COR2ED®

THE HEART OF MEDICAL EDUCATION

EVOLVING TREATMENT OF ADVANCED HCC IN THE ASIA–PACIFIC REGION: A REVIEW AND MULTIDISCIPLINARY EXPERT OPINION

Ogasawara S, et al. *Cancers*. 2021;13;2626

Prof. Pierce KH Chow

National Cancer Centre Singapore and Duke-NUS Medical School
Singapore, Singapore

JULY 2021

HCC, hepatocellular carcinoma

DISCLAIMER

COR2ED®
THE HEART OF MEDICAL EDUCATION

Please note: Views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution, organisation, or other group or individual.

This content is supported by an Independent Educational Grant from Roche.

Disclosures: Prof. Pierce KH Chow has received honoraria from the following: Sirtex Medical, Ipsen, Bristol-Myers Squibb, Oncosil, Bayer, New B Innovation, MSD, BTG Plc, Guerbet, Perspectum, IQVIA, Genentech, Roche, AstraZeneca, AUM Biosciences, L.E.K. Consulting Pte Ltd.

EPIDEMIOLOGY OF HCC & HEALTHCARE AND REIMBURSEMENT SYSTEMS IN THE ASIA-PACIFIC REGION

COR2ED®
THE HEART OF MEDICAL EDUCATION

- In primary liver cancer:
  - **HCC represents 75% to 85% of cases**
- HCC = **4th most common cause of cancer-related death worldwide**
- An estimated **72% of HCC cases in Asia**

Country	Reimbursement policy procedures
Japan	Patients pay 10–30% of medical costs (depending on age and income)
China	Patients pay 10–20% of the cost of drugs on the Chinese National Reimbursement Drug List
South Korea	National Health Insurance reimbursed approximately 80% of covered inpatient care and 50–70% of covered outpatient care
Taiwan	Similar to South Korea
Singapore	Healthcare costs are covered by nationalised life insurance schemes and deductions from compulsory savings plans

