



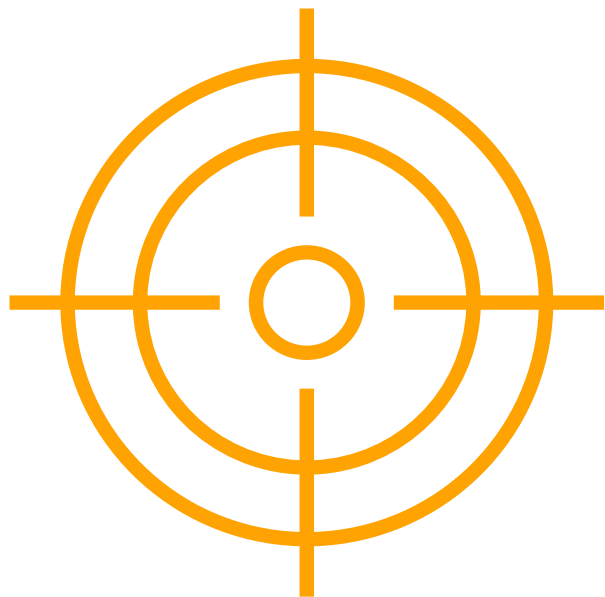
**EXPERTS KNOWLEDGE SHARE**

**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 11<sup>th</sup> 2021**

# 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



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**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

## DIAGNOSIS

Screening

Symptoms

## STAGE

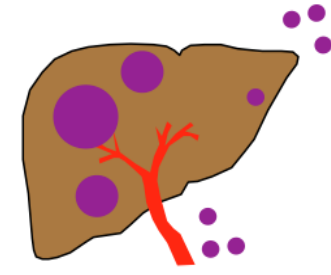
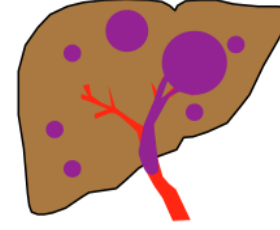
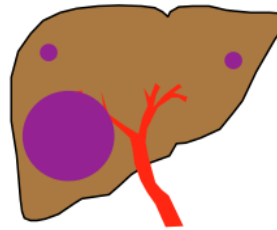
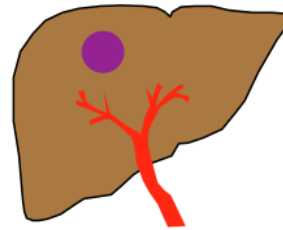
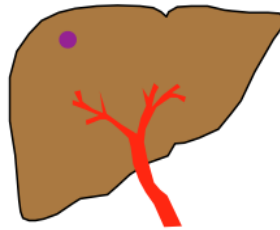
Very Early

Early

Intermediate

Advanced

## TUMOUR BURDEN



## TREATMENT

Resection  
Ablation

Intra-arterial Therapies

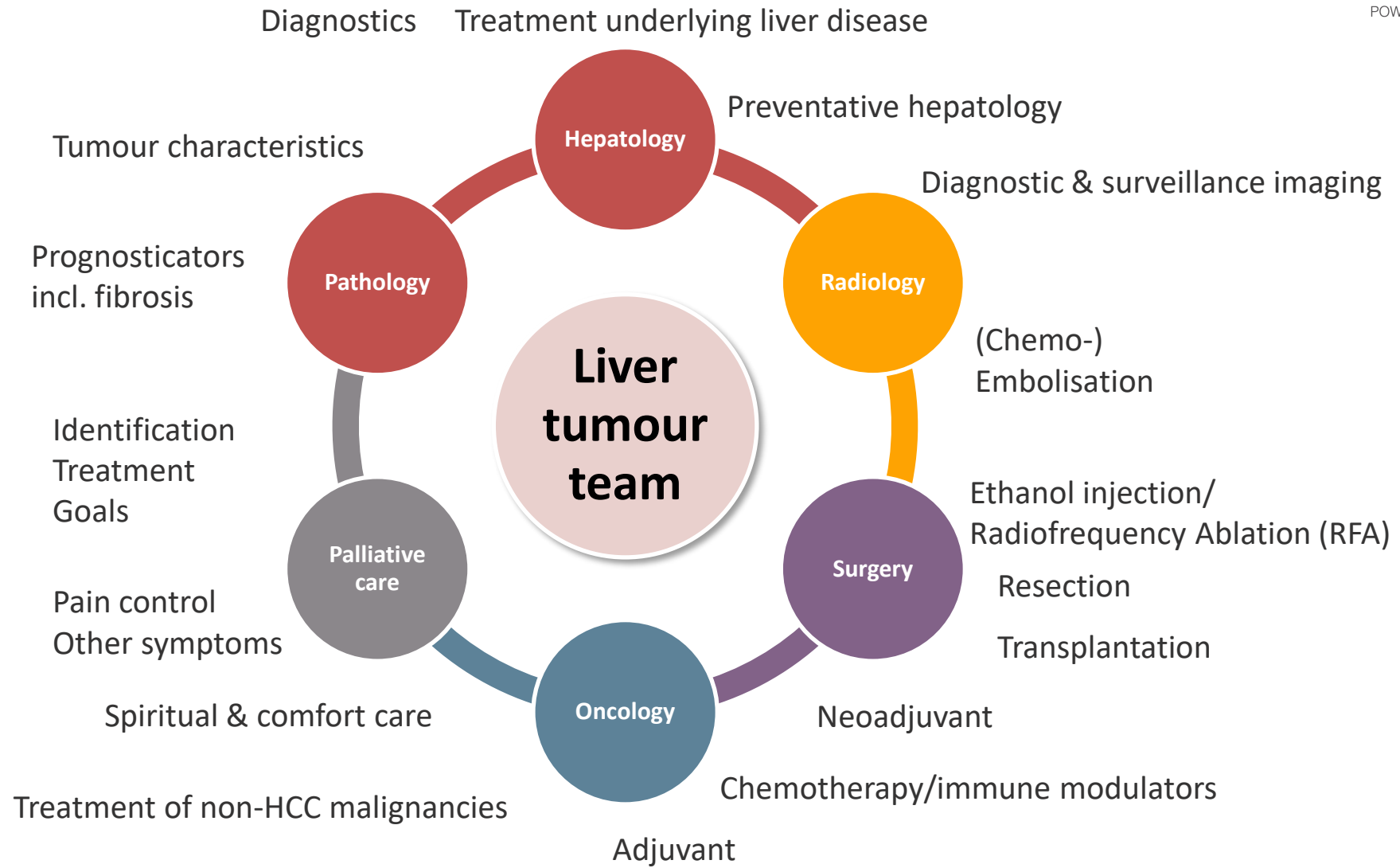
Systemic  
Therapies

## CIRRHOSIS

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

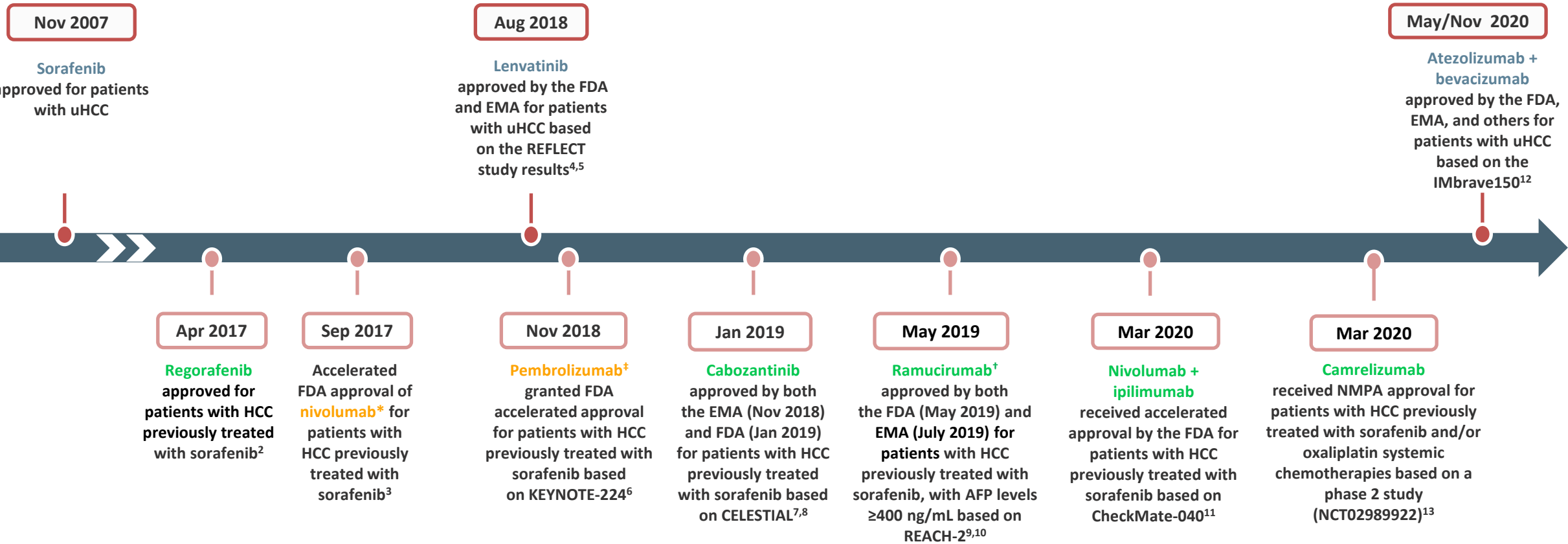


# MULTI-DISCIPLINARY TEAM APPROACH IN HCC PATIENTS



# THE HCC SYSTEMIC TREATMENT LANDSCAPE HAS RAPIDLY EVOLVED SINCE 2017

## First-line therapies



## 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<sup>19</sup>; <sup>†</sup>Patients with AFP ≥400 ng/mL; <sup>‡</sup> Pembrolizumab failed to significantly improve OS and PFS (co-primary endpoints) vs placebo in the phase 3 KEYNOTE-240 trial<sup>20,21</sup>

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.ipсен.com/media/press-releases/post\\_custom\\_datacustom\\_datapost\\_custom\\_dataeuropean-commission-approves-ipsens-cabometyx-cabozantinib-for-the-treatment-of-hepatocellular-carcinoma-in/](https://www.ipсен.com/media/press-releases/post_custom_datacustom_datapost_custom_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. Cymruza (ramucirumab) EMA approval. EMA summary of opinion. Available from: [https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-cymruza-ii-27\\_en.pdf](https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-cymruza-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. 10 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

