Advanced hepatocellular carcinoma (HCC): State of the Art

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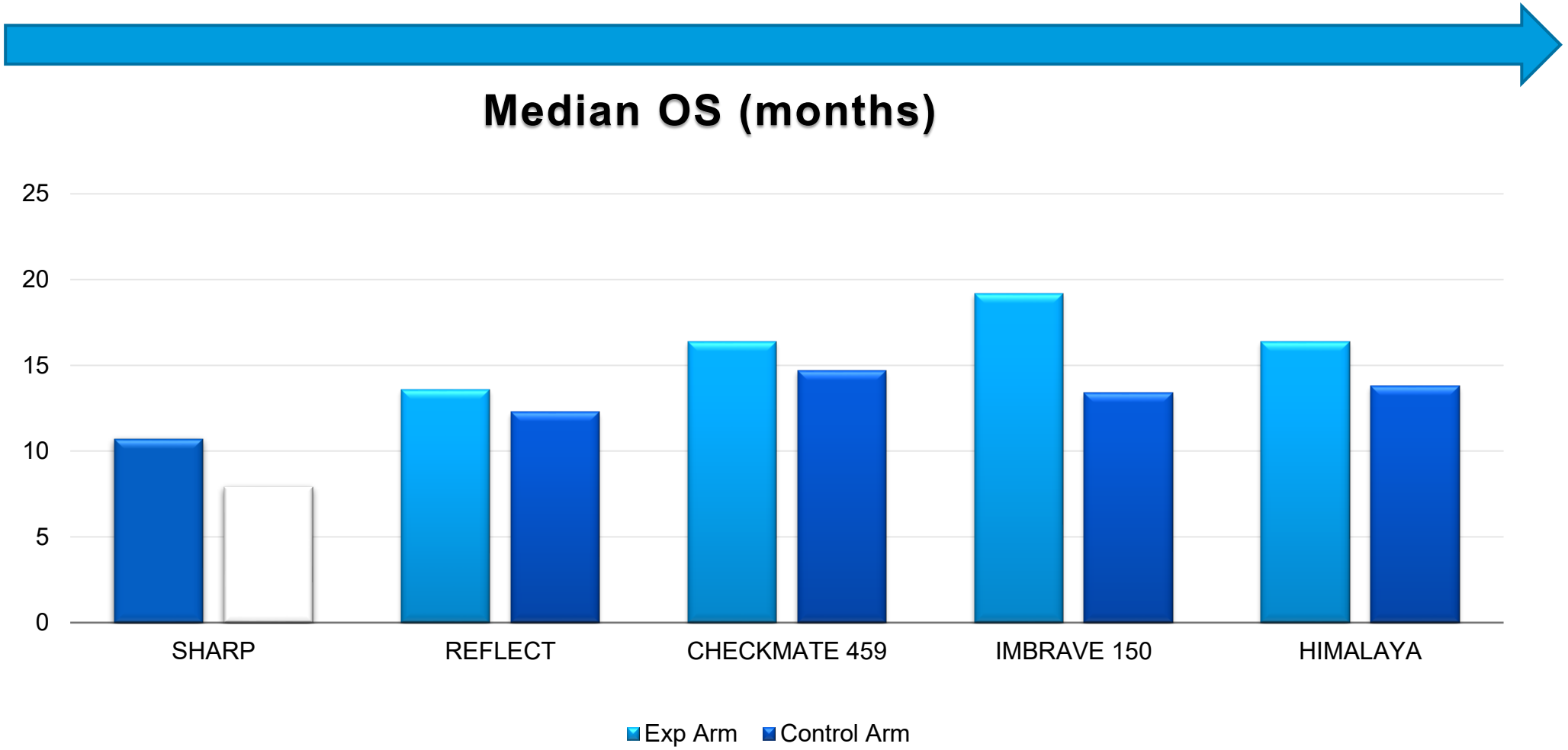
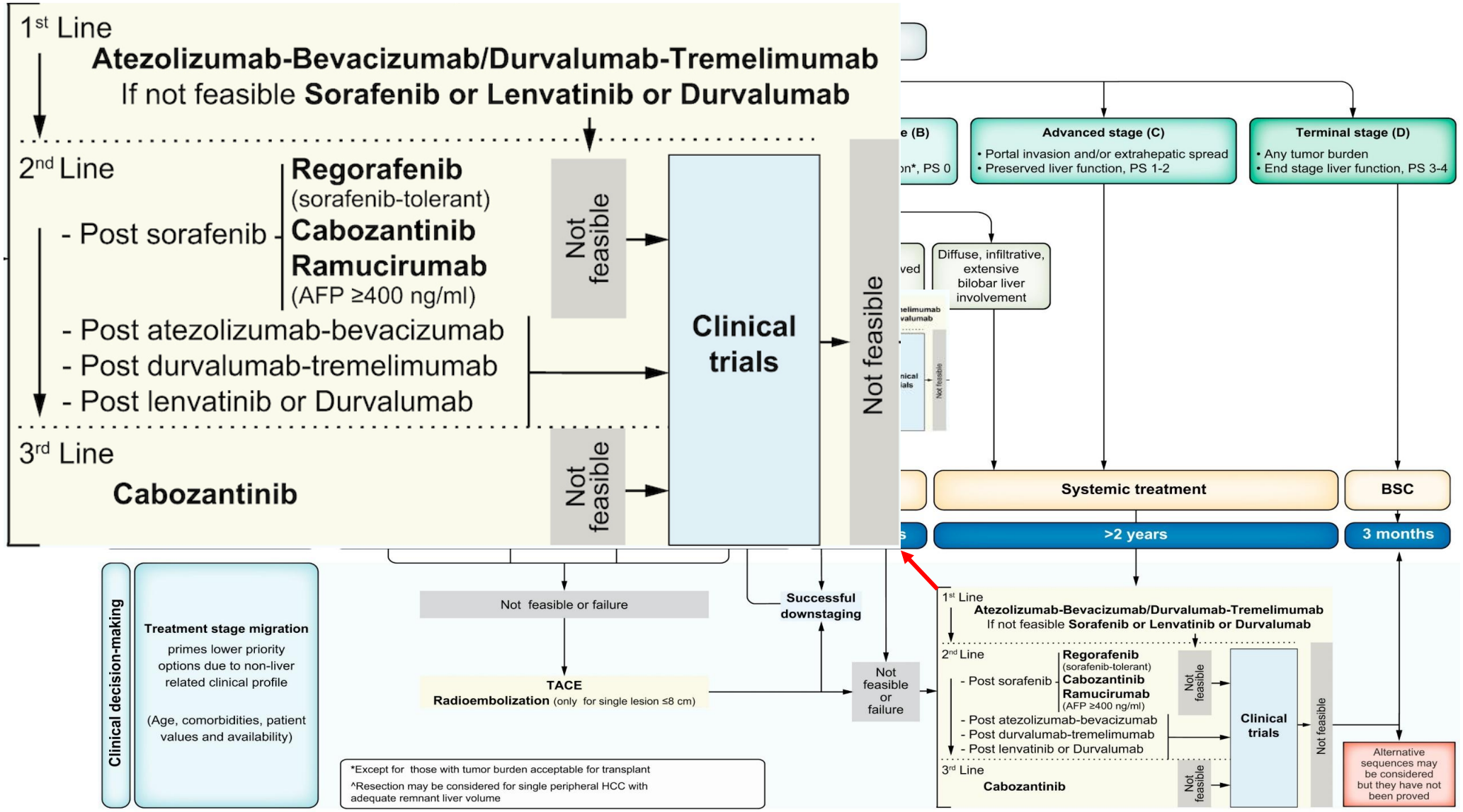
Historical snapshot

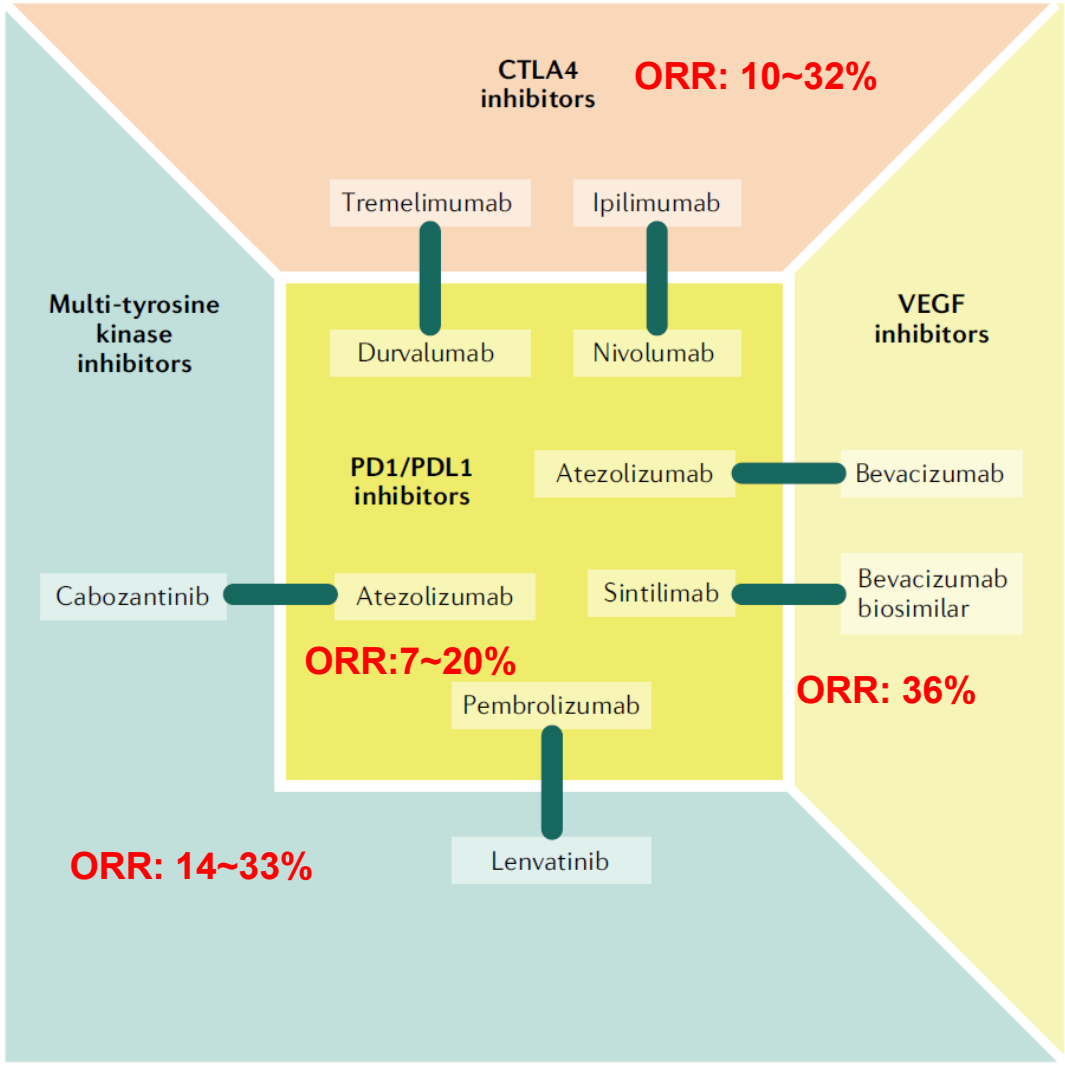


When is systemic therapy indicated for HCC ?