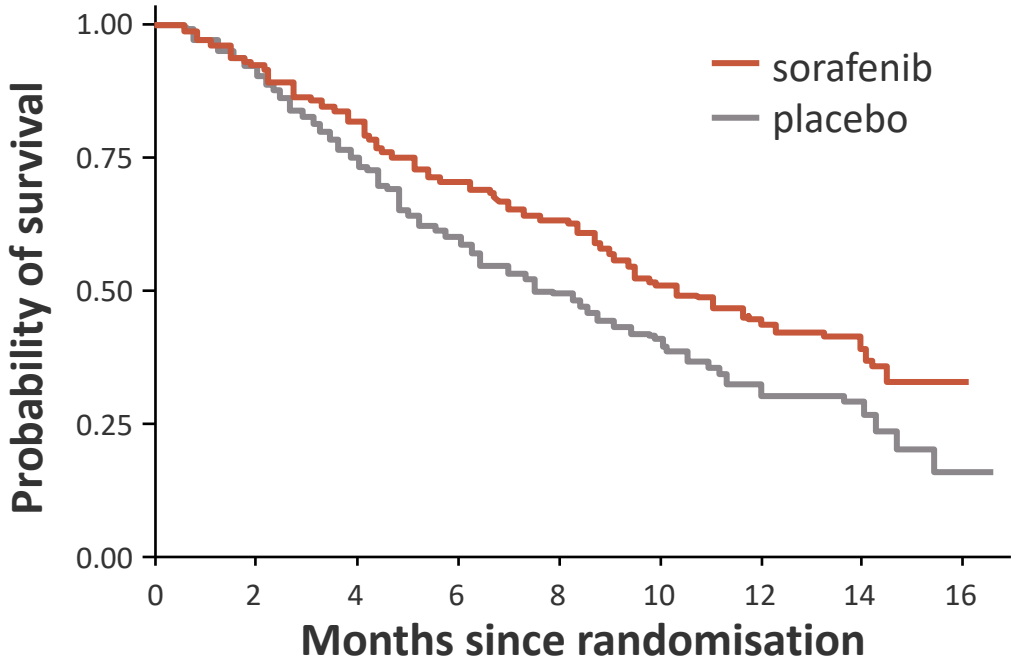
HCC, hepatocellular carcinoma

FIRST-LINE TREATMENT OPTIONS: SORAFENIB AND LENVATINIB

COR2ED®
THE HEART OF MEDICAL EDUCATION

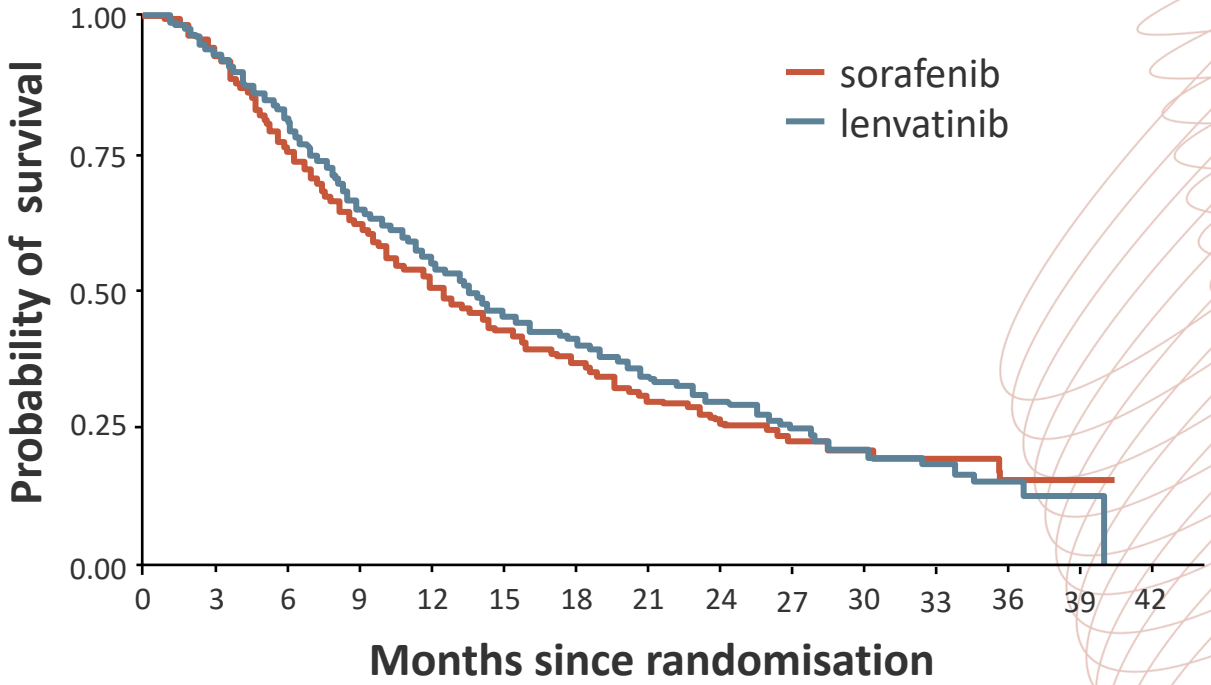
Overall survival in the SHARP trial[1]

Median OS: 10.7 months sorafenib *vs* 7.9 months placebo HR 0.69 (95% CI 0.55-0.87), p<0.001



Overall survival in the REFLECT* trial[2]

Median OS: 13.6 months lenvatinib *vs* 12.3 months sorafenib HR 0.92 (95% CI 0.79-1.06)



