinase inhibitor that targets VEGFR(1–3), FGFR(1–4), PDGFRα, RET, and KIT[1–4]
- There have been 4 failed phase 3 trials in front-line HCC in the past 10 years[5–8]
- In a global, randomized, open-label phase 3 noninferiority study, lenvatinib was noninferior to sorafenib for OS, and significantly improved PFS, TTP, and ORR in patients with untreated advanced HCC[9]

In vitro kinase inhibitory profiles[3]

IC_{50} (nmol/L)	Lenvatinib	Sorafenib
VEGFR1	4.7	21
VEGFR2	3.0	21
VEGFR3	2.3	16
FGFR1	61	340
FGFR2	27	150
FGFR3	52	340
FGFR4	43	3400
RET	6.4	15
KIT	85	140
PDGFRα	29	1.6
PDGFRβ	160	27
BRAF	8700	310
RAF1	1600	46

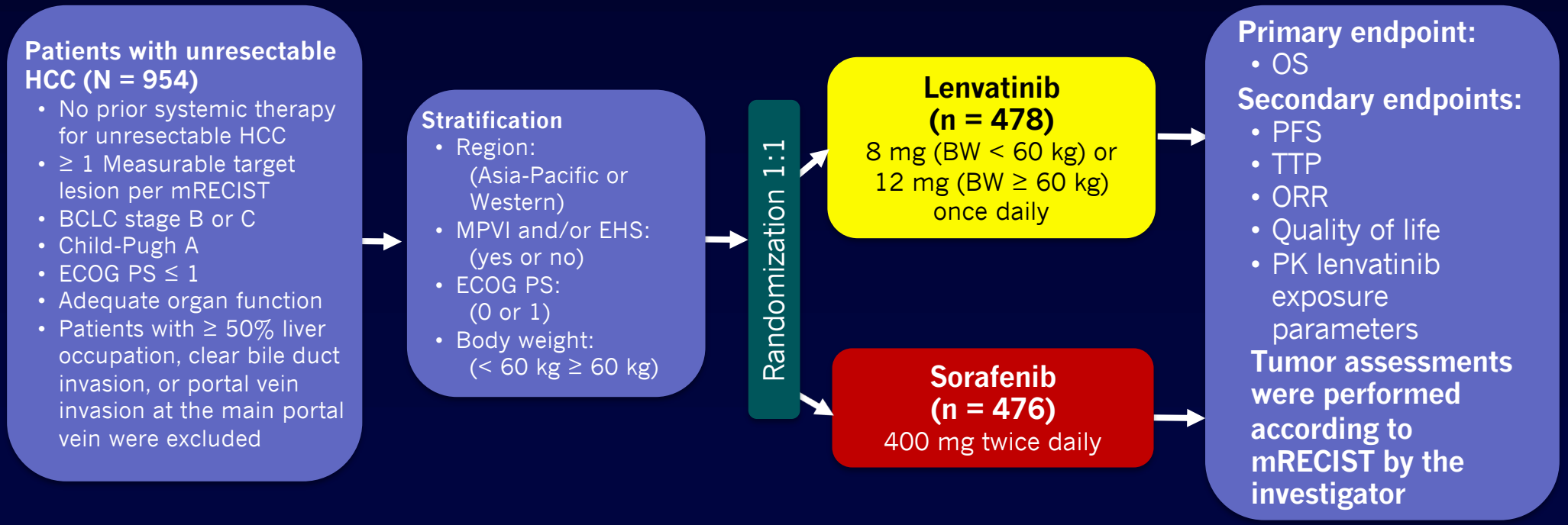
HCC, hepatocellular carcinoma; FGFR, fibroblast growth factor receptor; ORR, overall response rate; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; TTP, time to progression; VEGFR, vascular endothelial growth factor receptor;

1. Matsui et al. Int J Cancer 2008;122:664-71; 2. Matsui et al. Clin Cancer Res 2008;14:5459-65; 3. Tohyama et al. J Thyroid Res 2014;2014:638747; 4. Yamamoto et al. Vasc Cell 2014;6:18; 5. Cheng et al. J Clin Oncol 2013; 31: 4067-75; 6. Johnson et al. J Clin Oncol 2013; 31: 3517-24; 7. Cainap et al. J Clin Oncol 2015; 33: 172-9; 8. Zhu et al. J Clin Oncol 2015; 33: 559-66; 5. Cheng A.-L., ASCO 2017.

