Update on Hepatocellular Carcinoma

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Relevant disclosures

- Consulting and/or clinical trial funding:

-Astrazeneca
-Genentech
-Elevar
-Eisai
-Bayer
-Exelixis
-Tersera
-Eisai
-ITM
-Ipsen
-Merck
-Pfizer

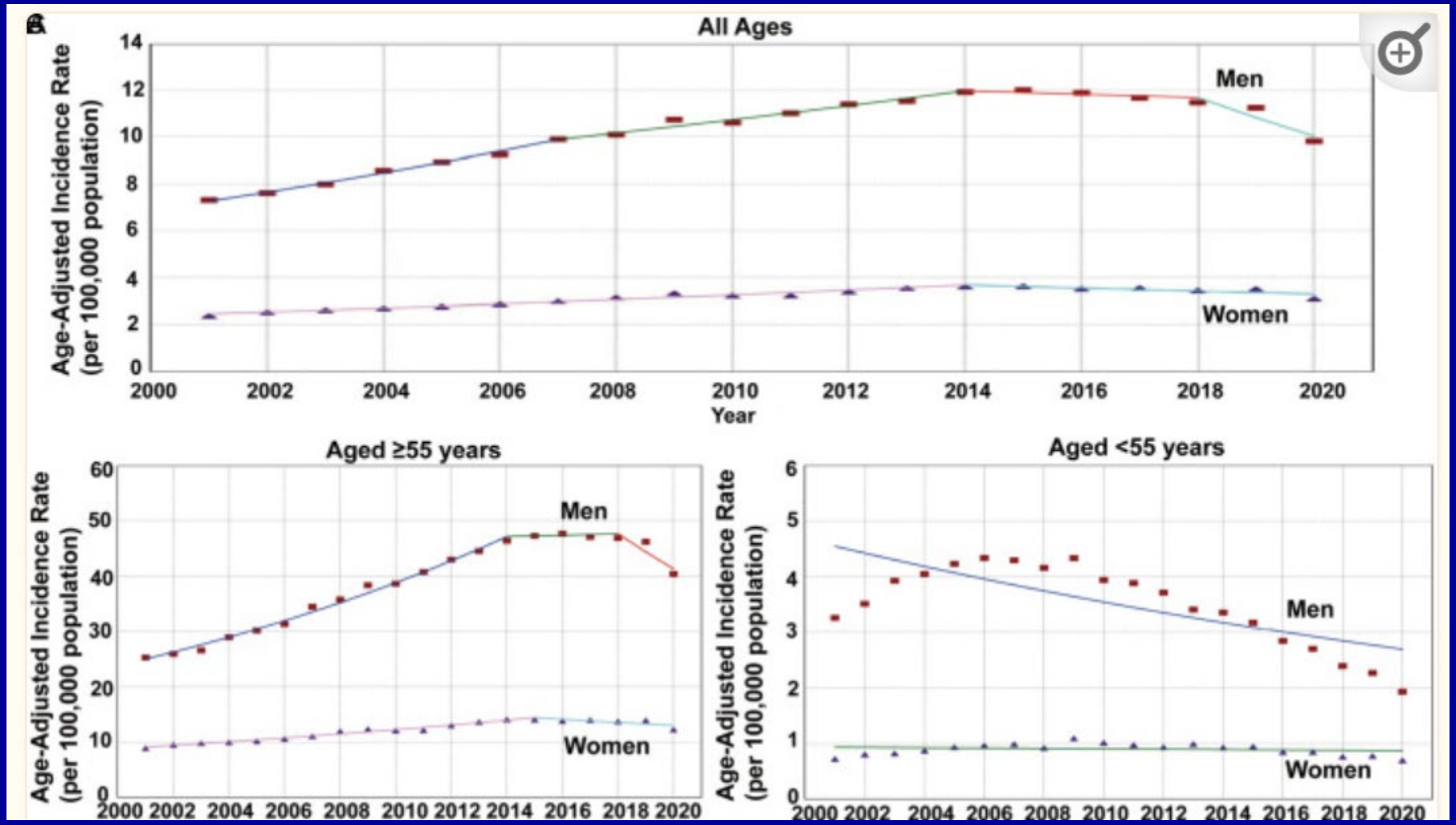
Off label uses of therapies will be mentioned

HCC: The bad news

- HCC is 3rd or 4th leading cause of cancer death worldwide
- In US it is 9th (5th in men)

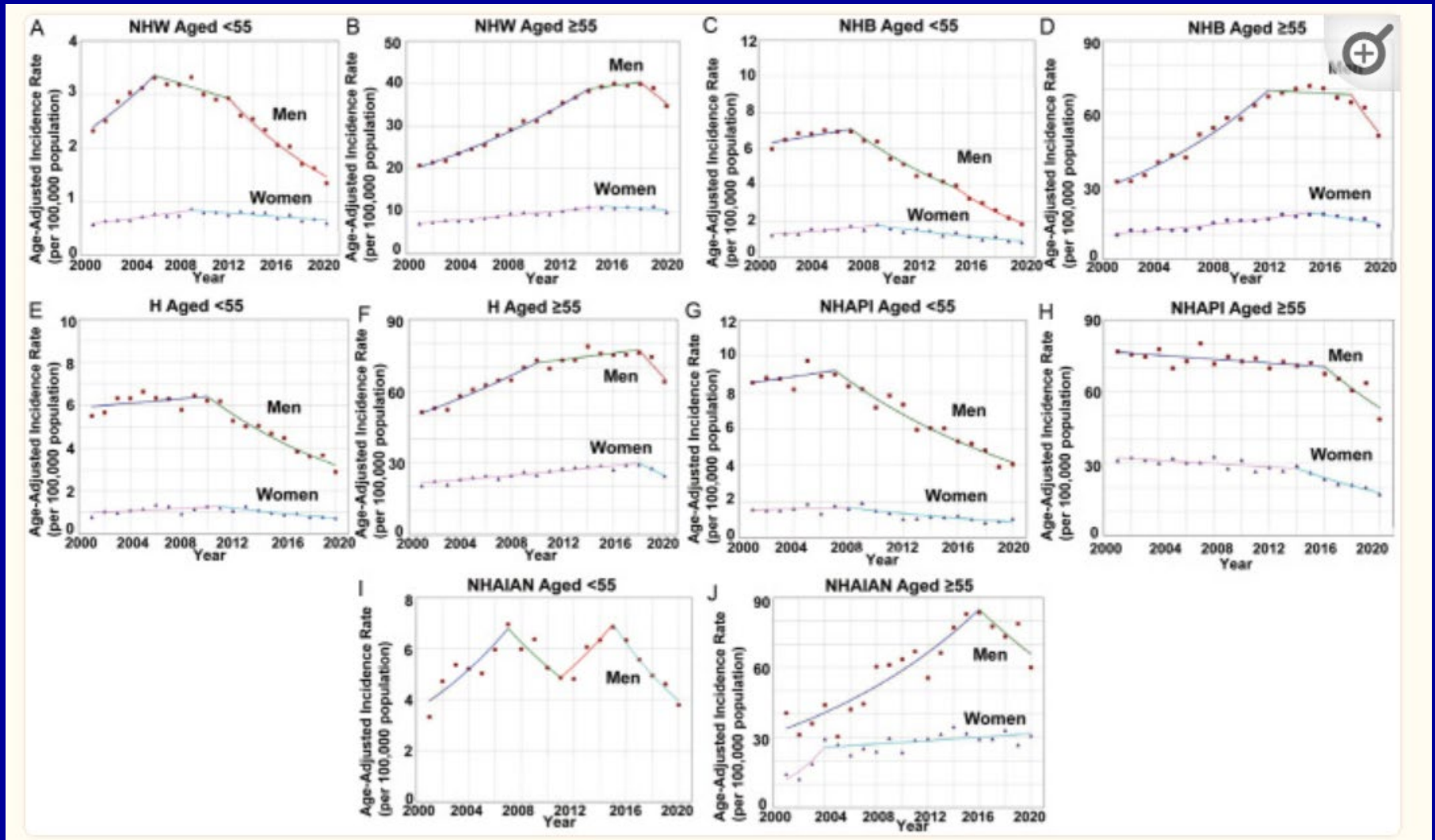
American Cancer Society. Cancer Facts & Figures 2024

The better news: Incidence is declining



J Clin Transl Hepatol. 2024 Feb 28;12(2):172-181

Incidence is declining in all groups



Work-up/evaluation

Diagnosis by imaging: OVERVIEW OF LIRADS

- American College of Radiology protocol for standardizing the reporting of imaging findings of HCC

- Only validated for patients at risk for HCC
  - Cirrhosis
    - NOT VALIDATED IN CARDIOGENIC CAUSES
  - History of HCC
  - Non cirrhotic chronic HBV with intermediate or high risk

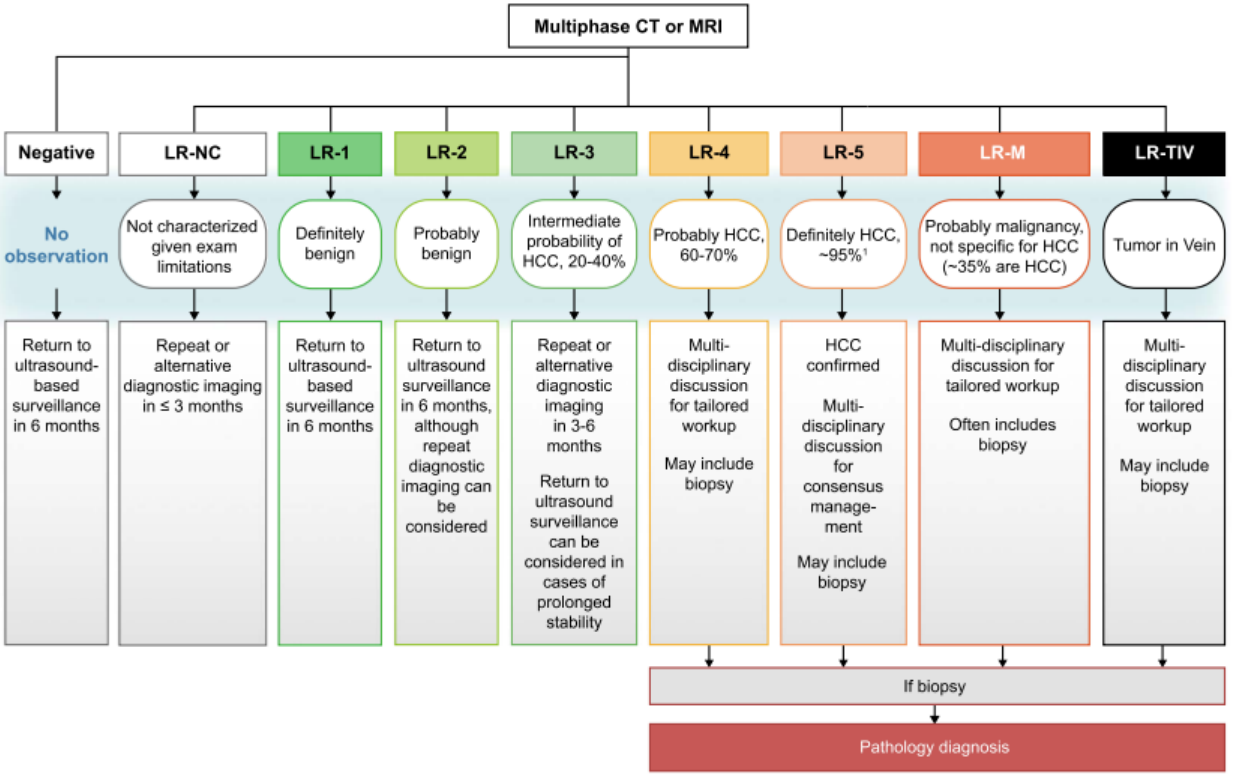
MAJOR IMAGING FEATURES

Non-rim APHE	• Greater enhancement of the lesion vs liver parenchyma • During AP (late > early) • Required for LR-5
Non-peripheral washout	• Perceived reduction in enhancement relative to surroundings • Assessed in extracellular phases (PVP or DP)
Enhancing "capsule"	• Uniform rim of hyperenhancement • Increases from early to late contrast phases
Size	• Largest edge-to-edge diameter • Influences staging and LT eligibility
Threshold growth	• Size increase by ≥50% in ≤ 6 months

Courtesy Dr. Bonike Oloruntoba-Sanders

HCC: DIAGNOSIS: LIRADS

- US + AFP
- Lesion >1CM or AFP >20 or AFP increasing
- Contrast enhanced multi-phased MRI or CT
- Liver Lesion
- Apply LIRADS



Courtesy Dr. Bonike Oloruntoba-Sanders

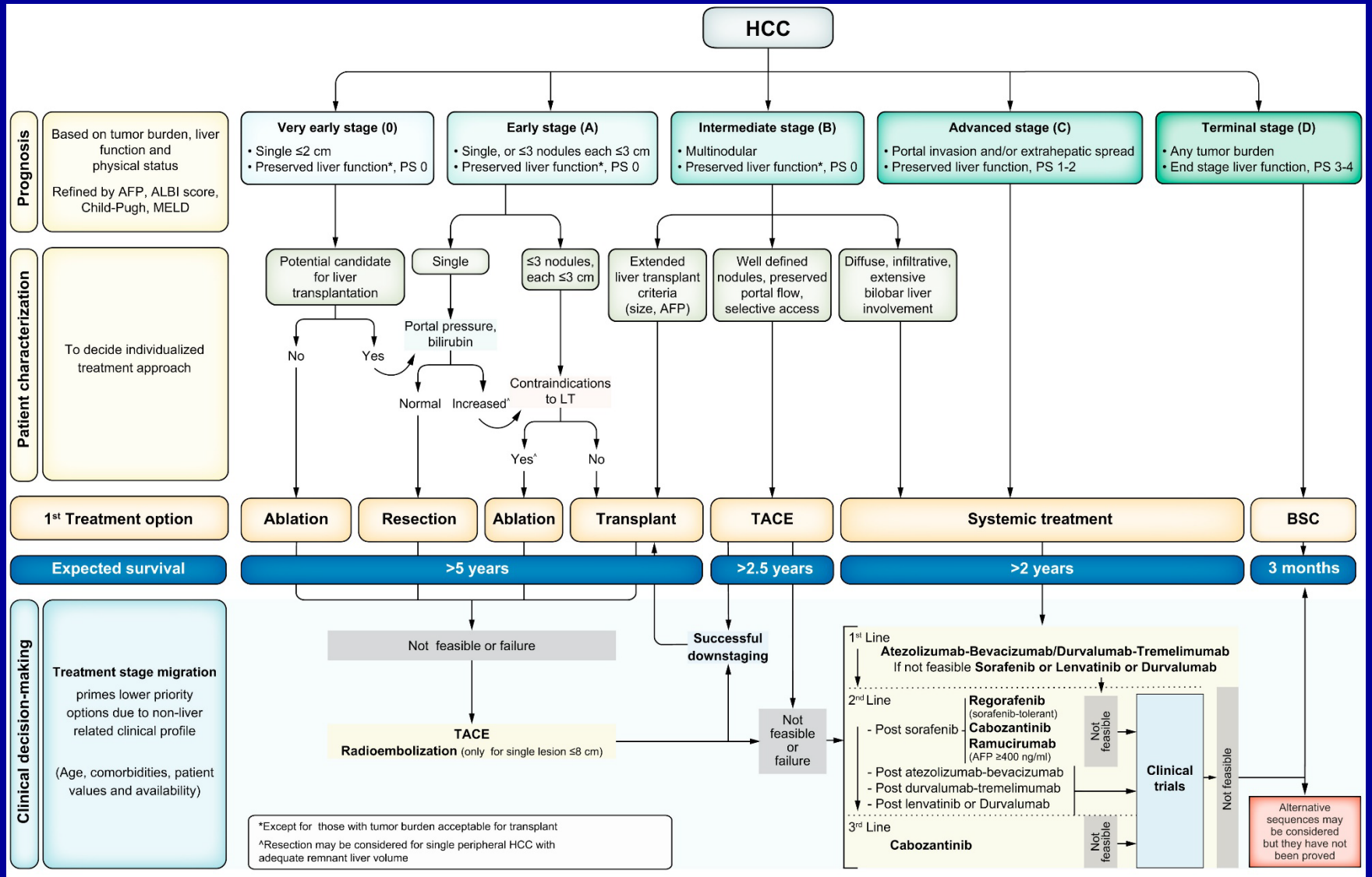
Is there a role for molecular testing?

