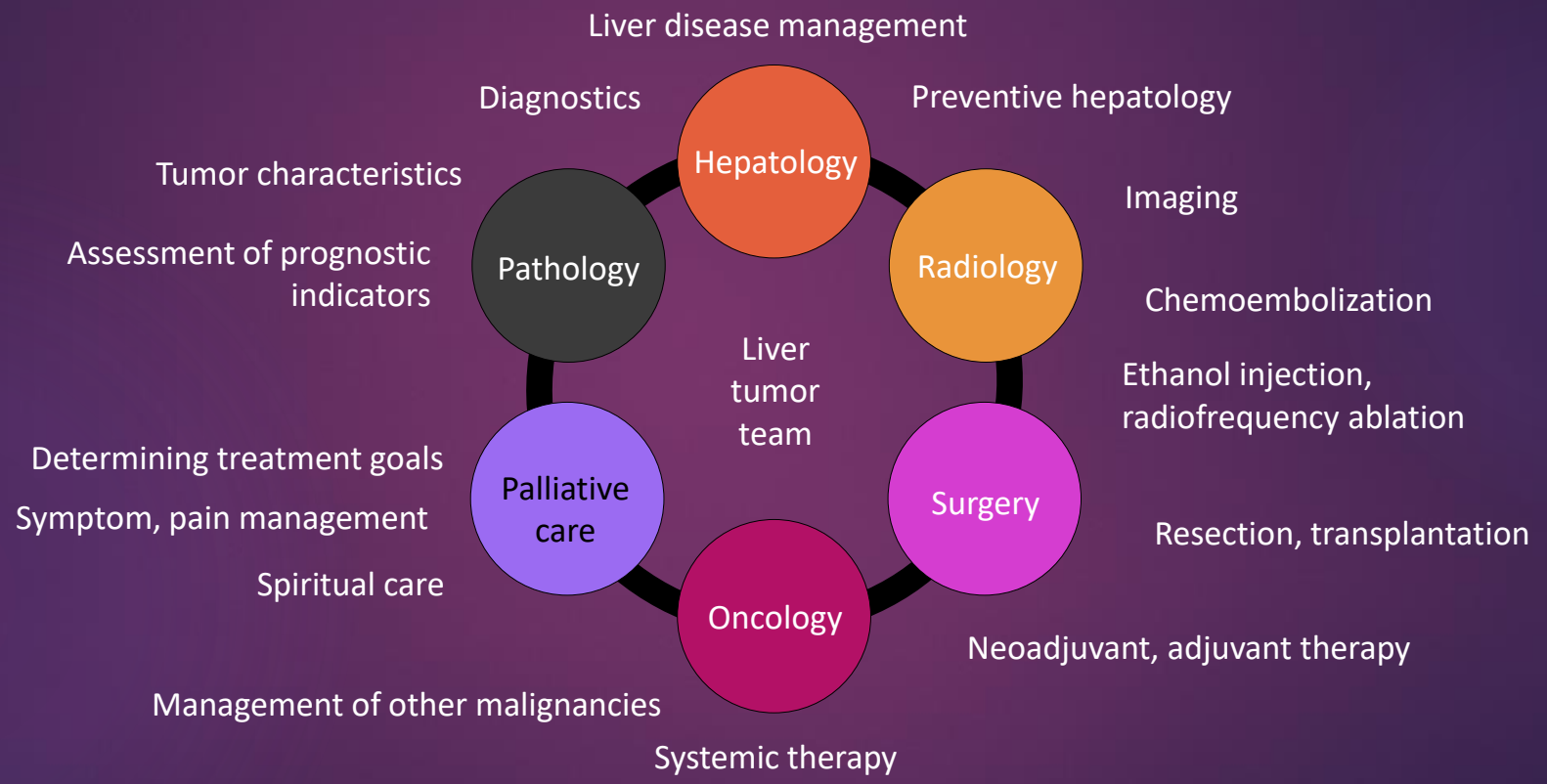
First Line Treatment In HCC

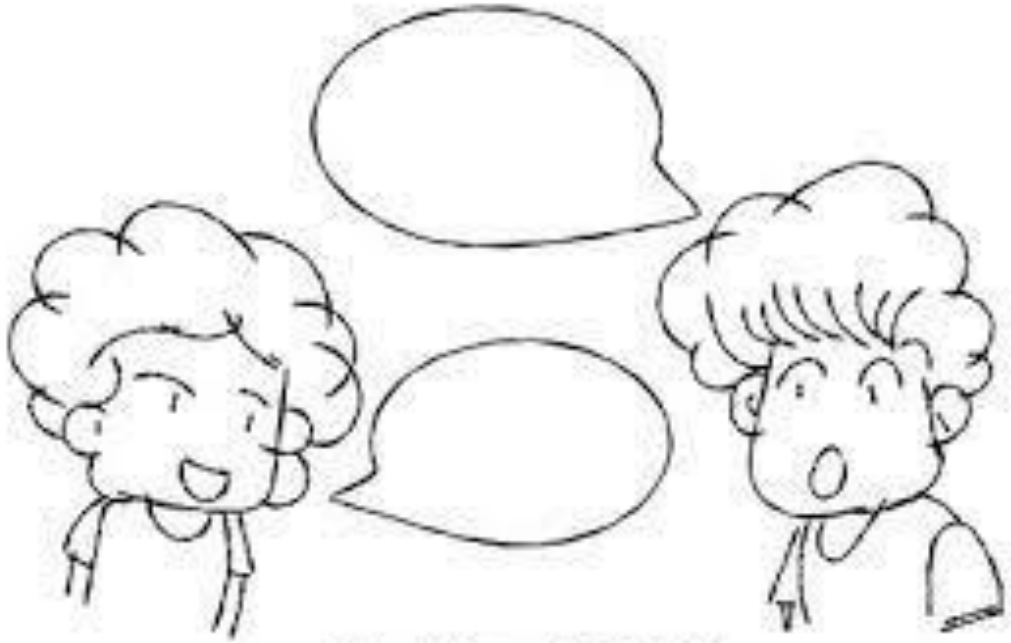
ASHWAQ ALOLAYAN
HEAD OF ADULT MEDICAL ONCOLOGY
MINISTRY OF NATIONAL GUARD

Management of HCC: Multidisciplinary Team

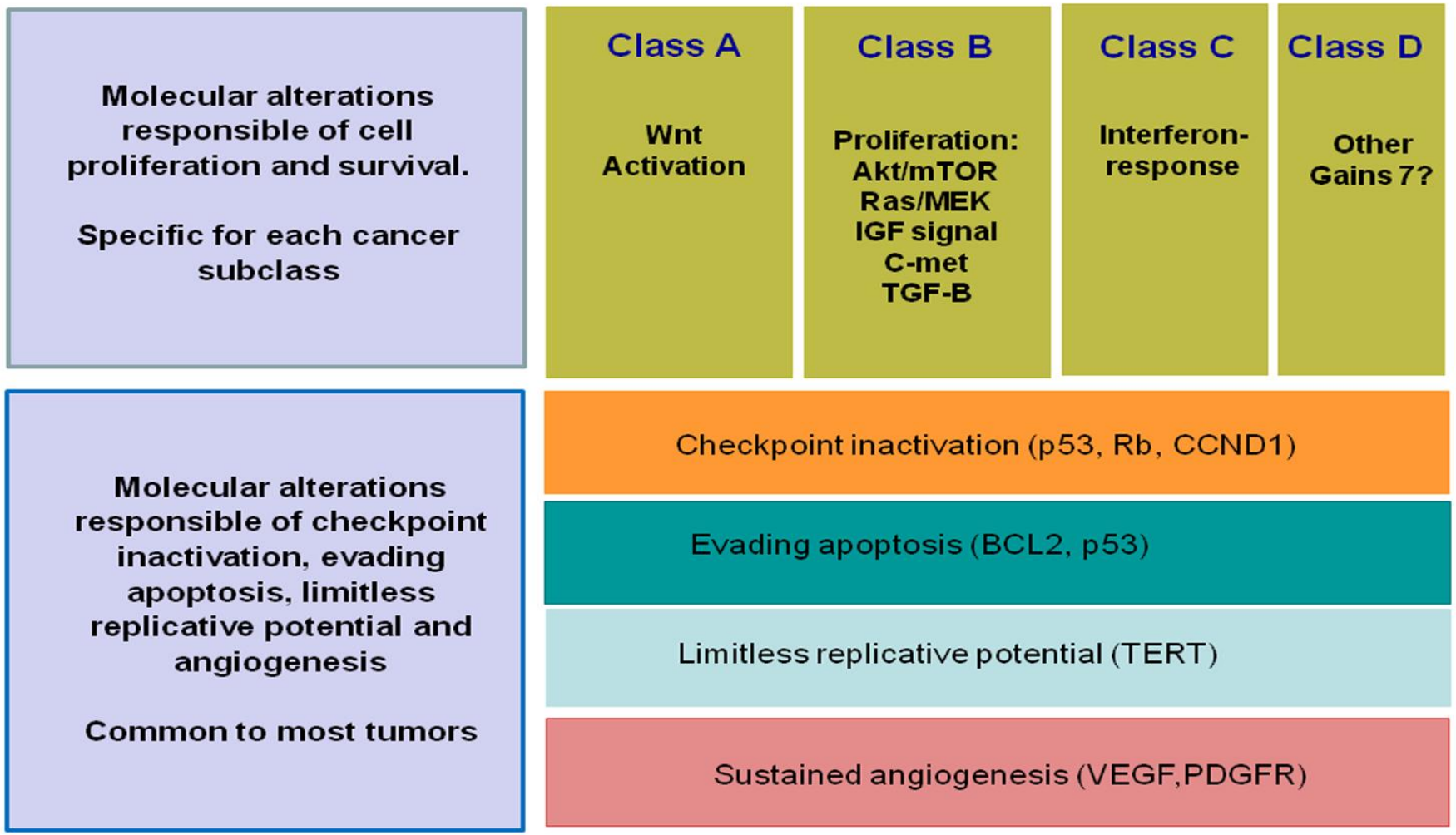


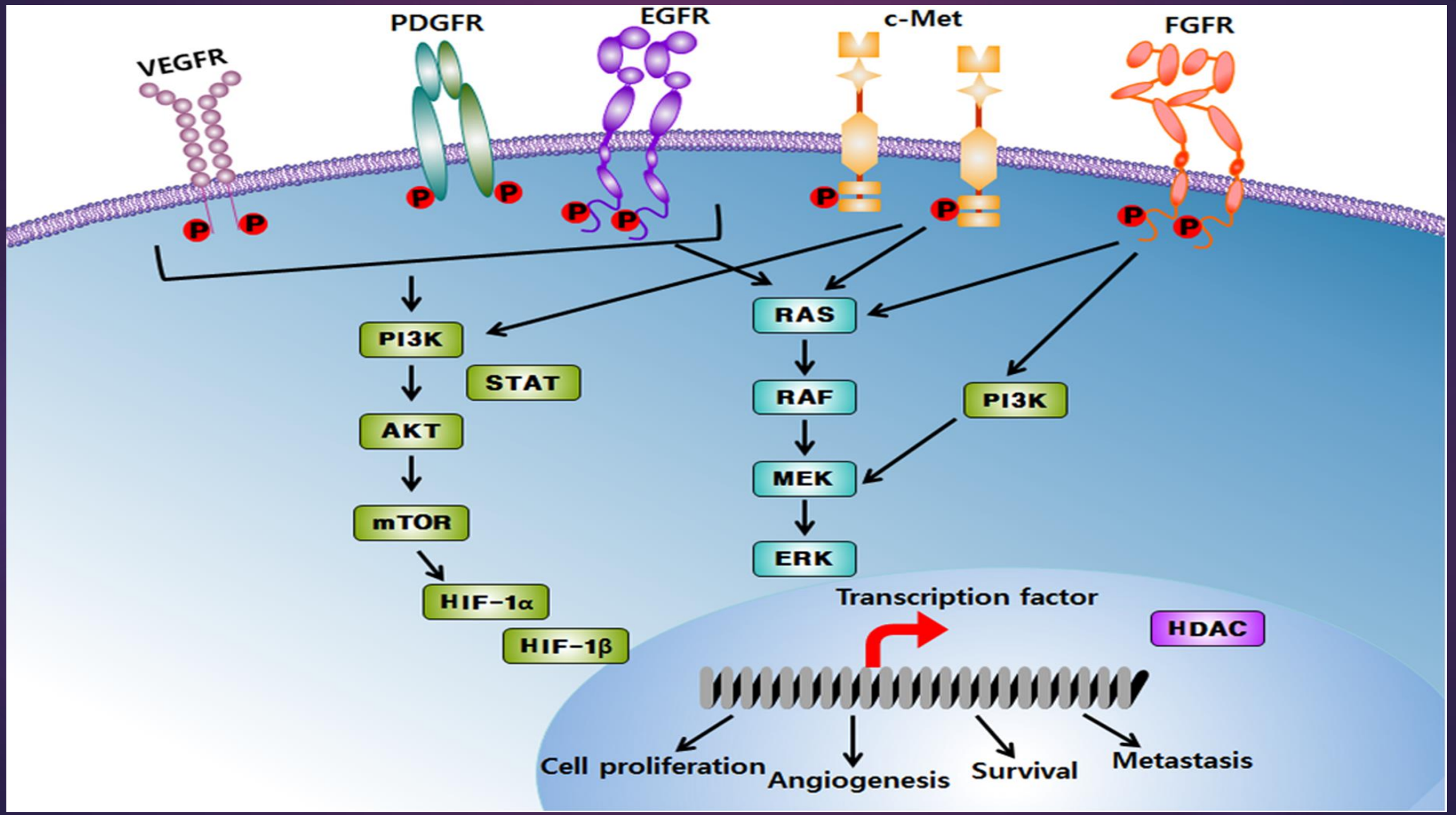
CS313362

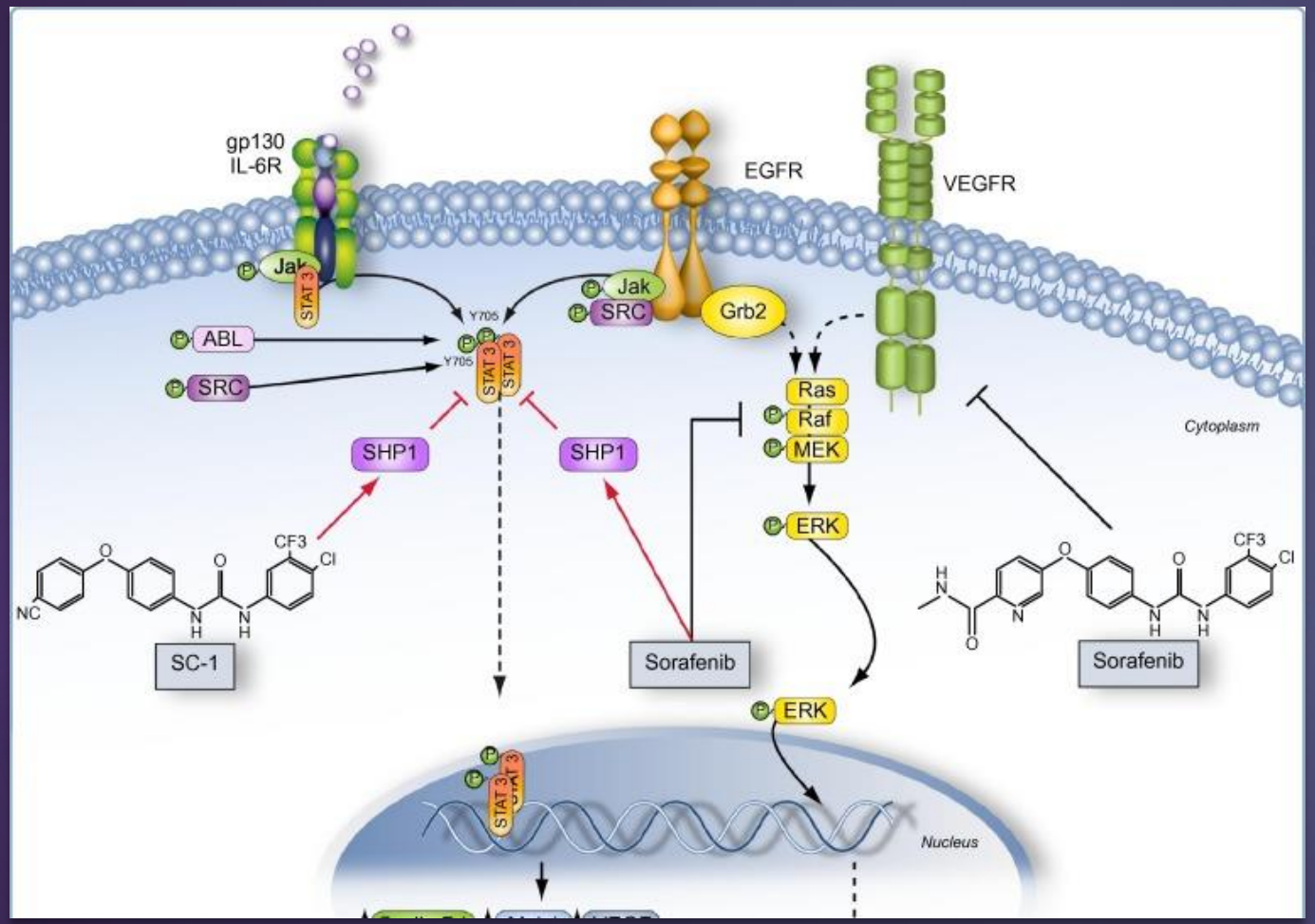
"You have an extremely, rare, hard-to-treat disease — are you trying to make me look bad?"



HCC SUBCLASSES




VEGFR
PDGFR
EGFR
c-Met
FGFR
P
PI3K
STAT
AKT
mTOR
HIF-1α
HIF-1β
RAS
RAF
MEK
ERK
PI3K
Transcription factor
HDAC
Cell proliferation
Angiogenesis
