COR2ED

THE HEART OF MEDICAL EDUCATION

THE USE OF IMMUNOTHERAPY IN HCC

MICRO LEARNING MODULE TWO:

IN-DEPTH SUBGROUP ANALYSES AND CHALLENGES

Dr Aiwu Ruth He, MD, PhD
Medstar Georgetown University Hospital, Washington DC, USA

Prof. Dr Peter R. Galle, MD, PhD
University Medical Centre Mainz, Mainz, Germany

JUNE 2023

THIS PROGRAMME HAS BEEN DEVELOPED BY TWO INTERNATIONAL EXPERTS

Dr Aiwu Ruth He
GI Medical Oncologist
Medstar Georgetown University Hospital, USA

Prof. Peter R. Galle
Hepatology Specialist
University Medical Centre Mainz, Germany

DEVELOPED BY HCC CONNECT

This programme is developed by HCC CONNECT, an international group of experts in the field of hepatocellular carcinoma.

HCC connect®
POWERED BY COR2ED

Acknowledgement and disclosures

This HCC CONNECT programme is supported through an independent educational grant from AstraZeneca. The programme is therefore independent, the content is not influenced by the supporter and is under the sole responsibility of the experts.

Please note: The views expressed within this programme are the personal opinions of the experts. They do not necessarily represent the views of the experts' institutions, or the rest of the HCC CONNECT group.

Expert disclaimers:

- **Dr Aiwu Ruth He** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: AstraZeneca, BMS, Boston Scientific, Eisai, Genentech, and Merck
- **Prof. Peter R. Galle** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: Adaptimmune, AstraZeneca, Bayer, BMS, Boston Scientific, Eisai, Guerbet, Ipsen, Lilly, MSD, Roche, and Sirtex

EDUCATIONAL OBJECTIVES

Upon completion of this micro learning you will:

1. Know how to **assess liver function** in patients with HCC using **the Albumin-Bilirubin (ALBI) scoring system**
   - To evaluate the eligibility for IO treatment

2. Understand **the data in the different subgroups of HCC patients** eligible for IO treatment
   - To study the efficacy and safety of IO combinations for these subgroups

HCC, hepatocellular carcinoma; IO, immunotherapy

CLINICAL TAKEAWAYS*

- **The Child-Pugh and ALBI scoring systems** are methods to assess liver function
  - The ALBI scoring system is more objective and easier to retrieve than the Child–Pugh score
  - The ALBI scoring system helps to further divide patients with compensated cirrhosis into subgroups **to predict clinical outcome of IO** in patients with HCC

- Given the expanding systemic treatment options for HCC, **including IO and IO combinations**, there is a need to understand whether **specific groups of patients** benefit more from one therapy than another

- Subgroup analyses in patients with HCC receiving **IO and IO combinations** show **variable hazard ratios (HRs) across etiologies and across liver function**
  - Data are not mature enough to guide treatment decisions

*These clinical takeaways are based on scientific literature that is discussed in greater detail and referred to in this slide deck

ALBI, Albumin-Bilirubin; HCC, hepatocellular carcinoma; IO, immunotherapy

LIVER FUNCTION: CHILD-PUGH AND ALBI SCORING SYSTEMS IN CLINICAL TRIALS IN HCC

ALBI, Albumin-Bilirubin; HCC, hepatocellular carcinoma

MEASURING LIVER FUNCTION IN PATIENTS WITH HCC[1]

THE CHILD-PUGH SCORING SYSTEM IS WIDELY USED TO GRADE LIVER FUNCTION

For patients with HCC, among several other factors, survival depends on tumour stage, **liver function**, and potentially on performance status

The Child–Pugh system was designed to predict mortality in cirrhosis patients[2]

The Child–Pugh system does not offer a wide degree of discrimination for patients with HCC[1]

The Child–Pugh system may be insufficient in defining the liver dysfunction and prognosis for patients with HCC categorised as Child–Pugh class A[1]

- Child-Pugh is based on 5 measures to grade liver function from class A to C (mild to severe):
  - Serum bilirubin, serum albumin, ascites status, prothrombin time, and degree of encephalopathy.

ALBI, Albumin-Bilirubin; HCC, hepatocellular carcinoma

1. Johnson PJ, et al. J Clin Oncol. 2015;33:550-8, 2. Tsoris A, Marlar CA, StatPearls Publishing LLC, 2023: PMID: 31194448

MEASURING LIVER FUNCTION IN PATIENTS WITH HCC

THE ALBI SCORING SYSTEM WAS DEVELOPED MORE RECENTLY TO GRADE LIVER FUNCTION[1]

- **Objective measures of liver function** were identified[1]
  - Using international databases
  - These objective measures influence survival independently in patients with HCC

- These measures were combined into the **ALBI scoring system**[1]
  - Combining **serum bilirubin** and **serum albumin** concentrations
  - ALBI score = −0.085 × (albumin g/L) + 0.66 × log(bilirubin µmol/L)

- The ALBI scoring system **was implemented** in the Barcelona Clinic Liver Cancer system in 2016[2]

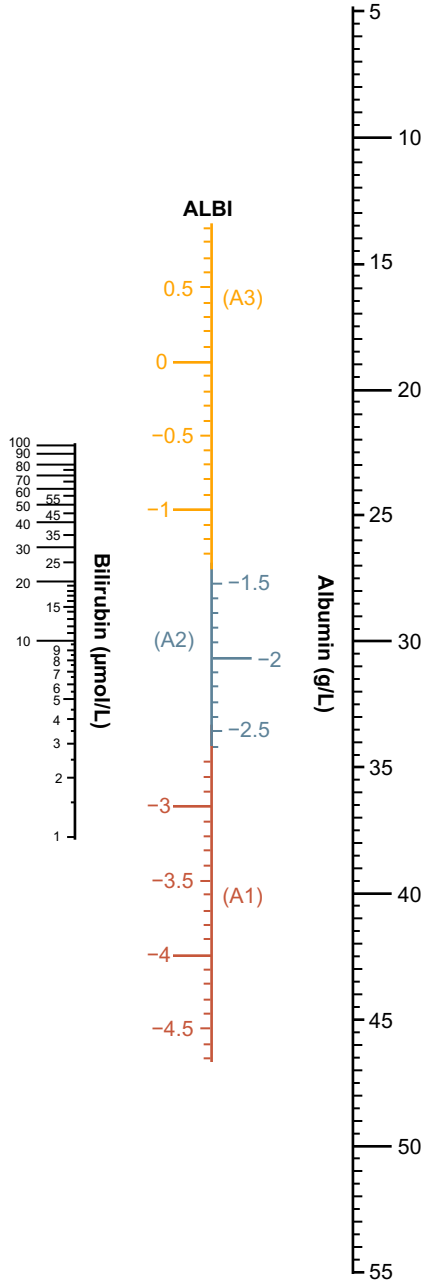


Figure adapted from Johnson PJ, et al.[1]; Nomogram to quickly assess the ALBI score
ALBI, Albumin-Bilirubin; HCC, hepatocellular carcinoma

1. Johnson PJ, et al. J Clin Oncol. 2015;33:550-8; 2. Chan AWH, et al. J Gastroenterol Hepatol. 2016;31:1300-6

PERFORMANCE OF THE ALBI SCORING SYSTEM
IN PATIENTS RECEIVING SORAFENIB TREATMENT

- Many HCC clinical trials **are limited** to Child–Pugh class A patients[1]
- Not all Child–Pugh class A patients are the same
  - **Heterogeneity** might impact survival findings[1]
- The ALBI scoring system may **highlight distinct prognostic subgroups** within Child–Pugh class A patients[1]
  - It allows for more precise patient selection for clinical trials of systemic treatments[2]

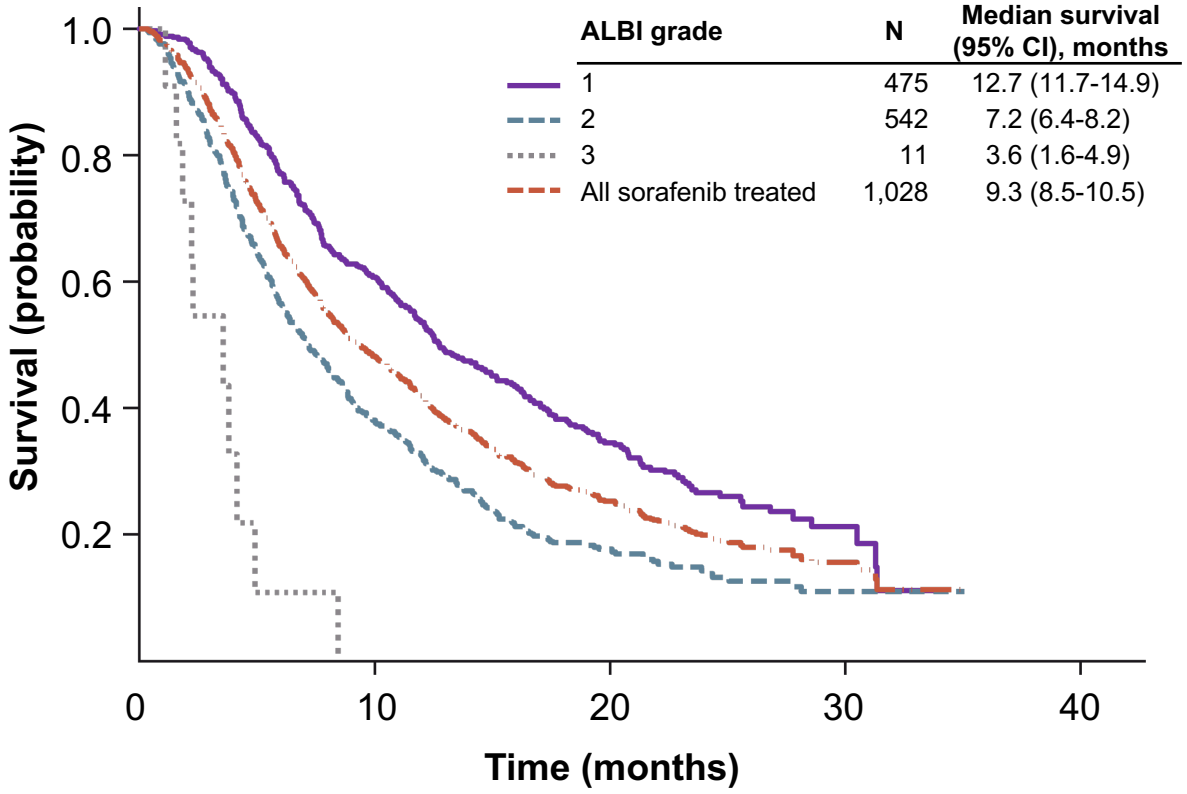


Figure adapted from Johnson PJ, et al.[1]; Median survival difference of nearly 6 months between patients with ALBI grade 1 and ALBI grade 2 treated with sorafenib
ALBI, Albumin-Bilirubin; CI, confidence interval; HCC, hepatocellular carcinoma

