MAYO CLINIC

HEPATOCELLULAR CARCINOMA: ARE WE FINALLY MAKING PROGRESS?

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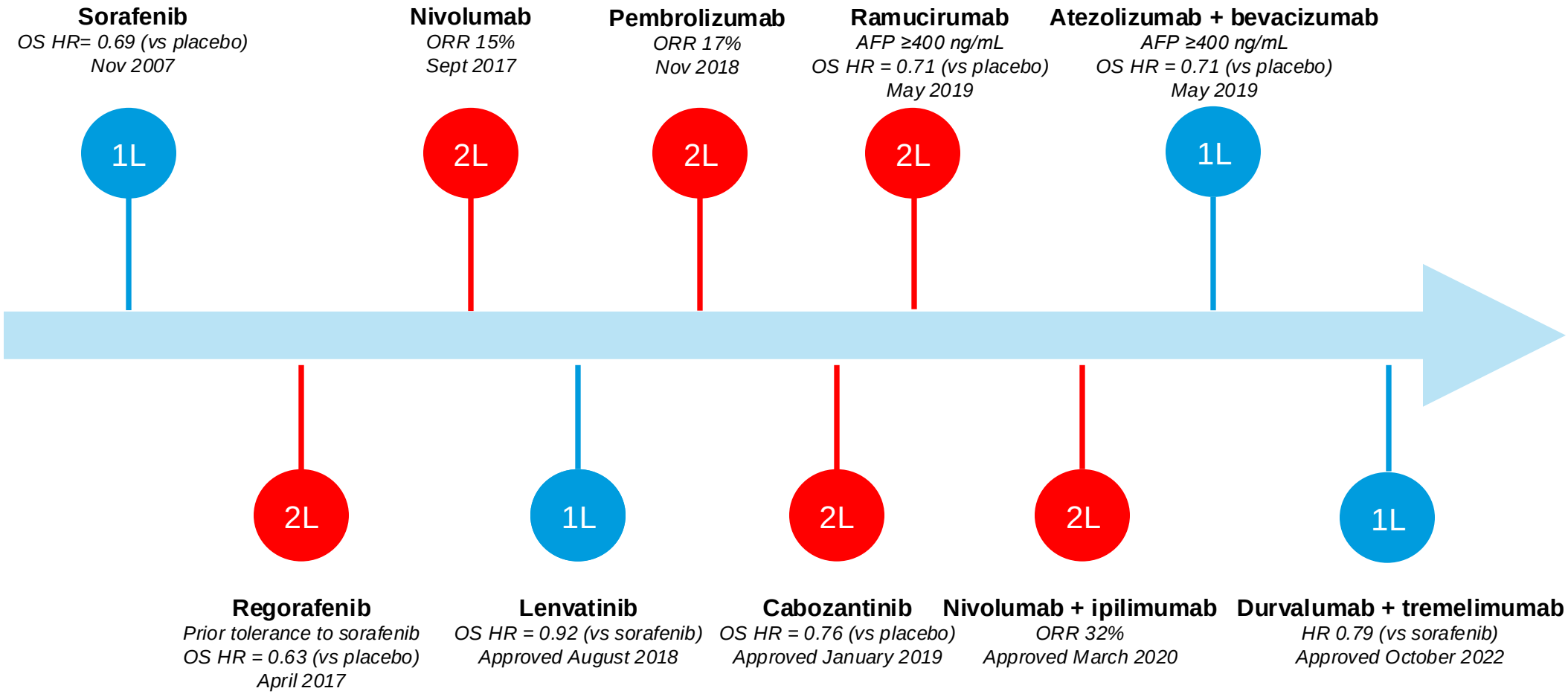
OUTLINE

- Updates in treatment landscape in HCC
  - First line clinical trials
  - Refractory clinical trials
- Future directions and considerations in HCC

TREATMENT LANDSCAPE IN HCC HAS RAPIDLY EVOLVED OVER THE PAST 7 YEARS

FROM A *"POST SORAFENIB AREA"* TO *"POST IO" ERA*



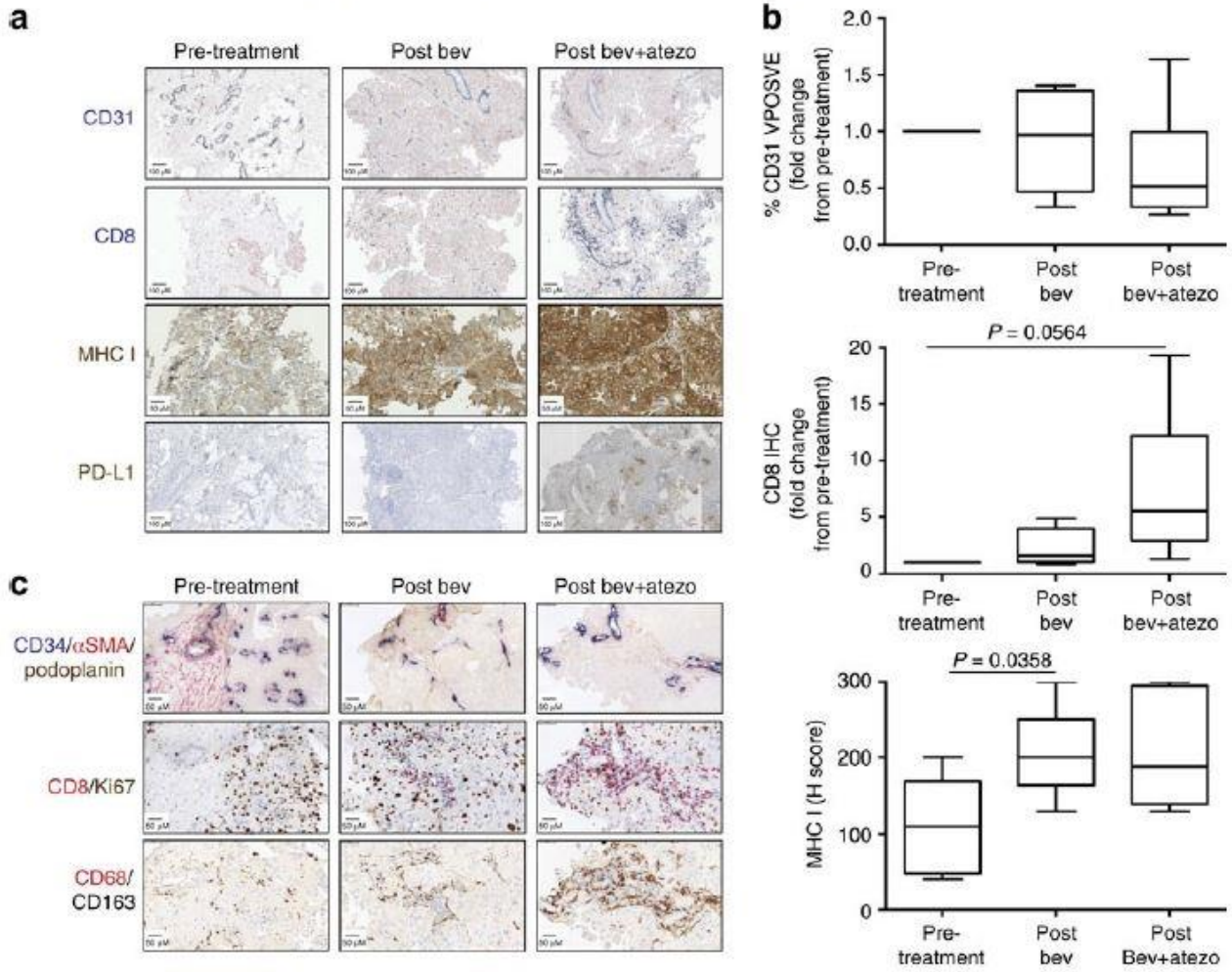
COMBINATION ANTI PD-1/PD-L1 AND ANTI VEGF

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

IMBRAVE 150: STUDY DESIGN

ELIGIBILITY CRITERIA **(N=501)***

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy for HCC
- ≥1 measurable untreated lesion
- Child-Pugh A
- ECOG PS 0/1
- Patients were required to be evaluated for the presence of varices within 6 months prior to treatment (assessed with EGD and treated according to local clinical practice), and were excluded if they had variceal bleeding, untreated or incompletely treated varices with bleeding, or high risk of bleeding

Atezolizumab 1200 mg IV q3w
+
Bevacizumab 15 mg/kg IV q3w
(N=336)

Randomization 2:1
No crossover allowed

Sorafenib 400 mg po bid
(N=165)

Treatment until loss of clinical benefit or unacceptable toxicity

Primary endpoint

- OS and PFS (IRF per RECIST v1.1)

Secondary endpoint

- PFS (investigator per RECIST v1.1, IRF per mRECIST)
- ORR, TTP, DOR (investigator per RECIST v1.1, IRF per RECIST v1.1, mRECIST)
- QOL and safety

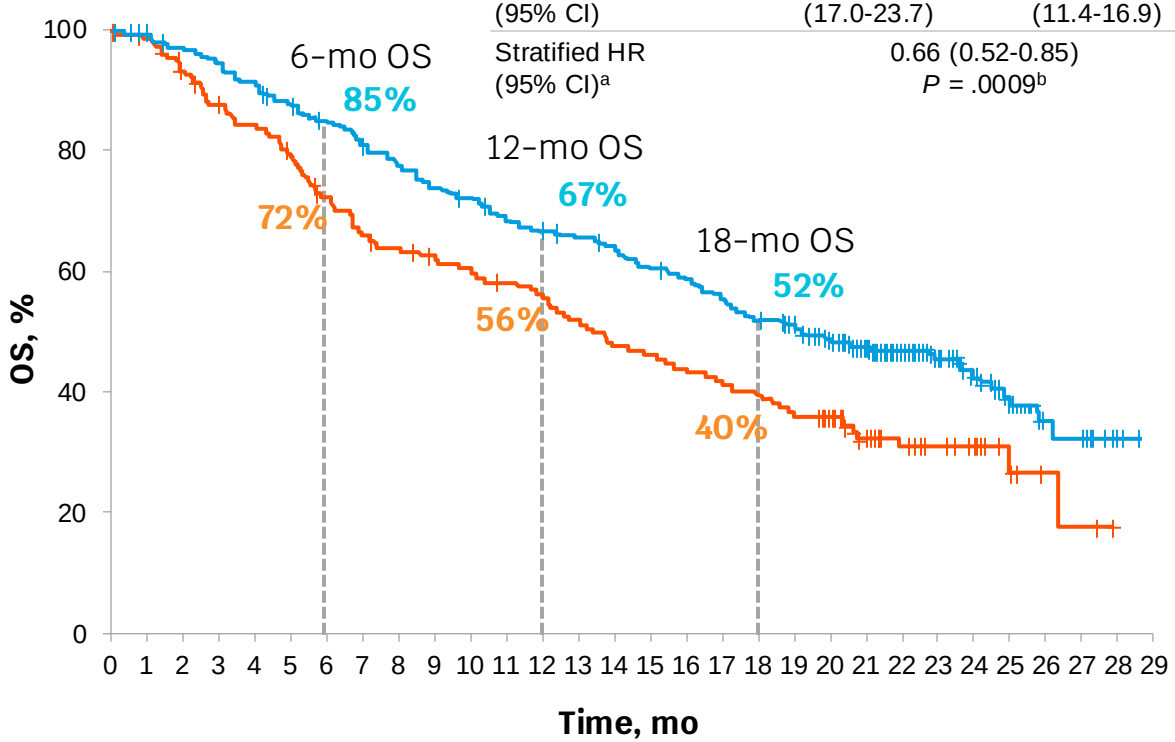
Label does not limit utilization by Child Pugh status.

Finn RS, et al. N Engl J Med. 2020;382(20):1894-1905. Cheng AL, et al. Presented at: ESMO Asia. 2019 (abstr LBA3).