Survival
Metastasis



Sorafenib

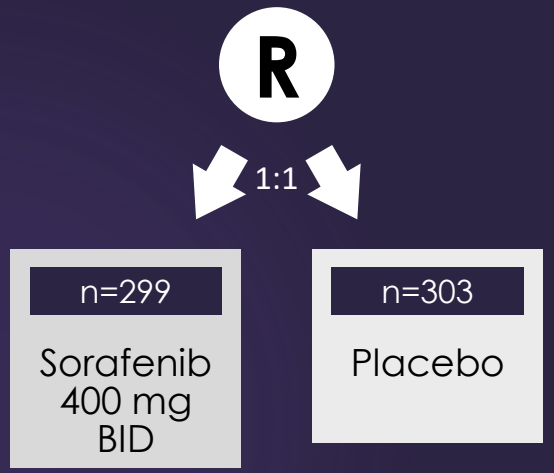
Raf-1, B-Raf, VEGFRs 1, 2, and 3 and PDGFR-β

Phase III SHARP and Asia-Pacific studies: Study designs

SHARP[1]

ELIGIBILITY

Advanced HCC, ECOG PS 0-2, Child-Pugh A, no prior systemic therapy



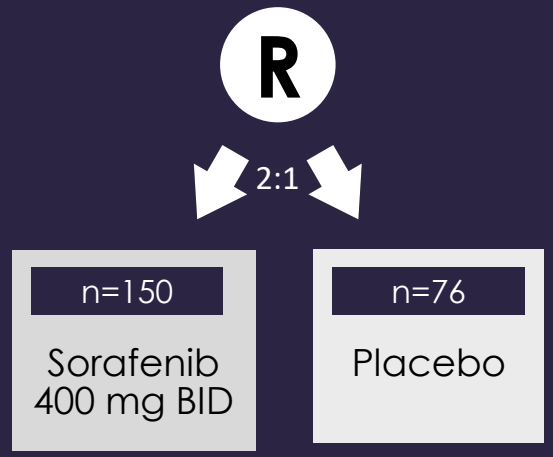
Primary Endpoints: OS, TTSP

Secondary Endpoints: TTP, DCR, safety

ASIA-PACIFIC[2]

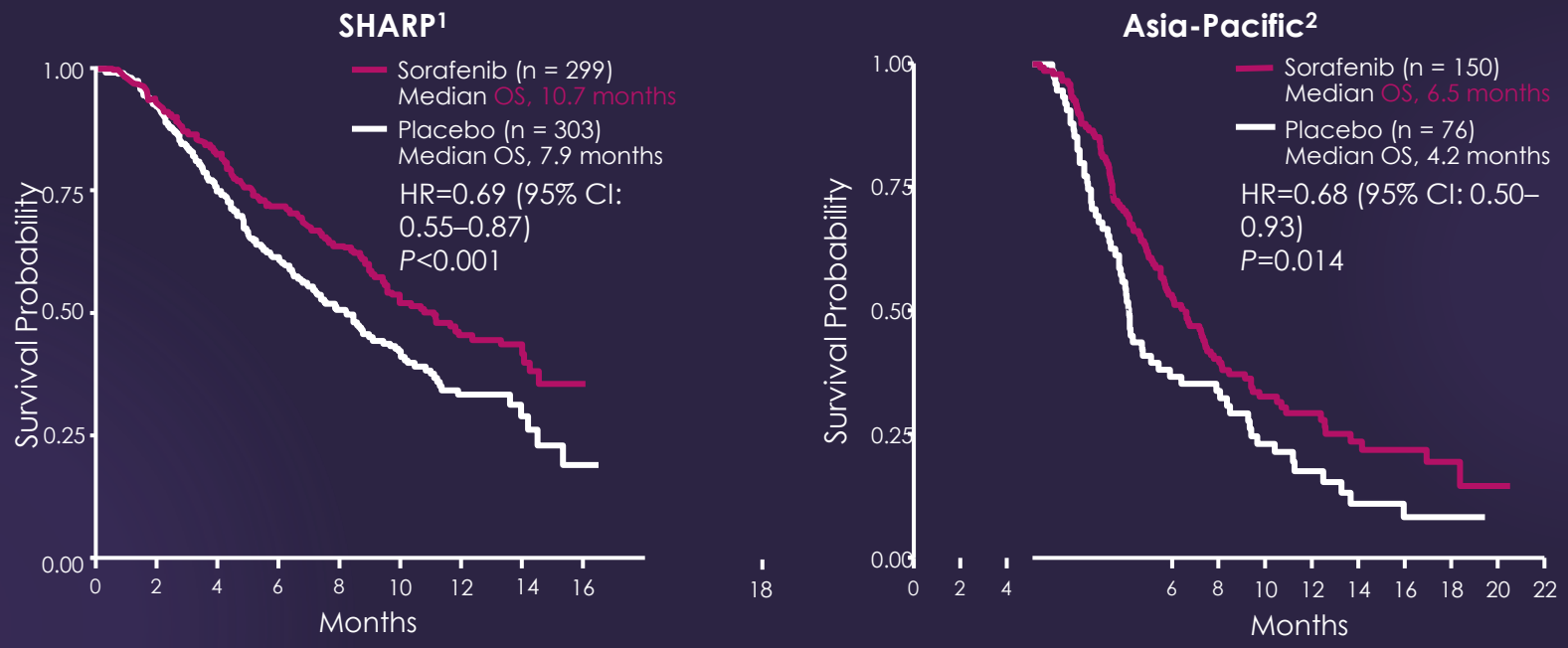
STRATIFICATION

MVI and/or EHS, ECOG PS (0 vs 1-2), geographic region

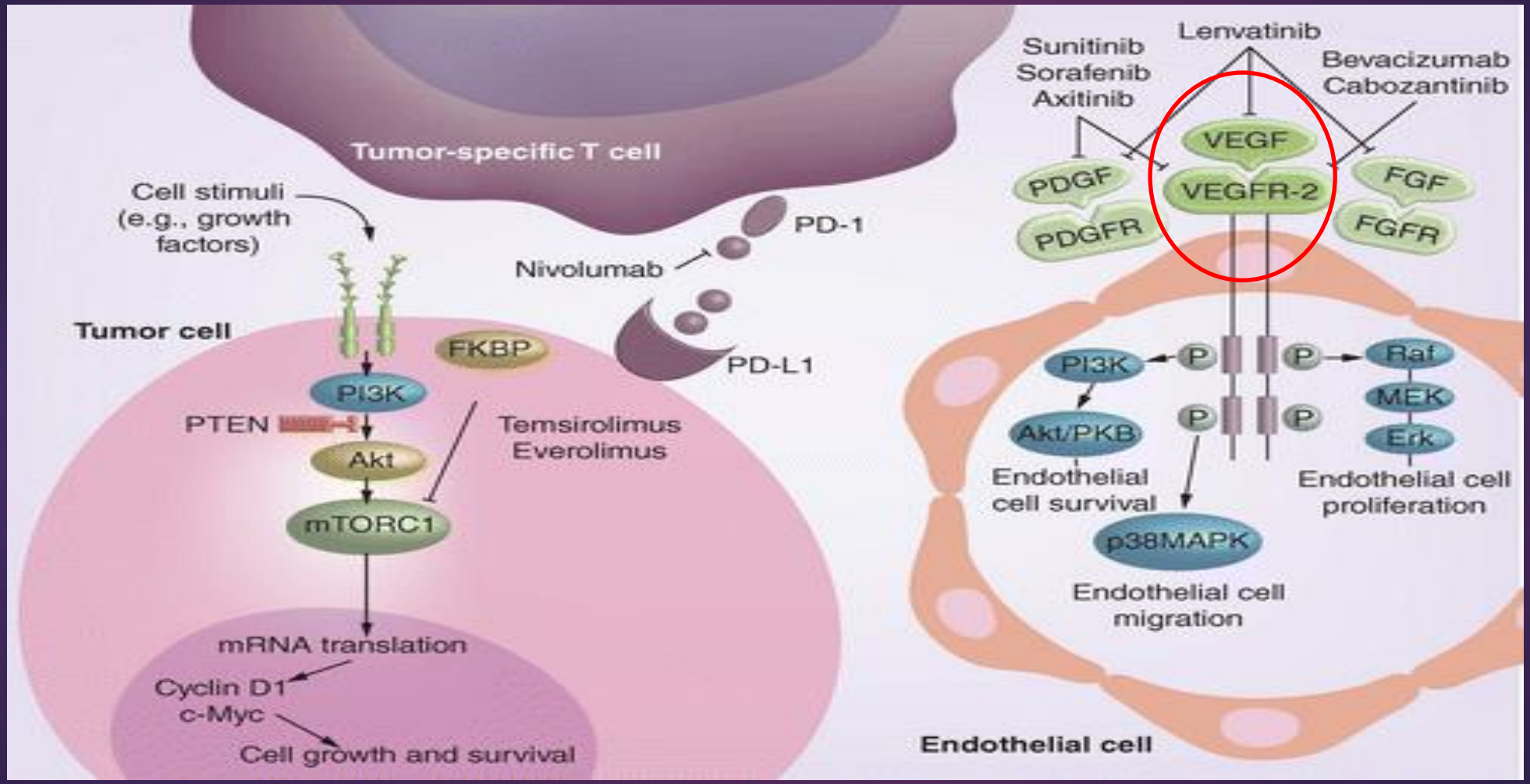


Endpoints: OS, TTSP, TTP, DCR, safety (no primary endpoint defined)