REFLECT Study

Study Schema

Global, randomized, open-label, phase 3 noninferiority study

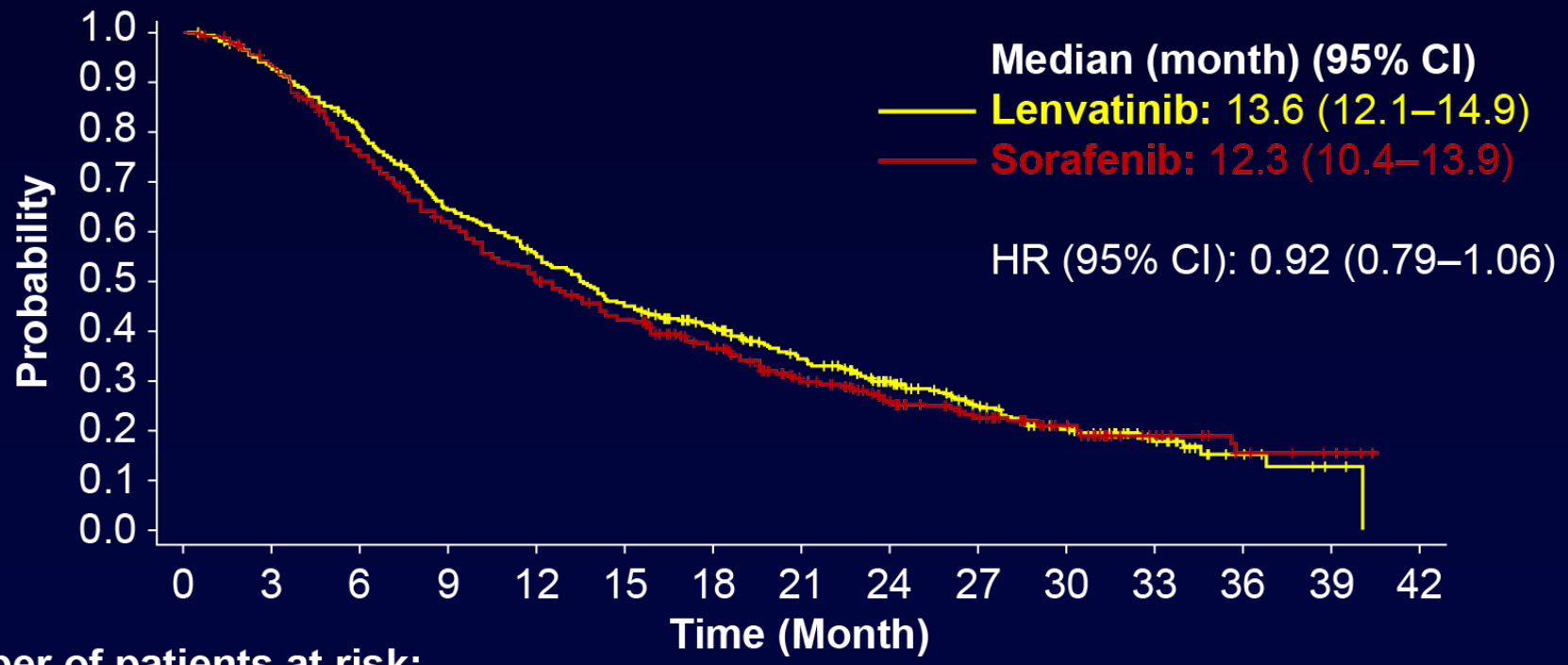


BCLC, Barcelona Clinic Liver Cancer; BW, body weight; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EHS, extrahepatic spread; MPVI, macroscopic portal vein invasion; mRECIST, modified Response Evaluation Criteria In Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.

Kudo M, Finn RS, Qin S et al. Lancet 2018

REFLECT Study

Primary Endpoint: Kaplan-Meier Estimate of OS



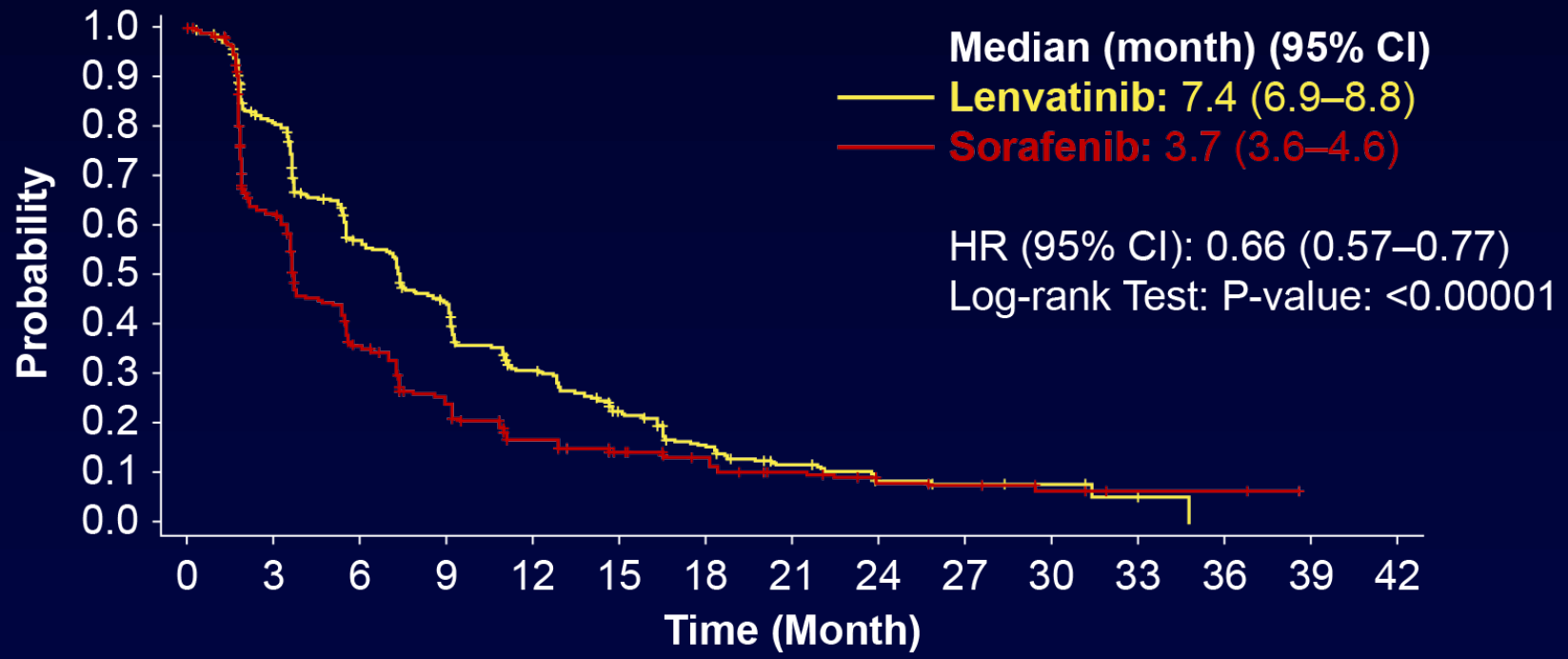
Number of patients at risk:

Lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
Sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

Kudo M, Finn RS, Qin S et al. Lancet 2018

REFLECT Study

Secondary Endpoint: Kaplan-Meier Estimate of PFS by mRECIST



Number of patients at risk:

Lenvatinib	478	345	223	172	106	69	44	28	14	9	4	2	0	0
Sorafenib	476	262	140	94	56	41	33	22	14	9	4	2	2	0

Kudo M, Finn RS, Qin S et al. Lancet 2018

Tumor assessments: Lenvatinib

Parameter	mRECIST by investigator	mRECIST by independent review	RECIST v1.1 by independent review
Lenvatinib (n = 478)			
ORR, n (%)	115 (24.1)	194 (40.6)	90 (18.8)
95% CI	20.2–27.9	36.2–45.0	15.3–22.3
Odds ratio (95%CI)[a]	3.13 (2.15–4.56)	5.01 (3.59–7.01)	3.34 (2.17–5.14)
BOR, n (%)			
Complete response	6 (1)	10 (2)	2 (<1)
Partial response	109 (23)	184 (38)	88 (18)
Stable disease	246 (51)	159 (33)	258 (54)
Durable stable disease[b]	167 (35)	84 (18)	163 (34)
Progressive disease	71 (15)	79 (17)	84 (18)
Not evaluable/unknown	46 (10)	46 (10)	46 (10)

[a]Lenvatinib vs sorafenib.
[b]Stable disease lasting ≥23 weeks.
BOR, best overall response; CI, confidence interval; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate.

REFLECT Study

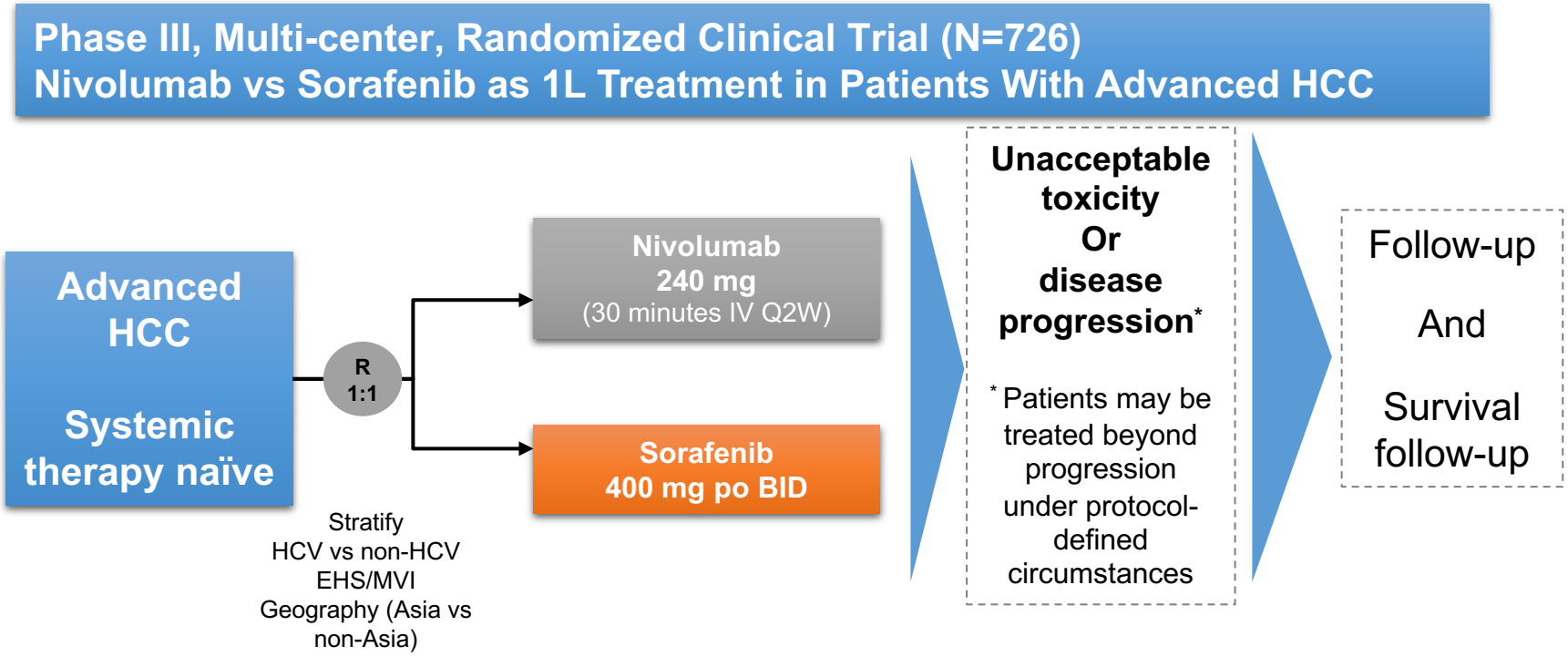
Most Frequent TEAEs (≥ 15%)