IMBRAVE150: EFFICACY

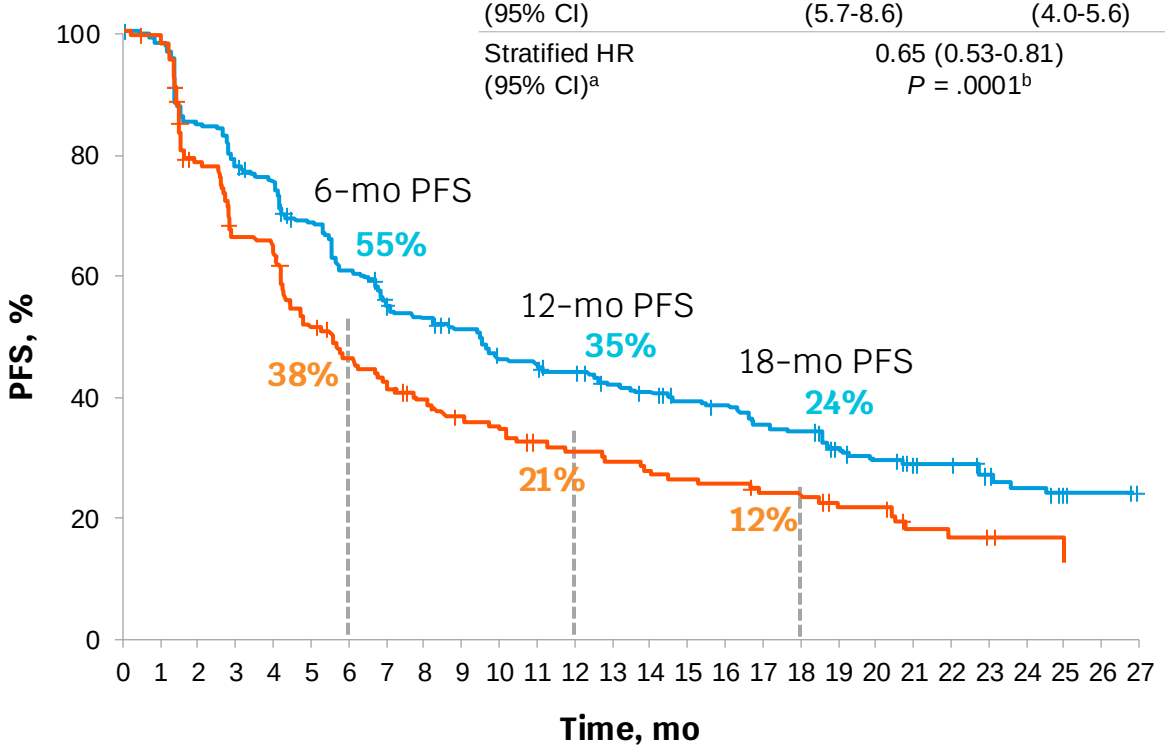
Overall Survival

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* = .0009[b]	



Progression-Free Survival

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* = .0001[b]	



- **With an additional 12 months of follow-up**
  - ORR/CR per RECIST v1.1: 30%/8% vs 11%/<1%
  - Safety and tolerability remains consistent with known safety profiles

1. Finn RS, et al. ASCO GI 2021 2. Finn, RS, et al. NEJM 2020

IMBRAVE 150: EFFICACY

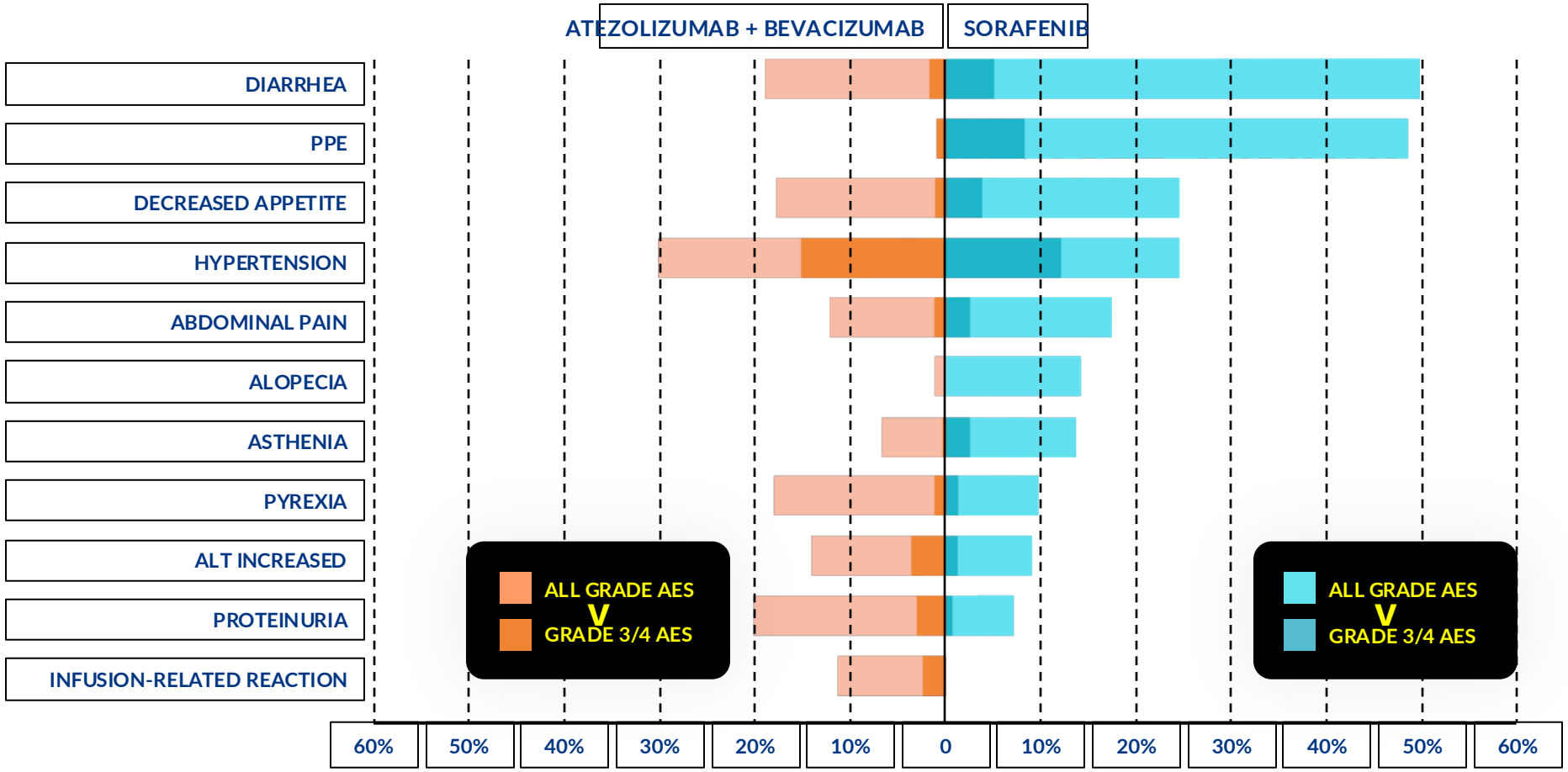
	Atezolizumab plus bevacizumab (n=326)	Sorafenib (n=159)
Objective response, n (%) [95% CI]	97 (30) [25-35]	18 (11) [7-17]
Complete response, n (%)	25 (8)	1 (<1)
Partial response, n (%)	72 (22)	17 (11)
Stable disease, n (%)	144 (44)	69 (43)
Disease control rate, n (%)	241 (74)	87 (55)
Progressive disease, n (%)	63 (19)	40 (25)
Patients with ongoing response, n (%)	54 (56)	5 (28)
Duration of response, median (95% CI), months*	18.1 (14.6-NE)	14.9 (4.9-17.0)
Range, months	2.5-25.6†	2.5†-21.8
Responders with duration of response, %		
≥12 months	69	65
≥18 months	51	22

*The Kaplan-Meier method was used to estimate the duration of response in confirmed responders for each treatment arm with 95% CIs.
†Censored.

Cheng, A. J Hepatol. 2022, 76, 862–873

SAFETY SUMMARY

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



	ATEZO + BEV VS SORAFENIB (N=336 VS 165)
Any grade AEs, %	98.2 vs 98.7
Grade 3/4 AEs, %	56.5 vs 55.1
Grade 5 TRAEs, n	6 vs 1

All grade bleeding/ hemorrhage occurred in 25.2% of patients treated with atezolizumab + bevacizumab† and 17.3% of patients treated with sorafenib

Grade 3/4 bleeding/hemorrhage occurred in 6.4% vs 5.8% of patients treated with atezolizumab + bevacizumab† vs sorafenib

**Safety-evaluable population. ≥10% frequency of AEs in either arm and >5% difference between arms. †Bevacizumab-related.*
ALT=alanine aminotransferase; PPE=palmar-plantar erythrodysesthesia.
Cheng AL, et al. Presented at: ESMO Asia. 2019 (abstr LBA3).

IMBRAVE 150: AESIs REQUIRING STEROIDS

Patients with ≥ 1 event, n (%)	Atezo + Bev (n = 329)	Sorafenib (n = 156)
Any AE	40 (12.2)	5 (3.2)
Grade 3-4 AE[a]	28 (8.5)	4 (2.6)

- 4 patients in the atezolizumab + bevacizumab arm required immunosuppressive treatments other than corticosteroids

Finn R et al, NEJM 2020; Chen AL et al, J Hepatol 2022

CARES310 TRIAL

Study Design

PARIS 2022 ESMO congress

Key eligibility criteria

- Unresectable or metastatic HCC
- BCLC Stage B (unsuitable for radical surgery and/or locoregional treatment) or C
- No prior systemic therapy
- ECOG PS 0 or 1
- Child-Pugh A
- At least one measurable lesion per RECIST v1.1

N=543

R 1:1

N=272 → Camrelizumab (200 mg, iv, Q2W) + rivoceranib (250 mg, po, QD)

N=271 → Sorafenib (400 mg, po, BID)

Treatment until loss of clinical benefits* or intolerable toxicity

Stratification factors

- MVI and/or EHS (yes *vs.* no)
- Geographical region (Asia *vs.* non-Asia)
- Baseline serum AFP (<400 *vs.* ≥ 400 ng/mL)

Primary endpoints

- PFS‡
- OS

Key secondary endpoint

- ORR‡

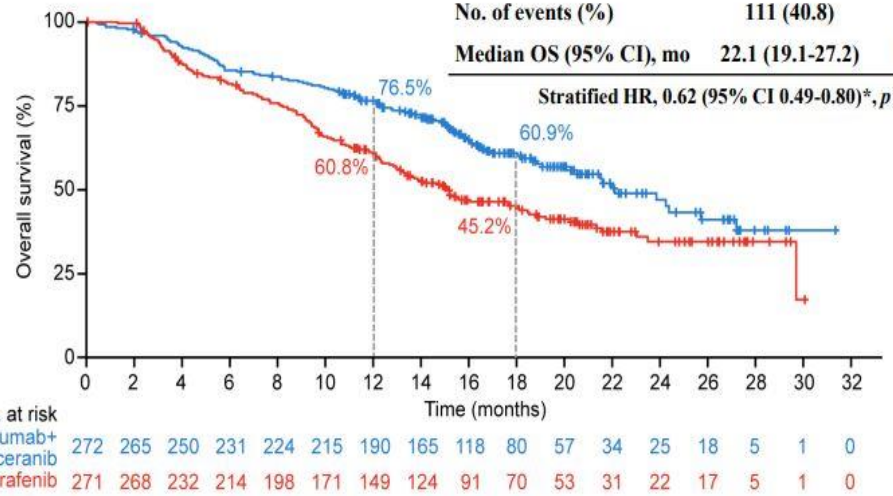
*Treatment beyond progression allowed if there was evidence of clinical benefits per investigator. ‡ By BIRC per RECIST v1.1. AFP=alpha-fetoprotein; BCLC=Barcelona Clinic Liver Cancer; BIRC=blinded independent review committee; ECOG PS=Eastern Cooperative Oncology Group performance status; EHS=extrahepatic spread; MVI=macrovascular invasion

OS AND PFS

Primary Endpoint: OS (ITT Population)

	Camrelizumab + rivoceranib	Sorafenib
No. of events (%)	111 (40.8)	151 (55.7)
Median OS (95% CI), mo	22.1 (19.1-27.2)	15.2 (13.0-18.5)

Stratified HR, 0.62 (95% CI 0.49-0.80)*, p <0.0001†

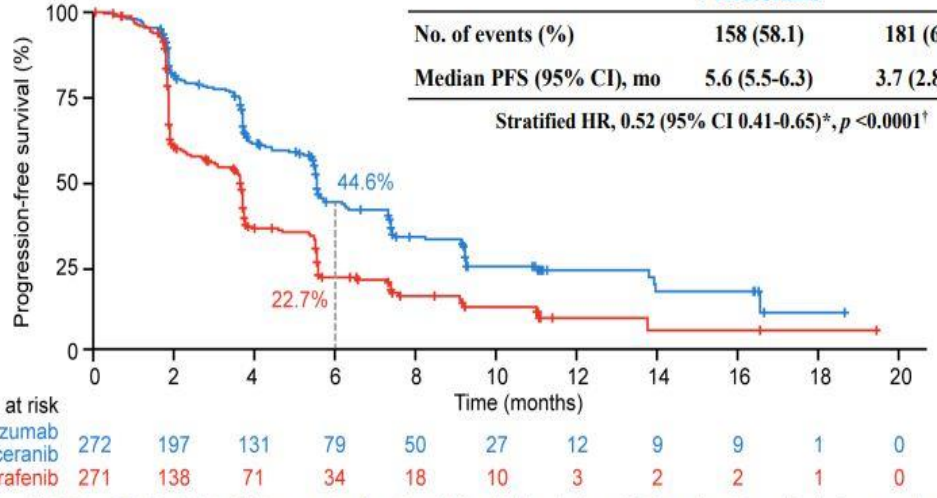


*Stratified Cox proportional hazards model. †One-sided based on the stratified log-rank test. The stratification factors were the randomization strata. Data cutoff: Feb. 8, 2022; median follow-up: 14.5 mo.