Overall survival from two phase III trials: SHARP and Asia-Pacific



Lenvatinib

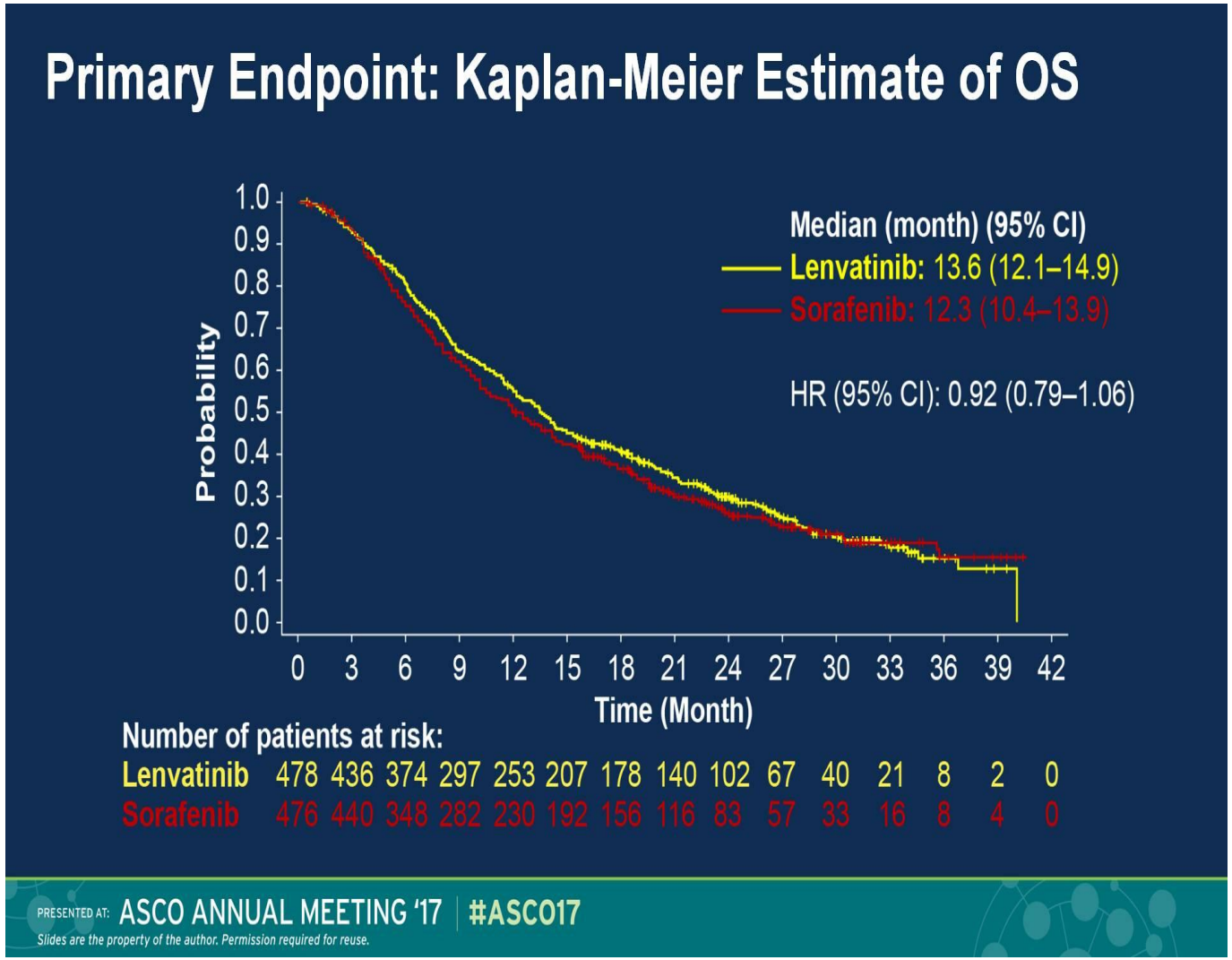

Tumor-specific T cell
Cell stimuli
(e.g., growth
factors)
PD-1
Nivolumab
PD-L1
Tumor cell
FKBP
PI3K
PTEN
Akt
Temsirolimus
Everolimus
mTORC1
mRNA translation
Cyclin D1
c-Myc
Cell growth and survival
Sunitinib
Sorafenib
Axitinib
Lenvatinib
Bevacizumab
Cabozantinib
VEGF
PDGF
VEGFR-2
FGF
PDGFR
FGFR
PI3K
P
P
Raf
MEK
Erk
Akt/PKB
P
P
Endothelial
cell survival
Endothelial cell
proliferation
p38MAPK
Endothelial cell
migration
Endothelial cell

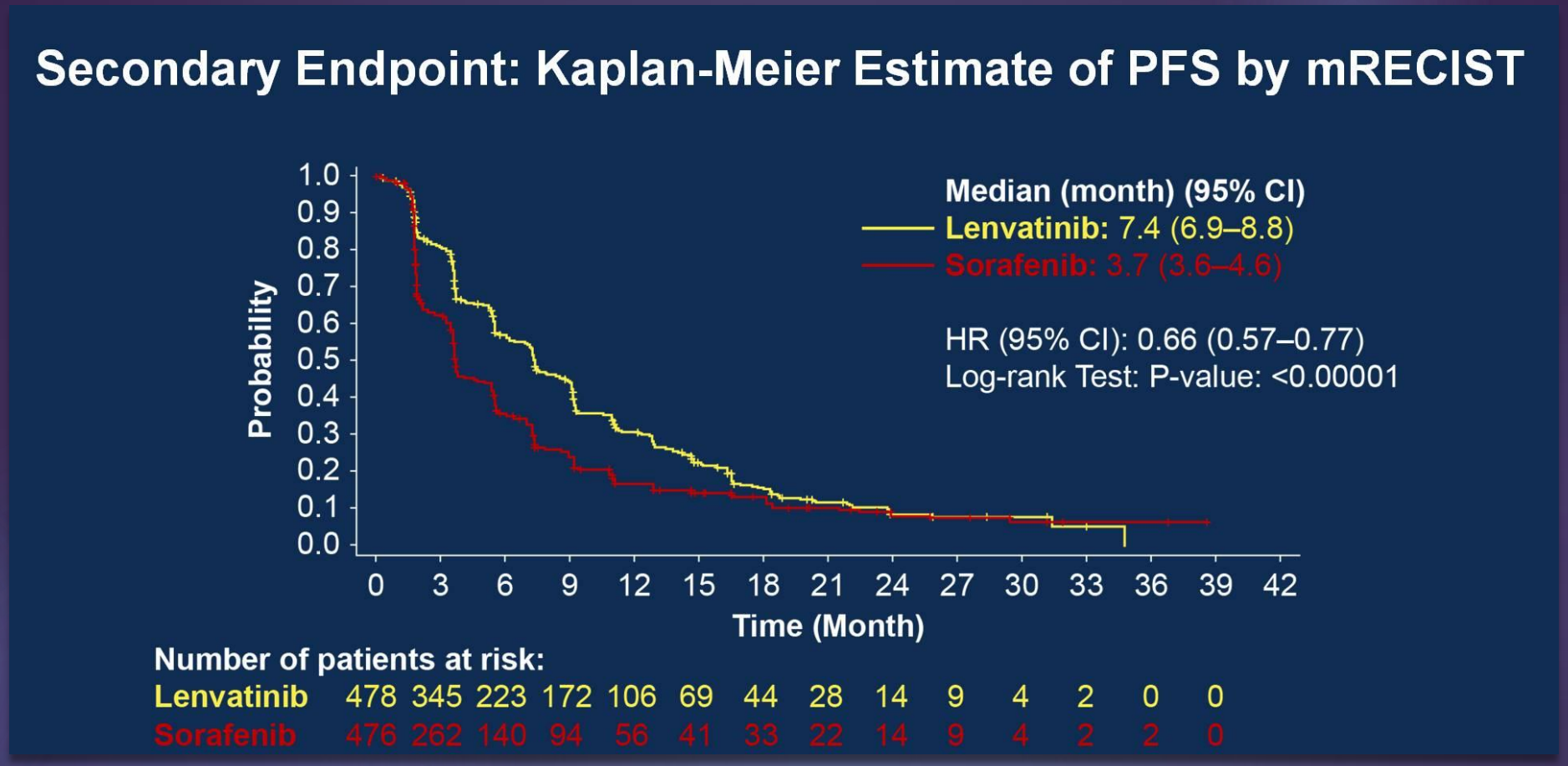
A Phase 3 Trial of Lenvatinib vs Sorafenib in First-line Treatment of Patients With Unresectable Hepatocellular Carcinoma (REFLECT Study)

PRESENTED BY ANN-LII CHENG AT 2017 ASCO ANNUAL MEETING

Primary Endpoint: Kaplan-Meier Estimate of OS

Presented By Ann-Lii Cheng at 2017 ASCO Annual Meeting





Secondary Endpoint: Kaplan-Meier Estimate of PFS by mRECIST

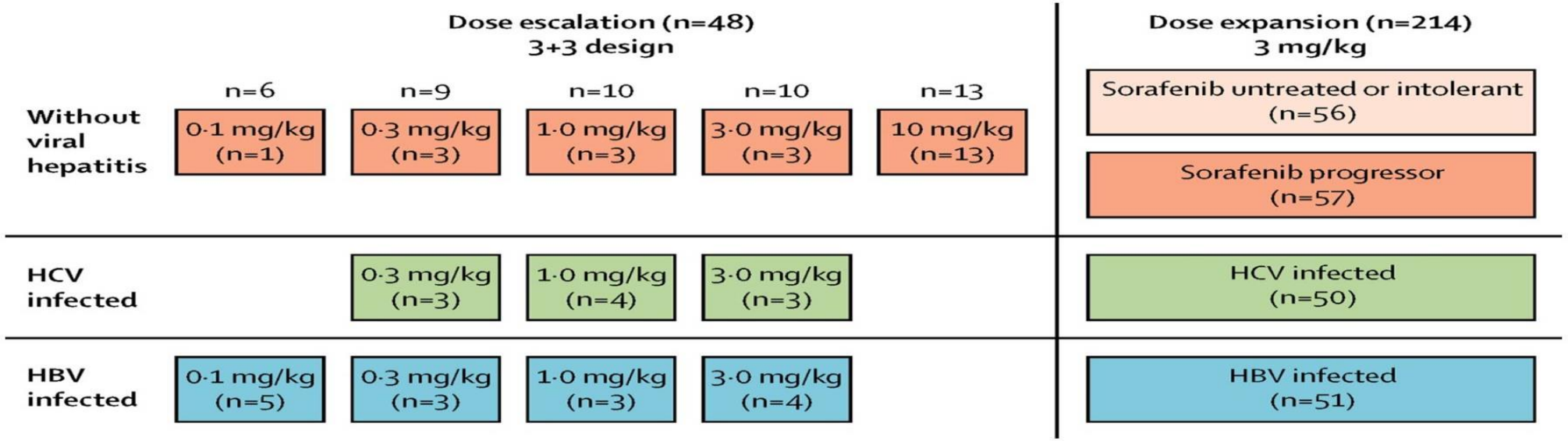
PRESENTED BY ANN-LII CHENG AT 2017 ASCO ANNUAL MEETING

Nivolumab

Nivolumab

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*

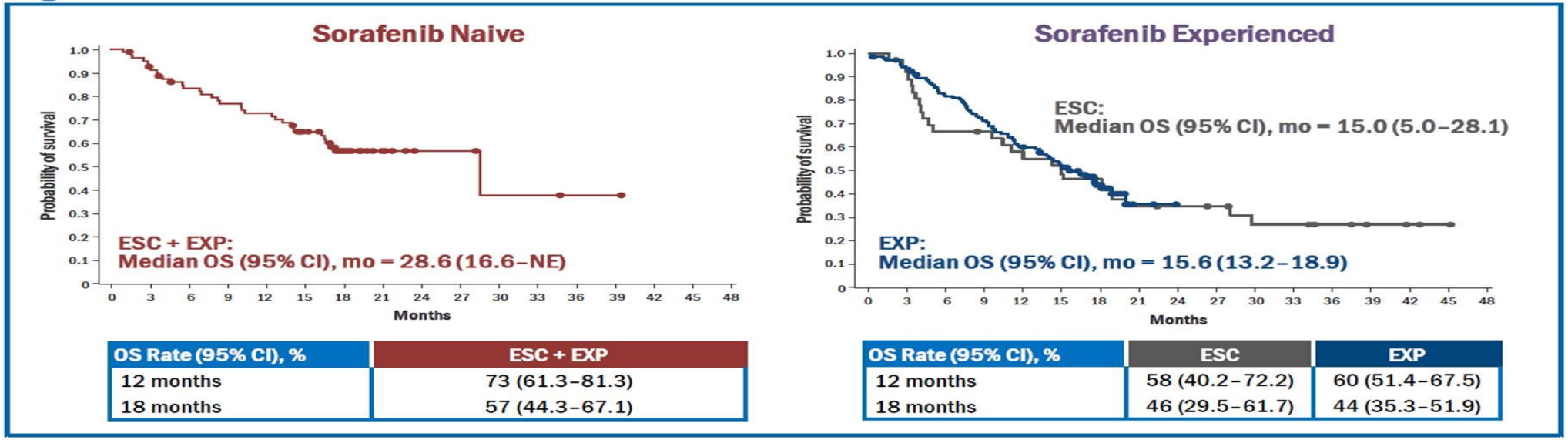


El-Khoueiry A et al, Lancet, online April 2017

Nivolumab

Survival update based on sorafenib exposure

Figure 4. Overall Survival



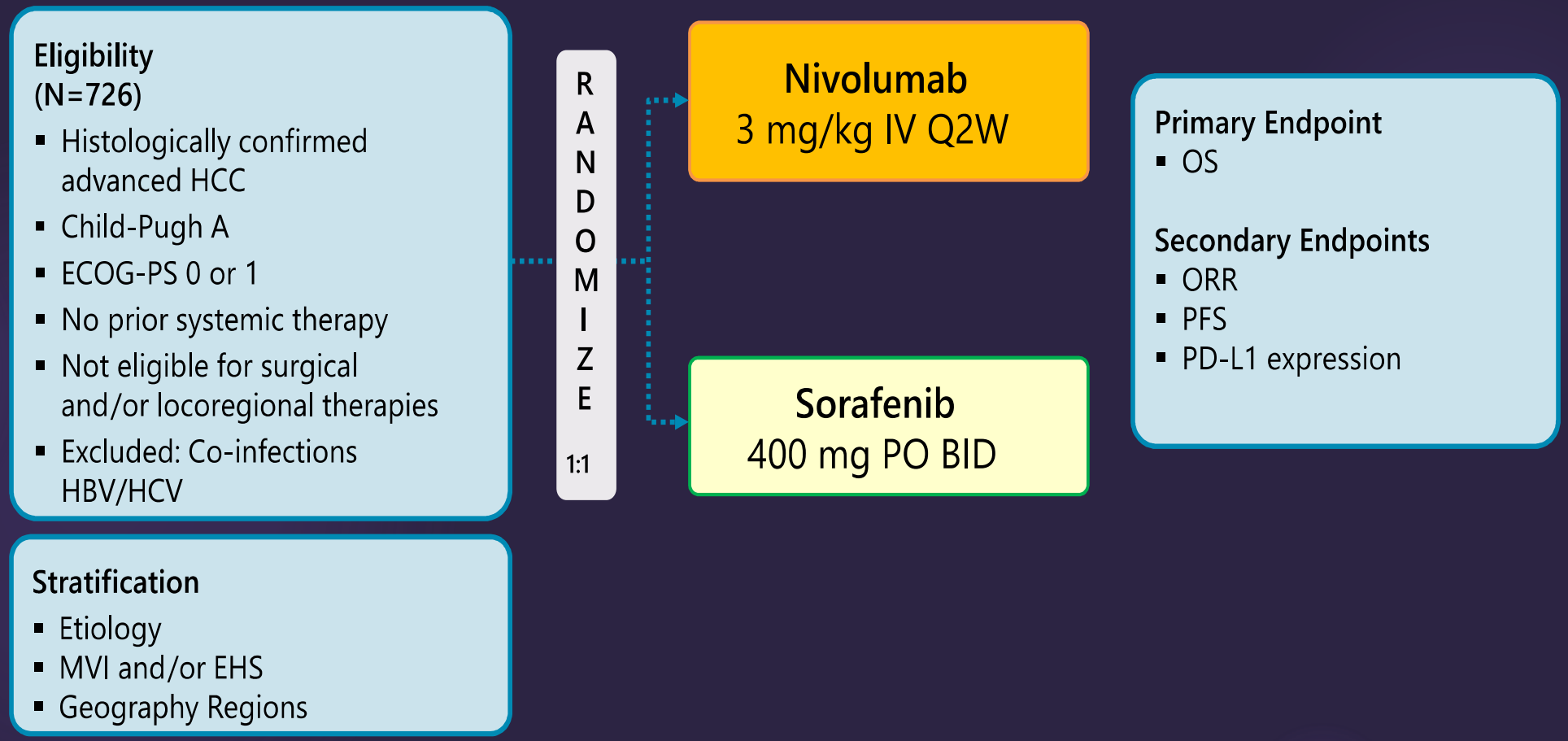
OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)

OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2–72.2)	60 (51.4–67.5)
18 months	46 (29.5–61.7)	44 (35.3–51.9)

Kaplan-Meier method; closed circles denote censored patients.

