
HCC
connect®
POWERED BY COR2ED

EXPERTS KNOWLEDGE SHARE

APPROPRIATE SELECTION OF PATIENTS FOR COMBINATION IMMUNOTHERAPY IN HCC: THE NOW AND THE NEXT

Prof. Peter Galle, Prof. Sammy Saab
and Prof. Amit Singal

Tuesday, May 11th 2021

EXPERTS KNOWLEDGE SHARE

HCC connect®
POWERED BY COR2ED

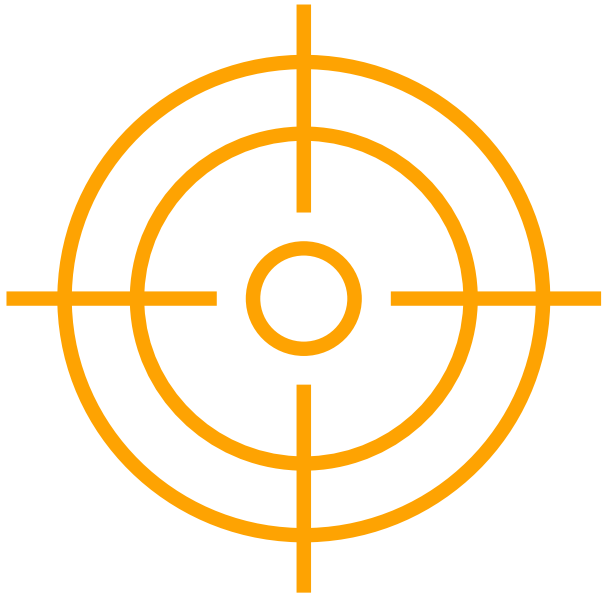
APPROPRIATE SELECTION OF PATIENTS FOR COMBINATION IMMUNOTHERAPY IN HCC: THE NOW AND THE NEXT

YOUR OPPORTUNITY TO **DISCUSS AND SHARE LEARNINGS** ON A CHALLENGING TOPIC WITHIN THE AREA OF HCC

A CHANCE TO HEAR THE **VIEWS OF EXPERTS** AND ALLOW THEM TO ANSWER THE QUESTIONS THAT ARE IMPORTANT TO YOU

REVIEW AND DISCUSS **PATIENT CASE STUDIES**, USING THE QUESTIONS THAT YOU HAVE SENT IN ADVANCE OF THIS EVENT

EXPERTS KNOWLEDGE SHARE EDUCATIONAL OBJECTIVES



To provide insights into the combination therapy for unresectable or advanced HCC patients, covering both approved therapies and those that are in clinical development

To define the HCC patient population who should benefit most from each available treatment option based on efficacy and safety profiles

To provide guidance on treatment sequencing

INTRODUCING THE SCIENTIFIC COMMITTEE

Peter Galle, MD, PhD

Department of Gastroenterology and Hepatology
University Medical Center Mainz
Mainz, Germany

Sammy Saab, MD

Department of Internal Medicine and Surgery
Head, Outcomes Research in Hepatology
David Geffen School of Medicine at UCLA

Amit Singal, MD, M.S

Department of Internal Medicine
UT Southwestern Medical Center
Dallas, USA

DISCLAIMER

This meeting is based on an independent medical educational grant from Bayer. The programme is therefore independent; the content is not influenced by Bayer and is the sole responsibility of the experts

Please note:

The views expressed within this presentation are the personal opinions of the experts. They do not necessarily represent the views of the experts' academic institutions or the rest of the faculty

EXTENDING THE REACH FOR THOSE NOT ABLE TO ATTEND TODAY

Experts Knowledge Share (EKS)

Newsletter

Newsletter #1:
Summarising video and slides from EKS

e-learning

Newsletter #2:
Link to e-learning:

- Videos, Slides and Supporting reading material
- Assessment test to obtain continuing medical education (CME) credit

EXPERTS KNOWLEDGE SHARE AGENDA

Appropriate selection of patients for combination immunotherapy in HCC: the now and the next

HCC connect® POWERED BY COR2ED

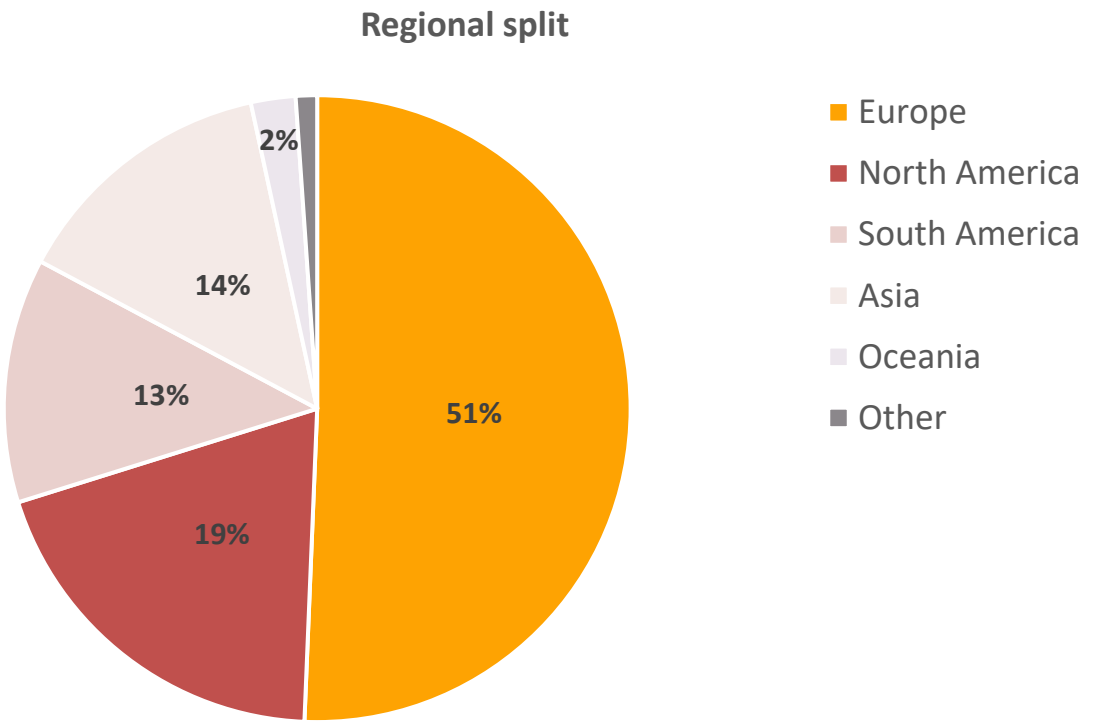
Time	Topic	Facilitator
5 minutes	Welcome and introductions	Peter Wallich COR2ED
15 minutes	Treating advanced and unresectable HCC today	Peter Galle
15 minutes	Sequencing guidelines in advanced and unresectable HCC: where do we stand?	Amit Singal
15 minutes	Stratification of patients with HCC: who needs what?	Sammy Saab
5 minutes	Lead-in to break-out sessions	Mahir Karababa COR2ED
20 minutes	Three break-out sessions Groups discussing questions and case studies and sharing experience	All
10 minutes	A look to future treatments and closing remarks	Peter Galle
5 minutes	Close	Peter Wallich COR2ED

HCC, hepatocellular carcinoma

PRE-MEETING SURVEY RESPONSES

A GLOBAL AUDIENCE

- Over 30 countries represented, spanning all regions
- Hepatologists and Oncologists primarily (50%) but also Haematology (16%) and other specialties



Source: Registrations (N=94) per 9 May 2021

EXPERTS KNOWLEDGE SHARE

TREATING ADVANCED AND UNRESECTABLE HCC TODAY

Prof. Peter Galle
Department of Gastroenterology and Hepatology
University Medical Center Mainz, Mainz, Germany

DISCLOSURES

- Adaptimmune
- Bayer
- BMS
- AstraZeneca
- Sirtex
- MSD
- Eisai
- Ipsen
- Roche
- Lilly
- Guerbet

HEPATOCELLULAR CARCINOMA

HCC connect®
POWERED BY COR2ED

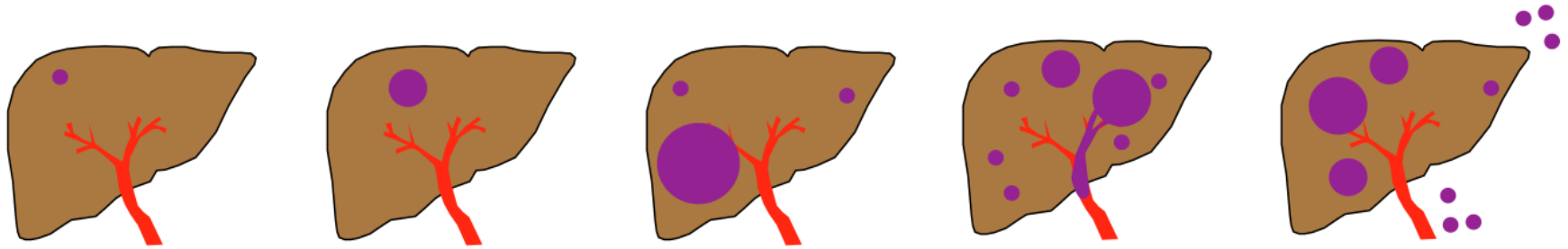
DIAGNOSIS

Screening → Symptoms

STAGE

Very Early | Early | Intermediate | Advanced

TUMOUR BURDEN



TREATMENT

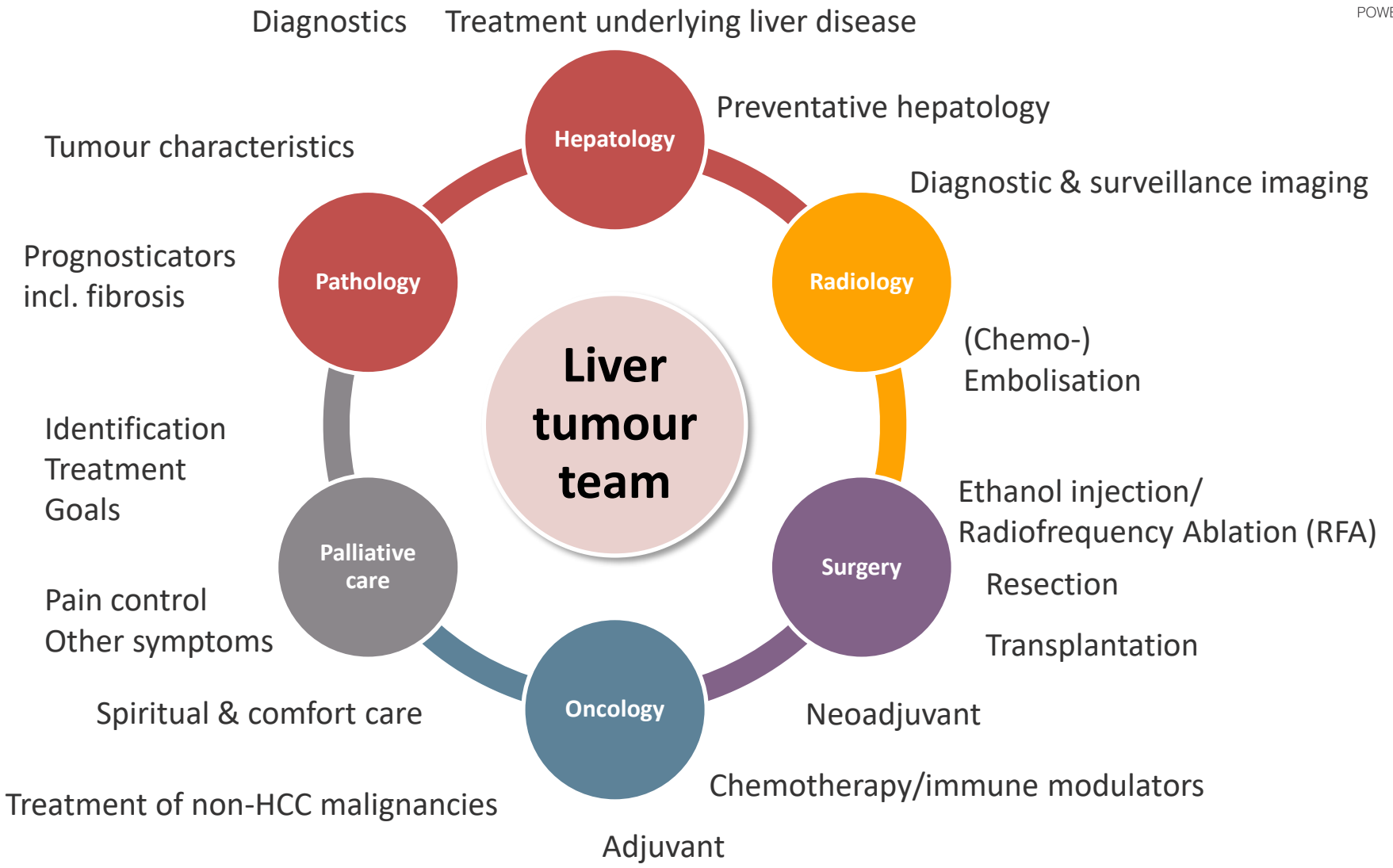
Resection Ablation ← Intra-arterial Therapies → Systemic Therapies

CIRRHOSIS

- Multifocal hepatocarcinogenesis (higher recurrence rates)
- Portal hypertension & impaired hepatic function (competing risk for death and toxicities)

Modifed from Sangro. ASCO GI 2019

MULTI-DISCIPLINARY TEAM APPROACH IN HCC PATIENTS



HCC, hepatocellular carcinoma

THE HCC SYSTEMIC TREATMENT LANDSCAPE HAS RAPIDLY EVOLVED SINCE 2017

HCC connect® POWERED BY COR2ED

First-line therapies

Nov 2007
Sorafenib approved for patients with uHCC

Apr 2017
Regorafenib approved for patients with HCC previously treated with sorafenib[2]

Sep 2017
Accelerated FDA approval of nivolumab* for patients with HCC previously treated with sorafenib[3]

Aug 2018
Lenvatinib approved by the FDA and EMA for patients with uHCC based on the REFLECT study results[4,5]

Nov 2018
Pembrolizumab‡ granted FDA accelerated approval for patients with HCC previously treated with sorafenib based on KEYNOTE-224[6]

Jan 2019
Cabozantinib approved by both the EMA (Nov 2018) and FDA (Jan 2019) for patients with HCC previously treated with sorafenib based on CELESTIAL[7,8]

May 2019
Ramucirumab† approved by both the FDA (May 2019) and EMA (July 2019) for patients with HCC previously treated with sorafenib, with AFP levels ≥400 ng/mL based on REACH-2[9,10]

Mar 2020
Nivolumab + ipilimumab received accelerated approval by the FDA for patients with HCC previously treated with sorafenib based on CheckMate-040[11]

Mar 2020
Camrelizumab received NMPA approval for patients with HCC previously treated with sorafenib and/or oxaliplatin systemic chemotherapies based on a phase 2 study (NCT02989922)[13]

May/Nov 2020
Atezolizumab + bevacizumab approved by the FDA, EMA, and others for patients with uHCC based on the IMbrave150[12]

Second-line therapies

Negative phase 3 trials in gold text.