Primary Endpoint: PFS (ITT Population)

	Camrelizumab + rivoceranib	Sorafenib
No. of events (%)	158 (58.1)	181 (66.8)
Median PFS (95% CI), mo	5.6 (5.5-6.3)	3.7 (2.8-3.7)

Stratified HR, 0.52 (95% CI 0.41-0.65)*, p <0.0001†



PFS was assessed by BIRC per RECIST v1.1. *Stratified Cox proportional hazards model. †One-sided based on the stratified log-rank test. The stratification factors were the randomization strata. Data cutoff: May. 10, 2021; median follow-up: 7.8 mo.

TRAES

Safety Summary

	Camrelizumab + rivoceranib (N=272)	Sorafenib (N=269)
Median exposure of treatment (IQR), mo		
Camrelizumab	6.9 (3.6-13.4)	–
Rivoceranib/sorafenib	6.5 (3.4-11.9)	3.8 (1.9-7.4)
Any TRAE*	265 (97.4)	249 (92.6)
Grade 3/4	219 (80.5)	140 (52.0)
Grade 5	1 (0.4)†	1 (0.4)‡
Serious TRAE	66 (24.3)	16 (5.9)
TRAEs leading to dose modification or interruption of any treatment component	219 (80.5)	135 (50.2)
TRAEs leading to discontinuation of any treatment component	66 (24.3)	12 (4.5)
TRAEs leading to discontinuation of all treatment components	10 (3.7)	12 (4.5)

Data are n (%) or otherwise indicated. *Causality to treatment was determined by the investigator. †Multiple organ dysfunction syndrome. ‡Respiratory failure and circulatory collapse. Data cutoff: Feb. 8, 2022. TRAE=treatment-related adverse event

Dose reductions in 47% in the combination arm

AESIs – Hepatotoxicity ≥ G3 33% (72% all grade); PPE ≥ G3 12.1% (37.5% all grade)

SUMMARY: VEGF + IO

- Atezolizumab + Bevacizumab continues to be a standard approved combination
- CARES-310: Camrelizumab/Rivoceranib

- Positive trial with PFS and OS improvement
- BUT
    - Asian, younger, hepatitis B population
    - Risk benefit ratio needs to be considered
    - No regulatory approval yet

- Other IO/TKI trials negative

COMBINATION OF ANTI PD-1/PD-L1 + 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%

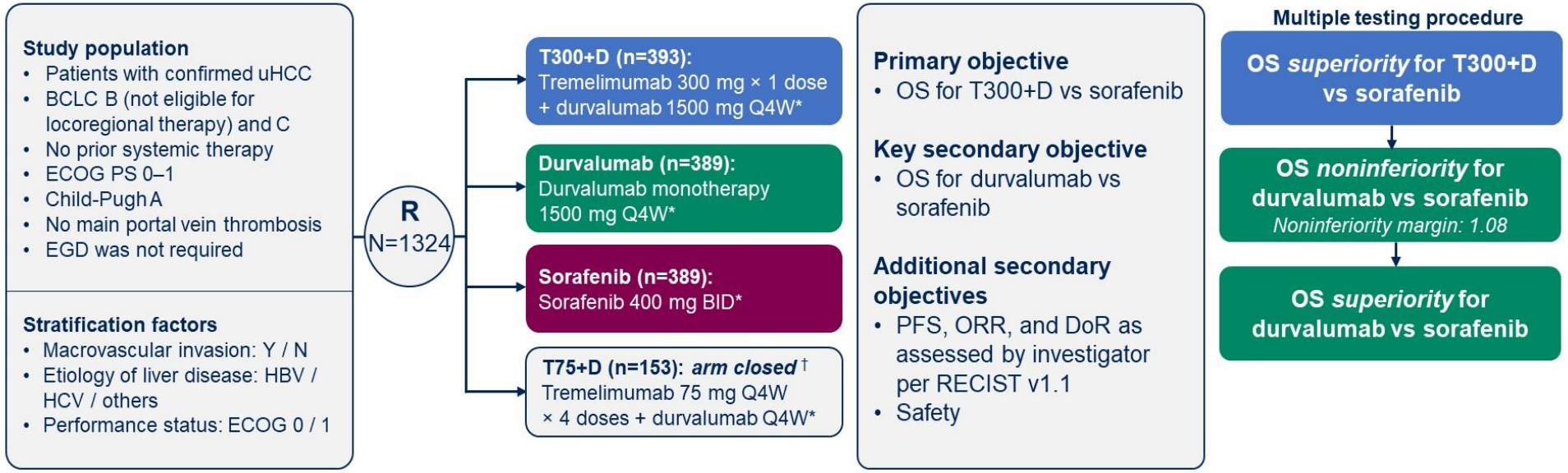
Targeting CTLA-4	• Blocks suppressive T cell signaling in lymph nodes
	• Modulates CD4 effector compartment
	  • Expands ICOS+Th1 like effector subsets
	• Single agent tremelimumab activity
	  • ORR 17.6%

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



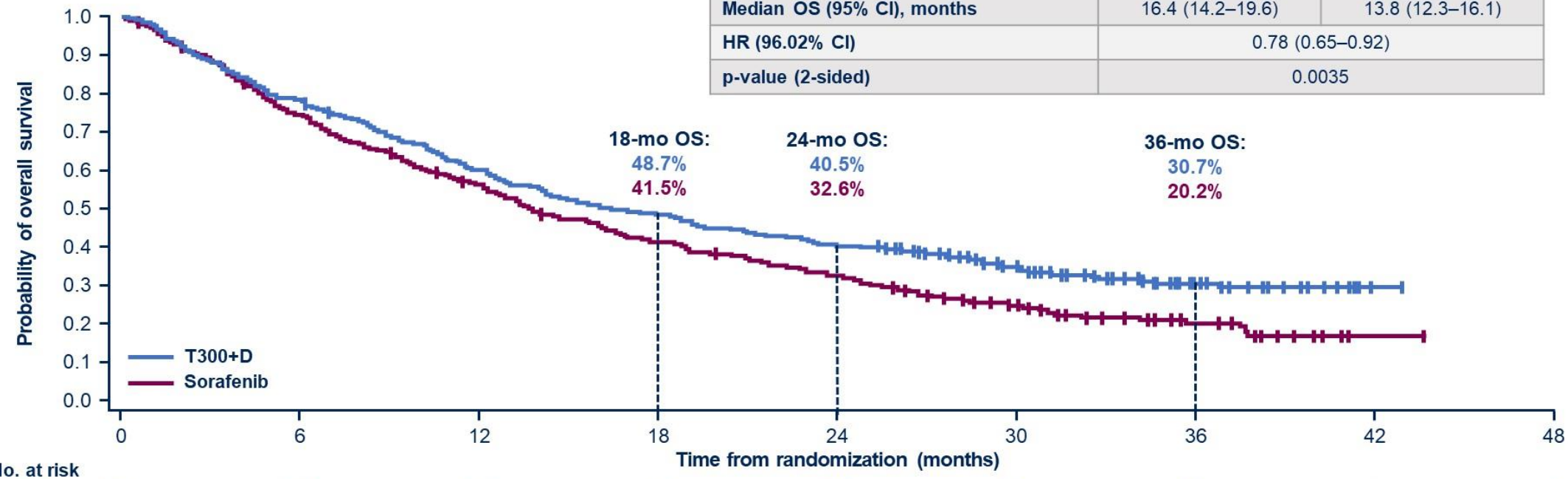
*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned 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.

Abou Alfa et al ASCO GI 2022, NEJM

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

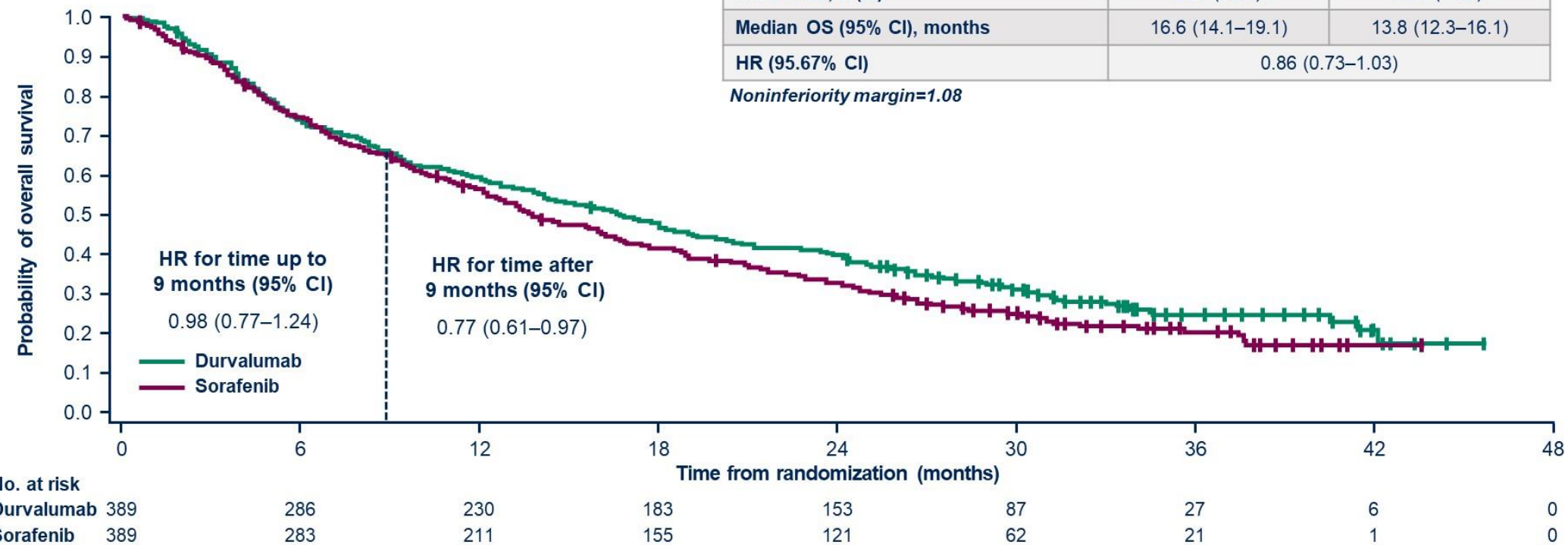
Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

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

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.

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.

Safety and tolerability

Event, n (%)	T300+D (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE*	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
Any TRAE leading to death	9 (2.3)†	0	3 (0.8)‡
Any TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)

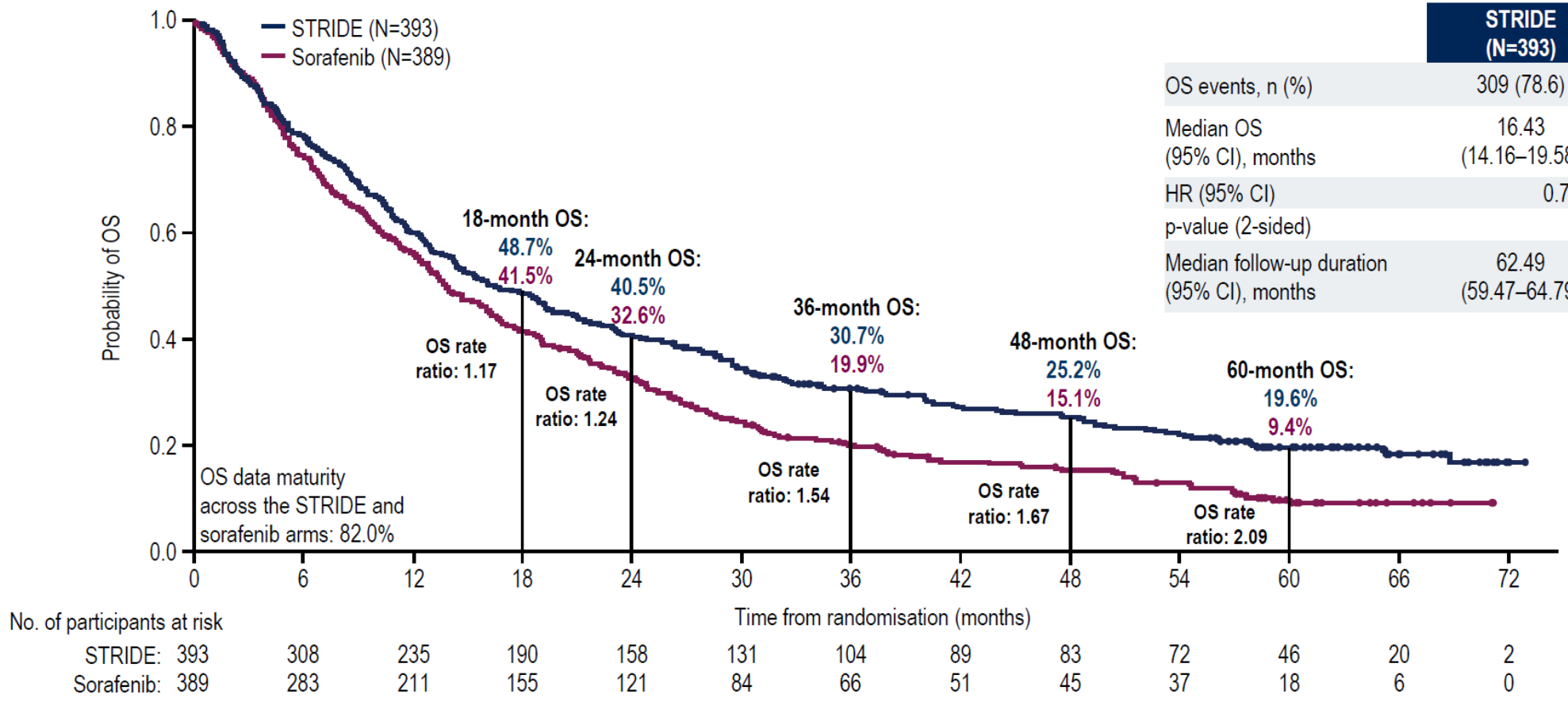
20% of patients that received D/T required corticosteroids

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy.