Crocenzi T et al, J Clin Oncol 35, 2017 (suppl; abstr 4013)

Nivolumab


Eligibility
(N=726)
Histologically confirmed advanced HCC
Child-Pugh A
ECOG-PS 0 or 1
No prior systemic therapy
Not eligible for surgical and/or locoregional therapies
Excluded: Co-infections HBV/HCV
Stratification
Etiology
MVI and/or EHS
Geography Regions
RANDOMIZE
1:1
Nivolumab
3 mg/kg IV Q2W
Sorafenib
400 mg PO BID
Primary Endpoint
OS
Secondary Endpoints
ORR
PFS
PD-L1 expression

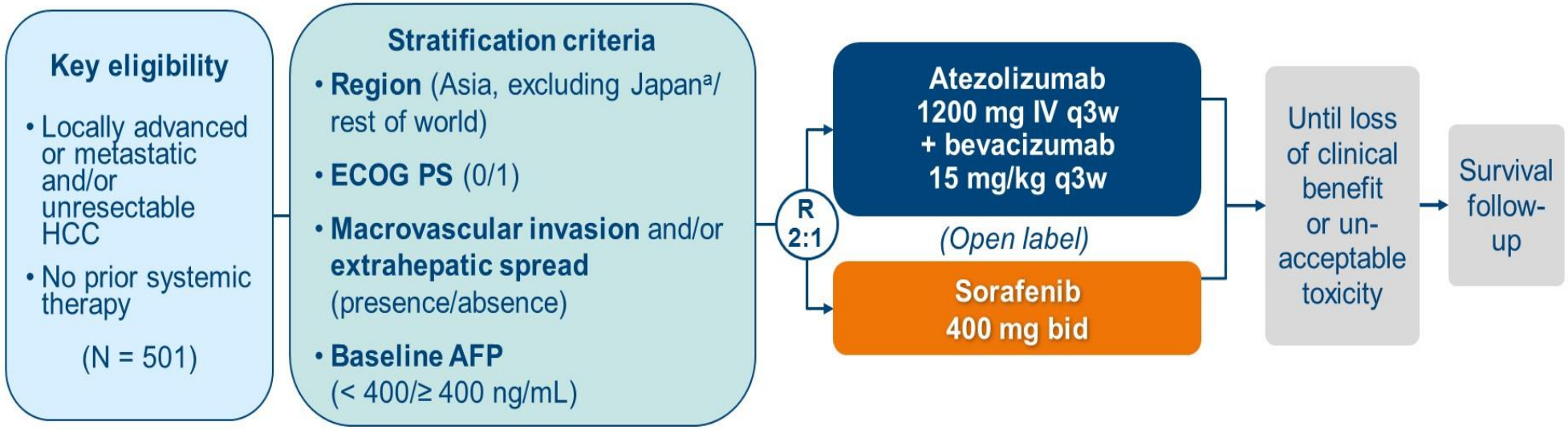
Check Mate 459: OS (Primary Endpoint)

Survival Outcome	Nivolumab (n = 371)	Sorafenib (n = 372)	HR
Median OS, mos (95% CI) (primary endpoint)	16.4 (13.9-18.4)	14.7 (11.9-17.2)	0.85 (95% CI: 0.72-1.02; *P* = .0752)
▪ 12-mo OS rate, %	59.7	55.1	
▪ 24-mo OS rate, %	36.8	33.1	
Patients with PD-L1 ≥ 1%			
▪ Median OS, mos (95% CI)	16.1 (8.4-22.3)	8.6 (5.7-16.3)	0.80 (0.54-1.19)
Patients with PD-L1 < 1%			
▪ Median OS, mos (95% CI)	16.7 (13.9-18.6)	15.2 (12.6-18.1)	0.84 (0.69-1.02)

Check Mate 459: PFS and Response

Outcome	Nivolumab	Sorafenib
Median PFS, mos (95% CI)	3.7 (3.1-3.9)	3.8 (3.7-4.5)
12-mo PFS rate, %	22	14
24-mo PFS rate, %	14	6
ORR, n (%)	57 (15)	26 (7)
Best objective response, n (%)		
▪ CR	14 (4)	5 (1)
▪ PR	43 (12)	21 (6)
ORR by PD-L1 expression, n/N (%)		
▪ PD-L1 ≥ 1%	20/71 (28)	6/64 (9)
▪ PD-L1 < 1%	36/295 (12)	20/300 (7)

IMbrave150 Study Design



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

Secondary endpoints include
- IRF-assessed ORR per RECIST 1.1 and HCC mRECIST
- PROs: TTD[b] of QOL, physical and role functioning (EORTC QLQ-C30)

Exploratory PRO endpoints
- TTD[c] of symptoms (EORTC QLQ-HCC18)
- Patients (%) with clinically meaningful deterioration in QOL, physical and role functioning

EORTC, European Organisation for Research and Treatment of Cancer; IRF, independent review facility; mRECIST, modified RECIST; TTD, time to deterioration.
[a] Japan is included in rest of world. [b] Time from randomization to first decrease from baseline of ≥ 10 points maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks. [c] Time from randomization to the first increase from baseline of ≥ 10 points in the symptom scales maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.

Baseline characteristics

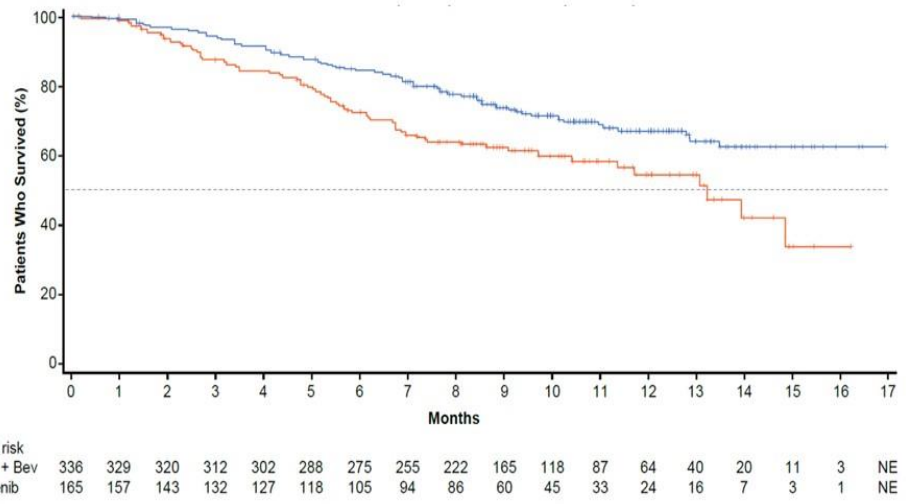
Characteristic	Updated analysis	
	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median age (range), years	64 (26-88)	66 (33-87)
Male, n (%)	277 (82)	137 (83)
Region, n (%)		
Asia (excluding Japan[a])	133 (40)	68 (41)
Rest of world	203 (60)	97 (59)
ECOG PS 1, n (%)	127 (38)	62 (38)
Child-Pugh class, n (%)		
A / B	333 (99) / 1 (< 1)	165 (100) / 0
BCLC staging at study entry, n (%)		
A / B / C	8 (2) / 51 (15) / 277 (82)	6 (4) / 25 (15) / 134 (81)
Etiology 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 (%)	131 (39)	70 (42)
Prior radiotherapy, n (%)	34 (10)	17 (10)

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.
[a] Japan is included in rest of world.

IMbrave150 Co-Primary Endpoints: OS and PFS[1]

OS

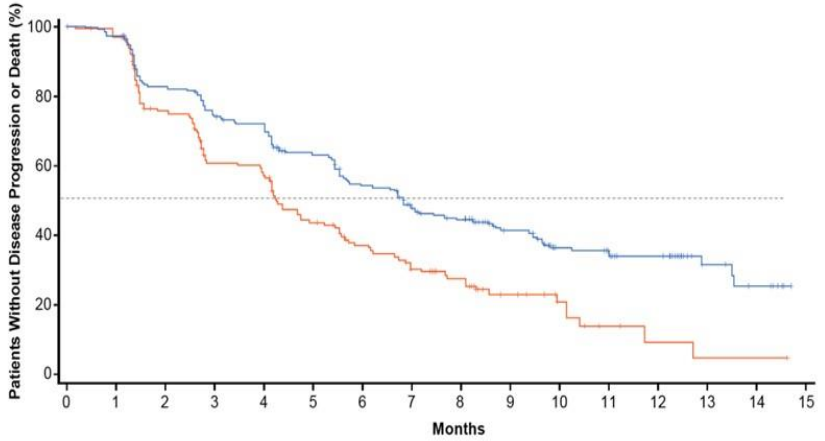
	Atezo + Bev	Sorafenib
Median (95% CI), mo	NE	13.2 (10.4, NE)
HR	0.58 (95% CI: 0.42, 0.79)[a]	
P value	0.0006[b]	



No. at risk																	
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

PFS (IRF assessed RECIST 1.1)

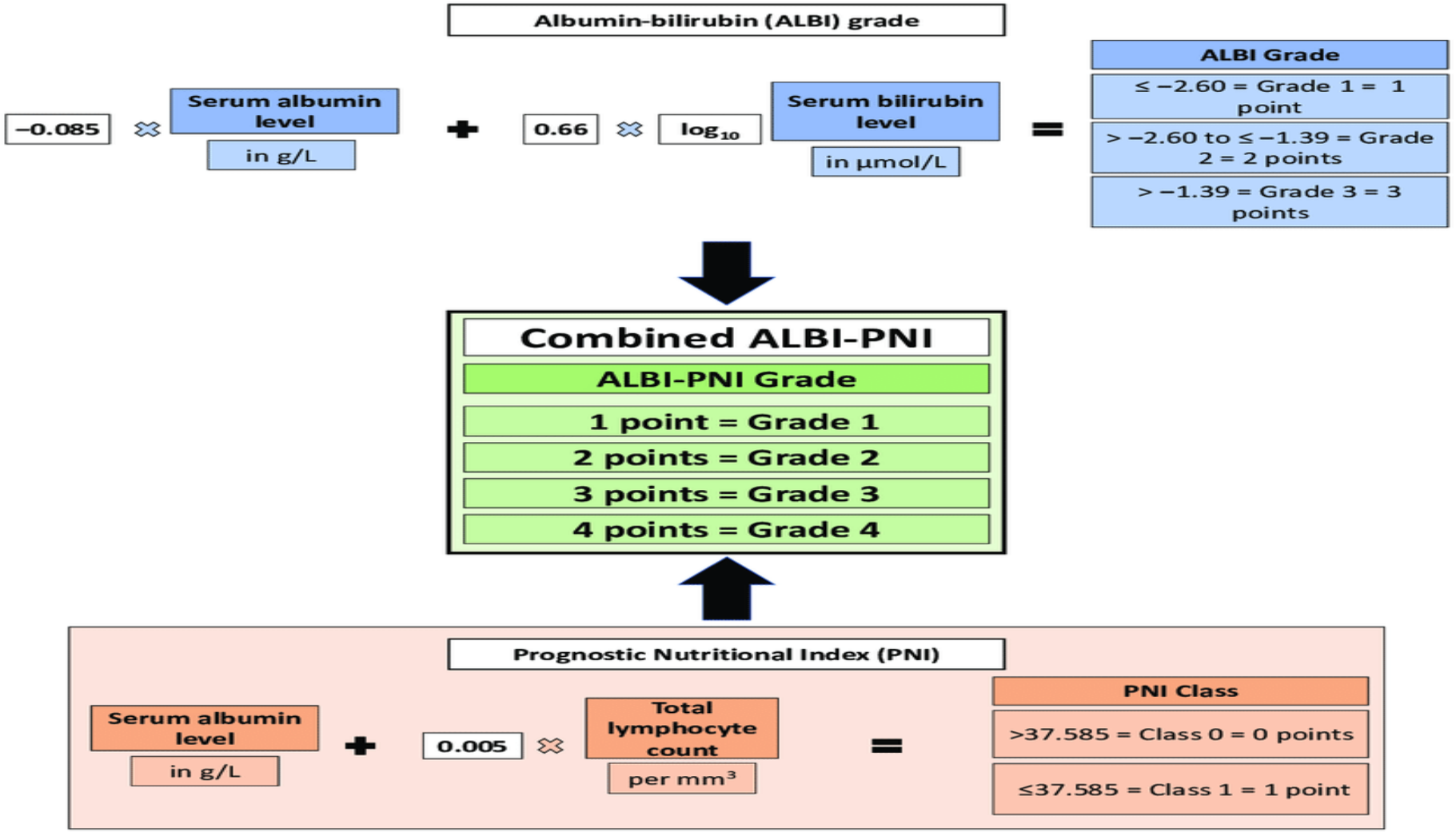
	Atezo + Bev	Sorafenib
Median (95% CI), mo	6.8 (5.7, 8.3)	4.3 (4.0, 5.6)
HR	0.59 (95% CI: 0.47, 0.76)[a]	
P value	< 0.0001[c]	



No. at risk																
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE

NE, not estimable.
Data cutoff, August 29, 2019; median survival follow-up, 8.6 months. [a] 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. [b] The 2-sided *P* value boundary based on 161 events is 0.0033. [c] The 2-sided *P* value boundary is 0.002. 1. Cheng A-L, et al. *Ann Oncol.* 2019;30(suppl 9) [abstract LBA3].

included and their weighting factors are shown in Figure 2. BCLC, HAP, mHAP-II, and Six-and-Twelve score were calculated as described in the original publications [3,8,16–



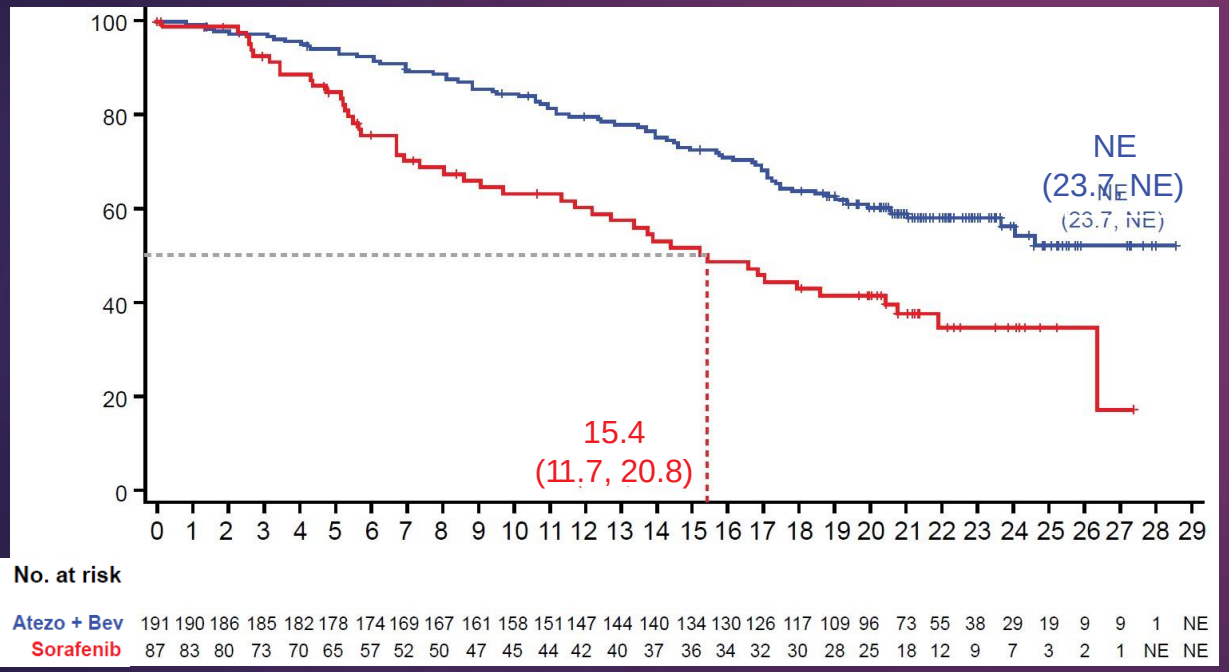
OS by ALBI grade

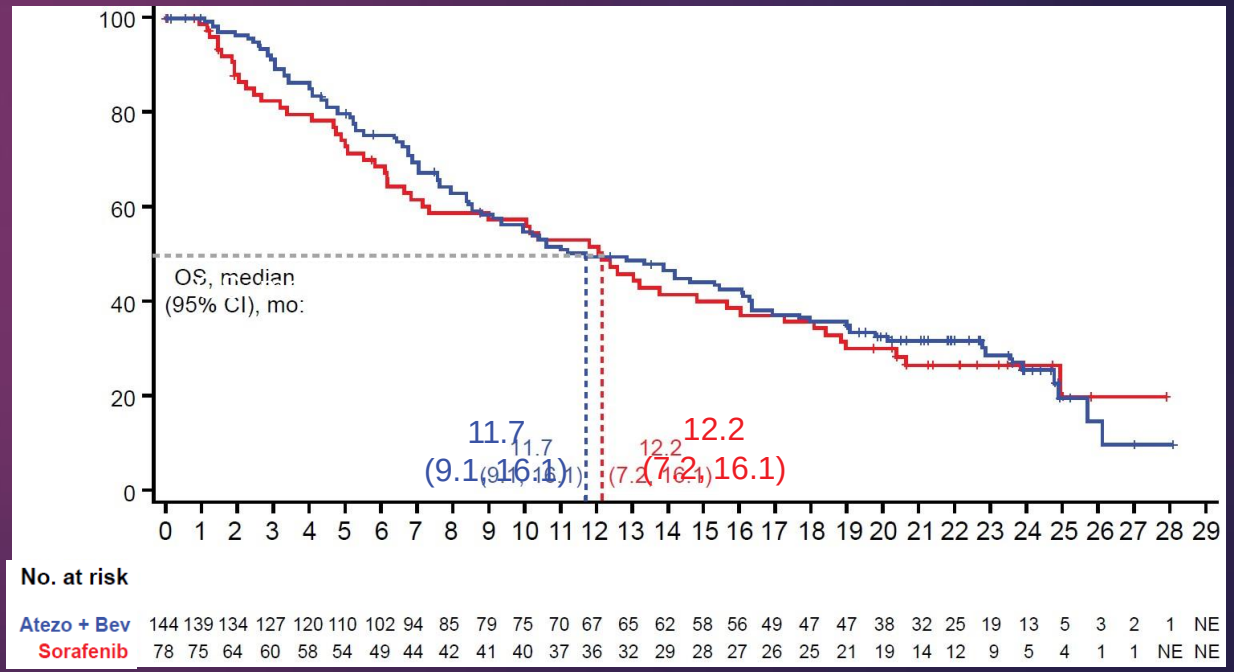
ALBI Grade 1

	Atezo + Bev (n=191)	Sorafenib (n=87)
OS events, n (%)	79 (41)	47 (54)
HR (95% CI)[a]	**0.50 (0.35, 0.72)**	

ALBI Grade 2

	Atezo + Bev (n=144)	Sorafenib (n=78)
OS events, n (%)	100 (69)	53 (68)
HR (95% CI)[a]	**0.92 (0.66, 1.29)**	



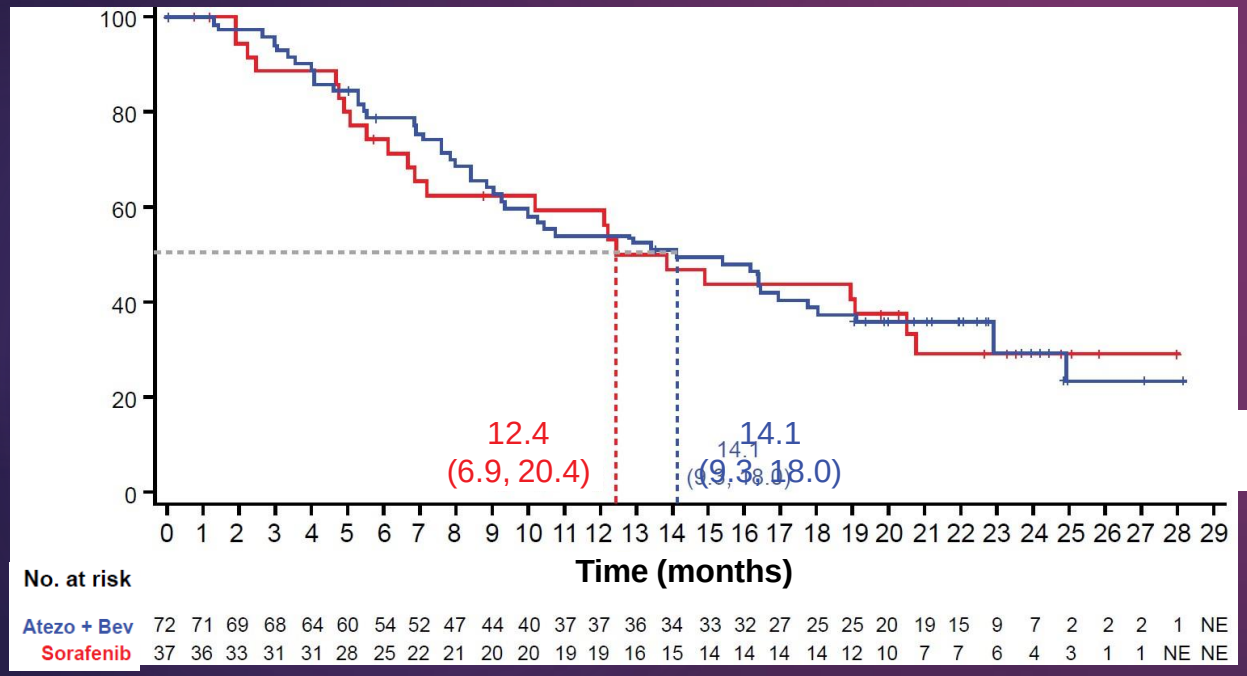


Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. NE, not estimable. [a] HR is unstratified.

OS by mALBI grade

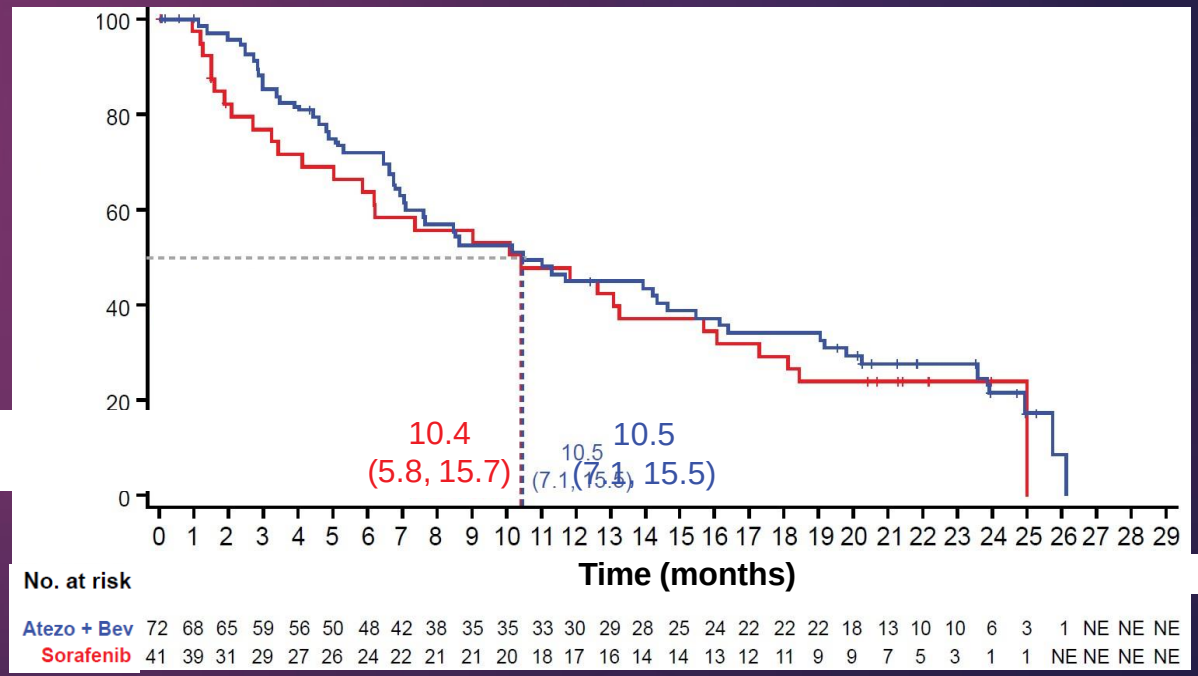
mALBI Grade 2a

	Atezo + Bev (n=72)	Sorafenib (n=37)
OS events, n (%)	47 (65)	23 (62)
HR (95% CI)[a]	**0.97 (0.59, 1.59)**	



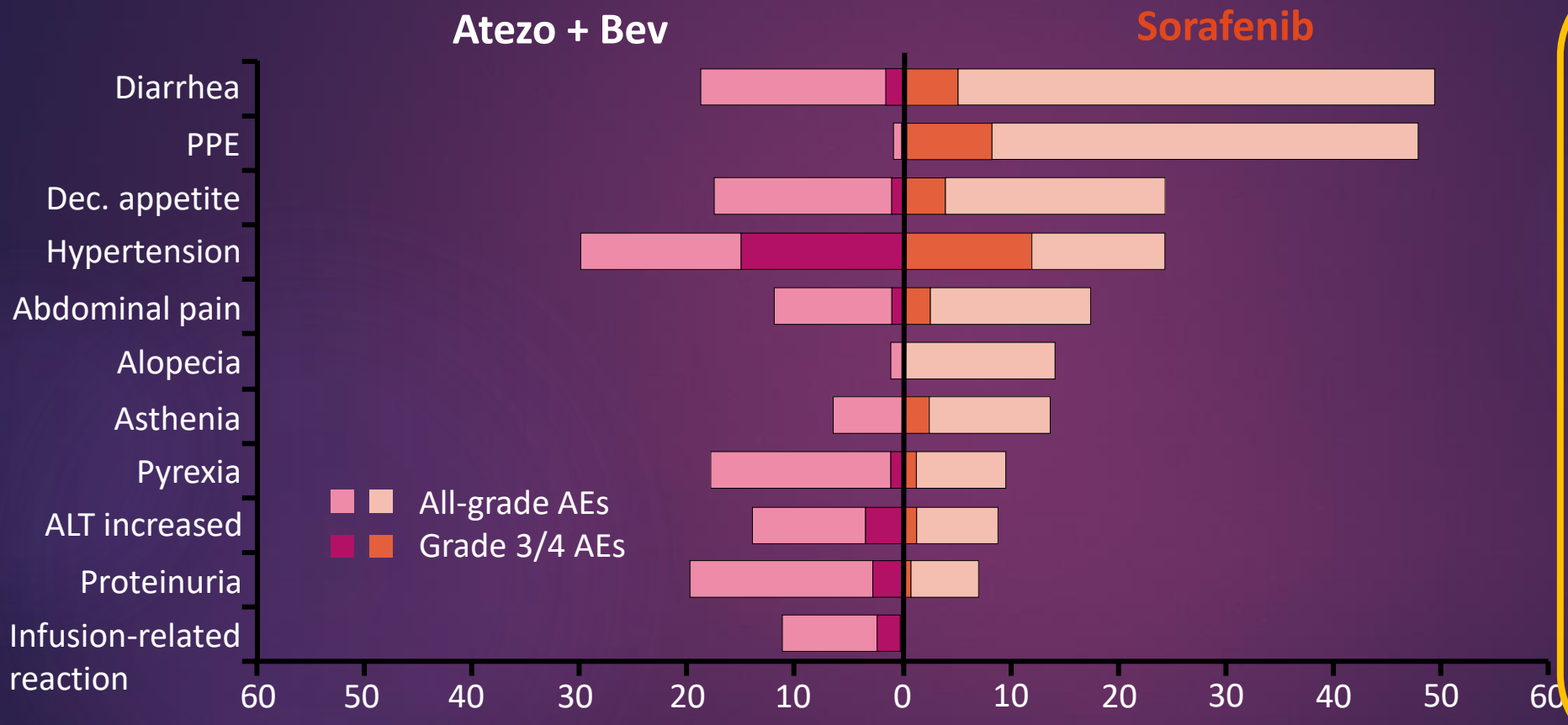
mALBI Grade 2b

	Atezo + Bev (n=72)	Sorafenib (n=41)
OS events, n (%)	53 (74)	30 (73)
HR (95% CI)[a]	**0.85 (0.54, 1.34)**	



Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. [a] HR is unstratified.