HCC are associated with a range of molecular alterations (*Wnt-TGFβ, PI3K-AKT-mTOR, RAS-MAPK, MET, IGF, Wnt-β-catenin; TP53* and *TERT* promotor mutations).
There are no treatments with differential benefit for specific molecularly defined subgroups of HCC.

There is no established indication for routine molecular profiling in HCC, but it should be considered on a case by-case basis.
Tumor molecular testing may be warranted in patients with atypical histology, cHCC-CCA histology, unusual clinical presentations, or for clinical trial enrollment.

Adapted from NCCN.org

BCLC staging and treatment strategy in 2022



Journal of Hepatology 2022 76681-693DOI: (10.1016/j.jhep.2021.11.018)

First line therapy for advanced HCC: Update on NCCN Guidelines

WAS

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy

Preferred Regimens

- Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1]
- Tremelimumab-actl + durvalumab (category 1)[b,2]

Other Recommended Regimens

- Sorafenib (Child-Pugh Class A [category 1] or B7)[d,e,3,4]
- Lenvatinib (Child-Pugh Class A only) (category 1)[5,6]
- Durvalumab (category 1)[b,2]
- Pembrolizumab (category 2B)[b,7]

Useful in Certain Circumstances

- Nivolumab (Child-Pugh Class B only)[b,8]
- Atezolizumab + bevacizumab (Child-Pugh Class B only)[9]
- For TMB-H tumors:
  - Nivolumab + ipilimumab (category 2B)[10]

Most recent

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Hepatocellular Carcinoma

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY[a,b,c]

First-Line Systemic Therapy

Preferred Regimens

- Atezolizumab + bevacizumab (category 1)[d,e,f,1]
- Tremelimumab-actl + durvalumab (category 1)[e,2]

Other Recommended Regimens

- Durvalumab (category 1)[e,2]
- Lenvatinib (category 1)[3,4]
- Sorafenib (category 1)[5,6]
- Pembrolizumab (category 2B)[e,7]

Useful in Certain Circumstances

- None

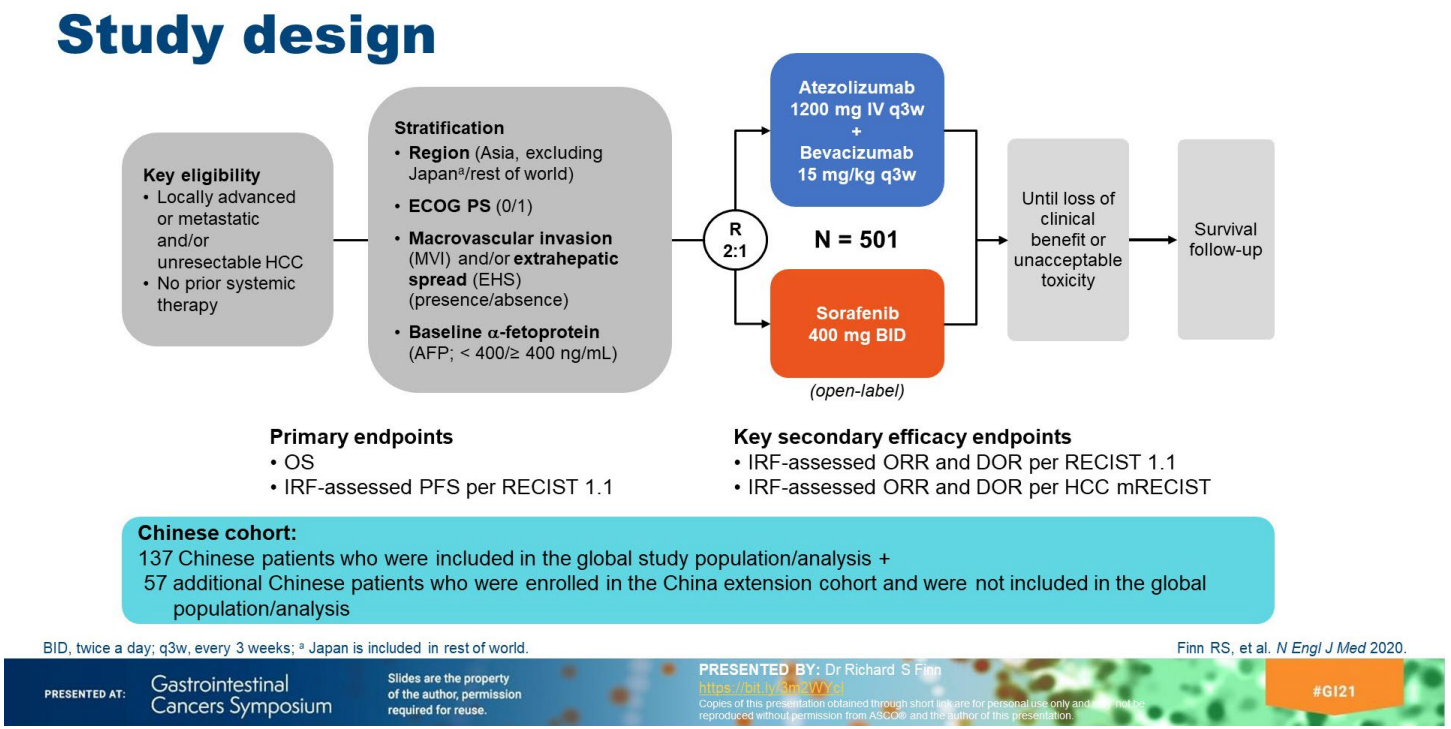
Research Article
Hepatic and Biliary Cancer

JOURNAL
OF HEPATOLOGY

Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab *vs.* sorafenib for unresectable hepatocellular carcinoma

Ann-Lii Cheng[1,*], Shukui Qin[2], Masafumi Ikeda[3], Peter R. Galle[4], Michel Ducreux[5], Tae-You Kim[6], Ho Yeong Lim[7], Masatoshi Kudo[8], Valeriy Breder[9], Philippe Merle[10], Ahmed O. Kaseb[11], Daneng Li[12], Wendy Verret[13], Ning Ma[14], Alan Nicholas[15], Yifan Wang[16], Lindong Li[17], Andrew X. Zhu[18,19], Richard S. Finn[20,*]

J Hepatol 2022;76(4):862-73.



Finn R: Presented at: 2021 ASCO Gastrointestinal Cancers Symposium.

* Patients had to be evaluated for the presence of varices before enrollment, and varices of any size were assessed and treated as needed according to local standards of care.

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)

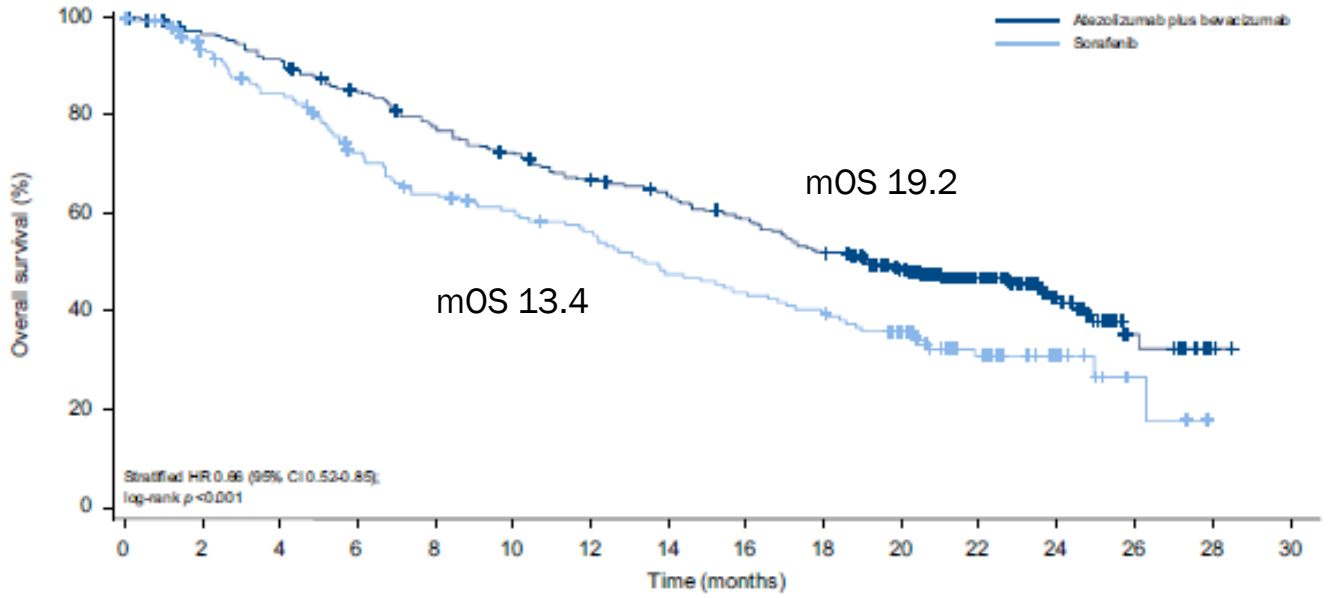
Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.
[a] Japan is included in rest of world.

Varices at baseline 26 vs 26%, treated 11 vs 14%

Finn R: Presented at: 2021 ASCO Gastrointestinal Cancers Symposium.

IMBRAVE 150: Updated OS

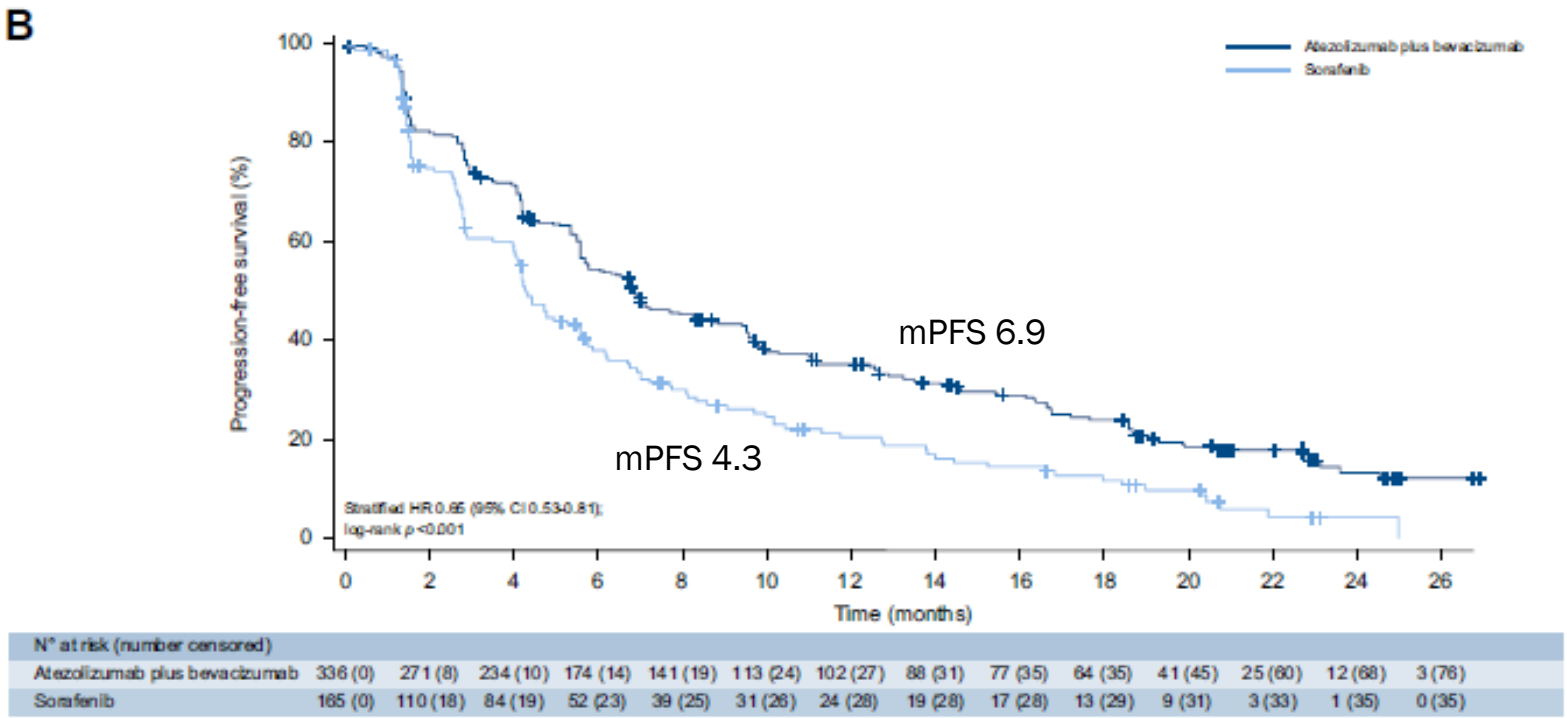
A



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)

J Cheng, J Hepatol 2022.

IMBRAVE 150: Updated PFS

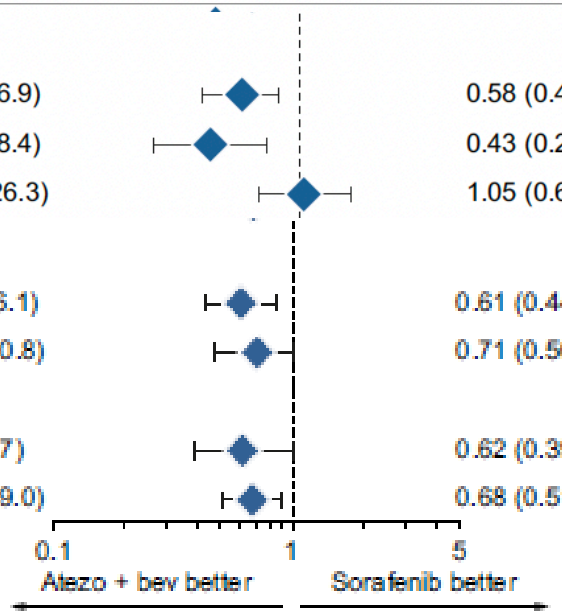


N° at risk (number censored)														
Atezolizumab plus bevacizumab	336 (0)	271 (8)	234 (10)	174 (14)	141 (19)	113 (24)	102 (27)	88 (31)	77 (35)	64 (35)	41 (45)	25 (60)	12 (68)	3 (76)
Sorafenib	165 (0)	110 (18)	84 (19)	52 (23)	39 (25)	31 (26)	24 (28)	19 (28)	17 (28)	13 (29)	9 (31)	3 (33)	1 (35)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

J Cheng, J Hepatol 2022.

OS: Subgroup analysis

Subgroup	Atezolizumab plus bevacizumab		Sorafenib		Hazard ratio for death (95% CI)
	Events/ patients	Median OS, months (95% CI)	Events/ patients	Median OS, months (95% CI)	
Etiology					
Hepatitis B	86/164	19.0 (16.1-NE)	46/76	12.4 (6.7-16.9)	0.58 (0.40-0.83)
Hepatitis C	31/72	24.6 (19.8-NE)	24/36	12.6 (7.4-18.4)	0.43 (0.25-0.73)
Non-viral	63/100	17.0 (11.7-22.8)	30/53	18.1 (11.7-26.3)	1.05 (0.68-1.63)
Prior local therapy					
No	95/175	19.4 (16.7-23.7)	52/80	13.1 (7.4-16.1)	0.61 (0.44-0.86)
Yes	85/161	19.0 (16.1-24.9)	48/85	14.4 (10.2-20.8)	0.71 (0.50-1.02)
High risk*					
Yes	44/64	7.6 (6.6-12.8)	29/37	5.5 (4.1-6.7)	0.62 (0.39-1.00)
No	136/272	22.8 (19.1-24.9)	71/128	15.7 (13.2-19.0)	0.68 (0.51-0.91)



*Defined as patients with Vp4 portal vein thrombus, bile duct invasion, or liver infiltration >50%.