Reig M et al, J of Hepatology 2022

Heterogeneous Response to ICI-based Therapies



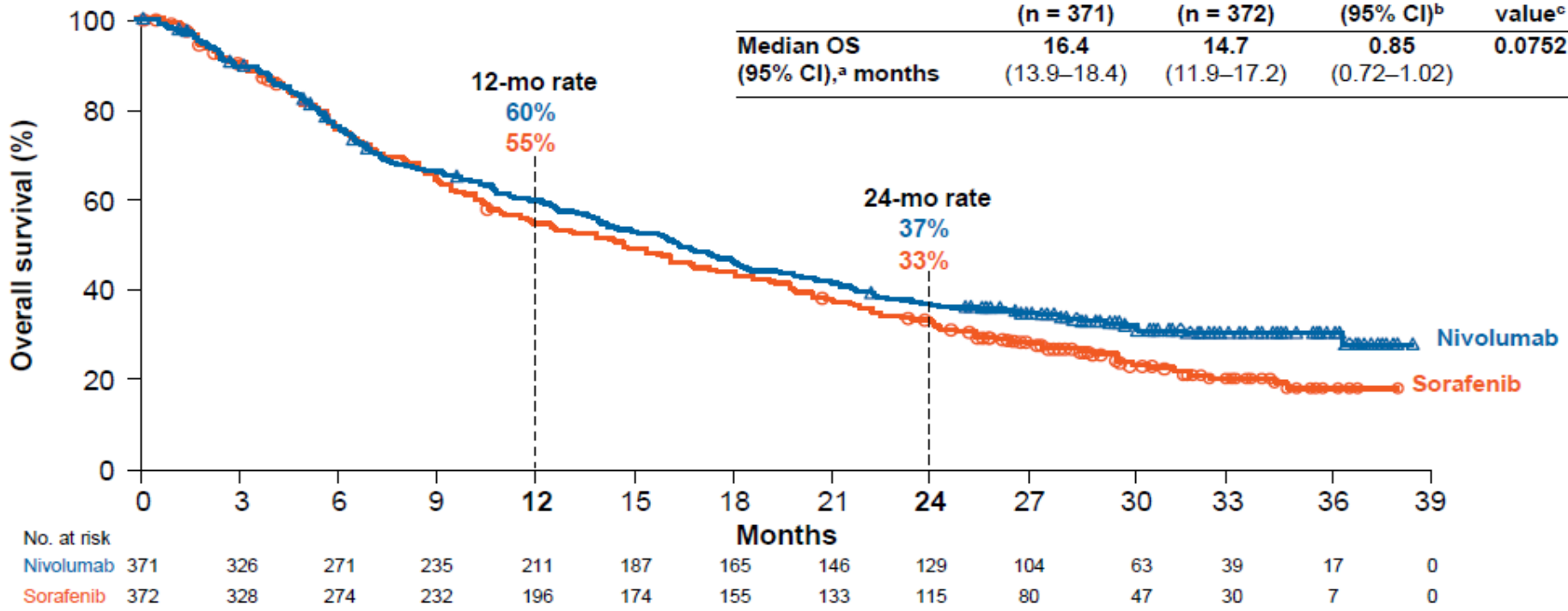
Sangro B et al. *Nat Rev Gastroenterol Hepatol*. 2021 Apr 13;1-19.

Checkmate 459: First line Nivolumab vs. Sorafenib

CheckMate 459

Overall Survival

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

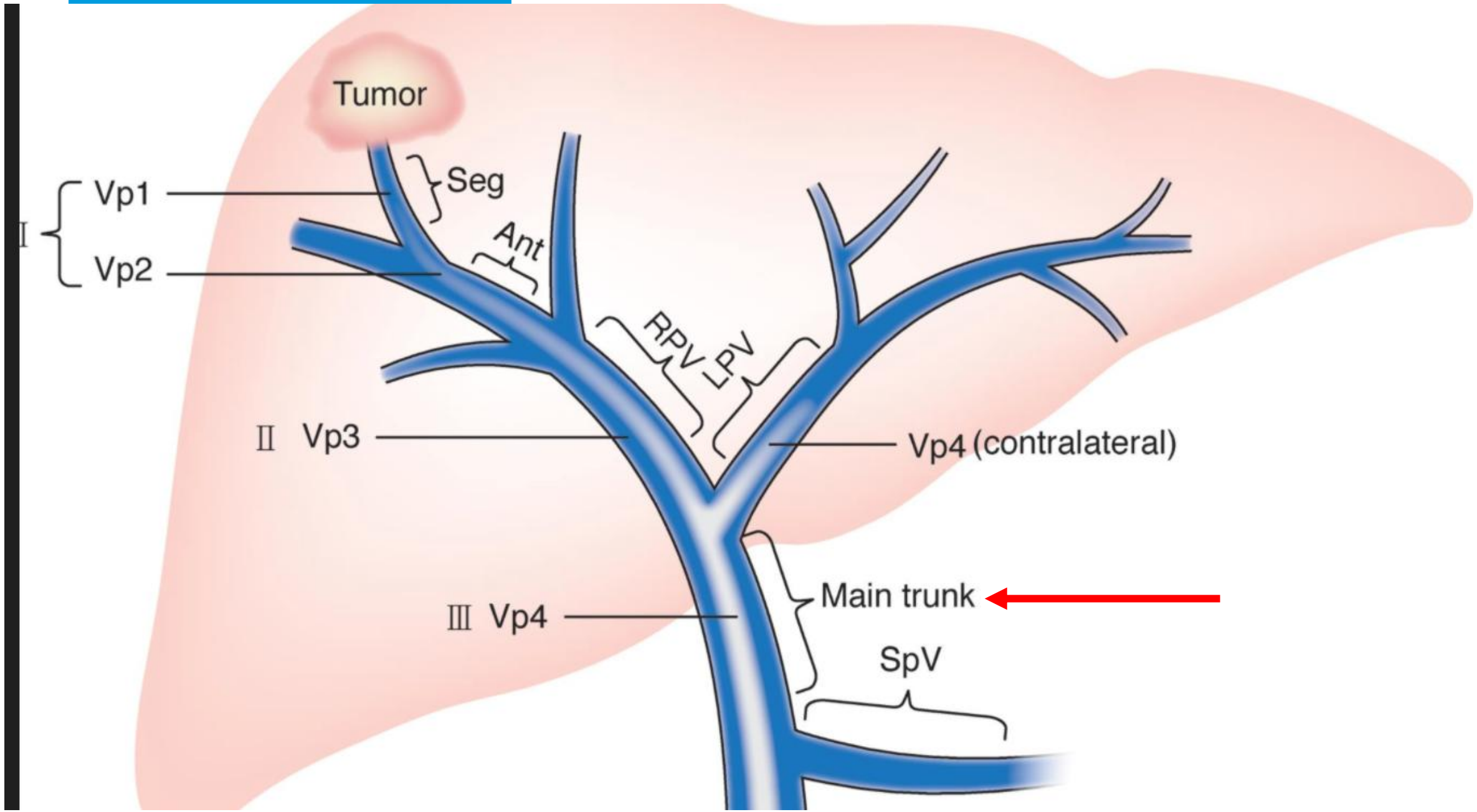


- The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit

[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.

8

Yau T et al, Lancet Oncol. 2022



Smart Combinations to Overcome Mechanisms of Resistance

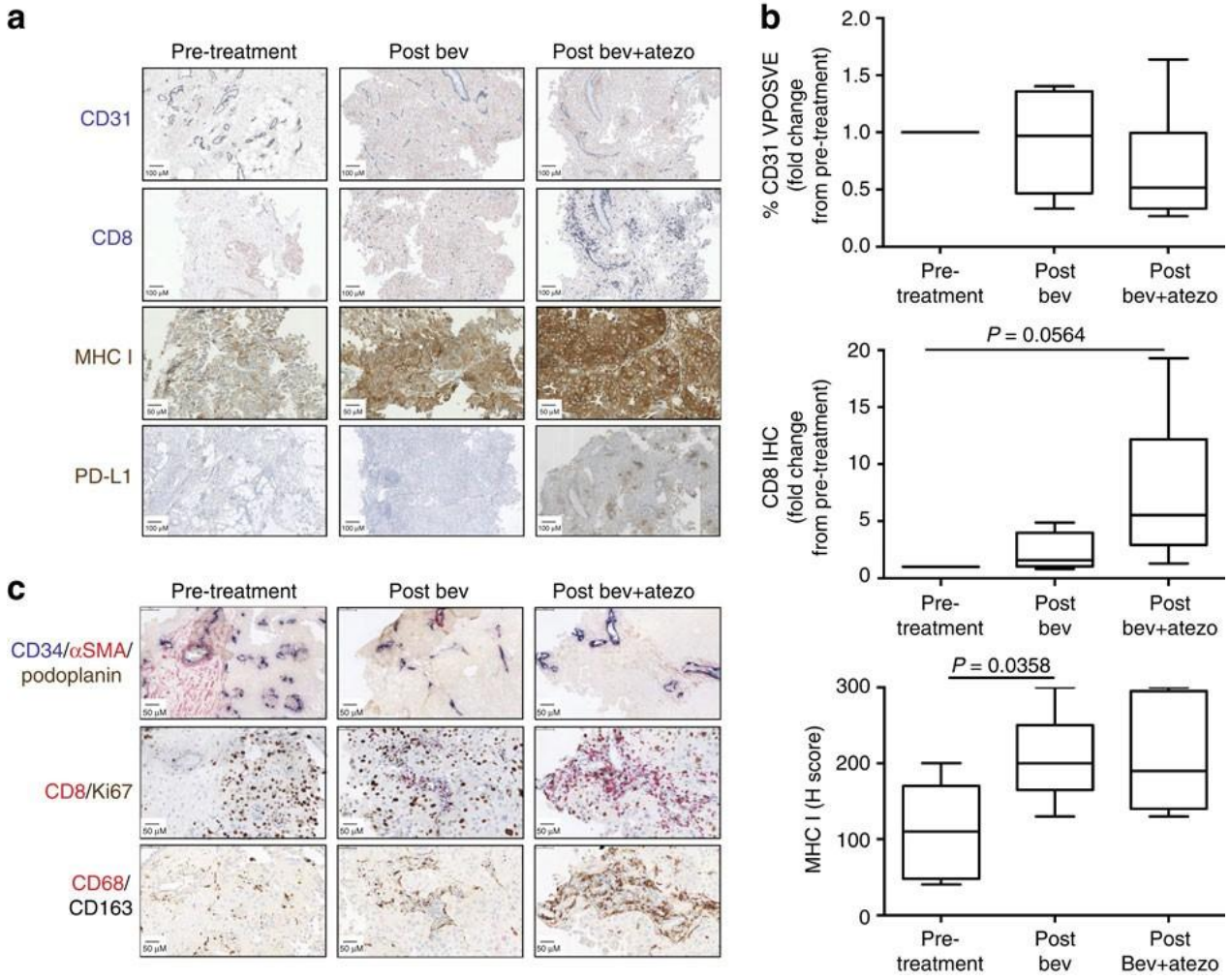
Combining anti PD-1/PD-L1 and anti VEGF

Targeting PD-1/ PD-L1

- Affects differentiated CD8+ T cells in tumor microenvironment
- Does not increase clonal diversity
- Does not move T cells into tumors
- Single agent activity in HCC
  - ORR 15 to 20%

Targeting VEGF

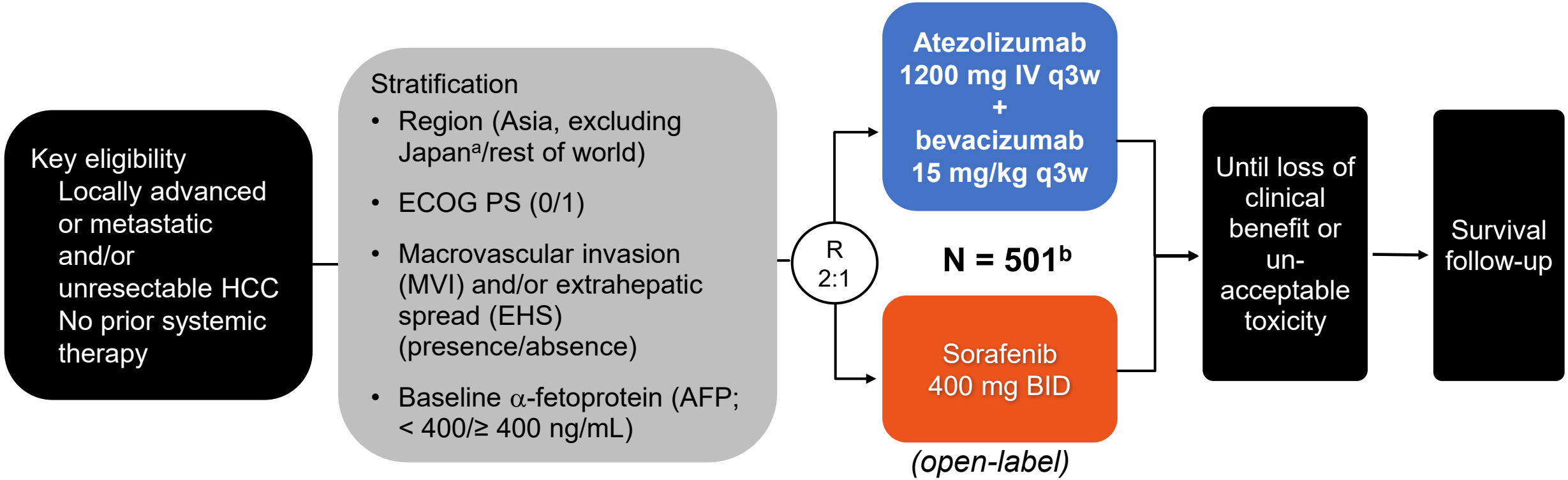
- Increases oxygenation and tumor perfusion
- Enhances delivery of CD8+ T cells into tumor
- TAM repolarization (M2 to M1)
- Suppresses MDSCs
- Multiple approve HCC tx target VEGF
- Single agent activity of bevacizumab
- ORR 13%; median PFS 6.9 mo;
- Median OS 12.4 mo