*CheckMate-459: Nivolumab did not achieve statistical significance for the primary endpoint of OS vs sorafenib[19]; †Patients with AFP ≥400 ng/mL; ‡ Pembrolizumab failed to significantly improve OS and PFS (co-primary endpoints) vs placebo in the phase 3 KEYNOTE-240 trial[20,21]

AFP, alpha-fetoprotein; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; NMPA, National Medical Products Administration; OS, overall survival; PFS, progression-free survival; uHCC, unresectable HCC

1. Nexavar (sorafenib) Full Prescribing Information. Bayer HealthCare Pharmaceuticals, Whippany, NJ. 2020 (accessed May 2020); 2. FDA regorafenib in HCC press release. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm555608.htm (accessed May 2020); 3. FDA press release. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm577166.htm (accessed May 2020); 4. FDA press release. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm617185.htm (accessed May 2020); 5. Merck press release. Available from: https://investors.merck.com/news/press-release-details/2018/Eisai-and-Merck-Announce-European-Commission-Grants-Marketing-Authorization-for-LENVIMA-lenvatinib-as-First-Line-Treatment-in-Adults-with-Advanced-or-Unresectable-Hepatocellular-Carcinoma/default.aspx (accessed May 2020); 6. FDA press release. Available from: https://www.fda.gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma (accessed May 2020): 7. Ipsen press release. Available from: https://www.ipsen.com/media/press-relases/post_custom_datacustom_datapost_custom_datacustom_dataeuropean-commission-approves-ipsens-cabometyx-cabozantinib-for-the-treatment-of-hepatocellular-carcinoma-in/ (accessed May 2020); 8. FDA press release. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm629512.htm (accessed May 2020): 9. FDA press release https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ramucirumab-hepatocellular-carcinoma (accessed May 2020); 10. Cyramza (ramucirumab) EMA approval. EMA summary of opinion. Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-cyramza-ii-27_en.pdf (accessed May 2020); 11. FDA press release. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma (accessed May 2020); 12. ASCO Post press release. Available from: https://www.ascopost.com/news/may-2020/fda-approves-atezolizumab-plus-bevacizumab-for-patients-with-unresectable-or-metastatic-hcc/ (accessed May 2020); 13. Qin S. et al, Lancet Oncol. 2020;21(4):571-580

1ST-LINE SYSTEMIC TREATMENT OPTIONS

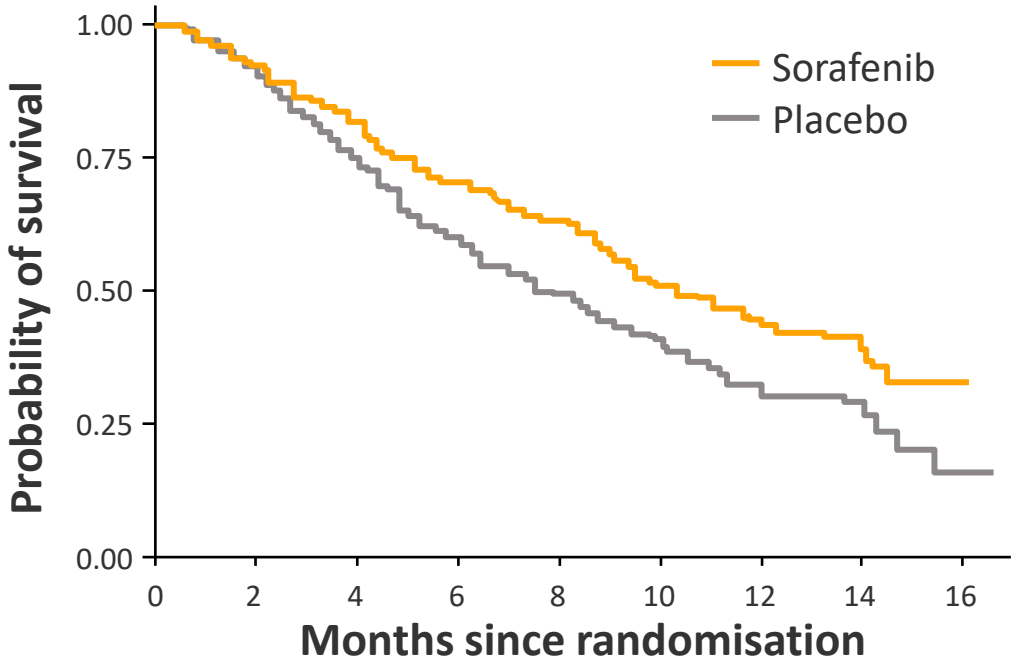
- Sorafenib
- Lenvatinib
- Atezolizumab + bevacizumab

1ST-LINE TREATMENT OPTIONS: SORAFENIB AND LENVATINIB

HCC connect® POWERED BY COR2ED

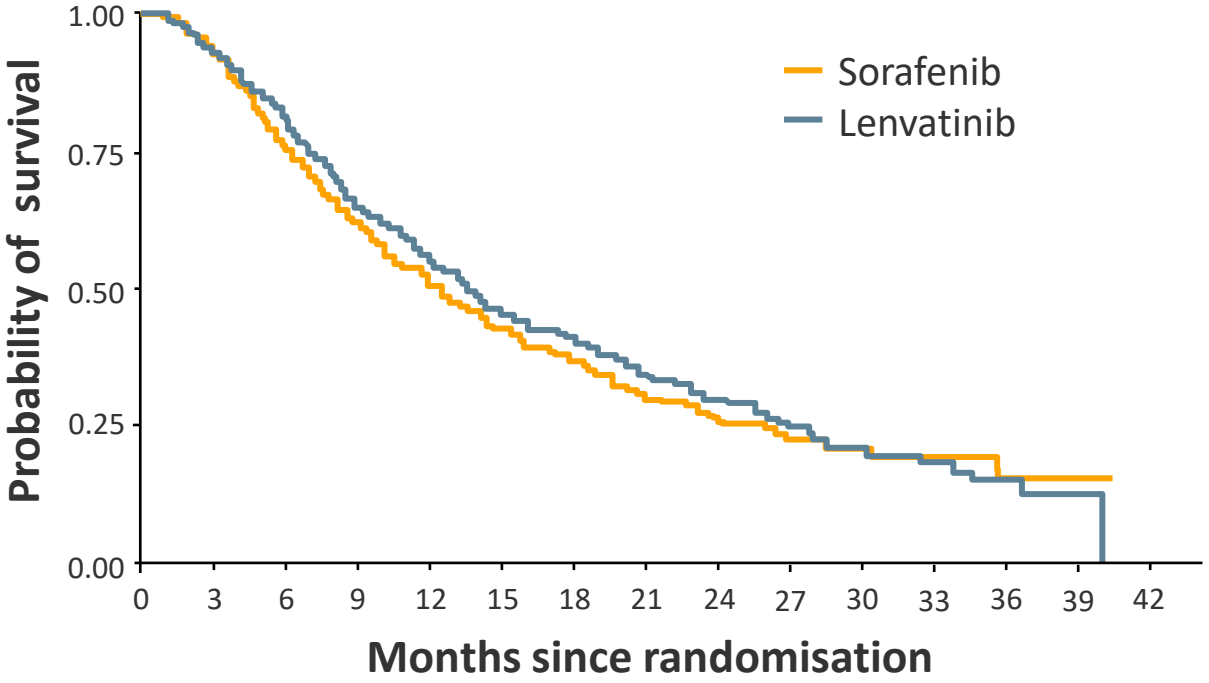
Overall survival in the SHARP trial[1]

Median OS: 10.7 months sorafenib *vs* 7.9 months placebo HR 0.69 (95% CI 0.55-0.87), p<0.001[1]



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)[2]

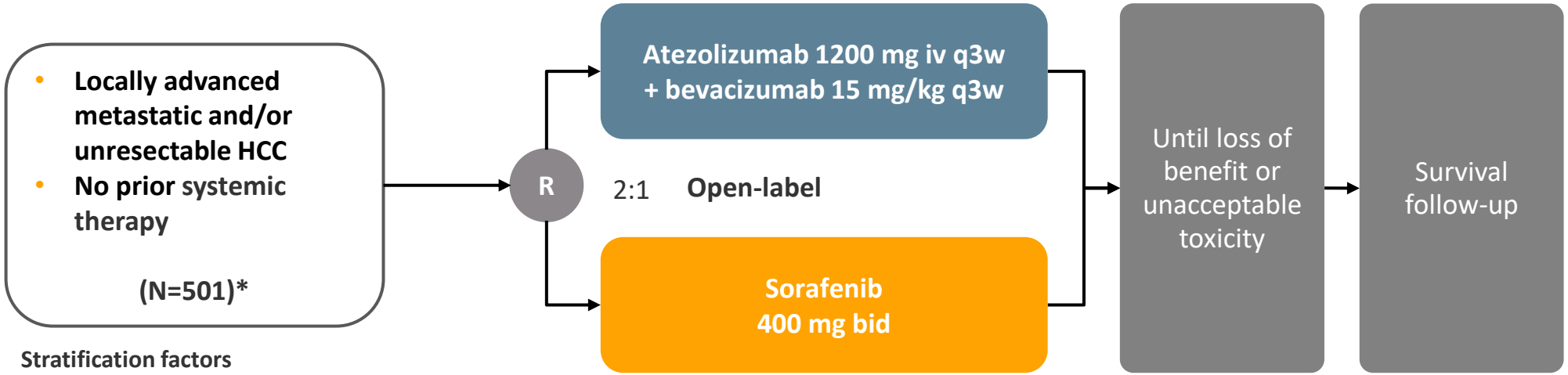


*REFLECT is a randomized phase 3 non-inferiority trial

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

1. Llovet JM, et al. N Engl J Med. 2008;359(4):378-90; 2. Kudo M, et al. Lancet. 2018;391(10126):1163-73

IMBRAVE150 IS A PHASE III TRIAL OF 1L ATEZOLIZUMAB + BEVACIZUMAB IN PATIENTS WITH UNRESECTABLE HCC[1]



Stratification factors

- **Region** (Asia excluding Japan‡/Rest of World)
- **ECOG PS** (0/1)
- **MVI** and/or **EHS** (presence/absence)
- **Baseline AFP** (<400/≥400 ng/ml)

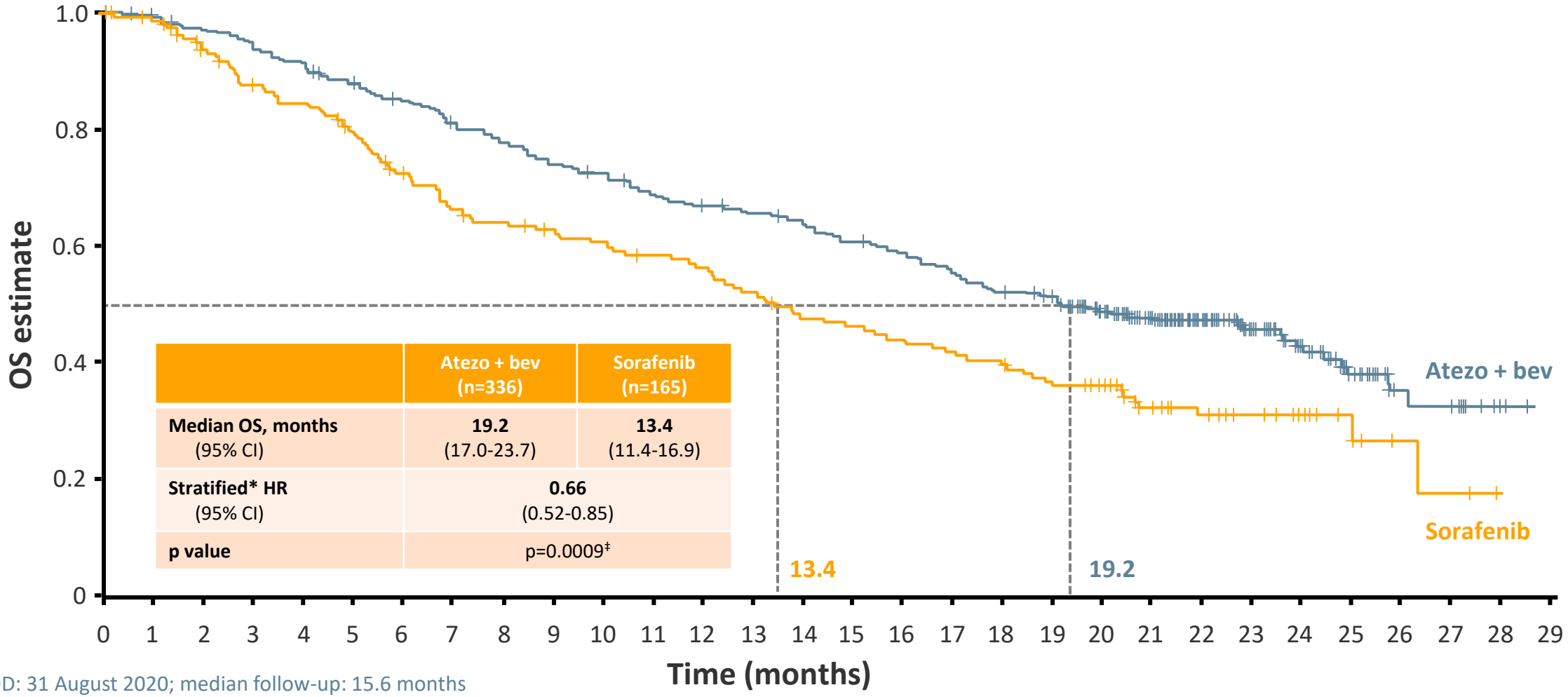
- **Co-primary endpoints:** OS and PFS IRF-assessed per RECIST v1.1
- **Key secondary endpoints** (in testing strategy): ORR IRF-assessed per RECIST v1.1 and HCC mRECIST

*There were an additional 57 Chinese patients in the China extension cohort that were not included in the global population/analysis; ‡Japan is included in Rest of World

1L, first-line; AFP, alpha-fetoprotein; bid, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; IRF, independent review facility; iv, intravenous; (m)RECIST, (modified) Response Evaluation Criteria in Solid Tumors; MVI, macrovascular invasion; ORR, objective response rate; OS, overall survival; q3w, every 3 weeks; PFS, progression-free survival.

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

UPDATED ANALYSIS: THE OS BENEFIT OBSERVED WITH ATEZOLIZUMAB + BEVACIZUMAB VS SORAFENIB WAS MAINTAINED



	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

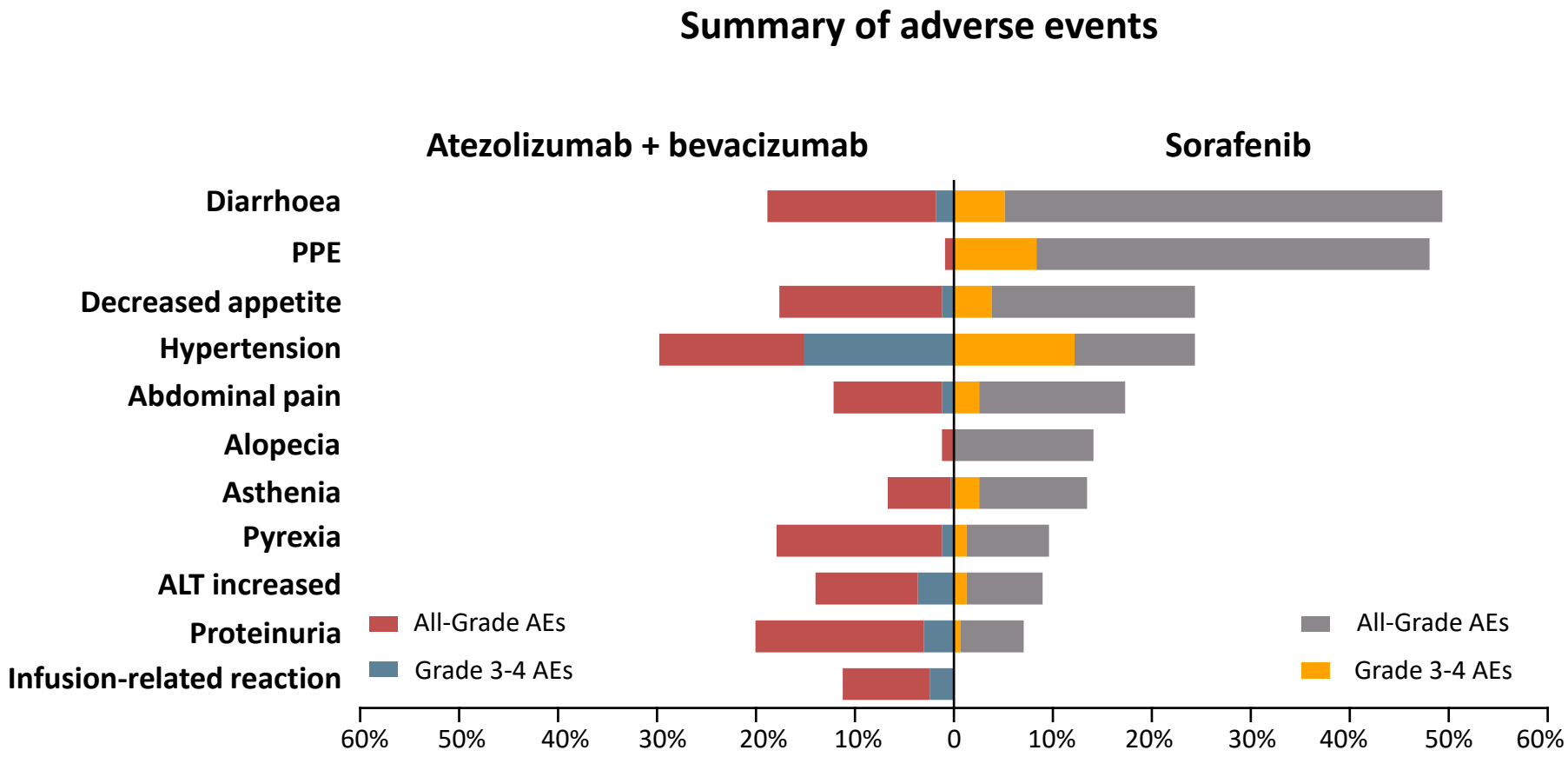
*Stratification factors included are geographic region (Asia excluding Japan vs RoW), AFP level (<400ng/mL vs ≥400ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS; ‡p value for descriptive purposes only

AFP, alpha-fetoprotein; Atezo, atezolizumab; bev, bevacizumab; CCOD, clinical cutoff date: CI, confidence interval; EHS, extrahepatic spread; HR, hazard ratio; 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)

SAFETY

≥10% FREQUENCY OF AEs IN EITHER ARM AND >5% DIFFERENCE BETWEEN ARMS



AE, adverse event; ALT, alanine aminotransferase; PPE, palmar-plantar erythrodysaesthesia

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

2ND-LINE SYSTEMIC TREATMENT OPTIONS

- Cabozantinib
- Regorafenib
- Ramucirumab
- Nivolumab
- Pembrolizumab
- Nivolumab + ipilimumab
- Camrelizumab

2ND-LINE TREATMENT OPTIONS: REGORAFENIB, CABOZANTINIB AND RAMUCIRUMAB*

	RESORCE[1]	CELESTIAL[2,3]	REACH-2[4]
Arms	Regorafenib vs placebo	Cabozantinib vs placebo	Ramucirumab vs placebo
Targets	VEGFR 1-3, RAF, KIT, RET, PDGFR, TIE 2, FGFR1	VEGFR, MET, AXL	VEGFR2
Class	TKI	TKI	mAb
Administration	Oral	Oral	IV
Previous treatment	Sorafenib	Sorafenib	Sorafenib
Reason for discontinuation of 1st-line	**Radiological progression**	**Progression or intolerance**	**Progression or intolerance**
Line	**2nd**	**2nd and 3rd**	**2nd**
Biomarker	–	–	AFP ≥400 ng/mL