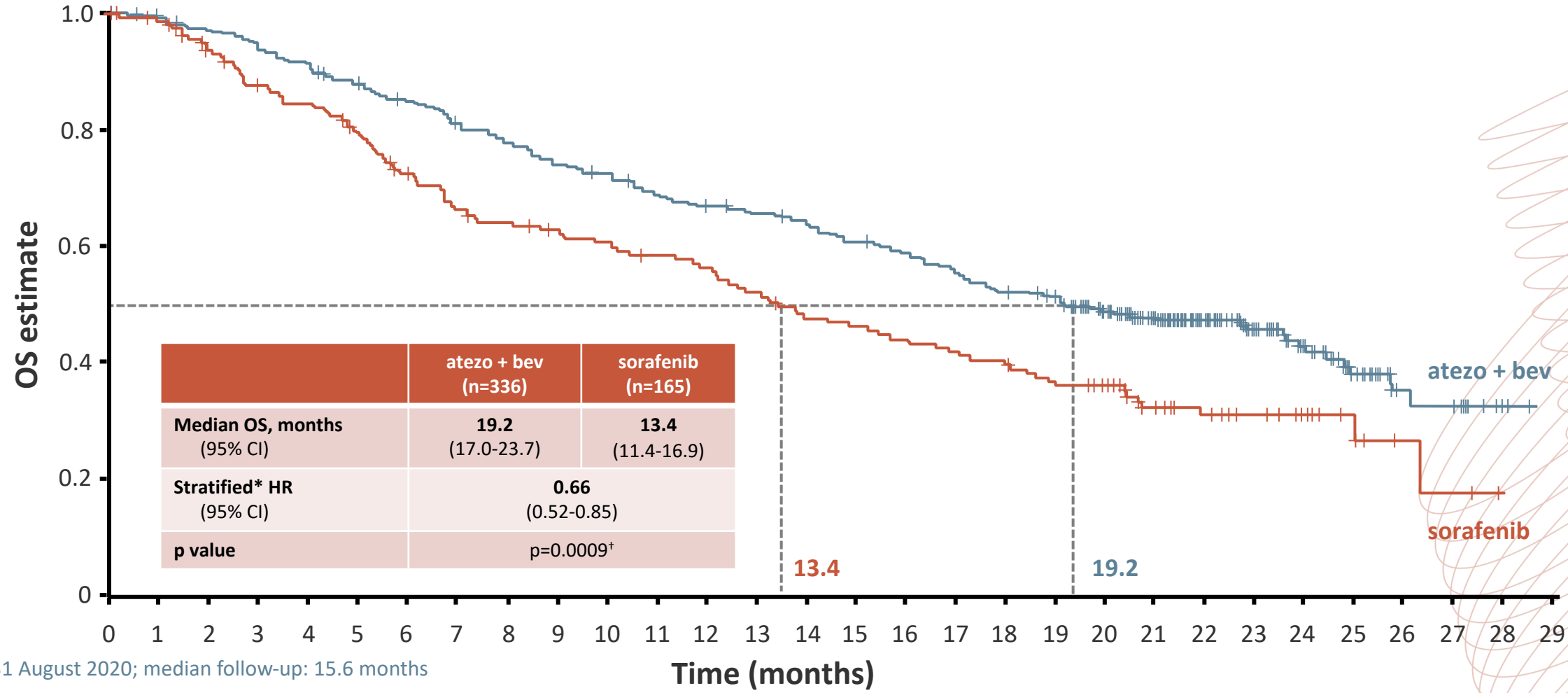
* REFLECT (NCT01761266) is a randomised phase 3 non-inferiority trial

CI, confidence interval; HR, hazard ratio; OS, overall survival

1. Llovet JM, et al. N Engl J Med. 2008;359:378-90; 2. Kudo M, et al. Lancet. 2018;391:1163-73

FIRST-LINE TREATMENT OPTIONS: ATEZOLIZUMAB + BEVACIZUMAB[1]

COR2ED®
THE HEART OF MEDICAL EDUCATION



	atezo + bev (n=336)	sorafenib (n=165)
Median OS, months (95% CI)	**19.2** (17.0-23.7)	**13.4** (11.4-16.9)
Stratified* HR (95% CI)	**0.66** (0.52-0.85)	
p value	p=0.0009†	

CCOD: 31 August 2020; median follow-up: 15.6 months

* Stratification factors included are geographic region (Asia excluding Japan vs RoW), AFP level (<400 ng/mL vs ≥400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS

† p value for descriptive purposes only

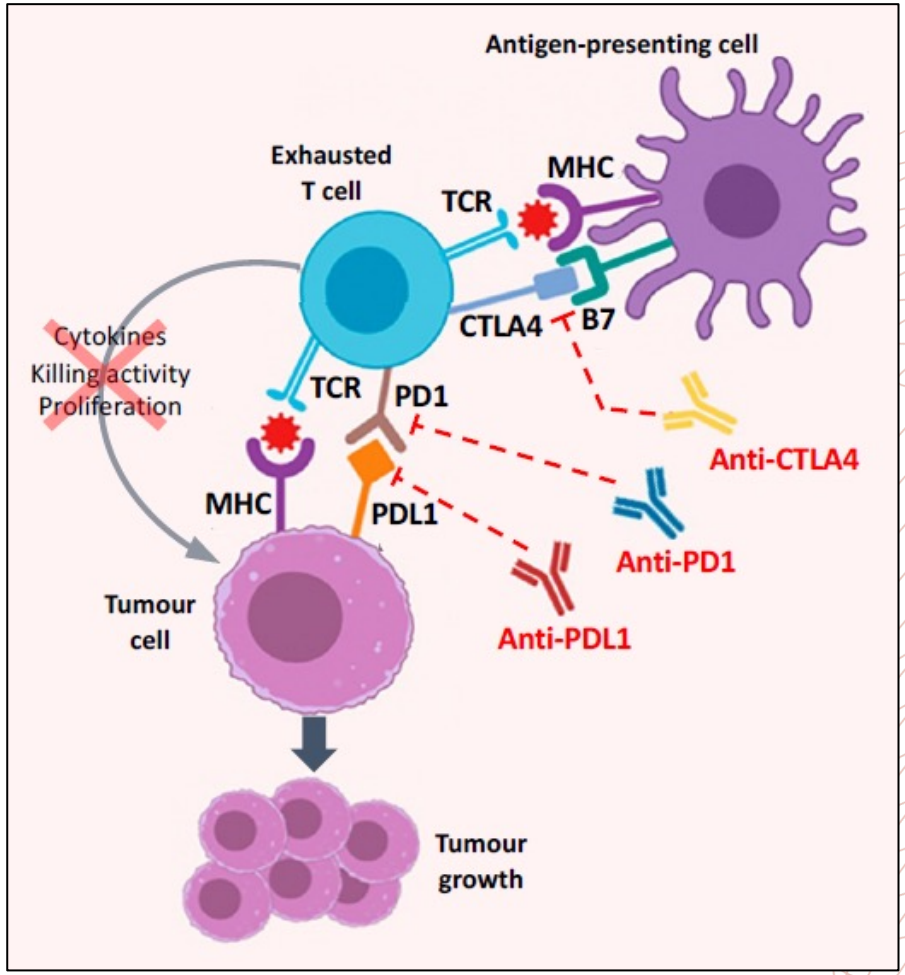
AFP, alpha-fetoprotein; atezo, atezolizumab; bev, bevacizumab; CCOD, clinical cutoff date; CI, confidence interval; EHS, extrahepatic spread; HR, hazard ratio; IxRS, Interactive voice/web response system; MVI, macrovascular invasion; OS, overall survival; RoW, Rest of World

1. Finn RS, et al. J Clin Oncol. 2021;39(3_suppl):267-267 (ASCO GI 2021 oral presentation)

MECHANISM OF ACTION OF IMMUNE CHECKPOINT INHIBITORS

COR2ED®
THE HEART OF MEDICAL EDUCATION

- Immune checkpoint inhibitors = Antibodies that target CTLA4, PD1, or PDL1
- In the HCC tumour microenvironment, chronic inflammation and cirrhosis lead to immune exhaustion
- Exhausted T cells have a reduced capacity to produce cytokines, to proliferate, and to kill tumour cells; tumour growth is facilitated by blockade of signalling resulting from interaction of the TCR with the MHC
- Key actionable drivers of immune exhaustion in HCC are the PD1–PDL1 pathway and CTLA4 signalling, and blockade of these pathways (i.e., immune checkpoint inhibition) enhances the immune reaction against the tumour cells