*Treatment-related was as assessed by investigator. †Nervous system disorder (n=1), acute respiratory distress syndrome (n=1), hepatitis (n=1), myocarditis (n=1), immune-mediated hepatitis (n=2), pneumonitis (n=1), hepatic failure (n=1), myasthenia gravis (n=1). ‡Hematuria (n=1), cerebral hematoma (n=1), hepatic failure (n=1).

AE, adverse event; SMQ, Standardized MedDRA Query; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TRAE, treatment-related adverse event.

HIMALAYA: 5-YEAR UPDATED OS SHOWED SUPERIORITY OVER SORAFENIB



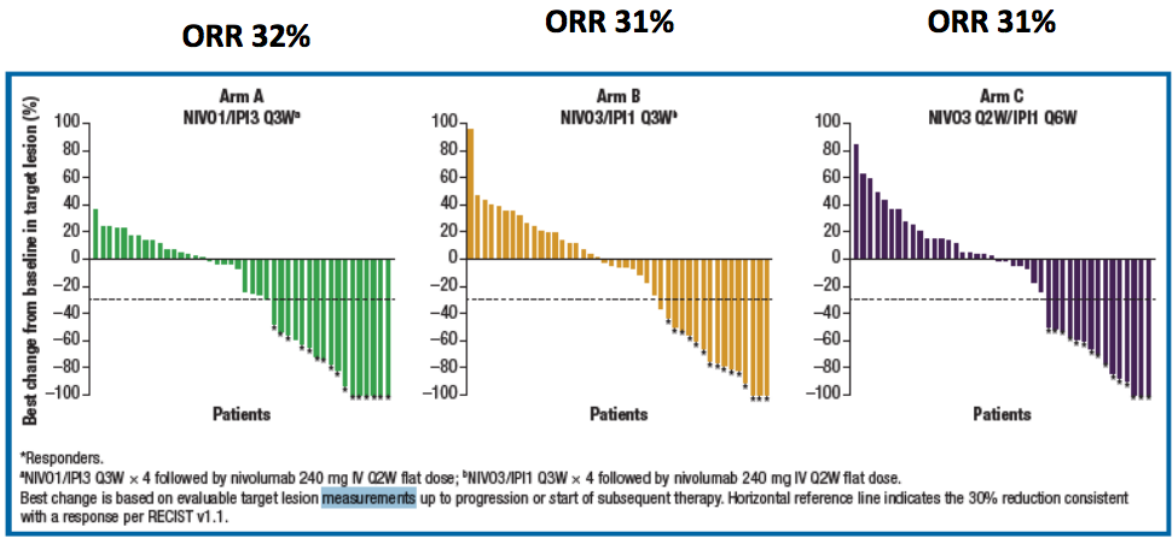
	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS (95% CI), months	16.43 (14.16–19.58)	13.77 (12.25–16.13)
HR (95% CI)	0.76 (0.65–0.89)	
p-value (2-sided)	0.0008	
Median follow-up duration (95% CI), months	62.49 (59.47–64.79)	59.86 (58.32–61.54)

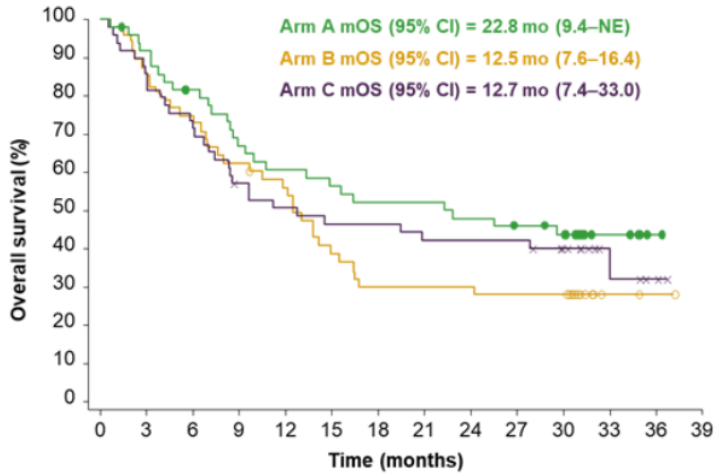
Updated analysis data cutoff: March 1, 2024.

Rimassa L, et al. ESMO 2024.

WHAT ABOUT MULTIPLE ANTI-CTLA4 DOSES?

NIVOLUMAB PLUS IPILIMUMAB IN PHASE 1/2 CHECKMATE-040 COHORT





- Treatment-related AE grade 3-4: 53%, 29%, 31% for Arms A-C
- Systemic steroid requirement: 51%, 24%, 23% for Arms A-C

Yau et al., *JAMA Oncol*, 2020.
Presented by Anthony El-Khoueiry, MD at GI 2021.

CHECKMATE 9DW: STUDY DESIGN

- CheckMate 9DW is a global, phase 3, randomized, open-label study of NIVO in combination with IPI compared with LEN or SOR as 1L treatment in patients with unresectable HCC[a]

Key eligibility criteria
- Unresectable HCC[b]
- At least 1 measurable lesion (RECIST v1.1)
- Systemic therapy naive
- Child-Pugh score 5 or 6
- ECOG PS 0 or 1
- No main portal vein invasion (Vp4)

N = 668

R 1:1

n = 335

NIVO 1 mg/kg IV + IPI 3 mg/kg IV Q3W (up to 4 cycles) then NIVO 480 mg Q4W[d]

n = 333

Investigator's choice of LEN 8 mg[e] or 12 mg[f] PO QD or SOR 400 mg PO BID

Primary endpoint:
- OS

Secondary endpoints:
- ORR and DOR by BICR per RECIST v1.1
- Time to symptom deterioration[g]

Key exploratory endpoints:
- PFS by BICR per RECIST v1.1
- Safety

Stratification factors:
- Etiology (HBV vs HCV vs uninfected)[c]
- MVI/EHS (present vs absent)
- AFP (< 400 vs ≥ 400 ng/mL)

Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO + IPI arm only)

Among 325 patients treated with LEN/SOR:
275 (85%) received LEN and 50 (15%) received SOR

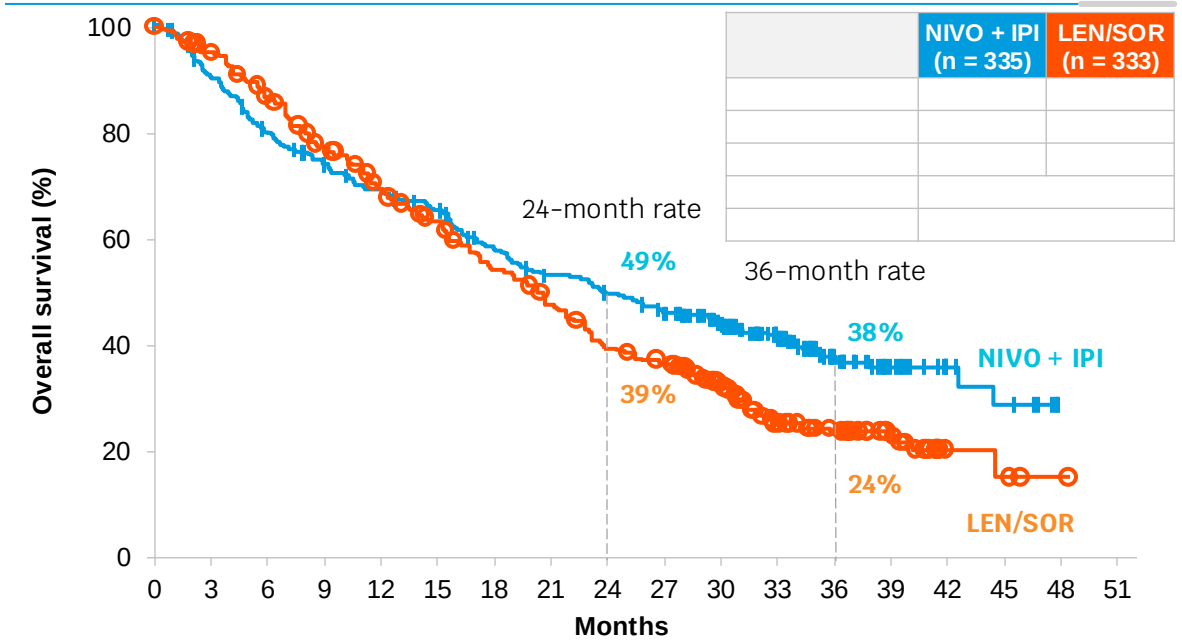
- At data cutoff (January 31, 2024), median (range) follow-up[h] was 35.2 (26.8-48.9) months

[a] ClinicalTrials.gov: NCT04039607. [b] Disease not eligible for, or progressive disease after, curative surgical and/or locoregional therapies. [c] Based on central lab serology results for stratification purpose. [d] Minimum of 1 dose of NIVO + IPI is required before proceeding to NIVO monotherapy. [e] If body weight < 60 kg. [f] If body weight ≥ 60 kg. [g] HCS subscale score of the FACT-Hep. [h] Time between randomization date and cutoff date.

Galle, P et al. ASCO 2024.

CHECKMATE 9DW: EFFICACY

Overall Survival



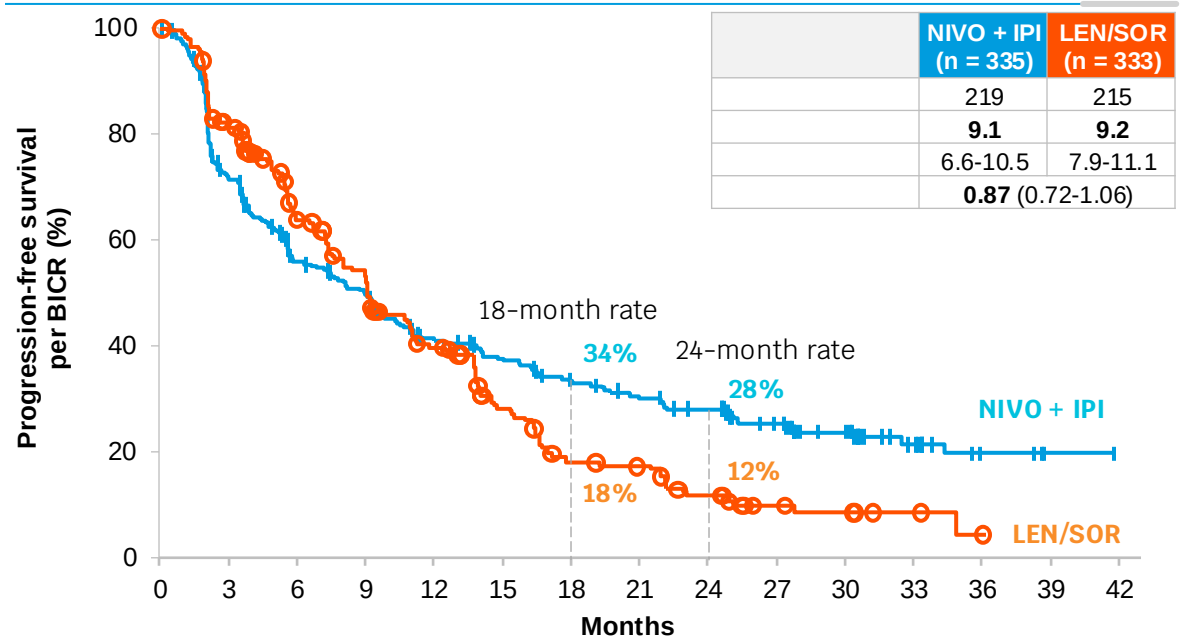
	NIVO + IPI (n = 335)	LEN/SOR (n = 333)

NIVO + IPI	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
LEN/SOR	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR
  - Longer median OS and long-term survival benefit with higher OS rates at 24 and 36 months

Median (range) follow-up, 35.2 (26.8-48.9) months. Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a] Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257.

