Unresectable Hepatocellular Carcinoma: Selecting the Optimal First-Line ICI Combination

Unmet Needs in Unresectable HCC

- Physicians can be confused about various frontline treatment options available to patients with unresectable HCC
- Patients with unresectable HCC do not always receive adequate frontline treatment according to the guidelines
- Lack of predictive biomarkers to select the optimal therapy for individual patients
- Lack of understanding of resistance mechanism to frontline therapy and need for continuing clinical research

Right now, we don't really have a validated biomarker that would recommend to patients which combination we should use.

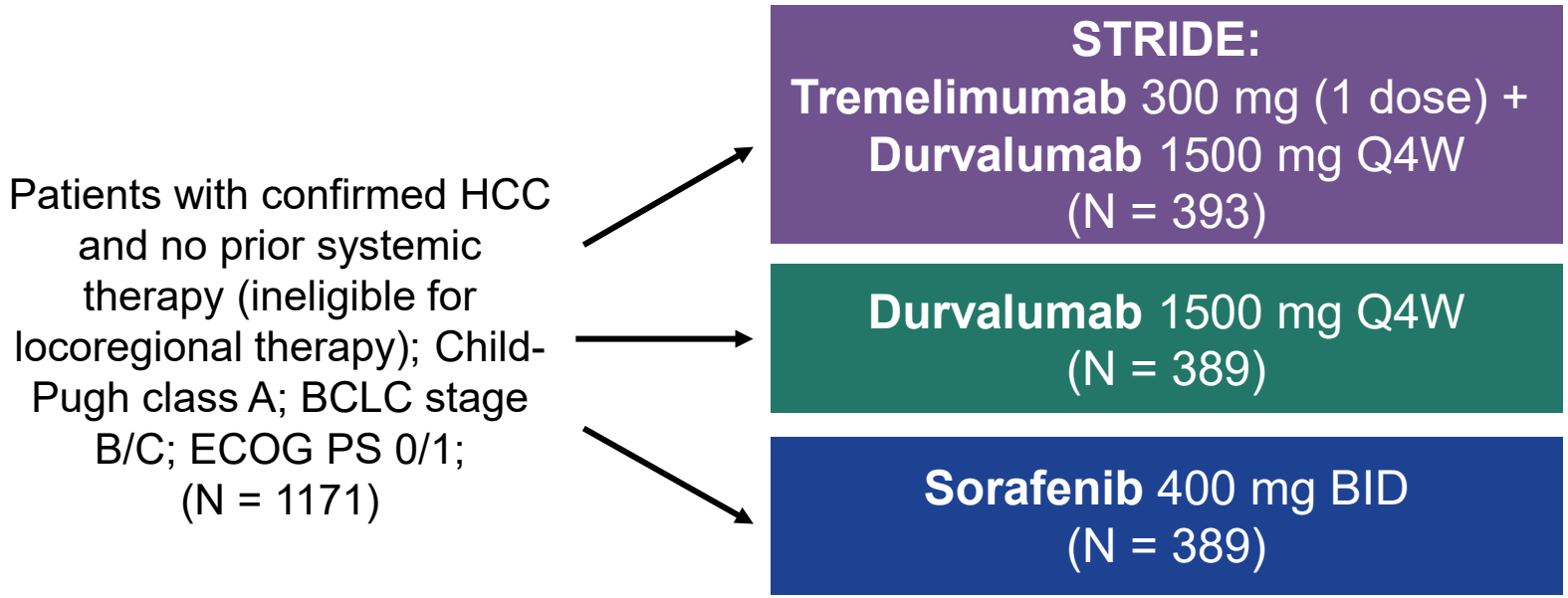
Aiwu Ruth He, MD

Checkpoint inhibitor therapies apply for everybody despite that we might see more benefit for certain populations versus the other.

Ghassan Abou-Alfa, MD

HIMALAYA: Study Design

Randomized, open-label, multicenter, global phase III trial

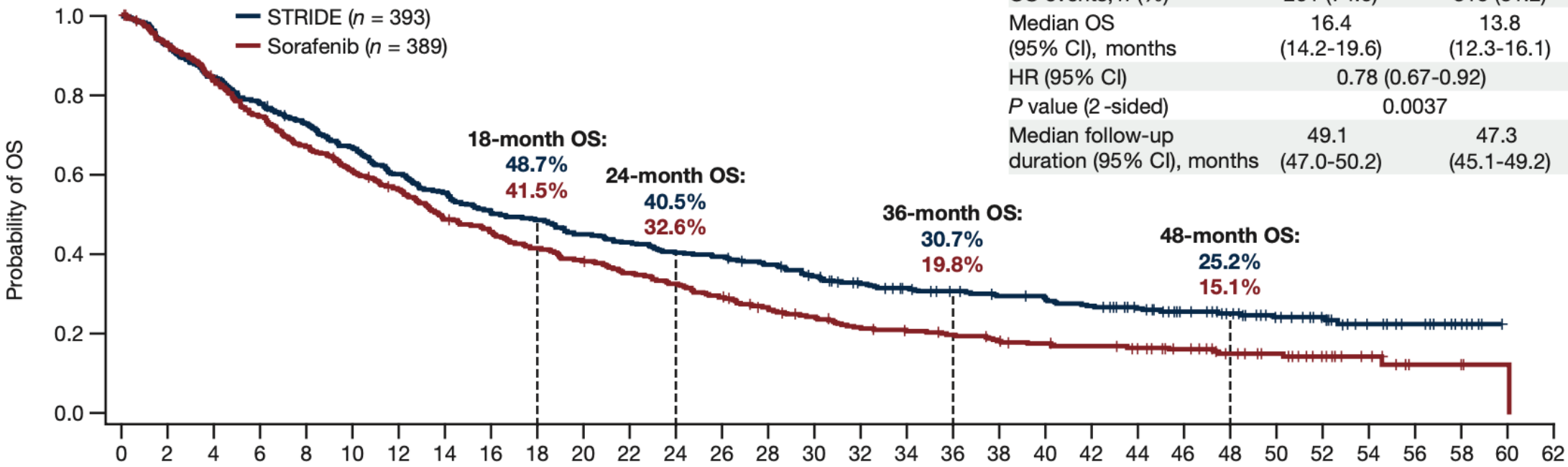


- **Primary endpoint:** OS (STRIDE vs sorafenib)
- **Key secondary endpoints:** OS (durvalumab vs sorafenib), PFS, ORR, safety

Abou-Alfa GK, et al. *NEJM Evid*. 2022;1(8):EVIDoa2100070.

HIMALAYA: 4-Year OS (STRIDE vs Sorafenib)

	STRIDE (*n* = 393)	Sorafenib (*n* = 389)
OS events, *n* (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), months	16.4 (14.2-19.6)	13.8 (12.3-16.1)
HR (95% CI)	0.78 (0.67-0.92)	
P value (2-sided)	0.0037	
Median follow-up duration (95% CI), months	49.1 (47.0-50.2)	47.3 (45.1-49.2)

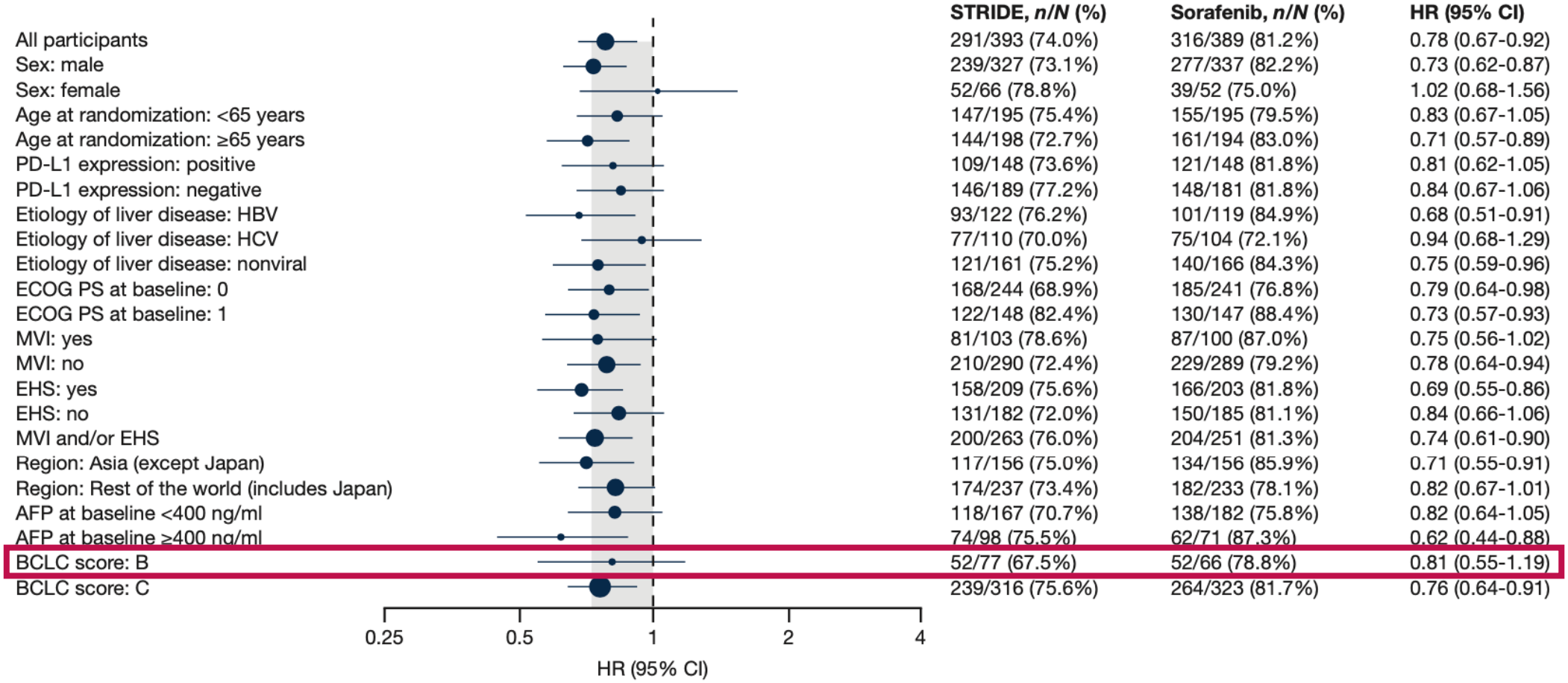


Number at risk

STRIDE:	393	365	333	308	285	262	235	217	197	190	176	168	158	154	144	131	118	110	103	97	94	88	75	62	54	40	31	19	13	5	0	0
Sorafenib:	389	356	319	283	255	231	211	183	170	155	142	131	121	108	93	83	73	69	64	56	53	50	45	36	28	21	14	9	3	1	1	0

Sangro B, et al. *Ann Oncol*. 2024;35(5):448-457.