Updated response and duration of response

Table 1. Clinical response by independent review facility-assessed RECIST 1.1.

	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.

J Cheng, J Hepatol 2022.

Time to deterioration in QOL

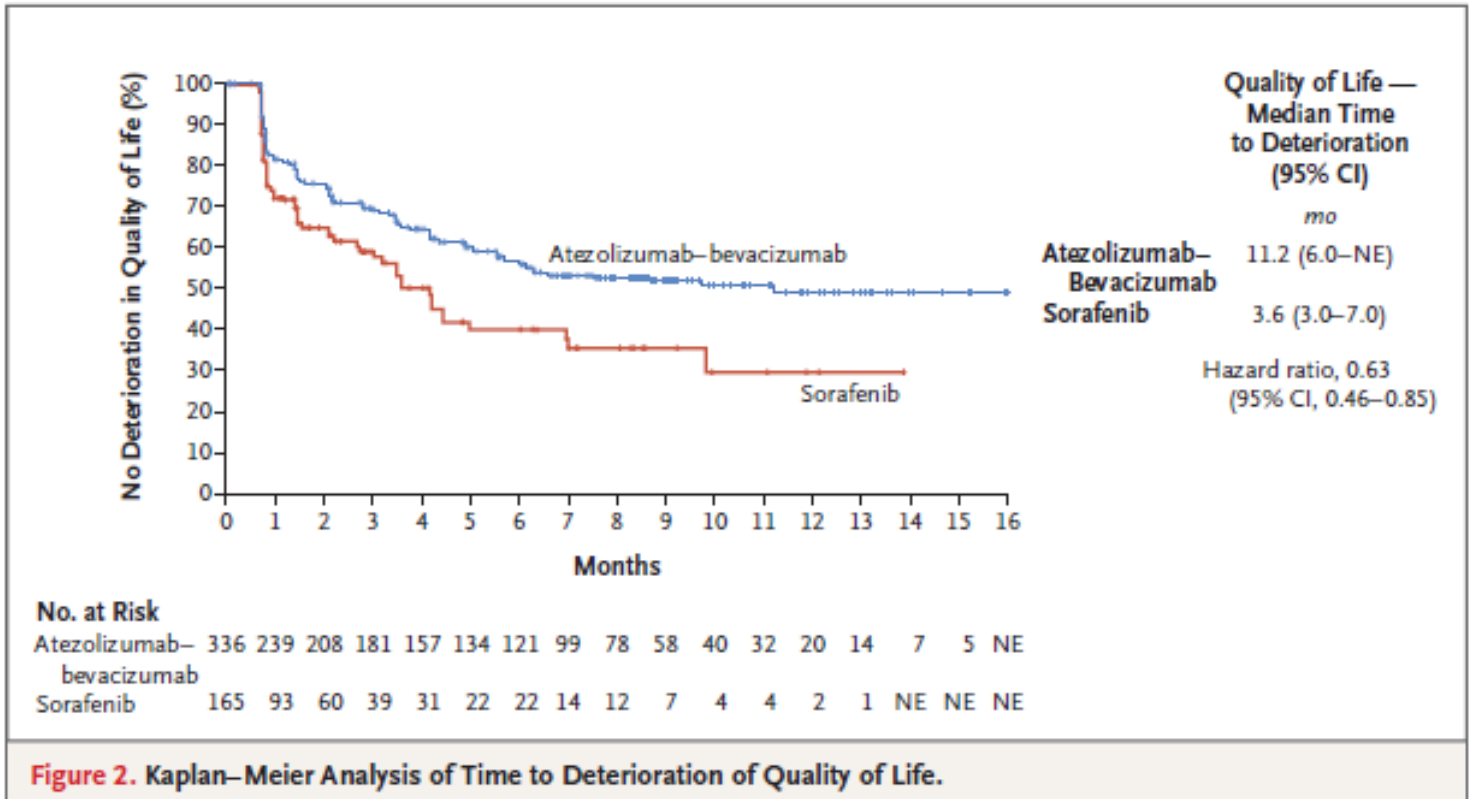


Figure 2. Kaplan–Meier Analysis of Time to Deterioration of Quality of Life.

Finn N Engl J Med 2020; 382;20

Treatment-Related Adverse Reactions

AEs % (All/Gr 3,4)	Atezo-Bev	Sorafenib
Tx-related AEs	86/43	95/46
HTN	30/15	24/12
Proteinuria	20/3	7/0.6
Palmar-plantar erythrodysesthesia	0.9/0	41/8
Diarrhea	19/2	49/5
Infusion rxn	11/2	N/A
Rash	13/0	17/3
Bleeding Gr 3/4	6.4	5.6
Autoimmune hepatitis Gr 3,4	0.6	N/A

Fatal GI bleeds (inc. Varices) 1.2% in Atezo-Bev

Adapted from: Finn R. N Engl J Med. 2020;382(20):1894-1905 & prescribing information

Future development

- A Study Evaluating Atezolizumab and Bevacizumab, With or Without Tiragolumab, in Participants With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma (IMbrave152) (SKYSCRAPER-14)
  - MORPHEUS-Liver study (ASCO2023:Abst 4010: ORR improved from 11.1% in the atezolizumab/bevacizumab arm to 42.5% in patients randomly assigned to the triplet of tiragolumab plus atezolizumab/bevacizumab.

The HIMALAYA TRIAL

NEJM Evidence

Published June 6, 2022

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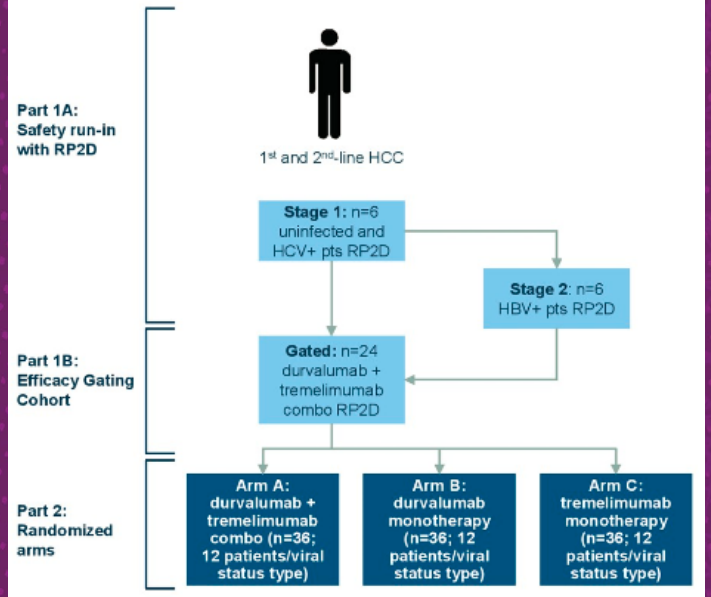
ORIGINAL ARTICLE

Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma

Ghassan K. Abou-Alfa, M.D., M.B.A.,[1,2] George Lau, M.D., F.R.C.P.,[3] Masatoshi Kudo, M.D., Ph.D.,[4] Stephen L. Chan, M.D.,[5] Robin Kate Kelley, M.D.,[6] Junji Furuse, M.D., Ph.D.,[7] Wattana Sukeepaisarnjaroen, M.D.,[8] Yoon-Koo Kang, M.D., Ph.D.,[9] Tu Van Dao, M.D., Ph.D.,[10] Enrico N. De Toni, M.D., Ph.D.,[11] Lorenza Rimassa, M.D.,[12,13] Valeriy Breder, M.D., Ph.D.,[14] Alexander Vasilyev, M.D.,[15] Alexandra Heurgué, M.D.,[16] Vincent C. Tam, M.D.,[17] Kabir Mody, M.D.,[18] Satheesh Chiradoni Thungappa, M.D.,[19] Yuriy Ostapenko, M.D.,[20] Thomas Yau, M.D.,[21] Sergio Azevedo, M.D.,[22] María Varela, M.D., Ph.D.,[23] Ann-Lii Cheng, M.D., Ph.D.,[24] Shukui Qin, M.D., Ph.D.,[25] Peter R. Galle, M.D., Ph.D.,[26] Sajid Ali, M.D.,[27] Michelle Marcovitz, Ph.D.,[27] Mallory Makowsky, Pharm.D.,[27] Philip He, Ph.D.,[27] John F. Kurland, Ph.D.,[27] Alejandra Negro, Ph.D.,[27] and Bruno Sangro, M.D., Ph.D.[28]

Phase 1/2 Study of Durvalumab and Tremelimumab in Patients with Unresectable Hepatocellular Carcinoma (HCC): Phase 1 Safety and Efficacy Analyses

Figure 2: Study Design



Kelley, ASCO2017;abstr 4073

TABLE 1: Outcomes With Tremelimumab/Durvalumab

Outcome	T300 + Durvalumab (n = 74)	Durvalumab Monotherapy (n = 101)	Tremelimumab Monotherapy (n = 69)	T75 + Durvalumab (n = 82)
Median OS	18.7 months	13.6 months	15.1 months	11.3 months
18-month OS	52.0%	35.3%	45.7%	34.7%
ORR	24.0%	10.6%	7.2%	9.5%
DCR	45.3%	37.5%	49.3%	36.9%
Median DOR	NR	11.7 months	23.9 months	13.2 months
Time to response	1.86 months	3.65 months	1.81 months	2.86 months
PFS	2.17 months	2.07 months	2.69 months	1.87 months

DCR = disease control rate; DOR = duration of response; NR = not reached; PFS = progression-free survival; ORR = objective response rate; OS = overall survival; T75 = 75 mg of tremelimumab; T300 = 300 mg of tremelimumab.

Kelley, ESMO World Congress on Gastrointestinal Cancer 2020 Virtual. Abst 0-6

HIMALAYA study design

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

Study population
- Patients aged ≥18 years with uHCC
- BCLC stage B (not eligible for locoregional therapy) and stage C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

R
N=1324

STRIDE (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*

Stratification factors
- Macrovascular invasion: yes vs no
- Etiology of liver disease: HBV vs HCV vs others
- Performance status: ECOG 0 vs 1

*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; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

PRESENTED BY: Ghassan K Abou-Alfa, MD, MBA

Baseline characteristics

Characteristic	STRIDE (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)
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)

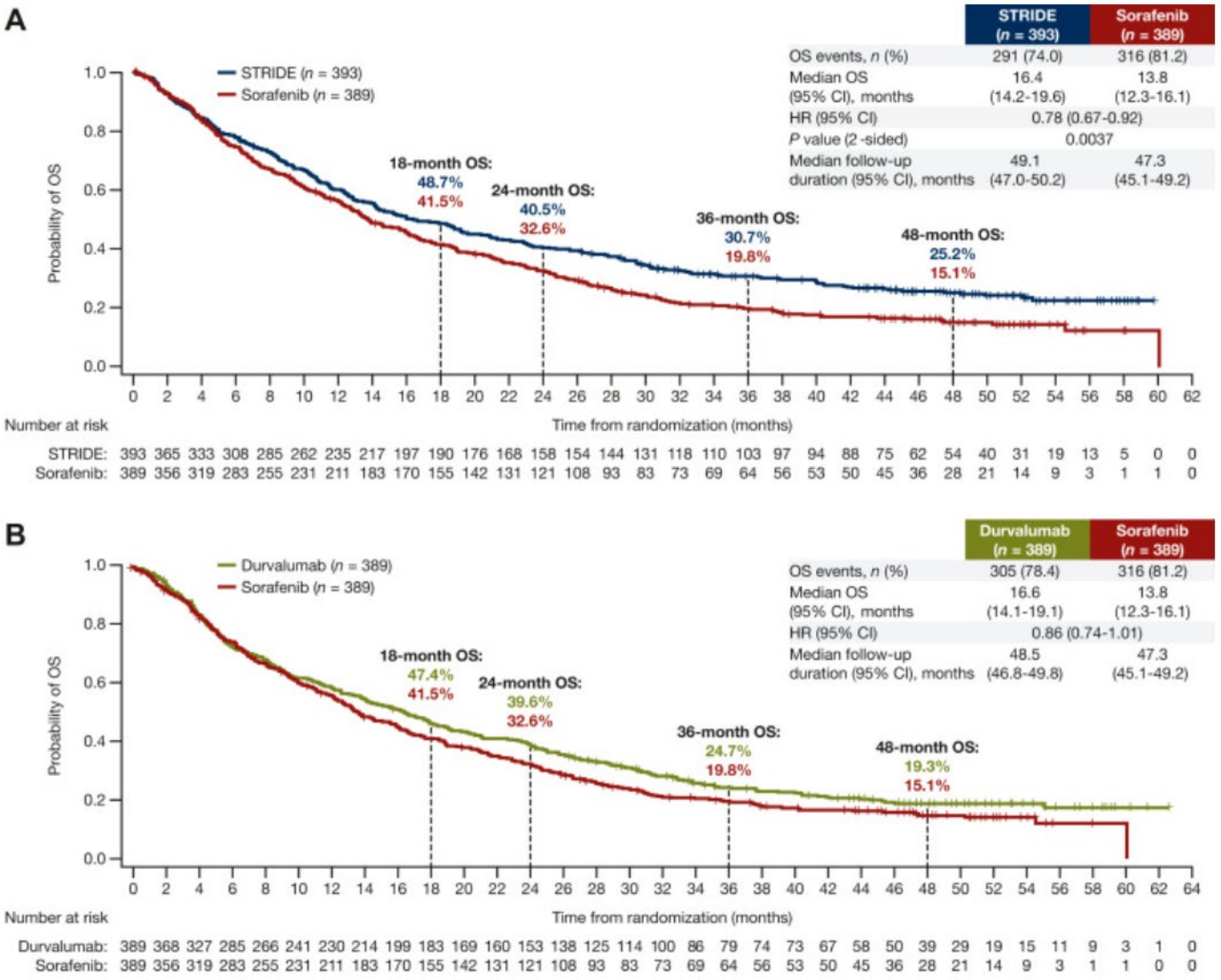
Biomarker evaluable samples were collected for all but 20 patients across all treatment arms.

*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.