CTLA4, cytotoxic T-lymphocyte antigen 4; HCC, hepatocellular carcinoma; MHC, major histocompatibility complex; PD1, programmed death 1; PDL1, programmed death ligand 1; TCR, T-cell receptor

Source figure: Giannini EG, et al. Cancers. 2019;11:1689

SUMMARY OF ASIAN GUIDELINES FOR THE TREATMENT OF ADVANCED HCC WITH MACROVASCULAR INVASION OR EXTRAHEPATIC METASTASES

COR2ED®
THE HEART OF MEDICAL EDUCATION

	Asia Pacific (APASL)		China		Hong Kong (HKLCS)		Japan (JSH)		Korea (KLCSG)		Singapore (NCCS)		Taiwan (TLCA)	
Disease features	MVI^+	EHM^+	MVI^+ (IIIa)	EHM^+ (IIIb)	Int. I or IIa + Vp 1–3 LA IIb or IIIa + Vp 1–3	EVM (IVa, IVb) Vp 4 or EHM (or both)	MVI^+	EHM^+	MVI^+ (IIc, IIIb, IVa) Single Multiple	EHM^+ IVa (LN), IVb (others)	MVI^+	EHM^+	MVI^+	EHM^+
First-line treatment	Systemic therapy, TACE	CP A or B: systemic therapy CP C: best supportive care	TACE ± (MKI or FOLFOX4, LR, RT)	MKI or FOLFOX4 ± (TACE, RT)	IIb or IIIa, CP A: LR	Systemic therapy	TACE, LR, HAIC, MKI	MKI	TACE (SIRT) ± EBRT sorafenib lenvatinib	sorafenib lenvatinib	SIRT, TACE	Systemic therapy	LR, MKI	Systemic therapy ± (TACE, SIRT, LR)
Second-line treatment			MKI	MKI	IIb or IIIa, CP B, or IIIb: TACE				(Vp 1–3: LR x 1–3)	(TACE, EBRT)	Systemic therapy		TACE + RT	Chemo-therapy
Later line of treatment									(CT, HAIC if MKI failed or not available)				SIRT, HAIC	

APASL, Asian Pacific Association for the Study of the Liver; CP, Child-Pugh; CT, computed tomography; EBRT, external beam radiation therapy; EHM, extrahepatic metastasis; EVM, extrahepatic vascular metastasis; FOLFOX4, folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HKLCS, Hong Kong Liver Cancer Staging system; Int., intermediate; JSH, Japan Society of Hepatology; KLCSG, Korean Liver Cancer Study Group; LA, locally advanced; LN, lymph node; LR, liver resection; MKI, multikinase inhibitor; MVI, macrovascular invasion; NCCS, National Cancer Centre Singapore; RT, radiation therapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation; TLCA, Taiwan Liver Cancer Association; Vp 1–3, portal vein thrombosis with involvement of unilateral 3rd (Vp1), 2nd (Vp2) or 1st branch (Vp3) of portal vein or bilateral 1st branches

APPROVAL AND REIMBURSEMENT FOR THE TREATMENT OF ADVANCED OR UNRESECTABLE HCC IN THE ASIA-PACIFIC REGION

COR2ED®
THE HEART OF MEDICAL EDUCATION

Country or Territory	First Line			Second Line (After sorafenib)						
	sorafenib	lenvatinib	atezolizumab + bevacizumab	cabozantinib	regorafenib	ramucirumab	nivolumab	pembrolizumab	nivolumab + ipilimumab	camrelizumab
China	A, R	A, R	A, NR[a]	NA, NR	A, R	NA, NR	NA, NR	NA, NR	NA, NR	A, R
Japan	A, R	A, R	A, R	A, R	A, R	A, R	NA, NR	NA, NR	NA, NR	NA, NR
Korea	A, R	A, R	A, NR	A, NR	A, R	A, NR	NA[b], NR	NA, NR	NA, NR	NA, NR
Singapore	A, NR	A, NR	A, NR	A, NR	A, NR	A, NR	NA[c], NR	NA[c], NR	NA, NR	NA, NR
Taiwan	A, R	A, R	A, NR	A, NR	A, R	A, NR	A[d], NR	A[d], NR	NA, NR	NA, NR