1. Johnson PJ, et al. J Clin Oncol. 2015;33:550-8; 2. Chan AWH, et al. J Gastroenterol Hepatol. 2016;31:1300-6

THE MODIFIED ALBI SCORING SYSTEM

MAY PROVIDE BETTER PROGNOSTIC AND PREDICTIVE VALUE FOR PATIENTS WITH HCC[1,2]

- The modified Albumin-Bilirubin (mALBI) scoring system is superior to the ALBI as:[1]
  - it produces a uniform distribution of patients among grades 2a and 2b
  - it improves stratification performance

- It is expected that the **mALBI scoring system** is now becoming widely used[1]

ALBI score	ALBI grade definition[3]	mALBI grade definition[2]	Liver dysfunction/decompensation
≤ −2.60	1	1	Mild
> −2.60 to < −2.270 ≥ −2.270 to ≤ −1.39	2 2	2a 2b	Moderate
> −1.39	3	3	Severe

ALBI, Albumin-Bilirubin; HCC, hepatocellular carcinoma

1. Kudo M. Liver Cancer. 2022;11:1-8; 2. Hiraoka A, et al. Liver Cancer. 2019;8:121-9; 3. Johnson PJ, et al. J Clin Oncol. 2015;33:550-8

SUBGROUP ANALYSES IN IO HCC TRIALS

HCC, hepatocellular carcinoma; IO, immunotherapy

SUBGROUP ANALYSES ARE IMPORTANT IF…

- There are **potential differences** in prognosis between subgroups, with or without treatment
- There is **potential heterogeneity of treatment effect** in relation to pathophysiology of underlying liver disease
- There are practical questions about **when to treat**
- There are **doubts about benefit** in specific groups, which are leading to potentially inappropriate treatment

Rothwell PM. Lancet. 2005;365:176-86

HETEROGENEITY OF PATIENTS WITH HCC

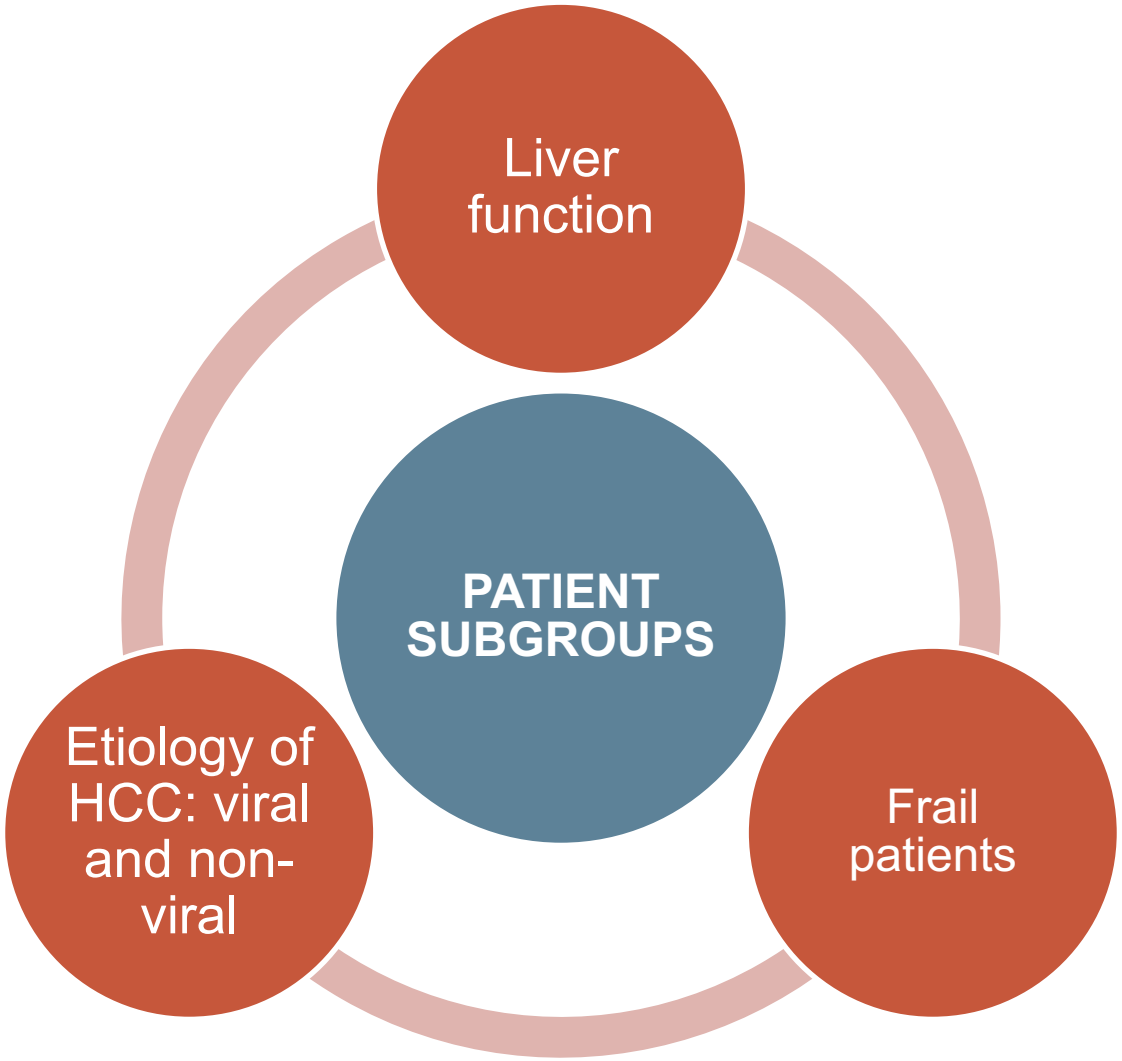
- There are **various patient groups with HCC** with specific comorbidities or disease features that require extra clinical attention[1], such as:
  - Solid organ transplantation, prior or active auto immune disease, or decompensated cirrhosis
- There are no **specific genetic biomarkers** to determine the prognosis or response to systemic treatment
- In general, these patient subgroups **are underrepresented** in clinical trials of systemic treatment[1]
  - Comorbidities, such as vascular invasion or decompensated cirrhosis, impact prognosis negatively and potentially confound outcomes
- This results in a **lack of robust safety and efficacy data** for these specific patient groups[1]