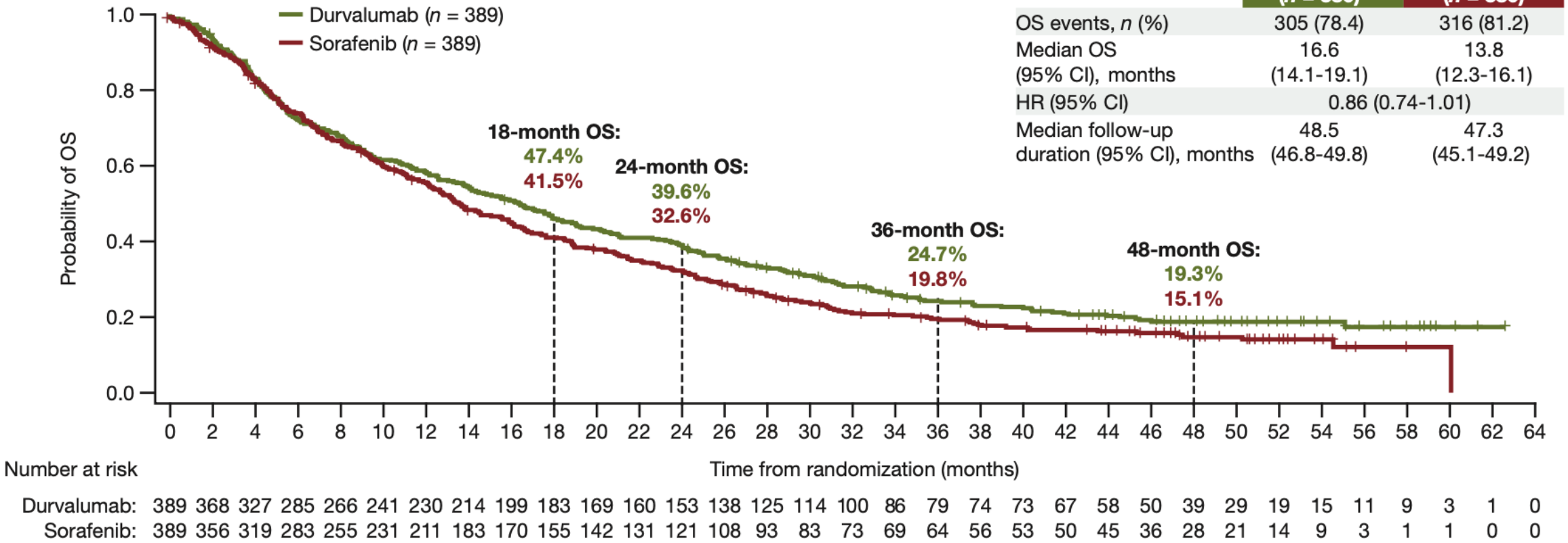
HIMALAYA: OS by Subgroups (STRIDE vs Sorafenib)



	STRIDE, *n/N* (%)	Sorafenib, *n/N* (%)	HR (95% CI)
All participants	291/393 (74.0%)	316/389 (81.2%)	0.78 (0.67-0.92)
Sex: male	239/327 (73.1%)	277/337 (82.2%)	0.73 (0.62-0.87)
Sex: female	52/66 (78.8%)	39/52 (75.0%)	1.02 (0.68-1.56)
Age at randomization: <65 years	147/195 (75.4%)	155/195 (79.5%)	0.83 (0.67-1.05)
Age at randomization: ≥65 years	144/198 (72.7%)	161/194 (83.0%)	0.71 (0.57-0.89)
PD-L1 expression: positive	109/148 (73.6%)	121/148 (81.8%)	0.81 (0.62-1.05)
PD-L1 expression: negative	146/189 (77.2%)	148/181 (81.8%)	0.84 (0.67-1.06)
Etiology of liver disease: HBV	93/122 (76.2%)	101/119 (84.9%)	0.68 (0.51-0.91)
Etiology of liver disease: HCV	77/110 (70.0%)	75/104 (72.1%)	0.94 (0.68-1.29)
Etiology of liver disease: nonviral	121/161 (75.2%)	140/166 (84.3%)	0.75 (0.59-0.96)
ECOG PS at baseline: 0	168/244 (68.9%)	185/241 (76.8%)	0.79 (0.64-0.98)
ECOG PS at baseline: 1	122/148 (82.4%)	130/147 (88.4%)	0.73 (0.57-0.93)
MVI: yes	81/103 (78.6%)	87/100 (87.0%)	0.75 (0.56-1.02)
MVI: no	210/290 (72.4%)	229/289 (79.2%)	0.78 (0.64-0.94)
EHS: yes	158/209 (75.6%)	166/203 (81.8%)	0.69 (0.55-0.86)
EHS: no	131/182 (72.0%)	150/185 (81.1%)	0.84 (0.66-1.06)
MVI and/or EHS	200/263 (76.0%)	204/251 (81.3%)	0.74 (0.61-0.90)
Region: Asia (except Japan)	117/156 (75.0%)	134/156 (85.9%)	0.71 (0.55-0.91)
Region: Rest of the world (includes Japan)	174/237 (73.4%)	182/233 (78.1%)	0.82 (0.67-1.01)
AFP at baseline <400 ng/ml	118/167 (70.7%)	138/182 (75.8%)	0.82 (0.64-1.05)
AFP at baseline ≥400 ng/ml	74/98 (75.5%)	62/71 (87.3%)	0.62 (0.44-0.88)
BCLC score: B	52/77 (67.5%)	52/66 (78.8%)	0.81 (0.55-1.19)
BCLC score: C	239/316 (75.6%)	264/323 (81.7%)	0.76 (0.64-0.91)

Sangro B, et al. *Ann Oncol*. 2024;35(5):448-457.

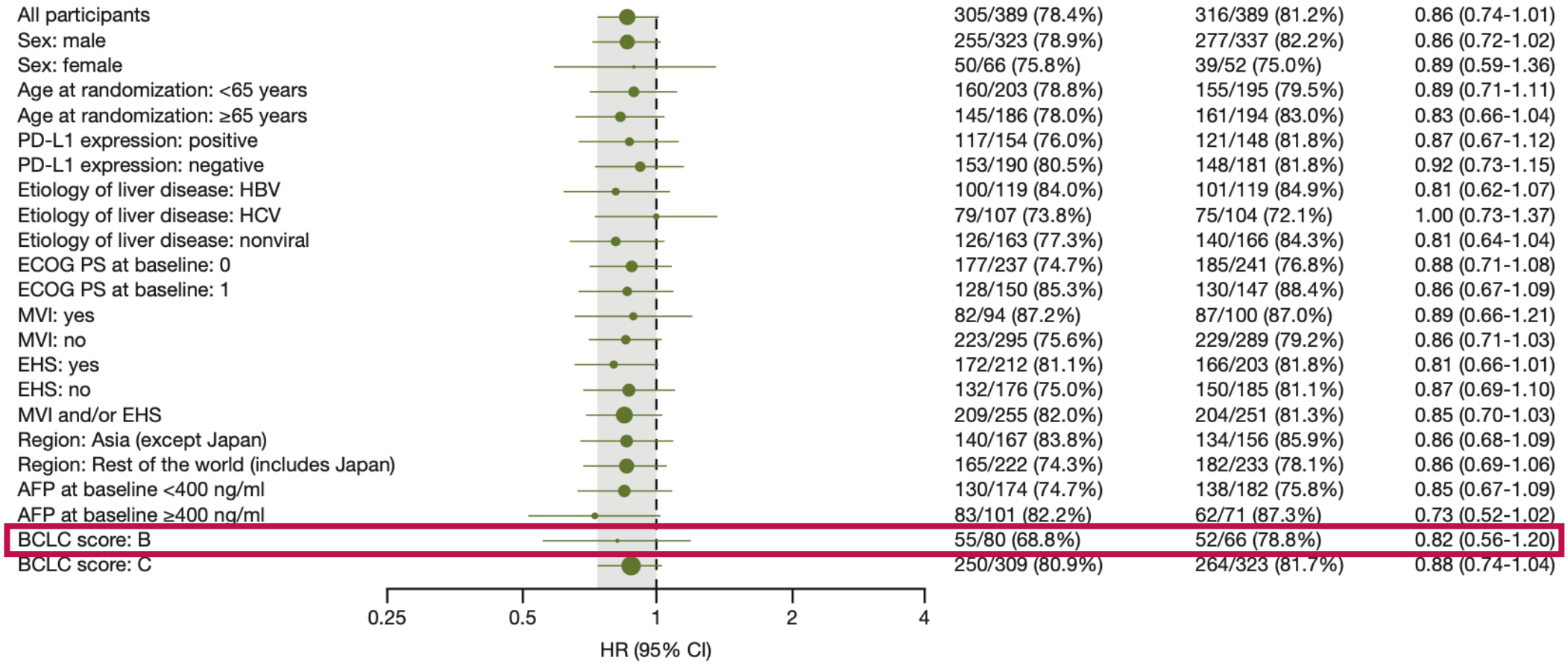
HIMALAYA: 4-Year OS (Durvalumab vs Sorafenib)



	Durvalumab (*n* = 389)	Sorafenib (*n* = 389)
OS events, *n* (%)	305 (78.4)	316 (81.2)
Median OS (95% CI), months	16.6 (14.1-19.1)	13.8 (12.3-16.1)
HR (95% CI)	0.86 (0.74-1.01)	
Median follow-up duration (95% CI), months	48.5 (46.8-49.8)	47.3 (45.1-49.2)

Sangro B, et al. *Ann Oncol*. 2024;35(5):448-457.