Adverse event, n (%)	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any grade	Grade 3/4	Any grade	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)
Palmar-plantar erythrodysesthesia	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (0)	57 (12)	0 (0)
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet count	87 (18)	26 (6)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Hypothyroidism	78 (16)	0 (0)	8 (2)	0 (0)
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0 (0)
Elevated aspartate aminotransferase	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0 (0)	76 (16)	2 (0)
Alopecia	14 (3)	0 (N/A)	119 (25)	0 (N/A)

Kudo M, Finn RS, Qin S et al. Lancet 2018

CheckMate 459: 1L Nivolumab vs Sorafenib

Phase 3 Study Design



- **Primary Endpoint:** OS

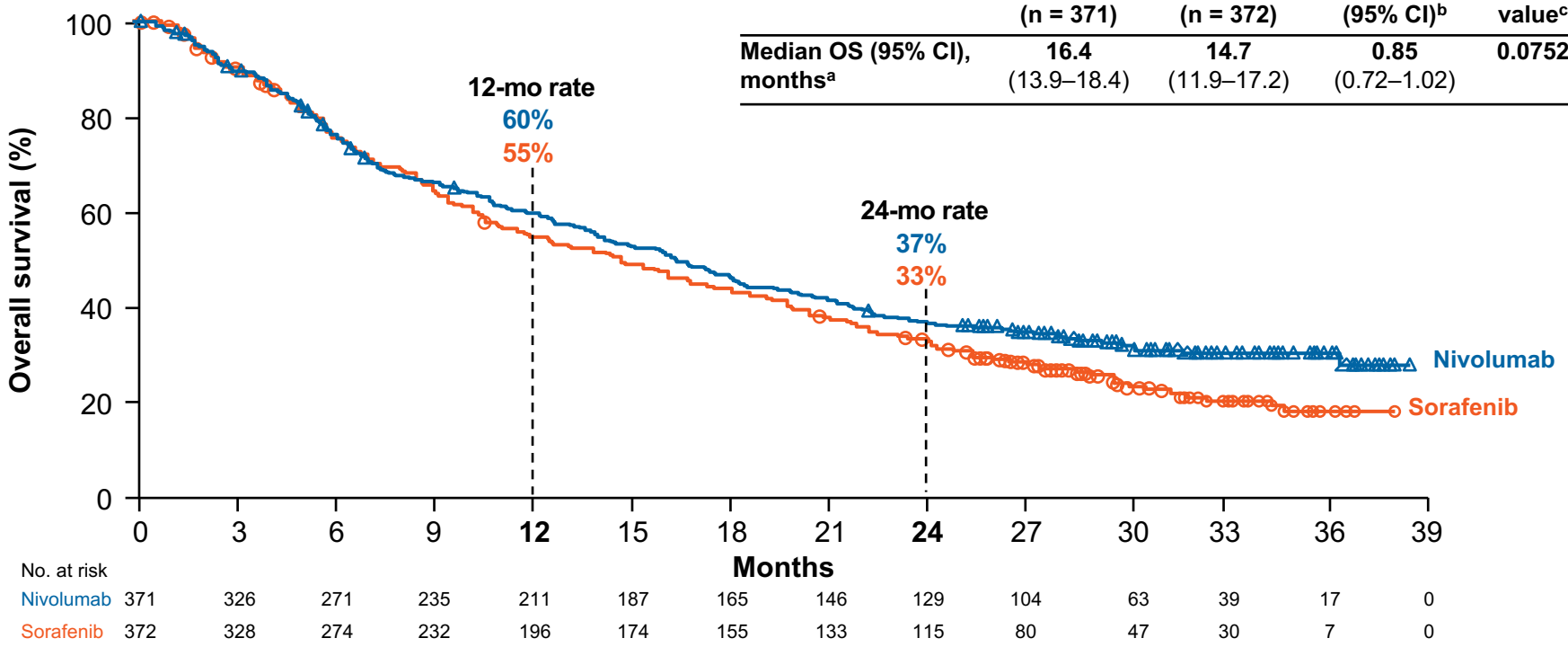
Countries	US, Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hong Kong, Japan, Korea, Poland, Singapore, Spain, Taiwan, UK
Status	Recruiting

Clinicaltrials.gov. NCT02576509. Accessed May 21, 2018.