HCC, hepatocellular carcinoma

1. Rimassa L, et al. J Hepatol. 2021;74:931-43

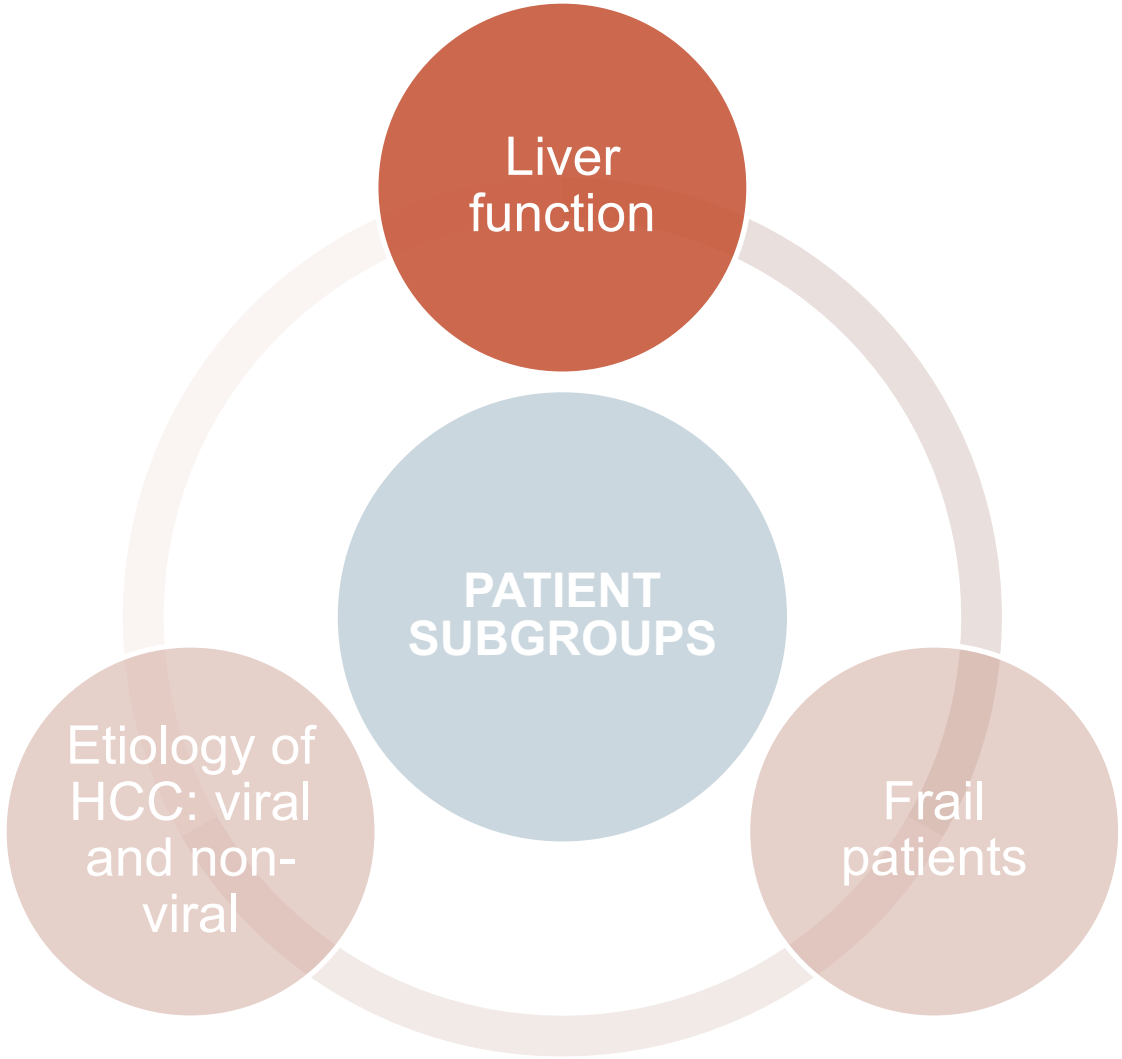
SUBGROUPS FOR IO TREATMENT IN HCC

AN OVERVIEW



HCC, hepatocellular carcinoma; IO, immunotherapy

SUBGROUP
LIVER FUNCTION



- Subgroup analyses by ALBI grade have been performed:
  - in IMbrave150 (atezolizumab + bevacizumab vs sorafenib)[1]
  - in HIMALAYA (tremelimumab + durvalumab vs sorafenib)[2]

ALBI, Albumin-Bilirubin

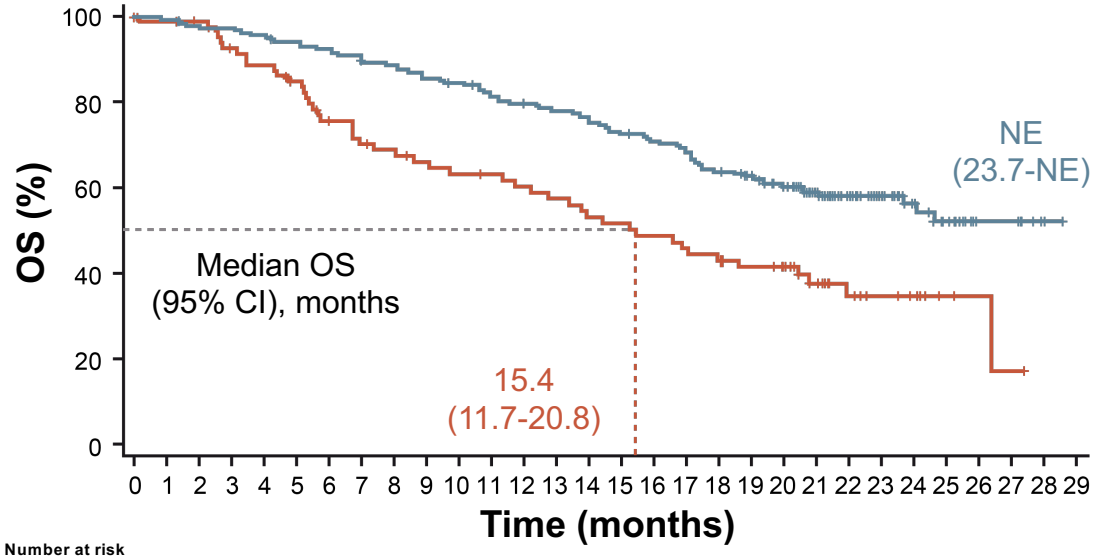
1. Kudo M, et al. ILCA (Virtual) 2021. Abstract #O-18. Oral presentation; 2. Vogel A, et al. Ann Oncol. 2022;33 suppl 9:S1454-84 (ESMO Asia 2022 poster presentation 79-P)

SUBGROUP: LIVER FUNCTION | ATEZOLIZUMAB + BEVACIZUMAB

ALBI GRADE 1 HAD A GREATER OVERALL SURVIVAL (OS) BENEFIT WITH ATEZOLIZUMAB + BEVACIZUMAB THAN WITH SORAFENIB[1]

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)**	

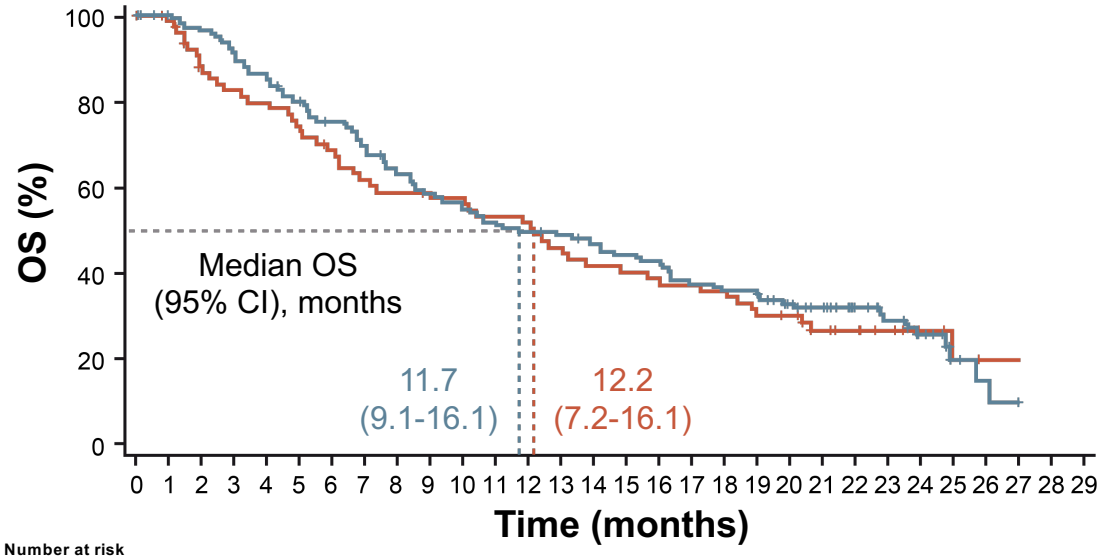


Number at risk

Atezo + Bev	191	190	186	185	182	178	174	169	167	161	158	151	147	144	140	134	130	126	117	109	96	73	55	38	29	19	9	9	1	NE
Sorafenib	87	83	80	73	70	65	57	52	50	47	45	44	42	40	37	36	34	32	30	28	25	18	12	9	7	3	2	1	NE	NE

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)**	



Number at risk

Atezo + Bev	144	139	134	127	120	110	102	94	85	79	75	70	67	65	62	58	56	49	47	47	38	32	25	19	13	5	3	2	1	NE
Sorafenib	78	75	64	60	58	54	49	44	42	41	40	37	36	32	29	28	27	26	25	21	19	14	12	9	5	4	1	1	NE	NE

Clinical cut-off date: 31 August 2020; Median follow-up: 15.6 months; [a] HR is unstratified.

Full analysis set - Updated IMbrave150 results (Cheng et al. J. Hepatol. 2022): Median OS was 5.8 months longer with atezolizumab +bevacizumab than sorafenib

ALBI, Albumin-Bilirubin; Atezo, atezolizumab; Bev, bevacizumab; CI, confidence interval; HR, hazard ratio; NE, not estimable

1. Kudo M, et al. ILCA (Virtual) 2021. Abstract #O-18. Oral presentation

SUBGROUP: LIVER FUNCTION | ATEZOLIZUMAB + BEVACIZUMAB

SAFETY PROFILES ACROSS SUBGROUPS BASED ON LIVER FUNCTION WERE GENERALLY CONSISTENT

	mALBI grade 1		mALBI grade 2a		mALBI grade 2b	
	Atezo + Bev (n=189)	Sorafenib (n=81)	Atezo + Bev (n=71)	Sorafenib (n=37)	Atezo + Bev (n=69)	Sorafenib (n=38)
Median treatment duration, months	Atezo: 10.4 (0-28); Bev: 9.6 (0-28)	2.9 (0-25)	Atezo: 6.9 (0-26); Bev: 5.1 (0-25)	1.9 (0-21)	Atezo: 4.3 (0-24); Bev: 4.7 (0-24)	2.8 (0-21)
All-grade AE, any cause, n (%)	185 (98)	79 (98)	70 (99)	37 (100)	67 (97)	38 (100)
Treatment-related	169 (89)	75 (93)	61 (86)	36 (97)	54 (78)	37 (97)
Grade 3 or 4 AE, n (%)[a]	122 (65)	47 (58)	46 (65)	21 (57)	39 (57)	21 (55)
Treatment-related[a]	90 (48)	37 (46)	27 (38)	21 (57)	26 (38)	14 (37)
Serious AE, n (%)	79 (42)	22 (27)	38 (54)	12 (32)	43 (62)	17 (45)
Treatment-related	41 (22)	10 (12)	12 (17)	5 (14)	23 (33)	10 (26)
Grade 5 AE, n (%)	7 (4)	3 (4)	5 (7)	2 (5)	11 (16)	4 (11)
Treatment-related	2 (1)	0	1 (1)	0	3 (4)	1 (3)
AE leading to withdrawal from any component, n (%)	33 (17)	7 (9)	18 (25)	5 (14)	21 (30)	6 (16)
AE leading to dose interruption of any study treatment, n (%)	122 (65)	28 (35)	37 (52)	19 (51)	36 (52)	21 (55)
AE leading to dose modification of sorafenib, n (%)[b]	0	30 (37)	0	14 (38)	0	14 (37)