HIMALAYA: OS by Subgroups (Durvalumab vs Sorafenib)



	Durvalumab, *n/N* (%)	Sorafenib, *n/N* (%)	HR (95% CI)
All participants	305/389 (78.4%)	316/389 (81.2%)	0.86 (0.74-1.01)
Sex: male	255/323 (78.9%)	277/337 (82.2%)	0.86 (0.72-1.02)
Sex: female	50/66 (75.8%)	39/52 (75.0%)	0.89 (0.59-1.36)
Age at randomization: <65 years	160/203 (78.8%)	155/195 (79.5%)	0.89 (0.71-1.11)
Age at randomization: ≥65 years	145/186 (78.0%)	161/194 (83.0%)	0.83 (0.66-1.04)
PD-L1 expression: positive	117/154 (76.0%)	121/148 (81.8%)	0.87 (0.67-1.12)
PD-L1 expression: negative	153/190 (80.5%)	148/181 (81.8%)	0.92 (0.73-1.15)
Etiology of liver disease: HBV	100/119 (84.0%)	101/119 (84.9%)	0.81 (0.62-1.07)
Etiology of liver disease: HCV	79/107 (73.8%)	75/104 (72.1%)	1.00 (0.73-1.37)
Etiology of liver disease: nonviral	126/163 (77.3%)	140/166 (84.3%)	0.81 (0.64-1.04)
ECOG PS at baseline: 0	177/237 (74.7%)	185/241 (76.8%)	0.88 (0.71-1.08)
ECOG PS at baseline: 1	128/150 (85.3%)	130/147 (88.4%)	0.86 (0.67-1.09)
MVI: yes	82/94 (87.2%)	87/100 (87.0%)	0.89 (0.66-1.21)
MVI: no	223/295 (75.6%)	229/289 (79.2%)	0.86 (0.71-1.03)
EHS: yes	172/212 (81.1%)	166/203 (81.8%)	0.81 (0.66-1.01)
EHS: no	132/176 (75.0%)	150/185 (81.1%)	0.87 (0.69-1.10)
MVI and/or EHS	209/255 (82.0%)	204/251 (81.3%)	0.85 (0.70-1.03)
Region: Asia (except Japan)	140/167 (83.8%)	134/156 (85.9%)	0.86 (0.68-1.09)
Region: Rest of the world (includes Japan)	165/222 (74.3%)	182/233 (78.1%)	0.86 (0.69-1.06)
AFP at baseline <400 ng/ml	130/174 (74.7%)	138/182 (75.8%)	0.85 (0.67-1.09)
AFP at baseline ≥400 ng/ml	83/101 (82.2%)	62/71 (87.3%)	0.73 (0.52-1.02)
BCLC score: B	55/80 (68.8%)	52/66 (78.8%)	0.82 (0.56-1.20)
BCLC score: C	250/309 (80.9%)	264/323 (81.7%)	0.88 (0.74-1.04)

Sangro B, et al. *Ann Oncol*. 2024;35(5):448-457.

HIMALAYA: Response

Response (%)	STRIDE (n = 393)	Durvalumab (n = 389)	Sorafenib (n = 389)
ORR	20.1	17.0	5.1
CR	3.1	1.5	0
PR	17.0	15.4	5.1
SD	39.9	37.8	55.5
DCR	60.1	54.8	60.7

Abou-Alfa GK, et al. *NEJM Evid*. 2022;1(8):EVIDoa2100070.

HIMALAYA: Safety

Event, n (%)	STRIDE (n = 388)	Durvalumab (n = 388)	Sorafenib (n = 374)
Any TEAE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 TEAE	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)
Any grade 3/4 hepatic TRAE	23 (5.9)	20 (5.2)	17 (4.5)
Any grade 3/4 hemorrhage TRAE	2 (0.5)	0	4 (1.1)
Any grade 3/4 immune-mediated TRAE	49 (12.6)	24 (6.2)	9 (2.4)
Any immune-mediated TEAE requiring high-dose steroids	78 (20.1)	37 (9.5)	7 (1.9)
Any immune-mediated TEAE leading to death	6 (1.5)	0	0

Abou-Alfa GK, et al. *NEJM Evid*. 2022;1(8):EVIDoa2100070.

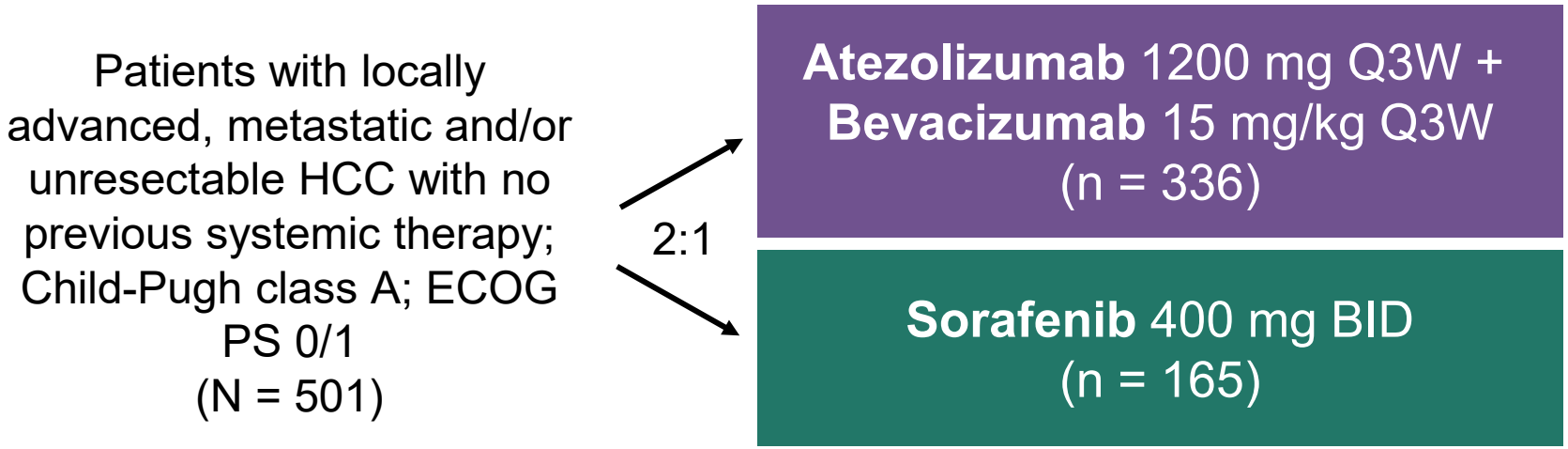
Key Trials in Progress

- SIERRA[1]
  - A phase IIIb, single-arm, multicentre study of tremelimumab plus durvalumab for first-line treatment of advanced uHCC (n = 140)
  - Co-primary endpoints
    - Incidence of grade 3/4 AEs possibly related to treatment
    - Investigator-assessed ORR
- MONTBLANC[2]
  - Randomized, 2-arm phase II study of durvalumab, tremelimumab, and bevacizumab in patients with advanced HCC (n = 83)
    - Arm A: STRIDE with the addition of bevacizumab upon progression or lack of response by month 4
    - Arm B: STRIDE + bevacizumab
  - Primary endpoint: ORR