Overall Survival

CheckMate 459

	Nivolumab (n = 371)	Sorafenib (n = 372)	HR (95% CI)[b]	P value[c]
Median OS (95% CI), months[a]	**16.4** (13.9–18.4)	**14.7** (11.9–17.2)	**0.85** (0.72–1.02)	**0.0752**



- The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit

[a]Based on Kaplan–Meier estimates; [b]Stratified Cox proportional hazards model. HR is nivolumab over sorafenib; [c]*P* value from log-rank test; final OS boundary: 0.0419 for a 2-sided nominal *P* value.
HR, hazard ratio.

Yau, Park, Finn et al ESMO 2019

Response, Disease Control, and Durability

	Nivolumab (n = 371)	Sorafenib (n = 372)
ORR,[a] n (%)	57 (15)	26 (7)
Best overall response, n (%)		
CR	14 (4)	5 (1)
PR	43 (12)	21 (6)
SD	130 (35)	180 (48)
Non-CR/non-PD	16 (4)	9 (2)
PD	136 (37)	105 (28)
Not evaluable	32 (9)	52 (14)
DCR,[b] n (%)	203 (55)	215 (58)
Median duration of disease control (95% CI), months	7.5 (6.5–10.7)	5.7 (5.6–7.4)
Median time to response (range), months	3.3 (1.6–19.4)	3.7 (1.5–11.1)
Median duration of response (range), months	23.3 (3.1 to 34.5+)	23.4 (1.9+ to 28.7+)

- Improvement in ORR was observed with nivolumab compared with sorafenib (odds ratio [95% CI], 2.41 [1.48–3.92])
  - Higher CR rate was observed with nivolumab compared with sorafenib

[a]Per blinded independent central review using RECIST v1.1. Defined as CR + PR. [b]Defined as CR + PR + SD + non-CR/non-PD.
CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Yau, Park, Finn et al ESMO 2019

Subsequent Therapy

CheckMate 459

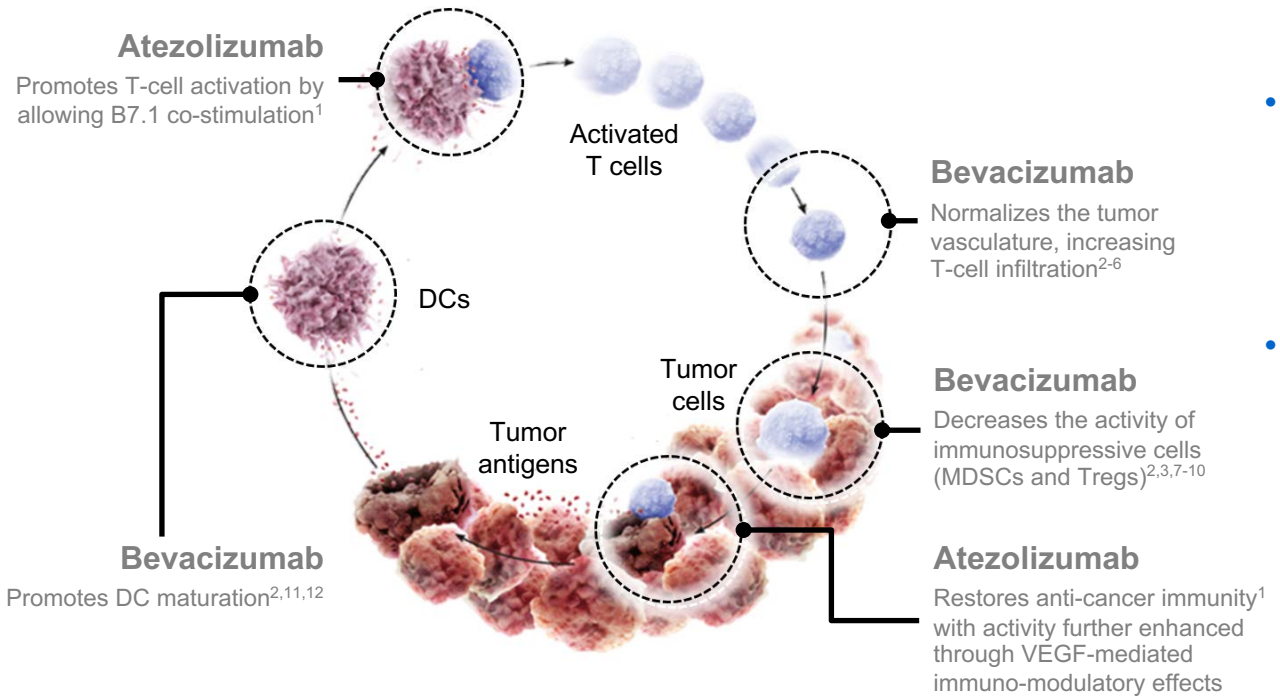
	Nivolumab (n = 371)	Sorafenib (n = 372)
Any subsequent therapy,[a] n (%)	181 (49)	196 (53)
Systemic therapy, n (%)	140 (38)	170 (46)
Tyrosine kinase inhibitor	132 (36)	86 (23)
Chemotherapy	15 (4)	25 (7)
Investigational agent[b]	10 (3)	40 (11)
I-O	7 (2)	76 (20)
Other	2 (1)	4 (1)
Local therapy, n (%)	63 (17)	61 (16)
Radiotherapy, n (%)	52 (14)	38 (10)
Surgery, n (%)	10 (3)	14 (4)