AFP, alfa-fetoprotein; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; PD-L1, programmed cell death ligand-1; PS, performance status; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

PRESENTED BY: Ghassan K Abou-Alfa, MD, MBA

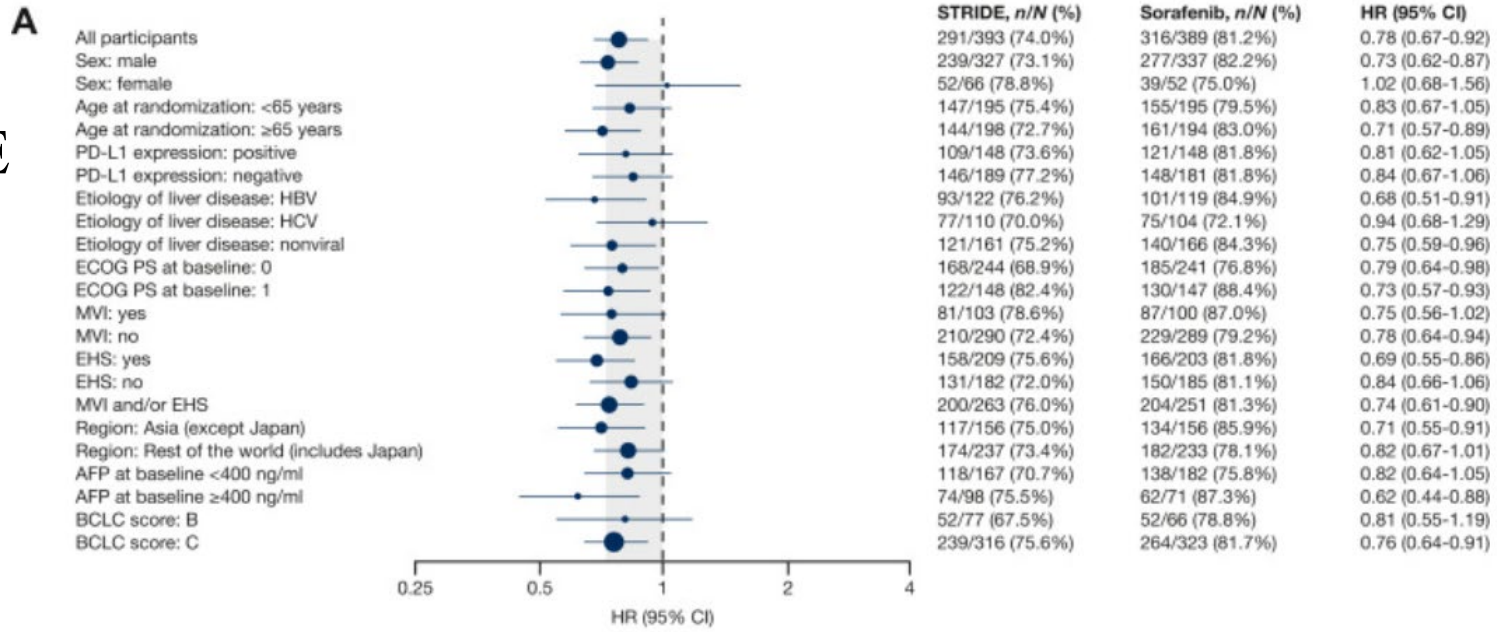
4 year OS data from HIMALAYA trial



Sangro, Ann Oncol. 2024 May;35(5):448-457

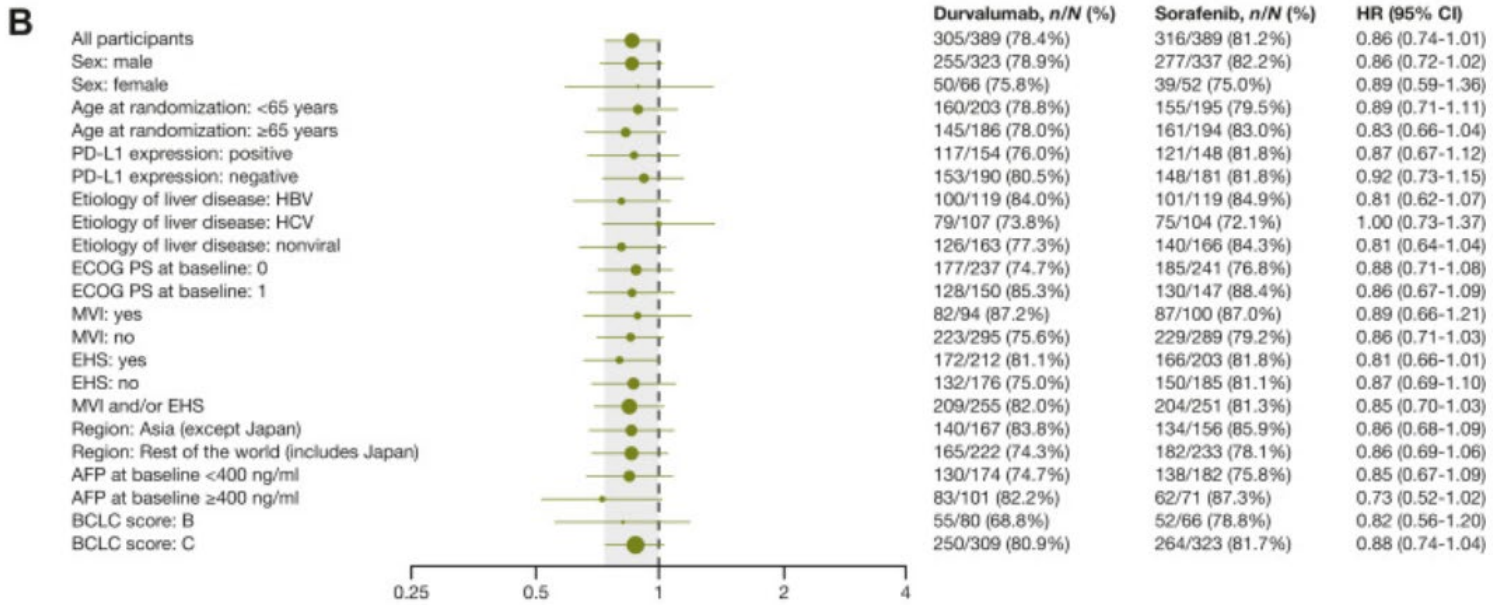
Subgroup analyses for Overall Survival

STRIDE



	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)

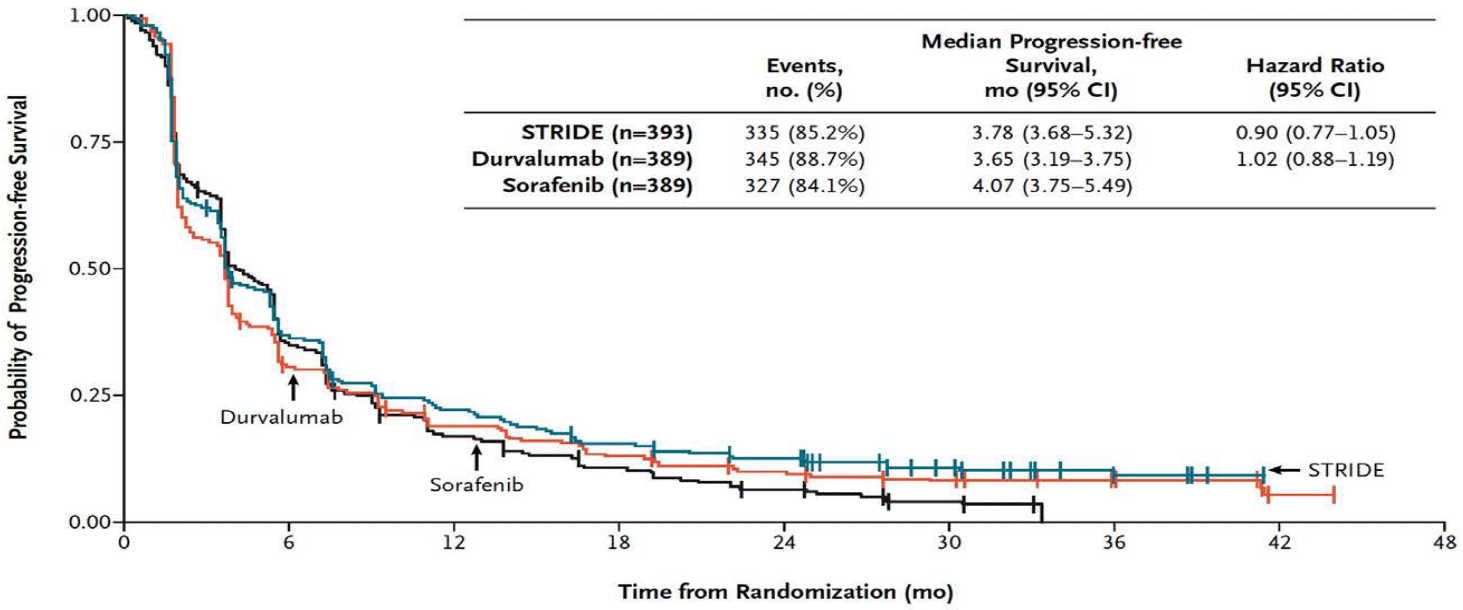
Durva



	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)

PFS

B



	Events, no. (%)	Median Progression-free Survival, mo (95% CI)	Hazard Ratio (95% CI)
STRIDE (n=393)	335 (85.2%)	3.78 (3.68–5.32)	0.90 (0.77–1.05)
Durvalumab (n=389)	345 (88.7%)	3.65 (3.19–3.75)	1.02 (0.88–1.19)
Sorafenib (n=389)	327 (84.1%)	4.07 (3.75–5.49)	

No. at Risk									
STRIDE	393	135	81	55	43	26	7	0	0
Durvalumab	389	115	68	47	34	20	6	1	0
Sorafenib	389	118	53	31	18	6	0	0	0

Tumor response

	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* %	20.1	17.0	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 moths	 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; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTR, time to response.

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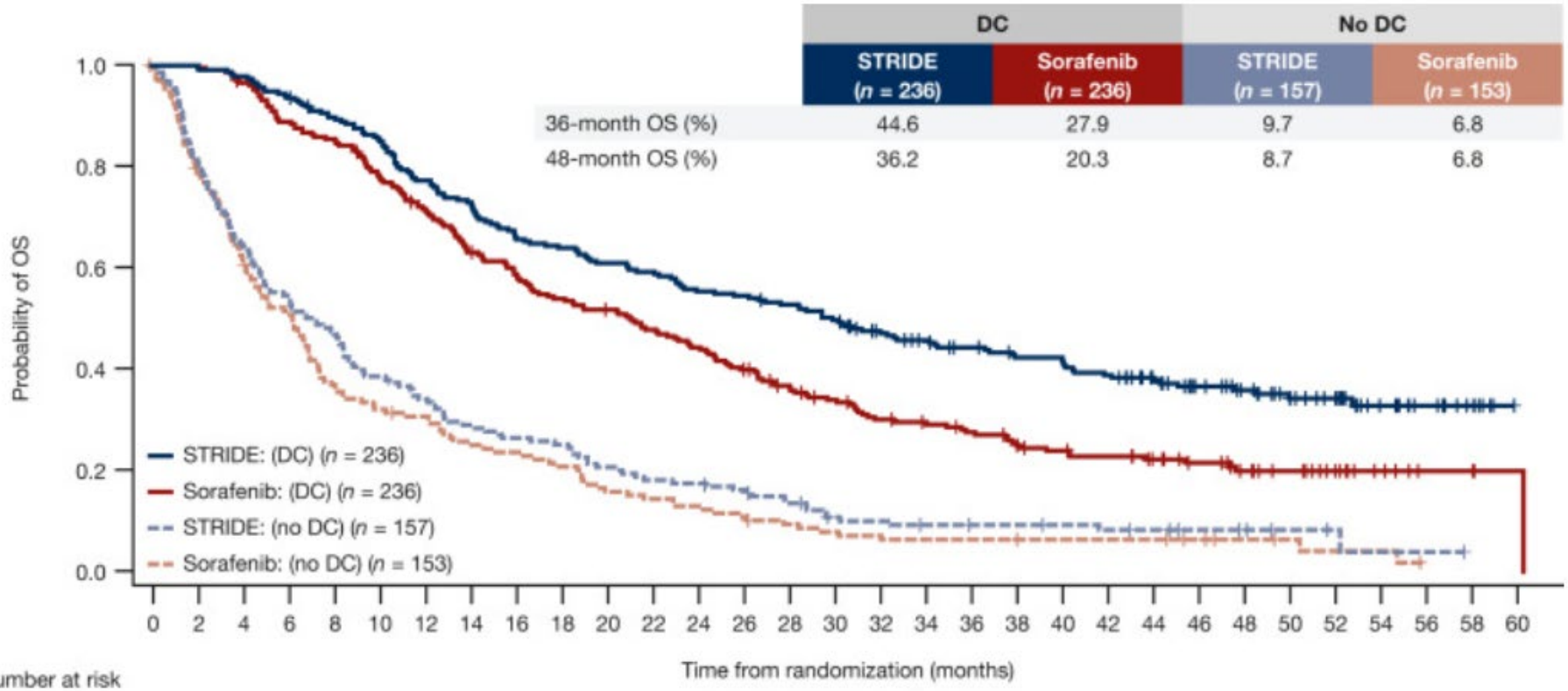
Overall survival by disease control



Number at risk

STRIDE (DC):	236	236	231	222	210	201	181	171	155	150	143	139	130	128	123	116	104	98	92	86	84	79	67	56	49	37	29	18	12	5	0
Sorafenib (DC):	236	236	227	209	201	184	167	147	136	125	119	110	102	92	80	72	63	60	55	48	45	42	37	30	24	18	12	7	3	1	1
STRIDE (no DC):	157	129	102	86	75	61	54	46	42	40	33	29	28	26	21	15	14	12	11	11	10	9	8	6	5	3	2	1	1	0	0
Sorafenib (no DC):	153	120	92	74	54	47	44	36	34	30	23	21	19	16	13	11	10	9	9	8	8	8	8	6	4	3	2	2	0	0	0

HIMALAYA: Response Outcomes in ALBI Grade Subgroups

Parameter	ALBI grade 1			ALBI grade 2/3			Full analysis set[1]		
	T300+D (n=217)	Durvalumab (n=198)	Sorafenib (n=203)	T300+D (n=175)	Durvalumab (n=191)	Sorafenib (n=186)	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* %	21.7	18.7	7.4	18.3	15.2	2.7	20.1	17.0	5.1
Median TTR‡ (IQR), mo	2.07 (1.84–3.94)	1.91 (1.81–3.98)	3.52 (1.84–5.49)	3.52 (1.91–5.40)	3.65 (1.94–3.94)	9.10 (7.79–11.01)	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Median DoR,†‡ (IQR), mo	22.34 (8.71–NR)	23.26 (7.43–NR)	22.06 (6.51–25.99)	26.55 (7.43–NR)	13.83 (7.43–27.43)	12.25 (7.69–NR)	22.34 (8.54–NR)	16.82 (7.43–NR)	18.43 (6.51–25.99)

- Similar to the full analysis set[1]:
  - ORR was higher for T300+D and durvalumab than for sorafenib in both ALBI subgroups
  - Median TTR was shorter for T300+D and durvalumab than for sorafenib in both ALBI subgroups

ORR = overall response rate; TTR = time to response; DoR = duration of response

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

Treatment-related hepatic or hemorrhage SMQ events

Event, n (%)	STRIDE (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

Includes adverse events 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.

SMQ, Standardized MedDRA Query; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TRAE, treatment-related adverse event.

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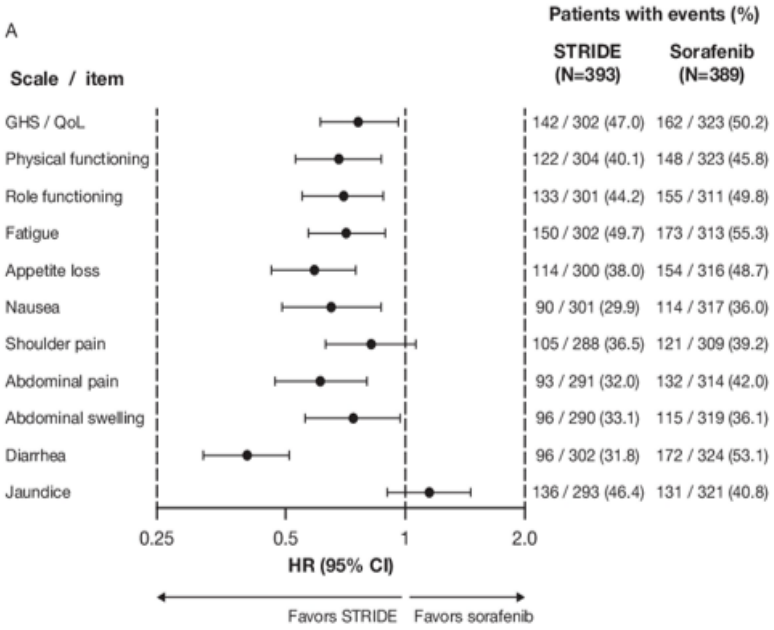
Immune-mediated adverse events

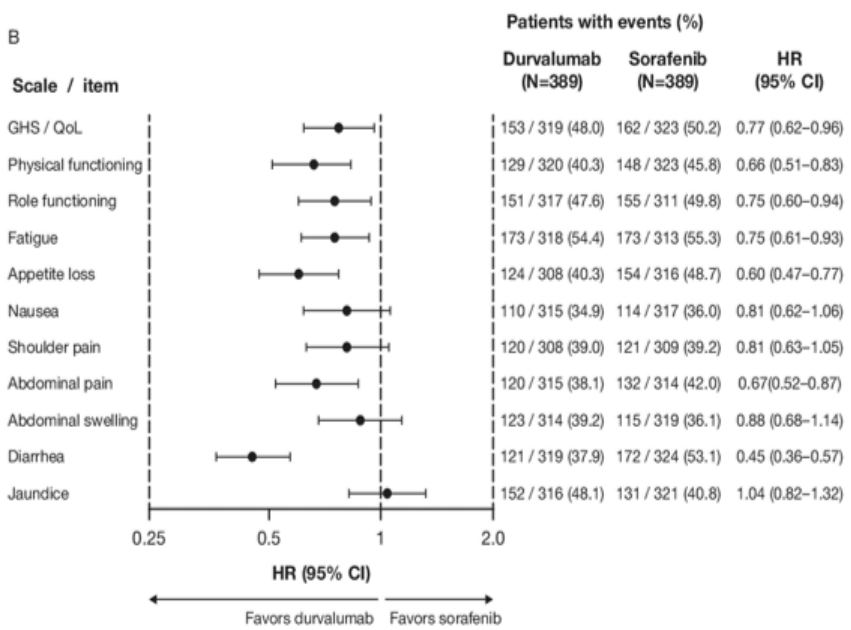
Event, n (%)	STRIDE (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (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

Includes adverse events 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. Patients may have had >1 event. Events include those that occurred in ≥1% of patients in either treatment arm.