J Immunother Cancer. 2018; 6
El-Khoueiry A et al, Lancet 2017
Zhu AX, et al. Lancet Oncol. 2018
Yamagushi R et al, Hepatology 1998
Park YN et al, Arch Pathol Lab Med 2000
Semela D et al, J hepatol 2004

Siegel A et al, J Clin Oncol 2008
Kusmartsev S et al, J Immunol 2008
Wada J et al, Anticancer Res 2009
Huang Y et al, Cancer Res 2013
Rolny C et al, Cancer Cell 2011
Chen D et al, The Cancer Journal 2018

IMbrave150 study design

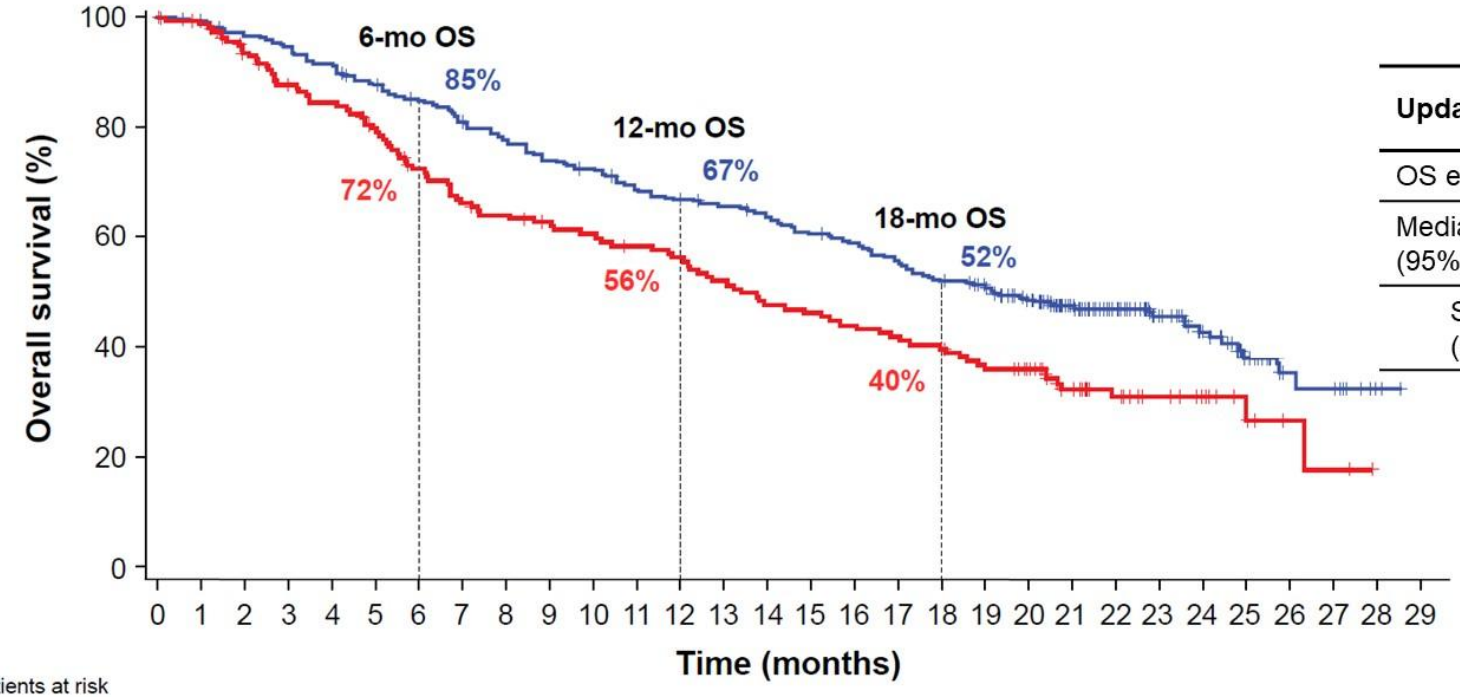


Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

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.

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]	

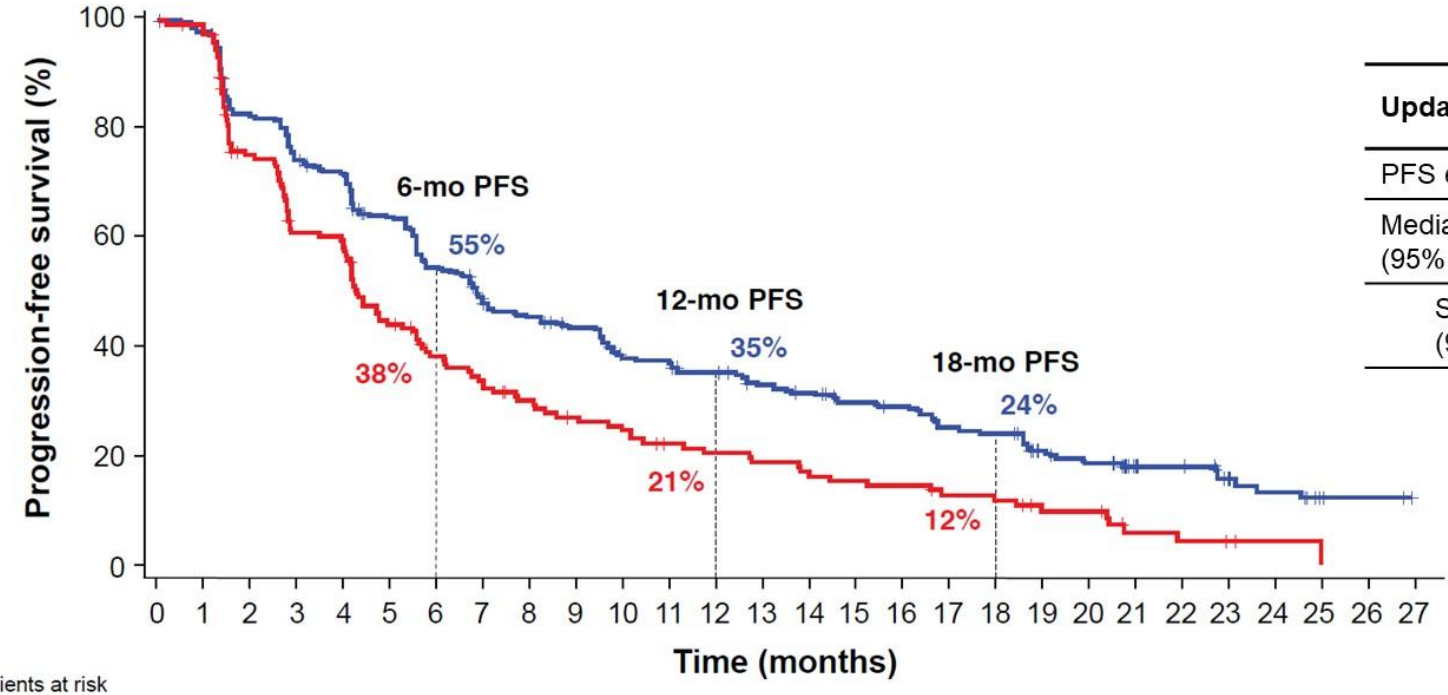
No. of patients at risk

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.

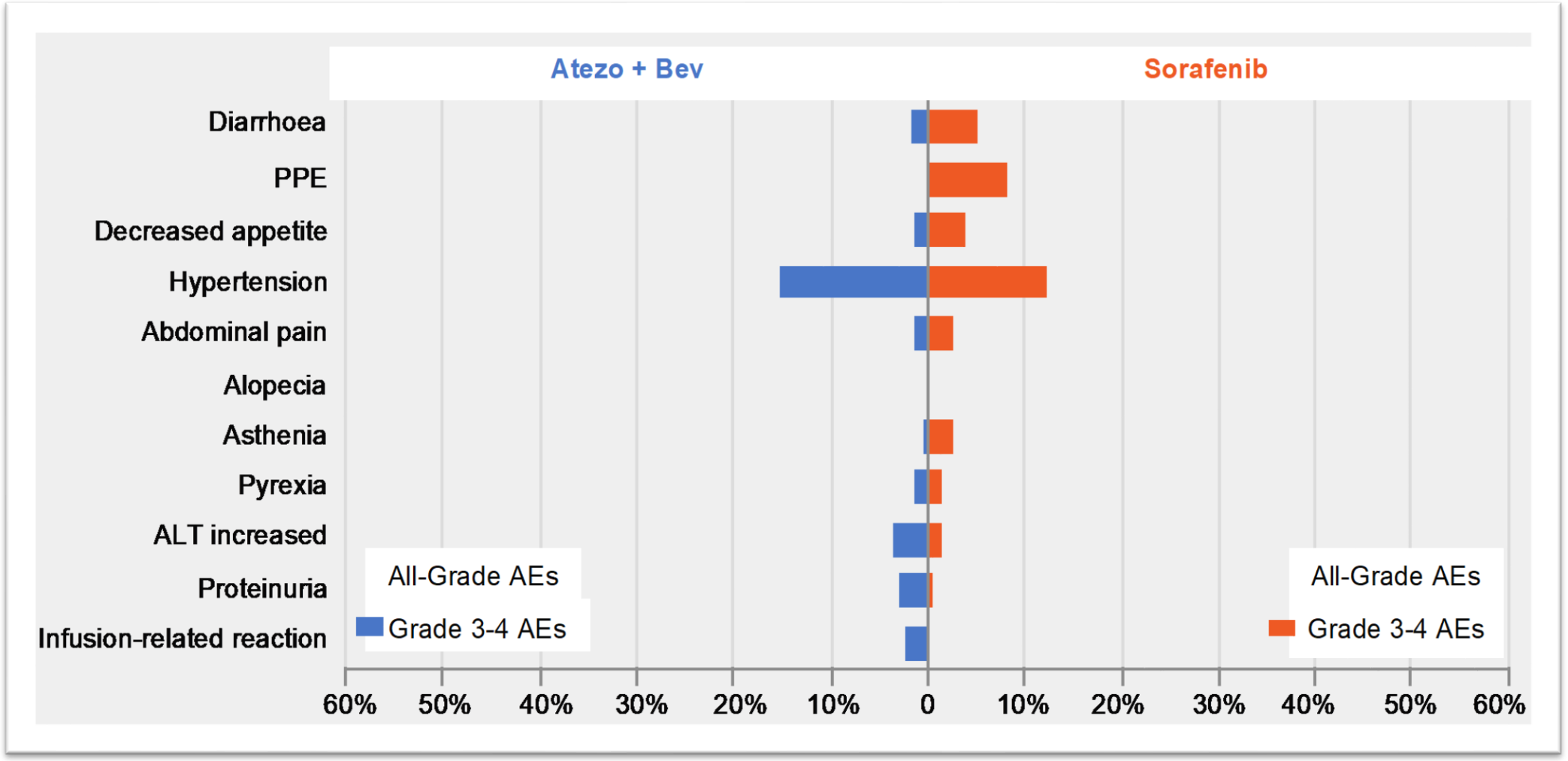
Updated response and duration of response

	Updated analysis[a]			
	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. DCR, disease control rate.
[a] Only patients with measurable disease at baseline were included in the analysis of ORR.
[b] Only confirmed responders were included in the analysis of ORR and DOR.