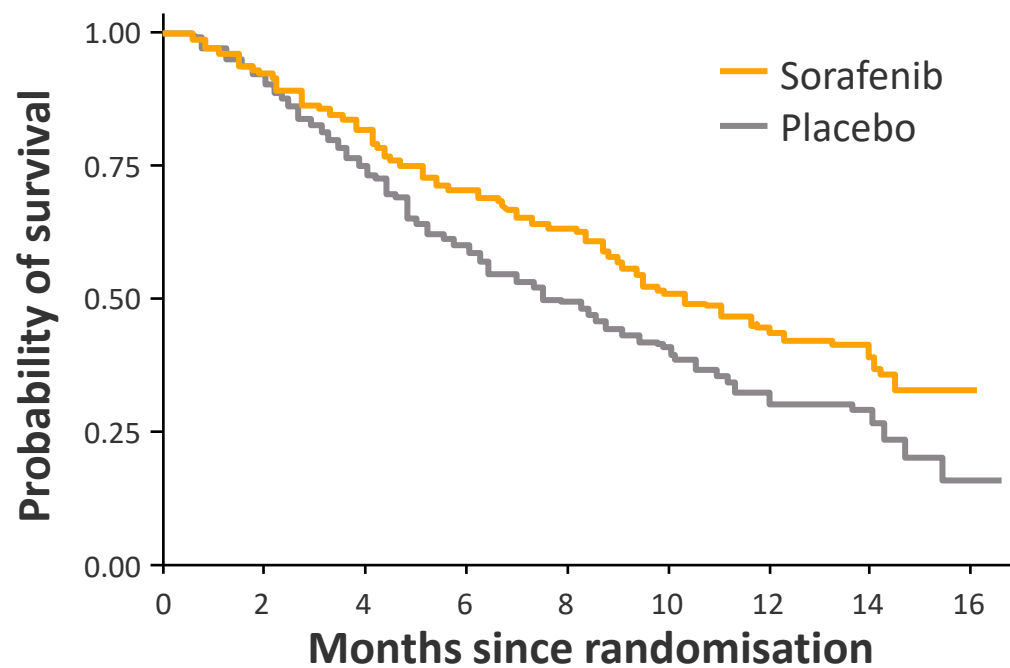
# 1<sup>ST</sup>-LINE SYSTEMIC TREATMENT OPTIONS

- Sorafenib
- Lenvatinib
- Atezolizumab + bevacizumab

# 1<sup>ST</sup>-LINE TREATMENT OPTIONS: SORAFENIB AND LENVATINIB

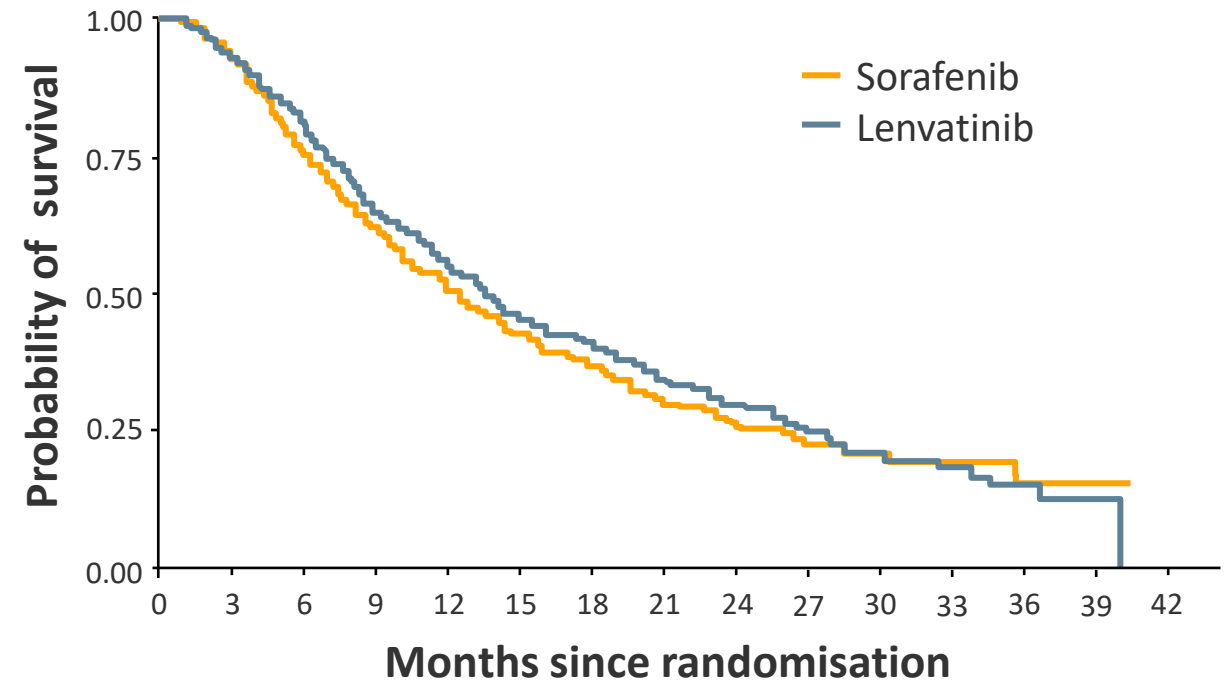
Overall survival in the SHARP trial<sup>1</sup>

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



Overall survival in the REFLECT\* trial<sup>2</sup>

Median OS: 13.6 months lenvatinib vs 12.3 months sorafenib HR 0.92 (95% CI 0.79-1.06)<sup>2</sup>

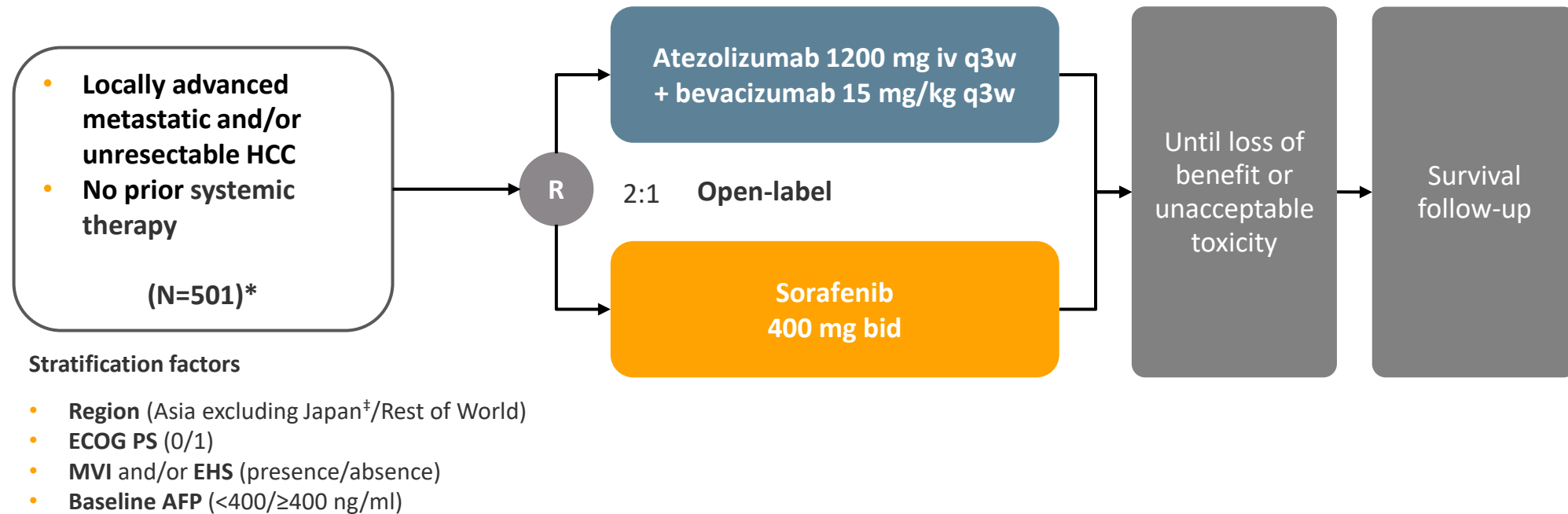


\*REFLECT is a randomized phase 3 non-inferiority trial

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<sup>1</sup>



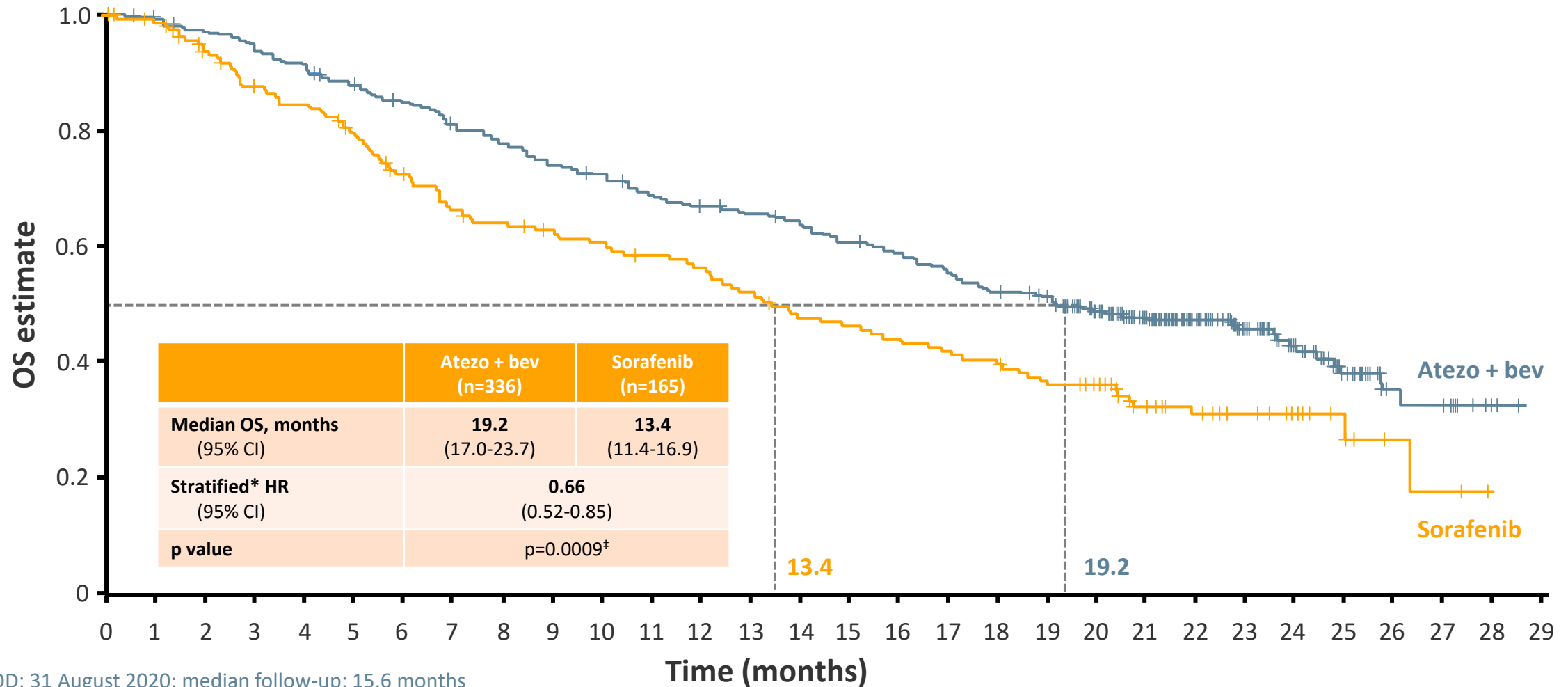
- **Co-primary endpoints:** OS and PFS IRF-assessed per RECIST v1.1
- **Key secondary endpoints** (in testing strategy): ORR IRF-assessed per RECIST v1.1 and HCC mRECIST

\*There were an additional 57 Chinese patients in the China extension cohort that were not included in the global population/analysis; <sup>‡</sup>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. 13

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



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)