[a] Patient access programme available (China Foundation of Cancer; http://www.cfchina.org.cn/show.php?contentid=2192, accessed on 20 January 2021 (in Mandarin))
[b] Off-label use is granted by the regulatory agency
[c] Readily available for use without approval
[d] Only for patients who received approval to use the drug before 1 April 2020 and meet requirements for application for renewal in follow-up evaluation

A, approved; HCC, hepatocellular carcinoma; NA, not approved; NR, not reimbursed; R, reimbursed

EXPERT OPINION (1/3): SORAFENIB & LENVATINIB REMAIN FIRST-LINE TREATMENT CHOICE

COR2ED®
THE HEART OF MEDICAL EDUCATION

Patients with advanced HCC

- poor liver function
- immune deficiency
- prior transplantation

→ immunotherapy is not appropriate →

sorafenib and lenvatinib remain treatments of choice until further clinical trial and real world evidence is obtained for immunotherapy approaches

- tumour-related symptoms
- high tumour volume

→ tumour shrinkage is important →

lenvatinib should be used

Both **sorafenib** and **lenvatinib** demonstrate **manageable toxicity profiles**

HCC; hepatocellular carcinoma

EXPERT OPINION (2/3): THE IMBRAVE150 TRIAL RESULTS ARE PRACTICE-CHANGING

COR2ED®
THE HEART OF MEDICAL EDUCATION

atezolizumab + bevacizumab = **new standard of care in the Asia-Pacific region**		
Strong and durable efficacy and safety profiles of the combination vs sorafenib in the first-line treatment of advanced HCC	May be **beneficial** for: – TACE-refractory BCLC-B HCC, or – TACE-unfeasible BCLC-B HCC	**PROs** in IMbrave150 trial: – reflect patients' experiences – have real-world validity

- **Local guidelines have been updated**:
  - In Taiwan: included the atezolizumab + bevacizumab combination for the treatment of unresectable HCC in patients who have not received prior systemic therapy and do not have a high risk of upper gastrointestinal bleeding
- **But**:
  - **Cost of the combination** could be an issue to provide patient access to the combination treatment

BCLC, Barcelona-Clinic Liver Cancer; HCC, hepatocellular carcinoma; PROs, patient-reported outcomes; TACE, transarterial chemoembolisation

EXPERT OPINION (3/3): PERSPECTIVES IN HCC

COR2ED®
THE HEART OF MEDICAL EDUCATION

The patient's perspective	The physician's perspective	The payer system's perspective
• Priority: Delay of disease progression • Priority: Prolongation of life	• Priority: Delay of disease progression • Importance of the multi-disciplinary tumour management board to define best treatment approach	• Balance between costs and benefits • Magnitude of benefit relative to the cost considered when assessing novel therapies

HCC, hepatocellular carcinoma

WHAT'S NEXT? ONGOING PHASE 3 CLINICAL TRIALS IN FIRST-LINE SYSTEMIC THERAPY COMBINATIONS FOR ADVANCED OR UNRESECTABLE HCC