1. ClinicalTrials.gov identifier: NCT05883644. 2. ClinicalTrials.gov identifier: NCT05844046.

IMbrave150: Study Design

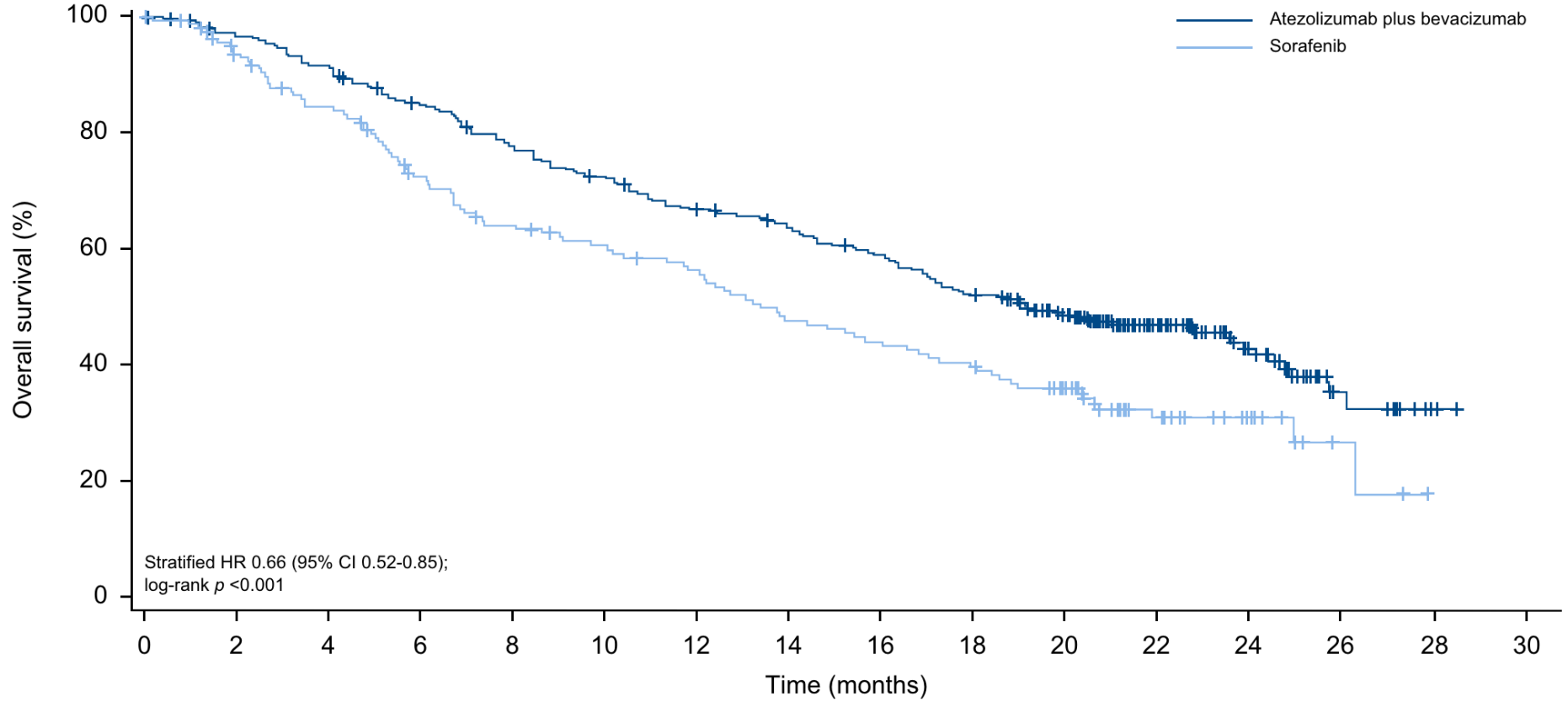
Randomized, open-label, multicenter, phase III trial



- **Co-primary endpoints:** OS and PFS
- **Key secondary endpoints:** ORR, DoR, safety

Finn RS, et al. *N Engl J Med*. 2020;382(20):1894-1905.

IMbrave150: OS

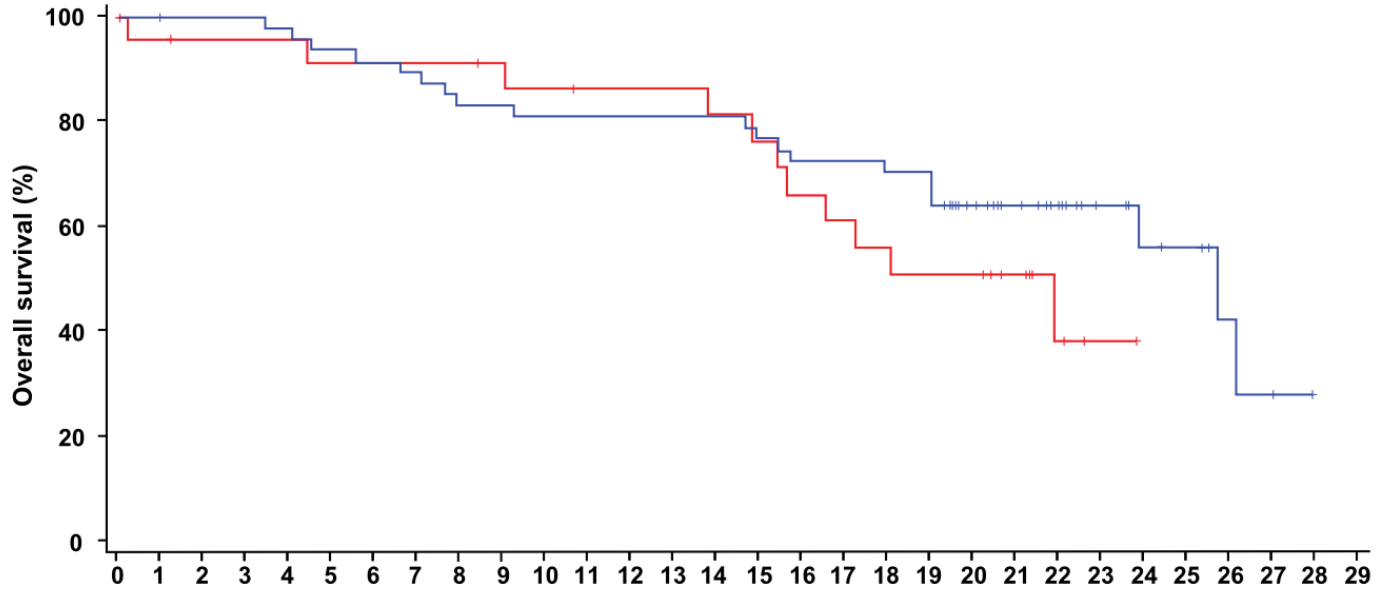


N° at risk (number censored)																
Atezolizumab plus bevacizumab	336 (0)	320 (6)	302 (6)	276 (10)	252 (11)	233 (12)	214 (14)	202 (16)	186 (17)	164 (17)	134 (37)	80 (87)	42 (120)	12 (145)	2 (154)	0 (156)
Sorafenib	165 (0)	144 (11)	128 (13)	106 (17)	92 (19)	85 (21)	78 (22)	66 (22)	61 (22)	55 (22)	44 (28)	24 (43)	12 (55)	3 (63)	0 (65)	0 (65)

Cheng A, et al. *J Hepatol*. 2022;76(4):862-873.

IMbrave150: OS (BCLC Stage B)

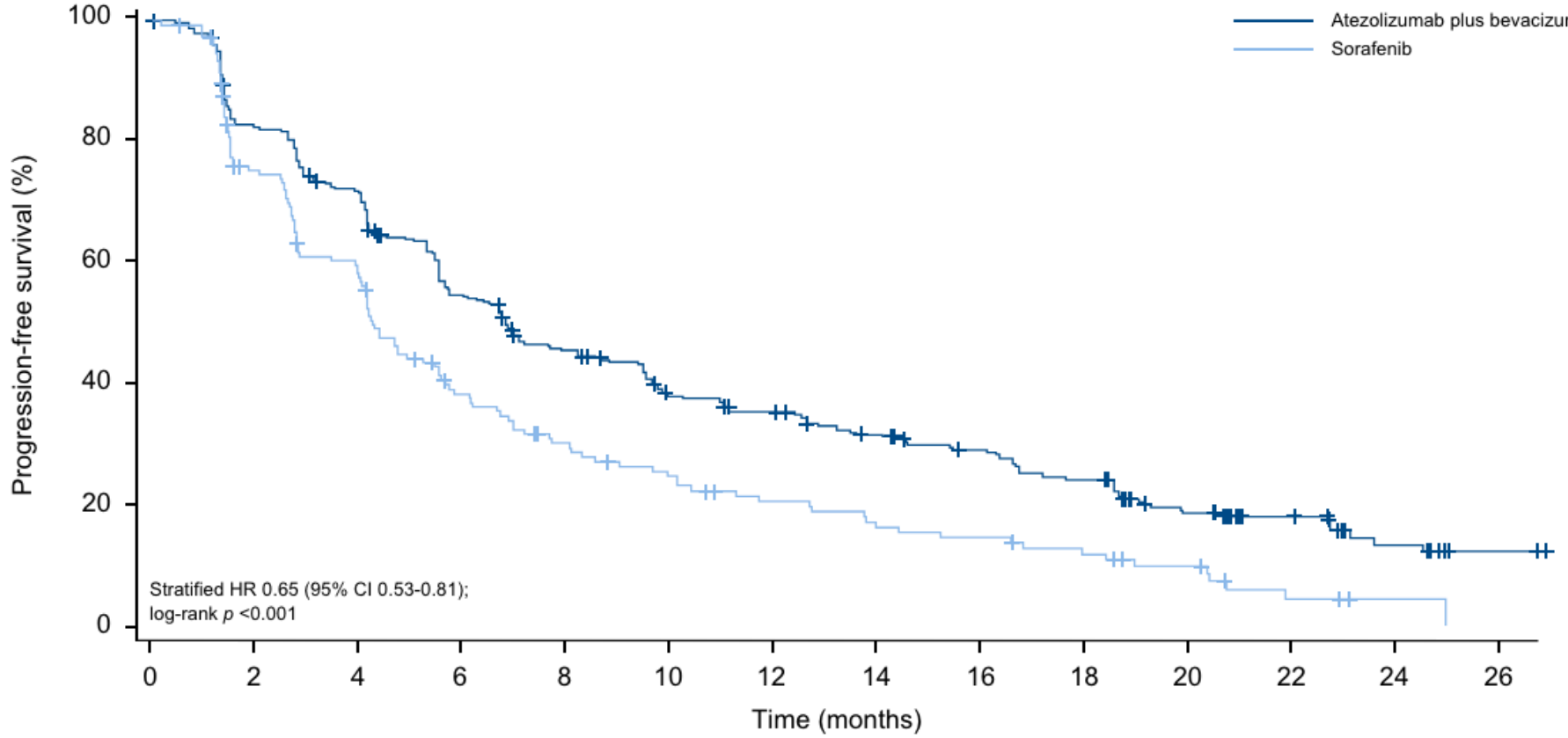
	Atezolizumab + bevacizumab (n=49)	Sorafenib (n=24)
Median OS (95% CI), months	25.8 (23.9, NE)	21.9 (15.7, NE)
HR (95% CI)	**0.63 (0.29, 1.34)**	



No. at risk																											
Atezolizumab + bevacizumab	49	47	47	47	46	44	43	42	39	39	38	38	38	38	38	36	34	34	33	33	25	20	16	10	7	6	3	2	NE	NE
Sorafenib	24	22	21	21	21	20	20	20	20	19	18	17	17	17	16	15	13	12	11	10	10	7	3	1	NE	NE	NE	NE	NE	NE

Kudo M, et al. *Liver Cancer*. 2022;12(3):238-250.