*Trials included different populations and should not be directly compared

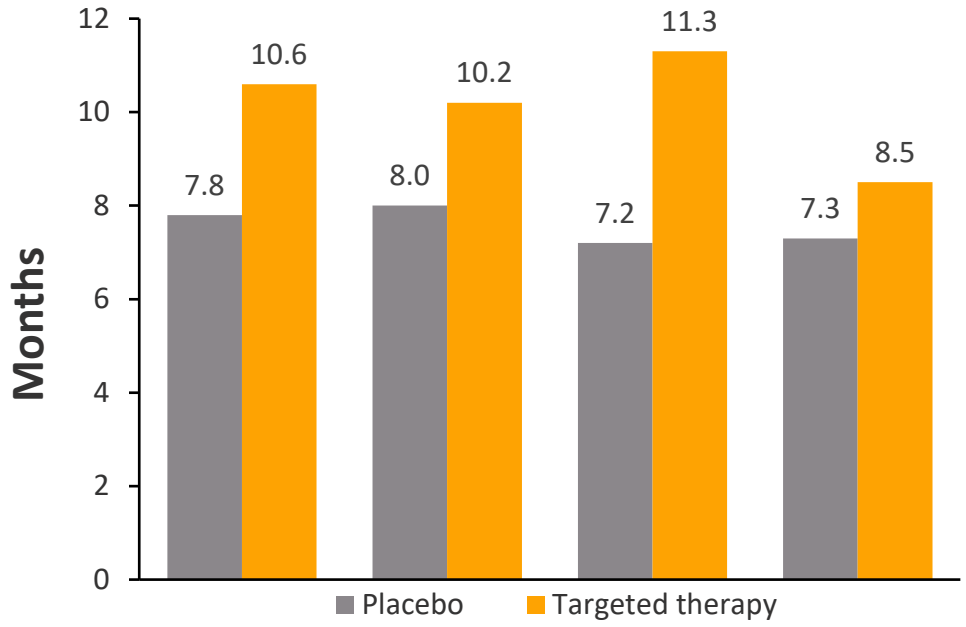
AFP, alpha-fetoprotein; AXL, anexelekto receptor; FGFR, fibroblast growth factor receptor; iv, intravenous; KIT, tyrosine-protein kinase gene; mAb, monoclonal antibody; MET, mesenchymal-epithelial transition factor; PDGFR, platelet-derived growth factor receptor; RAF, rapidly accelerated fibrosarcoma; RET, rearranged during transfection kinase; TIE, angiopoietin receptor; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

1. Bruix J, et al. Lancet. 2017;389:56-66; 2. Abou-Alfa GK, et al. N Engl J Med. 2018;379:54-63; 3. Kelley RK, et al. J Clin Oncol. 2018;36(15_suppl):4088-4088; 4. Zhu A, et al. Lancet Oncol. 2019;2:282-96

2ND-LINE TREATMENT OPTIONS: REGORAFENIB,[1] AND CABOZANTINIB[2,3] AND RAMUCIRUMAB,[4] VS PLACEBO

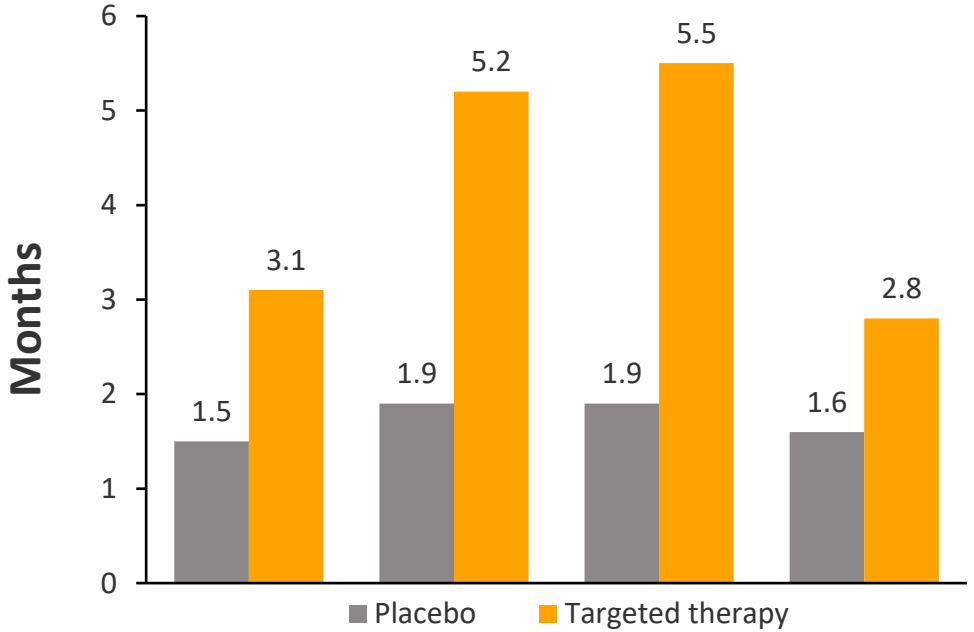
HCC connect® POWERED BY COR2ED

Overall survival



RESORCE	CELESTIAL	CELESTIAL**	REACH-2*
HR=0.63 95% CI: 0.50-0.79	HR=0.76 95% CI: 0.63-0.92	HR=0.70 95% CI: 0.55-0.88	HR=0.71 95% CI: 0.53-0.95

Progression-free survival



RESORCE	CELESTIAL	CELESTIAL**	REACH-2*
HR=0.46 95% CI: 0.37-0.56	HR=0.44 95% CI: 0.36-0.52	HR=0.40 95% CI: 0.32-0.50	HR=0.45 95% CI: 0.34-0.60

Trials included different populations and should not be directly compared

*AFP high population; **Pure 2nd-line population

AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio

1. Bruix J, et al. Lancet. 2017;389:56-66; 2. Abou-Alfa GK, et al. N Engl J Med. 2018;379:54-63; 3. Kelley RK, et al. J Clin Oncol. 2018;36(15_suppl):4088-4088; 4. Zhu A, et al. Lancet Oncol. 2019;2:282-96

2ND-LINE TREATMENT OPTIONS: RESORCE, CELESTIAL AND REACH-2 SAFETY SUMMARY

	RESORCE[1] (regorafenib)	CELESTIAL[2] (cabozantinib)	REACH-2[3,4] (ramucirumab)
Discontinuation due to TRAEs	10%	16%	11%
Dose modification due to AEs	68%	62%	35%
Median duration of treatment	3.6 months	3.8 months	2.8 months (AFP high)
Grade ≥3 TEAEs	67%	68%	59%
Toxicities (≥10%, grade ≥3)	Skin reactions, hypertension, increased bilirubin, AST increase	Skin reactions, hypertension, AST increase, fatigue, diarrhoea	Hypertension

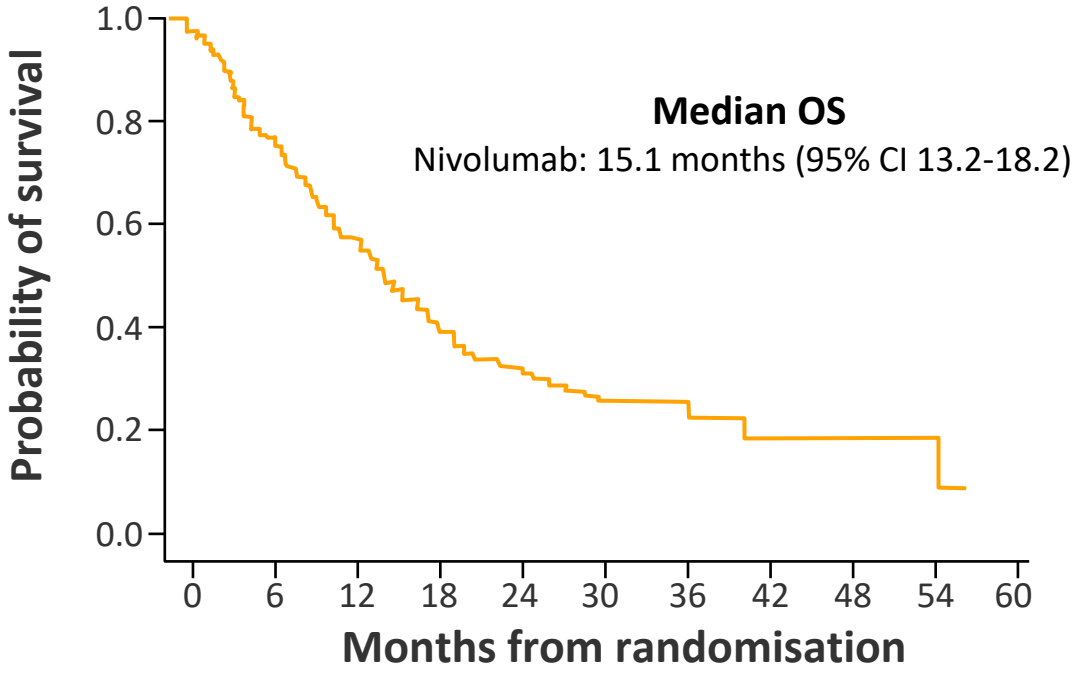
Trials included different populations and should not be directly compared

AE, adverse event; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; TEAE, treatment-emergent AE; TRAE, treatment-related AE

1. Bruix J, et al. Lancet. 2017;389:56-66; 2. Abou-Alfa GK, et al. N Engl J Med. 2018;379:54-63; 3. Zhu A, et al. Lancet Oncol. 2019;2:282-96; 4. Zhu A, et al. J Clin Oncol. 2018;36(15_suppl):4003-4003 (ASCO 2018 oral presentation)

2ND-LINE TREATMENT OPTIONS: NIVOLUMAB – RESULTS OF CHECKMATE-040

- This analysis of the Phase I/II study CheckMate-040 trial included 182 patients previously treated with sorafenib



Response, n (%)	Nivolumab (ITT) (n=182)
ORR	26 (14)
DCR	100 (55)

- Nivolumab had a manageable safety profile and no new signals were observed in patients with advanced HCC
- No maximum tolerated dose was found

CheckMate-040 did not meet the requirements for EMA approval of 2nd-line nivolumab in the treatment of HCC*

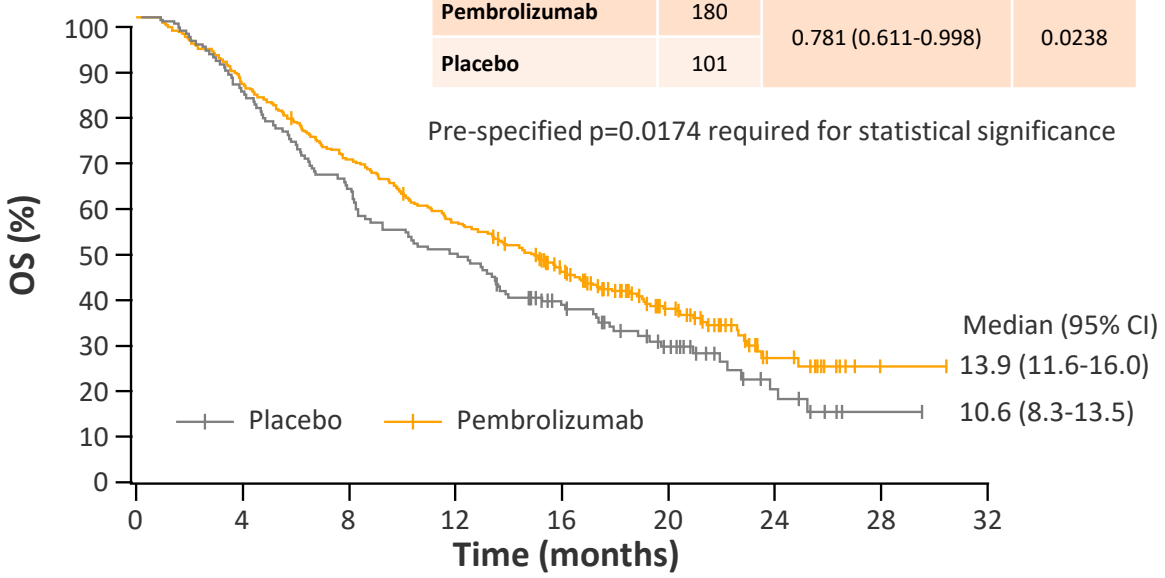
Nivolumab has been granted accelerated FDA approval in 2nd-line based on the results of CheckMate-040[2*]
In April 2021, FDA's Oncologic Drug Advisory Committee voted against the continued accelerated approval of nivolumab for the treatment of patients with HCC who were previously treated with sorafenib[3]

*Approved by the FDA, but not currently approved by the EMA
CI, confidence interval; DCR, disease control rate; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival
1. Yau T, et al. J Hepatol. 2019;71:543-52; 2. FDA Press release. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-hcc-previously-treated-sorafenib. Accessed May 2021; 3. https://www.fda.gov/media/147929/download. Accessed May 2021

2ND-LINE TREATMENT OPTIONS: PEMBROLIZUMAB – RESULTS OF KEYNOTE-240[1]

	Events	HR (95% CI)	p-value
Pembrolizumab	180	0.781 (0.611-0.998)	0.0238
Placebo	101		

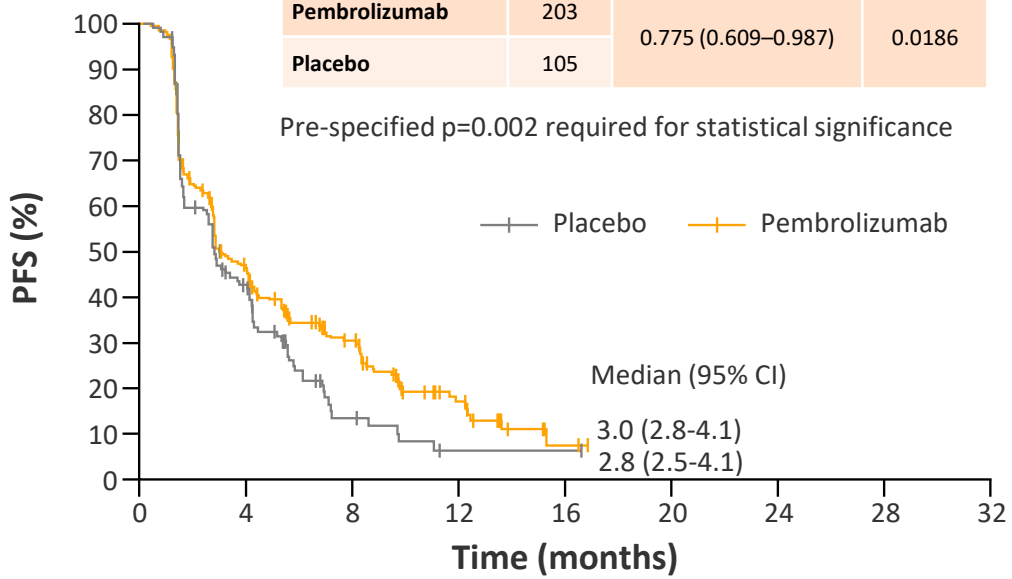
Pre-specified p=0.0174 required for statistical significance



KEYNOTE-240 did not meet the statistical criteria for either of the dual primary endpoints[2]

	Events	HR (95% CI)	p-value
Pembrolizumab	203	0.775 (0.609–0.987)	0.0186
Placebo	105		

Pre-specified p=0.002 required for statistical significance



Pembrolizumab received accelerated FDA approval in patients previously treated with sorafenib based on the results of KEYNOTE-224[3*]

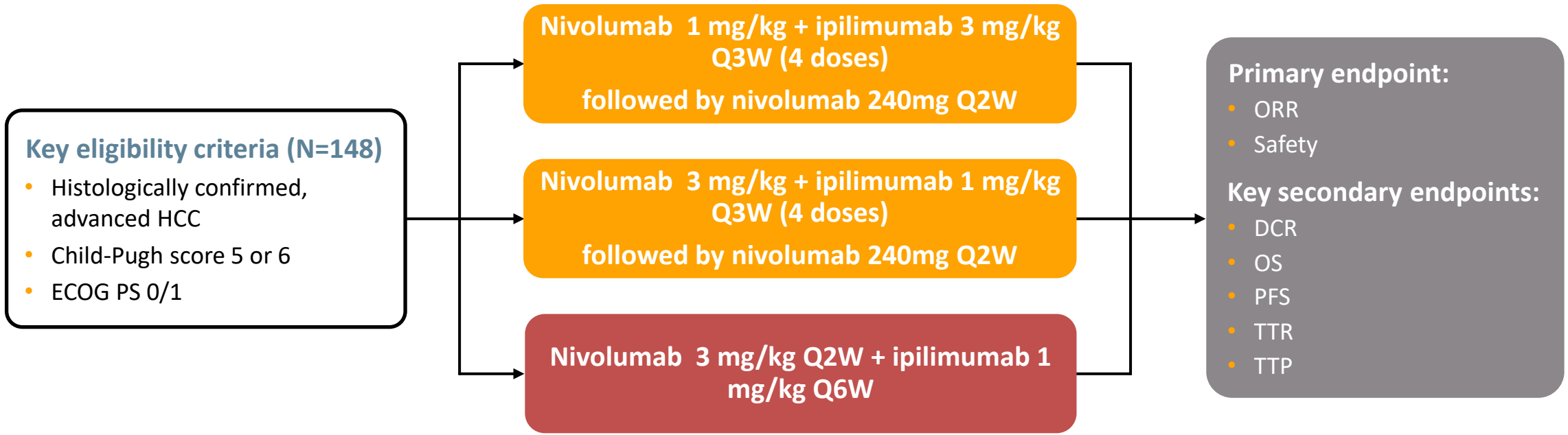
*Approved by the FDA, but not currently approved by the EMA

CI, confidence interval; FDA, Food and Drug Administration; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

1. NCT02702401. Available at clinicaltrials.gov. Accessed May 2021; 2. Finn R, et al. J Clin Oncol. 2020 20;38:193-202; 3. Pembrolizumab press release. Available at: www.fda.gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma. Accessed August 2020

2ND-LINE TREATMENT OPTIONS: NIVOLUMAB + IPILIMUMAB – CHECKMATE-040[1,2]

AIM: TO EVALUATE THE EFFICACY AND SAFETY OF 2L NIVOLUMAB + IPILIMUMAB IN SORAFENIB-TREATED PATIENTS WITH aHCC



2L, second-line; (a)HCC, (advanced) hepatocellular carcinoma; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; TTP, time to progression; TTR, time to response