COR2ED®
THE HEART OF MEDICAL EDUCATION

Study Drug(s)	Control Arm	Key Eligibility Criteria	Clinical Trials Identifier (Study Name)	Mechanism of Study Drug	Status
lenvatinib + pembrolizumab	lenvatinib + placebo	ECOG PS ≤1, BCLC stage B or C, CP A, ≥1 measurable lesion	NCT03713593 (LEAP-002)	MKI Anti-PD1	Active, not recruiting
sintilimab + bevacizumab biosimilar IBI305	sorafenib	ECOG PS ≤1, BCLC stage B or C, CP score ≤7, ≥1 measurable lesion	NCT03794440 (ORIENT-32)	Anti-PD1 Anti-VEGF	Active, not recruiting
atezolizumab + bevacizumab	sorafenib	ECOG PS ≤1, CP A, ≥1 measurable lesion	NCT03434379 (IMbrave150)	Anti-PDL1 Anti-VEGF	Active, not recruiting
cabozantinib + atezolizumab	sorafenib	ECOG PS ≤1, BCLC stage B or C, CP A, measurable disease	NCT03755791 (COSMIC-312)	Anti-VEGFR Anti-PDL1	Recruiting
camrelizumab (SHR-1210) + apatinib	sorafenib	ECOG PS ≤1, BCLC stage B or C, CP A, ≥1 measurable lesion	NCT03764293	Anti-PD1 Anti-VEGFR2	Recruiting
camrelizumab (SHR-1210) + FOLFOX4	Placebo + FOLFOX4	ECOG PS ≤1, CP score ≤7, measurable disease	NCT03605706	Anti-PD1 Chemotherapy	Recruiting
durvalumab ± tremelimumab	sorafenib	ECOG PS ≤1, BCLC stage B or C, CP A	NCT03298451 (HIMALAYA)	Anti-PDL1 Anti-CTLA4	Recruiting
IBI310 + sintilimab	sorafenib	ECOG PS ≤1, BCLC stage B or C, CP score ≤6, ≥1 measurable lesion	NCT04720716	Anti-CTLA4 Anti-PD1	Recruiting
lenvatinib ± CS1003	placebo	ECOG PS ≤1, BCLC stage B or C, CP A, ≥1 measurable lesion	NCT04194775	MKI Anti-PD1	Recruiting
nivolumab + ipilimumab	sorafenib or lenvatinib	ECOG PS ≤1, CP A, ≥1 measurable lesion	NCT04039607 (CheckMate 9DW)	Anti-PD1 Anti-CTLA4	Recruiting
SCT-I10A + bevacizumab biosimilar SCT-510	sorafenib	ECOG PS ≤1, BCLC stage B or C, CP score ≤7, ≥1 measurable lesion	NCT04560894	Anti-PD1 Anti-VEGF	Recruiting
penpulimab injection + anlotinib	sorafenib	ECOG PS ≤1, BCLC stage B or C, CP score ≤7, ≥1 measurable lesion	NCT04344158	Anti-PD1 MKI	Not yet recruiting
HLX10 + HLX04	sorafenib	BCLC stage B or C, ≥1 measurable lesion	NCT04465734	Anti-PD1 Anti-VEGF	Not yet recruiting

BCLC, Barcelona-Clinic Liver Cancer; CP, Child-Pugh; CTLA4, cytotoxic T-lymphocyte antigen 4; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX4, folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin; HCC, hepatocellular carcinoma; MKI, multikinase inhibitor; PD1, programmed death 1; PDL1, programmed death ligand 1; VEGF, vascular endothelial growth factor; VEGFR; vascular endothelial growth factor receptor

CONCLUSION

- **IMbrave150 study – significantly improved survival with atezolizumab + bevacizumab versus sorafenib**
  - effective new treatment option – potential to become the standard of care

- **Asia-Pacific region: complexity of therapeutic decision-making for advanced HCC is increasing**
  - variety of healthcare systems, treatment guidelines, approval patterns
- **Key unmet need: identification of patients who will benefit from the combination**
  - ideally through characterisation of validated prognostic biomarkers
- Treatment options increasing – need to optimise treatment sequencing for best outcomes

- If immunotherapy is not appropriate, sorafenib and lenvatinib remain first-line treatments of choice