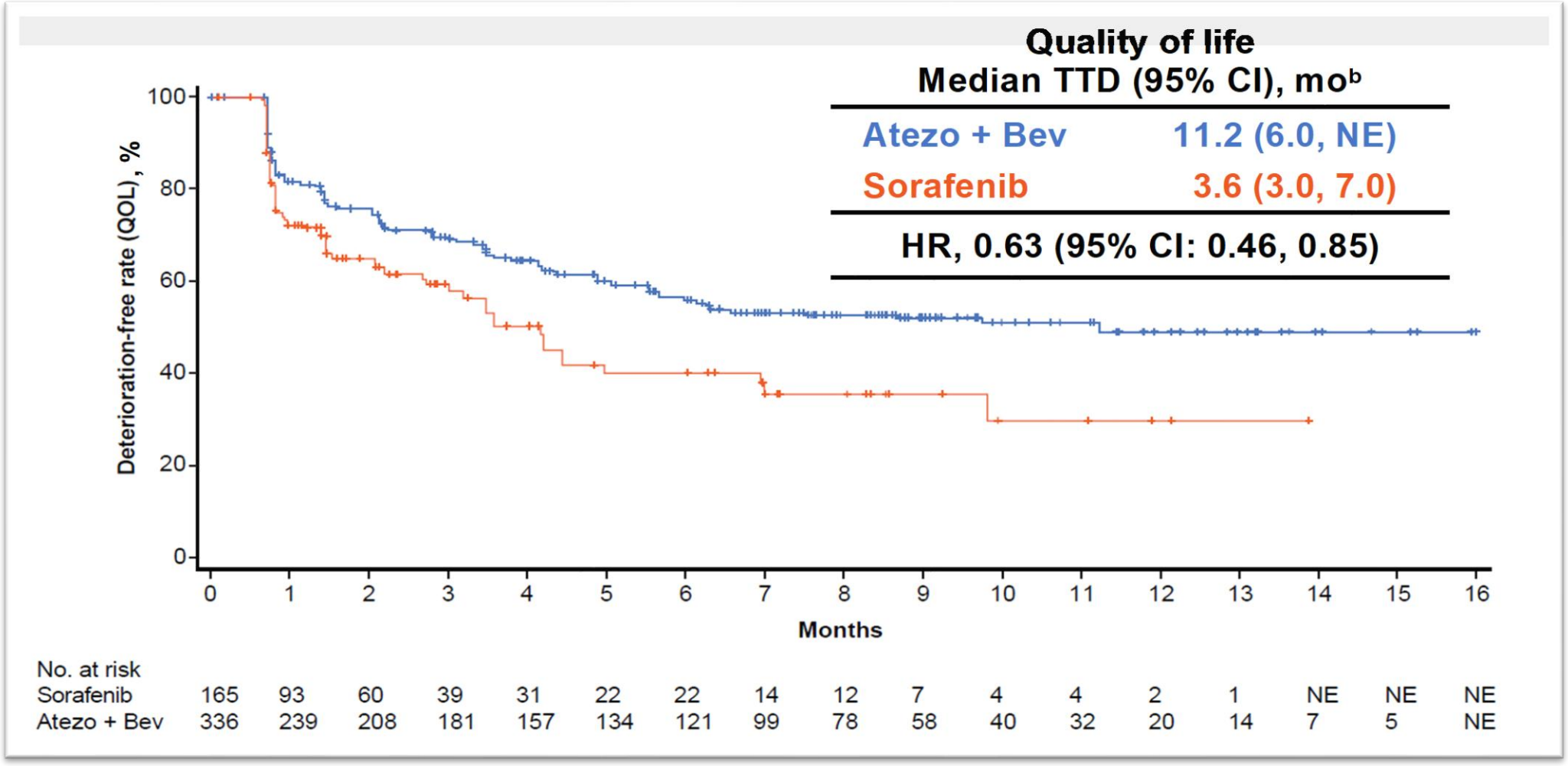
Safety

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



Finn R et al. N Engl J Med 2020; 382:1894-1905

Imbrave 150: Quality of Life – Median Time to Deterioration



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

Finn R et al. N Engl J Med 2020; 382:1894-1905

COSMIC-312: Cabozantinib ± Atezolizumab vs Sorafenib in Advanced HCC

- Multicenter, randomized, open-label phase III trial

Patients with HCC not amenable to curative treatment; no prior systemic therapy; BCLC stage B or C; Child-Pugh A; ECOG PS ≤ 1 (N = ~740)

→

Cabozantinib 40 mg PO QD + **Atezolizumab** 1200 mg IV Q3W

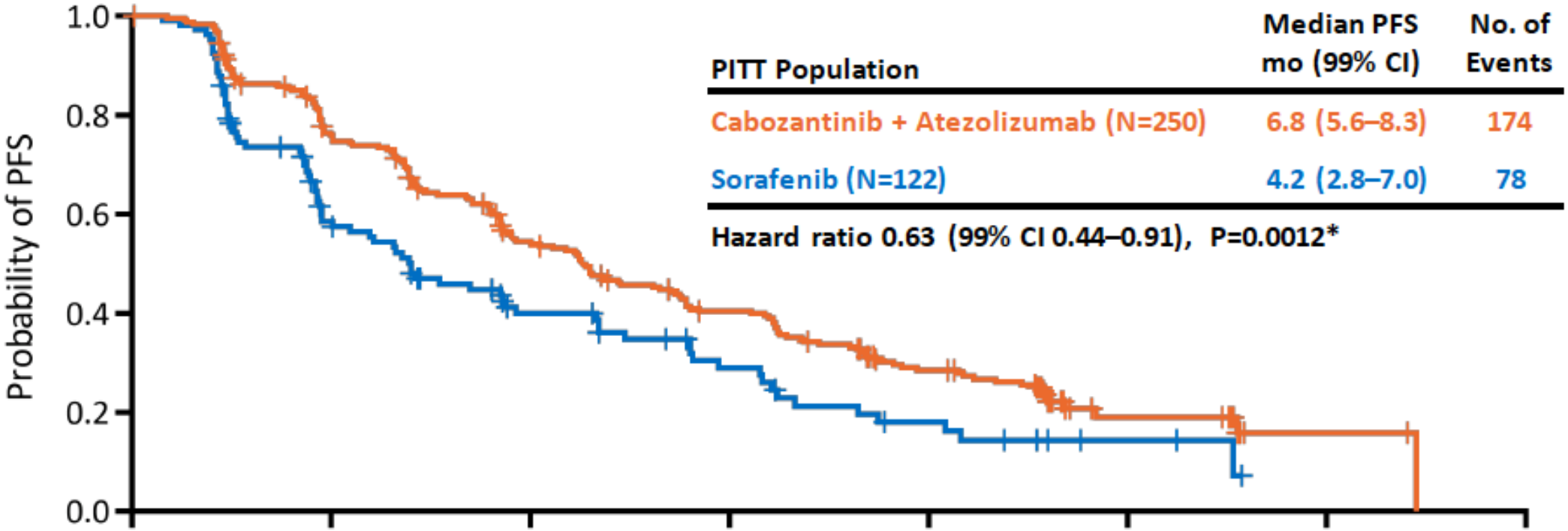
Sorafenib 400 mg PO BD

Cabozantinib 60 mg PO QD

- Primary endpoints: PFS (cabozantinib + atezolizumab vs sorafenib), OS
- Secondary endpoints: PFS (cabozantinib vs sorafenib), ORR, TTP, DoR, safety

Kelley. ASCO 2019. Abstr TPS4157. NCT03755791.

Primary Endpoint of PFS: Final Analysis Cabozantinib + Atezolizumab vs Sorafenib



PITT Population	Median PFS mo (99% CI)	No. of Events
Cabozantinib + Atezolizumab (N=250)	6.8 (5.6–8.3)	174
Sorafenib (N=122)	4.2 (2.8–7.0)	78

Hazard ratio 0.63 (99% CI 0.44–0.91), P=0.0012*

No. at risk								
Cabozantinib + Atezolizumab	250	177	119	84	51	11	2	0
Sorafenib	122	57	32	20	10	3	0	0

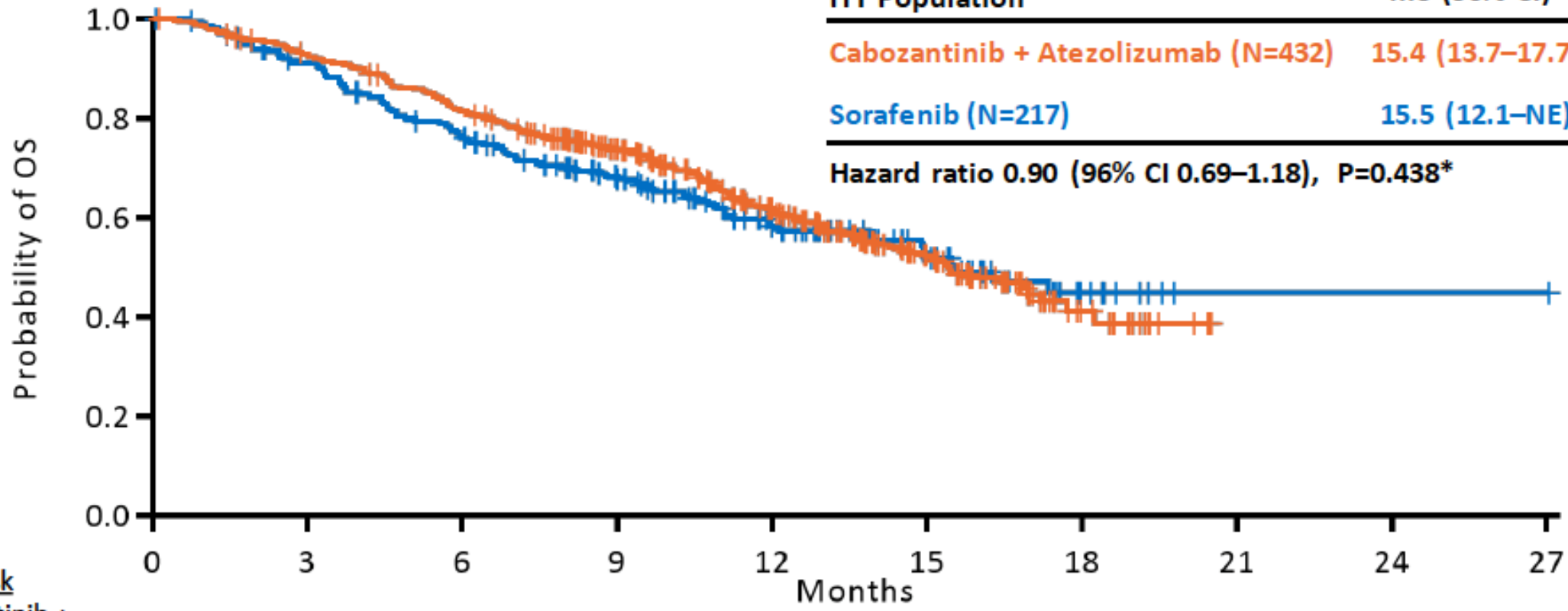
Median follow-up (range): 15.8 (12.8-27.0) months
PFS per RECIST v1.1 by BIRC

*Critical p-value 0.01

Primary Endpoint of Overall Survival: Interim Analysis Cabozantinib + Atezolizumab vs Sorafenib

ITT Population	Median OS mo (96% CI)	No. of Events
Cabozantinib + Atezolizumab (N=432)	15.4 (13.7–17.7)	183
Sorafenib (N=217)	15.5 (12.1–NE)	90

Hazard ratio 0.90 (96% CI 0.69–1.18), P=0.438*



No. at risk										
Cabozantinib + Atezolizumab	432	394	343	268	173	87	18	0	0	0
Sorafenib	217	190	156	116	74	42	12	1	1	1

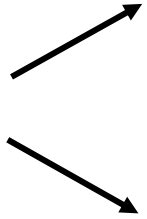
Median follow-up (range): 13.6 (6.4-27.0) months

*Critical p-value 0.01362 for the interim analysis

LEAP-002: First-Line Lenvatinib Plus Pembrolizumab Versus Lenvatinib Plus Placebo in Advanced HCC

- Multicenter, double-blind, phase III trial

Patients with HCC that is not amenable to curative treatment; no previous systemic therapy; Child-Pugh A and ECOG PS ≤ 1 (N = 750)



Lenvatinib PO QD* + **Pembrolizumab** 200 mg IV Q3W

Lenvatinib PO QD* + Placebo IV Q3W

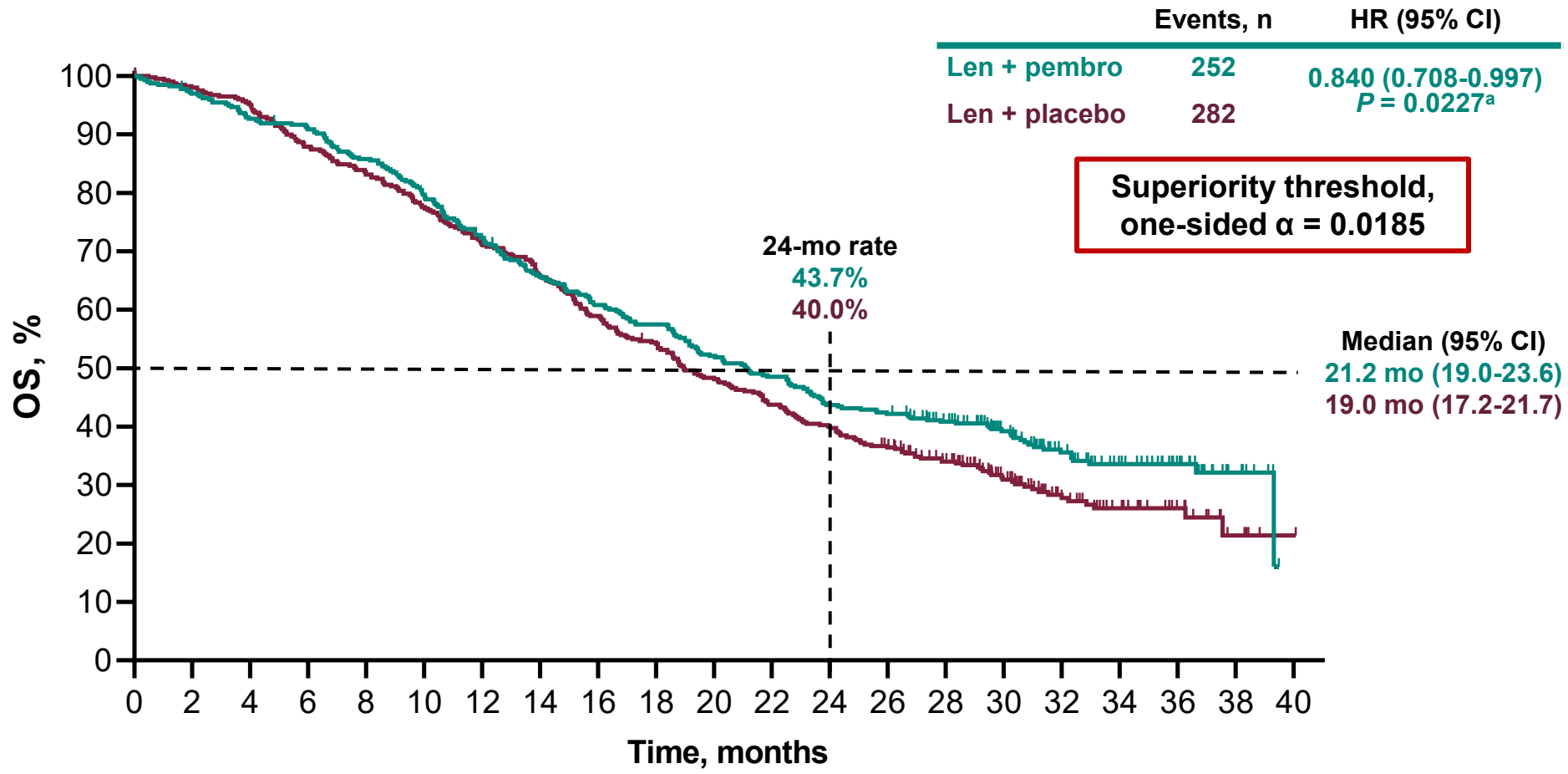
Treatment until PD, intolerable toxicity, or 36 cycles of pembrolizumab or placebo