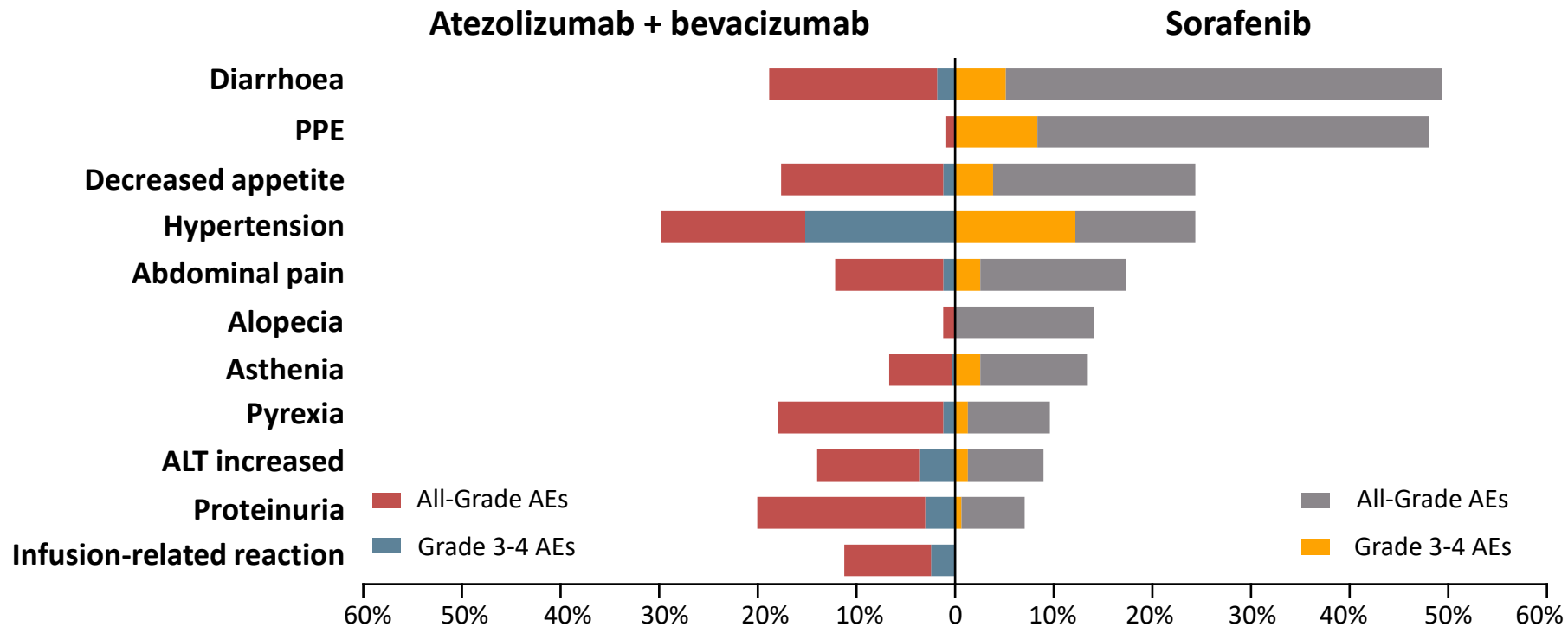
per IxRS; <sup>‡</sup>p value for descriptive purposes only

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)

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

### Summary of adverse events



# 2<sup>ND</sup>-LINE SYSTEMIC TREATMENT OPTIONS

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



# 2<sup>ND</sup>-LINE TREATMENT OPTIONS: REGORAFENIB, CABOZANTINIB AND RAMUCIRUMAB\*

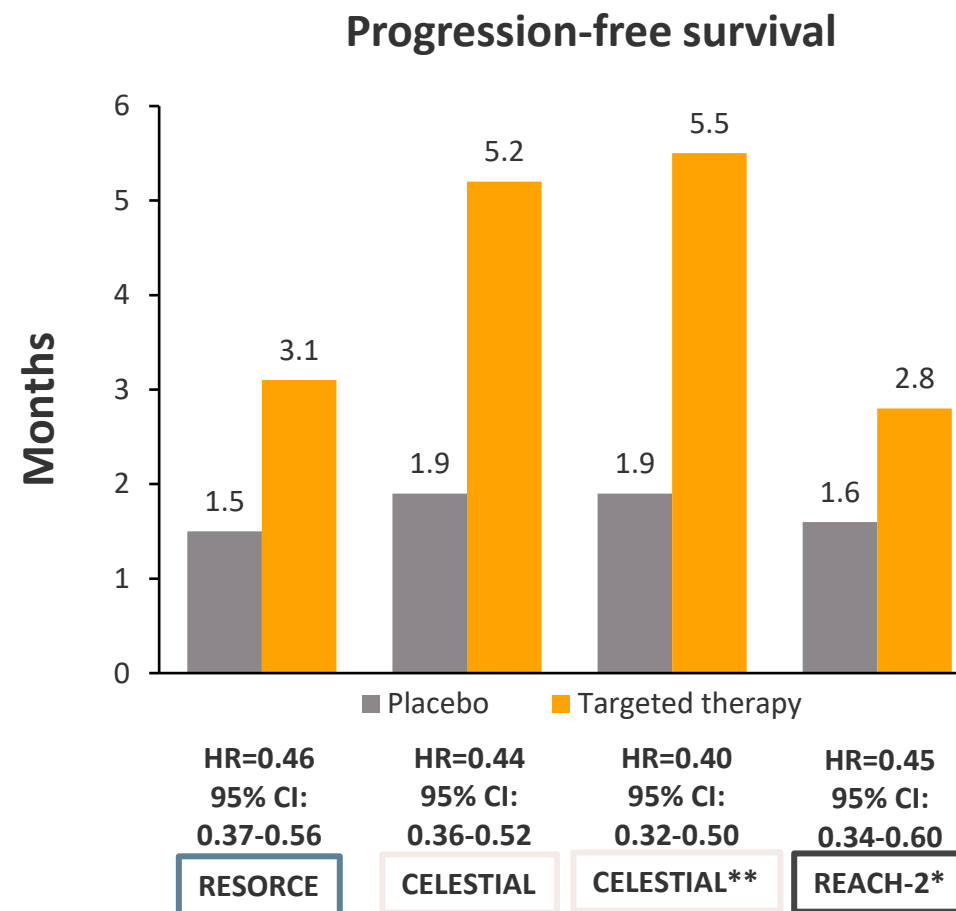
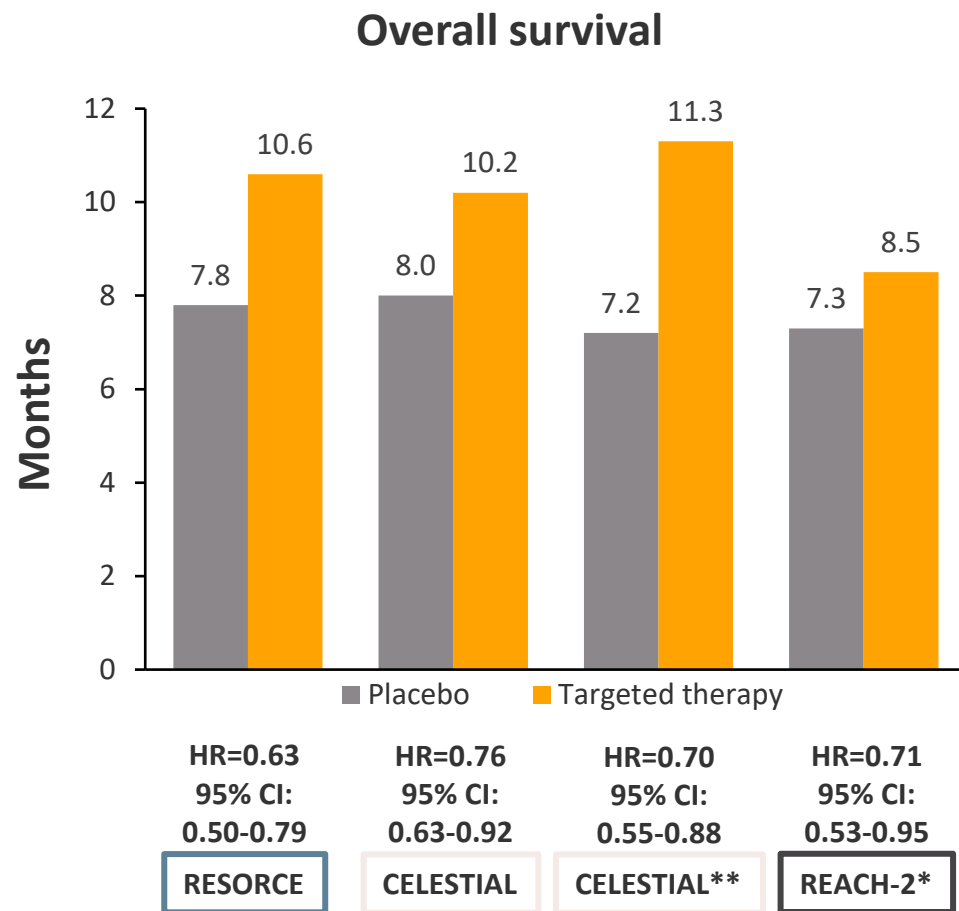
	RESORCE <sup>1</sup>	CELESTIAL <sup>2,3</sup>	REACH-2 <sup>4</sup>
<b>Arms</b>	Regorafenib vs placebo	Cabozantinib vs placebo	Ramucirumab vs placebo
<b>Targets</b>	VEGFR 1-3, RAF, KIT, RET, PDGFR, TIE 2, FGFR1	VEGFR, MET, AXL	VEGFR2
<b>Class</b>	TKI	TKI	mAb
<b>Administration</b>	Oral	Oral	IV
<b>Previous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

\*Trials included different populations and should not be directly compared

AFP, alpha-fetoprotein; AXL, anelexekto 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

# 2<sup>ND</sup>-LINE TREATMENT OPTIONS: REGORAFENIB,<sup>1</sup> AND CABOZANTINIB<sup>2,3</sup> AND RAMUCIRUMAB,<sup>4</sup> VS PLACEBO



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

# 2<sup>ND</sup>-LINE TREATMENT OPTIONS: RESORCE, CELESTIAL AND REACH-2 SAFETY SUMMARY

	RESORCE <sup>1</sup> (regorafenib)	CELESTIAL <sup>2</sup> (cabozantinib)	REACH-2 <sup>3,4</sup> (ramucirumab)
<b>Discontinuation due to TRAEs</b>	10%	16%	11%
<b>Dose modification due to AEs</b>	68%	62%	35%
<b>Median duration of treatment</b>	3.6 months	3.8 months	2.8 months (AFP high)
<b>Grade ≥3 TEAEs</b>	67%	68%	59%
<b>Toxicities (≥10%, grade ≥3)</b>	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