The safety and tolerability profile of atezolizumab + bevacizumab was consistent with the known safety profiles of each individual drug and with the underlying disease, regardless of mALBI grade

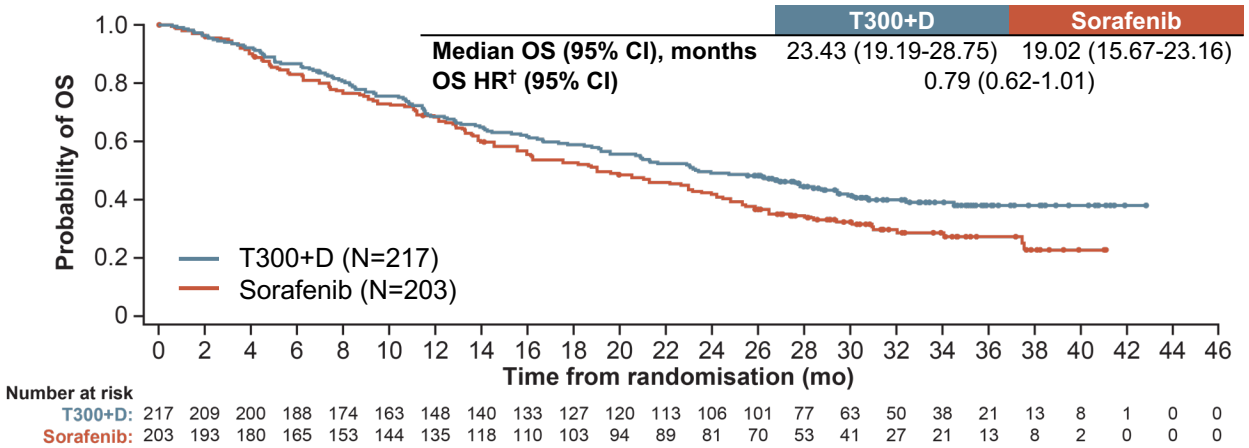
Clinical cut-off date: 31 August 2020; Median follow-up: 15.6 months; [a] Highest grade experienced; [b] No dose modification allowed for the atezolizumab + bevacizumab arm; AE, adverse event; Atezo, atezolizumab; Bev, bevacizumab; mALBI, modified Albumin-Bilirubin; SAE, serious adverse event

1. Kudo M, et al. ILCA (Virtual) 2021. Abstract #O-18. Oral presentation

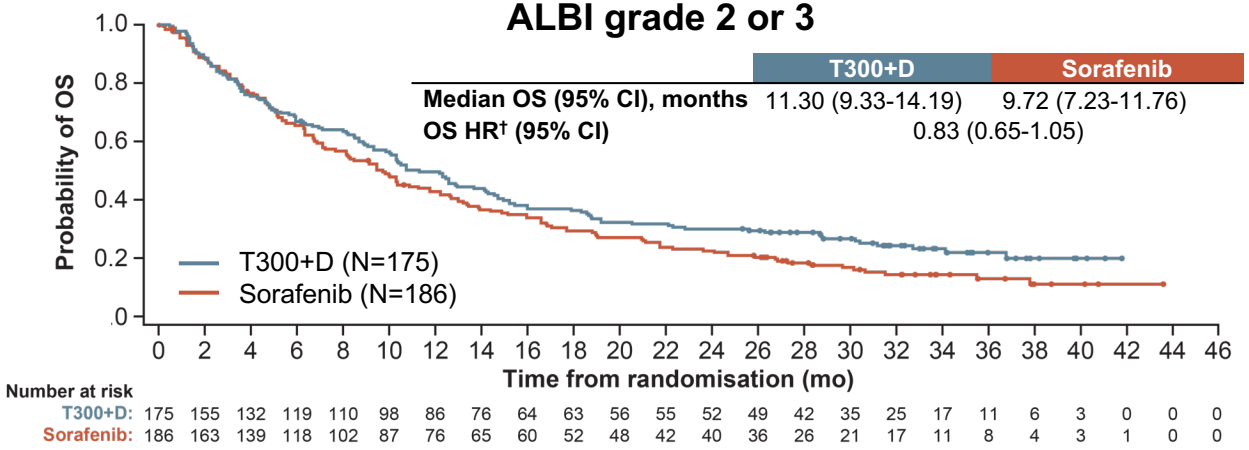
SUBGROUP: LIVER FUNCTION | TREMELIMUMAB + DURVALUMAB

OS IN BOTH SUBGROUPS WAS CONSISTENT WITH THE FULL ANALYSIS SET

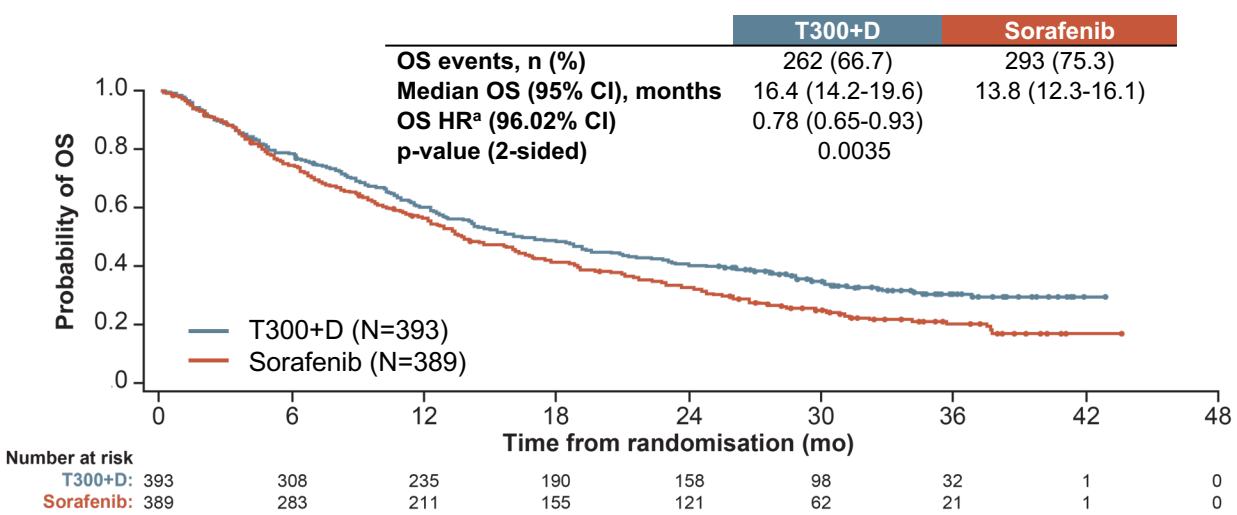
ALBI grade 1



ALBI grade 2 or 3



Full analysis set



Figures adapted from Vogel A, et al.[1]; data cut-off date: 27 August 2021; median follow-up (95% CI): 33.18 (31.74-34.53) months for T300+D, 32.56 (31.57-33.71) months for durvalumab, and 32.23 (30.42–33.71) months for sorafenib

[a] OS HRs and CIs were calculated using a Cox proportional hazards model adjusting for treatment, etiology, Eastern Cooperative Oncology Group performance status, and macrovascular invasion

ALBI, Albumin-Bilirubin; CI, confidence interval; HR, hazard ratio; mo, months; OS, overall survival; T300+D, tremelimumab 300 mg x 1 dose + durvalumab 1,500 mg every 4 weeks (Q4W)

1. Vogel A, et al. Ann Oncol. 2022;33 suppl 9:S1454-84 (ESMO Asia 2022 poster presentation 79-P)

SUBGROUP: LIVER FUNCTION | TREMELIMUMAB + DURVALUMAB

SAFETY PROFILES ACCORDING TO LIVER FUNCTION WERE GENERALLY CONSISTENT

- Tremelimumab + durvalumab had a similar safety profile in both ALBI subgroups, consistent with the safety analysis set
- Durvalumab had a similar safety profile in both ALBI subgroups, consistent with the safety analysis set

Patients with an event, n (%)	ALBI grade 1			ALBI grade 2 or 3			Safety analysis set		
	T300+D (n=216)	Durvalumab (n=198)	Sorafenib (n=197)	T300+D (n=171)	Durvalumab (n=190)	Sorafenib (n=177)	T300+D (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any TEAE	210 (97.2)	171 (86.4)	187 (94.9)	167 (97.7)	174 (91.6)	170 (96.0)	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE	166 (76.9)	99 (50.0)	168 (85.3)	127 (74.3)	103 (54.2)	149 (84.2)	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3 or 4 TEAE	111 (51.4)	63 (31.8)	102 (51.8)	85 (49.7)	81 (42.6)	94 (53.1)	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3 or 4 TRAE	59 (27.3)	17 (8.6)	76 (38.6)	41 (24.0)	33 (17.4)	62 (35.0)	100 (25.8)	50 (12.9)	138 (36.9)
Any TEAE leading to death	8 (3.7)	6 (3.0)	11 (5.6)	22 (12.9)	20 (10.5)	16 (9.0)	30 (7.7)	26 (6.7)	27 (7.2)
Any TRAE leading to death	5 (2.3)	0	1 (0.5)	4 (2.3)	0	2 (1.1)	9 (2.3)	0	3 (0.8)
Any serious TEAE	89 (41.2)	48 (24.2)	49 (24.9)	68 (39.8)	67 (35.3)	62 (35.0)	157 (40.5)	115 (29.6)	111 (29.7)
Any serious TRAE	44 (20.4)	14 (7.1)	15 (7.6)	24 (14.0)	18 (9.5)	20 (11.3)	68 (17.5)	32 (8.2)	35 (9.4)
Any TEAE leading to discontinuation	27 (12.5)	10 (5.1)	20 (10.2)	26 (15.2)	22 (11.6)	43 (24.3)	53 (13.7)	32 (8.2)	63 (16.8)
Any TRAE leading to discontinuation	20 (9.3)	4 (2.0)	15 (7.6)	12 (7.0)	12 (6.3)	26 (14.7)	32 (8.2)	16 (4.1)	41 (11.0)
Any immune-mediated TEAE	94 (43.5)	25 (12.6)	20 (10.2)	45 (26.3)	39 (20.5)	10 (5.6)	139 (35.8)	64 (16.5)	30 (8.0)