*Body weight < 60 kg, 8 mg; body weight ≥ 60 kg, 12 mg.

- Primary endpoints: PFS, OS
- Secondary endpoints: ORR, DoR, DCR, TTP, safety

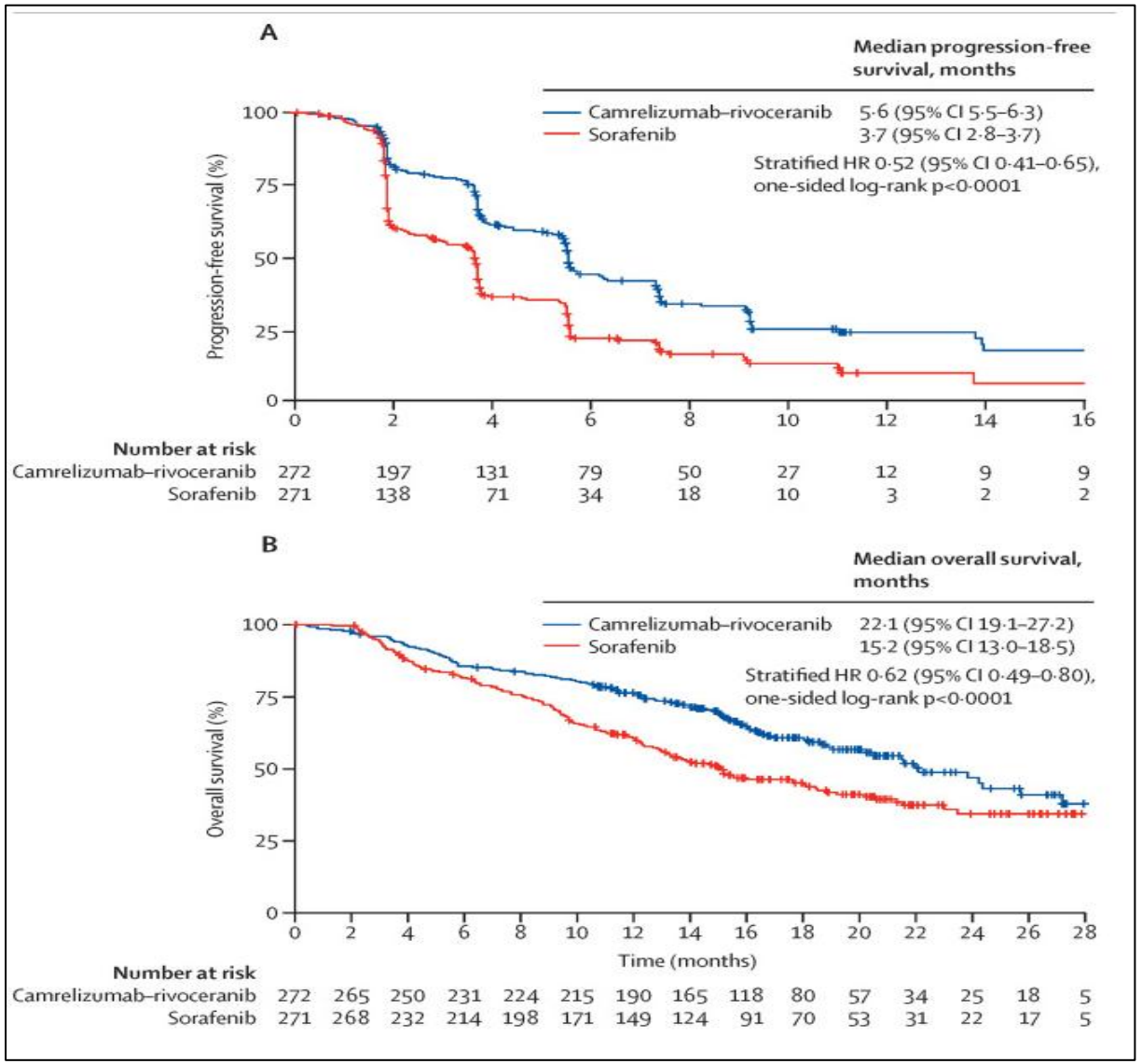
Llovet. ASCO 2019. Abstr TPS4152. NCT03713593.

Overall Survival, ITT, FA



[a]Did not reach superiority threshold, one-sided α=0.0185.
Data cutoff date for FA: 21 June 2022; median follow-up: 32.1 months.

Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310)



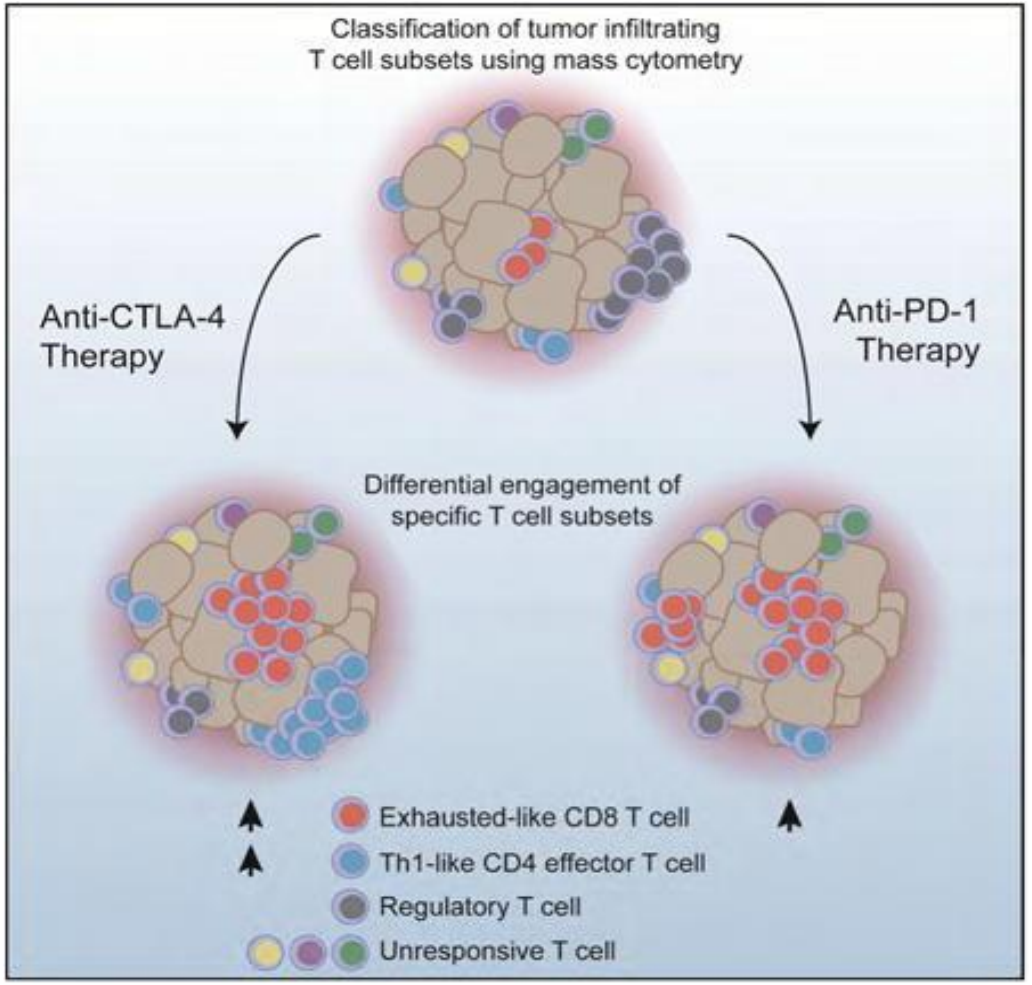
Combination of anti PD-1/PD-L1 and anti CTLA-4

Targeting PD-1/ PD-L1

- Affects differentiated CD8+ T cells in tumor microenvironment
- Does not increase clonal diversity
- Does not move T cells into tumors
- Single agent activity in HCC
  - ORR 15 to 20%

Targeting CTLA-4

- Blocks suppressive T cell signaling in lymph nodes
- Modulates CD4 effector compartment
  - Expands ICOS+Th1 like effector subsets
- Single agent tremelimumab activity
  - ORR 17.6%



J Immunother Cancer. 2018; 6
Wei SC et al, Cell 2017
Rotte A, J Exp Clin Cancer Res 2019

Sangro B et al. J Hepatol. 2013
El-Khoueiry A et al, Lancet 2017
Zhu AX, et al. Lancet Oncol. 2018
Kelley RK et al, J Clin Oncol. 2021

HIMALAYA study design

HIMALAYA was an open-label, multicenter, global, Phase 3 trial

Study population
- Patients with confirmed uHCC
- BCLC B (not eligible for locoregional therapy) and C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

Stratification factors
- Macrovascular invasion: Y / N
- Etiology of liver disease: HBV / HCV / others
- Performance status: ECOG 0 / 1

R
N=1324

T300+D (n=393):
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

Durvalumab (n=389):
Durvalumab monotherapy 1500 mg Q4W*

Sorafenib (n=389):
Sorafenib 400 mg BID*

T75+D (n=153): *arm closed* †
Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

Primary objective
- OS for T300+D vs sorafenib

Key secondary objective
- OS for durvalumab vs sorafenib

Additional secondary objectives
- PFS, ORR, and DoR as assessed by investigator per RECIST v1.1
- Safety

Multiple testing procedure

OS *superiority* for T300+D vs sorafenib

↓

OS *noninferiority* for durvalumab vs sorafenib
Noninferiority margin: 1.08

↓

OS *superiority* for durvalumab vs sorafenib

*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.