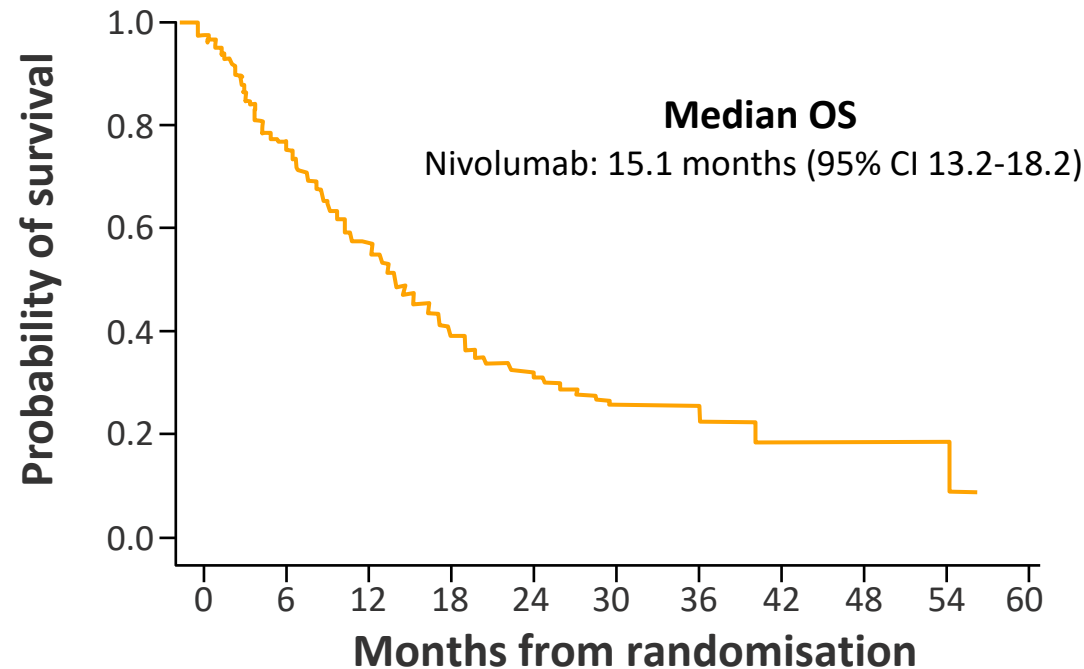
AE, adverse event; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; TEAE, treatment-emergent AE; TRAE, treatment-related AE

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)

# 2<sup>ND</sup>-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

Nivolumab has been granted accelerated FDA approval in 2<sup>nd</sup>-line based on the results of CheckMate-040<sup>2\*</sup>  
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<sup>3</sup>



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



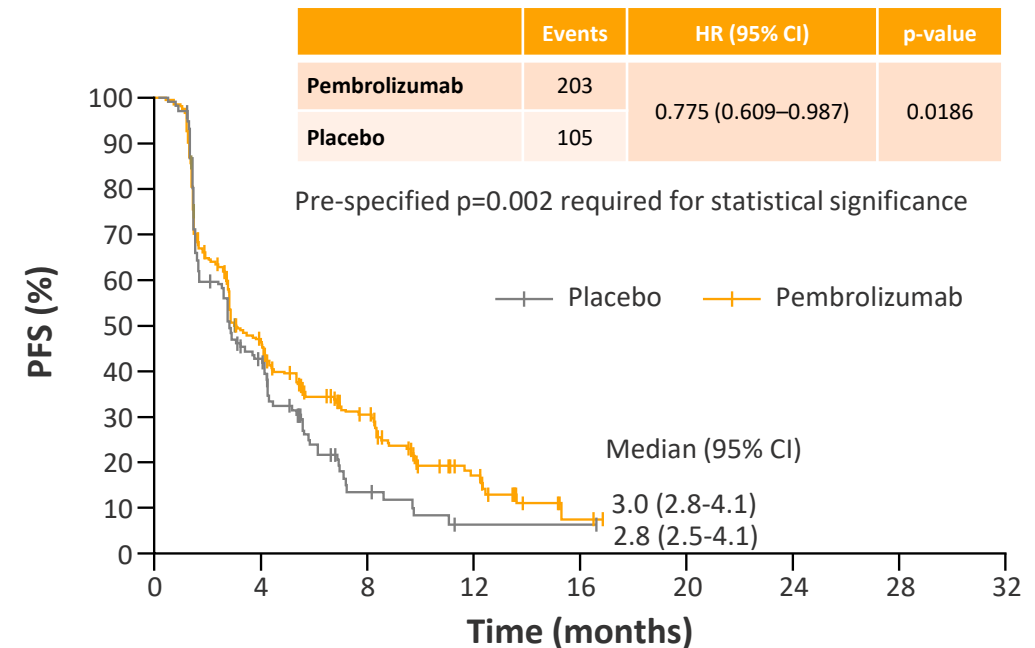
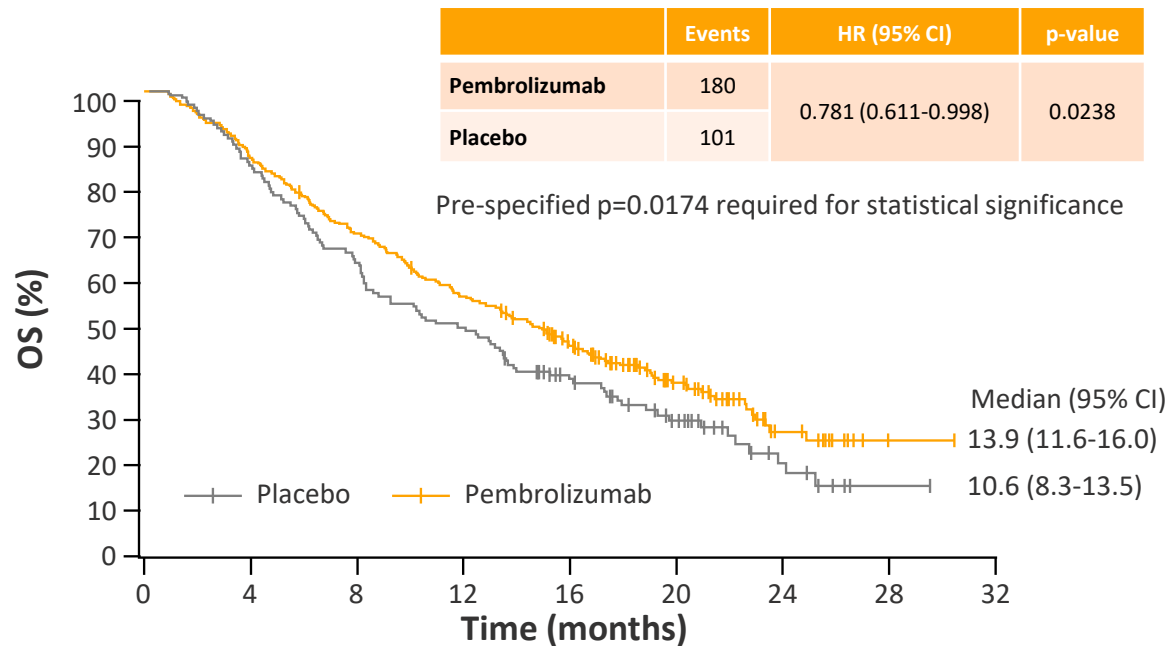
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\*Approved by the FDA, but not currently approved by the EMA

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

# 2<sup>ND</sup>-LINE TREATMENT OPTIONS: PEMBROLIZUMAB – RESULTS OF KEYNOTE-240<sup>1</sup>



**KEYNOTE-240 did not meet the statistical criteria for either of the dual primary endpoints<sup>2</sup>**

Pembrolizumab received accelerated FDA approval in patients previously treated with sorafenib based on the results of KEYNOTE-224<sup>3\*</sup>

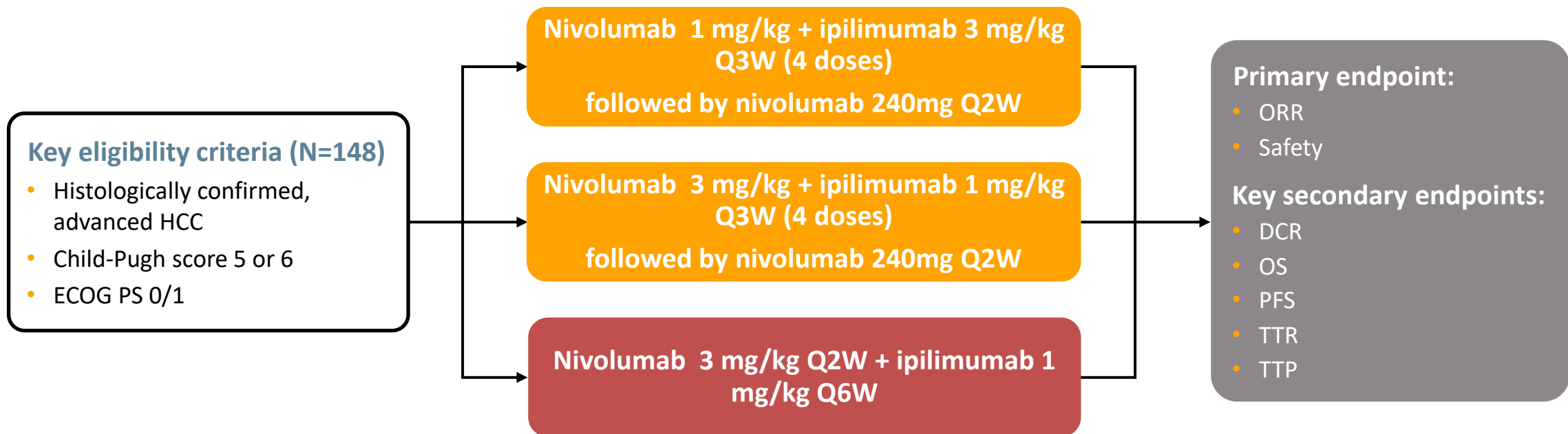
\*Approved by the FDA, but not currently approved by the EMA

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

1. NCT02702401. Available at [clinicaltrials.gov](https://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](https://www.fda.gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma). Accessed August 2020

# 2<sup>ND</sup>-LINE TREATMENT OPTIONS: NIVOLUMAB + IPIILIMUMAB – CHECKMATE-040<sup>1,2</sup>

**AIM: TO EVALUATE THE EFFICACY AND SAFETY OF 2L NIVOLUMAB + IPIILIMUMAB 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](https://clinicaltrials.gov). Accessed August 2020; 2. Yau T, et al. J Clin Oncol. 2019;37(15\_suppl):4012-4012

# 2<sup>ND</sup>-LINE TREATMENT OPTIONS: NIVOLUMAB + IPIILIMUMAB – 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)
<b>ORR, n (%)</b>	<b>16 (32)</b>	<b>15 (31)</b>	<b>15 (31)</b>	<b>46 (31)</b>
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)
<b>DCR, n (%)</b>	<b>27 (54)</b>	<b>21 (43)</b>	<b>24 (49)</b>	<b>72 (49)</b>
<b>Median TTR, months (range)</b>	<b>2.0 (1.1-2.8)</b>	<b>2.6 (1.2-5.5)</b>	<b>2.7 (1.2-8.7)</b>	–
<b>Median DoR, months (range)</b>	<b>17.5 (4.6-30.5+)</b>	<b>22.2 (4.2-29.9+)</b>	<b>16.6 (4.1+-32.0+)</b>	–
<b>ORR by investigator, n (%)</b>	<b>16 (32)</b>	<b>13 (27)</b>	<b>14 (29)</b>	–

**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**

# 2<sup>ND</sup>-LINE TREATMENT OPTIONS: CAMRELIZUMAB (ANTI-PD-1 INHIBITOR)

**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)
<b>Primary endpoints</b>			
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)
<b>Secondary endpoints</b>			
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)