HCC, hepatocellular carcinoma

COR2ED®

THE HEART OF MEDICAL EDUCATION

COR2ED
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

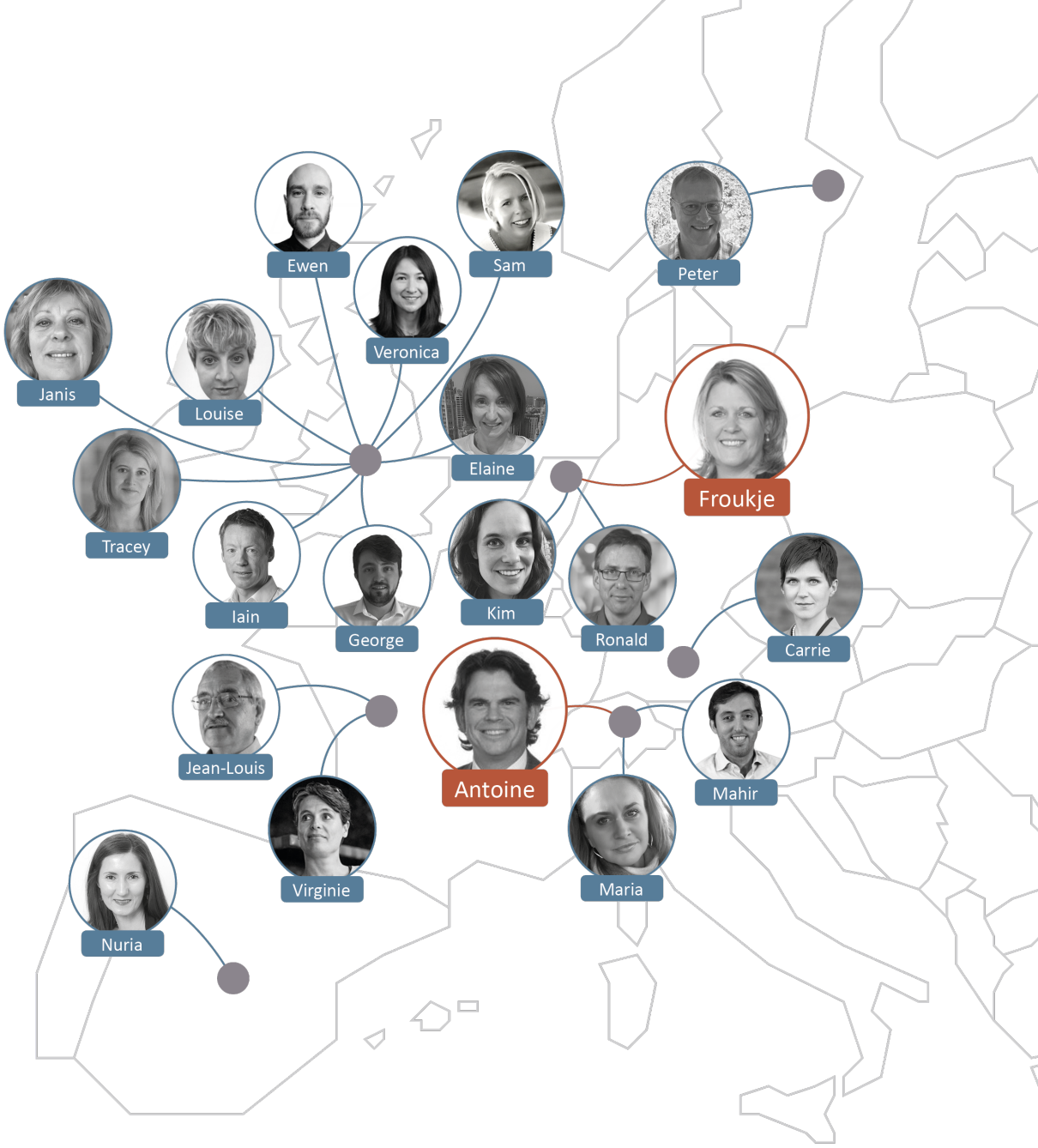
antoine.lacombe@cor2ed.com

Connect on
LinkedIn @COR2ED

Watch on
Vimeo @COR2ED

Visit us at
cor2ed.com

Follow us on
Twitter @COR2EDMedEd



Heading to the heart of Independent Medical Education Since 2012