1. NCT01658878. Available at clinicaltrials.gov. Accessed August 2020; 2. Yau T, et al. J Clin Oncol. 2019;37(15_suppl):4012-4012

2ND-LINE TREATMENT OPTIONS: NIVOLUMAB + IPILIMUMAB – CHECKMATE-040

	Arm A Nivo1/Ipi3 Q3W (n=50)	Arm B Nivo3/Ipi1 Q3W (n=49)	Arm C Nivo3 Q2W/Ipi1 Q6W (n=49)	Total (N=148)
ORR, n (%)	**16 (32)**	**15 (31)**	**15 (31)**	**46 (31)**
Complete response	4 (8)	3 (6)	0	7 (5)
Partial response	12 (24)	12 (24)	15 (31)	39 (26)
Stable disease	9 (18)	5 (10)	9 (18)	23 (16)
Progressive disease	20 (40)	24 (49)	21 (43)	65 (44)
Unable to determine	3 (6)	4 (8)	4 (8)	11 (7)
DCR, n (%)	27 (54)	21 (43)	24 (49)	72 (49)
Median TTR, months (range)	2.0 (1.1-2.8)	2.6 (1.2-5.5)	2.7 (1.2-8.7)	–
Median DoR, months (range)	17.5 (4.6-30.5+)	22.2 (4.2-29.9+)	16.6 (4.1+-32.0+)	–
ORR by investigator, n (%)	16 (32)	13 (27)	14 (29)	–

Nivolumab plus ipilimumab led to robust and durable responses in sorafenib-treated patients, with higher ORRs (>30% in each treatment arm) than the ORR observed with nivolumab monotherapy (14%)

The nivolumab plus ipilimumab combination led to clinically meaningful responses and had an acceptable safety profile in patients with previous exposure to sorafenib

DCR, disease control rate; DoR, duration of response; Ipi, ipilimumab; ORR, objective response rate; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; TTR, time to response; Nivo, nivolumab

Yau T, et al. J Clin Oncol. 2019;37(15_suppl):4012-4012 (ASCO 2019 oral presentation)

2ND-LINE TREATMENT OPTIONS: CAMRELIZUMAB (ANTI-PD-1 INHIBITOR)

HCC connect® POWERED BY COR2ED

OPEN-LABEL CHINESE MULTICENTER PHASE 2 STUDY (NCT02989922): 217 EVALUABLE PRETREATED PATIENTS WITH ADVANCED HCC WERE RANDOMLY ASSIGNED BETWEEN NOVEMBER 2016 AND NOVEMBER 2017 TO RECEIVE CAMRELIZUMAB AT 3 MG/KG EVERY 2 WEEKS (N=109) OR EVERY 3 WEEKS (N=108)

Cut off date: 16 November 2018	All treated patients (n=217)	Every 2 weeks (n=109)	Every 3 weeks (n=108)
Primary endpoints			
BICR-assessed objective response*, n (%, 95% CI)	32 (14.7%; 10.3-20.2)	13 (11.9%; 6.5-19.5)	19 (17.6%; 10.9-26.1)
6-month overall survival**, % (95% CI)	74.4% (68.0-79.7)	75.9% (66.6-82.9)	73.0% (63.6-80.4)
Secondary endpoints			
Disease control, n (%, 95% CI)	96 (44.2%; 37.5-51.1)	52 (47.7%; 38.1-57.5)	44 (40.7%; 31.4-50.6)
Median time to response, months (IQR)	2.0 (1.9-3.4)	2.0 (1.9-2.0)	2.1 (2.0-3.5)
Median duration of response, month (IQR)	NR (3.7-14.0)	NR (2.9-12.5)	NR (4.1-14.5)
Median OS, months (95% CI)	13.8 (11.5-16.6)	14.2 (11.5-NR)	13.2 (9.4-17.0)

Camrelizumab showed antitumour activity in pretreated Chinese patients with advanced HCC, preliminary survival benefit and a manageable safety profile

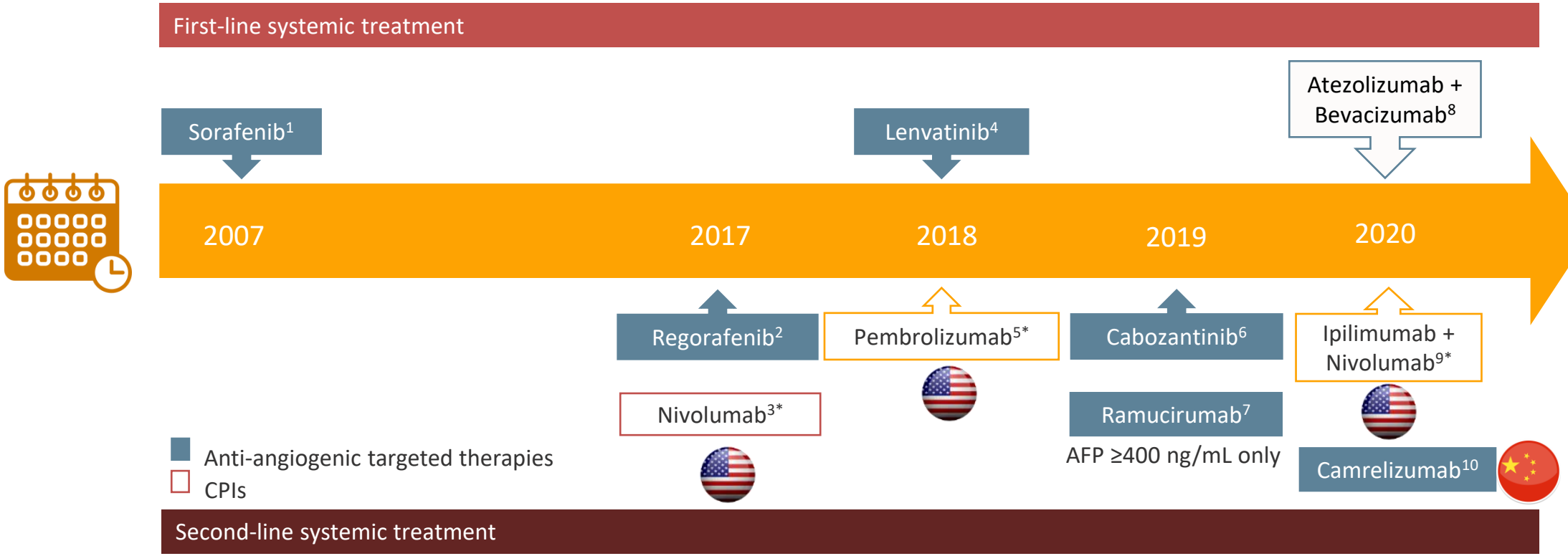
*Defined as the percentage of patients whose best overall response was confirmed complete or partial response; **Defined as cumulative overall survival at 6 months from the first dose

BICR, blinded independent central review; CI, confidence interval; HCC, hepatocellular carcinoma; IQR, interquartile range; NR, not reached; PD-1, programmed cell death 1

Qin S, et al. Lancet Oncol. 2020;21(4):571-80

CLOSING REMARKS

THE EVOLVING LANDSCAPE OF SYSTEMIC TREATMENT FOR HCC



*Approved by the FDA, but not currently approved by the EMA

AFP, alpha-fetoprotein; CPI, checkpoint inhibitor; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma

1. Nexavar Press release. Available at: www.drugs.com/nda/nexavar_070820.html. Accessed August 2020; 2. Regorafenib Press release. Available at: www.cancer.gov/news-events/cancer-currents-blog/2017/fda-regorafenib-liver. Accessed August 2020; 3. Opdivo Press release. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-hcc-previously-treated-sorafenib. Accessed August 2020; 4. Lenvatinib Press release. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-unresectable-hepatocellular-carcinoma. Accessed August 2020; 5. Pembrolizumab Press release. Available at: www.fda.gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma. Accessed August 2020; 6. Cabometyx Press release. Available at: www.fda.gov/drugs/fda-approves-cabozantinib-hepatocellular-carcinoma. Accessed August 2020; 7. Cyramza Press release. Available at: https://investor.lilly.com/news-releases/news-release-details/lillys-cyramzar-ramucirumab-becomes-first-fda-approved-biomarker. Accessed August 2020; 8. FDA Press release. Available at: www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-plus-bevacizumab-unresectable-hepatocellular-carcinoma. Accessed August 2020. 9. FDA Press release. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma. Accessed August 2020.
10. Qin S. et al, Lancet Oncol. 2020;21(4):571-580

EXPERTS KNOWLEDGE SHARE

SEQUENCING GUIDELINES IN ADVANCED AND UNRESECTABLE HCC: WHERE DO WE STAND?

Prof. Amit Singal
Department of Internal Medicine
UT Southwestern Medical Center
Dallas, USA

DISCLOSURES

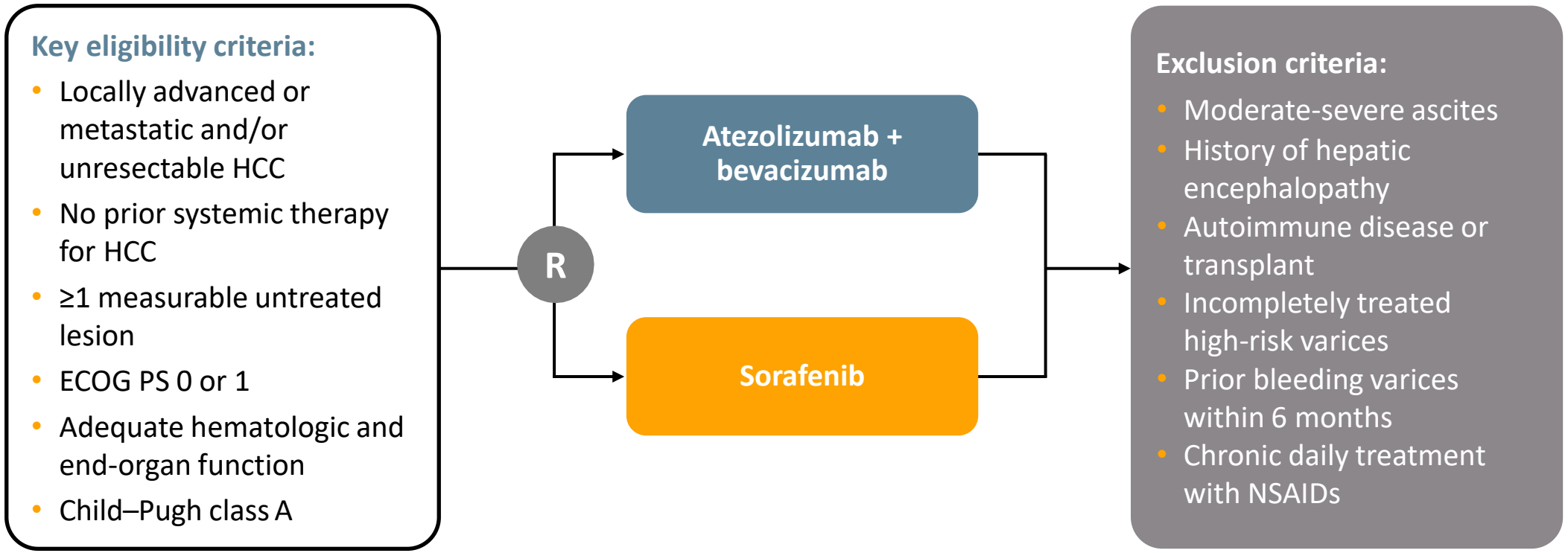
- Bayer
- Eisai
- Genentech
- AstraZeneca
- Exelixis
- BMS

SUMMARY OF NCCN: RECOMMENDATIONS

First-Line Therapy	Subsequent-Line Therapy
Preferred Regimens • Atezolizumab + bevacizumab • Sorafenib • Lenvatinib **Useful in Certain Circumstances** • Nivolumab	• Sorafenib • Lenvatinib • Regorafenib • Cabozantinib • Ramucirumab • Nivolumab • Pembrolizumab • Nivolumab + ipilimumab

NCCN, National Comprehensive Cancer Network
NCCN Guidelines. Hepatobiliary Cancers. V2.2021. Issued April 16, 2021

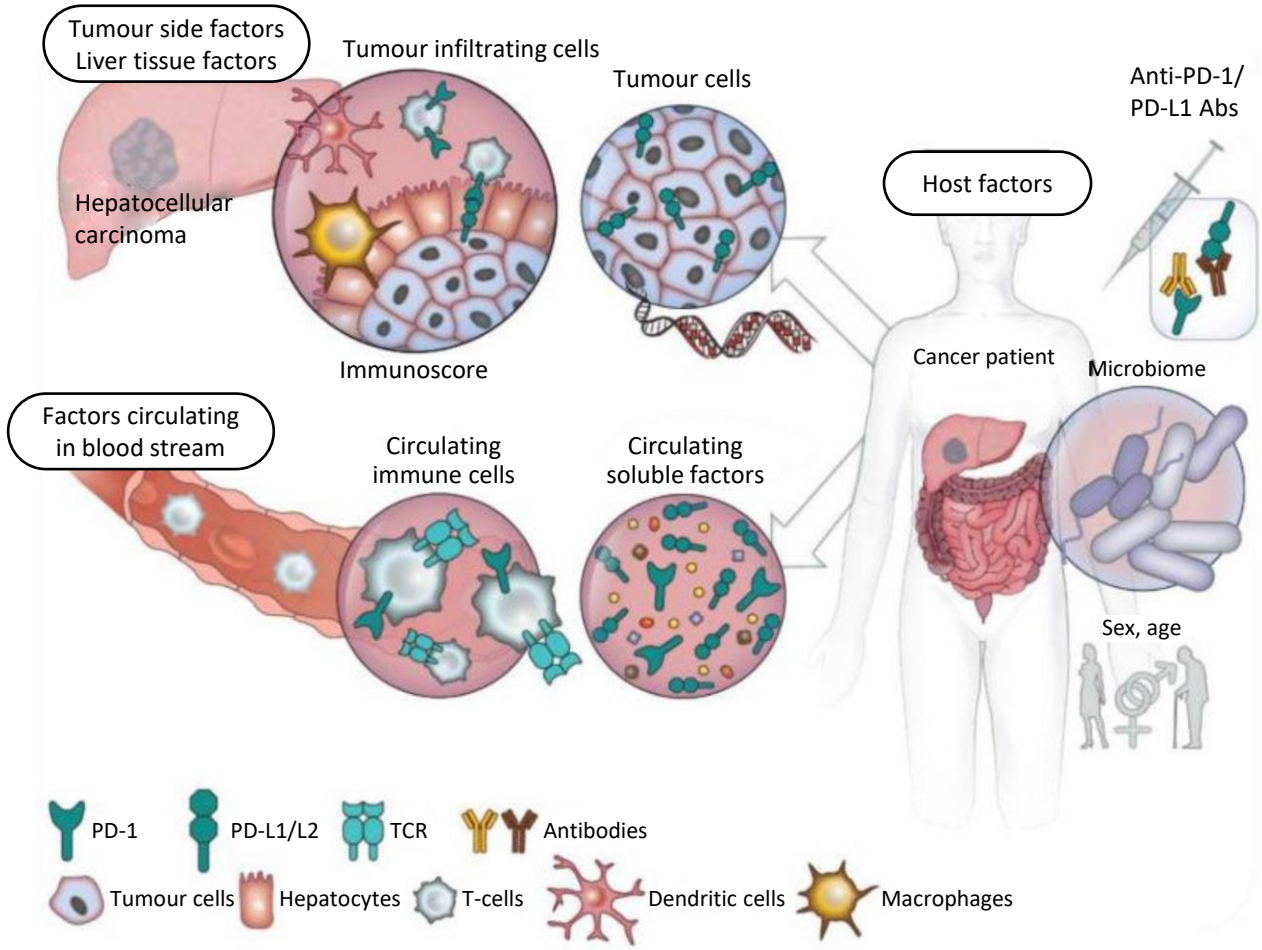
ATEZOLIZUMAB/BEVACIZUMAB WILL BE PREFERRED IN MOST BUT NOT ALL PATIENTS



ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; NSAIDs, nonsteroidal anti-inflammatory drugs

Finn RS, et al. N Engl J Med. 2020;382(20):1894-1905. Finn RS, et al. J Clin Oncol. 2021;39(3_suppl):267-267. Source: https://clinicaltrials.gov/ct2/show/NCT03434379.