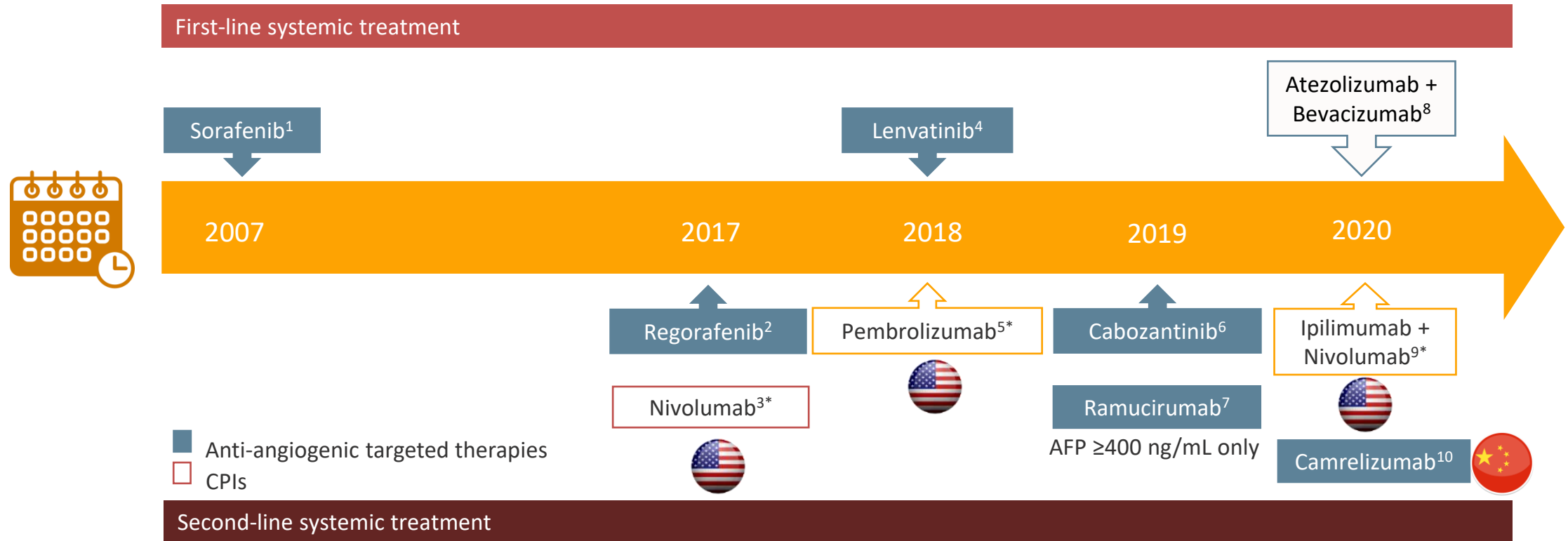
**Camrelizumab showed antitumour activity in pretreated Chinese patients with advanced HCC, preliminary survival benefit and a manageable safety profile**

\*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



# 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](http://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](http://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](http://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](http://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](http://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](http://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](http://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](http://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**

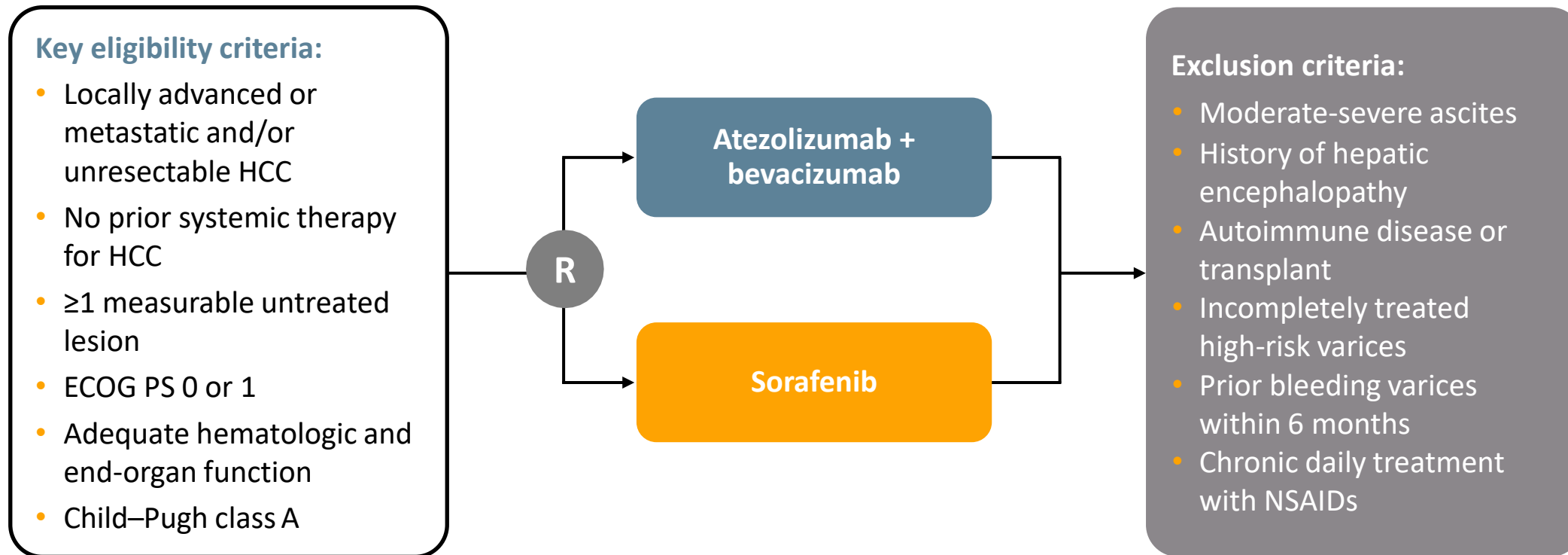
# DISCLOSURES

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

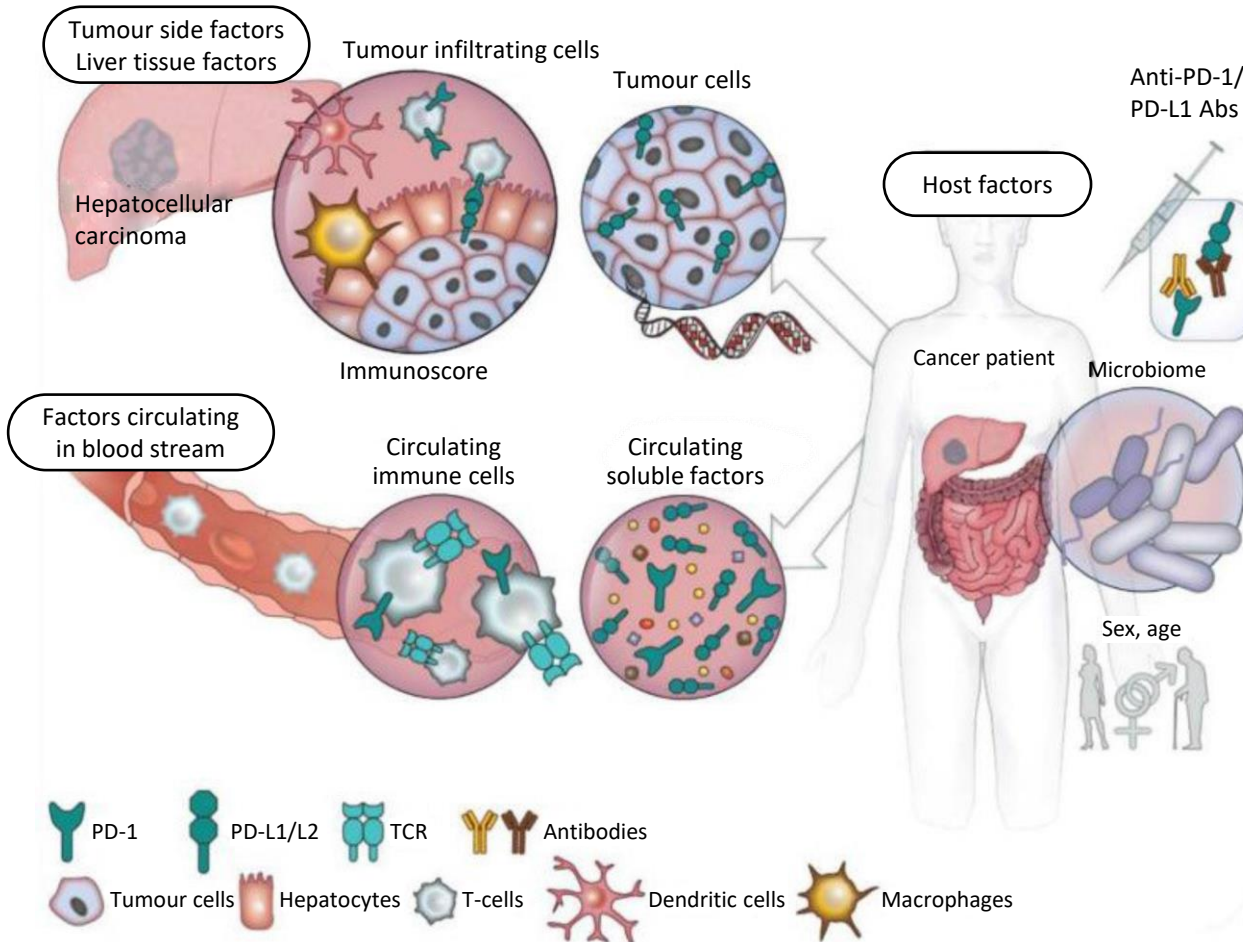
# SUMMARY OF NCCN: RECOMMENDATIONS

First-Line Therapy	Subsequent-Line Therapy
<p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"><li>• Atezolizumab + bevacizumab</li><li>• Sorafenib</li><li>• Lenvatinib</li></ul> <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"><li>• Nivolumab</li></ul>	<ul style="list-style-type: none"><li>• Sorafenib</li><li>• Lenvatinib</li><li>• Regorafenib</li><li>• Cabozantinib</li><li>• Ramucirumab</li><li>• Nivolumab</li><li>• Pembrolizumab</li><li>• Nivolumab + ipilimumab</li></ul>