IMbrave150: PFS

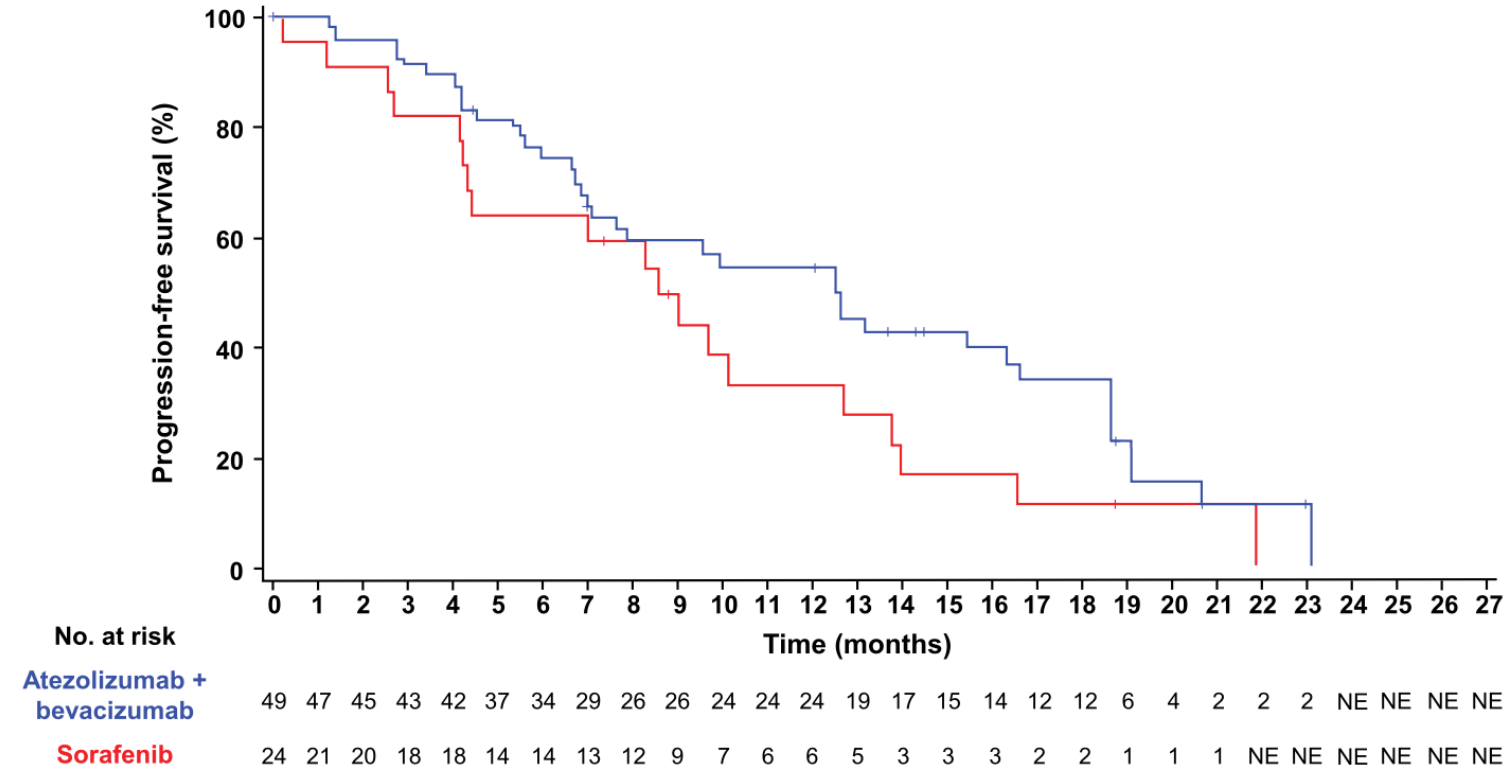


N° at risk (number censored)														
Atezolizumab plus bevacizumab	336 (0)	271 (8)	234 (10)	174 (14)	141 (19)	113 (24)	102 (27)	88 (31)	77 (35)	64 (35)	41 (45)	25 (60)	12 (68)	3 (76)
Sorafenib	165 (0)	110 (18)	84 (19)	52 (23)	39 (25)	31 (26)	24 (28)	19 (28)	17 (28)	13 (29)	9 (31)	3 (33)	1 (35)	0 (35)

Cheng A, et al. *J Hepatol*. 2022;76(4):862-873.

IMbrave150: PFS (BCLC Stage B)

	Atezolizumab + bevacizumab (n=49)	Sorafenib (n=24)
Median PFS (95% CI), months	12.6 (7.1, 16.7)	8.6 (4.3, 12.7)
HR (95% CI)	**0.64 (0.36, 1.12)**	



Kudo M, et al. *Liver Cancer*. 2022;12(3):238-250.

IMbrave150: Response

Response, n (%)	Atezolizumab + Bevacizumab (n = 326)	Sorafenib (n = 159)
ORR	97 (30)	18 (11)
CR	25 (8)	1 (<1)
PR	72 (22)	17 (11)
SD	144 (44)	69 (43)
DCR	241 (74)	87 (55)

Cheng A, et al. *J Hepatol*. 2022;76(4):862-873.

IMbrave150: Safety

Adverse Events, n (%)	Atezolizumab + Bevacizumab (n = 329)	Sorafenib (n = 156)
Any grade AE	322 (98)	154 (99)
Treatment-related AE	284 (86)	148 (95)
Grade 3/4 AE	207 (63)	89 (57)
Treatment-related grade 3/4 AE	143 (43)	72 (46)
Serious AE	160 (49)	51 (33)
Treatment-related serious AE	76 (23)	25 (16)
Grade 5 AE	23 (7)	9 (6)
Treatment-related grade 5 AE	6 (2)	1 (<1)
AE leading to withdrawal of any component	72 (22)	18 (12)
AE leading to dose interruption of any study treatment	195 (59)	68 (44)

Cheng A, et al. *J Hepatol*. 2022;76(4):862-873.

It's very important for our colleagues to make sure that they scope the patients before using any of the anti-VEGF therapies like bevacizumab.

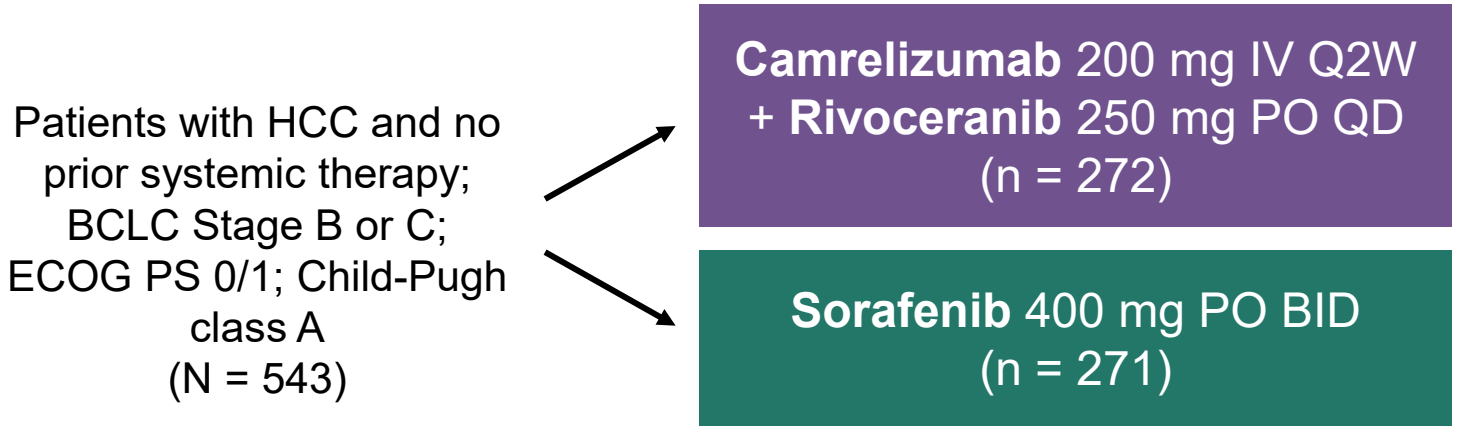
Ghassan Abou-Alfa, MD

I also realize a lot of patients actually have proteinuria as a result of hypertension or diabetes. And anti-VEGF therapy may increase the risk of having worsening proteinuria.