- 140 patients (38%) in the nivolumab arm and 170 patients (46%) in the sorafenib arm received subsequent systemic therapy
  - 20% of patients in the sorafenib arm received subsequent I-O therapy

[a]Patient may have received more than 1 type of subsequent therapy; [b]Includes indeterminate therapies received in subsequent clinical trials, including I-O.
I-O, immuno-oncology.

Yau, Park, Finn et al ESMO 2019

Combining VEGF Inhibition and PD-1/PD-L1

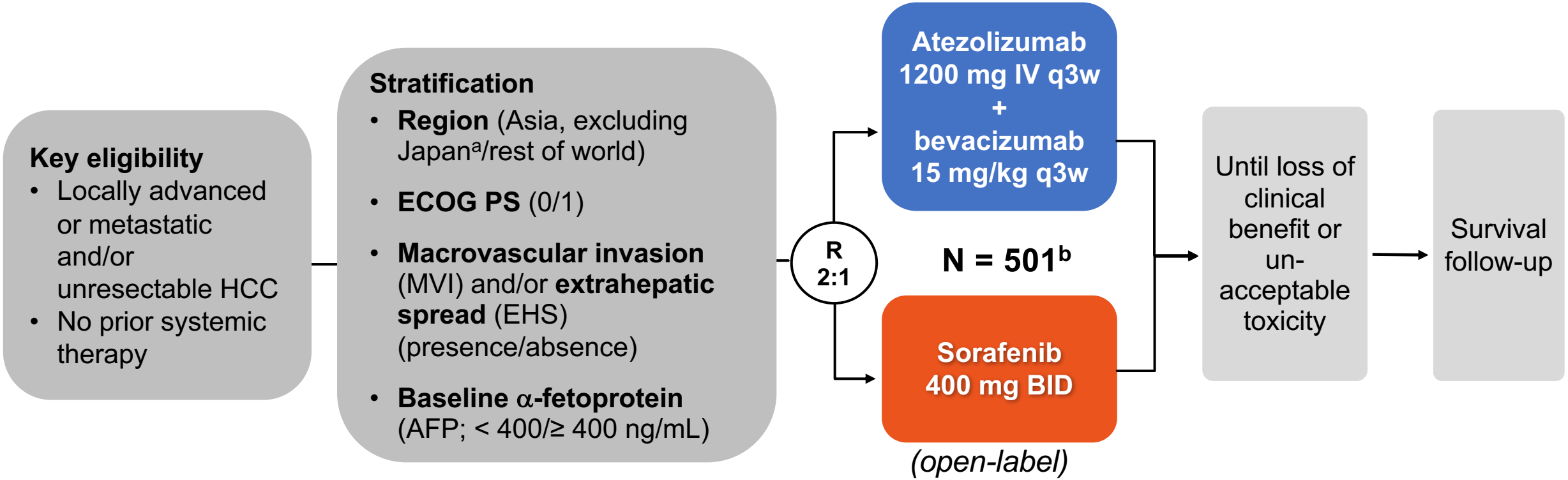


- Bevacizumab (anti-VEGF) is an antiangiogenic agent with additional immuno-modulatory effects
- In combination, bevacizumab may further enhance atezolizumab's efficacy by reversing VEGF-mediated immuno-suppression to promote T-cell infiltration into the tumor

DC, dendritic cell; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

1. Chen and Mellman. Immunity 2013. 2. Hegde et al. Semin Cancer Biol 2017.
3. Wallin et al. Nat Commun 2016. 4. Goel et al. Physiol Rev 2011. 5. Motz et al. Nat Med 2014.
6. Hodi et al. Cancer Immunol Res 2014. 7. Gabrilovich et al. Nat Rev Immunol 2009.
8. Roland et al. PLoS One 2009. 9. Facciabene et al. Nature 2011. 10. Voron et al. J Exp Med 2015.
11. Gabrilovich et al. Nat Med 1996. 12. Oyama et al. J Immunol 1998.

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.