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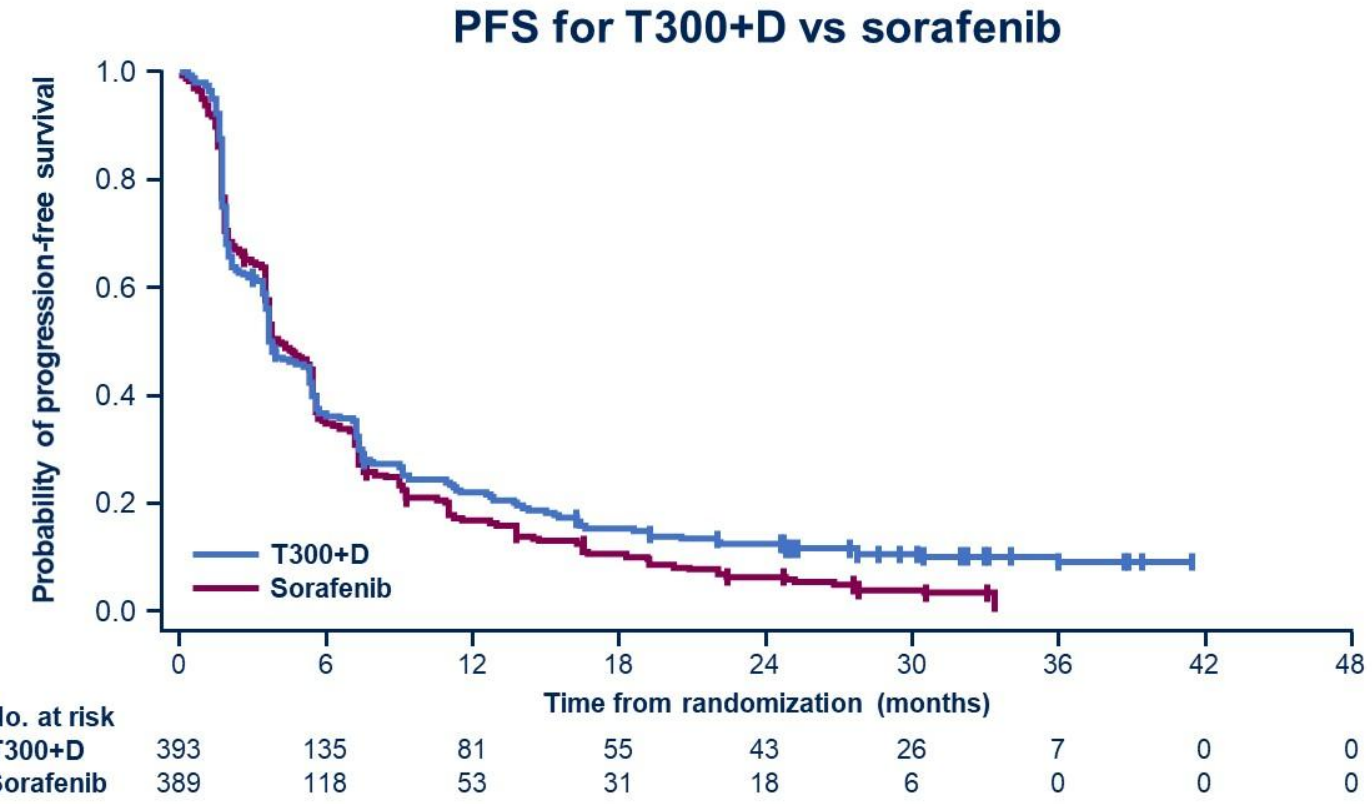
Progression-free survival

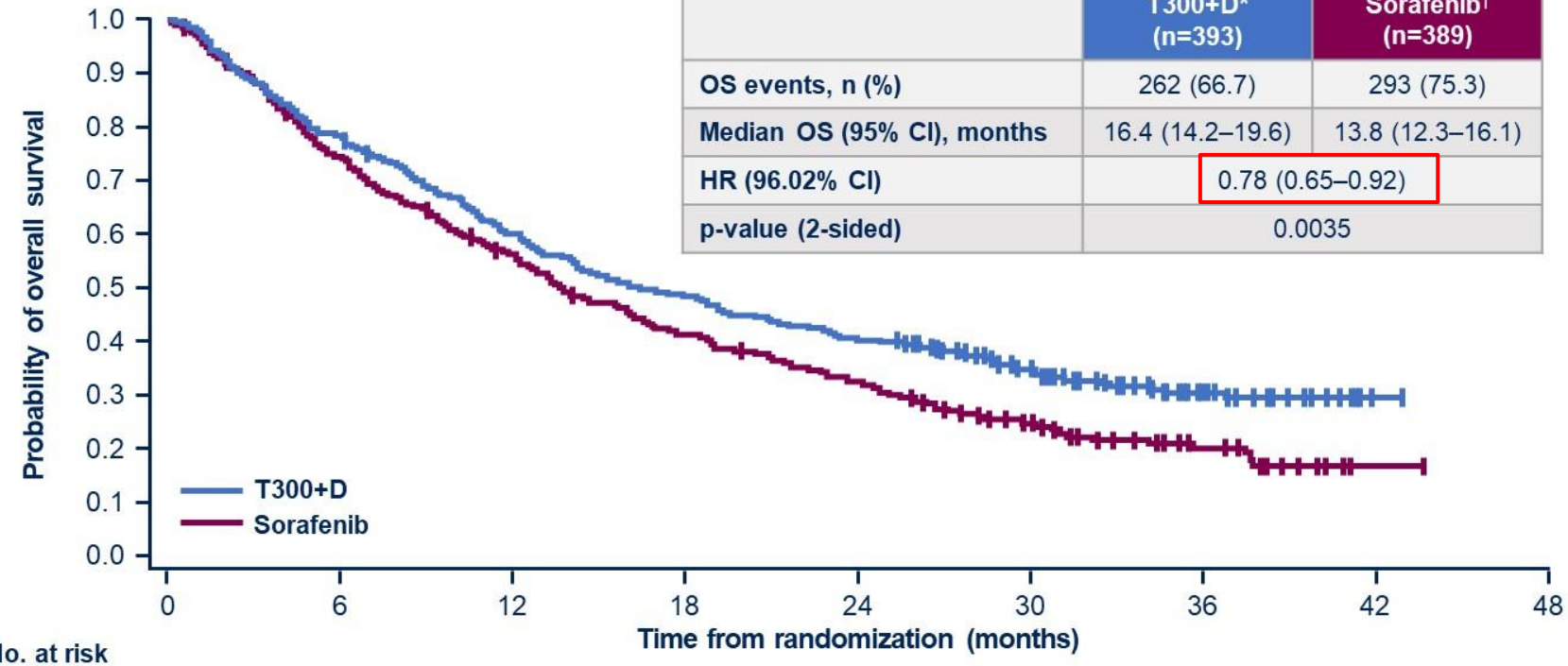


	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
PFS events, n (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68–5.32)	3.65 (3.19–3.75)	4.07 (3.75–5.49)
PFS HR* (95% CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	–
Progression-free at DCO, n (%)	49 (12.5)	32 (8.2)	19 (4.9)
Median TTP (95% CI), months	5.42 (3.81–5.62)	3.75 (3.68–5.42)	5.55 (5.13–5.75)
Treated ≥1 cycle beyond progression, n (%)†	182 (46.9)	188 (48.5)	134 (34.4)

*Versus sorafenib. †Percent calculated from total patients in the safety analysis set: T300+D, N=388; durvalumab, N=388, sorafenib, n=374.
CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTP, time to progression.

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

- HIMALAYA met its primary endpoint: T300+D was superior to sorafenib for OS
- T300+D appeared to have a long-term survival benefit in this mature dataset with substantial follow-up time

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. *Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W. †Sorafenib 400 mg BID.

CI, confidence interval; HR, hazard ratio; OS, overall survival.

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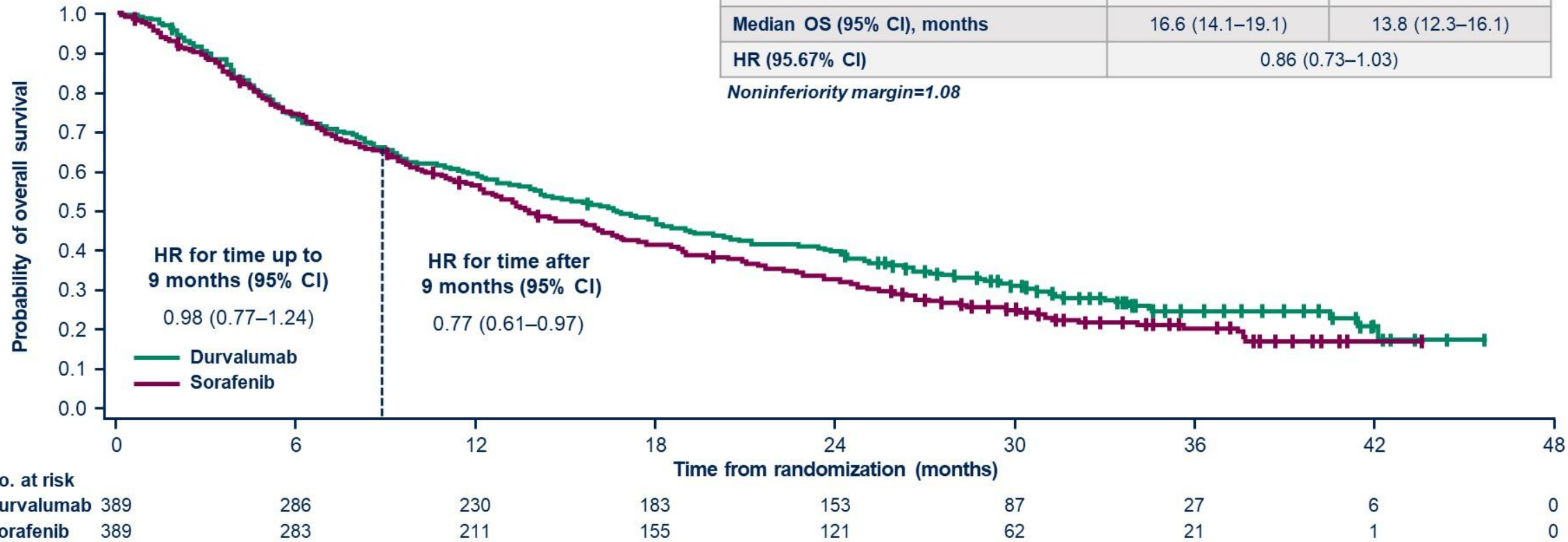
Secondary objective: overall survival for durvalumab vs sorafenib

	Durvalumab (n=389)	Sorafenib (n=389)
OS events, n (%)	280 (72.0)	293 (75.3)
Median OS (95% CI), months	16.6 (14.1–19.1)	13.8 (12.3–16.1)
HR (95.67% CI)	0.86 (0.73–1.03)	

Noninferiority margin=1.08



No. at risk									
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 32.56 (95% CI, 31.57–33.71) months for durvalumab and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

CI, confidence interval; HR, hazard ratio; NI, noninferiority; OS, overall survival.

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Tumor response

	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* n (%)	**79 (20.1)**	**66 (17.0)**	**20 (5.1)**
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months 25th percentile 75th percentile	22.34 8.54 NR	16.82 7.43 NR	18.43 6.51 25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ % 6 months 12 months	 82.3 65.8	 81.8 57.8	 78.9 63.2

*By investigator assessment according to RECIST v1.1. Responses are confirmed. †Defined as neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD. ‡Calculated using Kaplan-Meier technique.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTR, time to response.

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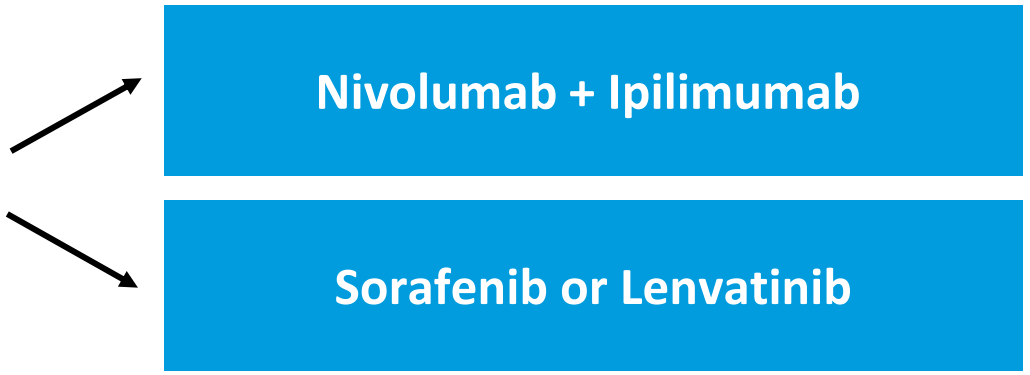
Himalaya: immune mediated events

Event, n (%)	STRIDE (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypophysitis	4 (1.0)	0	1 (0.3)	0	1 (0.3)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Thyroiditis	6 (1.5)	0	1 (0.3)	0	2 (0.5)	0	0	0
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0

CheckMate 9DW: Nivolumab + Ipilimumab vs Sorafenib or Lenvatinib as First-Line Treatment for Advanced HCC

- Multicenter, randomized, open-label, phase III trial

Patients with advanced HCC; no previous systemic therapy,
Child-Pugh 5 or 6;
ECOG PS ≤ 1
(Planned N = 1084)