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



# 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

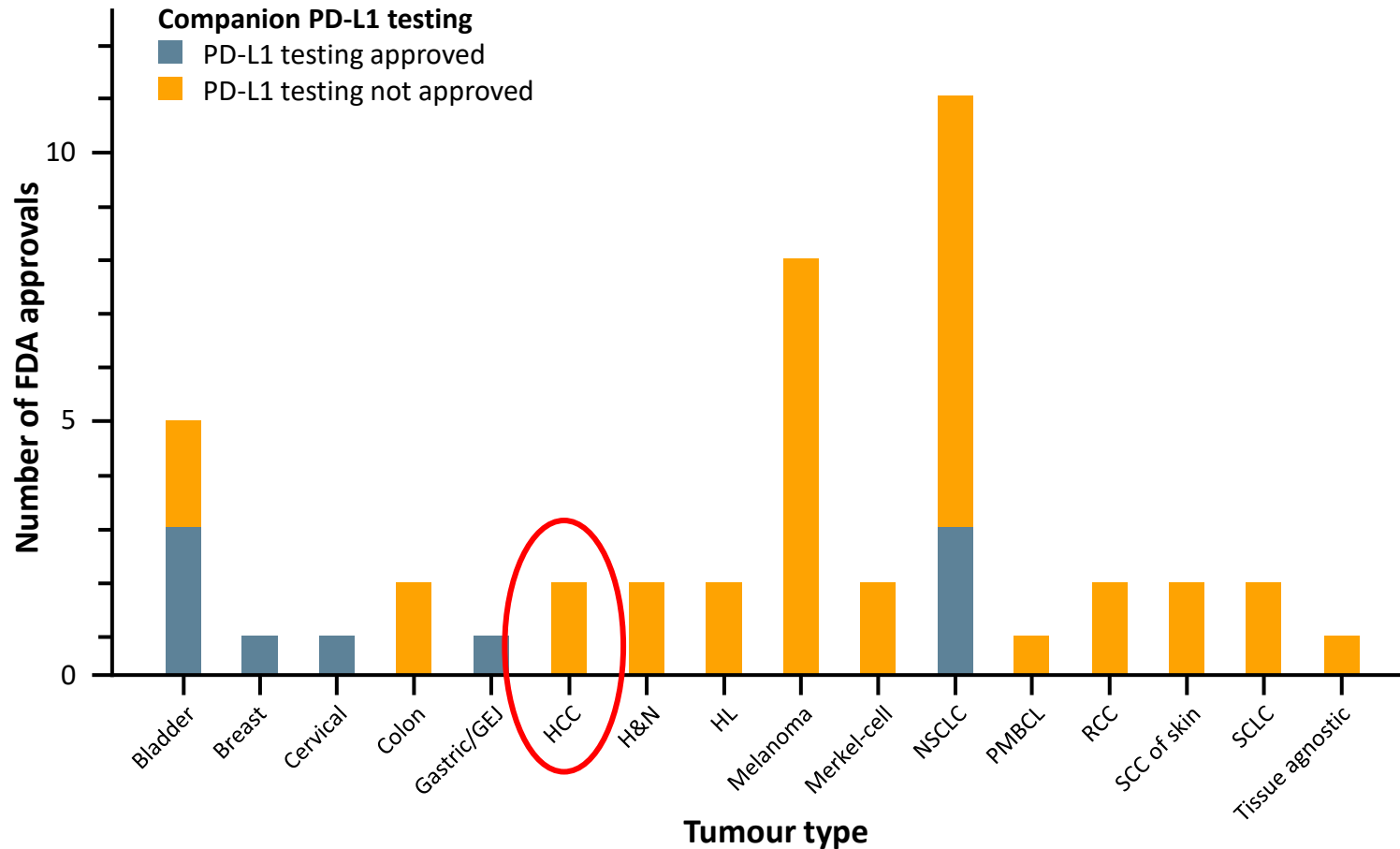
## Circulating factors

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

## Host factors

- Male sex and older age
- Gut microbiome

# 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



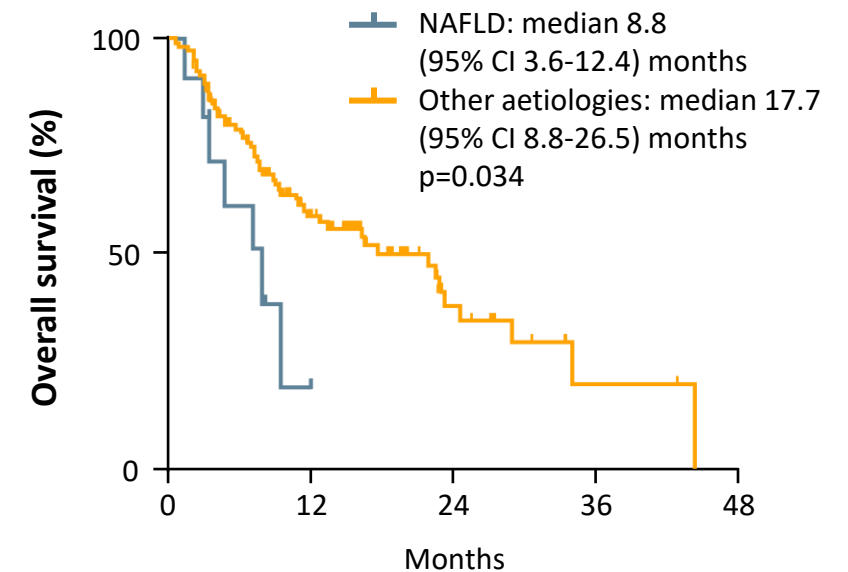
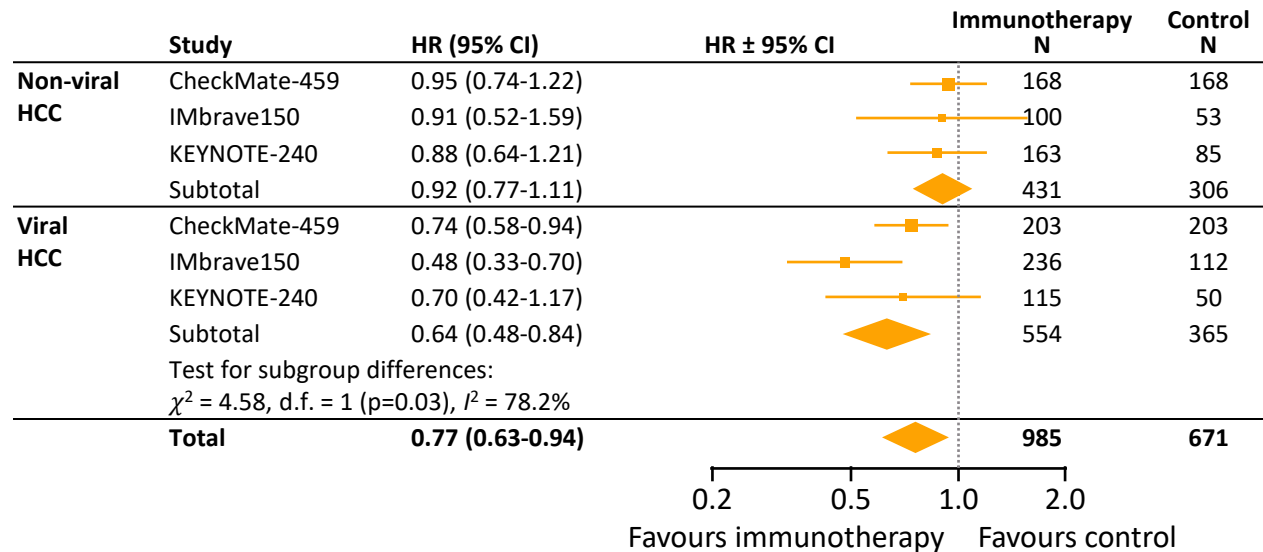
# TKIs HIT DIFFERENT TARGETS BUT DOES NOT TRANSLATE TO PRACTICE

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

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

AXL, anexelekt 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, angiotensin receptor; TKI, tyrosine kinase inhibitor; 33 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<sup>+</sup> T-cells but did not induce tumour regression, indicating impaired tumour immune surveillance

# CLINICAL FACTORS CAN HELP SELECT BETWEEN SORAFENIB AND LENVATINIB

	Sorafenib	Lenvatinib
<b>Level of evidence</b>	Phase 3	Phase 3
<b>Inclusion criteria</b>	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
<b>Efficacy</b>	Improved survival vs placebo	Non-inferior survival vs sorafenib Improved objective responses and time to progression compared to sorafenib
<b>AE profile</b>	Increased hand-foot skin reaction	Increased hypertension, proteinuria, anorexia
<b>Logistics</b>	Oral, twice daily Taken 1-2 hours removed from food	Oral, once daily Can be taken with or without food
<b>Miscellaneous</b>	Real-world effectiveness data in populations including Child B cirrhosis	

# 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)
<b>Dose reduction rate, n (%)</b>	<b>784 (40)</b>	<b>194 (29)</b>	<b>19 (26)</b>
AEs (all grades), n (%)	1,653 (84)	590 (89)	68 (92)
<b>All grade 3 or 4 AEs, n (%)</b>	<b>638 (33)</b>	<b>210 (32)</b>	<b>13 (18)</b>

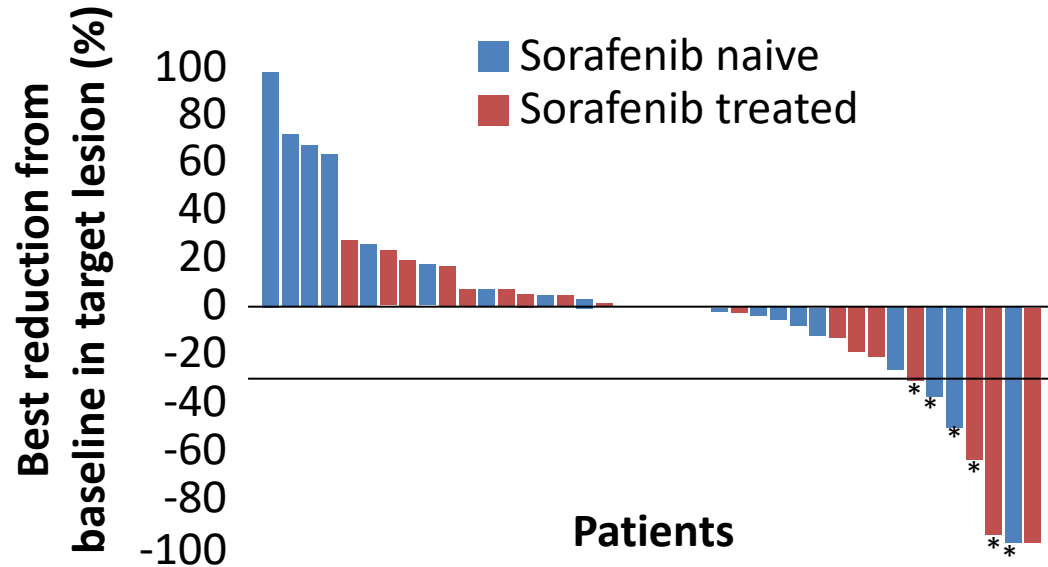
\*Three patients recorded as having Child-Pugh B but specific score not recorded

AE, adverse event

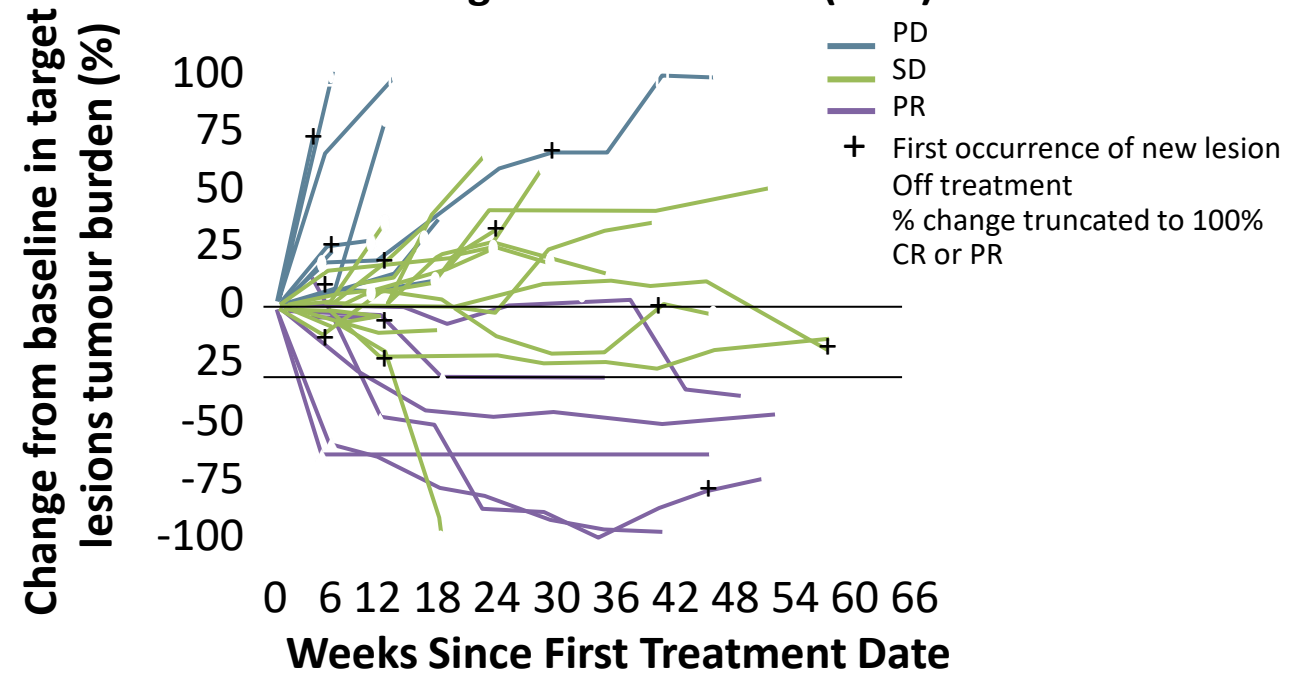
Marrero JA, et al. J Hepatol. 2016;65(6):1140-7