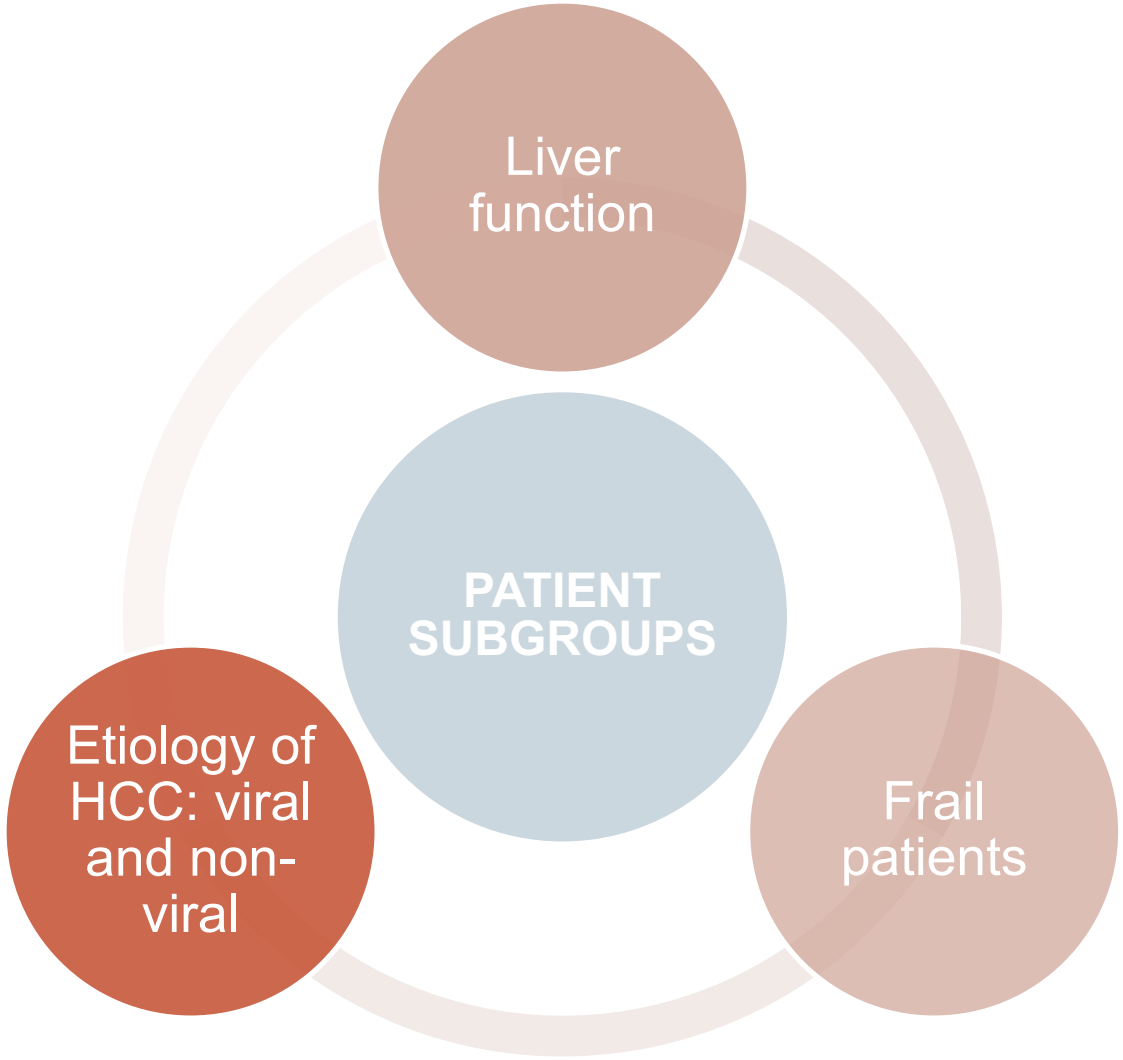
TEAEs include AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy; Treatment-related was as assessed by the investigator

AE, adverse event; ALBI, albumin-bilirubin; T300+D, tremelimumab 300 mg x 1 dose + durvalumab 1,500 mg Q4W; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

Vogel A, et al. Ann Oncol. 2022;33 suppl 9:S1454-84 (ESMO Asia 2022 poster presentation 79-P)

SUBGROUP

ACCORDING TO ETIOLOGY OF HCC: VIRAL AND NON-VIRAL HCC



- HCC can have **viral and non-viral** causes
- Non-viral causes of HCC include **non-alcoholic steatohepatitis (NASH),** non-alcoholic fatty liver disease (NAFLD) and alcohol use
- Viral causes of HCC **are hepatitis B (HBV) and hepatitis C (HCV)**

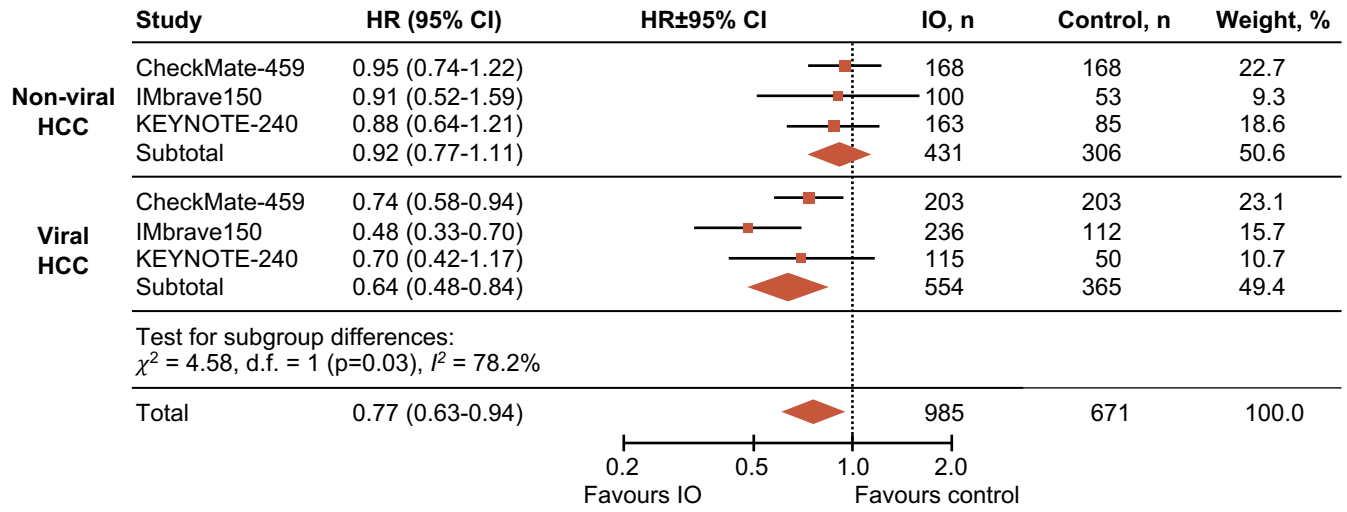
HCC, hepatocellular carcinoma

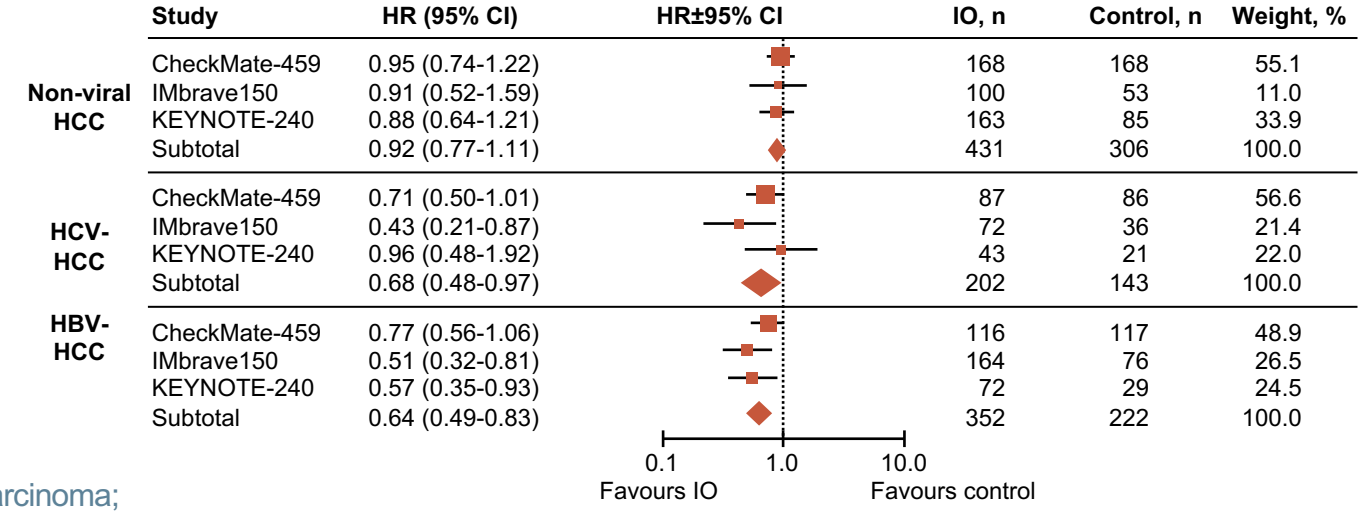
Pfister D, et al. Nature. 2021;592:450-6

SUBGROUP: THE CAUSE OF HCC – VIRAL AND NON-VIRAL HCC[1]