Progression-Free Survival



	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
	219	215
	9.1	**9.2**
	6.6-10.5	7.9-11.1
	0.87 (0.72-1.06)	

NIVO + IPI	335	224	160	140	103	92	78	69	61	45	29	16	6	1	0
LEN/SOR	333	242	164	131	82	52	30	26	16	8	6	3	1	0	0

- Numerically higher PFS rates with NIVO + IPI vs LEN/SOR at 18 and 24 months

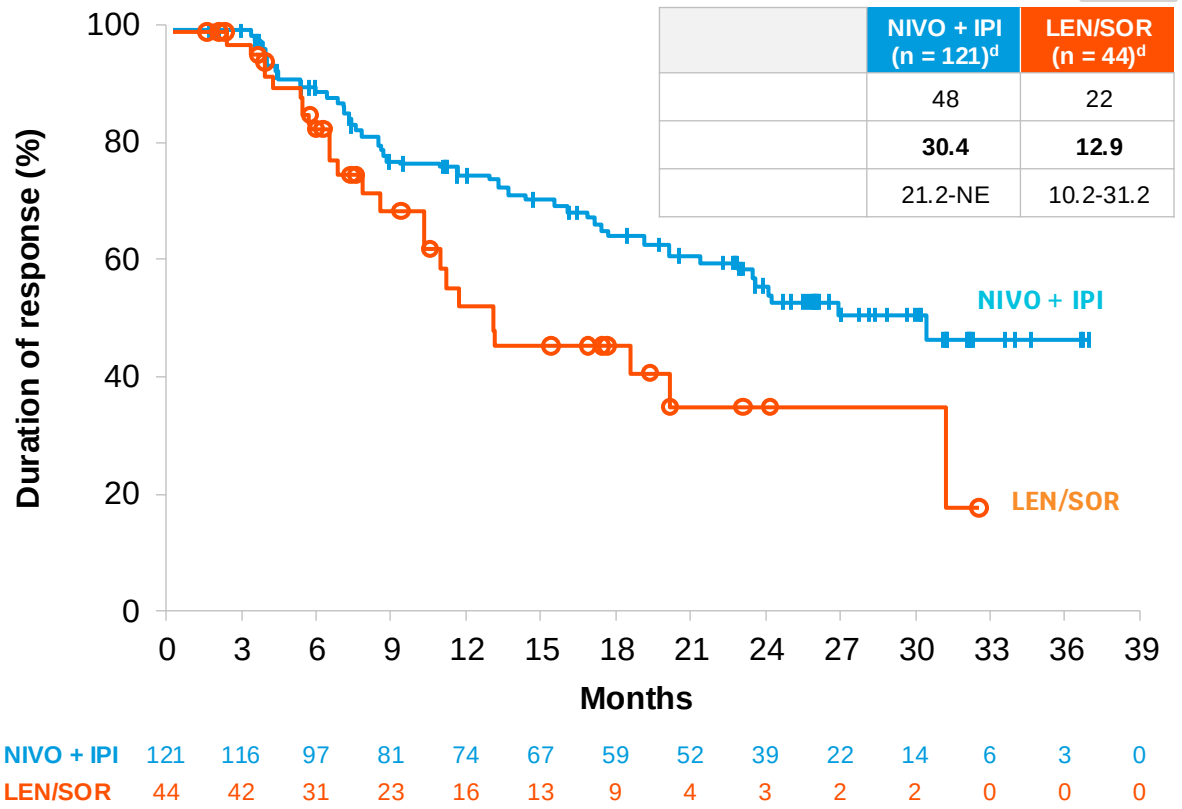
Median (range) follow-up, 35.2 (26.8-48.9) months. Median PFS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a] Assessed by BICR based on RECIST v1.1.

Galle, P et al. ASCO 2024.

RESPONSE AND DURATION OF RESPONSE

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
ORR,[a] %	36	13
95% CI	31-42	10-17
P value[b]	< 0.0001	
Best overall response,[a] %		
Complete response	7	2
Partial response	29	11
Stable disease[c]	32	62
Progressive disease	20	14
Not evaluable	12	11
Median TTR (range),[a] mo	2.2 (1.1-11.6)	3.7 (0.6-11.2)

Duration of Response



- Statistically significant and clinically meaningful improvement in ORR with NIVO + IPI vs LEN/SOR, with a higher complete response rate (7% vs 2%, respectively) and durable responses

Median (range) follow-up, 35.2 (26.8-48.9) months. Symbols represent censored observations. [a] Assessed by BICR based on RECIST v1.1. [b] Two sided *P* value from stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: *P* value ≤ 0.025. [c] Includes non-CR/non-PD: NIVO + IPI, n = 6 (2%); LEN/SOR, n = 7 (2%). Non-CR/non-PD refers to patients with persistence of one or more non-target lesion(s). [d] Number of confirmed responders.

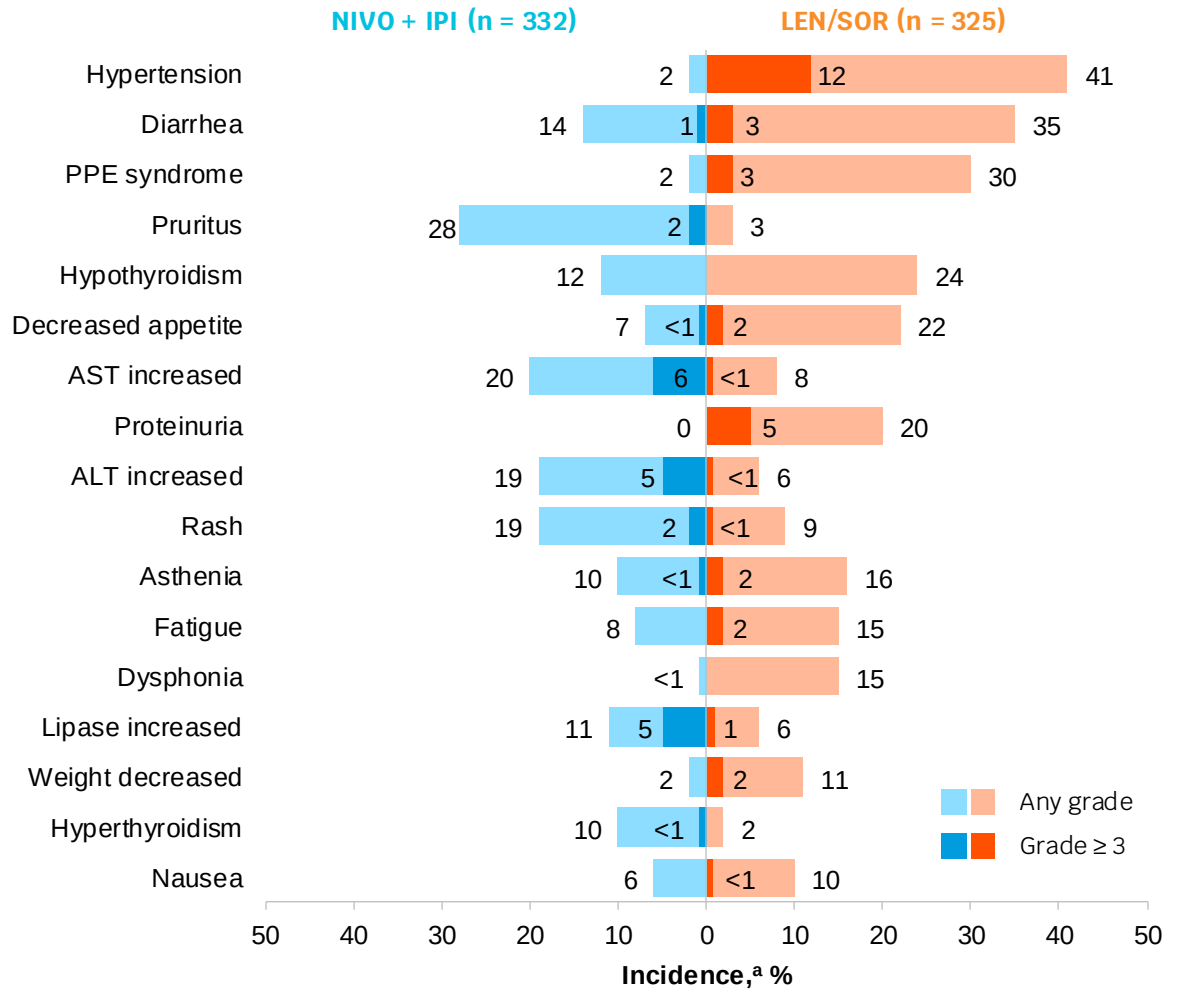
Galle, P et al. ASCO 2024.

TREATMENT-RELATED ADVERSE EVENTS

All treated patients, n (%)	NIVO + IPI (n = 332)	LEN/SOR (n = 325)
Median (range) duration of treatment, mo	4.7 (< 1 to 24.4)	6.9 (< 1 to 45.8)

All treated patients, n (%)	NIVO + IPI (n = 332)		LEN/SOR (n = 325)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs[a]				
Any TRAEs	278 (84)	137 (41)	297 (91)	138 (42)
Serious TRAEs	94 (28)	83 (25)	47 (14)	42 (13)
TRAEs leading to discontinuation	59 (18)	44 (13)	34 (10)	21 (6)
Treatment-related deaths[b]	12 (4)[c]		3 (< 1)[d]	

TRAES occuring in ≥ 10% of patients



Galle, P et al. ASCO 2024.

IMAES

All treated patients, n (%)	NIVO + IPI (n = 332)			
	Any grade	Grade 3/4	Received high-dose steroids	Leading to discontinuation
Patients with IMAEs[†]	191 (58)	93 (28)	96 (29)	42 (13)
Hepatitis	63 (19)	51 (15)	56 (17)	19 (6)
Hypothyroidism/thyroiditis	62 (19)	1 (< 1)	2 (< 1)	0
Rash	51 (15)	14 (4)	10 (3)	1 (< 1)
Hyperthyroidism	36 (11)	2 (< 1)	3 (< 1)	0
Diarrhea/colitis	28 (8)	15 (5)	27 (8)	9 (3)
Adrenal insufficiency	18 (5)	6 (2)	2 (< 1)	4 (1)
Hypophysitis	9 (3)	4 (1)	3 (< 1)	4 (1)
Pneumonitis	7 (2)	3 (< 1)	6 (2)	3 (< 1)
Nephritis and renal dysfunction	5 (2)	3 (< 1)	3 (< 1)	2 (< 1)
Hypersensitivity	4 (1)	0	3 (< 1)	0
Diabetes mellitus	2 (< 1)	2 (< 1)	0	0

- **The majority of IMAES were grade 1 or 2, were manageable, and did not result in treatment discontinuation**
- **29% of patients required corticosteroids**

[†] IMAEs are specific events considered as potential immune-mediated events by investigator, occurring within 100 days after the last dose of study treatment, regardless of causality, and, with the exception of endocrine events, are treated with immune-modulating medication

SUMMARY 2: IO + IO (CLTA4)

Tremelimumab+Durvalumab represents another standard first line option for advanced HCC

• Advantages of “maintenance” single agent durvalumab q 4 weeks with favorable safety profile

• No PFS improvement
• Longest follow-up data at 5 years with persistent benefit

Checkmate 9DW: Nivolumab+Ipilimumab (3mg/kg)
• Positive trial with ORR and OS improvement BUT • Higher rates of IMAEs and grade 3/4 TRAEs
• Curves “flip” at 12 months: why?
• No regulatory approval yet

SUMMARY OF EFFICACY AND SAFETY DATA ACROSS SELECT FIRST-LINE PHASE III STUDIES IN HCC

	VARIABLE	REFLECT[2]	CHECKMATE 9DW[1]	IMBRAVE150[4,5]	HIMALAYA[6]	CARES310[7]
		PHASE III, NONINFERIORITY	PHASE III	PHASE III	PHASE III	PHASE III
		LENVATINIB VS SORAFENIB (N=478 VS 476)	IPI/NIVO vs TKI (N=335 VS 333)	ATEZOLIZUMAB + BEVACIZUMAB VS SORAFENIB (N=336 VS 165)	DURVALUMAB/TREMELIMUMAB VS SORAFENIB	CAMRELIZUMAB/RIVOCERANIB VS SORAFENIB
EFFICACY	**Median OS, months** **HR (95% CI); *P* value**	13.6 vs 12.3 0.92 (0.79-1.06)	23.7 vs 20.6 0.79 (0.65-0.96); 0.018	19.2 vs 13.4 0.66 (0.52-0.85); <0.0009	16.4 vs 13.8 (vs 16.6) 0.79 (0.65-0.92); 0.0035	22.1 vs 15.2 0.62 (0.49-0.80); 0.0001
EFFICACY	**Median TTP, months** **HR (95% CI); *P* value**	7.4 vs 3.7 0.61 (0.51-0.72); <0.0001	–	–	–	–
EFFICACY	**Median PFS†, months** **HR (95% CI); *P* value**	7.3 vs 3.6 0.65 (0.56-0.77); <0.0001	9.1 vs 9.2 0.87 (0.72-1.06)	6.8 vs 4.3 0.59 (0.47-0.76); <0.001	3.78 vs 4.07 (vs 3.65) 0.90 (0.77 – 1.05);	5.6 vs 3.7 0.52 (0.41-0.65)
EFFICACY	**ORR†, %** **PD, %**	18.8 vs 6.5 18 vs 32	36 vs 13 20 vs 14	27.3 vs 11.9‡ 19.6 vs 24.5‡	20.1 vs 5.1 (vs 17.0)	25.4 vs 5.9
EFFICACY	**Median DOR†, months**	–	30.4 vs 12.9	NE vs 6.3	22.3 vs 18.4	14.8 vs 9.2
		(n=476 vs 475)	**(n=335 vs 333)**	**(n=329 vs 156)**	**(n=393 vs 389)**	**(n=272 vs 269)**
SAFETY	**Any grade AEs, %**	99 vs 99	–	98.2 vs 98.7	97.4 vs 95.5	97.4 vs 92.6
SAFETY	**Grade 3/4 AEs, %**	75 vs 67	41 vs 42	56.5 vs 55.1	50.5 vs 52.4	80.5 vs 50.2
SAFETY	**Grade 5 TRAEs, n**	11 vs 4	12 vs 3	6 vs 1	9 vs 3.	1 vs 1.