STRIDE, Single Tremelimumab Regular Interval Durvalumab.

HIMALAYA: Time To Deterioration Patient Reported Outcomes





CI, confidence interval; **GHS**, global health status; **QoL**, quality of life
Reference: Sangro B. et al. ASCO 2022.

CARES-310: Camrelizumab plus rivoceranib vs Sorafenib

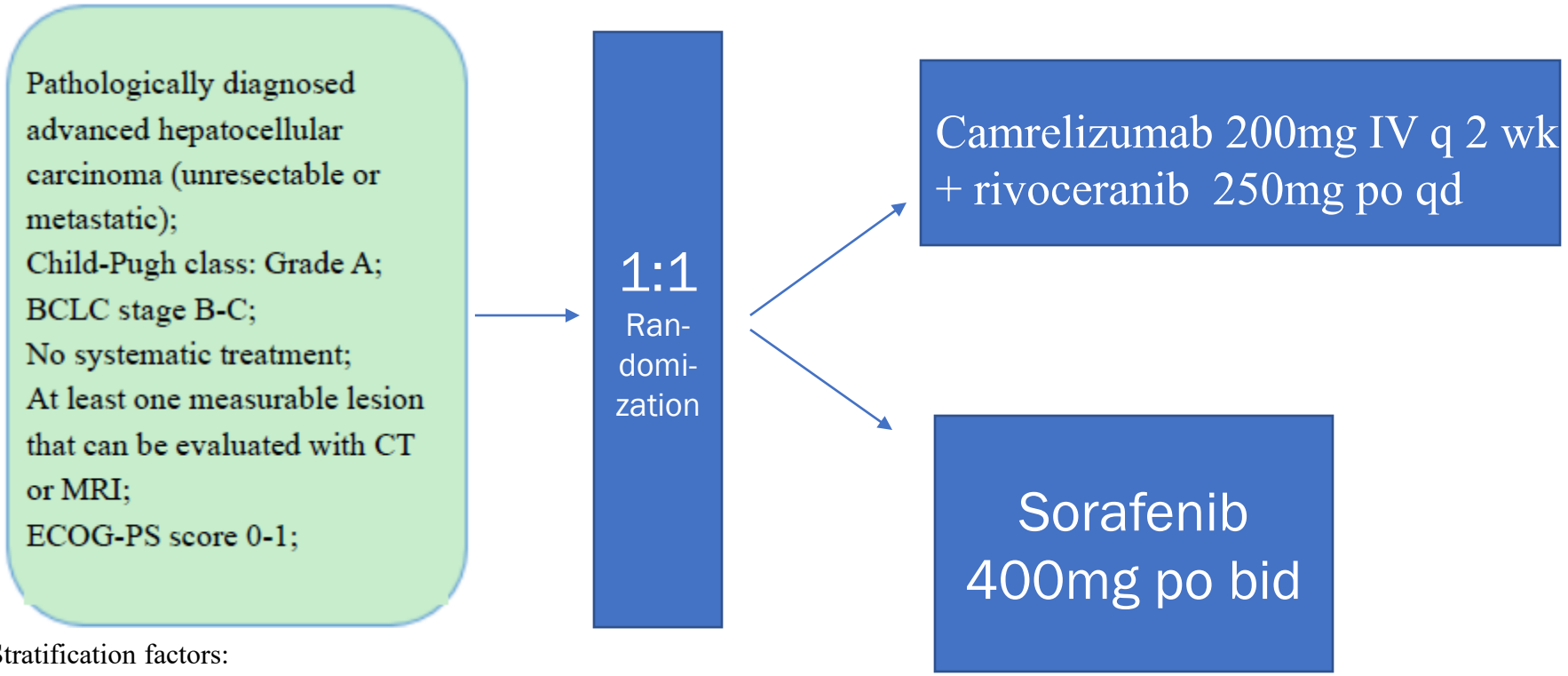
Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study

Shukui Qin, Stephen L Chan*, Shanzhi Gu, Yuxian Bai, Zhenggang Ren, Xiaoyan Lin, Zhendong Chen, Weidong Jia, Yongdong Jin, Yabing Guo, Xiaohua Hu, Zhiqiang Meng, Jun Liang, Ying Cheng, Jianping Xiong, Hong Ren, Fang Yang, Wei Li, Yajin Chen, Yong Zeng, Alexander Sultanbaev, Monika Pazgan-Simon, Margaryta Pisetska, Davide Melisi, Dmitriy Ponomarenko, Yurii Osypchuk, Ivan Sinielnikov, Tsai-Sheng Yang, Xiao Liang, Chunxia Chen, Linna Wang, Ann-Lii Cheng†, Ahmed Kaseb†, Arndt Vogel†, for the CARES-310 Study Group‡*

Lancet 2023; 402: 1133–46

Randomization/endpoints

Primary endpoints PFS and OS



Stratification factors:
1. Macrovascular invasion and/or extrahepatic metastasis (presence vs. absence)
2. Geographical region (Asia vs. countries outside of Asia)
3. Baseline AFP (AFP < 400 ng/mL vs. AFP ≥ 400 ng/mL)

Tumor radiological evaluation will be performed every 8 weeks

Demographics-CARES-310

	Camrelizumab–rivoceranib (n=272)	Sorafenib (n=271)
Age, years	58 (48–66)	56 (47–64)
<65	191 (70%)	210 (77%)
≥65	81 (30%)	61 (23%)
Sex		
Male	227 (83%)	230 (85%)
Female	45 (17%)	41 (15%)
Geographical region		
Asia*	225 (83%)	224 (83%)
Non-Asia†	47 (17%)	47 (17%)
Race		
Asian	226 (83%)	224 (83%)
White	44 (16%)	46 (17%)
Black or African American	1 (<1%)	0
Other	1 (<1%)	1 (<1%)
Ethnicity		
Hispanic or Latinx	4 (1%)	2 (<1%)
Eastern Cooperative Oncology Group performance status		
0	120 (44%)	116 (43%)
1	152 (56%)	155 (57%)
Alpha-fetoprotein		
<400 ng/mL	176 (65%)	171 (63%)
≥400 ng/mL	96 (35%)	100 (37%)
Barcelona Clinic Liver Cancer stage		
Stage B	38 (14%)	40 (15%)
Stage C	234 (86%)	231 (85%)
Child-Pugh score		
Class A (5 points)	236 (87%)	230 (85%)
Class A (6 points)	36 (13%)	41 (15%)
Albumin–bilirubin grade		
1	153 (56%)	165 (61%)
2	117 (43%)	106 (39%)
3	2 (<1%)	0

(Table 1 continues in next column)

	Camrelizumab–rivoceranib (n=272)	Sorafenib (n=271)
(Continued from previous column)		
Macrovascular invasion, extrahepatic metastasis, or both	200 (74%)	200 (74%)
Macrovascular invasion‡	40 (15%)	52 (19%)
Extrahepatic metastasis	175 (64%)	180 (66%)
Aetiology§		
Hepatitis B virus	208 (76%)	197 (73%)
Hepatitis C virus	22 (8%)	29 (11%)
Non-viral¶	42 (15%)	45 (17%)
Previous local therapy for hepatocellular carcinoma	161 (59%)	150 (55%)
PD-L1 expression		
TPS <1%	220 (81%)	212 (78%)
TPS ≥1%	32 (12%)	39 (14%)
CPS <1	190 (70%)	180 (66%)
CPS ≥1	62 (23%)	71 (26%)
Unknown	20 (7%)	20 (7%)

PFS and OS: CARES-310

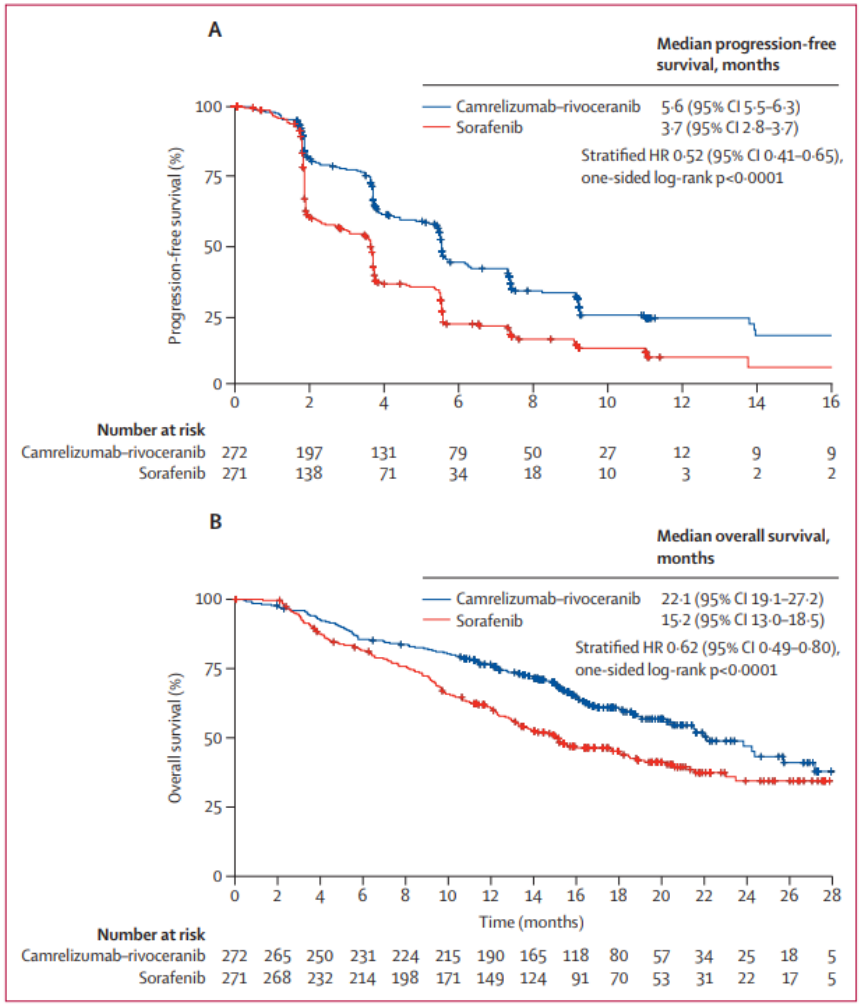
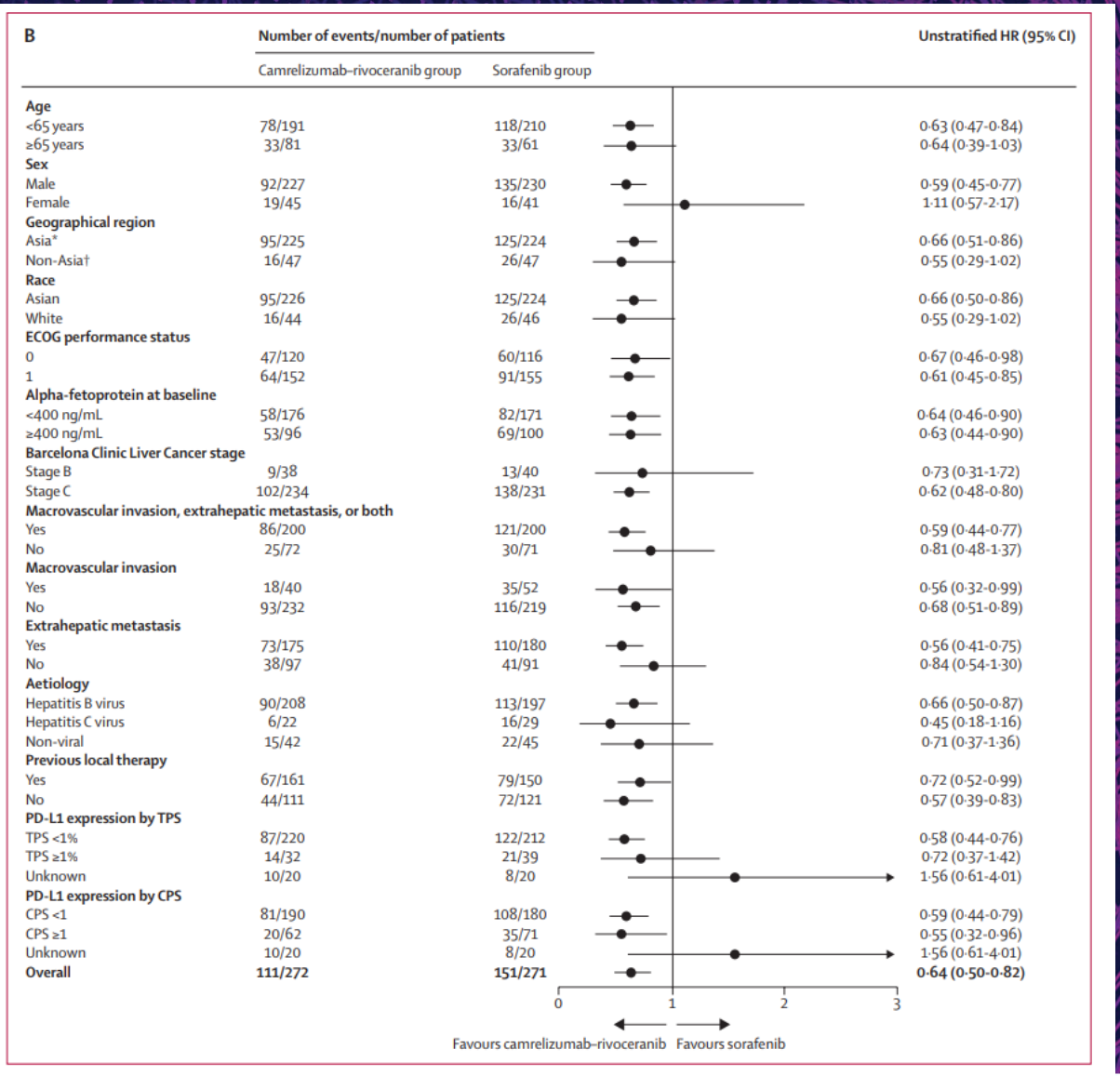


***Figure 2*: Kaplan-Meier plot of progression-free survival at the primary analysis of progression-free survival and overall survival at the interim analysis of overall survival**

(A) Kaplan-Meier curve of progression-free survival as assessed by the blinded independent review committee according to Response Evaluation Criteria in Solid Tumors 1.1. (B) Kaplan-Meier curve of overall survival. HR=hazard ratio.