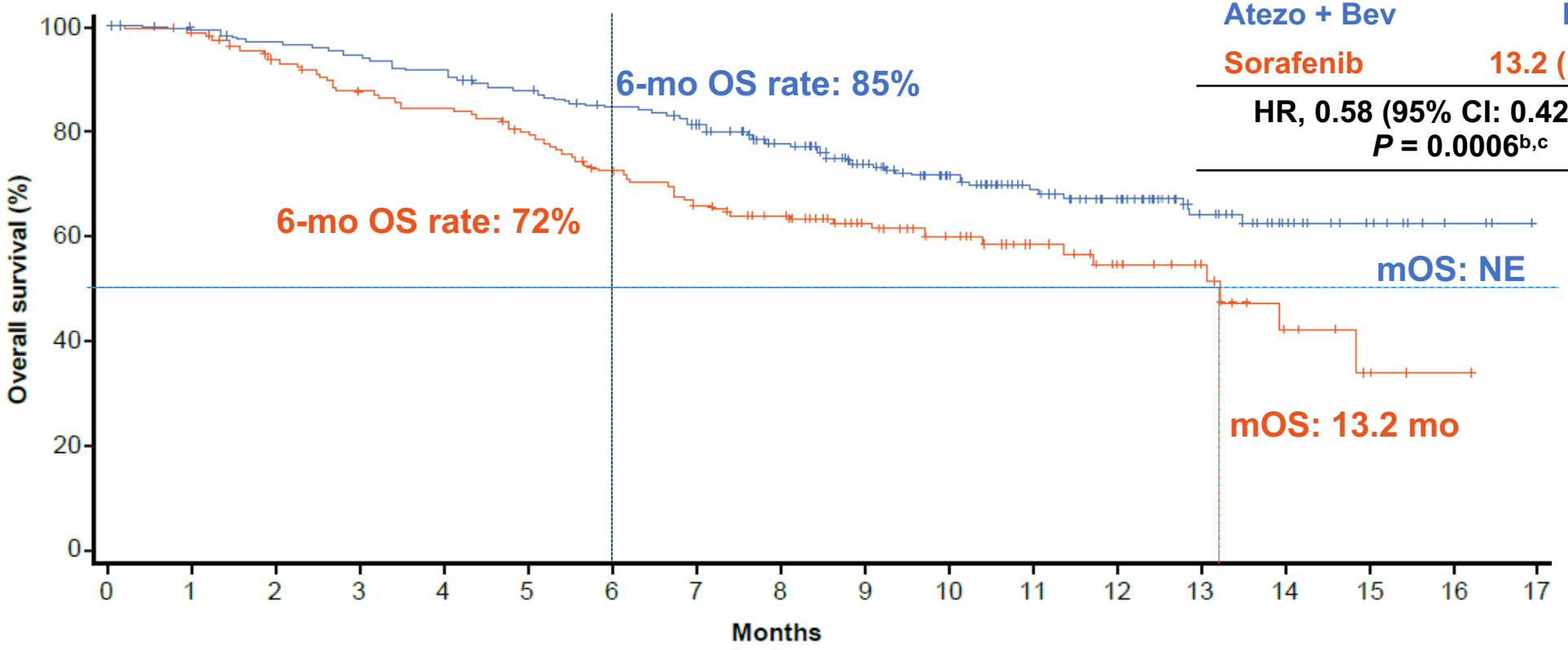
IMbrave150 baseline characteristics (ITT)

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

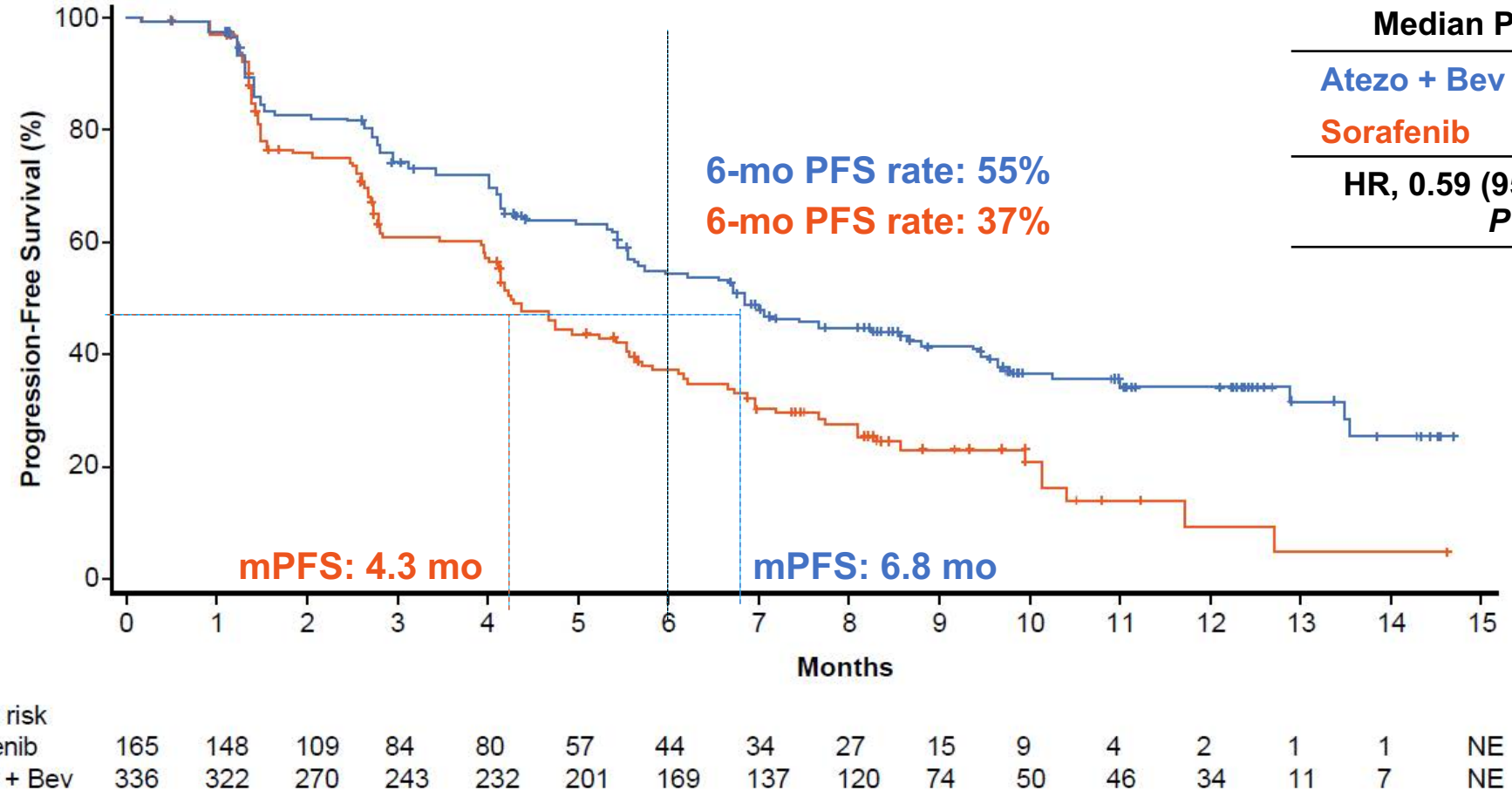
Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b] *P* = 0.0006[b,c]	