# CHECKMATE-040: NIVOLUMAB IN CHILD-PUGH B COHORT

Best change in target lesion per investigator assessment



Tumour burden change per investigator assessment (DoR)



- 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

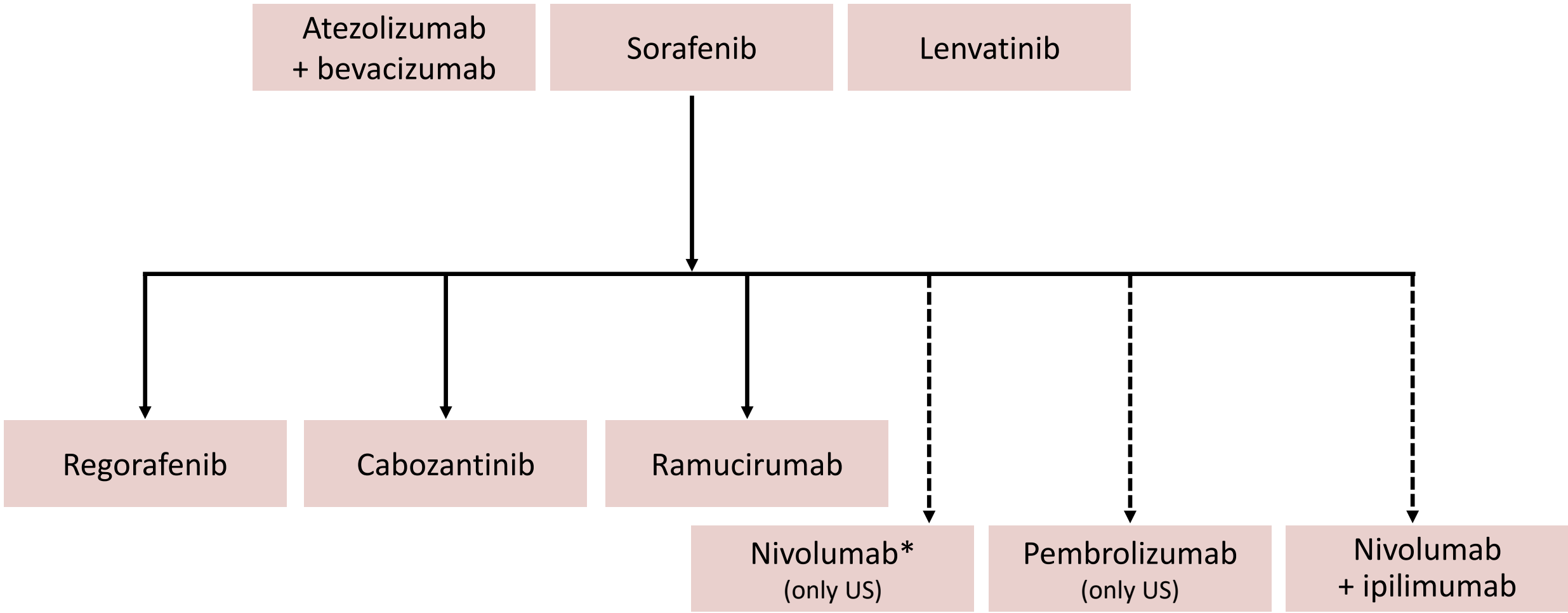
• FDA recommended to remove the accelerated approval of nivolumab for the treatment of HCC in 2<sup>nd</sup> line\*

\*<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

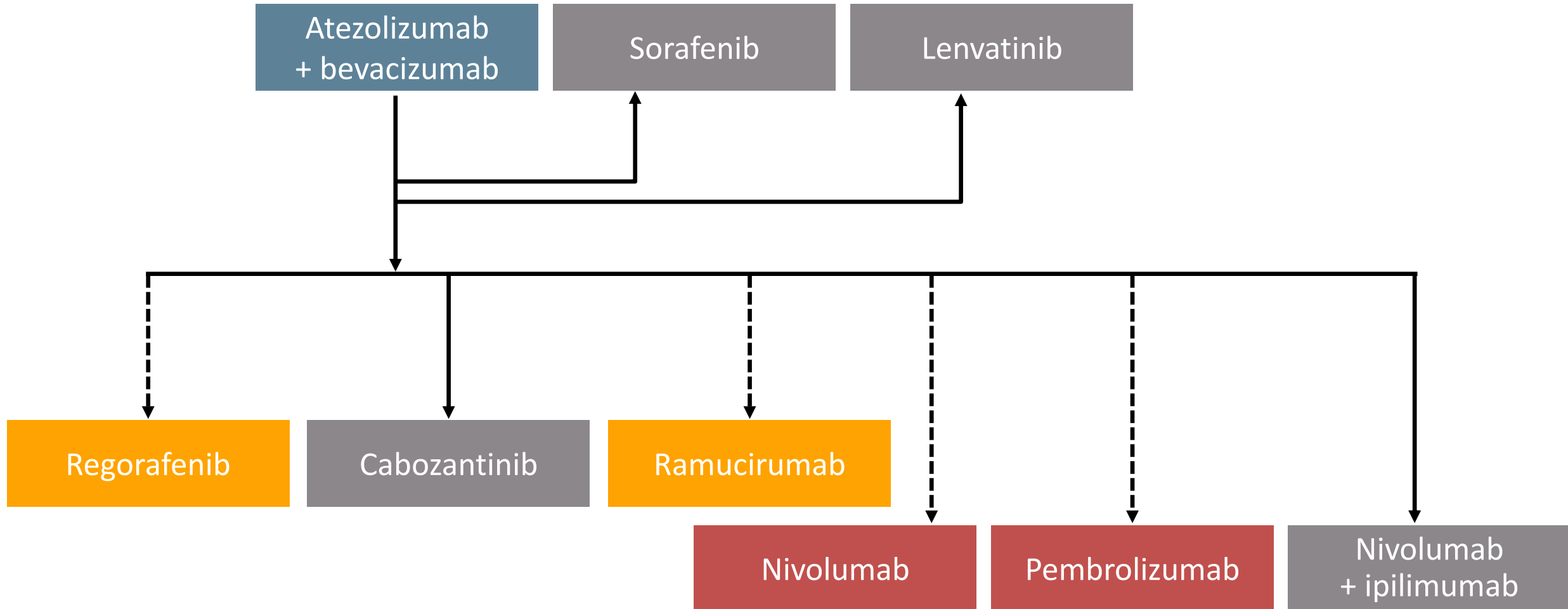


\*In April 2021, FDA recommended rescinding nivolumab approval in 2<sup>nd</sup> line HCC treatment (Source: <https://www.fda.gov/media/147929/download>. Accessed May 2021).

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

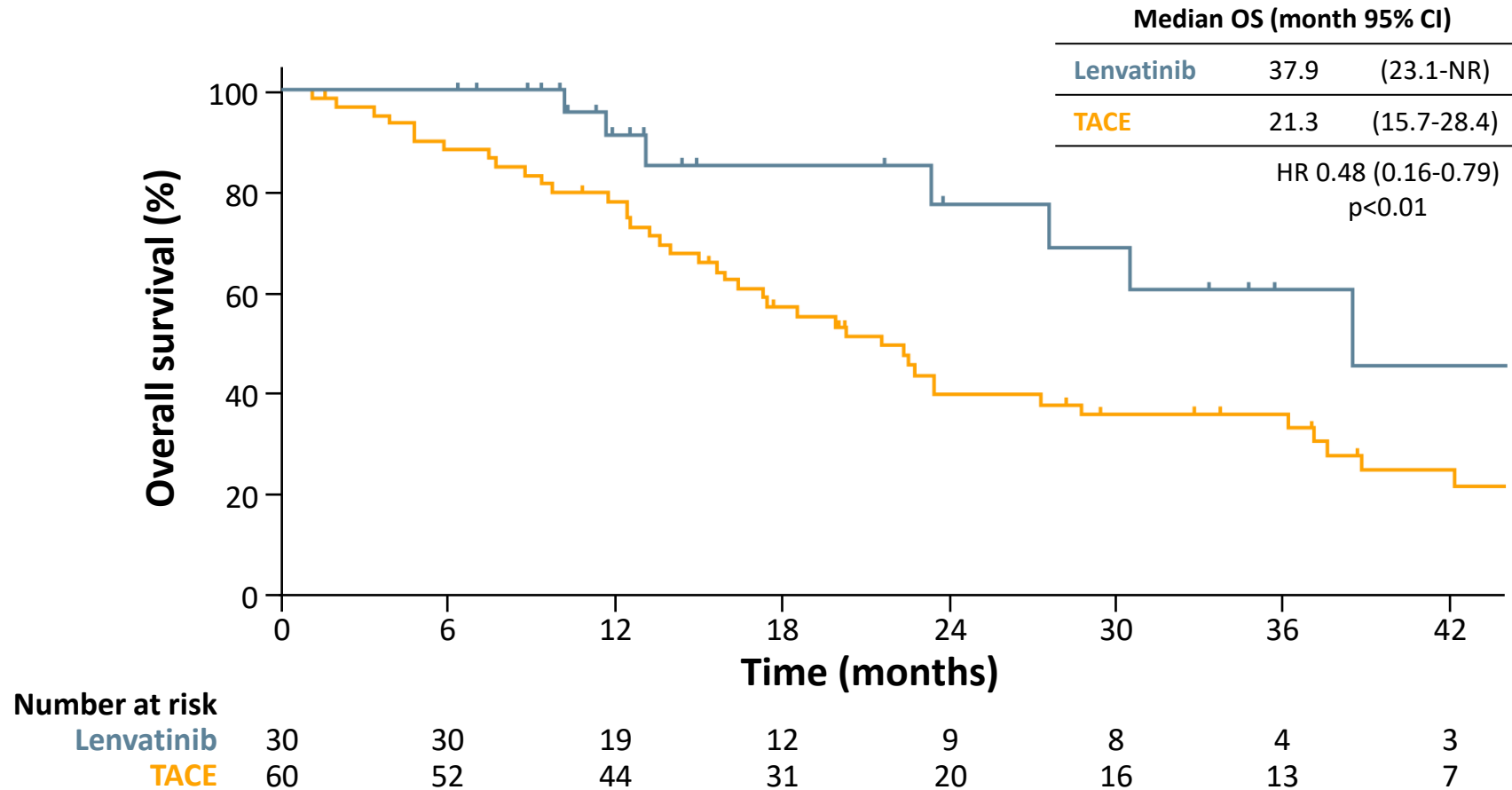
	Regorafenib	Cabozantinib	Ramucirumab
<b>Level of evidence</b>	Phase 3	Phase 3	Phase 3
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>Tolerated sorafenib but with radiographic progression</li> </ul>	<ul style="list-style-type: none"> <li>Intolerant to sorafenib or with radiographic progression</li> <li>Could have received an additional line of systemic therapy</li> </ul>	<ul style="list-style-type: none"> <li>Intolerant to sorafenib or with radiographic progression</li> <li>Patients with AFP <math>\geq</math>400 ng/mL</li> </ul>
<b>Efficacy</b>	<ul style="list-style-type: none"> <li>Improved OS</li> </ul>	<ul style="list-style-type: none"> <li>Improved OS</li> </ul>	<ul style="list-style-type: none"> <li>Improved OS</li> </ul>
<b>AE profile</b>	<ul style="list-style-type: none"> <li>Similar to AE profile of other TKIs</li> </ul>	<ul style="list-style-type: none"> <li>Similar to AE profile of other TKIs</li> </ul>	<ul style="list-style-type: none"> <li>Well tolerated with low rates of dose reductions or discontinuations</li> </ul>
<b>Logistics</b>	<ul style="list-style-type: none"> <li>Orally daily for 3 weeks with 1-week holiday</li> </ul>	<ul style="list-style-type: none"> <li>Orally once daily</li> </ul>	<ul style="list-style-type: none"> <li>IV infusion every 2 weeks</li> </ul>