IMbrave150: Safety

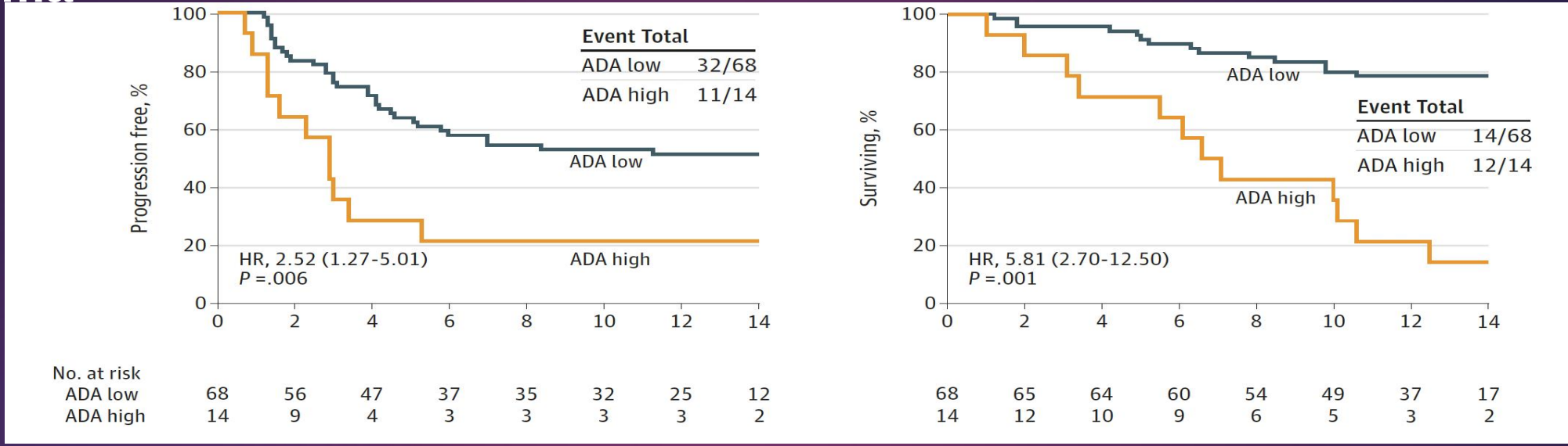


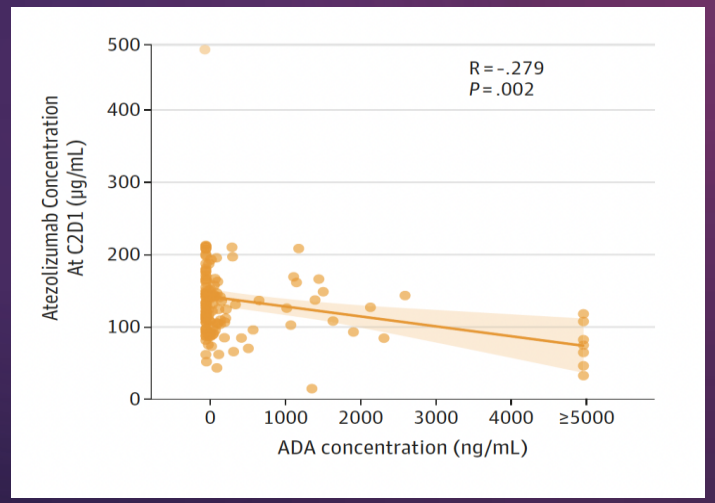
- EGD within 6 mo of initiating treatment required to evaluate for varices; varices of any size according to local standards of care
- Upper GI bleeding rate in atezo + bev vs sorafenib groups: 7% vs 4.5%; this was consistent with historical data in other studies of bevacizumab in HCC

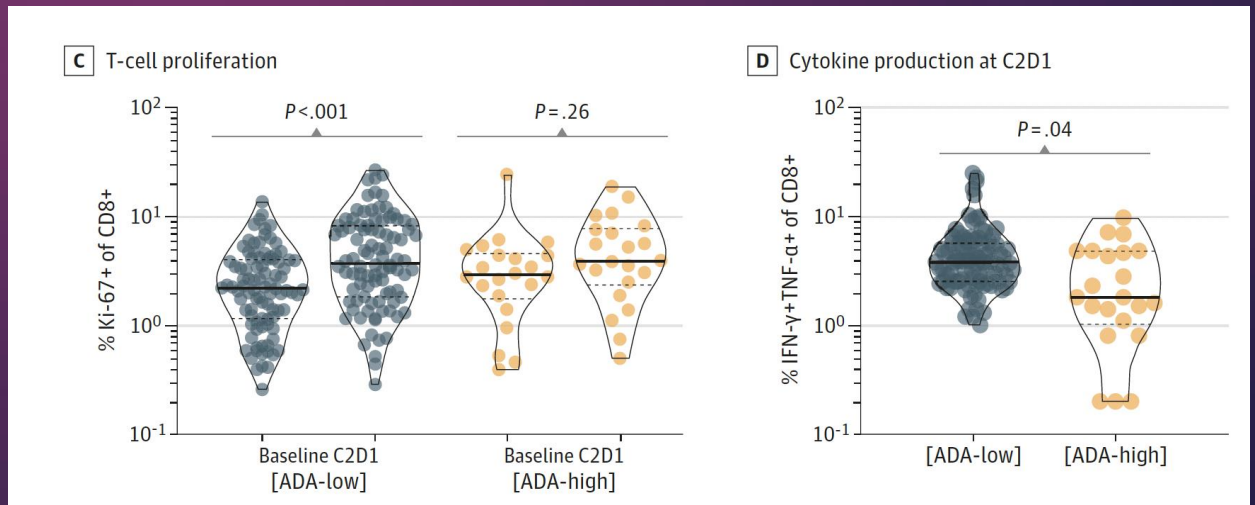
≥10% frequency in either arm and >5% difference between arms.

Cheng. ESMO Asia 2019. Abstr LBA3. Finn. NEJM. 2020;382:1894.

Association of High Levels of Antidrug Antibodies Against Atezolizumab With Clinical Outcomes and T-Cell Responses in Patients With Hepatocellular Carcinoma







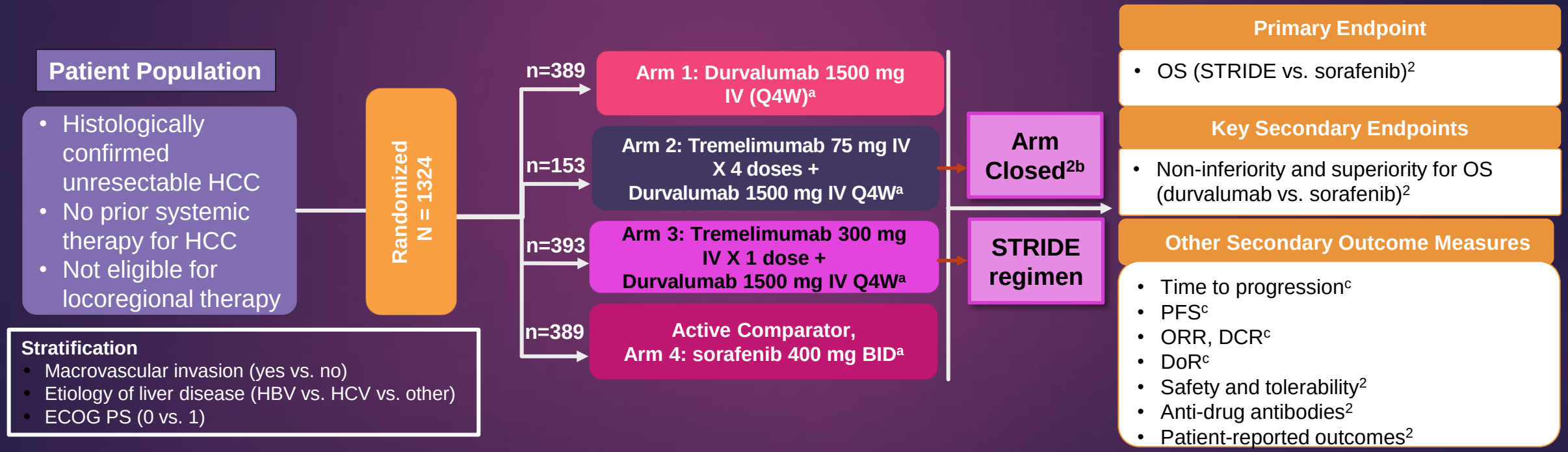
Kim et al. Jama Oncology 2022


HIMALAYA

HIMALAYA: Study Design[1,2]

Phase III, randomized, open-label, multicenter, global study

To evaluate the efficacy and safety of durvalumab plus tremelimumab combination therapy and durvalumab monotherapy versus sorafenib in the 1L treatment of patients with unresectable HCC



*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; [b]Arm 2 was closed following a preplanned analysis of a Phase II study. The protocol was amended to randomly assign patients 1:1:1 to receive STRIDE, durvalumab, or sorafenib. Patients randomized to this arm could continue treatment. Results from this arm are not reported here; [c]According to RECISTv1.1 per investigator assessment.

1L = first-line; BID = twice daily; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; HBV = hepatitis B virus; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; IV = intravenous; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; Q4W = every 4 weeks; STRIDE = Single Tremelimumab Regular Interval Durvalumab; vs. = versus.

1. Study NCT03298451. ClinicalTrials.gov website. 2. Abou-Alfa GK, et al. *NEJM Evid.* 2022. doi:10.1056/EVIDoa2100070.

Baseline characteristics

Characteristic	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Male sex, n (%)	327 (83.2)	323 (83.0)	337 (86.6)
Median age (range), years	65.0 (22–86)	64.0 (20–86)	64.0 (18–88)
Region, n (%)			
Asia (excluding Japan)	156 (39.7)	167 (42.9)	156 (40.1)
Rest of world (including Japan)	237 (60.3)	222 (57.1)	233 (59.9)
Viral etiology,*,† n (%)			
HBV	122 (31.0)	119 (30.6)	119 (30.6)
HCV	110 (28.0)	107 (27.5)	104 (26.7)
Nonviral	161 (41.0)	163 (41.9)	166 (42.7)
ECOG PS, n (%)			
0	244 (62.1)	237 (60.9)	241 (62.0)
1	148 (37.7)	150 (38.6)	147 (37.8)
BCLC,† n (%)			
B	77 (19.6)	80 (20.6)	66 (17.0)
C	316 (80.4)	309 (79.4)	323 (83.0)

Characteristic	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Child-Pugh classification,† n (%)			
A	392 (99.7)	388 (99.7)	386 (99.2)
B	0	1 (0.3)	3 (0.8)
Missing	1 (0.3)	0	0
ALBI grade, n (%)			
1	217 (55.2)	198 (50.9)	203 (52.2)
2	174 (44.3)	189 (48.6)	185 (47.6)
3	1 (0.3)	2 (0.5)	1 (0.3)
MVI,† n (%)	103 (26.2)	94 (24.2)	100 (25.7)
EHS,† n (%)	209 (53.2)	212 (54.5)	203 (52.2)
PD-L1 positive,‡ n (%)	148 (37.7)	154 (39.6)	148 (38.0)
AFP ≥400 ng/ml,† n (%)	145 (36.9)	137 (35.2)	124 (31.9)

*HBV: patients who tested positive for HBsAg or anti-HBc with detectable HBV DNA; HCV: patients who tested positive for HCV or had history of HCV infection; Nonviral: no active viral hepatitis identified. †Determined at screening. ‡Defined as tumor area positivity score ≥1%.