*Did not achieve statistical significance. † By independent radiologic/imaging review according to RECIST v1.1. ‡n=326 vs 159. §TRAEs.

DOR=duration of response; HCC=hepatocellular carcinoma; NE=not estimable; TRAE=treatment-related adverse event; TTP=time to progression.

1. Galle P et al ASCO 2024 . 2. Kudo M, et al. Lancet. 2018;391(10126):1163-1173.

3. Yau T, et al. Presented at: ESMO. 2019 (abstr 6572). 4. Finn RS, et al. N Engl J Med. 2020;382(20):1894-1905.

5. Cheng AL, et al. Presented at: ESMO Asia. 2019 (abstr LBA3).

6. Abou Alfa et al NEJM

7. Qin et al Lancet Oncology

Cross-trial comparisons do not constitute substantial evidence as varying study designs, methodology, and patient populations limit the ability to draw conclusions of comparative efficacy and safety. This slide includes cross-trial comparisons to facilitate treatment and strategic discussion regarding the current HCC landscape.

OPPORTUNITIES FOR DATA GENERATION IN FIRST-LINE HCC SETTING

• Evaluation of QOL and organ function change over time while on first line therapy • Opportunities for maintenance approaches?

• New approaches to biomarker development
• Combination of clinical characteristics, biology (HCC subclasses), and immune microenvironment
• Opportunities for AI?

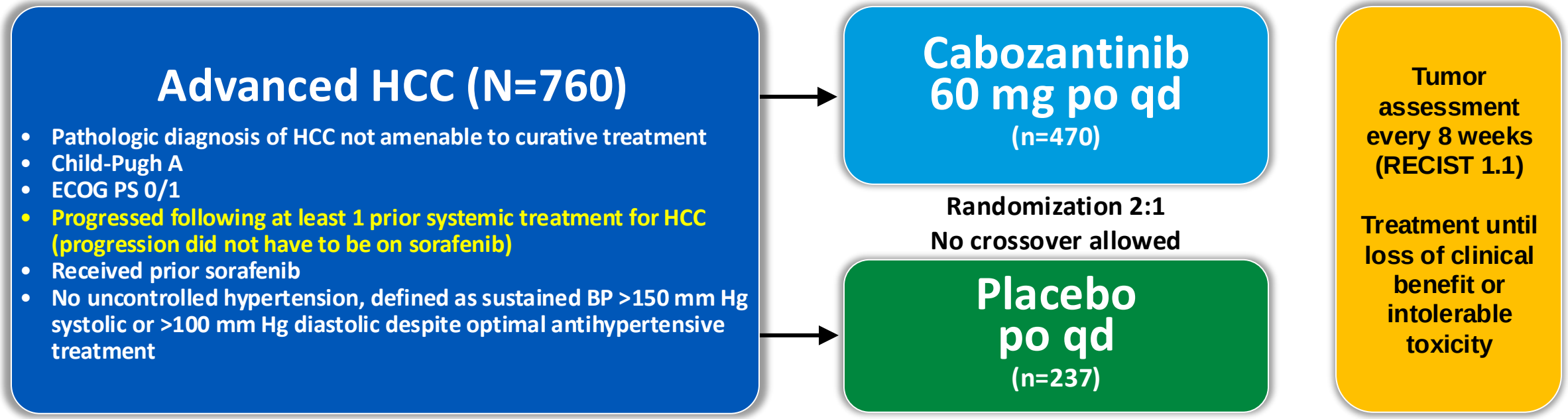
• Safety and efficacy data beyond child-pugh A

• Drug development:
• Careful evaluation of triplets
• Majority of current efforts use atezolizumab/bevacizumab as backbone

• Role of liver-directed therapy and intrahepatic control in setting of advanced HCC • Cost to benefit ratio

SECOND-LINE AND SUBSEQUENT THERAPY FOR ADVANCED HCC

CELESTIAL: RANDOMIZED, DOUBLE-BLIND, PHASE III TRIAL OF CABOZANTINIB VS PLACEBO IN PATIENTS WITH ADVANCED HCC AFTER PRIOR SORAFENIB



Primary endpoint

- OS

Secondary endpoints

- PFS and ORR (investigator-assessed per RECIST 1.1)

Stratification

- Etiologic factor (HBV +/- HCV, HCV without HBV, other)
- Geographic region (Asia, other)
- Evidence of extrahepatic spread of disease, macrovascular invasion or both (yes or no)

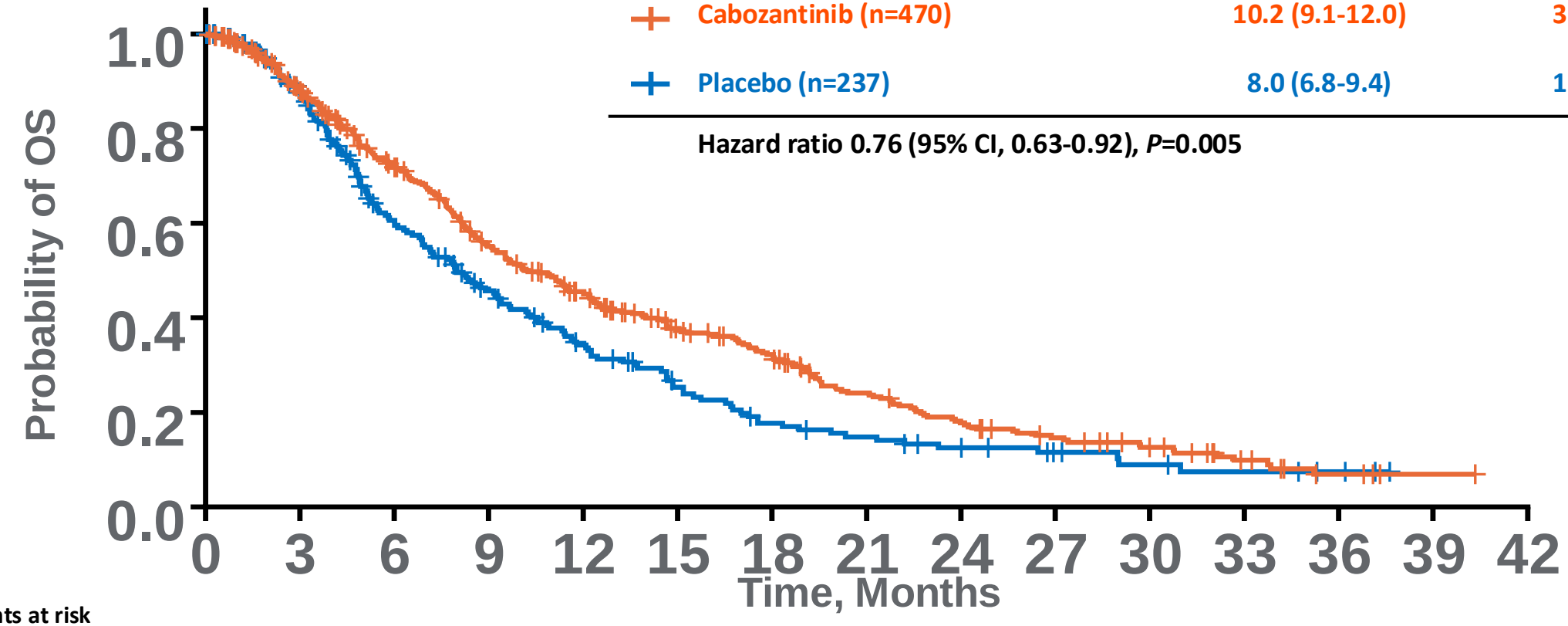
BP=blood pressure; ECOG PS=Eastern Cooperative Oncology Group performance status; HBV=hepatitis B virus; HCV=hepatitis C virus; po=orally; qd=every day; RECIST=Response Evaluation Criteria in Solid Tumors.

Abou-Alfa GK, et al. *N Engl J Med*. 2018;379:54-63. Abou-Alfa GK, et al. Presented at: ASCO. 2018 (abstr 4019).
Abou-Alfa GK, et al. Presented at: ASCO GI. 2018 (abstr 207).

CELESTIAL: OVERALL SURVIVAL IN ITT POPULATION

	Median OS (95% CI), Months	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*=0.005



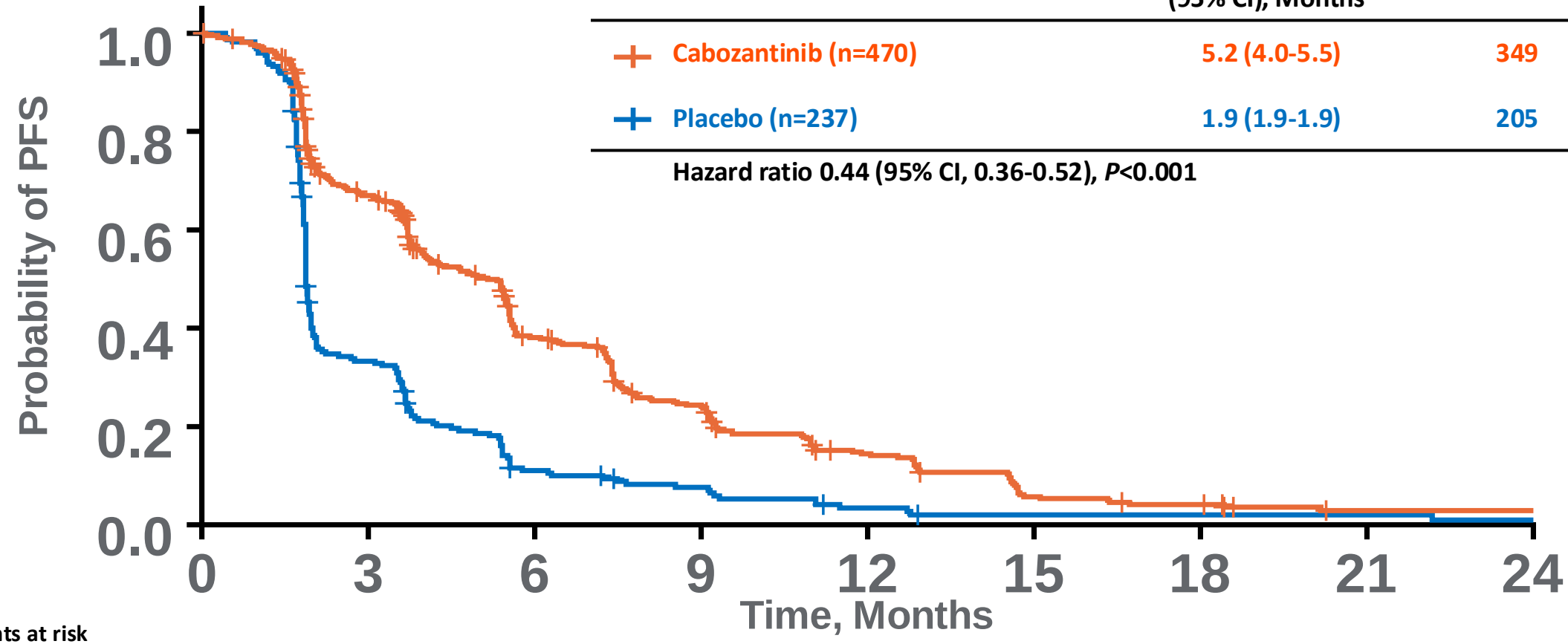
Patients at risk															
Cabozantinib	470	382	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

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

CELESTIAL: PROGRESSION-FREE SURVIVAL IN ITT POPULATION

	Median PFS (95% CI), Months	No. of Events
Cabozantinib (n=470)	5.2 (4.0-5.5)	349
Placebo (n=237)	1.9 (1.9-1.9)	205