Subgroup analyses: OS



B

	Number of events/number of patients		Unstratified HR (95% CI)
	Camrelizumab–rivoceranib group	Sorafenib group	
Age			
<65 years	78/191	118/210	0·63 (0·47-0·84)
≥65 years	33/81	33/61	0·64 (0·39-1·03)
Sex			
Male	92/227	135/230	0·59 (0·45-0·77)
Female	19/45	16/41	1·11 (0·57-2·17)
Geographical region			
Asia*	95/225	125/224	0·66 (0·51-0·86)
Non-Asia†	16/47	26/47	0·55 (0·29-1·02)
Race			
Asian	95/226	125/224	0·66 (0·50-0·86)
White	16/44	26/46	0·55 (0·29-1·02)
ECOG performance status			
0	47/120	60/116	0·67 (0·46-0·98)
1	64/152	91/155	0·61 (0·45-0·85)
Alpha-fetoprotein at baseline			
<400 ng/mL	58/176	82/171	0·64 (0·46-0·90)
≥400 ng/mL	53/96	69/100	0·63 (0·44-0·90)
Barcelona Clinic Liver Cancer stage			
Stage B	9/38	13/40	0·73 (0·31-1·72)
Stage C	102/234	138/231	0·62 (0·48-0·80)
Macrovascular invasion, extrahepatic metastasis, or both			
Yes	86/200	121/200	0·59 (0·44-0·77)
No	25/72	30/71	0·81 (0·48-1·37)
Macrovascular invasion			
Yes	18/40	35/52	0·56 (0·32-0·99)
No	93/232	116/219	0·68 (0·51-0·89)
Extrahepatic metastasis			
Yes	73/175	110/180	0·56 (0·41-0·75)
No	38/97	41/91	0·84 (0·54-1·30)
Aetiology			
Hepatitis B virus	90/208	113/197	0·66 (0·50-0·87)
Hepatitis C virus	6/22	16/29	0·45 (0·18-1·16)
Non-viral	15/42	22/45	0·71 (0·37-1·36)
Previous local therapy			
Yes	67/161	79/150	0·72 (0·52-0·99)
No	44/111	72/121	0·57 (0·39-0·83)
PD-L1 expression by TPS			
TPS <1%	87/220	122/212	0·58 (0·44-0·76)
TPS ≥1%	14/32	21/39	0·72 (0·37-1·42)
Unknown	10/20	8/20	1·56 (0·61-4·01)
PD-L1 expression by CPS			
CPS <1	81/190	108/180	0·59 (0·44-0·79)
CPS ≥1	20/62	35/71	0·55 (0·32-0·96)
Unknown	10/20	8/20	1·56 (0·61-4·01)
Overall	**111/272**	**151/271**	**0·64 (0·50-0·82)**

Toxicity: CARES-310

LFT In-crease

	Camrelizumab–rivoceranib (n=272)				Sorafenib (n=269)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-related adverse event	45 (17%)	193 (71%)	26 (10%)	1 (<1%)	128 (48%)	128 (48%)	12 (4%)	1 (<1%)
Hypertension	87 (32%)	100 (37%)	2 (1%)	0	76 (28%)	40 (15%)	0	0
Aspartate aminotransferase increased	102 (38%)	42 (15%)	3 (1%)	0	85 (32%)	14 (5%)	0	0
Proteinuria	118 (43%)	16 (6%)	0	0	67 (25%)	5 (2%)	0	0
Alanine aminotransferase increased	92 (34%)	34 (13%)	1 (<1%)	0	72 (27%)	8 (3%)	0	0
Platelet count decreased	94 (35%)	28 (10%)	4 (1%)	0	85 (32%)	4 (1%)	0	0
Blood bilirubin increased	92 (34%)	24 (9%)	0	0	71 (26%)	4 (1%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	69 (25%)	33 (12%)	0	0	122 (45%)	41 (15%)	0	0
Diarrhoea	77 (28%)	6 (2%)	0	0	91 (34%)	14 (5%)	0	0
Reactive cutaneous capillary endothelial proliferation	72 (26%)	7 (3%)	0	0	0	0	0	0
Neutrophil count decreased	57 (21%)	14 (5%)	2 (1%)	0	24 (9%)	1 (<1%)	2 (1%)	0
White blood cell count decreased	66 (24%)	7 (3%)	0	0	35 (13%)	3 (1%)	0	0
Gamma-glutamyltransferase increased	39 (14%)	25 (9%)	2 (1%)	0	29 (11%)	15 (6%)	5 (2%)	0
Hypothyroidism	58 (21%)	0	0	0	16 (6%)	0	0	0
Fatigue	46 (17%)	7 (3%)	0	0	20 (7%)	1 (<1%)	0	0
Blood alkaline phosphatase increased	44 (16%)	3 (1%)	0	0	30 (11%)	3 (1%)	0	0
Conjugated blood bilirubin increased	34 (13%)	10 (4%)	2 (1%)	0	28 (10%)	6 (2%)	2 (1%)	0
Rash	40 (15%)	5 (2%)	0	0	47 (17%)	3 (1%)	0	0
Anaemia	41 (15%)	4 (1%)	0	0	19 (7%)	2 (1%)	0	0
Decreased appetite	39 (14%)	3 (1%)	0	0	31 (12%)	3 (1%)	0	0
Unconjugated blood bilirubin increased	33 (12%)	2 (1%)	0	0	20 (7%)	1 (<1%)	0	0
Hypoalbuminaemia	34 (13%)	0	0	0	21 (8%)	0	0	0
Weight decreased	28 (10%)	4 (1%)	0	0	33 (12%)	6 (2%)	0	0
Asthenia	29 (11%)	3 (1%)	0	0	15 (6%)	0	0	0
Haematuria	31 (11%)	0	0	0	12 (4%)	0	0	0
Nausea	31 (11%)	0	0	0	14 (5%)	0	0	0
Headache	28 (10%)	2 (1%)	0	0	4 (1%)	1 (<1%)	0	0
Blood lactate dehydrogenase increased	26 (10%)	1 (<1%)	0	0	29 (11%)	0	0	0
Lymphocyte count decreased	18 (7%)	8 (3%)	0	0	14 (5%)	3 (1%)	0	0
Amylase increased	15 (6%)	9 (3%)	1 (<1%)	0	6 (2%)	0	1 (<1%)	0
Hyponatraemia	13 (5%)	8 (3%)	0	0	8 (3%)	1 (<1%)	0	0
Lipase increased	7 (3%)	7 (3%)	6 (2%)	0	6 (2%)	4 (1%)	1 (<1%)	0
Hypophosphataemia	17 (6%)	2 (1%)	0	0	27 (10%)	12 (4%)	0	0
Upper gastrointestinal haemorrhage	2 (1%)	6 (2%)	0	0	0	0	0	0
Alopecia	4 (1%)	0	0	0	52 (19%)	0	0	0

Data are n (%). Treatment-related adverse events of grade 1–2 occurring in at least 10% of patients or of grade 3–5 occurring in at least 2% of patients in either group are reported.

Table 2: **Treatment-related adverse events in the safety analysis set at the interim analysis for overall survival**

Bristol Myers Squibb Announces CheckMate -9DW Trial Evaluating Opdivo (nivolumab) Plus Yervoy (ipilimumab) Meets Primary Endpoint of Overall Survival for the First-Line Treatment of Advanced Hepatocellular Carcinoma

03/20/2024

CATEGORY: Corporate/Financial News

Opdivo *plus* Yervoy *demonstrates statistically significant and clinically meaningful improvement in overall survival compared to investigator's choice of sorafenib or lenvatinib*

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced the Phase 3 CheckMate -9DW trial evaluating *Opdivo* (nivolumab) plus *Yervoy* (ipilimumab) as a first-line treatment for patients with advanced hepatocellular carcinoma (HCC) who have not received prior systemic therapy met its primary endpoint of improved overall survival (OS) compared to investigator's choice of sorafenib or lenvatinib at a pre-specified interim analysis.

The dual immunotherapy combination of *Opdivo* plus *Yervoy* demonstrated a statistically significant and clinically meaningful improvement in OS compared to investigator's choice of sorafenib or lenvatinib. The safety profile for the combination of *Opdivo* plus *Yervoy* remained consistent with previously reported data and was manageable with established protocols, with no new safety signals identified.

Take-away messages from recent pivotal trials

Bevacizumab plus atezolizumab

Durvalumab plus tremelimumab

Camrelizumab plus rivoceranib

Nivolumab plus ipilimumab

show overall survival benefit compared with sorafenib and have different side effect profiles

Therapy for Child B Patients?

- IMBrave150 and HIMALAYA enrolled Child A patients
- Data for use in Child B for lenvatinib and sorafenib
  - Clin Exp Gastroenterol. 2020 Oct 1;13:385-396. Safety and Efficacy of Lenvatinib Treatment in Child-Pugh A and B Patients with Unresectable Hepatocellular Carcinoma in Clinical Practice: A Multicenter Analysis. Ogushi K.
  - J Hepatol. 2016 Dec;65(6):1140-1147. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. Marrero JA.
- Nivolumab has been studied in Child B (Kudo M. J Hepatol. 2021 Sep;75(3):600-609.)

There may be a role for immune monotherapy

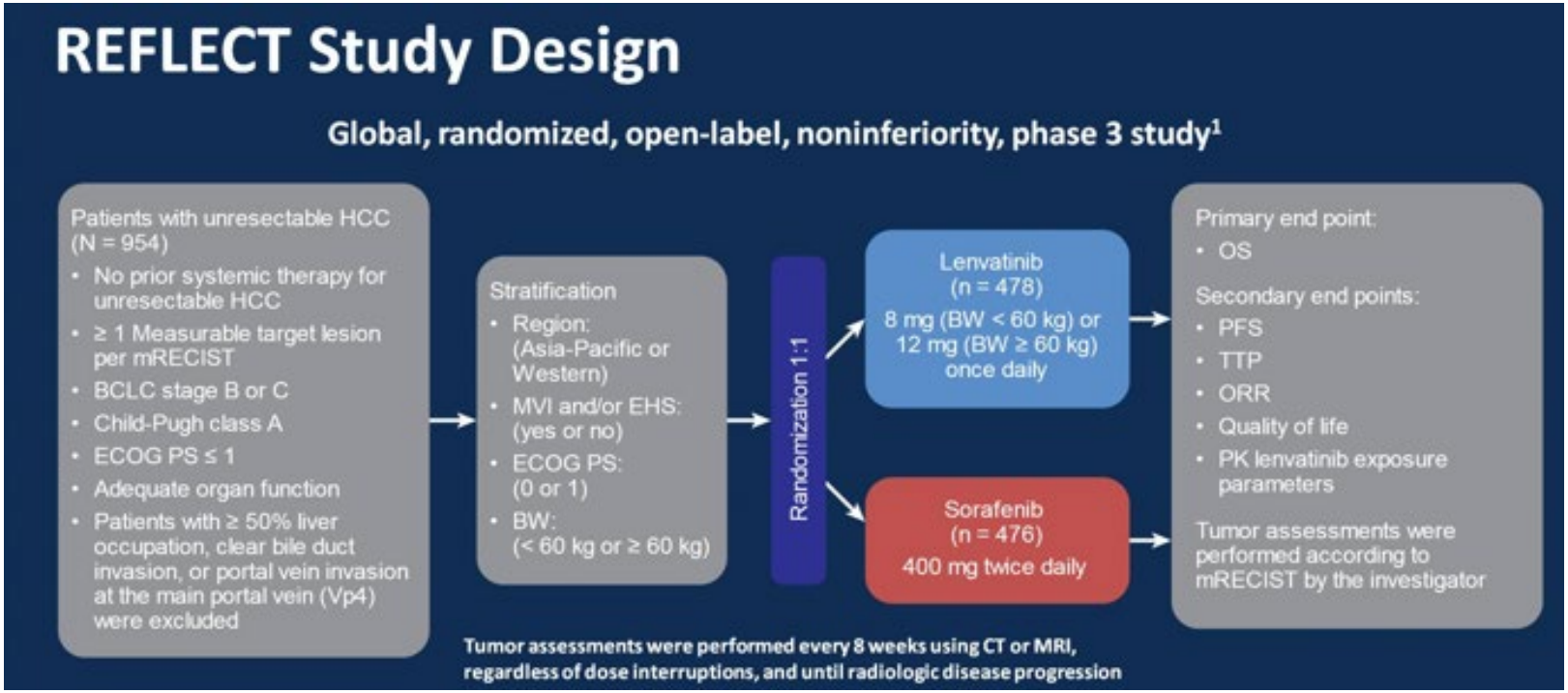
Drug(s)	Trial	Active therapy	Control	HR
Durvalumab	HIMALAYA	16.6mth	13.8mth	HR=0.86^
Durvalumab + tremelimumab		16.4mth		HR=0.78, p=0.0035
Tislelizumab	Rationale-301	15.9mth	14.1mth	HR=0.85^
Nivolumab	Checkmate-459	16.4mth	14.7mth	HR=0.85, p=0.075

TKIs in 1st line

Drug(s)	Trial	Active	Control	Stats
Sorafenib	SHARP	10.7mth	Placebo 7.9mth*	HR=0.69, p=0.00058
Lenvatinib	REFLECT	13.6mth	Sorafenib 12.3mth	HR=0.92^
Camrelizumab + rivoceranib	CARES-310	22.1mth	Sorafenib 15.2mth	HR=0.62, p<0.0001
pembrolizumab + lenvatinib	LEAP-002	21.2mth	Len 19.0mth**	HR=0.84, p=0.0227

Current 1st line option: Lenvatinib

TKI targeting VEGFR1-3, FGFR1-4, RET, KIT and PDGFRβ



Kudo M, Lancet 2018; 391: 1163–73; Kudo ASCO GI 2019; Abstr 186.

Lenvatinib: Noninferior overall survival; better ORR and PFS

Category	Lenvatinib (n = 478)	Sorafenib (n = 476)
Median OS, months	13.6	12.3
95% CI	12.1–14.9	10.4–13.9
ORR†, n (%)	115 (24.1)	44 (9.2)
95% CI	20.2–27.9	6.6–11.8
Median PFS†, months	7.4	3.7
95% CI	6.9–8.8	3.6–4.6

*Data cutoff: November 13, 2016
†Investigator review according to mRECIST

Kudo ASCO GI 2019; Abstr 186

Adverse events

	Lenvatinib (n=476)	Sorafenib (n=475)
Total treatment-emergent adverse events	470 (99%)	472 (99%)
Total treatment-related treatment-emergent adverse events	447 (94%)	452 (95%)
Treatment-emergent adverse events of grade ≥3	357 (75%)	316 (67%)
Treatment-related treatment-emergent adverse events of grade ≥3	270 (57%)	231 (49%)
Serious treatment-emergent adverse events	205 (43%)	144 (30%)
Serious treatment-related treatment-emergent adverse events	84 (18%)	48 (10%)
Treatment-emergent adverse events occurring in ≥15% of patients in either treatment group		
Palmar-plantar erythrodysaesthesia		
Any grade	128 (27%)	249 (52%)
Grade ≥3	14 (3%)	54 (11%)
Diarrhoea		
Any grade	184 (39%)	220 (46%)
Grade ≥3	20 (4%)	20 (4%)
Hypertension		
Any grade	201 (42%)	144 (30%)
Grade ≥3	111 (23%)	68 (14%)
Decreased appetite		
Any grade	162 (34%)	127 (27%)
Grade ≥3	22 (5%)	6 (1%)
Decreased weight		
Any grade	147 (31%)	106 (22%)
Grade ≥3	36 (8%)	14 (3%)
Fatigue		
Any grade	141 (30%)	119 (25%)
Grade ≥3	18 (4%)	17 (4%)

Less HFS →

More HTN →

	Lenvatinib (n=476)	Sorafenib (n=475)
(Continued from previous column)		
Alopecia		
Any grade	14 (3%)	119 (25%)
Grade ≥3	0	0
Proteinuria		
Any grade	117 (25%)	54 (11%)
Grade ≥3	27 (6%)	8 (2%)
Dysphonia		
Any grade	113 (24%)	57 (12%)
Grade ≥3	1 (<1%)	0
Nausea		
Any grade	93 (20%)	68 (14%)
Grade ≥3	4 (1%)	4 (1%)
Abdominal pain		
Any grade	81 (17%)	87 (18%)
Grade ≥3	8 (2%)	13 (3%)
Decreased platelet count		
Any grade	87 (18%)	58 (12%)
Grade ≥3	26 (5%)	16 (3%)
Elevated aspartate aminotransferase		
Any grade	65 (14%)	80 (17%)
Grade ≥3	24 (5%)	38 (8%)
Hypothyroidism		
Any grade	78 (16%)	8 (2%)
Grade ≥3	0	0
Vomiting		
Any grade	77 (16%)	36 (8%)
Grade ≥3	6 (1%)	5 (1%)
Constipation		
Any grade	76 (16%)	52 (11%)
Grade ≥3	3 (1%)	0
Rash		
Any grade	46 (10%)	76 (16%)
Grade ≥3	0	2 (<1%)
Increased blood bilirubin		
Any grade	71 (15%)	63 (13%)
Grade ≥3	31 (7%)	23 (5%)