T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Baseline liver function in the HIMALAYA study population

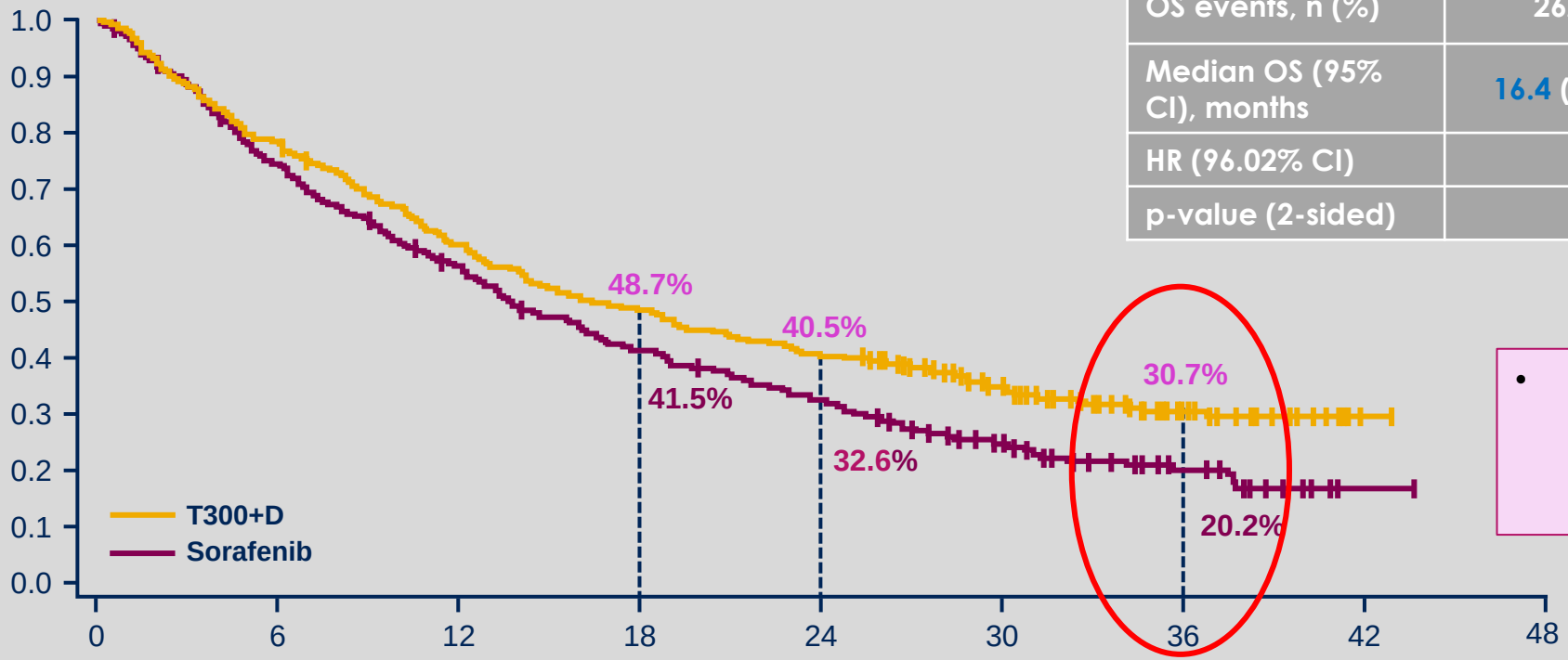
Characteristic	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Mean Child-Pugh score* (SD)	5.3 (0.52)	5.3 (0.50)	5.3 (0.51)
Child-Pugh class/score, n (%)			
A/5	295 (75.1)	284 (73.0)	277 (71.2)
A/6	92 (23.4)	96 (24.7)	102 (26.2)
B/7	4 (1.0)	8 (2.1)	10 (2.6)
Other	2 (0.5)	1 (0.3)	0
ALBI grade, n (%)			
1	217 (55.2)	198 (50.9)	203 (52.2)
2	174 (44.3)	189 (48.6)	185 (47.6)
3	1 (0.3)	2 (0.5)	1 (0.3)
Missing	1 (0.3)	0	0

- Baseline liver function was similar across treatment arms
- In the HIMLAYA study population, 52.8% of patients were in the ALBI grade 1 subgroup and 47.1% were in the ALBI grade 2/3 subgroup

Abou-Alfa et al NEJM Evidence 2022

HIMALAYA: Primary Endpoint – OS for T300+D (STRIDE) vs Sorafenib[a]

	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	

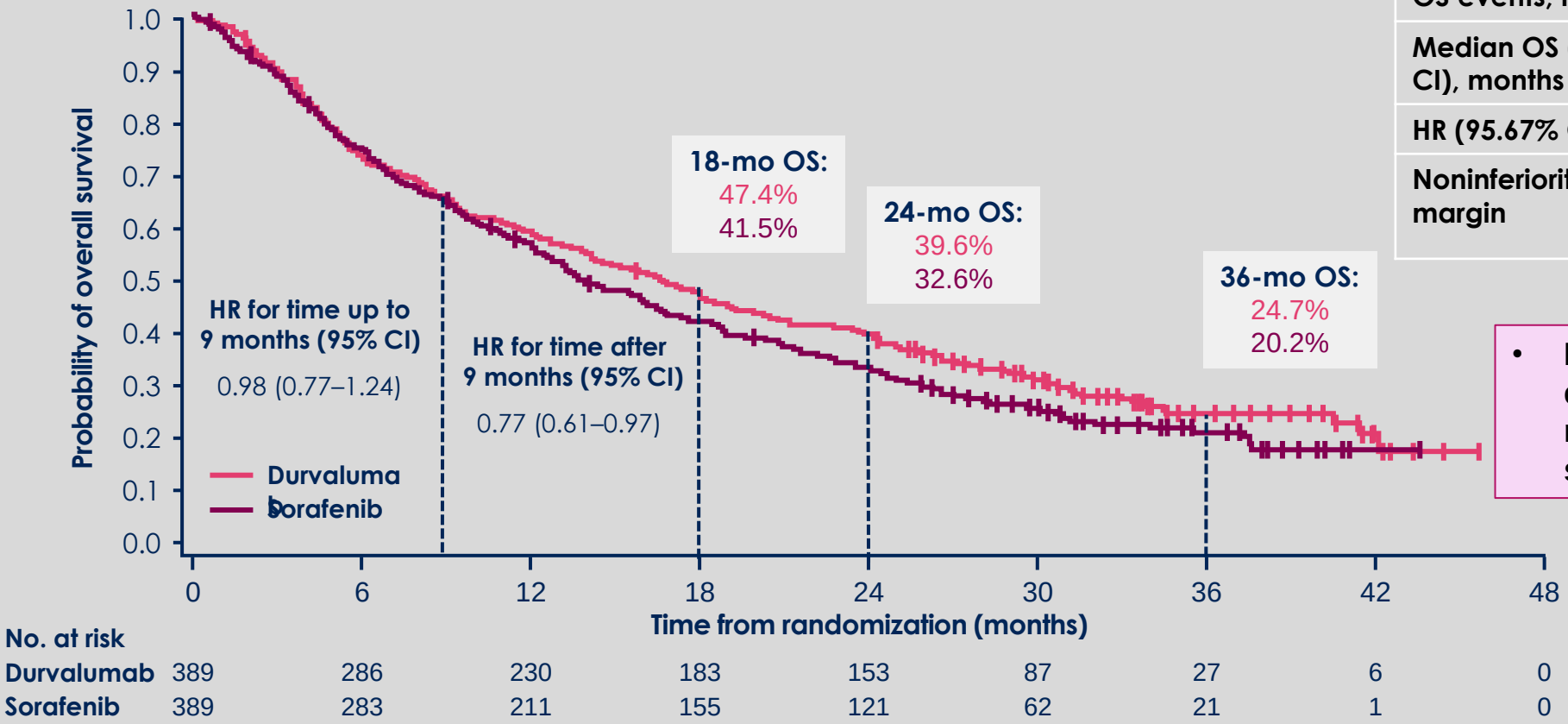


Number at risk									
STRIDE	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

- HIMALAYA met its primary endpoint: the T300+D (STRIDE) regimen was superior to sorafenib for OS

HIMALAYA: Secondary Endpoint – OS 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	

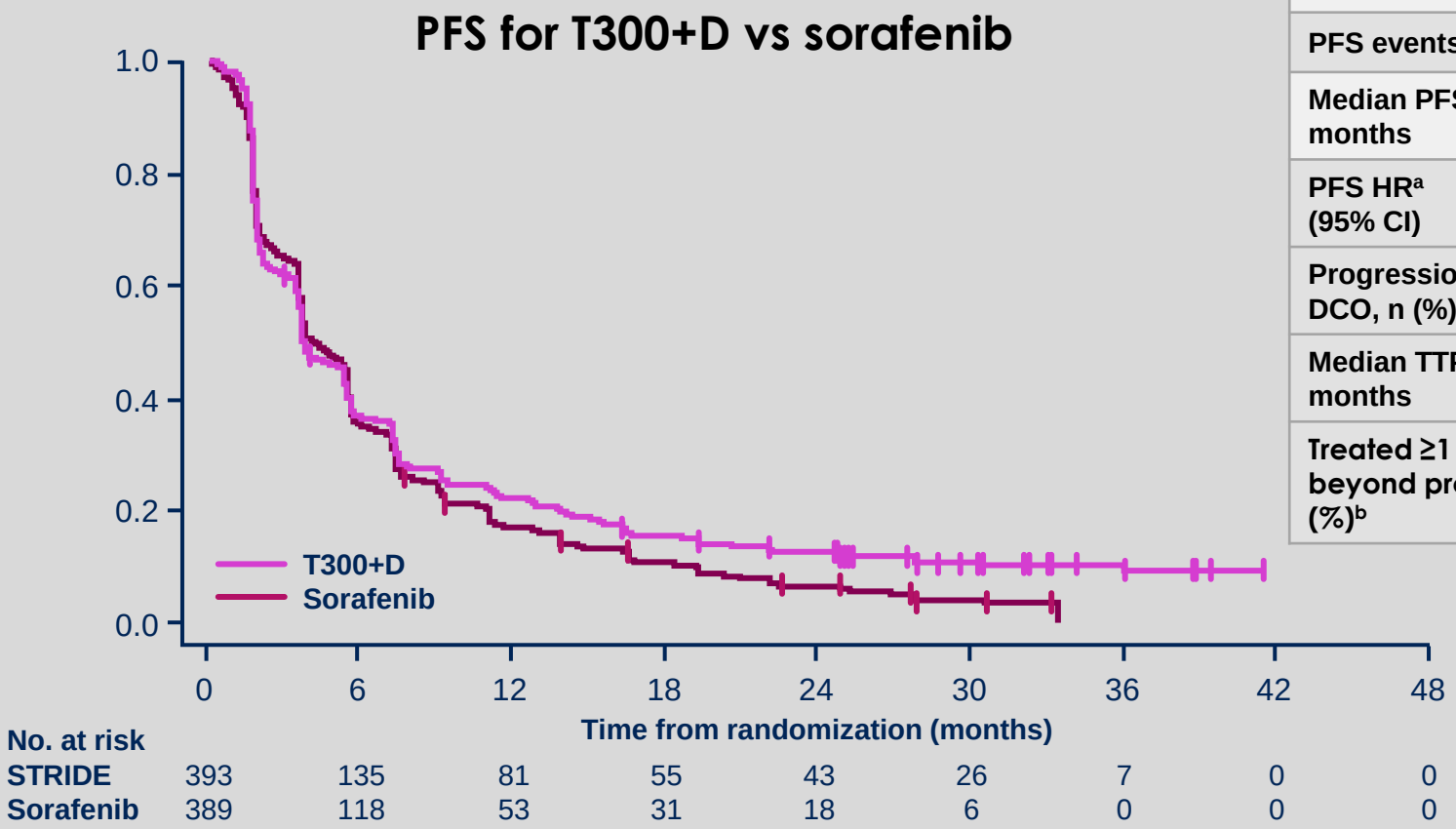


No. at risk

Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

- HIMALAYA met a key secondary endpoint: durvalumab monotherapy was noninferior to sorafenib for OS

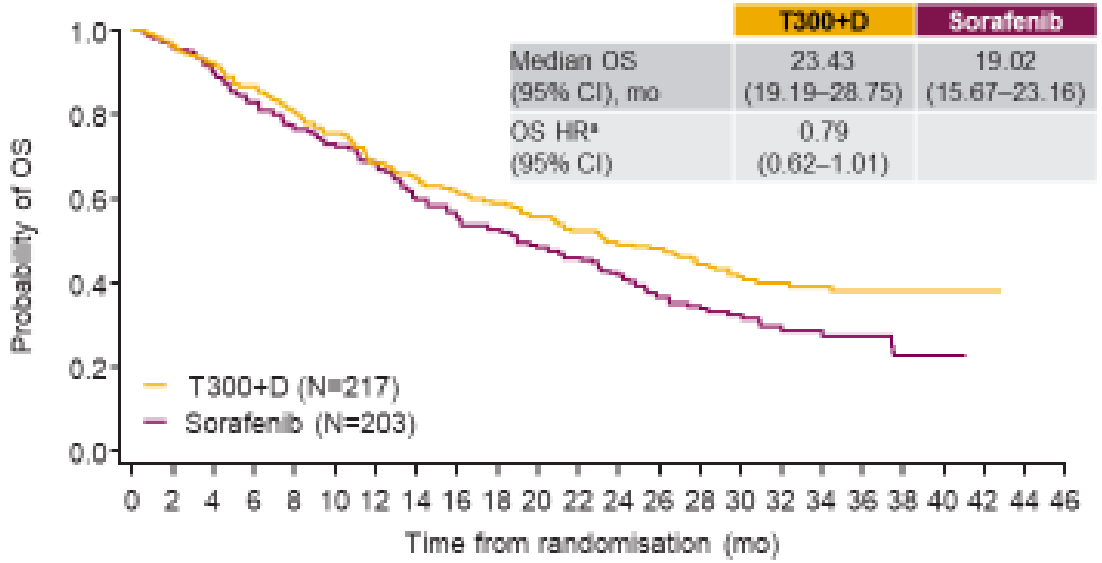
HIMALAYA: Secondary Endpoint – Summary of PFS



	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[a] (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 (%)[b]	182 (46.9)	188 (48.5)	192 (51.3)

HIMALAYA: OS for STRIDE (T300+D) Versus Sorafenib by ALBI Grade[1,2]

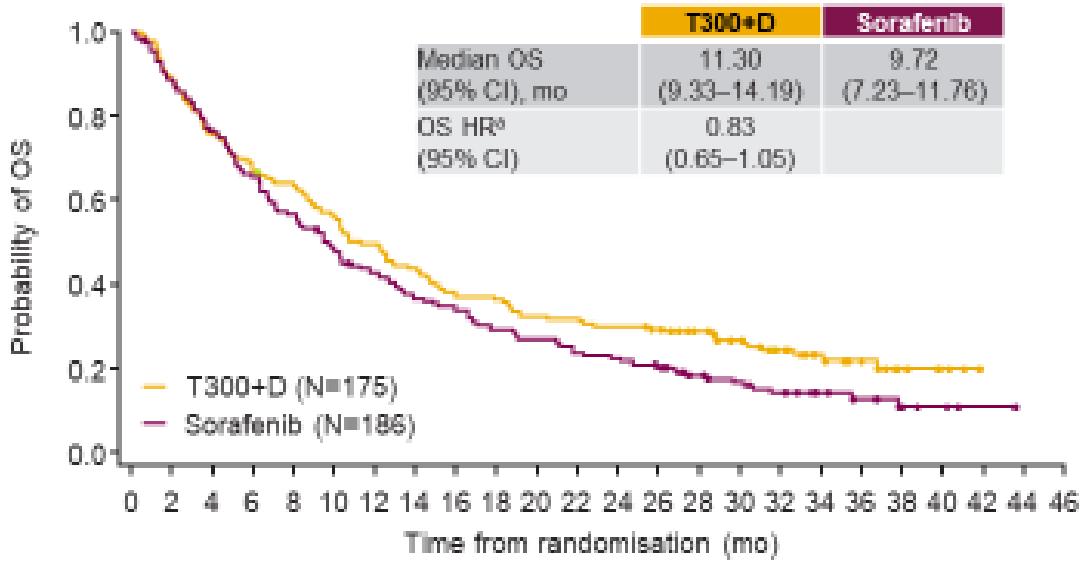
ALBI grade 1



Number at risk

T300+D:	217	209	200	188	174	163	148	140	133	127	120	113	106	101	77	63	50	38	21	13	8	1	0	0
Sorafenib:	203	193	180	165	153	144	135	118	110	103	94	89	81	70	53	41	27	21	13	8	2	0	0	0