SEVERAL TREATMENT RESPONSE BIOMARKERS OF INTEREST



Tumour and Immunologic Factors

- PD-L1 expression by tumour and immune infiltrate
- Features of intra-tumoural lymphoid infiltrates

Tumour mutations and microsatellite instability

- Tumour mutation burden
- MSI-high status

Circulating factors

- Circulating immune cells
- Circulating soluble factors, e.g. TGF-*B*
- Extracellular vesicles, such as exosomes

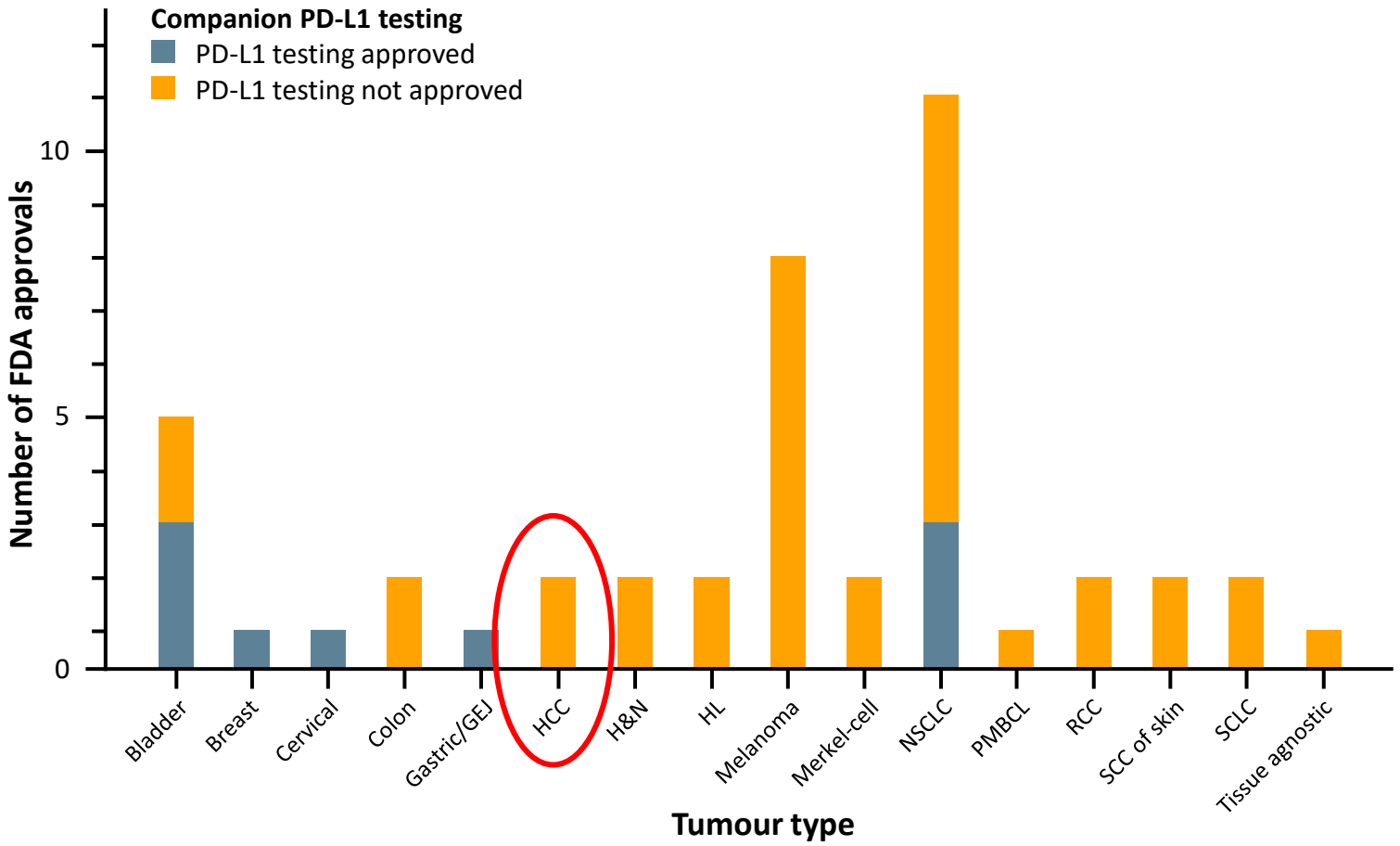
Host factors

- Male sex and older age
- Gut microbiome

MSI, microsatellite instability; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TGF, transforming growth factor; TCR, T-cell receptor

Jilkova ZM, et al. Cancers. 2019;11(10):1554

PD-L1: ROLE AS A TREATMENT RESPONSE BIOMARKER



- Among 45 approvals thru April 2019:
  - PD-L1 predictive in 28.9%
  - PD-L1 not predictive in 53.3%
  - PD-L1 not tested in 17.8%
- Heterogeneity in threshold, types of cells expressing PD-L1 (tumour infiltrating cells, tumour cells, or composite score) and companion diagnostics
- MSI has also been approved, albeit rare in HCC

FDA, Food and Drug Administration; GEJ, gastro-esophageal junction; H&N, head and neck; HCC, hepatocellular carcinoma; HL, Hodgkin's Lymphoma; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; PMBCL, primary mediastinal B-cell lymphoma; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer

Davis A, et al. J Immunother Cancer. 2019;7(1):278

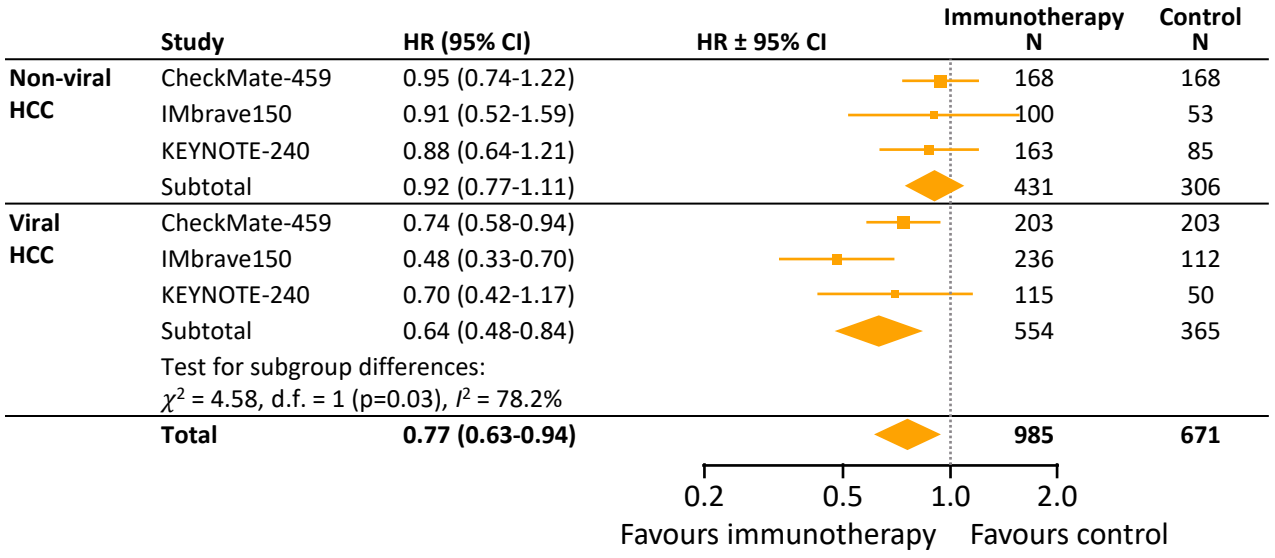
TKIs HIT DIFFERENT TARGETS BUT DOES NOT TRANSLATE TO PRACTICE

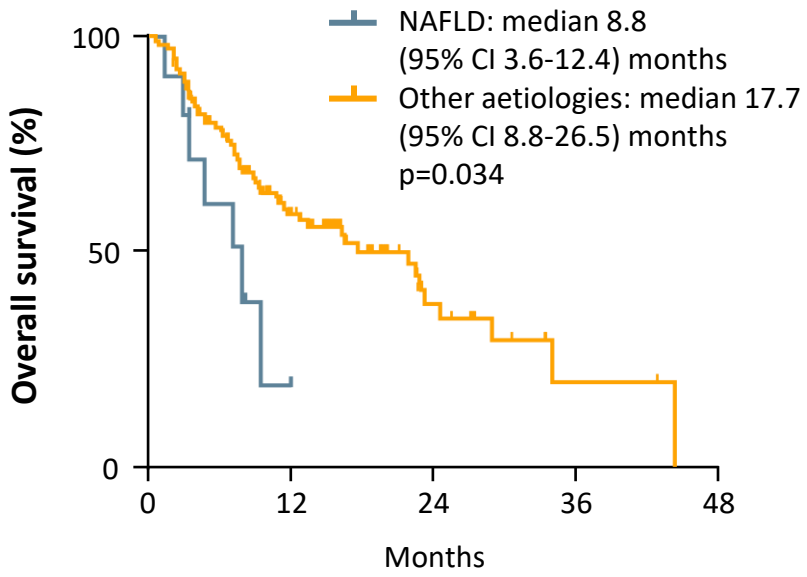
TKI	Therapy Line	VEGFA	VEGFR1	VEGFR2	VEGFR3	PDGFB	Other
Bevacizumab*	1st Line	X					
Sorafenib	1st Line		X	X	X	X	BRAF, FLT3, c-Kit, FGFR1
Lenvatinib	1st Line		X	X	X	X	**FGFR1,** Kit
Regorafenib	2nd Line		X	X	X	X	BRAF, Ret, Kit
Cabozantinib	2nd Line			X		X	**c-Met,** Ret, Kit, Flt-1/3/4, Tie2, and **AXL**
Ramucirumab	2nd Line			X			

*bevacizumab is approved in combination with atezolizumab for the treatment of patient with HCC in first line.

AXL, anexelekto receptor; BRAF, v-raf murine sarcoma viral oncogene homolog B1; FGFR, fibroblast growth factor receptor; FLT, fms-related tyrosine kinase; KIT, tyrosine-protein kinase; MET, mesenchymal-epithelial transition factor; PDGFB, platelet-derived growth factor subunit B; Ret, rearranged during transfection kinase; TIE, angiopoietin receptor; TKI, tyrosine kinase inhibitor; VEGFA, vascular endothelial growth factor A; VEGFR, vascular endothelial growth factor receptor

IS CIRRHOSIS ETIOLOGY ASSOCIATED WITH RESPONSE TO IMMUNE CHECKPOINT INHIBITORS?





- In preclinical HCC models in the setting of NASH, PD-1 inhibitors expanded $CD8^+$ T-cells but did not induce tumour regression, indicating impaired tumour immune surveillance

CI, confidence interval; d.f., degrees of freedom; HCC, hepatocellular carcinoma; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

Pfister D, et al. Nature. 2021;592(7854):450-6

CLINICAL FACTORS CAN HELP SELECT BETWEEN SORAFENIB AND LENVATINIB

	Sorafenib	Lenvatinib
Level of evidence	Phase 3	Phase 3
Inclusion criteria	Child A cirrhosis, ECOG 0-1	Child A cirrhosis, ECOG 0-1 Excluded patients with >50% liver involvement, main portal vein or bile duct invasion
Efficacy	Improved survival vs placebo	Non-inferior survival vs sorafenib Improved objective responses and time to progression compared to sorafenib
AE profile	Increased hand-foot skin reaction	Increased hypertension, proteinuria, anorexia
Logistics	Oral, twice daily Taken 1-2 hours removed from food	Oral, once daily Can be taken with or without food
Miscellaneous	Real-world effectiveness data in populations including Child B cirrhosis	

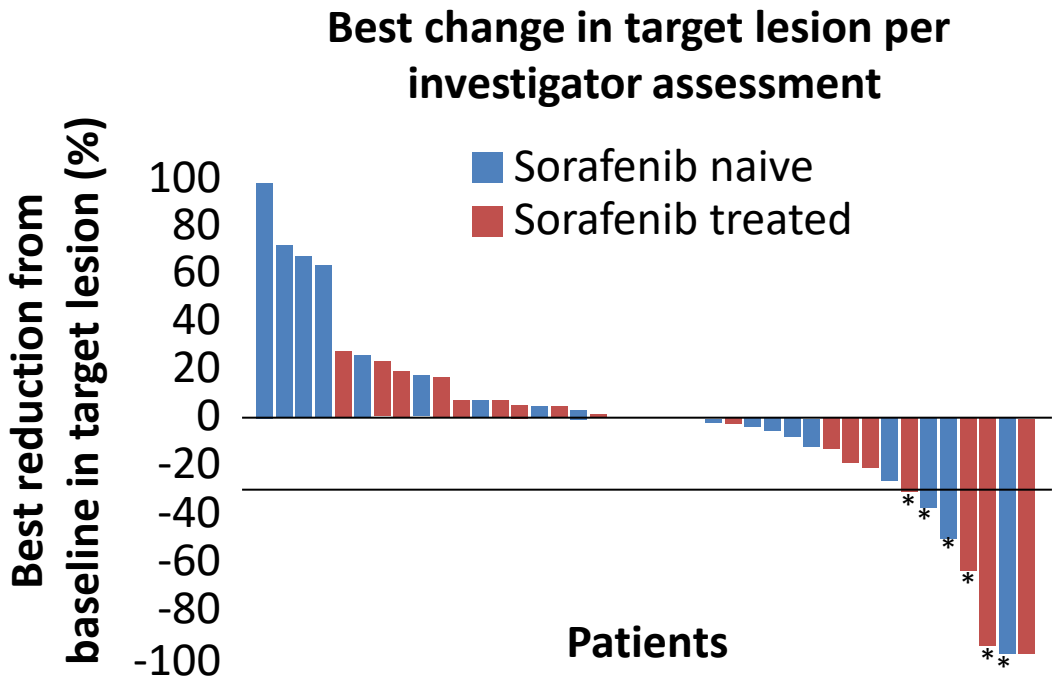
AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group Performance Status

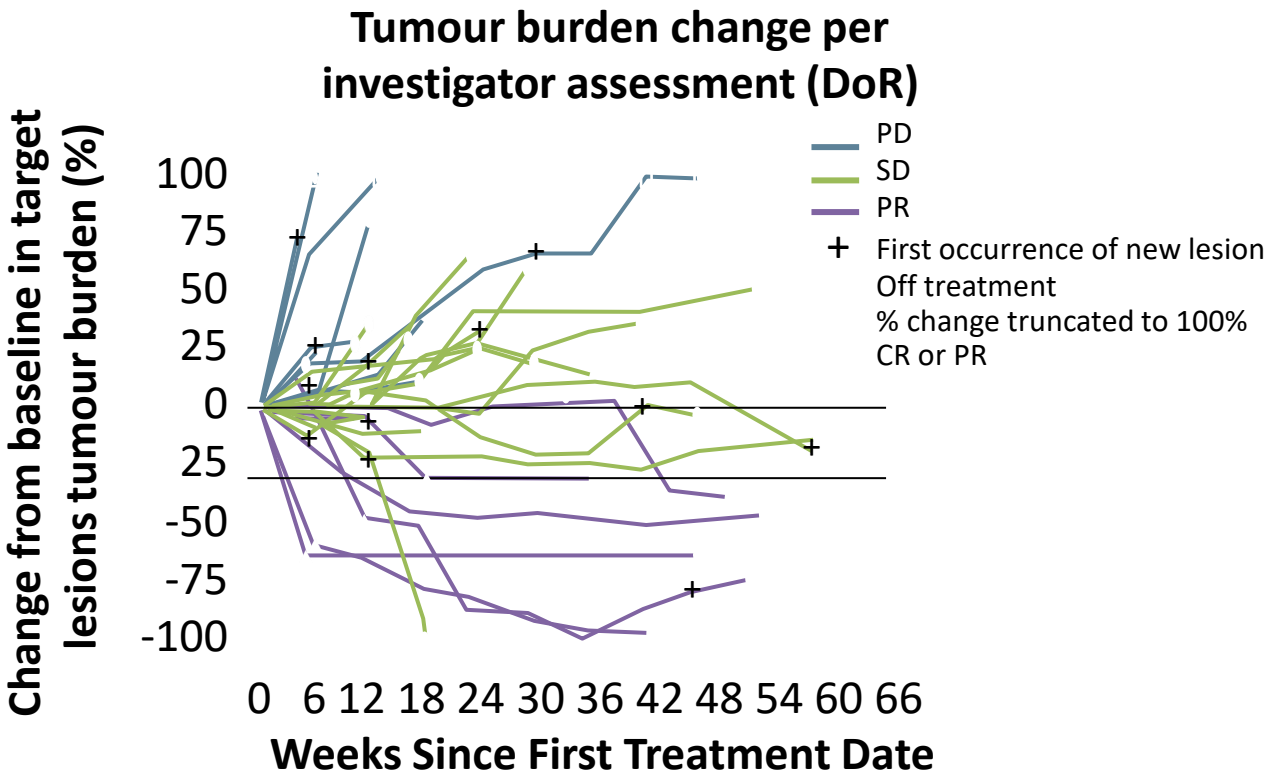
GIDEON PROVIDES REAL-WORLD DATA FOR SORAFENIB

	Child-Pugh A (N=1,968)	Child-Pugh B (N=666)	Child-Pugh C (N=74)
Median treatment duration,* weeks	17.6	9.9	5.6
Initial dose, n (%)			
800 mg	1,415 (72)	464 (70)	46 (62)
400 mg	482 (25)	173 (26)	21 (28)
Dose reduction rate, n (%)	**784 (40)**	**194 (29)**	**19 (26)**
AEs (all grades), n (%)	1,653 (84)	590 (89)	68 (92)
All grade 3 or 4 AEs, n (%)	**638 (33)**	**210 (32)**	**13 (18)**

*Three patients recorded as having Child-Pugh B but specific score not recorded
AE, adverse event
Marrero JA, et al. J Hepatol. 2016;65(6):1140-7