Aiwu Ruth He, MD

CARES-310: Study Design

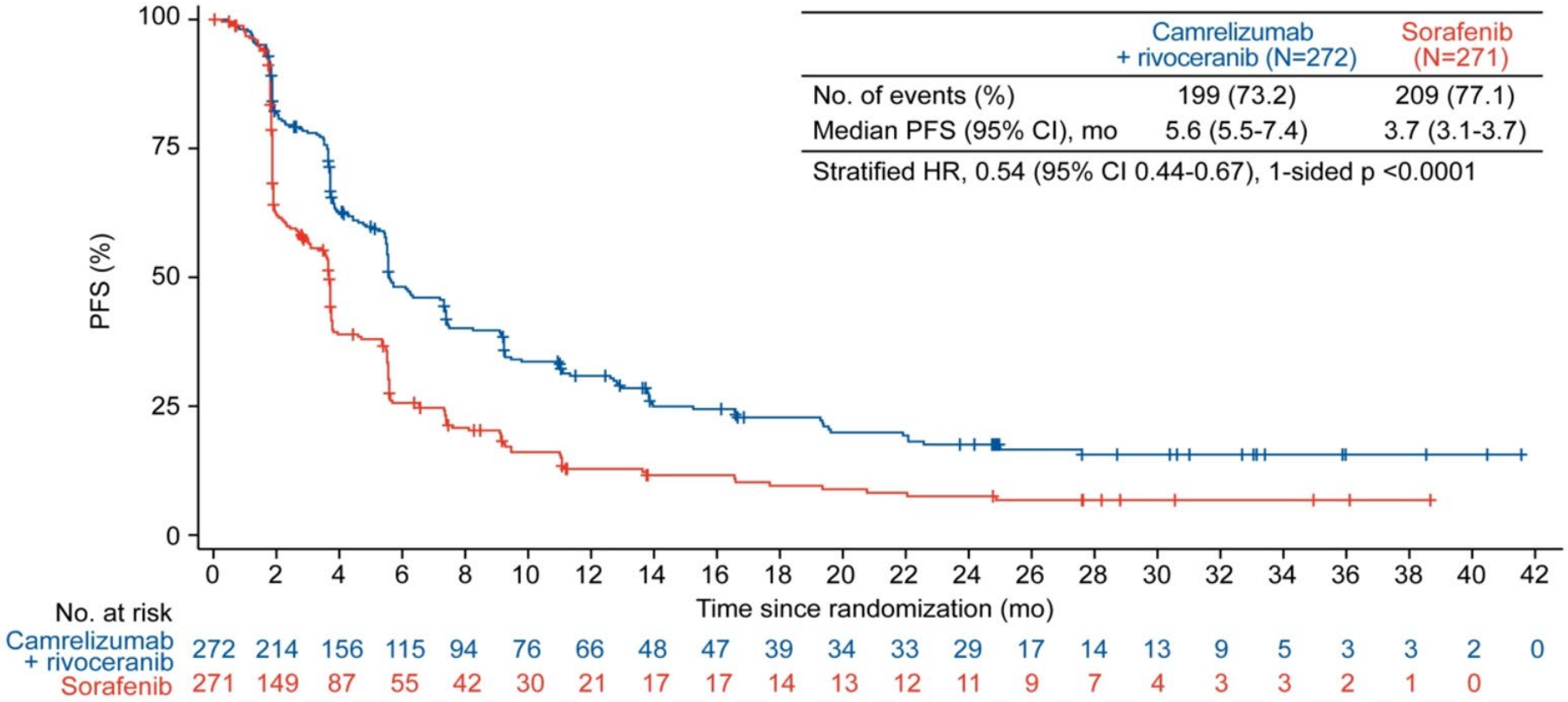
Randomized, open-label, multicenter, international phase III trial



- **Primary endpoint:** PFS and OS
- **Key secondary endpoints:** ORR, DCR, DoR, safety

Qin S, et al. *Lancet*. 2023;402(10408):1133-1146.

CARES-310: PFS

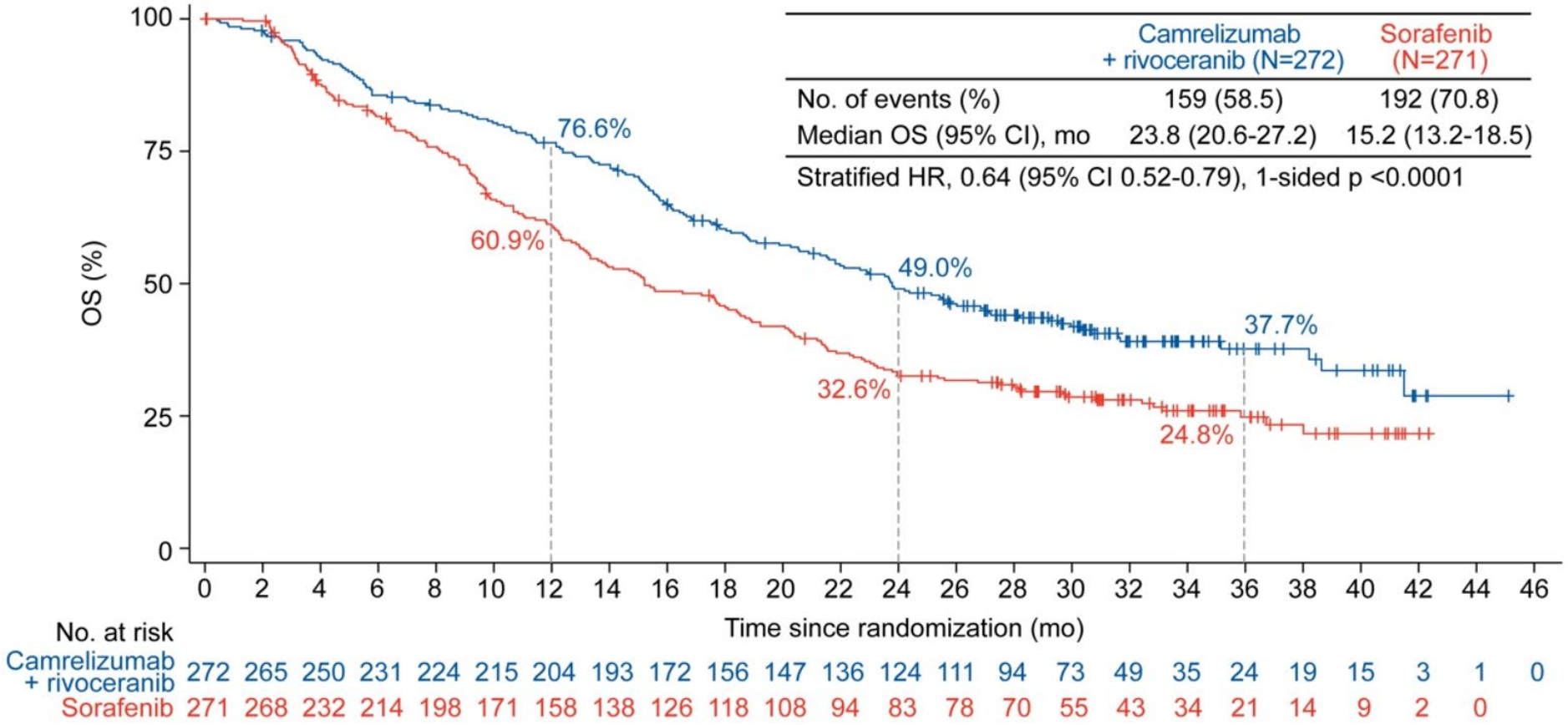


	Camrelizumab + rivoceranib (N=272)	Sorafenib (N=271)
No. of events (%)	199 (73.2)	209 (77.1)
Median PFS (95% CI), mo	5.6 (5.5-7.4)	3.7 (3.1-3.7)

Stratified HR, 0.54 (95% CI 0.44-0.67), 1-sided p <0.0001

Vogel A, et al. ASCO 2024. Abstract 4110.

CARES-310: OS



Vogel A, et al. ASCO 2024. Abstract 4110.

CARES-310: Safety

Adverse Events, n (%)	Camrelizumab + Rivoceranib (n = 272)	Sorafenib (n = 269)
Any grade AE	271 (99)	265 (99)
Treatment-related AE	265 (97)	249 (93)
Grade ≥3 AE	238 (88)	182 (68)
Treatment-related grade ≥3 AE	220 (81)	141 (52)
Treatment-related serious AE	66 (24)	16 (6)
Treatment-related grade 5 AE	1 (<1)	1 (<1)
TRAE leading to discontinuation of any study medication	66 (24)	12 (4)
TRAE leading to dose reduction of any study medication	128 (47)	87 (32)

Qin S, et al. *Lancet*. 2023;402(10408):1133-1146.