Hazard ratio 0.44 (95% CI, 0.36-0.52), *P*<0.001

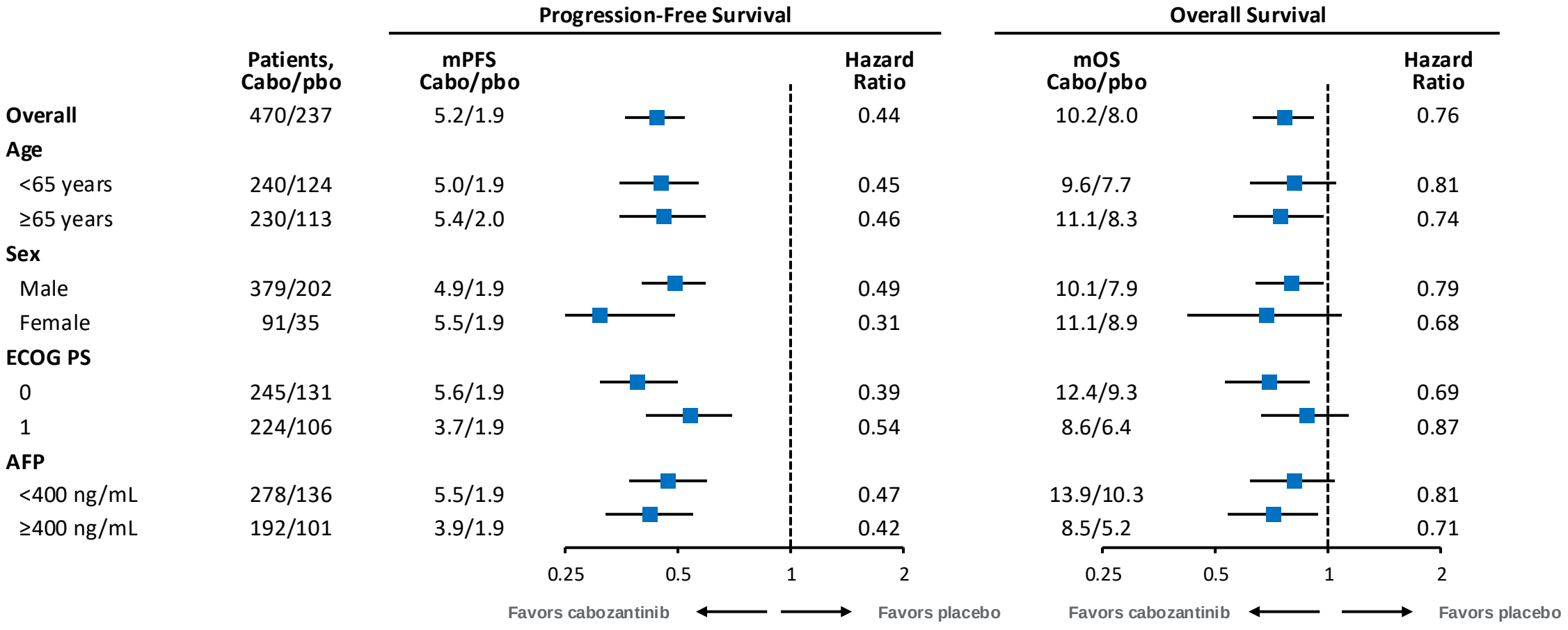


Patients at risk

Cabozantinib	470	266	131	80	39	15	10	3	3
Placebo	237	70	21	13	5	2	2	2	1

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

CELESTIAL: PFS AND OS IN SUBGROUPS

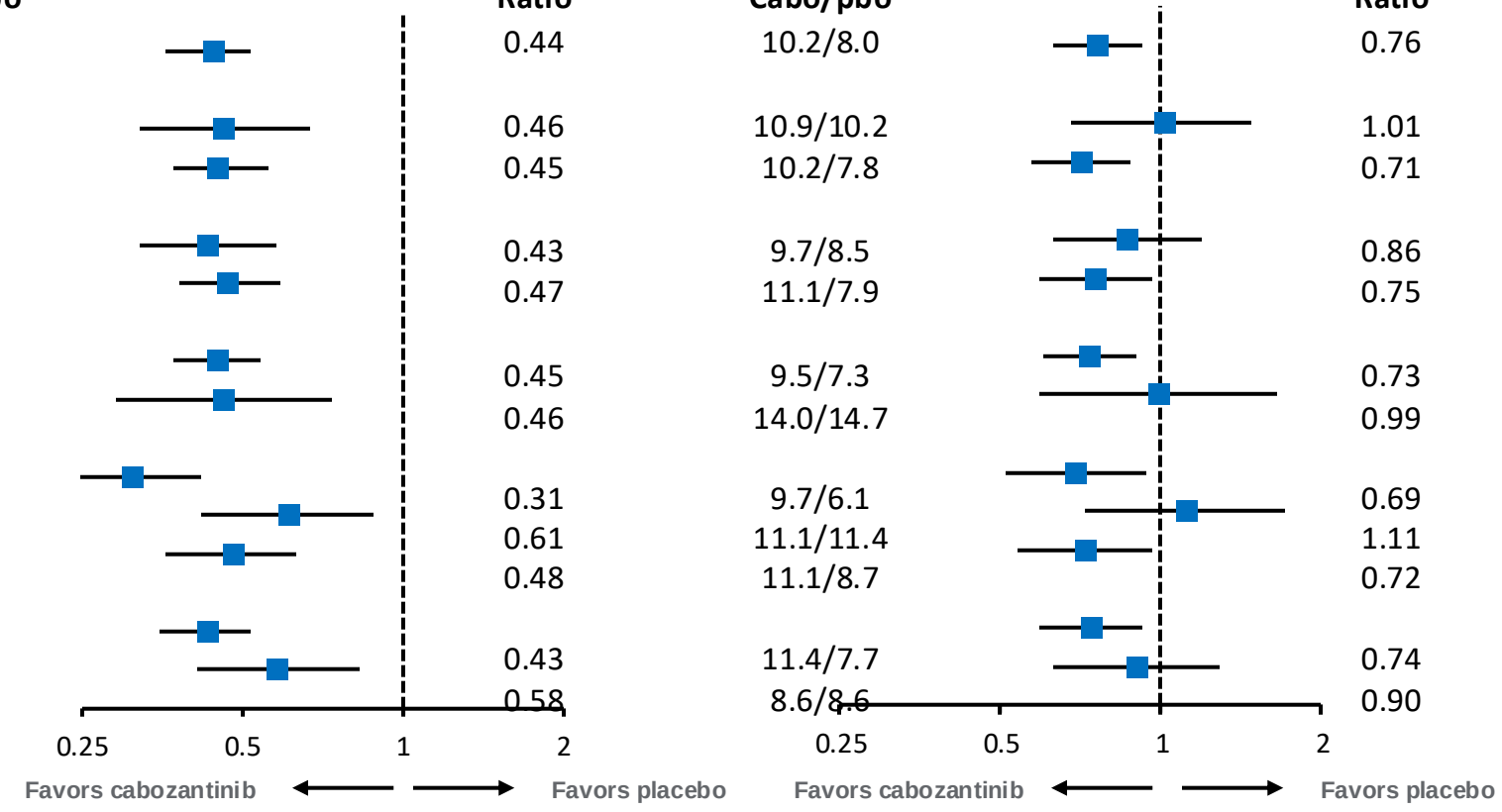


AFP=alpha-fetoprotein; Cabo=cabozantinib; ECOG PS=Eastern Cooperative Oncology Group performance status; pbo=placebo.

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

CELESTIAL: PFS AND OS IN SUBGROUPS (CONT.)

	Patients, Cabo/pbo	mPFS Cabo/pbo	Hazard Ratio	mOS Cabo/pbo	Hazard Ratio
		Progression-Free Survival		Overall Survival	
Overall	470/237	5.2/1.9	0.44	10.2/8.0	0.76
Region					
Asia	116/59	5.4/1.8	0.46	10.9/10.2	1.01
Other regions	354/178	5.2/1.9	0.45	10.2/7.8	0.71
Race					
Asian	159/82	5.4/1.8	0.43	9.7/8.5	0.86
Non-Asian	280/143	5.2/1.9	0.47	11.1/7.9	0.75
EHS and/or MVI					
Yes	398/200	5.0/1.9	0.45	9.5/7.3	0.73
No	72/37	5.6/2.0	0.46	14.0/14.7	0.99
Etiology					
HBV	178/89	4.4/1.8	0.31	9.7/6.1	0.69
HCV	105/51	4.1/1.9	0.61	11.1/11.4	1.11
Other	187/97	5.5/2.0	0.48	11.1/8.7	0.72
Prior lines of therapy*					
One prior regimen	335/174	5.5/1.9	0.43	11.4/7.7	0.74
Two prior regimens	130/62	3.7/1.9	0.58	8.6/8.6	0.90



*Prior systemic anticancer regimens for advanced HCC.

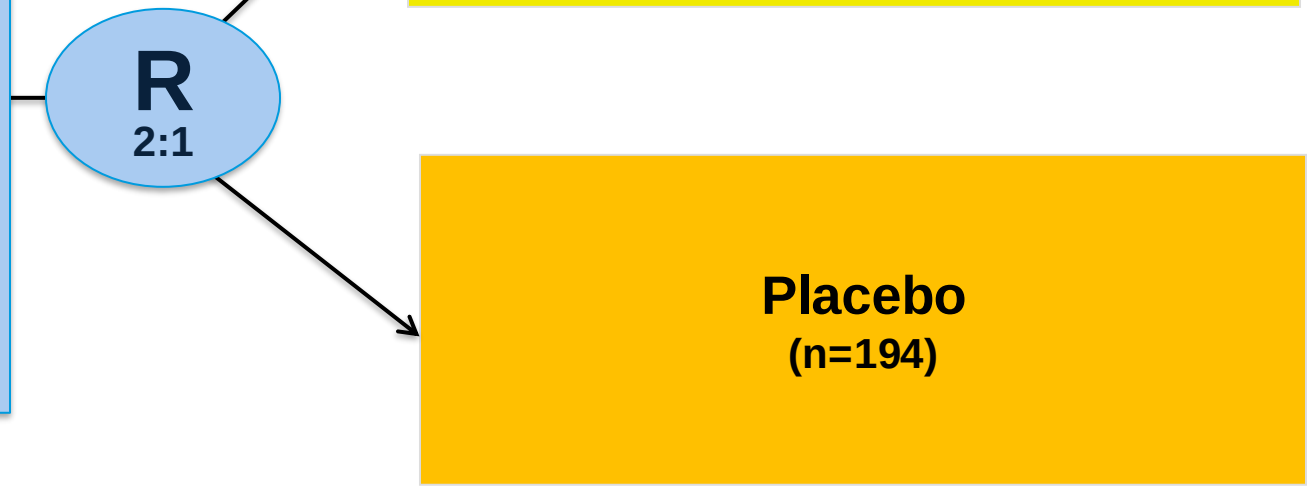
Cabo=cabozantinib; EHS=extrahepatic spread of disease; HBV=hepatitis B virus; HCV=hepatitis C virus; MVI=macrovascular invasion; pbo=placebo.