CHECKMATE-040: NIVOLUMAB IN CHILD-PUGH B COHORT



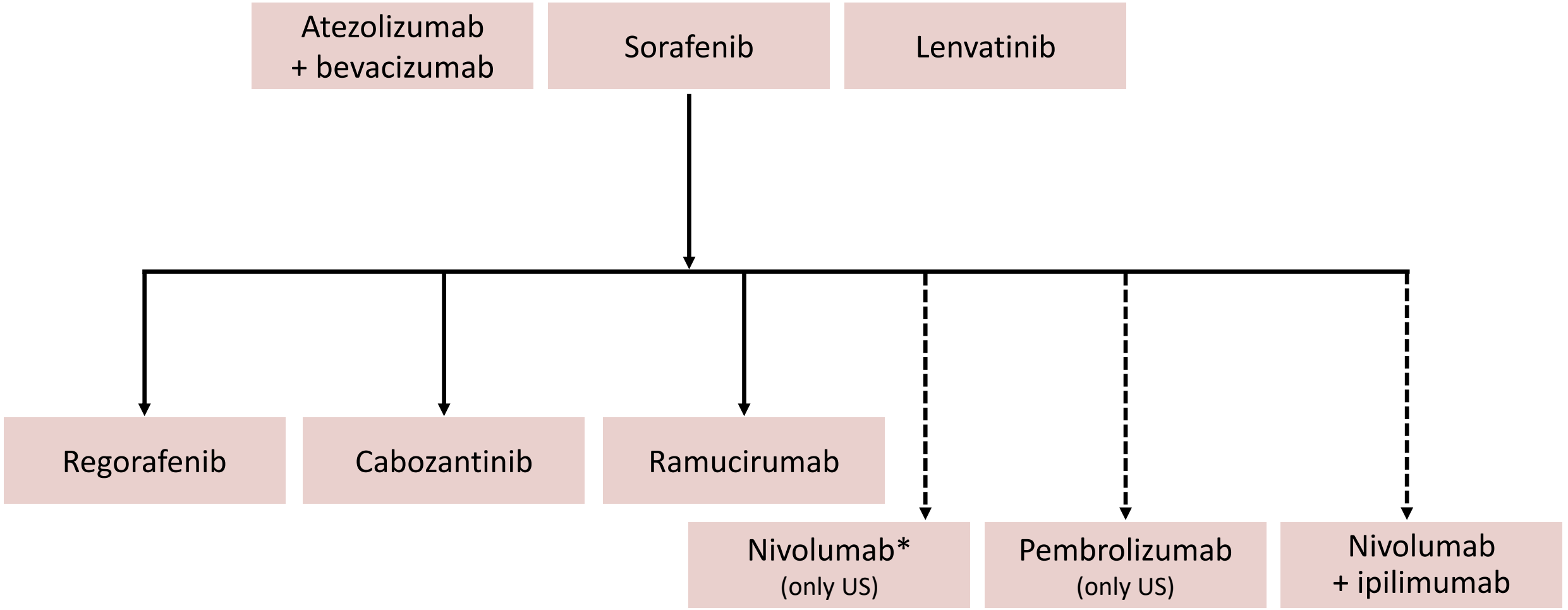


- Patient population: 49 patients; 76% Child Pugh B7 and 24% Child Pugh B8
- TRAEs manageable and not higher vs Child-Pugh A cohort
- ORR 10.2%; mOS 7.6 months; mOS in sorafenib-naïve and previously treated patients 9.8 and 7.4 months

- The phase 3 CheckMate-459 (NCT02576509) did not show significant benefit of nivolumab over sorafenib
- FDA recommended to remove the accelerated approval of nivolumab for the treatment of HCC in 2nd line*

*https://www.fda.gov/media/147929/download. Accessed May 2021.
CR, complete response; DoR, duration of response; mOS, median overall survival; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease; TRAE, treatment-related adverse events
Kudo. ASCO GI 2019; Kudo M, et al. J Clin Oncol. 2019;37(4_suppl):327-327

MULTIPLE SECOND-LINE TREATMENT OPTIONS AFTER SORAFENIB



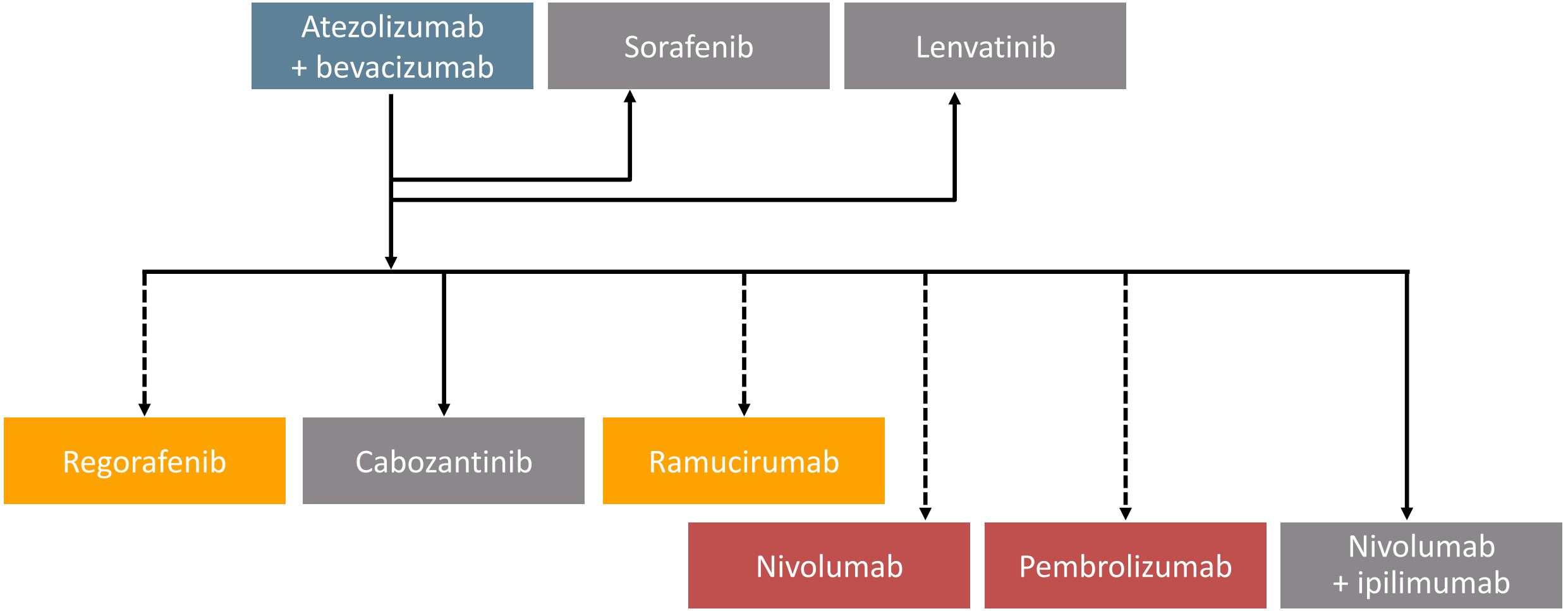
*In April 2021, FDA recommended rescinding nivolumab approval in 2nd line HCC treatment (Source: https://www.fda.gov/media/147929/download. Accessed May 2021).

DIFFERENCES IN SECOND-LINE TARGETED TREATMENT OPTIONS (EXPERT COMMENTS)

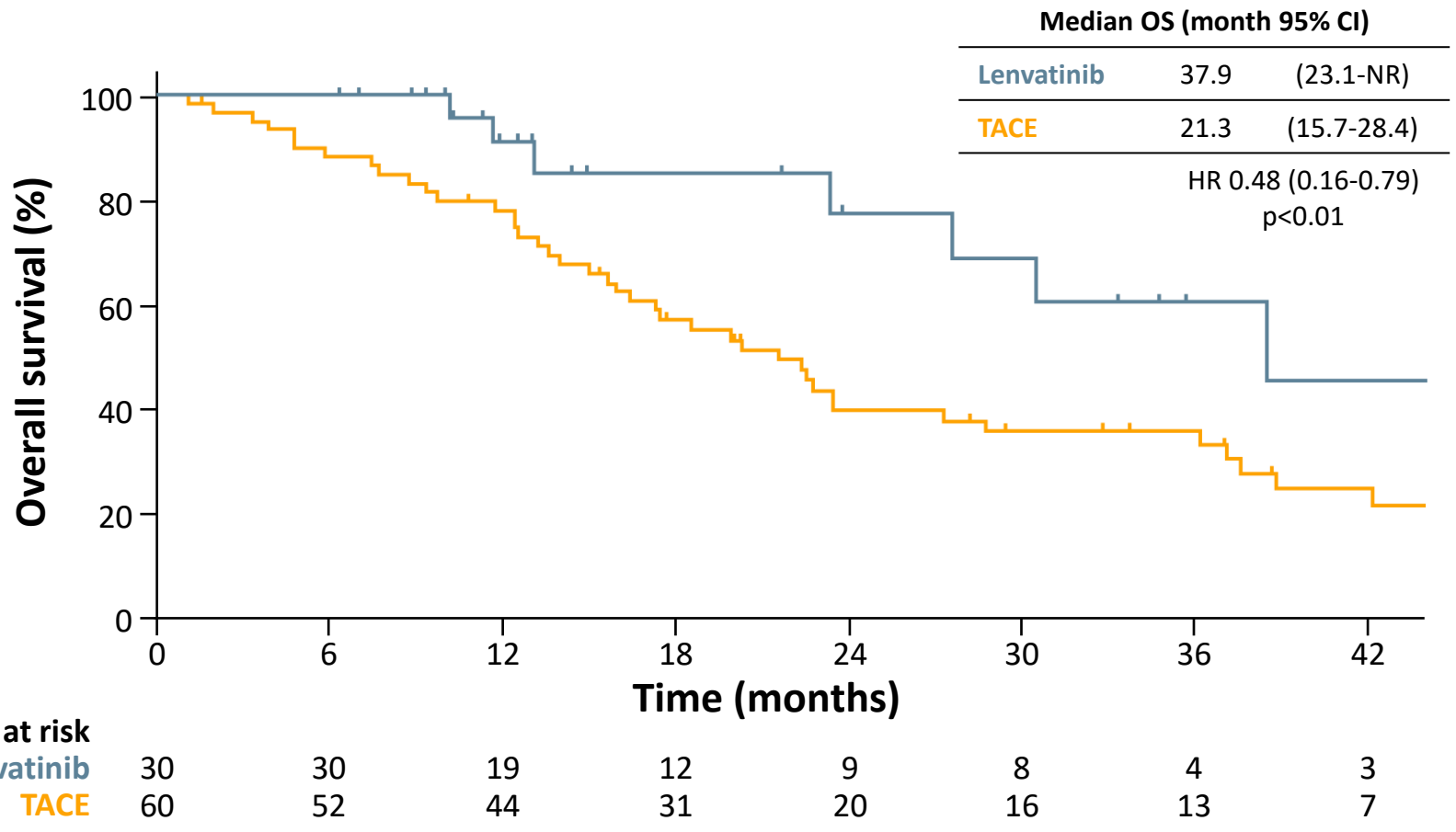
	Regorafenib	Cabozantinib	Ramucirumab
Level of evidence	Phase 3	Phase 3	Phase 3
Inclusion criteria	• Tolerated sorafenib but with radiographic progression	• Intolerant to sorafenib or with radiographic progression • Could have received an additional line of systemic therapy	• Intolerant to sorafenib or with radiographic progression • Patients with AFP ≥400 ng/mL
Efficacy	• Improved OS	• Improved OS	• Improved OS
AE profile	• Similar to AE profile of other TKIs	• Similar to AE profile of other TKIs	• Well tolerated with low rates of dose reductions or discontinuations
Logistics	• Orally daily for 3 weeks with 1-week holiday	• Orally once daily	• IV infusion every 2 weeks

AE, adverse event; AFP, alpha-fetoprotein; iv, intravenous; OS, overall survival; TKI, tyrosine kinase inhibitor

CAN THEY BE APPLIED AFTER ATEZOLIZUMAB AND BEVACIZUMAB?



ABILITY TO SEQUENCE REQUIRES STARTING SYSTEMIC THERAPY AT THE APPROPRIATE TIME



CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; TACE, transcatheter arterial chemoembolisation

Kudo M, et al. Cancers. 2019;11(8):1084

SUMMARY

- Interest in precision medicine and identifying best therapy for each patient
- Given a lack of proven biomarkers, we must rely on clinical factors to determine optimal therapies and sequencing strategies
- Although atezolizumab/bevacizumab should be first-line systemic therapy in most patients, there are patient population who will continue to receive TKI therapy
- TKIs could play an important role in second line after atezolizumab and bevacizumab
- Patient population with unique algorithms including patients with Child B, high risk of bleeding, or post-transplant
- Sequencing starts with transition from LRT to systemic therapy

AE, adverse event; AFP, alpha-fetoprotein; iv, intravenous; LRT, local regional treatment; OS, overall survival; TKI, tyrosine kinase inhibitor

EXPERTS KNOWLEDGE SHARE

STRATIFICATION OF PATIENTS WITH HCC: WHO NEEDS WHAT?

Sammy Saab, MD, MPH, AGAF, FACG, FAASLD
Professor of Medicine and Surgery
Head, Outcomes Research in Hepatology
David Geffen School of Medicine at UCLA

DISCLOSURES

- AbbVie
- BMS
- Bayer
- Gilead
- Eisai
- Exilisi
- Intercept
- Dova
- Saliix

IMPACT OF CIRRHOSIS ON THE MANAGEMENT OF HEPATOCELLULAR CARCINOMA (HCC)

- Cirrhosis independently associated with survival
  - Dealing with two disorders: cirrhosis and HCC
- Certain causes of cirrhosis can reactivate during treatment of HCC
- Patients with cirrhosis can have unique complications not seen in patients with other cancers
  - Manifestations of portal hypertension
  - Drug toxicity
- Patients with cirrhosis require additional preparatory work prior to the treatment of HCC
  - Variceal endoscopy

HCC, hepatocellular carcinoma

EVALUATION PRIOR TO STARTING HCC SYSTEMIC THERAPY

HCC connect® POWERED BY COR2ED

Laboratory tests

- CBC with platelets
- Complete Metabolic Panel
- Prothrombin time/INR
- HBsAg
- HBcAb
- Urine analysis
- TSH
- AFP

Other

- Upper endoscopy

AFP, alpha-fetoprotein; CBC, complete blood count; HBcAb, Hepatitis B core antibody test; HBsAg, Hepatitis B surface antigen; INR, international normalised ratio; TSH, thyroid stimulating hormone

AVAILABLE SYSTEMIC THERAPIES*

Sequence	Agent	Administration	Class
First Line	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	Lenvatinib	Oral	VEGF Inhibitor
	Bevacizumab**	Injection	VEGF Inhibitor
	Atezolizumab**	Injection	PD-L1 Inhibitor
Second Line	Regorafenib	Oral	Tyrosine Kinase Inhibitor
	Cabozantinib	Oral	Tyrosine Kinase Inhibitor
	Nivolumab	Injection	PD-1 Inhibitor
	Pembrolizumab	Injection	PD-1 Inhibitor
	Ramucirumab***	Injection	VEGFR2 inhibitor

*nivolumab + ipilimumab combination is not mentioned as this slide will support the illustration of treatment selection by patient population. **Bevacizumab/atezolizumab are used in combination; *** for HCC patients with AFP levels ≥400 ng/mL

PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2

Source: NCCN Guidelines. Hepatobiliary Cancers. V2.2021. Issued April 16, 2021

CLASSIFICATION OF CIRRHOSIS SEVERITY DETERMINANTS FOR CHILD-TURCOTTE-PUGH (CTP)

HCC connect® POWERED BY COR2ED

	Points		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds prolonged)	<4	4-6	>6

Total Numerical Score	Child-Pugh Class
5-6	A
7-9	B
10-15	C

Patients in Class A are considered **"compensated"**

Patients in Classes B and C are considered **"decompensated"**

Adapted from Garcia-Tsao G, et al. Am J Gastroenterol. 2009;104(7):1802-29

RECOMMENDED SYSTEMIC HCC THERAPIES FOR: PATIENTS WITH CHILD-CLASS B CIRRHOSIS

Sequence	Agent	Administration	Class
First Line	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	Lenvatinib	Oral	VEGF Inhibitor
	Bevacizumab**	Injection	VEGF Inhibitor
	Atezolizumab**	Injection	PD-L1 Inhibitor
Second Line	Regorafenib	Oral	Tyrosine Kinase Inhibitor
	Cabozantinib	Oral	Tyrosine Kinase Inhibitor
	Nivolumab	Injection	PD-1 Inhibitor
	Pembrolizumab	Injection	PD-1 Inhibitor
	Ramucirumab***	Injection	VEGFR2 inhibitor

Bevacizumab/atezolizumab are used in combination; * for HCC patients with AFP levels ≥400 ng/mL

HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2

Source: NCCN Guidelines. Hepatobiliary Cancers. V2.2021. Issued April 16, 2021

RECOMMENDED SYSTEMIC HCC THERAPIES FOR: TRANSPLANT RECIPIENTS OR IMMUNE CONTRAINDICATIONS

Sequence	Agent	Administration	Class
First Line	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	Lenvatinib	Oral	VEGF Inhibitor
	Bevacizumab	Injection	VEGF Inhibitor
	Atezolizumab	Injection	PD-L1 Inhibitor
Second Line	Regorafenib	Oral	Tyrosine Kinase Inhibitor
	Cabozantinib	Oral	Tyrosine Kinase Inhibitor
	Nivolumab	Injection	PD-1 Inhibitor
	Pembrolizumab	Injection	PD-1 Inhibitor
	Ramucirumab***	Injection	VEGFR2 inhibitor

Bevacizumab/atezolizumab are used in combination; * for HCC patients with AFP levels ≥400 ng/mL

HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2

Source: NCCN Guidelines. Hepatobiliary Cancers. V2.2021. Issued April 16, 2021

RECOMMENDED SYSTEMIC HCC THERAPIES FOR: INTOLERANT TO SORAFENIB

Sequence	Agent	Administration	Class
First Line	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	Lenvatinib	Oral	VEGF Inhibitor
	Bevacizumab**	Injection	VEGF Inhibitor
	Atezolizumab**	Injection	PD-L1 Inhibitor
Second Line	Regorafenib	Oral	Tyrosine Kinase Inhibitor
	Cabozantinib	Oral	Tyrosine Kinase Inhibitor
	Nivolumab	Injection	PD-1 Inhibitor
	Pembrolizumab	Injection	PD-1 Inhibitor
	Ramucirumab***	Injection	VEGFR2 inhibitor

Bevacizumab/atezolizumab are used in combination; * for HCC patients with AFP levels ≥400 ng/mL

HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2

Source: NCCN Guidelines. Hepatobiliary Cancers. V2.2021. Issued April 16, 2021

RECOMMENDED SYSTEMIC HCC THERAPIES FOR: MAIN PORTAL VEIN HCC INVASION

Sequence	Agent	Administration	Class
First Line	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	~~Lenvatinib~~	~~Oral~~	~~VGEF Inhibitor~~
	Bevacizumab**	Injection	VGEF Inhibitor
	Atezolizumab**	Injection	PD-L1 Inhibitor
Second Line	Regorafenib	Oral	Tyrosine Kinase Inhibitor
	Cabozantinib	Oral	Tyrosine Kinase Inhibitor
	Nivolumab	Injection	PD-1 Inhibitor
	Pembrolizumab	Injection	PD-1 Inhibitor
	Ramucirumab***	Injection	VEGFR2 inhibitor

Bevacizumab/atezolizumab are used in combination; * for HCC patients with AFP levels ≥400 ng/mL
HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2
Source: NCCN Guidelines. Hepatobiliary Cancers. V2.2021. Issued April 16, 2021

AREAS NEEDING FURTHER RESEARCH WHEN CHOOSING SYSTEMIC THERAPY

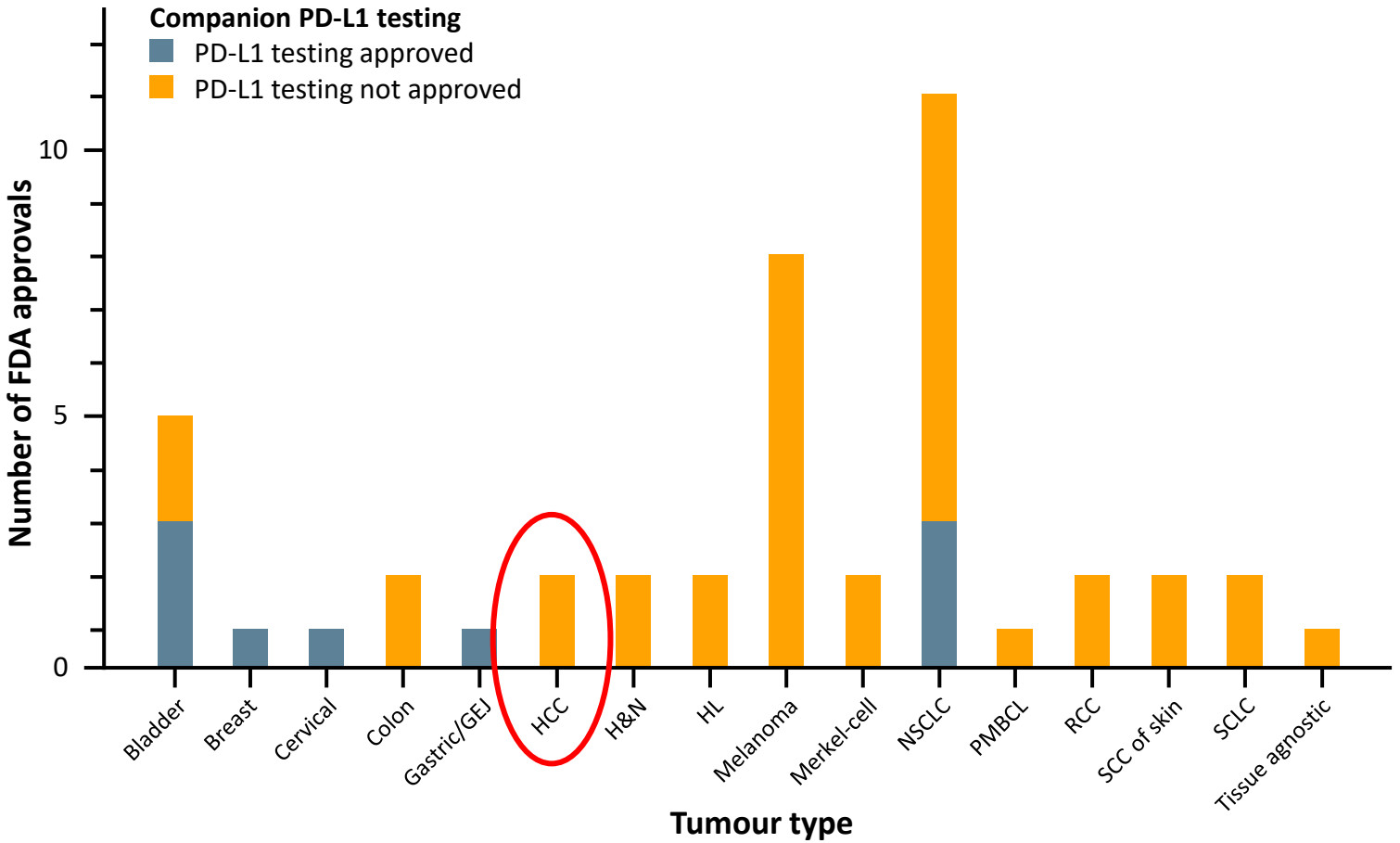
- Impact of underlying liver disease on treatment efficacy
  - Viral vs non-viral causes?
- Sequential therapy after immunotherapy nonresponse
- Biomarkers predicting treatment response
  - Ramucirumab and AFP, PD-L1 expression?
- Utility of systemic therapy in Child-Class B cirrhosis

AFP, alpha-fetoprotein; PD-L1, programmed cell death ligand 1

SELECTION BIOMARKERS CONSIDERATIONS IN TREATMENT OF HCC

Biomarkers	Clinical Relevance
PD-L1 Expression	• Expression low in HCC (~ 10%) • Not found to be robust predictor
Tumor mutational burden (TMB)	• Infrequent occurrence • Results inconsistent
Tumor-infiltrating lymphocytes (TIL)	• ~20% HCC tumors well infiltrated • Additional studies needed

The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration approvals of immune checkpoint inhibitors



FDA, Food and Drug Administration; GEJ, gastro-esophageal junction; H&N, head and neck; HCC, hepatocellular carcinoma; HL, Hodgkin's Lymphoma; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; PMBCL, primary mediastinal B-cell lymphoma; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer

El Khoueiry et al Lancet 2017; 389(10088):2492-2502 - Zhu AX et al. Lancet Oncol 2018; 19(7):940-952 - Tai D, et al. Cancers. 2019;11:1926 - Davis A, et al. J Immunother Cancer. 2019;7(1):278

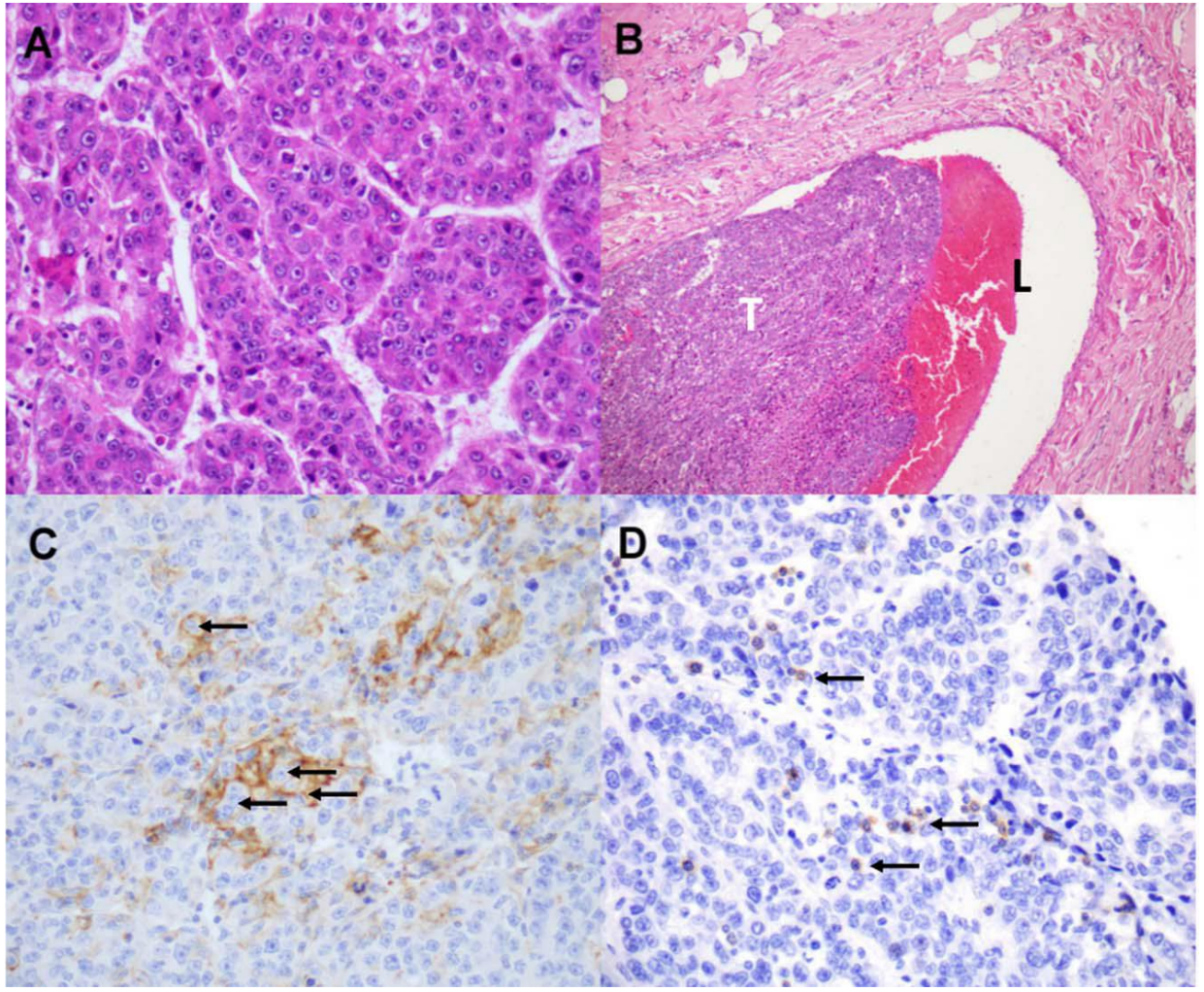
PATHOLOGICAL FEATURES OF HCC

(A) A case of poorly differentiated HCC, with a macrotrabecular architectural pattern and a high degree of nuclear atypia (hematein-eosin-saffron, x 400).

(B) Massive vascular invasion at the tumor margin, with tumoral thrombi within vessel lumens (hematein-eosin-saffron, x 100).

(C) Membranous PD-L1 expression by neoplastic cells (arrows, x 400).

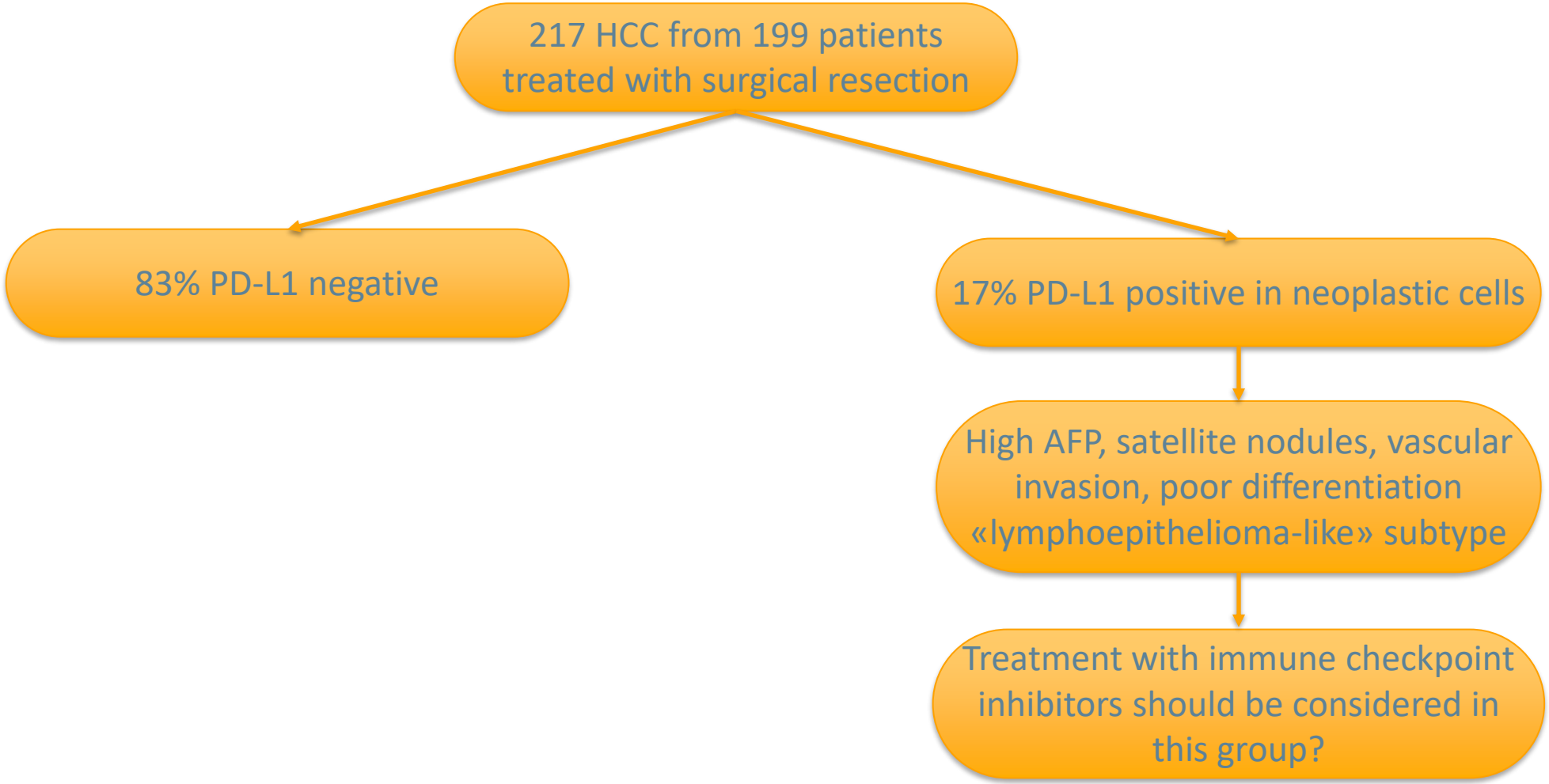
(D) Diffuse tumoral infiltration by PD-1–positive lymphocytes (arrows, x 400).



HCC, hepatocellular carcinoma; PD-1, programmed cell death 1

Calderaro J, et al. Hepatology 2016; 64(6):2038-2046

POSSIBLE THERAPEUTIC STRATIFICATION OF THE PATIENTS BASED ON PD-L1 EXPRESSION IN THE HCC SPECIMENS



AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; PD-L1, programmed cell death ligand 1

Solinas A & Calvisi DF. Hepatology. 2016; 64(6):1847-1849

CONCLUSIONS

- Treatment of hepatocellular carcinoma (HCC) does not occur in a vacuum
- Coordinated care with gastroenterology/hepatology is essential for preparing and managing patients with cirrhosis in the treatment of HCC
- No currently available predictive biomarkers for re-stratification and for tailoring therapy options

HCC, hepatocellular carcinoma

EXPERTS KNOWLEDGE SHARE

A LOOK TO FUTURE TREATMENTS AND CLOSING REMARKS

Prof. Peter Galle

Department of Gastroenterology and Hepatology
University Medical Center Mainz, Mainz, Germany

THE CLINICAL BENEFIT OBSERVED WITH ATEZOLIZUMAB + BEVACIZUMAB HAS SPARKED MULTIPLE ONGOING 1L CIT COMBINATION TRIALS

HCC connect® POWERED BY COR2ED

Cancer immunotherapy combinations combinations with anti-VEGF or a TKI

Anti-PDL1	**Atezolizumab + cabozantinib** (COSMIC-312; phase III) *Anti-PD-L1 + TKI*	**Avelumab + axitinib** (VEGF Liver 100; phase Ib) *Anti-PD-L1 + TKI*	**Durvalumab + tivozanib** (DEDUCTIVE; phase Ib/II) *Anti-PD-L1 + VEGFR TKI*	**Durvalumab + lenvatinib*** (Dulect2020-1; N/A) *Anti-PD-L1 + TKI*	
Anti-PD1	**Pembrolizumab + lenvatinib** (LEAP-002; phase III) *Anti-PD-1 + TKI*	**Pembrolizumab + regorafenib** (KEYNOTE-743; phase Ib) *Anti-PD-1 + TKI*	**Penpulimab + anlotinib*** (phase III) *Anti-PD-1 + TKI*	**CS1003 + lenvatinib*** (phase III) *Anti-PD-1 + TKI*	**Camrelizumab + apatinib*** (phase III) *Anti-PD-1 + TKI*
	Nivolumab + lenvatinib (IMMUNIB; phase II) *Anti-PD-1 + TKI*	**Sintilimab + bev-biosimilar*** (ORIENT-32;‡ phase II/III) *Anti-PD-1 + anti-VEGF*	**Nivolumab + lenvatinib** (Study 117; phase Ib) *Anti-PD-1 + TKI*	**Toripalimab + lenvatinib*** (phase III) *Anti-PD-1 + TKI*	**HLX10 + bev-biosimilar*** (phase III) *Anti-PD-1 + anti-VEGF*
	SCT-I10A + bev-biosimilar* (phase II/III) *Anti-PD-1 + anti-VEGF*	**Toripalimab + bevacizumab*** (phase II) *Anti-PD-1 + anti-VEGF*	**Nivolumab + regorafenib** (RENOBATE; phase II) *Anti-PD-1 + TKI*	**Nivolumab + sorafenib** (phase II) *Anti-PD-1 + TKI*	**Tislelizumab + lenvatinib*** (phase II) *Anti-PD-1 + TKI*
	Camrelizumab + lenvatinib* (phase I/II) *Anti-PD-1 + TKI*	**Toripalimab + sorafenib*** (phase I/II) *Anti-PD-1 + TKI*	**Spartalizumab + sorafenib** (phase Ib) *Anti-PD-1 + TKI*		