← More proteinuria

← More Hypo-thyroidism

Second-line therapy in advanced HCC

NCCN Guidelines for Subsequent Line Therapy

Subsequent-Line Systemic Therapy if Disease Progression[g,h,i]

Options

- Cabozantinib (category 1)[8]
- Regorafenib (category 1)[9]
- Lenvatinib
- Sorafenib

Other Recommended Regimens

- Nivolumab + ipilimumab[e,j,10,11]
- Pembrolizumab[e,j,k,12-14]

Useful in Certain Circumstances

- Ramucirumab (AFP ≥400 ng/mL) (category 1)[15]
- Nivolumab[e,j,16-19]
- For MSI-H/dMMR tumors
  - Dostarlimab-gxly (category 2B)[e,j,l,20]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib (category 2B)[21]

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Comparison of Mechanism of Action

	PD-1	VEGF1	VEGF2	VEGFr	Tie2	PDGF Rb	FGFR	Kit	Ret	RAF	MET	AXL	Flt1,3, 4
Sor		+	+	+		+	+	+	+	+			+
Len		+	+	+		+			+				
Rego		+	+	+	+	+	+	+	+	+			
Cabo			+		+			+	+		+	+	+
Ram			+										
Nivo Pembro	+												

Overall Survival in Second-Line Studies

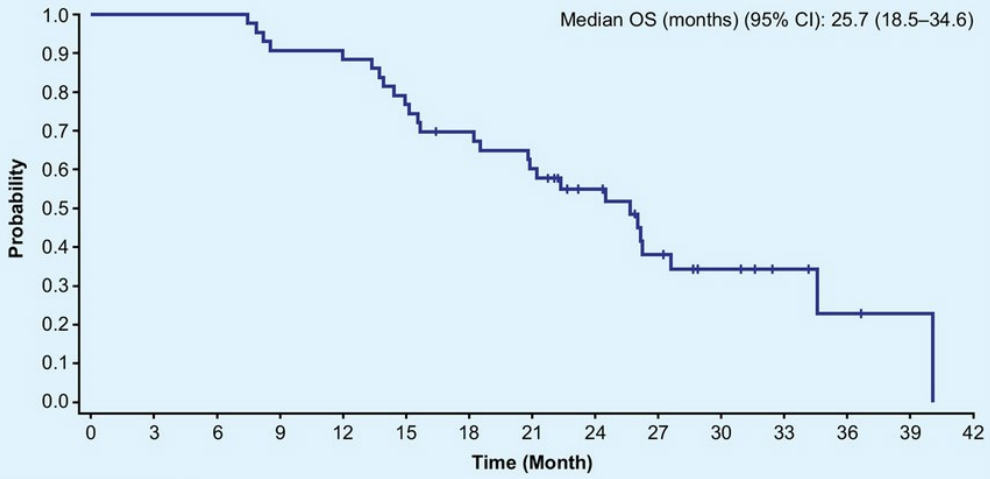
Regorafenib vs Placebo	Nivolumab 1/Ipilimumab 3	Pembrolizumab vs Placebo	Pembrolizumab vs Placebo
10.6 vs 7.8 0.63 (0.50-0.79) <0.0001	22.1 mo	13.9 vs 10.6 0.781 (0.611-0.998) 0.0238*	14.6 vs 13 0.79 0.0032

Cabozantinib vs Placebo	Ramucirumab vs Placebo
10.2 vs 8.0 0.76 (0.63-0.92) 0.005	8.5 vs 7.3 0.710 (0.531-0.949) 0.0199

BruixJ. Lancet. 2017 Jan 7;389(10064):56-66. Abou-Alfa. N Engl J Med. 2018;379:54-63. Zhu. Lancet Oncol. 2019;20:282-296. Finn R. J Clin Oncol. 2020;38:193-202. Yau. JAMA Oncol. 2020;6:e204564. ASCOGI2022;abstract 383

Patients Who Receive 2nd-Line Have Prolonged Survival

Figure 3. Kaplan-Meier Estimate of OS for Lenvatinib Responders Who Received any Poststudy Anticancer Medication



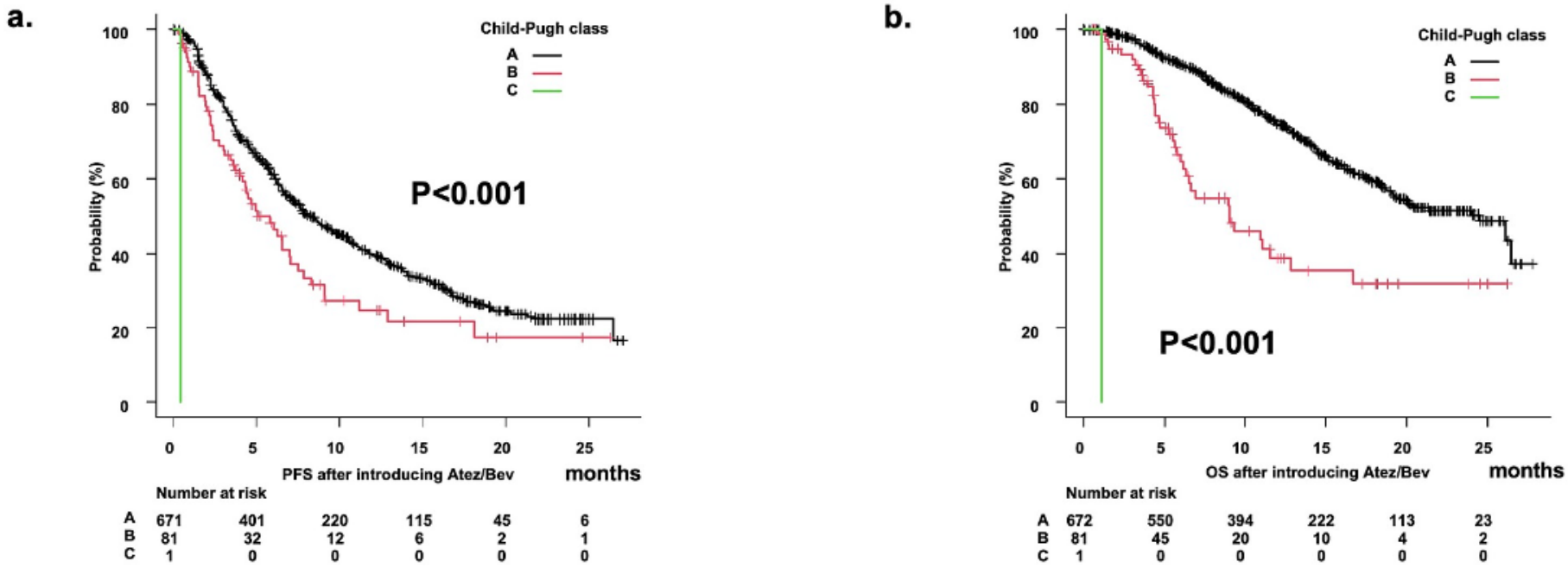
Presented at: ASCO GI 2019, Abstract 371.

Exploratory Analysis from RESORCE	Regorafenib (n=374)	Placebo (n=193)
Median OS from start of prior sorafenib to death (95% CI), months	26.0 (22.6-28.1)	19.2 (16.3-22.8)

Bruix J. Lancet. 2017;389(10064):56-66.

Choice of Second-Line After Atezolizumab + Bevacizumab?

Outcome for lenvatinib or other MTA after Atezo/Bev



Median PFS (mPFS) was 8.3 months (95% CI 7.3-9.6) for Child-Pugh A, 5.0 months (95% CI 4.0-7.0) for Child-Pugh B, and 0.4 months [95% CI not applicable (NA)] for Child-Pugh C patients (P<0.00001). Median OS (mOS) was 24.5 months (95% CI 19.3-NA) for Child-Pugh A, 9.1 months (95% CI 6.2-12.9) for Child-Pugh B, and 1.1 months (95% CI NA-NA) for Child-Pugh C patients (P<0.001).

Oncology (2023) 101 (10): 624–633.

Future directions

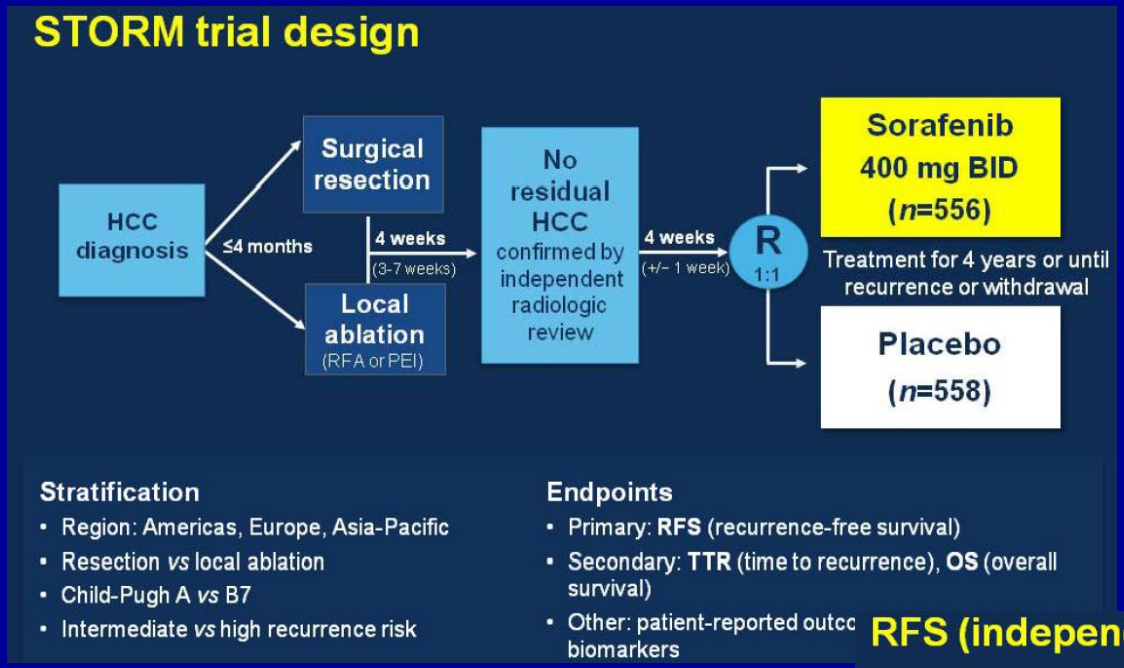
- Formally establishing role of TKIs in second line after current first line options
  - Phase II trial of second-line regorafenib in patients with unresectable hepatocellular carcinoma after progression on first-line atezolizumab plus bevacizumab: REGONEXT trial.
  - ACCRU-GI-2008: A phase II randomized study of atezolizumab (Atezo) plus a multi-kinase inhibitor (MKI) versus MKI alone in patients with unresectable advanced hepatocellular carcinoma (aHCC) who previously received atezolizumab plus bevacizumab (Bev).

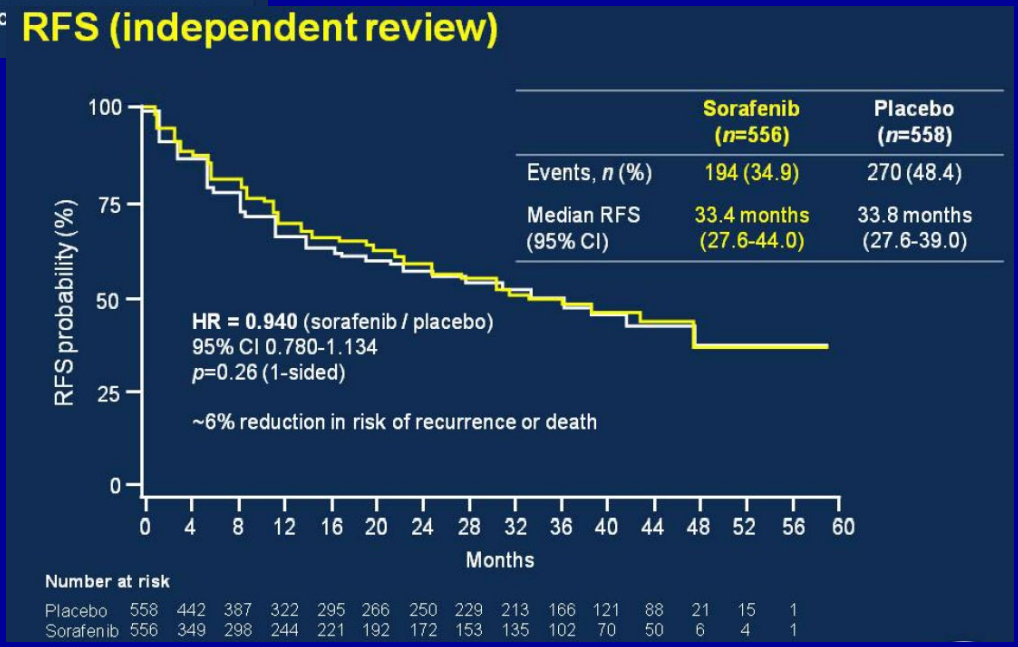
Update on

ADJUVANT THERAPIES:

ADJUVANT THERAPY AFTER SURGERY OR ABLATION IN HIGH RISK HCC

STORM trial: adjuvant sorafenib was negative



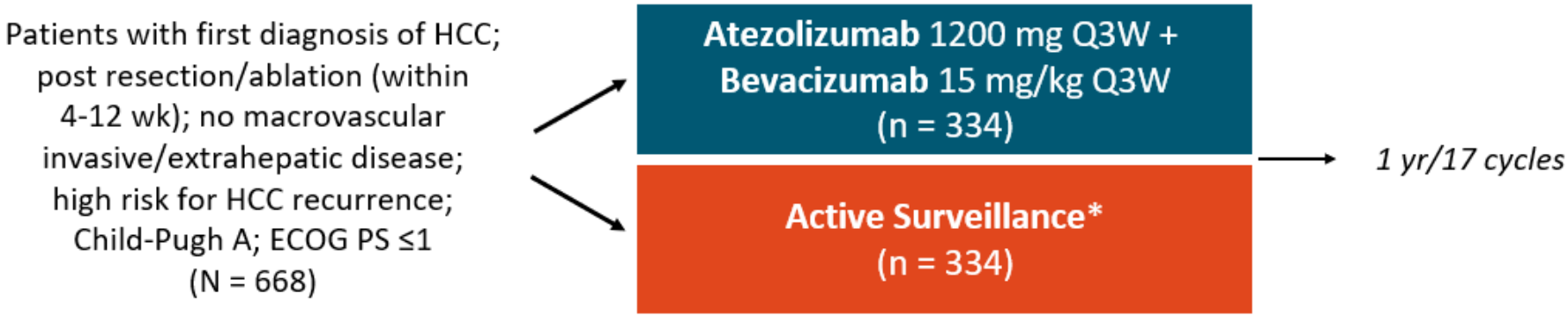


Lancet Oncol. 2015 Oct;16(13):1344-54.