OS MAY BE RELATED TO UNDERLYING LIVER DISEASE

- Meta-analysis of 1,656 patients
  - OS improved with immunotherapy
- Separate meta-analyses were subsequently performed for each of the three etiologies: non-viral (NASH and alcohol intake), hepatitis C virus (HCV), and hepatitis B virus (HCV)
  - Survival was superior to the control arm in patients with HBV-related HCC (n=574; p=0.0008) and HCV-related HCC (n=345; p=0.04)
  - Survival was not superior to the control arm in patients with non-viral HCC (n=737; p=0.39)





CI, confidence interval; d.f., degrees of freedom; HCC, hepatocellular carcinoma; HR, hazard ratio; IO, immunotherapy; NASH, non-alcoholic steatohepatitis; OS, overall survival

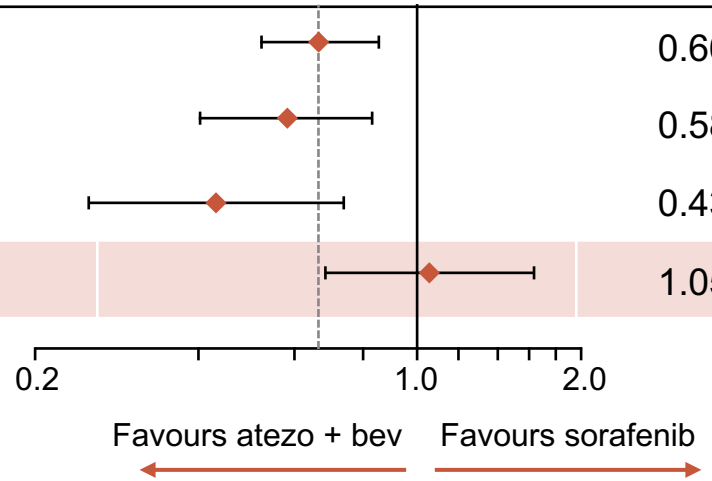
1. Pfister D, et al. Nature. 2021;592:450-6

SUBGROUP: VIRAL/NON-VIRAL | ATEZOLIZUMAB + BEVACIZUMAB

OS (UPDATED IMbrave150)

The atezolizumab + bevacizumab combination seems to be **less effective in non-viral HCC**

Characteristic (n)	Median OS, months		HR[a] (95% CI)
	Atezo + Bev	Sorafenib	
All patients (501)	19.2	13.4	0.66 (0.52-0.85)
HBV-HCC (240)	19.0	12.4	0.58 (0.40-0.83)
HCV-HCC (108)	24.6	12.6	0.43 (0.25-0.73)
Non-viral HCC (153)	17.0	18.1	1.05 (0.68-1.63)



Clinical cut-off date: 31 August 2020; Median follow-up: 15.6 months; [a] HRs are from unstratified analyses
atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; OS, overall survival

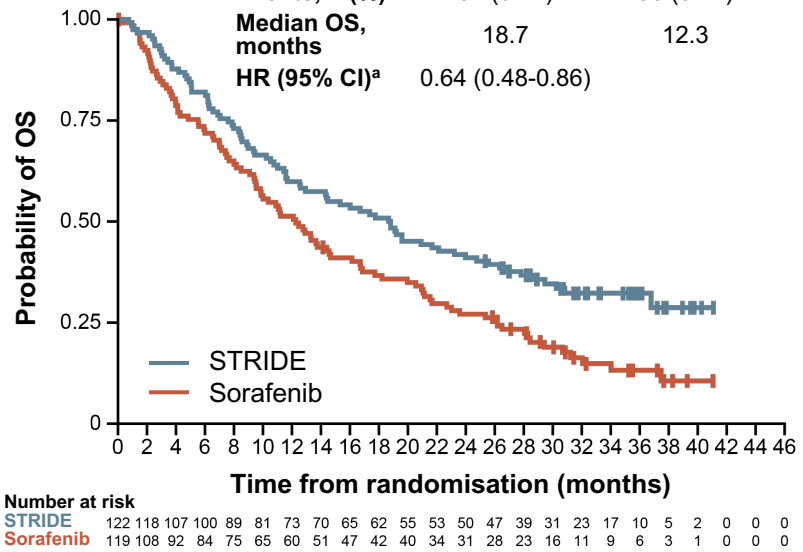
1. Cheng A-L, et al. J Hepatol. 2022;76:862-73

SUBGROUP: VIRAL/NON-VIRAL | TREMELIMUMAB + DURVALUMAB

SURVIVAL BENEFIT OF IO IN PATIENTS WITH NON-VIRAL HCC AND HBV-INFECTED HCC

HBV

	STRIDE (n=122)	Sorafenib (n=119)
Events, n (%)	82 (67.2)	98 (82.4)
Median OS, months	18.7	12.3
HR (95% CI)[a]	0.64 (0.48-0.86)	

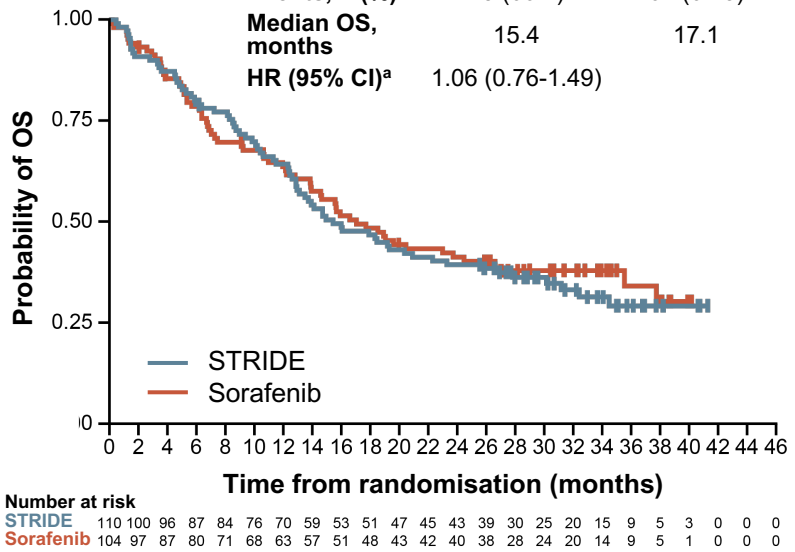


Number at risk

STRIDE	122	118	107	100	89	81	73	70	65	62	55	53	50	47	39	31	23	17	10	5	2	0	0	0
Sorafenib	119	108	92	84	75	65	60	51	47	42	40	34	31	28	23	16	11	9	6	3	1	0	0	0

HCV

	STRIDE (n=110)	Sorafenib (n=104)
Events, n (%)	73 (66.4)	64 (61.5)
Median OS, months	15.4	17.1
HR (95% CI)[a]	1.06 (0.76-1.49)	

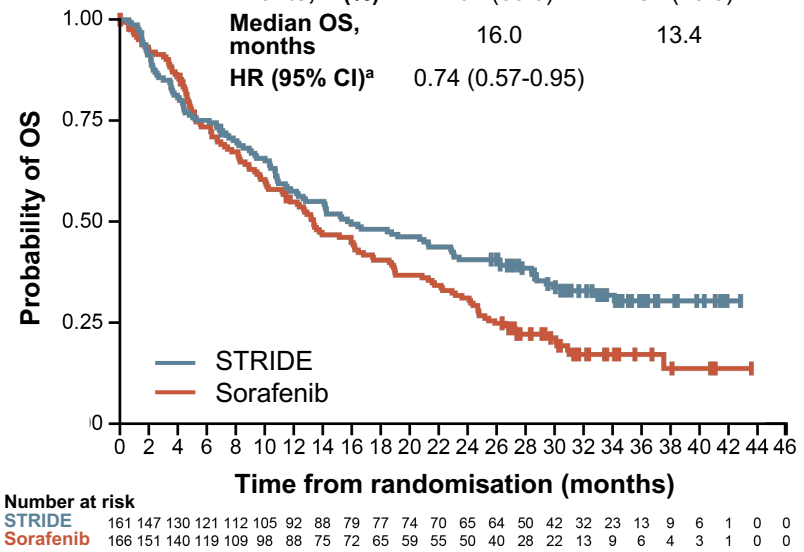


Number at risk

STRIDE	110	100	96	87	84	76	70	59	53	51	47	45	43	39	30	25	20	15	9	5	3	0	0	0
Sorafenib	104	97	87	80	71	68	63	57	51	48	43	42	40	38	28	24	20	14	9	5	1	0	0	0

Non-viral

	STRIDE (n=161)	Sorafenib (n=166)
Events, n (%)	107 (66.5)	131 (78.9)
Median OS, months	16.0	13.4
HR (95% CI)[a]	0.74 (0.57-0.95)	



Number at risk

STRIDE	161	147	130	121	112	105	92	88	79	77	74	70	65	64	50	42	32	23	13	9	6	1	0	0
Sorafenib	166	151	140	119	109	98	88	75	72	65	59	55	50	40	28	22	13	9	6	4	3	1	0	0

[a] HR and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and using the Efron method to control for ties

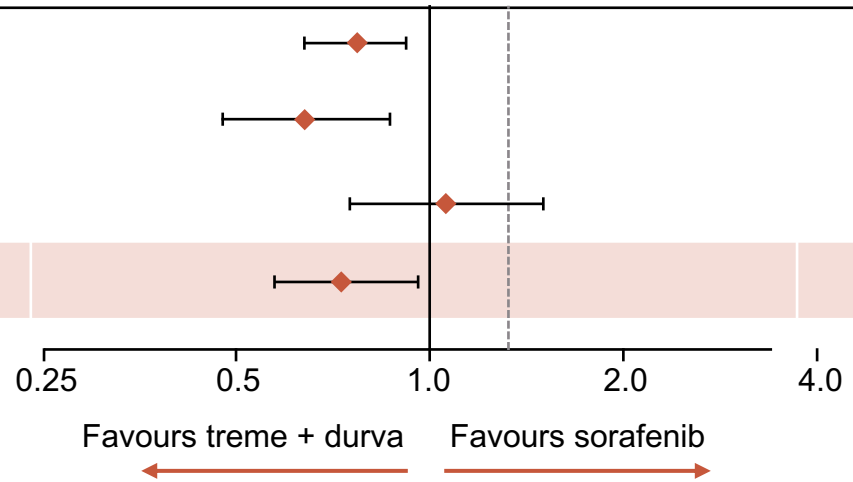
CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IO, immunotherapy; OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab

Chan LS, et al. Ann Oncol. 2022;33 suppl 9:S869-70 (ESMO 2022 poster presentation 714-P)

SUBGROUP: VIRAL/NON-VIRAL | TREMELIMUMAB + DURVALUMAB

SURVIVAL BENEFIT OF IO IN PATIENTS WITH NON-VIRAL HCC AND HBV-INFECTED HCC

Characteristic	Median OS, months		HR[a] (95% CI)
	Durva + Treme	Sorafenib	
All patients	16.4	13.8	0.77 (0.65-0.91)
HBV-HCC	18.7	12.3	0.64 (0.48-0.86)
HCV-HCC	15.4	17.1	1.06 (0.76-1.49)
Non-viral HCC	16.0	13.4	0.73 (0.57-0.95)



[a] HR and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and using the Efron method to control for ties. Please refer to the original publication for the stratified results

Durva, durvalumab; treme, tremelimumab; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IO, immunotherapy;

Chan LS, et al. Ann Oncol. 2022;33 suppl 9:S869-70 (ESMO 2022 poster presentation 714-P)

SUBGROUP: VIRAL VERSUS NON-VIRAL ETIOLOGY | TREMELIMUMAB + DURVALUMAB

INCIDENCES OF trAEs WERE LOWER ACROSS ETIOLOGY SUBGROUPS

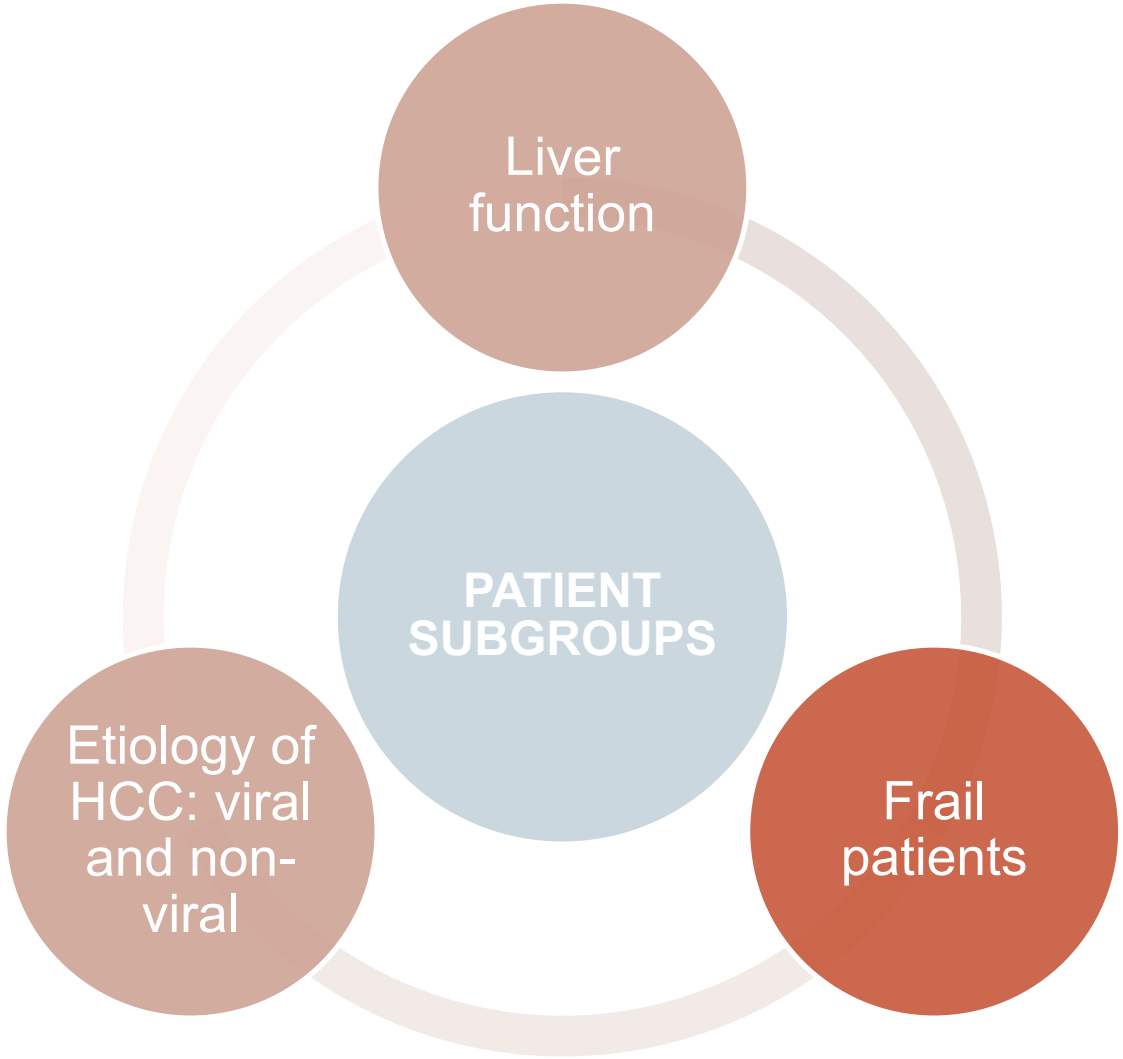
- The incidences of trAEs or grade 3 or 4 trAEs were **generally lower** for durvalumab + tremelimumab and durvalumab than for sorafenib **across etiology subgroups**

Participants with event, n (%)	HBV (N=354)			HCV (N=315)			Non-viral (N=481)		
	STRIDE (n=122)	Durvalumab (n=117)	Sorafenib (n=115)	STRIDE (n=108)	Durvalumab (n=107)	Sorafenib (n=100)	STRIDE (n=158)	Durvalumab (n=164)	Sorafenib (n=159)
Any AE	116 (95.1)	96 (82.1)	108 (93.9)	105 (97.2)	99 (92.5)	97 (97.0)	157 (99.4)	150 (91.5)	152 (95.6)
Any trAE	88 (72.1)	57 (48.7)	98 (85.2)	82 (75.9)	64 (59.8)	85 (85.0)	124 (78.5)	81 (49.4)	134 (84.3)
Any grade 3 or 4 AE	53 (43.4)	35 (29.9)	52 (45.2)	54 (50.0)	47 (43.9)	57 (57.0)	89 (56.3)	62 (37.8)	87 (54.7)
Any grade 3 or 4 trAE	26 (21.3)	14 (12.0)	32 (27.8)	26 (24.1)	19 (17.8)	39 (39.0)	48 (30.4)	17 (10.4)	67 (42.1)
Any serious trAE	16 (13.1)	9 (7.7)	7 (6.1)	12 (11.1)	11 (10.3)	9 (9.0)	40 (25.3)	12 (7.3)	19 (11.9)
Any trAE leading to death	0	0	1 (0.9)	2 (1.9)	0	0	7 (4.4)	0	2 (1.3)
Any trAE leading to discontinuation	4 (3.3)	2 (1.7)	5 (4.3)	8 (7.4)	8 (7.5)	18 (18.0)	20 (12.7)	6 (3.7)	18 (11.3)
Any immune-mediated AE	38 (31.1)	13 (11.1)	6 (5.2)	39 (36.1)	30 (28.0)	14 (14.0)	62 (39.2)	21 (12.8)	10 (6.3)

AE, adverse event; HBV, hepatitis B virus; HBC, hepatitis C virus; STRIDE, Single Tremelimumab Regular Interval Durvalumab; trAE, treatment-related adverse event

Chan LS, et al. Ann Oncol. 2022;33 suppl 9:S869-70 (ESMO 2022 poster presentation 714-P)

SUBGROUP
FRAIL PATIENTS



- **Frail patients may not tolerate** the high risk of immune-related adverse events and have **routinely been excluded** from clinical trials*
- **More studies are needed** (e.g. real-world evidence studies) on the efficacy and safety of new treatments such as **tremelimumab + durvalumab**

HCC, hepatocellular carcinoma

* For general efficacy and safety of IO in HCC, please refer to Micro learning module 1 (COR2ED 2023) of this series

FRAIL PATIENTS WITH CHILD–PUGH CLASS B OR C

THESE PATIENTS ARE USUALLY EXCLUDED FROM CLINICAL TRIALS

There is a **lack of evidence** on the safety and efficacy of immunotherapy in the **Child–Pugh class B** patient population

- Available data come from **retrospective cohorts or single-arm Phase 2 trials**
- Atezolizumab + bevacizumab and nivolumab **are the most evaluated immunotherapies** in Child–Pugh class B patients