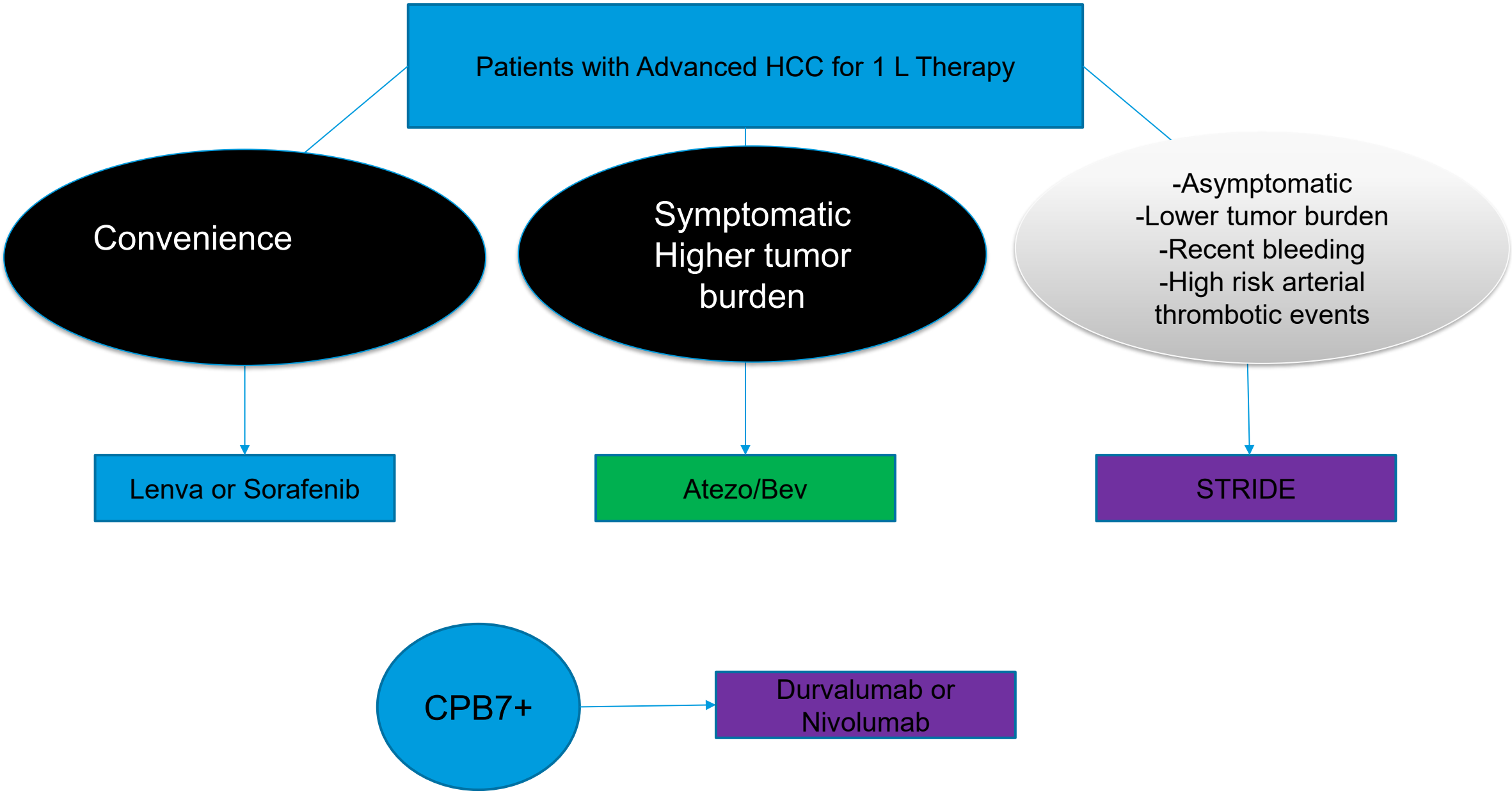
- Primary endpoints: OS
- Secondary endpoints: ORR, DOR, TTSD

NCT04039607.

Approved combinations in 1L HCC

	IMBRAVE 150		HIMALAYA	
	Atezo/Bev	Sorafenib	STRIDE	Sorafenib
mOS (mo)	19.2 HR 0.66 (0.52,0.85)	13.4	16.4 HR 0.78 (0.65-0.92)	13.8
mPFS (mo)	6.9 HR 0.65(0.53,0.81)	4.3	3.78 HR 0.9 (0.77-1.05)	4.07
ORR (RECIST 1.1)	30%	11%	20.1%	5.1%
CR	8%		3.1%	
PD	19%		39.9%	
Median DoR (months)	18.1	14.9	22.3	18.4
DCR	74%	55%	60.1%	60.7%
Discontinuation due to AEs	22%		13.4%	
≥ Grade 3 TRAEs	43%		25.8%	
IMAEs requiring steroids	12.2%		20.1%	
All grade bleeding events	25%	17.3%	1.8%	4.8%
Grade 3/4 bleeding events	6.4%	5.8%	0.5%	1.6%

Bleeding events less common in HIMALAYA but trial did exclude patients with main PVT who are at highest risk for bleeding



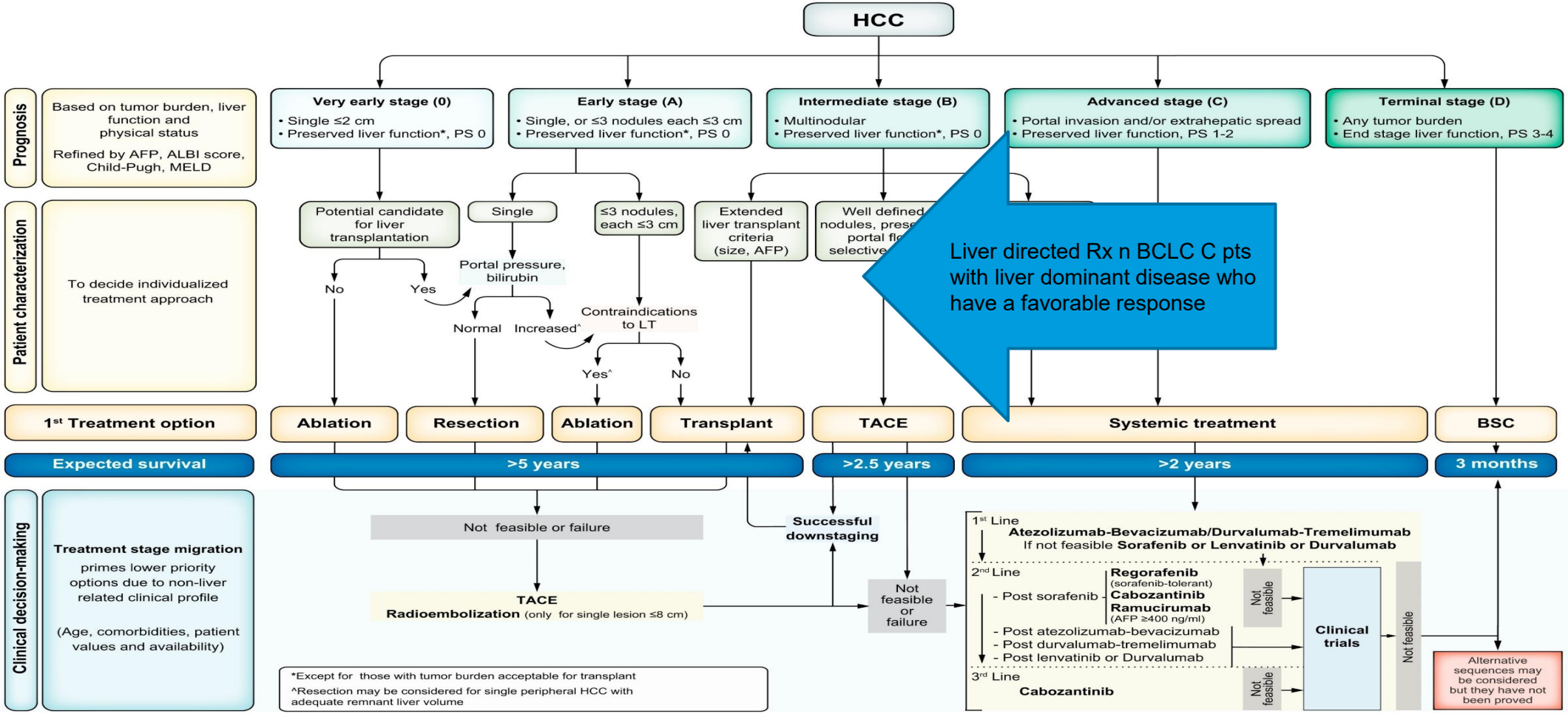
SUMMARY OF EFFICACY AND SAFETY DATA ACROSS SECOND-LINE ANTI-VEGF STUDIES IN HCC

		CELESTIAL[1]		RESORCE[2]	REACH-2[3,4]
		PHASE III		PHASE III	PHASE III
		CABOZANTINIB VS PLACEBO		REGORAFENIB VS PLACEBO (N=379 VS 194)	RAMUCIRUMAB VS PLACEBO (N=197 VS 95)
		ITT (N=470 VS 237)	2L (N=331 VS 164)		
EFFICACY	**MEDIAN OS, MONTHS** **HR (95% CI); *P* VALUE**	10.2 VS 8.0 0.76 (0.63-0.92); 0.005	11.3 VS 7.2 0.70 (0.55-0.88)	10.6 VS 7.8 0.63 (0.50-0.79); <0.0001	8.5 VS 7.3 0.710 (0.531-0.949); 0.0199
EFFICACY	**MEDIAN TTP, MONTHS** **HR (95% CI); *P* VALUE**	–	–	3.9 VS 1.5 0.41 (0.34-0.51); <0.0001	3.0 VS 1.6 0.427 (0.313-0.582); <0.0001
EFFICACY	**MEDIAN PFS*, MONTHS** **HR (95% CI); *P* VALUE**	5.2 VS 1.9 0.44 (0.36-0.52); <0.001	5.5 VS 1.9 0.40 (0.32-0.50)	3.4 VS 1.5 0.43 (0.35-0.52); <0.0001	2.8 VS 1.6 0.452 (0.339-0.603); <0.0001
EFFICACY	**ORR*, %** **PD, %**	4 VS <1 21 VS 55	–	7 VS 3 22 VS 57	4.6 VS 1.1 33.5 VS 50.5
EFFICACY	**MEDIAN DOR†, MONTHS**	–	–	3.5 VS 2.7	–
SAFETY		**(N=467 VS 237)**	**–**	**(N=374 VS 193)**	**(N=197 VS 95)**
SAFETY	**ANY GRADE AES, %**	99 VS 92	–	100 VS 93	97.0 VS 86.3
SAFETY	**GRADE 3/4 AES, %**	68 VS 36	–	66 VS 39	58.9 VS 44.2

Future Practical Considerations

- Child's Pugh B score HCC patients remain a challenge
- Biomarker Discovery is key to better selection of patients with HCC
- Explore in earlier disease stages: LR combination, adjuvant and neoadjuvant settings etc …

Intersectionality of Systemic and LR Modalities : "Reverse" Treatment Stage Migration



Reig M et al, J of Hepatology 2022

Intersectionality of Systemic and LR Modalities : More Questions Needing an Answer

- Positive adjuvant data (IMBRAVE 050): impact on treatment after recurrence
- Positive data from EMERALD-1 combining systemic and liver directed therapy

IMbrave050 study design

Patient Population
- Confirmed first diagnosis of HCC and had undergone curative resection or ablation
- Disease free
- Child-Pugh class A
- High risk of recurrence[a]
- No extrahepatic disease or macrovascular invasion (except Vp1/Vp2)
- ECOG PS 0 or 1

4-12 weeks

1 cycle of TACE, if indicated

R 1:1

12 months or 17 cycles

Atezolizumab 1200 mg q3w + bevacizumab 15 mg/kg q3w (n=334)

Active surveillance (n=334)

Recurrence[b] or unacceptable toxicity

Survival follow-up

Crossover permitted

Stratification
- Region (APAC excluding Japan vs rest of world)
- High-risk features and procedures:
  - Ablation
  - Resection, 1 risk feature, adjuvant TACE (yes vs no)
  - Resection, ≥2 risk features, adjuvant TACE (yes vs no)

Primary endpoint
- Recurrence-free survival assessed by the independent review facility[b]