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

RESORCE trial design

Clinicaltrials.gov NCT01774344

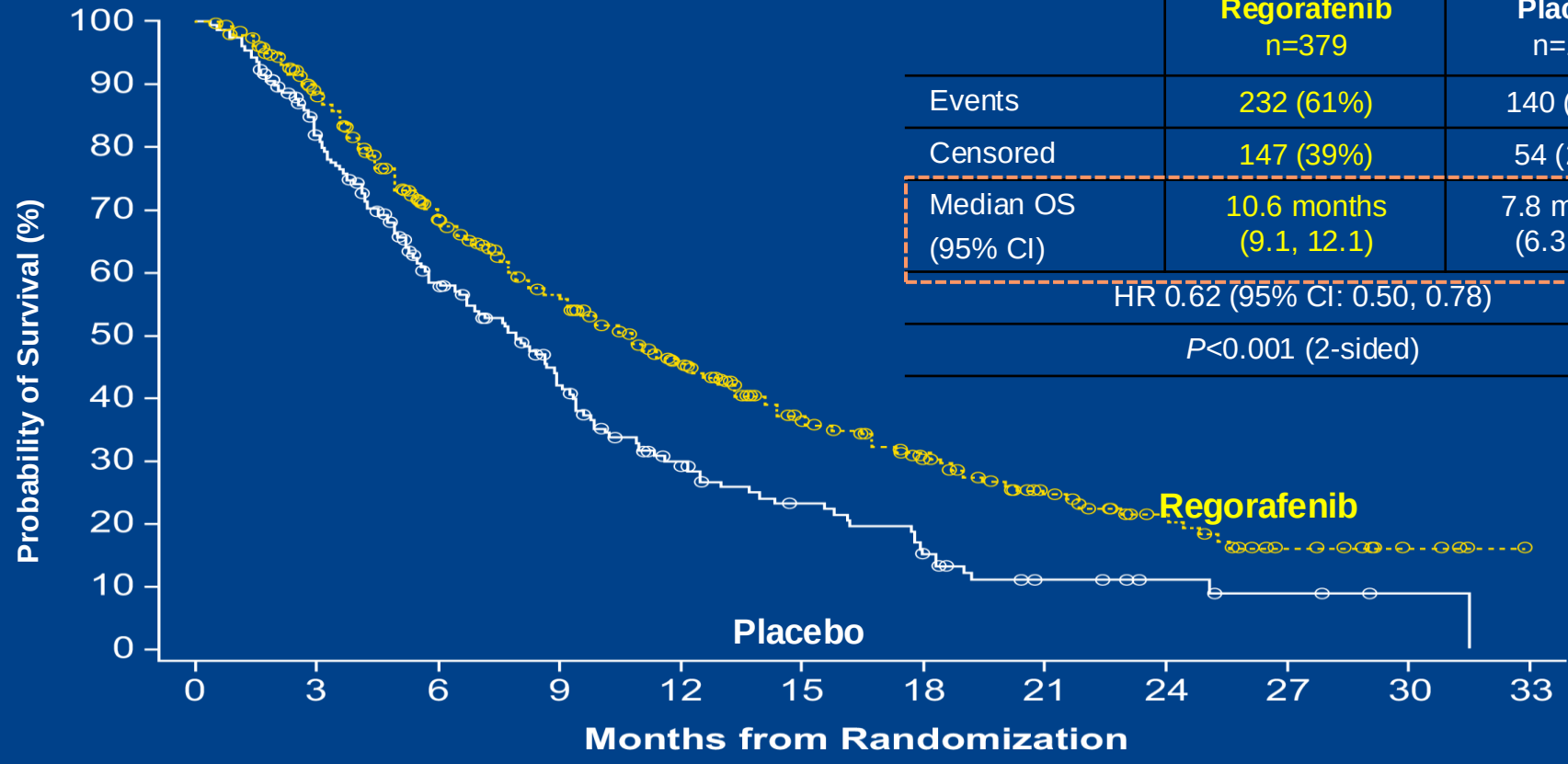
- HCC patients with documented radiological progression during sorafenib treatment
- Stratified by:
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)



- 152 centers in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

ROW, rest of the world; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein

OVERALL SURVIVAL (OS)
PRIMARY ENDPOINT

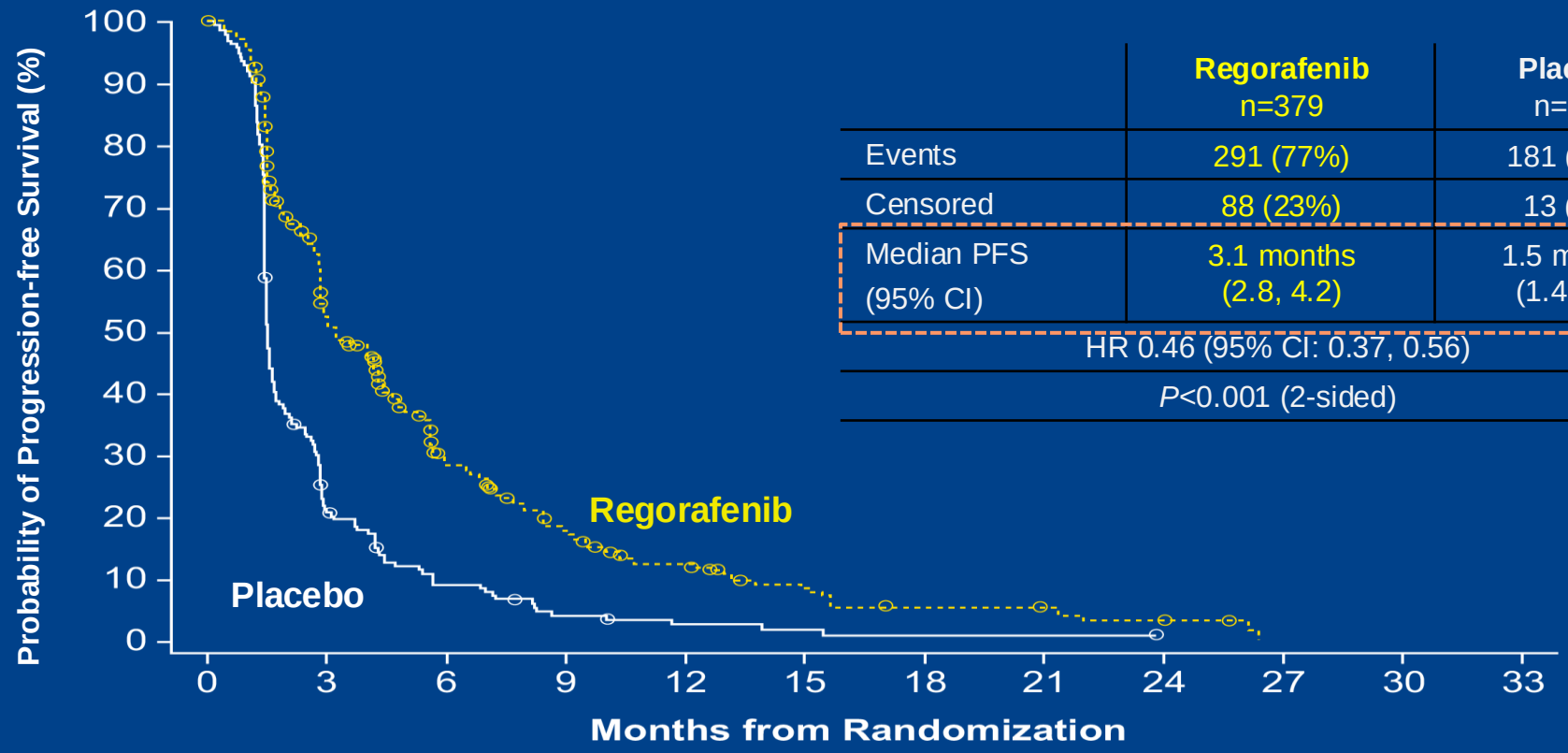


	Regorafenib n=379	Placebo n=194
Events	232 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS (95% CI)	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
HR 0.62 (95% CI: 0.50, 0.78)		
P<0.001 (2-sided)		

Number 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

PROGRESSION-FREE SURVIVAL (PFS)



	Regorafenib n=379	Placebo n=194
Events	291 (77%)	181 (93%)
Censored	88 (23%)	13 (7%)
Median PFS (95% CI)	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.6)
HR 0.46 (95% CI: 0.37, 0.56)		
P<0.001 (2-sided)		

Number at risk

Regorafenib	379	165	76	42	26	14	8	7	4	0	0	0
Placebo	194	37	15	6	3	2	1	1	0	0	0	0

Based on mRECIST

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

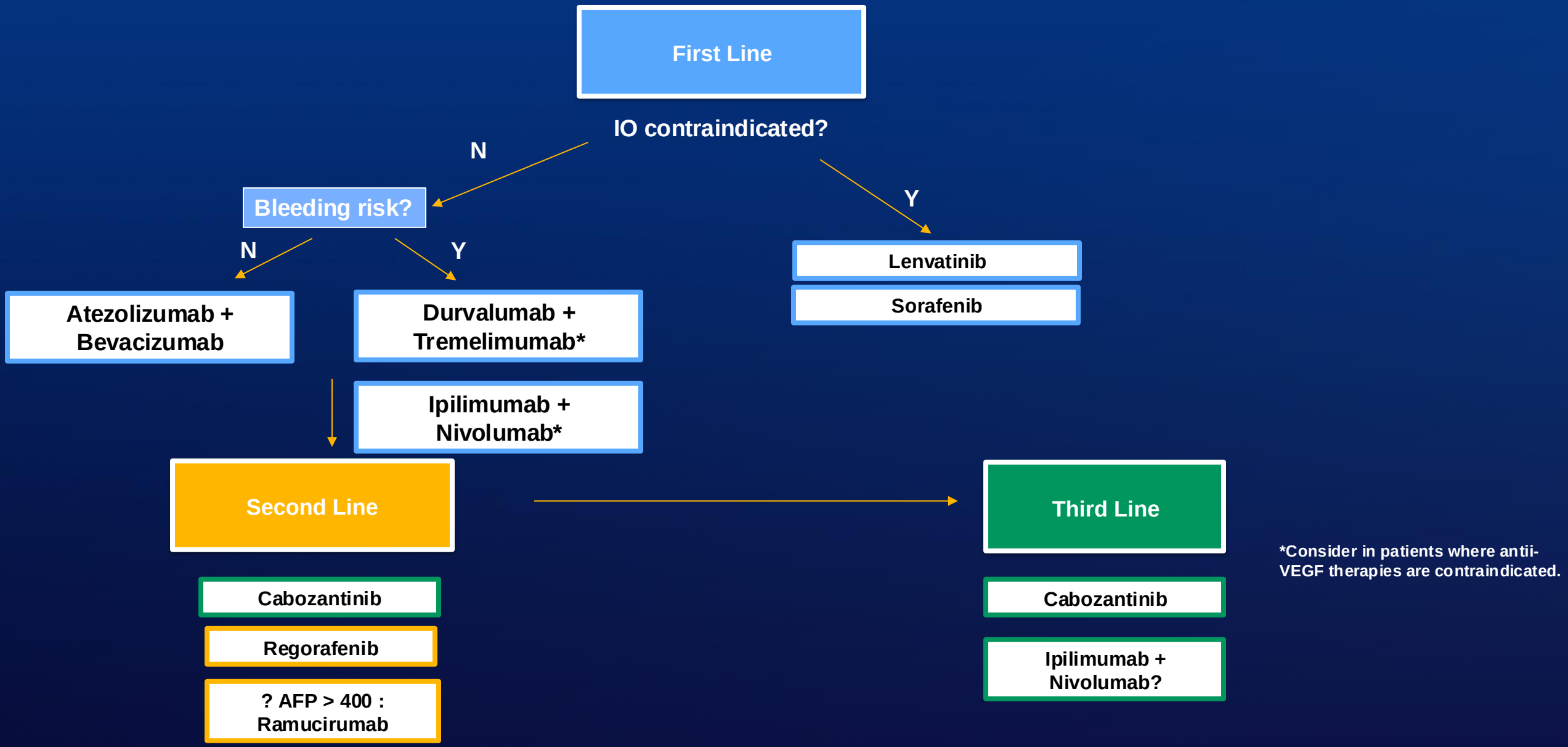
		CELESTIAL[1]		RESORCE[2]	REACH-2[3,4]
		PHASE III		PHASE III	PHASE III
		CABOZANTINIB VS PLACEBO		REGORAFENIB VS PLACEBO (N=379 VS 194)	RAMUCIRUMAB VS PLACEBO (N=197 VS 95)
		ITT (N=470 VS 237)	2L (N=331 VS 164)		
EFFICACY	**MEDIAN OS, MONTHS** HR (95% CI); *P* VALUE	10.2 VS 8.0 0.76 (0.63-0.92); 0.005	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
	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
	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
	ORR*, % **PD, %**	4 VS <1 21 VS 55	–	7 VS 3 22 VS 57	4.6 VS 1.1 33.5 VS 50.5
	MEDIAN DOR†, MONTHS	–	–	3.5 VS 2.7	–
SAFETY		(N=467 VS 237)	–	(N=374 VS 193)	(N=197 VS 95)
	ANY GRADE AES, %	99 VS 92	–	100 VS 93	97.0 VS 86.3
	GRADE 3/4 AES, %	68 VS 36	–	66 VS 39	58.9 VS 44.2

1. Abou-Alfa GK, et al. N Engl J Med. 2018;379(1):54-63. 2. Bruix J, et al. Lancet. 2017;389(10064):56-66.
3. Zhu AX, et al. Lancet Oncol. 2019;20(2):282-296. 4. Zhu AX, et al. Presented at: ASCO. 2018 (abstr 4003).

How do you pick a TKI post atezolizumab-bevacizumab or durvalumab-tremelimumab?

	VEGF/ VEGFR	PDGFR / c-Kit	RAF	FGFR	RET	MET	AXL FLT3 TRKb	TIE-2	Immune Modulation
Bevacizumab	X								?
Lenvatinib	X	X		X	X				?
Sorafenib	X	X	X						?
Regorafenib	X	X	X	X	X			X	?
Cabozantinib	X				X	X	X	X	?
Ramucirumab	X								?

How to Best Sequence Patients With Advanced Disease



*Consider in patients where antii-VEGF therapies are contraindicated.

Summary and Conclusions

- Combination therapy is the preferred treatment strategy for patients with advanced HCC
  - Atezo/bev is the de facto gold standard for eligible patients
  - Dual CPI strategy for patients ineligible to receive anti-angiogenic therapies
- Upfront treatment strategies should include considerations for sequencing in subsequent lines of therapy (MOA, toxicities)
- Important considerations:
  - CPB/C
  - Potential (downstaging) and post transplant patients
  - Biomarker development
  - Heterogeneity of patient population
  - Multiple therapeutic options (BUT not compared to one another)

THANK YOU!