CheckMate 9DW: Study Design

Randomized, open-label, multicenter, global, phase III trial

Patients with advanced HCC;
no previous systemic therapy;
Child-Pugh class A;
ECOG PS 0/1
(N = 668)

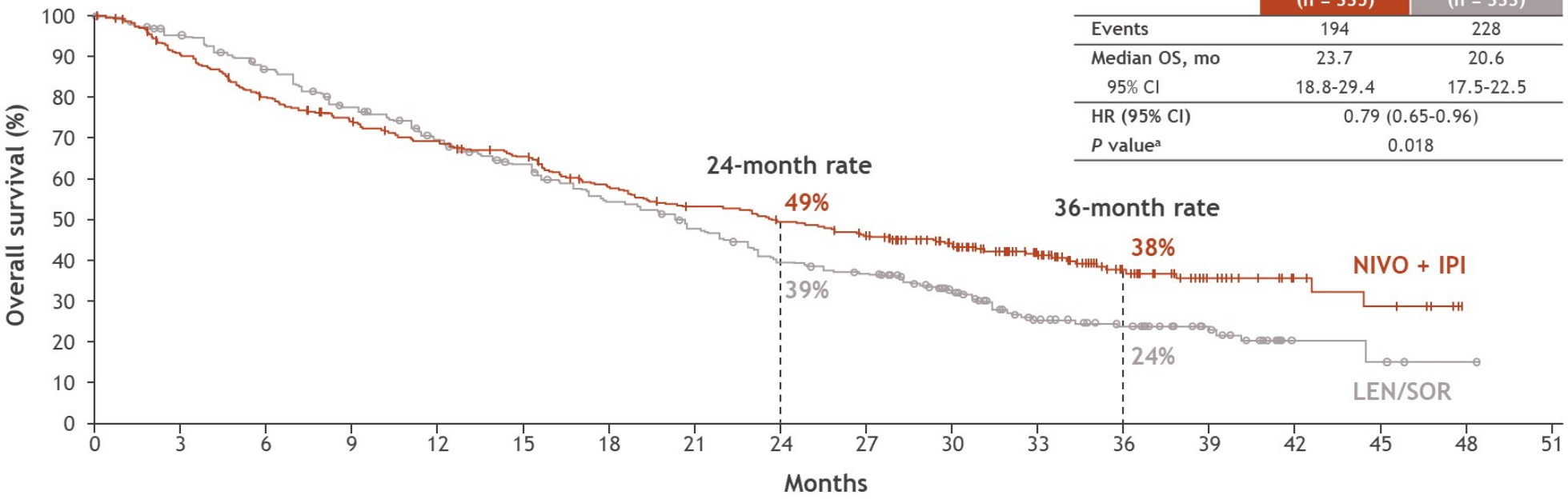
→ **Nivolumab** 1 mg/kg + **Ipilimumab** 3 mg/kg Q3W (4 doses) followed by **Nivolumab** monotherapy

→ **Sorafenib** or **Lenvatinib**

- **Primary endpoint:** OS
- **Key secondary endpoints:** ORR, DoR, time to symptom deterioration

Galle P, et al. ASCO 2024. Abstract LBA4008.
ClinicalTrials.gov identifier: NCT04039607.

CheckMate 9DW: OS



	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	194	228
Median OS, mo	23.7	20.6
95% CI	18.8-29.4	17.5-22.5
HR (95% CI)	0.79 (0.65-0.96)	
P value[a]	0.018	

No. at risk

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

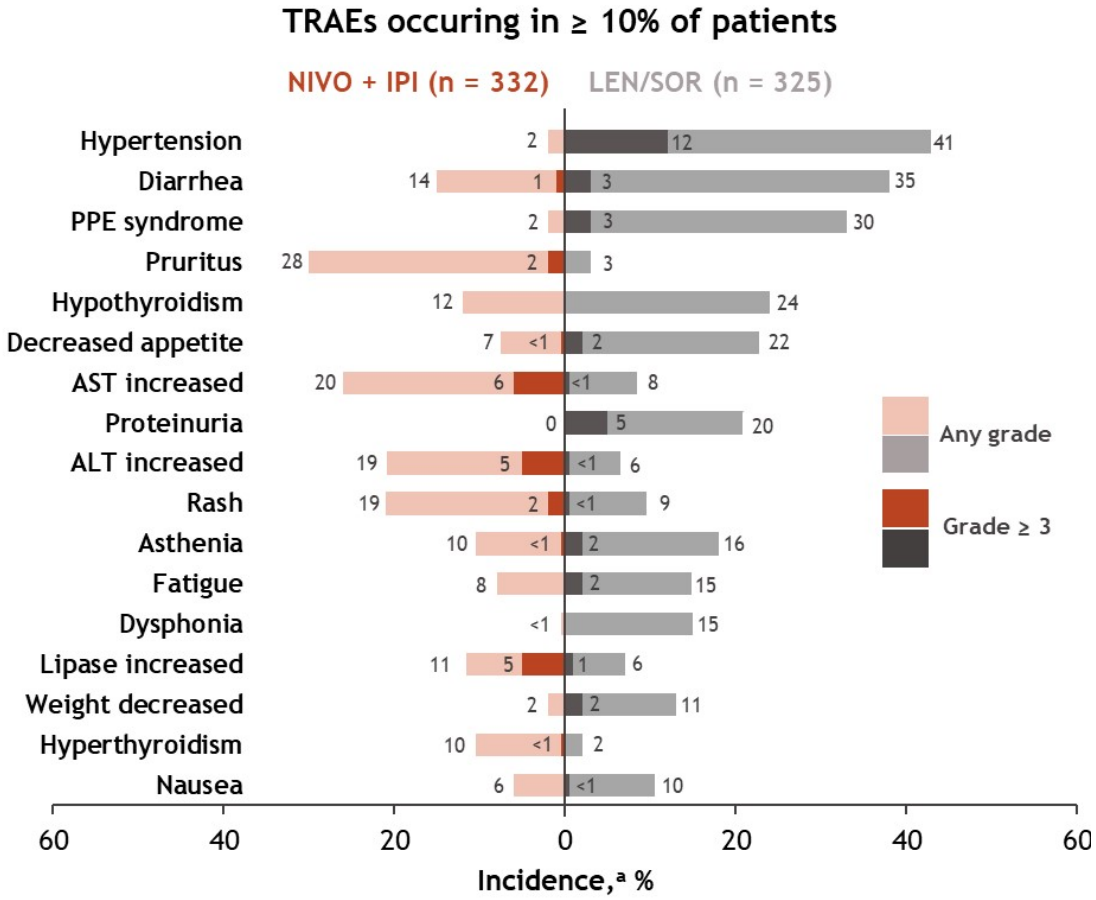
Median (range) follow-up, 35.2 (26.8-48.9) months. Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Two-sided *P* value from stratified log-rank test. Boundary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

Galle P, et al. ASCO 2024. Abstract LBA4008.

CheckMate 9DW: Safety

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]	



[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Treatment-related deaths were reported regardless of time frame. [c]TRAEs leading to death in the NIVO + IPI arm included immune-mediated hepatitis (n = 4), hepatic failure (n = 3), hepatic insufficiency (n = 1), decompensated cirrhosis (n = 1), diarrhea-colitis (n = 1), autoimmune hemolytic anemia (n = 1), and dysautonomia (n = 1). [d]TRAEs leading to death in the LEN/SOR arm included hepatorenal syndrome (n = 1), ischemic stroke (n = 1), and acute kidney injury (n = 1).

Galle P, et al. ASCO 2024. Abstract LBA4008.

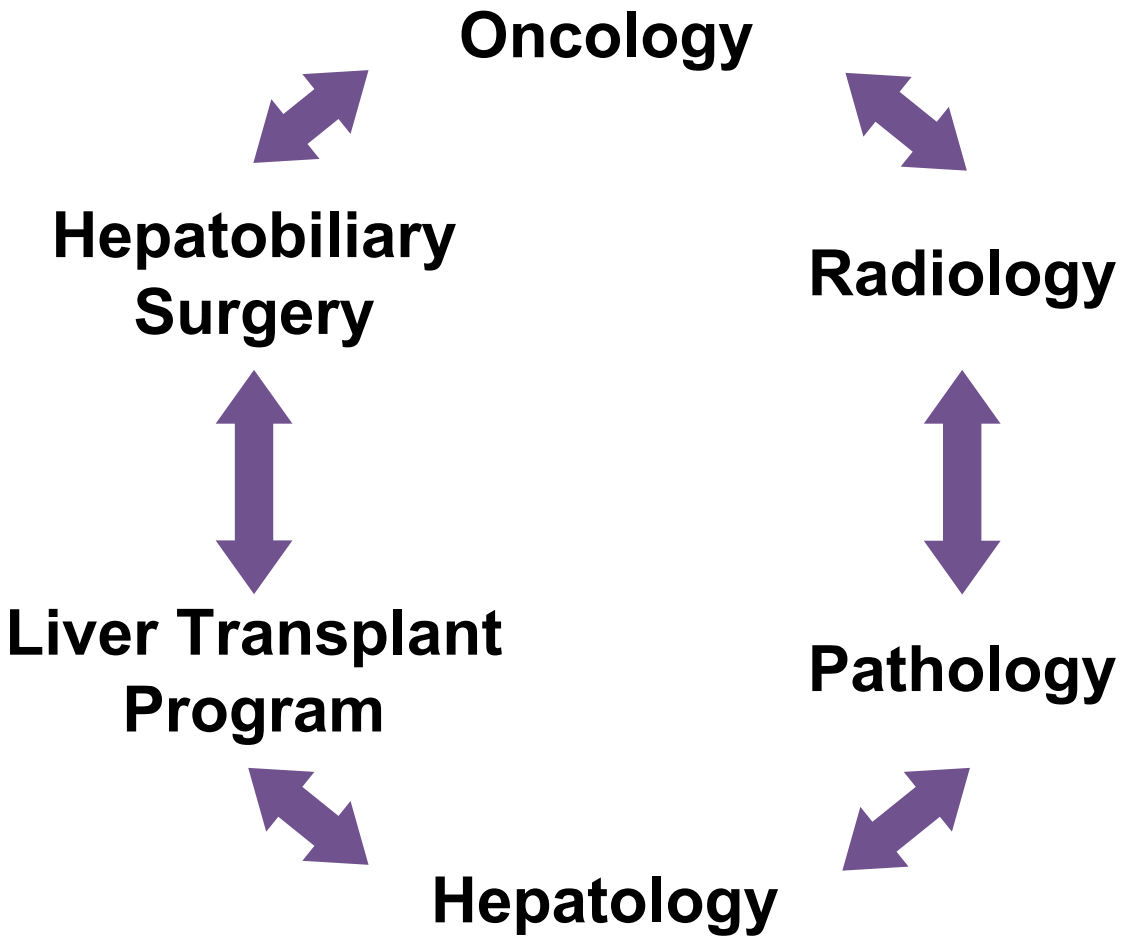
I always try to educate patients about the signs of liver failure. And we always need to watch for patients' liver function.