Atezolizumab + Bevacizumab as adjuvant therapy

IMbrave050: Adjuvant Atezolizumab + Bevacizumab vs Surveillance for HCC After Resection or Ablation

- Multicenter, randomized, open-label phase III trial



- **Primary endpoint:** RFS (independent review)
- **Key secondary endpoints:** OS, RFS by PD-L1 status, time to recurrence, safety

Kudo. ASCO 2023. Abstr 4002. Qin. Lancet. 2023;402:1835

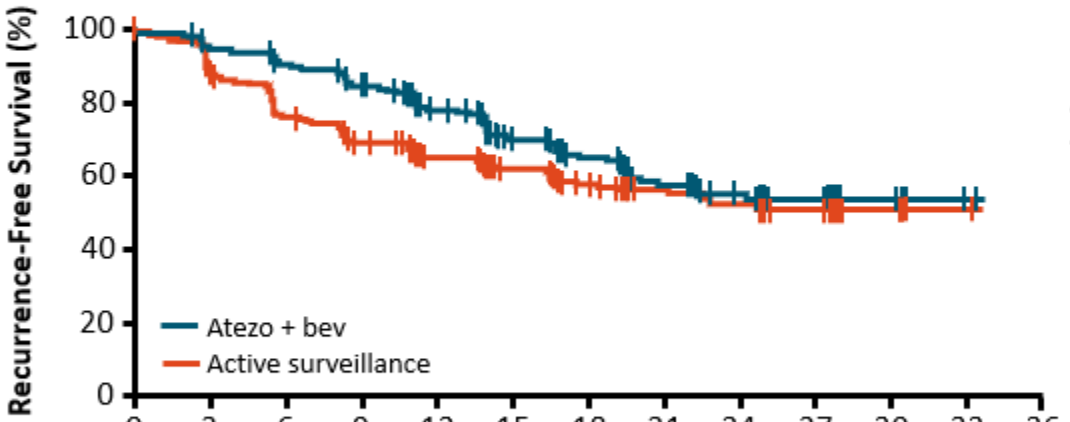
High-risk criteria by curative treatment

Curative treatment	Criteria for high risk of HCC recurrence
Resection	▪ ≤3 tumors, with **largest tumor >5 cm** regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) ▪ **≥4 tumors**, with largest tumor ≤5 cm regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) ▪ ≤3 tumors, with largest tumor ≤5 cm with **vascular invasion**,[a] and/or **poor tumor differentiation** (Grade 3 or 4)
Ablation[b]	▪ 1 tumor >2 cm but ≤5 cm ▪ Multiple tumors (≤4 tumors), all ≤5 cm

[a] Microvascular invasion or minor macrovascular portal vein invasion of the portal vein—Vp1/Vp2.
[b] Ablation must be radiofrequency ablation or microwave ablation.

RFS (IRF)

	Atezo + Bev (n = 334)	Active Surveillance (n = 334)
Patients with events, n (%)	110 (33)	133 (40)
Median RFS, mo (95% CI)	NE (22.1-NE)	NE (21.4-NE)
12-mo IRF-RFS event-free rate, % (95% CI)	78 (73-82)	65 (60-71)
Stratified HR (adjusted 95% CI)	0.72 (0.53-0.98)	
P value (log-rank)	.012	



Patients at Risk (No. Censored)													
Atezo + bev	334	305	290	268	211	139	97	63	37	22	9	1	NE
	(0)	(10)	(12)	(15)	(53)	(105)	(139)	(164)	(188)	(202)	(215)	(223)	(NE)
Active surveillance	334	283	245	214	179	131	93	57	36	20	6	1	NE
	(0)	(12)	(12)	(20)	(44)	(84)	(114)	(148)	(166)	(181)	(195)	(200)	(NE)

More toxicity in the atezo/bev arm of the study

AE, n (%)	Atezo + Bev (n = 332)			Active Surveillance (n = 330)		
	Any Gr	Gr 3-4	Gr 5	Any Gr	Gr 3-4	Gr 5
Any AE	326 (98)	135 (41)	6 (2)	205 (62)	44 (13)	1 (<1)
Related AE	293 (88)	116 (35)	2 (<1)	NA	NA	NA
Serious AE	80 (24)	53 (16)	6 (2)	34 (10)	26 (8)	1 (<1)
Related serious AE	44 (13)	32 (10)	2 (<1)	NA	NA	NA
AE leading to withdrawal from both atezo and bev	29 (9)	23 (7)	0	NA	NA	NA
AE leading to withdrawal from atezo	31 (9)	24 (7)	0	NA	NA	NA
AE leading to withdrawal from bev	62 (19)	38 (11)	0	NA	NA	NA

Adjuvant (Post-resection or Ablation) Studies Ongoing

Table 4. Current clinical trials on adjuvant systemic treatments after surgery or ablation.

Trial	Identifier	Phase	BCLC Stage	Treatment Arms	Primary Endpoint(s)	Setting
CheckMate 9DX	NCT03383458	Phase 3	0 or A	• Nivolumab • Placebo	• RFS	Adjuvant
KEYNOTE-937	NCT03867084	Phase 3	0 or A	• Pembrolizumab • Placebo	• RFS • OS	Adjuvant
IMbrave050	NCT04102098	Phase 3	0 or A	• Atezolizumab + bevacizumab • Active surveillance	• RFS	Adjuvant
EMERALD-2	NCT03847428	Phase 3	0 or A	• Durvalumab + bevacizumab • Durvalumab • Placebo	• RFS	Adjuvant

BCLC, Barcelona Clinic Liver Cancer; OS, overall survival; RFS, recurrence-free survival.

Cancers. 2021;13,1962.

Update on

ADJUVANT THERAPIES:

ADJUVANT THERAPY IN CONJUNCTION WITH TACE

Mostly negative: adjuvant sorafenib after TACE

TACE Combination Trials with Sorafenib

Trial	Ph3 Post-TACE[1]	Ph2 SPACE[2]	Ph3 TACE-2[3]	Ph2 TACTICS
Author	Kudo M, et al Eur J Cancer 2011	Lencioni R, et al J Hepatol 2016	Tim Meyer, et al Lancet GH 2017	Kudo M, et al ASCO-GI 2018
Child-Pugh	A	A(No ascites)	A	A5-B7
ECOG-PS	0-1	0	0-1	0-1
Tumor burden	≤7 cm ≤10 tumors	Unresectable multinodular	Not a candidate for resection or transplantation	≤10 cm ≤10 tumors
TACE procedure	cTACE, on demand	DEB-TACE, scheduled	DEB-TACE, on demand	cTACE, on demand
Endpoint	TTP (5.4M)	TTP (6.0M)	PFS (8.5M)	PFS (25.2M)
Criteria of progression	RECICL 2004	mRECIST	RECIST 1.1	Criteria for UnTACEable progression/TACE Failure New lesion: not PD
Sorafenib duration(w)	17.0	21.0	17.1	38.7
Median f/u period (w)	NA	38.6	88.6	123.6

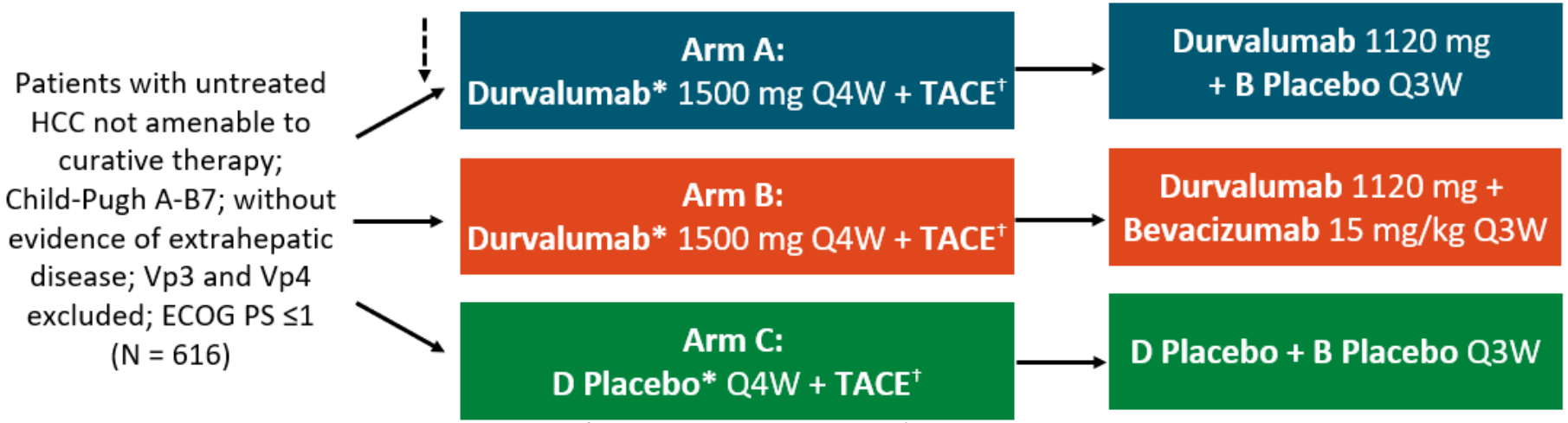
cTACE: conventional Lipiodol TACE, RECICL: Response evaluation criteria in the Cancer of Liver (JSH), UP: UnTACEable Progression, DOT: Duration of Treatment

[1]Kudo M, et al. Eur J Cancer 2011;47:2117-2127; [2]Lencioni R, et al. J Hepatol 2016;64:1090-1098; [3]Meyer T, et al. Lancet Gastroenterol Hepatol 2017;2:565-575

EMERALD-1: TACE and Durvalumab ± Bevacizumab for Unresectable HCC

- Global, double-blind, placebo-controlled phase III trial

Stratified by TACE modality (DEB-TACE vs cTACE), geographic region (Japan vs Asia [excluding Japan] vs other), portal vein invasion (Vp1 or Vp2+/-Vp1 vs none)

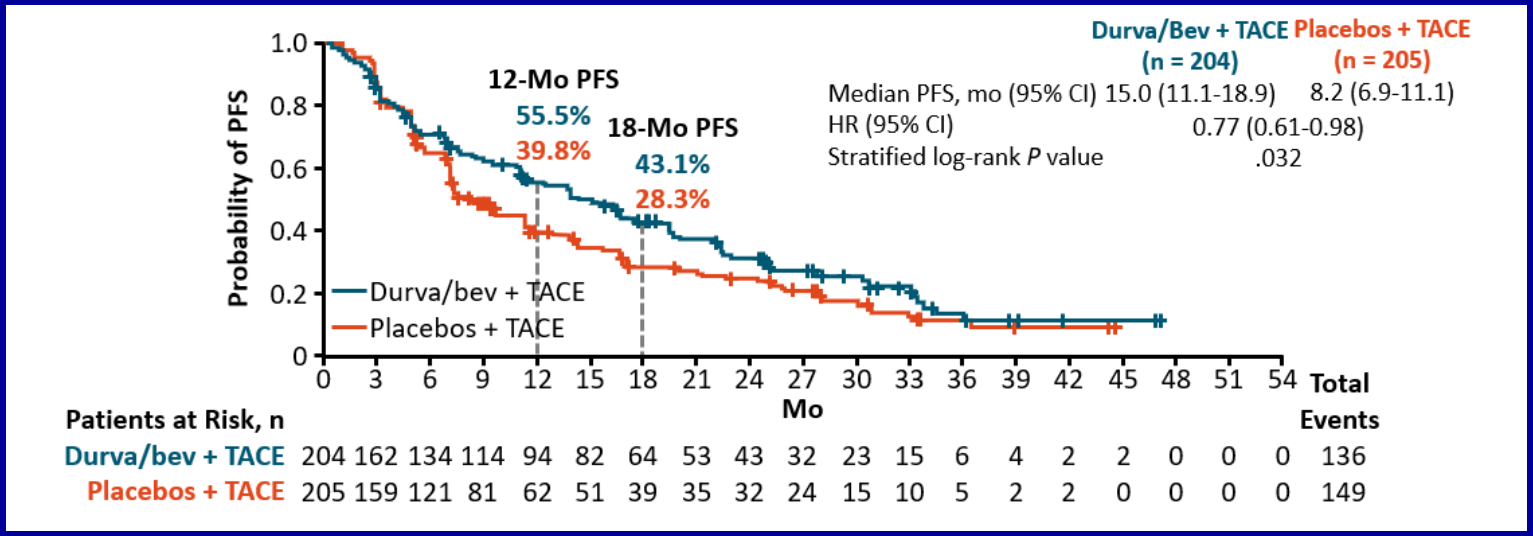


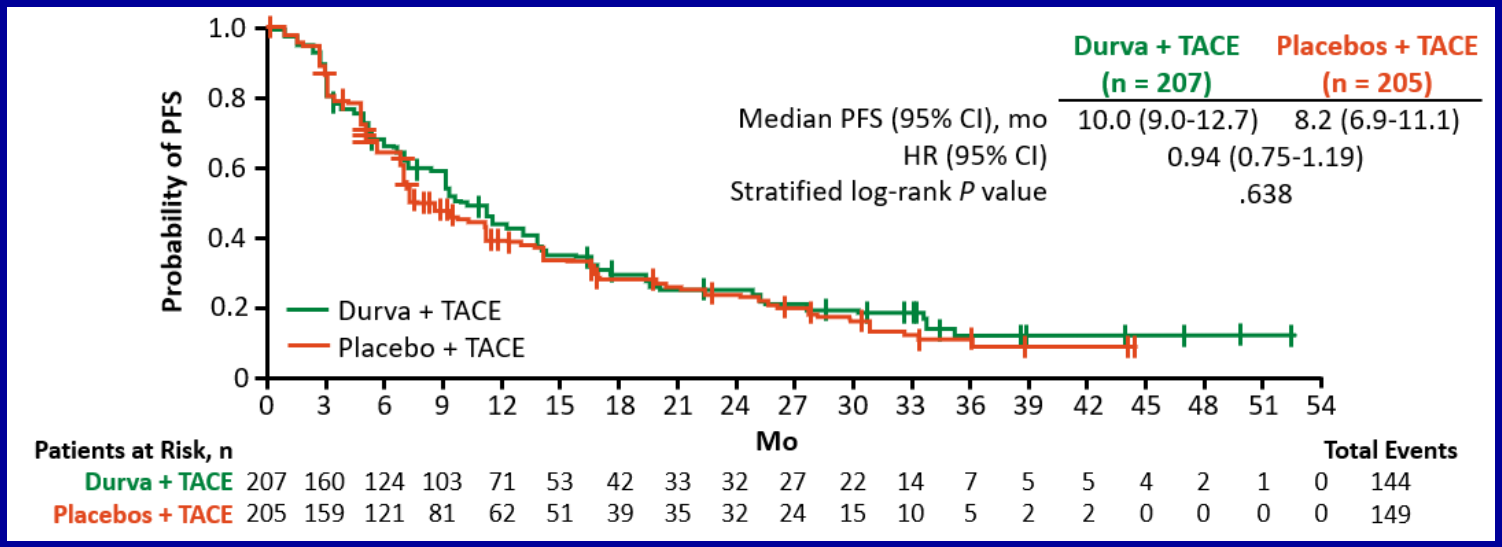
*Durvalumab/placebo started ≥7 days after TACE. †TACE = cTACE or DEB-TACE. Up to 4 TACE procedures within 16 wk following Day 1 of first TACE.

- **Primary endpoints:** PFS for arm B vs arm C per BICR
- **Secondary endpoints:** PFS for arm A vs arm C, OS, ORR, TTP, QoL, safety

Lencioni. ASCO GI 2023. Abstr LBA432.

PFS improved with Durva/Bev but not Durva





Adjuvant after TA(C)E: Studies ongoing

Table 3. Current clinical trials combining or comparing systemic treatments with TACE.

Trial	Identifier	Phase	BCLC Stage	Treatment Arms	Primary Endpoint(s)	Setting
LEAP-012	NCT04246177	Phase 3	B	• Lenvatinib + pembrolizumab + TACE • TACE	• PFS per RECIST 1.1 • OS	First-line
EMERALD-1	NCT03778957	Phase 3	B	• Durvalumab + TACE • Durvalumab + bevacizumab + TACE • TACE	• PFS per RECIST 1.1	First-line
CheckMate 74W	NCT04340193	Phase 3	B	• Nivolumab + ipilimumab + TACE • Nivolumab + TACE • TACE	• Time to TACE progression • OS	First-line
ABC-HCC	NCT04803994	Phase 3	B	• Atezolizumab + bevacizumab • TACE	• Time to failure of treatment strategy	First-line
RENOTACE	NCT04777851	Phase 3	B	• Regorafenib + nivolumab • TACE	• PFS per mRECIST	First-line

BCLC, Barcelona Clinic Liver Cancer; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; TACE, transarterial chemoembolization.

Cancers. 2021;13,1962.

tremelimumab (T) plus durvalumab (D) with or without lenvatinib combined with concurrent transarterial chemoembolisation (TACE) versus TACE alone in patients (pts) with locoregional hepatocellular carcinoma (HCC): EMERALD-3

Summary

- First line therapy for uHCC will soon have 4 treatment options: Future directions are adding novel therapies to standard backbones
- Second line therapy remains TKIs but role of continuing IO unclear
- A number of adjuvant clinical trials remain to be read out but there does appear to be benefit for immunotherapy based combinations.
- Child Pugh B patients benefit, but benefit less on an absolute basis from systemic therapies