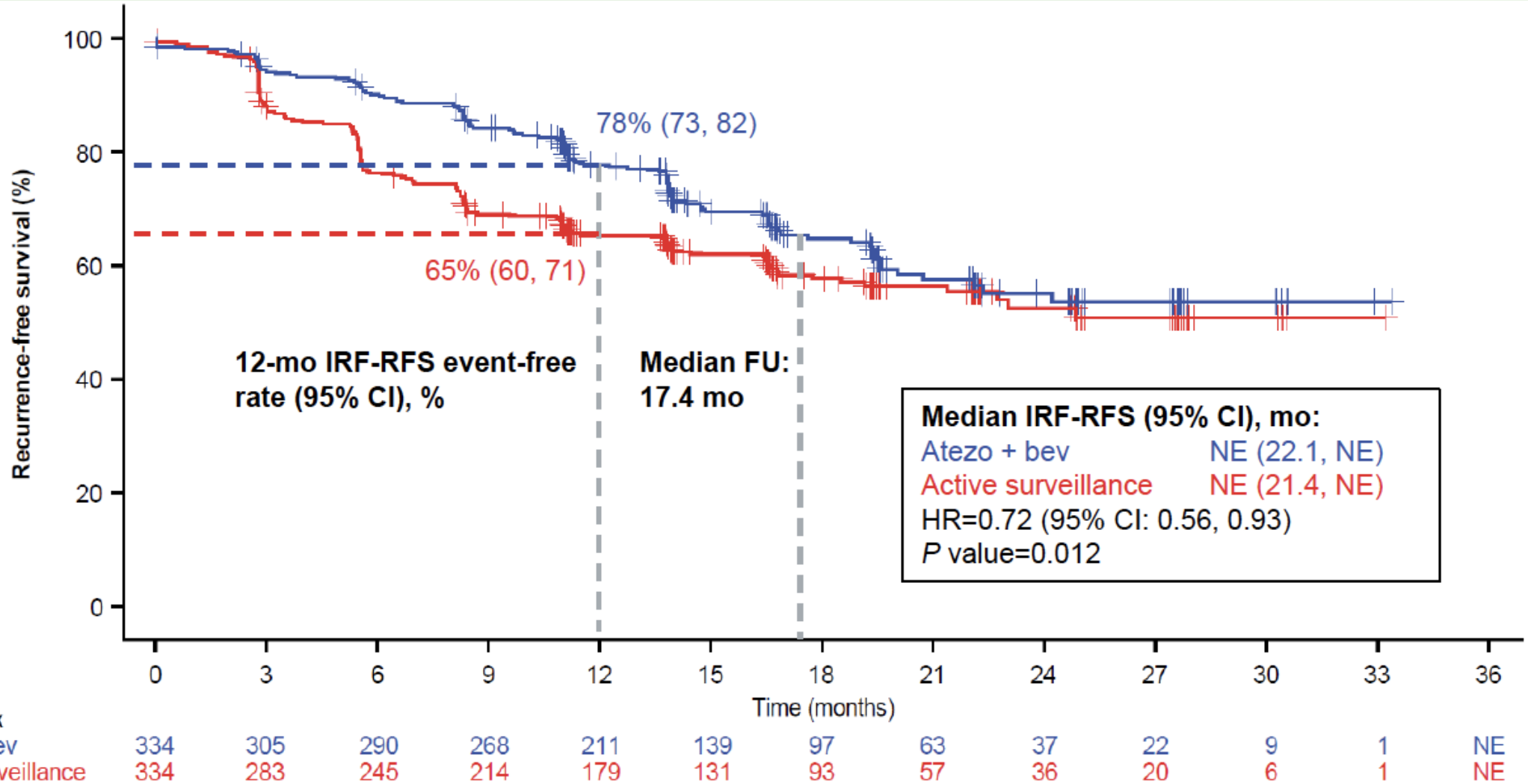
ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; R, randomization; TACE, transarterial chemoembolization.

[a] **High-risk features** include: tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology.

[b] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.

Chow et al IMbrave050
https://bit.ly/3ZPKzqM 5

Primary endpoint: IRF-assessed RFS was significantly improved with atezo + bev vs active surveillance



No. at risk

Atezo + bev	334	305	290	268	211	139	97	63	37	22	9	1	NE
Active surveillance	334	283	245	214	179	131	93	57	36	20	6	1	NE

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

Chow et al IMbrave050
https://bit.ly/3ZPKzgM 12

Imbrave 050: Initial thoughts

- Is RFS clinically meaningful endpoint?
- OS pending
- How about lower risk patients?

Intersectionality of Systemic and LR Modalities : More Questions Needing an Answer

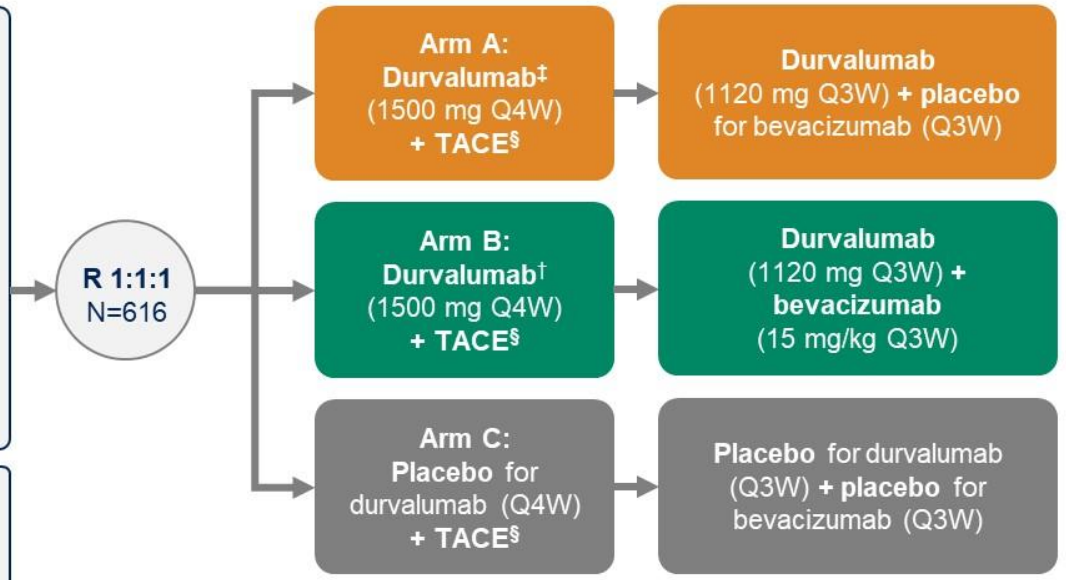
- Positive adjuvant data (IMBRAVE 050): impact on treatment after recurrence
- Positive data from EMERALD-1 combining systemic and liver directed therapy

EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)



Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

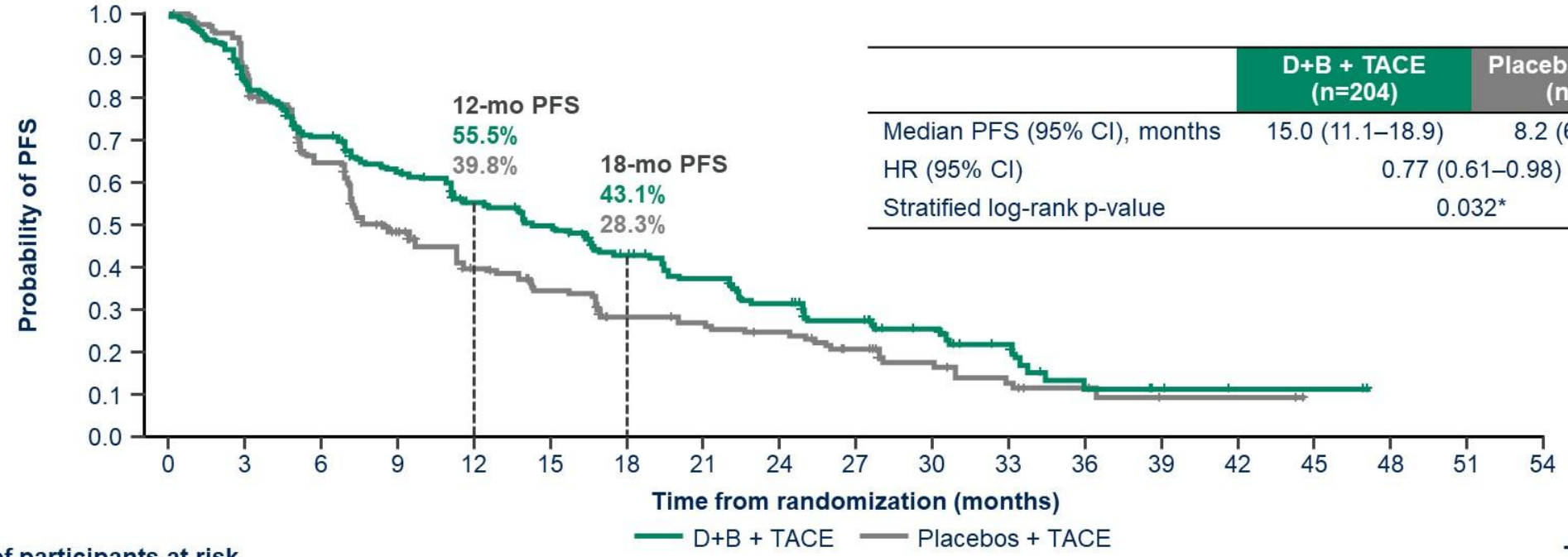
*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡Durvalumab / placebo started ≥7 days after TACE. §DEB-TACE or cTACE. Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure. ‖Only new lesions consistent with progression that were not eligible for TACE occurring prior to the first on study imaging at 12 weeks were considered progression events; standard mRECIST progression criteria were used after the 12-week imaging.

BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead-transarterial chemoembolization; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W / Q4W, every 3 / 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

PRESENTED BY: Riccardo Lencioni, MD

PFS with D+B + TACE versus placebos + TACE: primary endpoint

Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

No. of participants at risk																			Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

Median (range) duration of follow-up in censored participants, D+B + TACE 16.7 (0.03–47.1) months, Placebos + TACE 10.3 (0.03–44.3) months. **Median (95% CI) duration of follow-up** in all participants using the reverse Kaplan-Meier method, D+B + TACE 22.2 (16.7–27.3) months, Placebos + TACE 26.3 (16.7–30.4) months. PFS was assessed by BICR (RECIST v1.1)

*The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mo, months, PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

PRESENTED BY: Riccardo Lencioni, MD

Future Directions

Adjuvant phase III studies (end-point: RFS)

- KEYNOTE 937: Pembrolizumab vs placebo
- CheckMate 9DX: Nivolumab vs placebo
- EMERALD-2: Durvalumab +/- bevacizumab vs placebo
- JUPITER 04: Toripalimab vs placebo

Phase III studies

- LEAP 012: Lenvatinib + pembrolizumab + TACE vs TACE
- EMERALD-3: Durvalumab+ tremelimumab+/- lenvatinib + TACE vs TACE
- REPLACE: Regorafenib + Pembrolizumab vs TACE/TARE
- ABC-HCC: Atezolizumab +bevacizumab vs TACE

Llovet J . ASCO GI 2024

CASES

CASE-HCC

54-year-old with a history of hepatitis C was diagnosed with multifocal HCC March 17, 2022. One of the larger liver lesion biopsy confirmed HCC.

- Tecentriq, Avastin (April 28, 2022 Feb 2023- Progressed)
- Cabozantinib (February - April 20, 2023; held d/t worsening hand-foot syndrome)
- Cabozantinib 20mg (May 11, 2023 - August 15, 2023)
- Lenvatinib (August 22, 2023 -November 13, 2023; progressed)
- Regorafenib (November 14, 2023 Feb 2024- Progressed)
- Palliative RT to right upper anterior chest wall mass (November 20, 2023 - December 13, 2023)
- Enrolled in hospice in February 2024, but started to feel better and came off hospice to consider further therapy. (AFP prior to palliative XRT was 48232, went down to 31115 post XRT and recently on 3/26/2024 was down to 2995)
- Restaging scans on 4/4/2024 showed mixed pattern of response and progression pulmonary metastatic disease and multifocal HCC.

- What treatment options patient has at this point?

Reedy

Thank you

CASE - HCC

70 y/o male with History of hepatitis C with underlying cirrhosis, status post resection of a T1b hepatocellular carcinoma involving the left side of the liver, moderately differentiated, measuring 7.4 cm with extensive background liver cirrhosis with no vascular involvement and negative margins, status post surgical resection December 2022, followed by observation.

- Disease recurrence, March 2024, with right adrenal mass.
- Surgical resection, March 15, 2024, with right adrenal gland excision with well to moderately differentiated hepatocellular carcinoma with tumor present at inked resection margin with tumor involving the retroperitoneum and part of the liver with extensive need for blood transfusion.
- Postoperative course complicated by right upper extremity radial artery thrombosis and jugular venous system thrombosis treated with anticoagulation.

Questions

- How do we choose between stride regimen and Atezo/bev if paient eligible for both regimens?
- Does the underlying cause of liver disease factor into decision making?

Brenner

Q :

1. Review standard of care for 1st, 2nd and 3rd line treatment of advanced HCC
2. Understand how HCPs think about the differences between the results of 1L IO uHCC trial design and inclusion criteria, efficacy and safety data. What has value
    - Does rapidity of response matter? (T+A; OS KM curve separation at 2 mos)
    - Patient characteristics: included patients with VP4; Patient reported outcomes available)
3. Assess Impact of Emerald One Clinical trial
    - Is VEGF the multiplier that makes the difference in outcomes. 40% dont receive Atezo-Bev
4. Is EGD still barrier to Atezo-Bev use
5. Interactive case discussions to highlight key objectives and gain strategic insights (for consideration: include a Patient with manageable varices/CP-B/VP4 patient)
6. Is treatment of B different than A?

Thank you