Management of advanced HCC in Child–Pugh class B patients

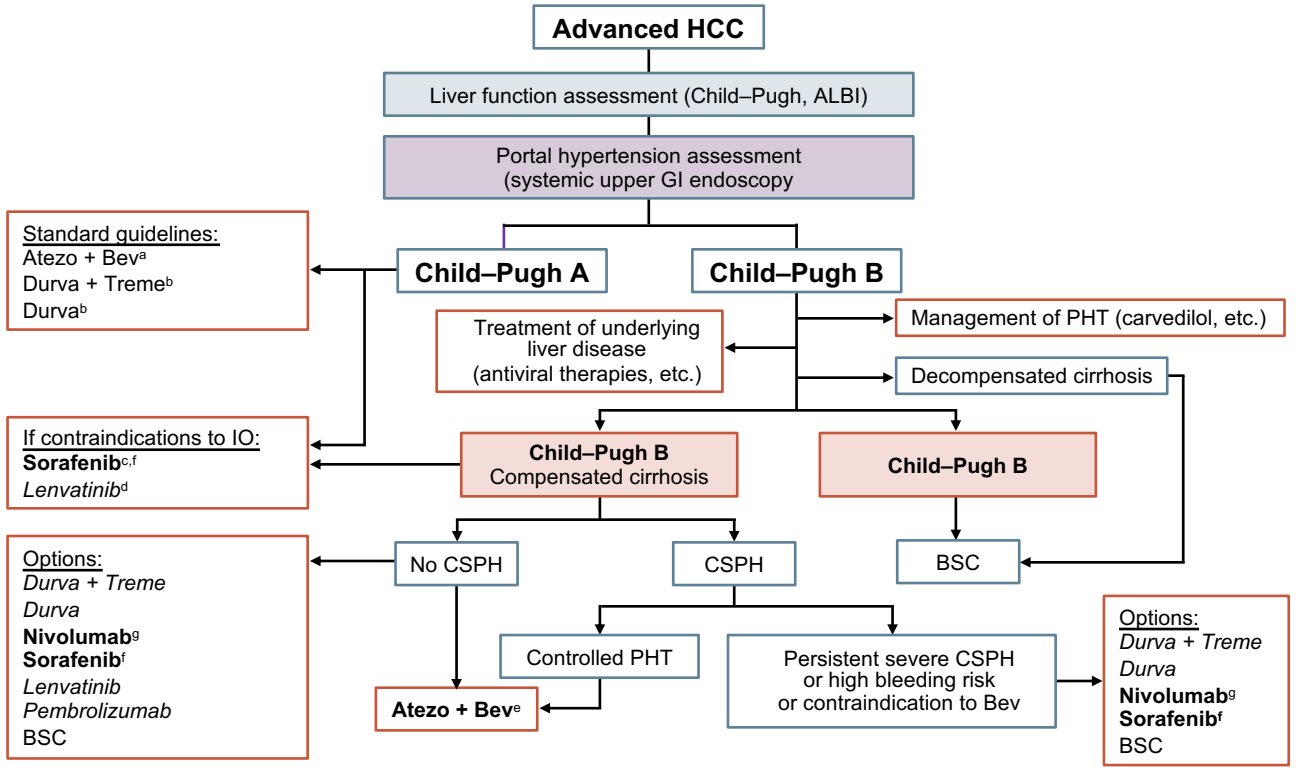


Figure adapted from Roth GS, et al.[1]; Standards of care validated in Child–Pugh class B patients by published prospective studies or multicentre retrospective cohort studies are written in **bold**; Standards of care lacking evidence in Child–Pugh class B patients but are considered as reasonable treatment options (expert opinion) are in *italics;* [a] IMbrave150 Phase 3 study; [b] HIMALAYA Phase 3 study; [c] SHARP Phase 3 study; [d] REFLECT Phase 3 study and its post hoc analysis in Child–Pugh class B patients; [e] Multicentre, retrospective cohort study by D'Alessio et al. (2022); [f] GIDEON prospective, observational registry study; [g] CheckMate-040 Phase 2 study

ALBI, Albumin-Bilirubin; Atezo, atezolizumab; Bev, bevacizumab; BSC, best supportive care; CSPH, clinically significant portal hypertension; Durva, durvalumab; GI, gastrointestinal; HCC, hepatocellular carcinoma; IO, immunotherapy; PTH, portal hypertension; Treme, tremelimumab

1. Roth GS, et al. Liver Int. 2023;43:546-57

FRAIL PATIENTS WITH CARDIOVASCULAR MORBIDITY

PATIENTS WITH A RECENT CARDIOVASCULAR EVENT WERE EXCLUDED FROM IMbrave150

Bevacizumab may expose patients to bleeding complications

rhosis and hepatocellular carcinoma. In this trial, 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. Overall, the inci-

All-causality AEs of special interest by medical concept[a*]	Atezolizumab + bevacizumab (n=329)		Sorafenib (n=156)	
	All grade	Grade 3 or 4	All grade	Grade 3 or 4
Patients with at least one event, n (%)	190 (57.8)	76 (23.1)	76 (48.7)	29 (18.6)
Hypertension	102 (31.0)	50 (15.2)	40 (25.6)	19 (12.2)
Bleeding/haemorrhage	83 (25.2)	21 (6.4)	27 (17.3)	9 (5.8)
Proteinuria	70 (21.3)	10 (3.0)	13 (8.3)	1 (0.6)
Thromboembolic event–venous	10 (3.0)	5 (1.5)	5 (3.2)	2 (1.3)
Thromboembolic event–arterial	9 (2.7)	4 (1.2)	2 (1.3)	1 (0.6)
Congestive heart failure	1 (0.3)	0	2 (1.3)	0

[a] Grouped Medical Dictionary for Regulatory Activities preferred terms;

* Bevicizumab-related AEs only;

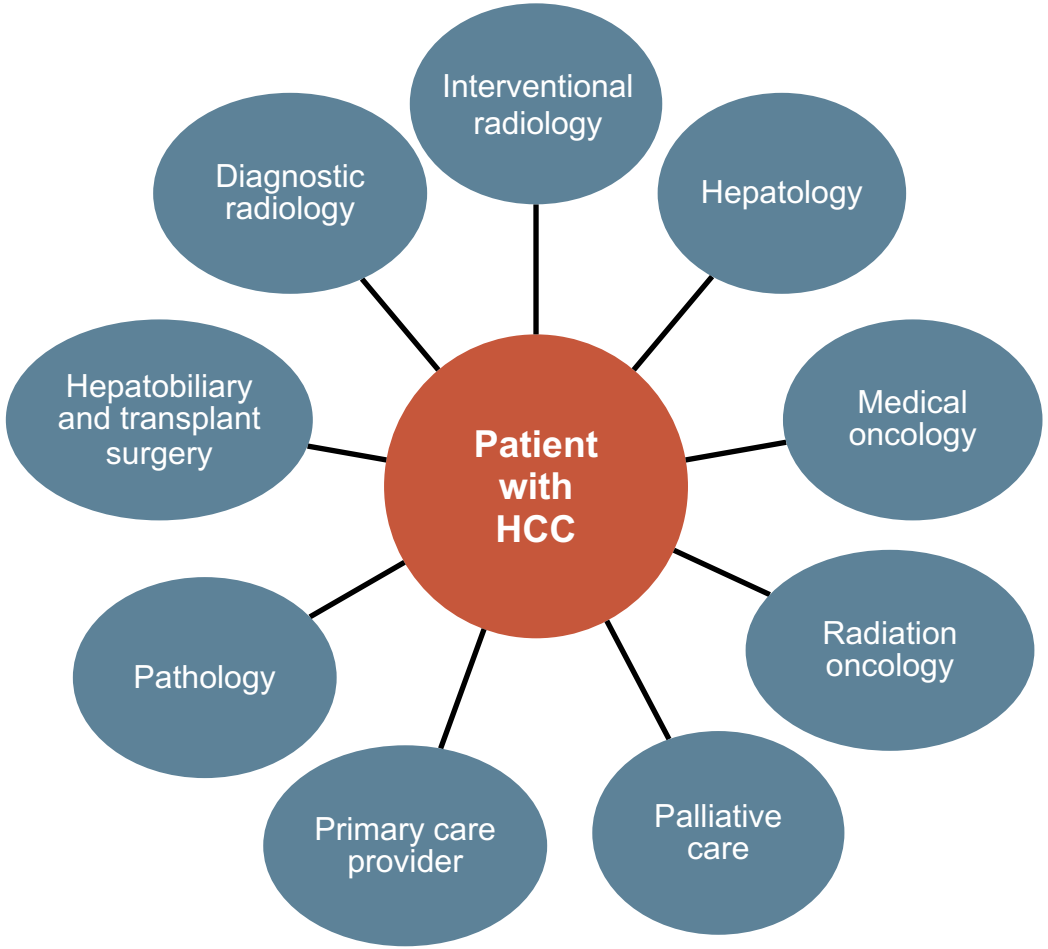
AE, adverse event

Finn R, et al. N Engl J Med. 2020;382:1894-905

IN CONCLUSION

MULTIDISCIPLINARY TEAM

IMPORTANT TO DETERMINE THE COURSE OF THERAPY FOR PATIENTS WITH HCC



HCC, hepatocellular carcinoma

IN CONCLUSION

- **Liver function** in patients with HCC is a critical prognostic factor
- The ALBI scoring system is a method to **assess liver function** based on albumin and bilirubin levels
  - It helps to further divide patients with compensated cirrhosis into subgroups to **predict clinical outcome of IO**
- There is a need to understand whether **specific patient groups** benefit more from one therapy rather than another one
- **Subgroup analysis according to liver function** has been performed
  - For IMbrave150, ALBI grade 1 had a greater OS benefit with atezolizumab + bevacizumab than with sorafenib
  - For HIMALAYA, all ALBI grades had a consistent OS with tremelimumab + durvalumab compared to the full analysis set
- **Subgroup analysis according to underlying liver disease** has been performed
  - IMbrave150 showed that atezolizumab + bevacizumab may be **less effective in non-viral HCC**
  - HIMALAYA showed a survival benefit of tremelimumab + durvalumab in **non-viral HCC** and HBV-infected HCC
- There are **not enough mature data** available to guide treatment decisions for these patient groups
  - **Predictive biomarkers** for therapeutic decision making are urgently needed

ALBI, Albumin-Bilirubin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IO, immunotherapy; OS, overall survival; NASH, non-alcoholic steatohepatitis

COR2ED

THE HEART OF MEDICAL EDUCATION

For more information visit

HCC connect®

POWERED BY COR2ED

Connect on
LinkedIn @HCC CONNECT

Watch on
YouTube @COR2ED

Email
info@cor2ed.com

Visit us at
https://cor2ed.com/

Follow us on
Twitter @hccconnectinfo

Heading to the heart of Independent Medical Education Since 2012