- ■ Phase Ib/II data available
- ■ No data available
- ☐ Ongoing global phase III trials

Cancer immunotherapy combinations with two CPIs

Durvalumab + tremelimumab (HIMALAYA; phase III) *Anti-PD-L1 + anti-CTLA-4*	**TSR-042 + TSR-022** (phase II) *Anti-PD-1 + anti-TIM3*
Nivolumab + ipilimumab (CheckMate 9DW; phase III) *Anti-PD-1 + anti-CTLA-4*	**Relatlimab ± nivolumab** (phase I/II) *Anti-LAG3 ± anti-PD-1*

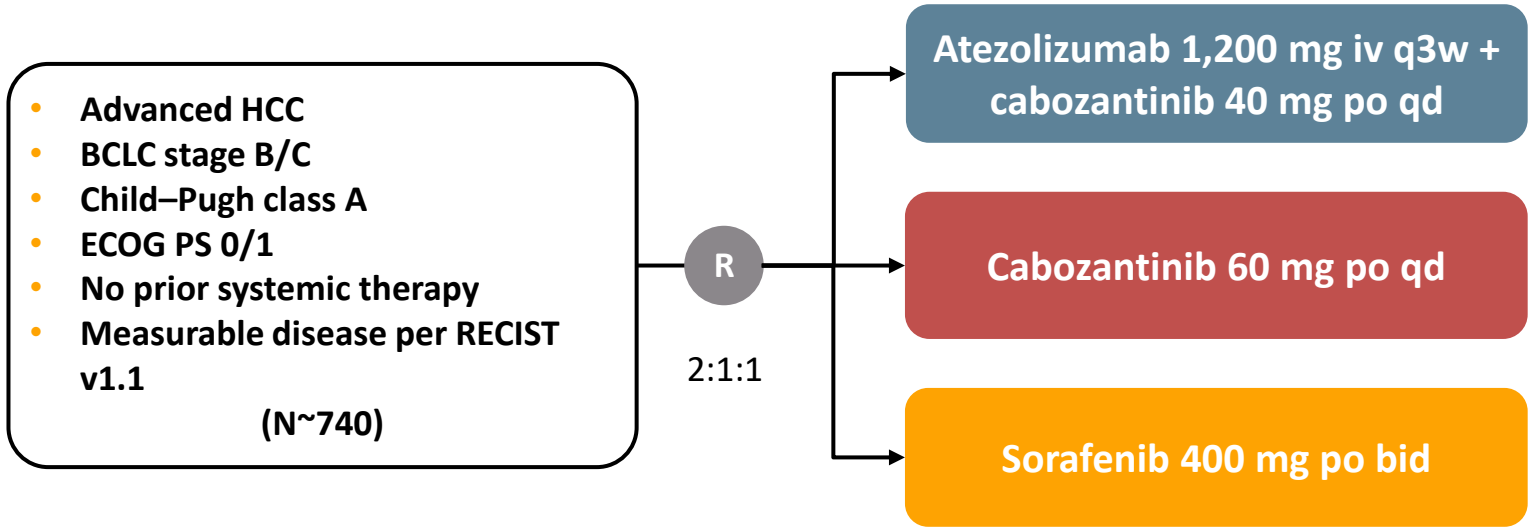
Bispecific antibody combinations

XmAb22841 ± pembrolizumab (DUET-4; phase I) *Anti-CTLA-4 × anti-LAG3 ± anti-PD-1*	**AK104 + lenvatinib*** (phase I/II) *Anti-PD-1 × anti-CTLA-4 + TKI*

*China only; ‡Met primary endpoints (OS and PFS) at interim analysis

1L, first-line; CIT, cancer immunotherapy; CPI, checkpoint inhibitor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LAG3, lymphocyte activation gene-3; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TIM3, T-cell immunoglobulin and mucin-domain containing gene-3; TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor)

COSMIC-312 (PHASE III): 1L ATEZOLIZUMAB + CABOZANTINIB IS CURRENTLY BEING INVESTIGATED IN ADVANCED HCC

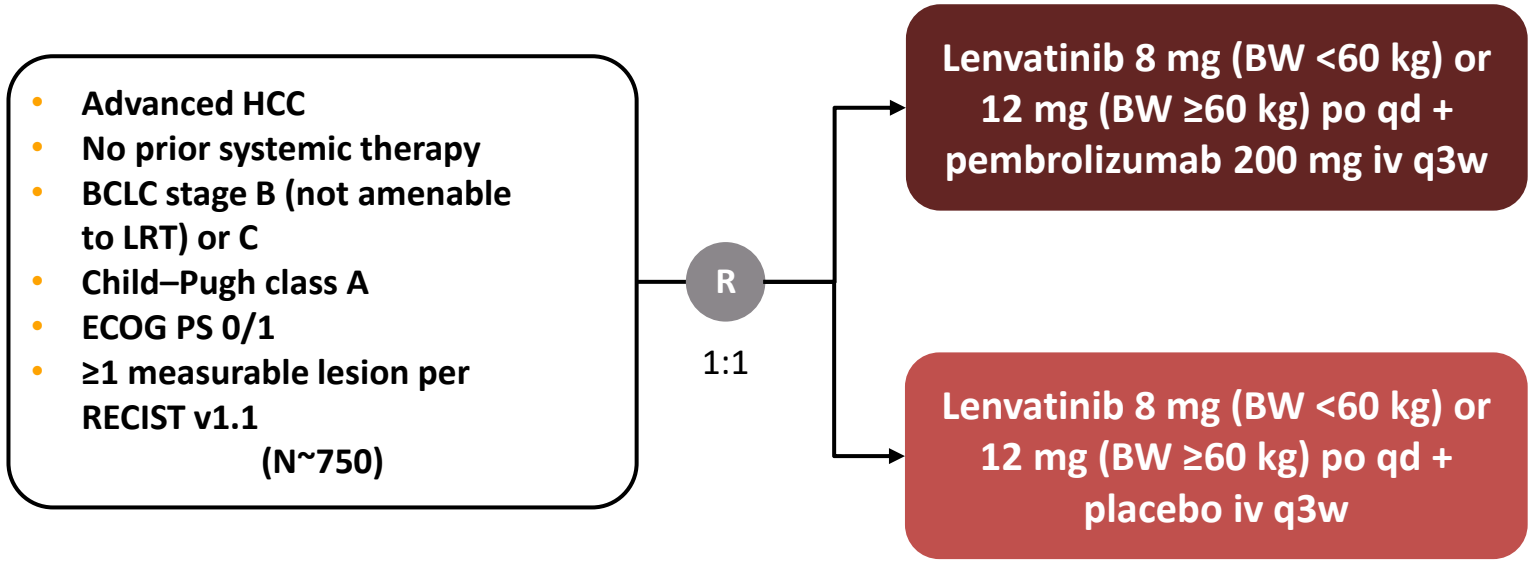


- **Co-primary endpoints:** PFS by BIRC RECIST v1.1 and OS for atezolizumab + cabozantinib vs sorafenib
- **Secondary endpoint:** Duration of PFS by BIRC RECIST v1.1 for cabozantinib vs sorafenib

1L, first-line; BCLC, Barcelona Clinic Liver Cancer; bid, twice daily; BIRC, blinded independent radiology committee; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; iv, intravenous; OS, overall survival; PFS, progression-free survival; po, orally; q3w, every 3 weeks; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumors

Source: https://clinicaltrials.gov/ct2/show/NCT03755791

LEAP-002 (PHASE III): ONGOING 1L TRIAL OF LENVATINIB + PEMBROLIZUMAB IN ADVANCED HCC



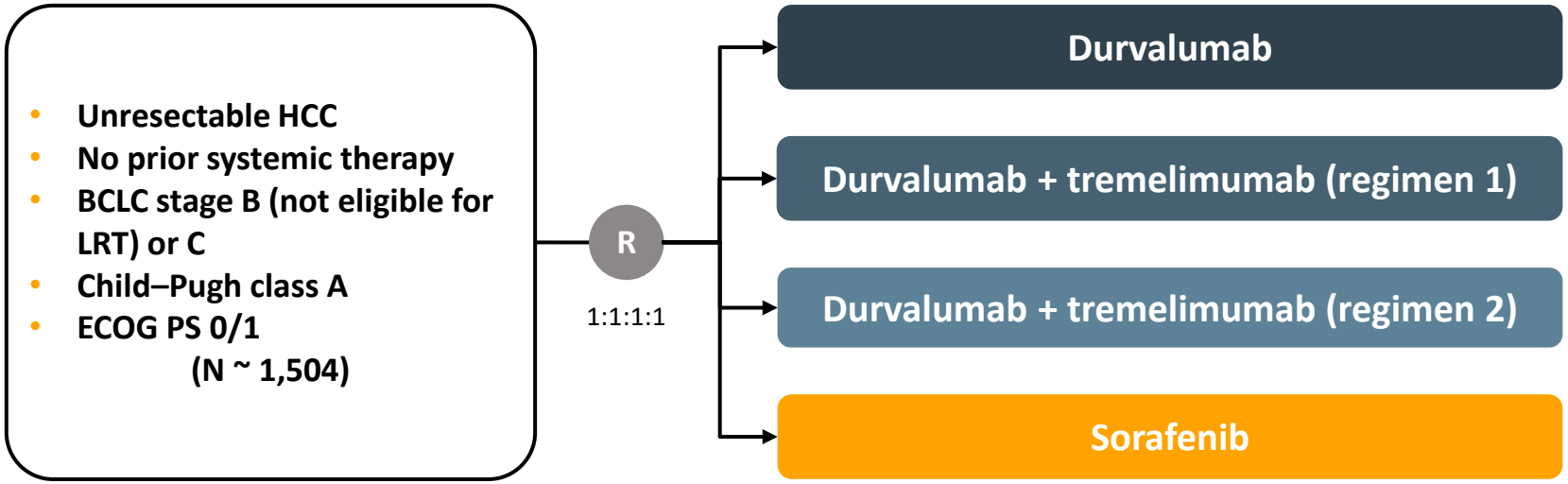
- **Co-primary endpoints:** PFS BICR assessed by RECIST v1.1, OS
- **Secondary/exploratory endpoints includes:** ORR,* DoR,* DCR,* TTP,* PFS,‡ safety, PK

*Per RECIST v1.1 or HCC mRECIST; ‡Per HCC mRECIST

1L, first-line; BCLC, Barcelona Clinic Liver Cancer; BIRC, blinded independent radiology committee; BW, body weight; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; iv, intravenous; LRT, local regional treatment; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; po, orally; q3w, every 3 weeks; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to disease progression

Source: https://clinicaltrials.gov/ct2/show/NCT03713593

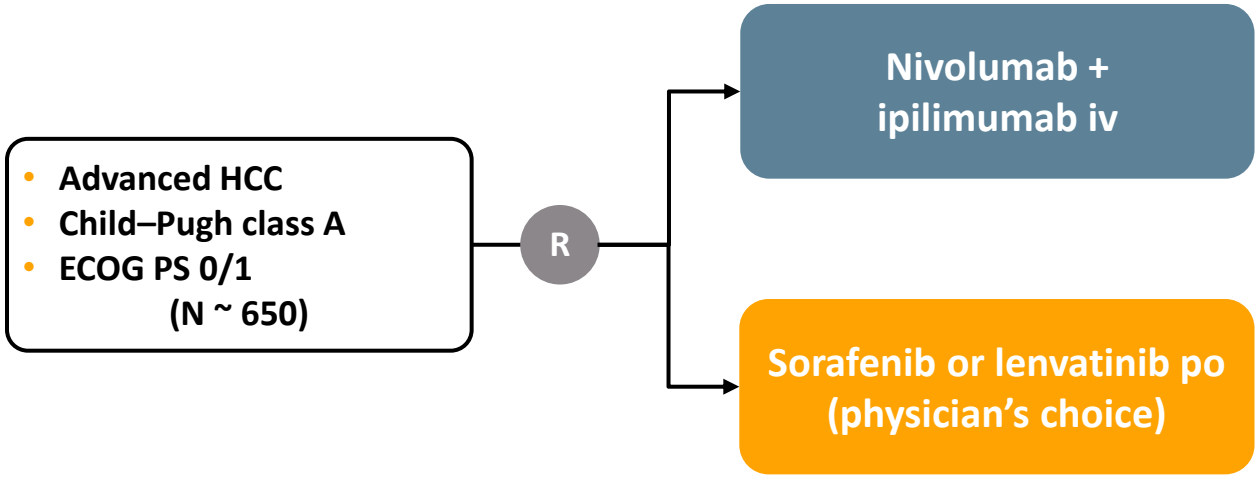
HIMALAYA (PHASE III): DATA FOR 1L DURVALUMAB ± TREMELIMUMAB IN UNRESECTABLE HCC



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

1L, first-line; BCLC, Barcelona Clinic Liver Cancer; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; LRT, local regional treatment; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression
Source: https://clinicaltrials.gov/ct2/show/NCT03298451

CHECKMATE-9DW (PHASE III): 1L TRIAL OF NIVOLUMAB + IPILIMUMAB IN ADVANCED HCC IS CURRENTLY RECRUITING



- **Co-primary endpoints:** OS
- **Secondary endpoints:** ORR by RECIST v1.1, DoR, TTSD

1L, first-line; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; ORR, objective response rate; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; TTSD, time to symptom deterioration
Source: https://www.clinicaltrials.gov/ct2/show/NCT04039607

REACH HCC CONNECT VIA TWITTER, LINKEDIN, VIMEO & EMAIL OR VISIT THE GROUP'S WEBSITE

http://www.hccconnect.info

Follow us on Twitter
@hccconnectinfo

Follow the
HCC CONNECT
group on LinkedIn

Watch us on the
Vimeo Channel
HCC CONNECT

Email
froukje.sosef@cor2ed.com

HCC connect®
POWERED BY COR2ED

HCC CONNECT
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

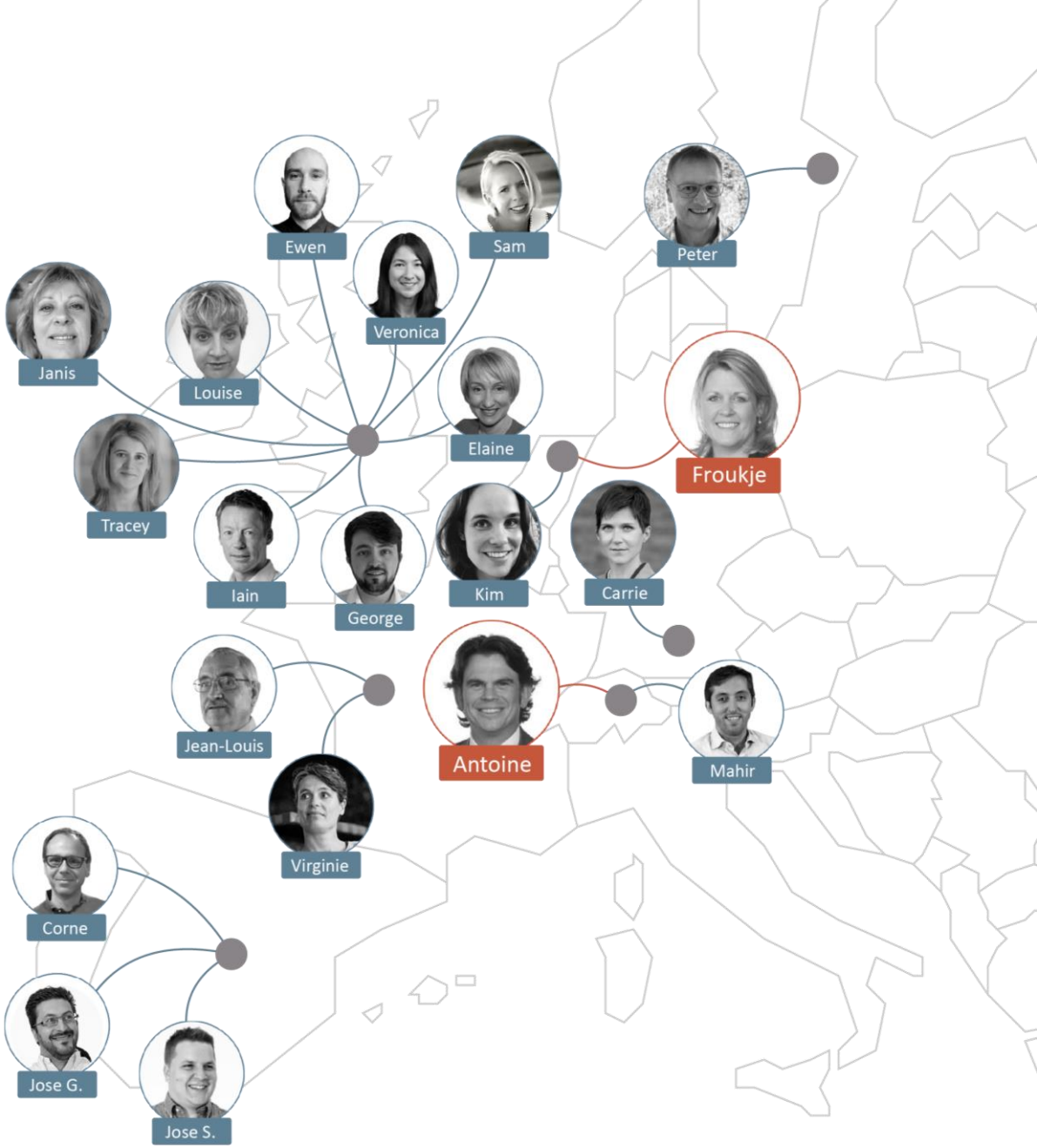
antoine.lacombe@cor2ed.com

Connect on
LinkedIn @HCC CONNECT

Watch on
Vimeo @HCC CONNECT

Visit us at
hccconnect.info

Follow us on
Twitter @hccconnectinfo



Heading to the heart of Independent Medical Education Since 2012