ALBI grade 2/3



Number at risk

T300+D:	175	156	132	119	110	98	86	76	64	63	56	55	52	49	42	35	25	17	11	6	3	0	0	0
Sorafenib:	186	163	139	118	102	87	76	65	60	52	48	42	40	36	26	21	17	11	8	4	3	1	0	0

- OS HRs for STRIDE (T300+D) versus sorafenib in the ALBI Grade 1 and ALBI Grade 2/3 subgroups were generally consistent with the full analysis set (0.78; 96.02% CI, 0.65–0.93)[2]

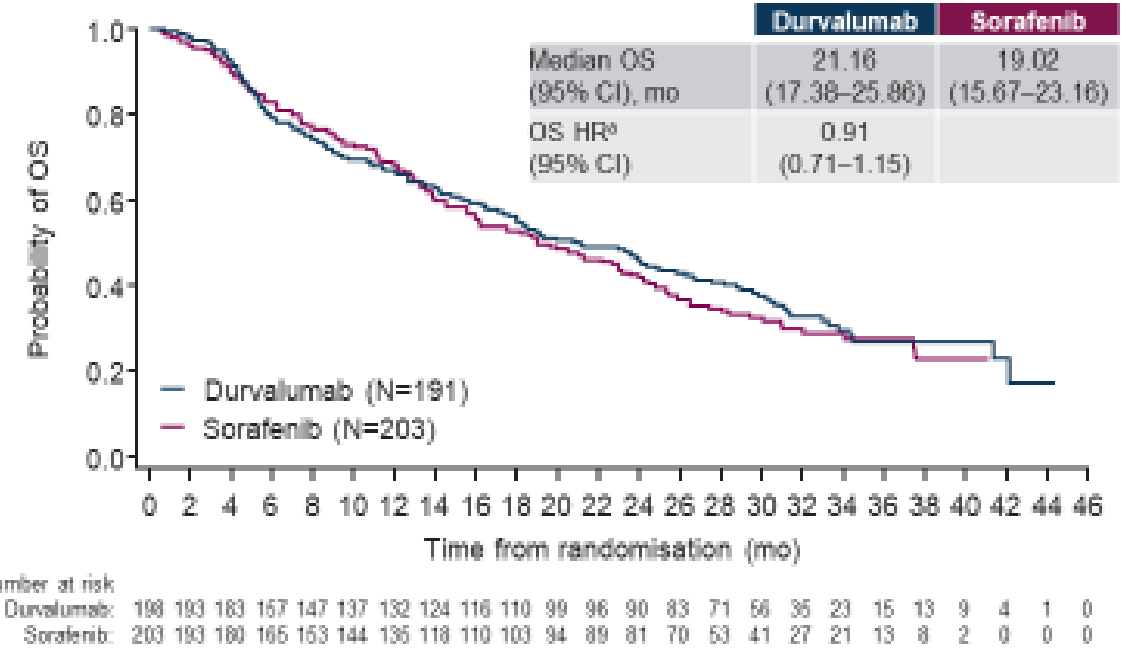
[a]OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, etiology, ECOG performance status, and macrovascular invasion.

ALBI = albumin-bilirubin; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; mo = months; OS = overall survival; STRIDE = Single Tremelimumab Regular Interval Durvalumab; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; Q4W = every 4 weeks.

1. Vogel A, et al. Presented at: World GI, June 29- July 2, 2022. 2. Abou-Alfa GK, et al. *N EJM Evid*. 2022. doi:10.1056/EVIDoa2100070.

HIMALAYA: OS for Durvalumab Versus Sorafenib by ALBI Grade[1,2]

ALBI grade 1

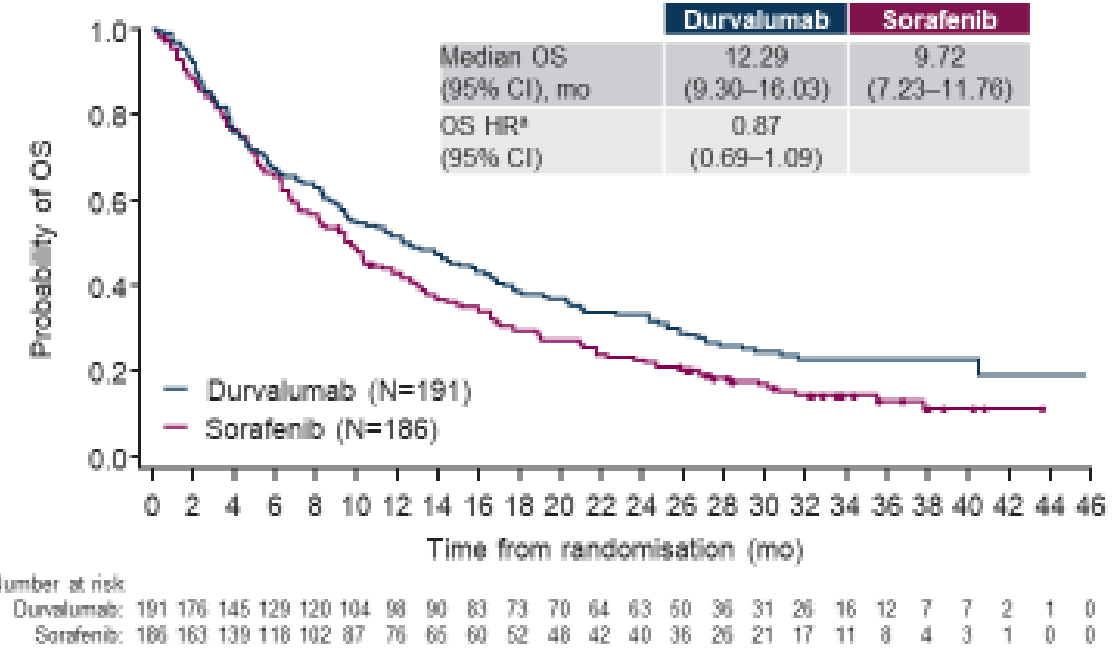


	Durvalumab	Sorafenib
Median OS (95% CI), mo	21.16 (17.38–25.86)	19.02 (15.67–23.16)
OS HR[a] (95% CI)	0.91 (0.71–1.15)	

Number at risk

Durvalumab:	198	193	183	167	147	137	132	124	116	110	99	96	90	83	71	56	35	23	15	13	9	4	1	0
Sorafenib:	203	193	180	165	153	144	135	118	110	103	94	89	81	70	53	41	27	21	13	8	2	0	0	0

ALBI grade 2/3



	Durvalumab	Sorafenib
Median OS (95% CI), mo	12.29 (9.30–16.03)	9.72 (7.23–11.76)
OS HR[a] (95% CI)	0.87 (0.69–1.09)	

Number at risk

Durvalumab:	191	176	145	129	120	104	98	90	83	73	70	64	63	50	36	31	26	16	12	7	7	2	1	0
Sorafenib:	186	163	139	118	102	87	76	65	60	52	48	42	40	36	26	21	17	11	8	4	3	1	0	0

- OS HRs for durvalumab versus sorafenib in the ALBI grade 1 and ALBI grade 2/3 subgroups were generally consistent with the full analysis set (0.86; 95.67% CI, 0.73–1.03)[2]

[a]OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, etiology, ECOG performance status, and macrovascular invasion.

ALBI = albumin-bilirubin; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; mo = months; OS = overall survival.

1. Vogel A, et al. Presented at: World GI, June 29- July 2, 2022. 2. Abou-Alfa GK, et al. *N EJM Evid.* 2022. doi:10.1056/EVIDoa2100070.

HIMALAYA: Safety

Event, n (%)	Durva + Trem (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)
Grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
TRAE leading to death	9 (2.3)	0	3 (0.8)
TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)
Immune-mediated AE requiring treatment with high-dose steroids	78 (20.1)	37 (9.5)	7 (1.9)
Immune-mediated AE leading to discontinuation of study treatment	22 (5.7)	10 (2.6)	6 (1.6)

Abou-Alfa. ASCO GI 2022. Abstr 379. Abou-Alfa. NEJM Evid. 2022;1(8).

HIMALAYA: Treatment-related Hepatic or Hemorrhage SMQ Events[a]

Event, n (%)	T300+D (n=388)		Durvalumab (n=388)		Sorafenib (n=374)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Patients with hepatic SMQ TRAE	66 (17.0)	27 (7.0)	55 (14.2)	20 (5.2)	46 (12.3)	18 (4.8)
Patients with hemorrhage SMQ TRAE	7 (1.8)	2 (0.5)	3 (0.8)	0	18 (4.8)	6 (1.6)
Alanine aminotransferase increased	18 (4.6)	4 (1.0)	22 (5.7)	5 (1.3)	8 (2.1)	3 (0.8)
Aspartate aminotransferase increased	22 (5.7)	9 (2.3)	25 (6.4)	9 (2.3)	10 (2.7)	6 (1.6)
Blood bilirubin increased	6 (1.5)	1 (0.3)	6 (1.5)	0	10 (2.7)	2 (0.5)
Ascites	1 (0.3)	0	0	0	2 (0.5)	0
Hepatic encephalopathy	0	0	0	0	2 (0.5)	1 (0.3)
Activated partial thromboplastin time prolonged	1 (0.3)	0	0	0	0	0
International normalized ratio increased	4 (1.0)	1 (0.3)	0	0	0	0
Esophageal varices hemorrhage	0	0	0	0	0	0

1L and 2L Treatment Options in Unresectable HCC

Advanced stage (BCLC C: *Portal invasion* and/or *extrahepatic spread*)
Intermediate stage (BCLC B: *Multinodular*) **progressing upon loco-regional therapies**[1,2]

1st line

atezolizumab + bevacizumab	sorafenib	lenvatinib	Tremelimumab Durvalumab
Child-Pugh A-ECOG PS ≤1 No prior systemic therapy	Child-Pugh A-ECOG PS ≤2 *Higher benefit in HCV Infection and lack of EHS	Child-Pugh A-ECOG PS ≤1 No invasion main portal vein	Child-Pugh A-ECOG PS ≤1 No prior systemic therapy

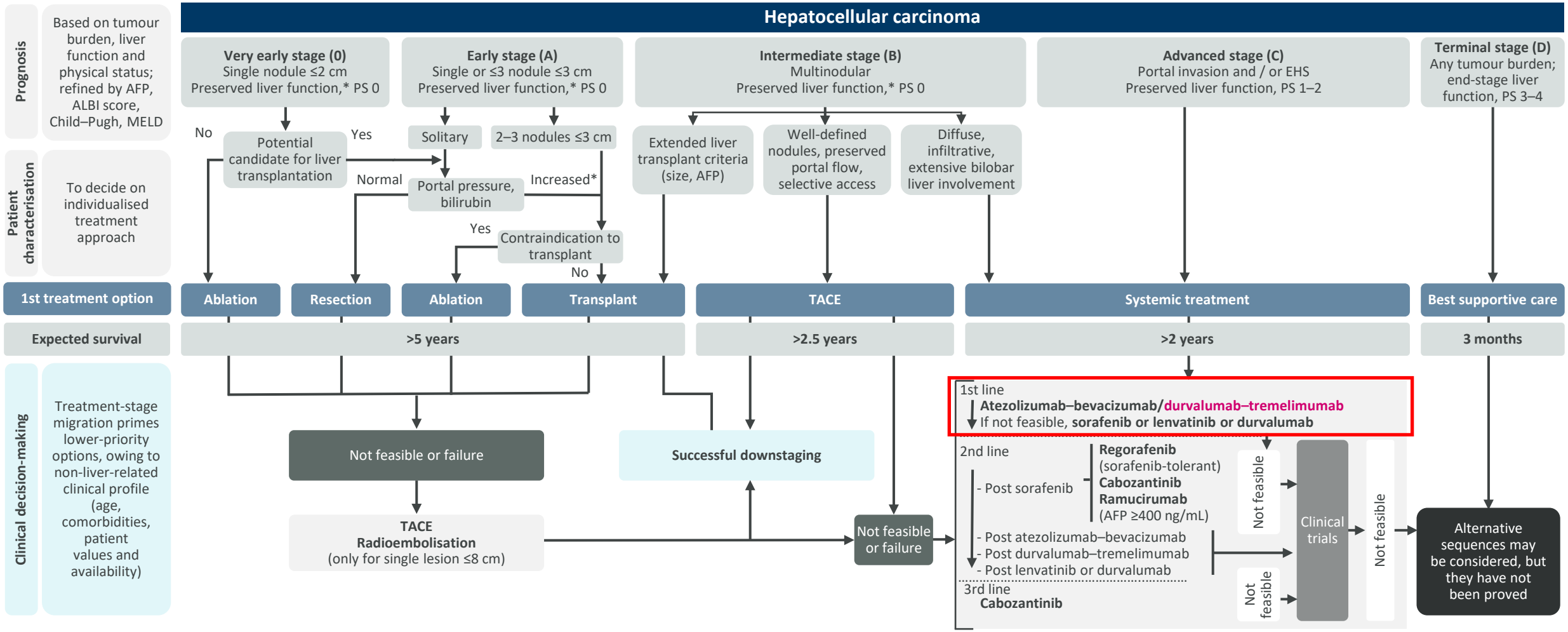
2nd line

regorafenib	cabozantinib	ramucirumab	nivolumab + ipilimumab	nivolumab pembrolizumab
Child-Pugh A-ECOG PS ≤1 Tolerant to sorafenib (85%)	Child-Pugh A-ECOG PS ≤1	Child-Pugh A-ECOG PS ≤1 AFP ≥400 ng/ml	Child-Pugh A-ECOG PS ≤1	Child-Pugh A-ECOG PS ≤1 *PDL1 IHC not a predictive biomarker

Figure. FDA Approved Drugs in Unresectable HCC

Thanks

Anti-PD-L1 (atezolizumab) plus anti-VEGF (bevacizumab) combination therapy and the STRIDE regimen are recommended 1L treatments for patients with unresectable HCC



*Except for those with tumour burden acceptable for transplant.

See slide notes for abbreviations and references