Aiwu Ruth He, MD

Adverse Events Associated With ICI Combinations

- Immune-mediated adverse events
  - Worsening of liver function
    - Increased ALT and AST
    - Repeat liver function test before each treatment
  - Colitis
    - Refer patients to a GI doctor
    - Treat with high-dose steroids
    - Infliximab for steroid-refractory colitis
  - Endocrine disorders
- VEGF-related adverse events
  - Risk of bleeding in patients with varices
  - Proteinuria
    - Follow up with urinalysis
    - Hold therapy if getting worse

Multidisciplinary Care for Unresectable HCC Is Important



The involvement of Medical Oncology right from the start will be very critical.

We know that it will give the opportunity to help build the big picture and ensure that we get the right therapy for the patient at the right time.

Ghassan Abou-Alfa, MD

Multidisciplinary Care Improves OS

Study	Outcomes
Single-day multidisciplinary team conference (N = 6619)[1]	Improves survival
VA hospital or multispecialty evaluation (N = 3988)[2]	Increases treatment receipt and improves survival
Single-day multidisciplinary clinic and conference (N = 355)[3]	Improves early detection, curative treatment, time to treatment, and survival
Multidisciplinary treatment team for fluid referrals and joint conferences (N = 121)[4]	Improves referrals, early detection, curative treatment, and survival

1. Sinn DH, et al. *PLoS One*. 2019;14(1):e0210730. 2. Serper M, et al. *Gastroenterol*. 2017;152(8):1954-1964.
3. Yopp AC, et al. *Ann Surg Onc*. 2014;21(4):1287-1295. 4. Chang TT, et al. *HPB (Oxford)*. 2008;10(6):405-411.

We would want to share information with patients so that they can also take part in the decision-making. I think that will increase the satisfaction of the patient.

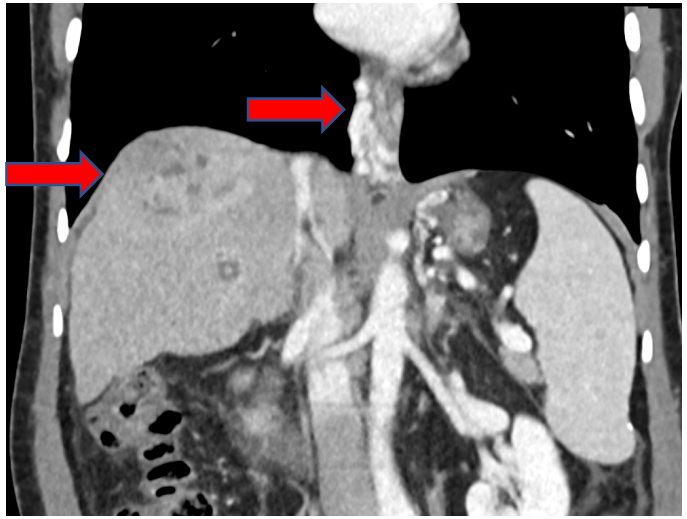
Aiwu Ruth He, MD

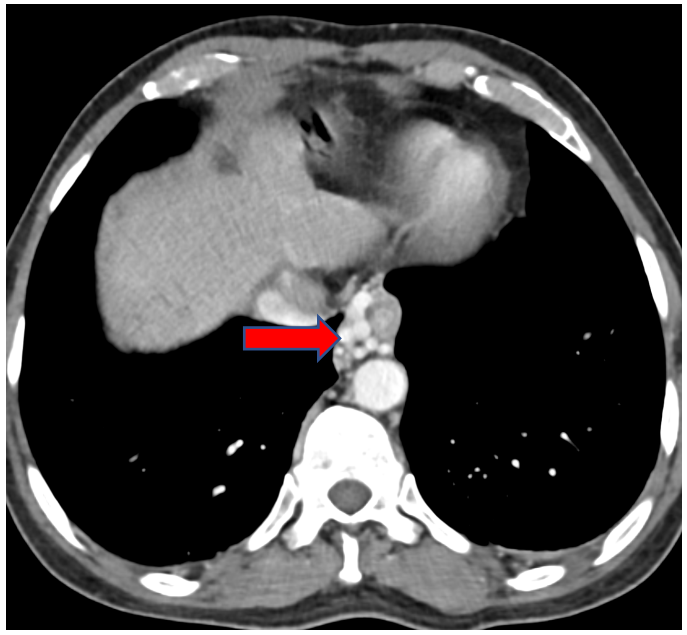
It’s teamwork. We cannot engage the patients without involving and hearing the patient perspective.

Ghassan Abou-Alfa, MD

Case Presentation

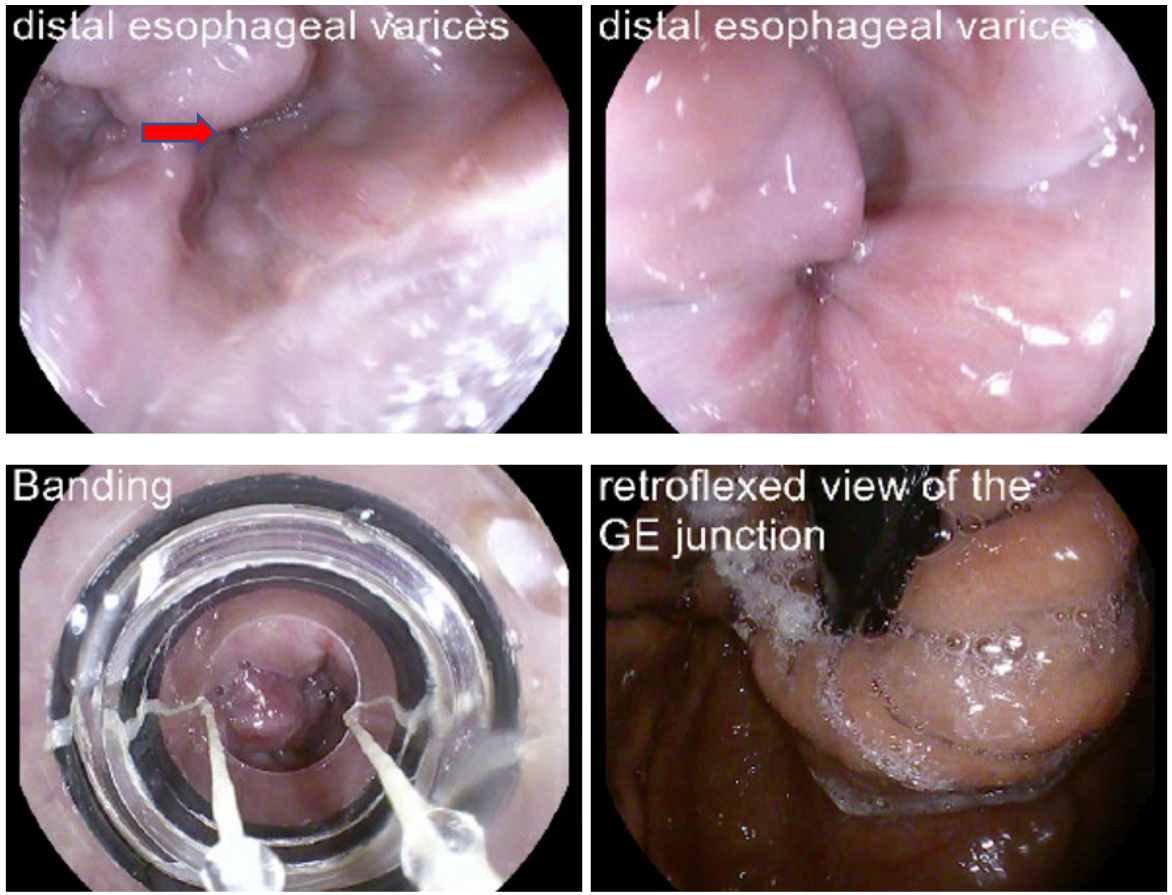
- 66-year-old man with a history of cryptogenic cirrhosis diagnosed in 2016
- Monitored with routine surveillance for HCC
- A recent scan on 11/3/2023 showed LIRAD5 lesion of approximately 2.3 x 1.7 cm, bridging segments 7 and 8
- Thrombosis of the right portal vein and questionable tumor in vein
- AFP on 11/22/2023 was 2998
- WBC 3.65, Hgb 13.3, HCT 40.7, platelets 54,000
- Child-Pugh A liver function
- Normal blood pressure
- Enlarged liver and spleen
- BCLC stage C disease





Case Presentation (Continued)

EGD



Case Presentation (Continued)

- Patient was treated with the STRIDE regimen on 12/18/2023
- Repeat CT scan on 4/13/2024 showed tumor shrinkage to 1.2 x 0.9 cm
- Ongoing right-sided portal vein thrombosis with overall decreased tumor in vein
- AFP has declined