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]	

[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.

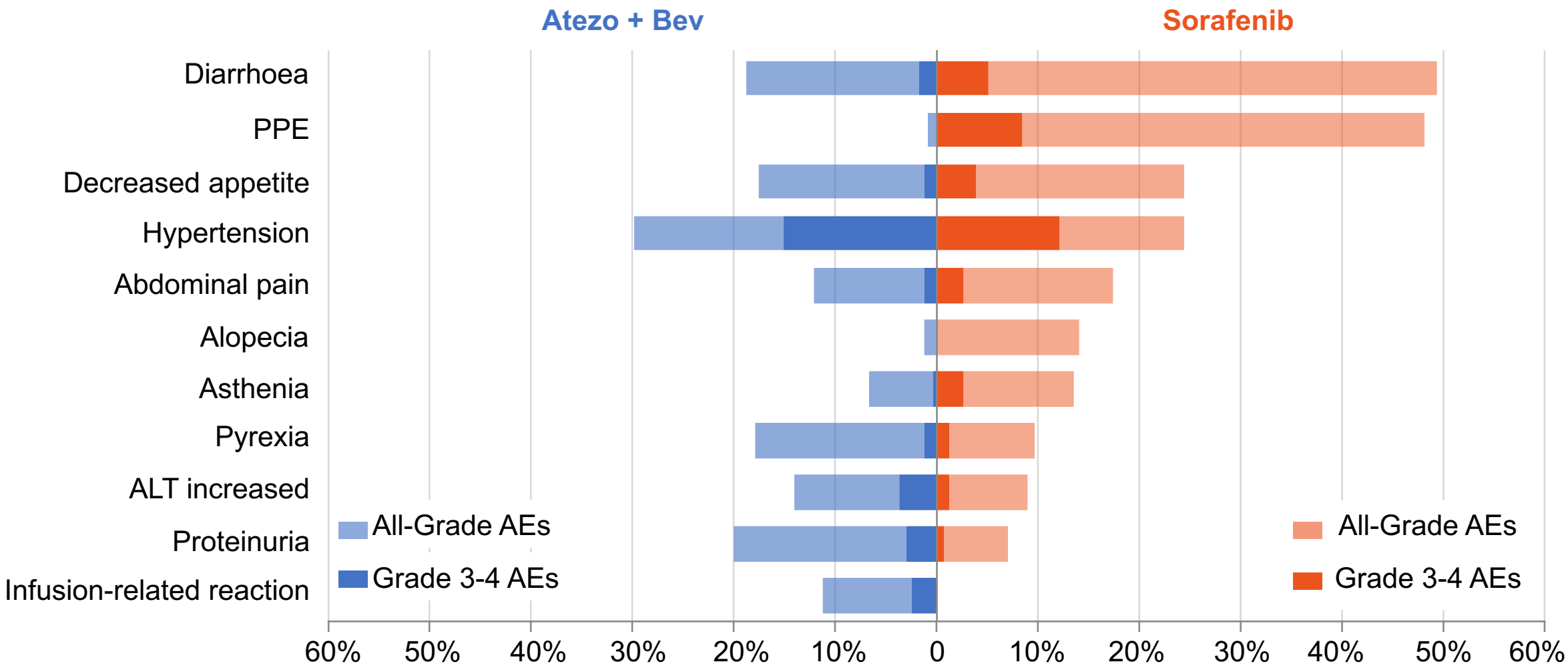
Response rate and duration of response

	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.

Safety[a]

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



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