# CAN THEY BE APPLIED AFTER ATEZOLIZUMAB AND BEVACIZUMAB?





# ABILITY TO SEQUENCE REQUIRES STARTING SYSTEMIC THERAPY AT THE APPROPRIATE TIME



# 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

**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

# EVALUATION PRIOR TO STARTING HCC SYSTEMIC THERAPY

## Laboratory tests

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

## Other

- Upper endoscopy

# AVAILABLE SYSTEMIC THERAPIES\*

Sequence	Agent	Administration	Class
<b>First Line</b>	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	Lenvatinib	Oral	VEGF Inhibitor
	Bevacizumab**	Injection	VEGF Inhibitor
	Atezolizumab**	Injection	PD-L1 Inhibitor
<b>Second Line</b>	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  $\geq 400$  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 47

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

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

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



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

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

\*\*Beverizumab/atezolizumab are used in combination; \*\*\* for HCC patients with AFP levels  $\geq 400$  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
<b>First Line</b>	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	Lenvatinib	Oral	VEGF Inhibitor
	Bevacizumab	Injection	VEGF Inhibitor
	Atezolizumab	Injection	PD-L1 Inhibitor
<b>Second Line</b>	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  $\geq 400$  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
<b>First Line</b>	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	Lenvatinib	Oral	VEGF Inhibitor
	Bevacizumab**	Injection	VEGF Inhibitor
	Atezolizumab**	Injection	PD-L1 Inhibitor
<b>Second Line</b>	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  $\geq 400$  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
<b>First Line</b>	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	Lenvatinib	Oral	VEGF Inhibitor
	Bevacizumab**	Injection	VEGF Inhibitor
	Atezolizumab**	Injection	PD-L1 Inhibitor
<b>Second Line</b>	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  $\geq 400$  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

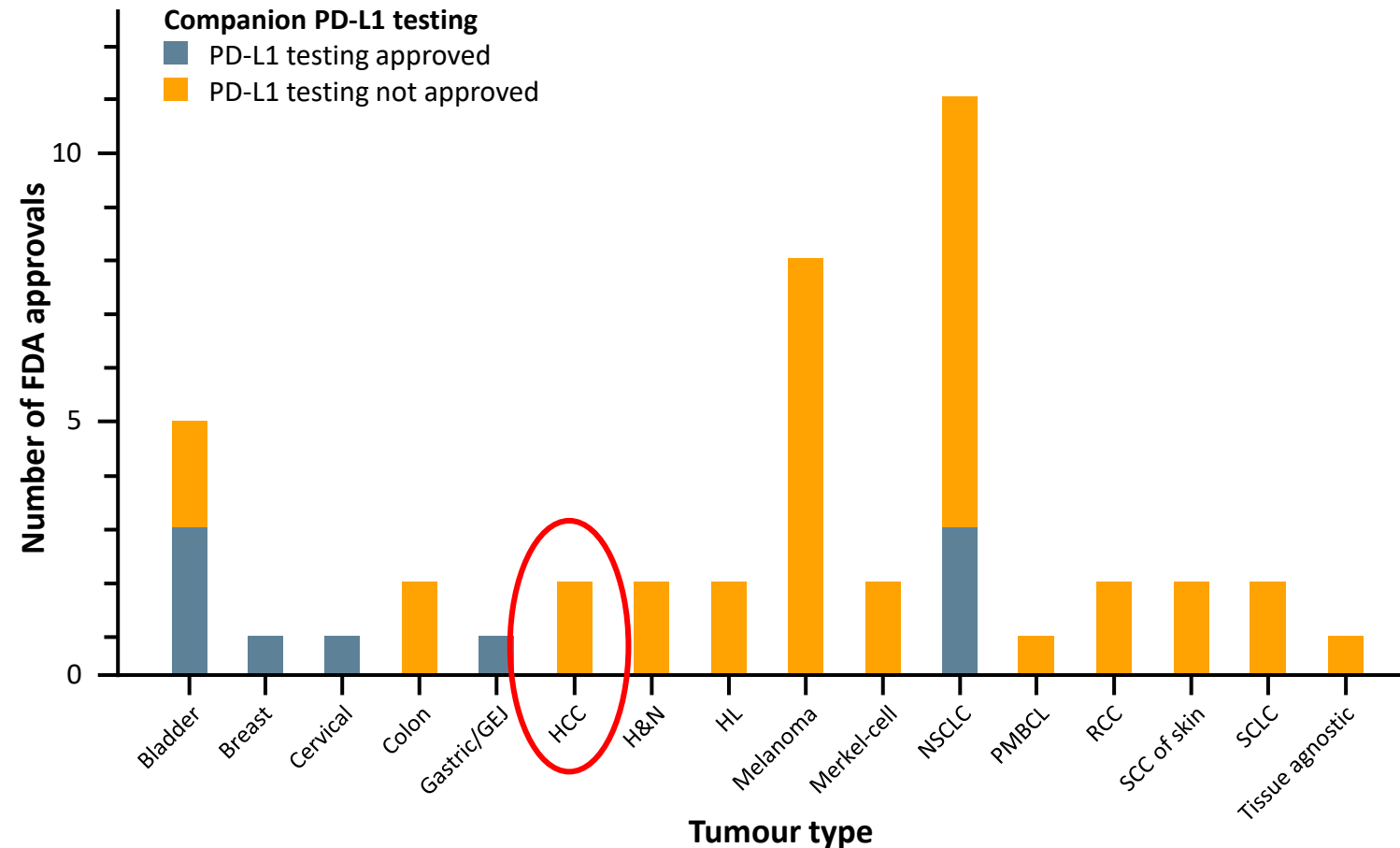
# AREAS NEEDING FURTHER RESEARCH WHEN CHOOSING SYSTEMIC THERAPY

- 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

# SELECTION BIOMARKERS CONSIDERATIONS IN TREATMENT OF HCC

Biomarkers	Clinical Relevance
PD-L1 Expression	<ul style="list-style-type: none"> <li>• Expression low in HCC (~ 10%)</li> <li>• Not found to be robust predictor</li> </ul>
Tumor mutational burden (TMB)	<ul style="list-style-type: none"> <li>• Infrequent occurrence</li> <li>• Results inconsistent</li> </ul>
Tumor-infiltrating lymphocytes (TIL)	<ul style="list-style-type: none"> <li>• ~20% HCC tumors well infiltrated</li> <li>• Additional studies needed</li> </ul>

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 Khouairy 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

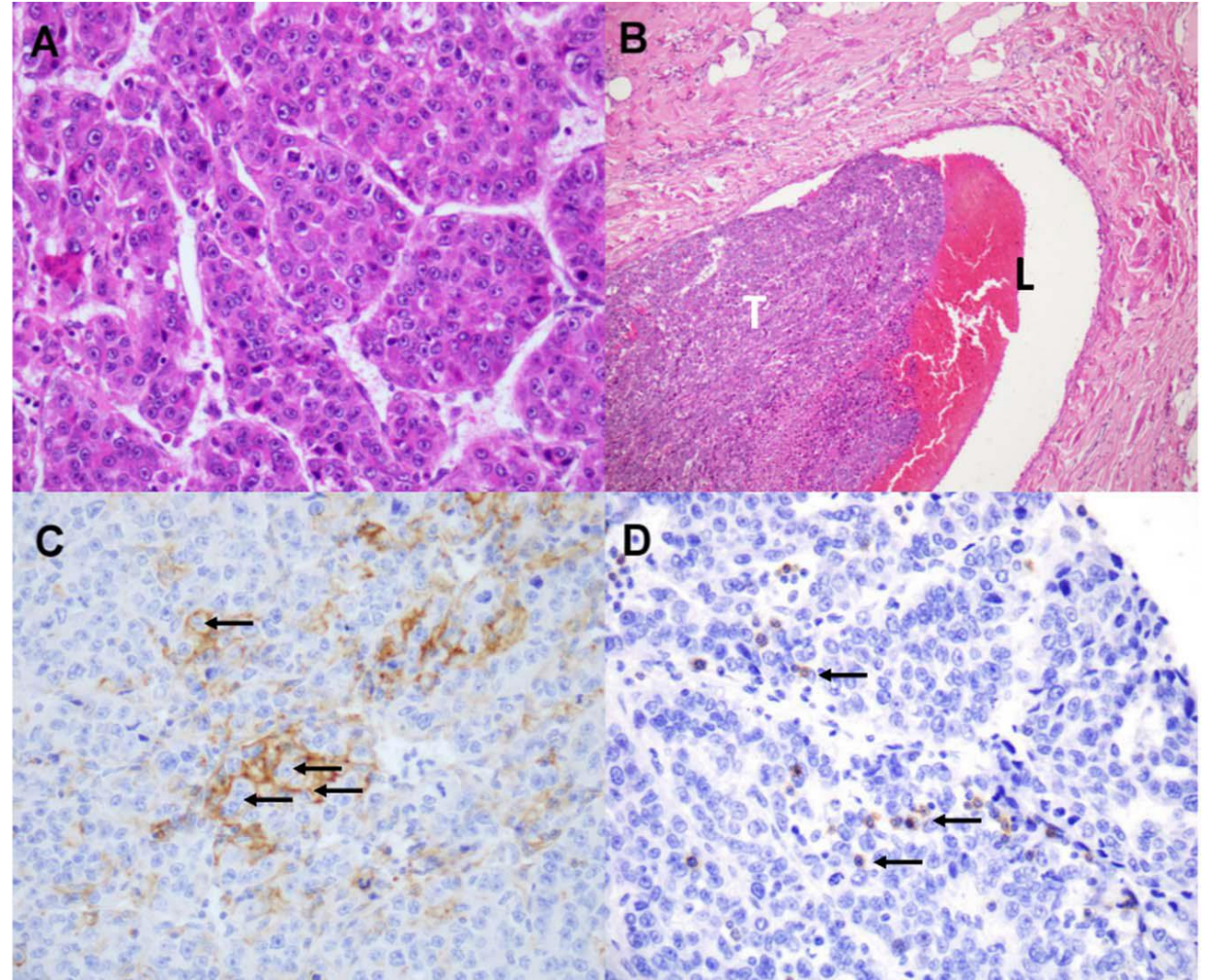
# PATHOLOGICAL FEATURES OF HCC

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

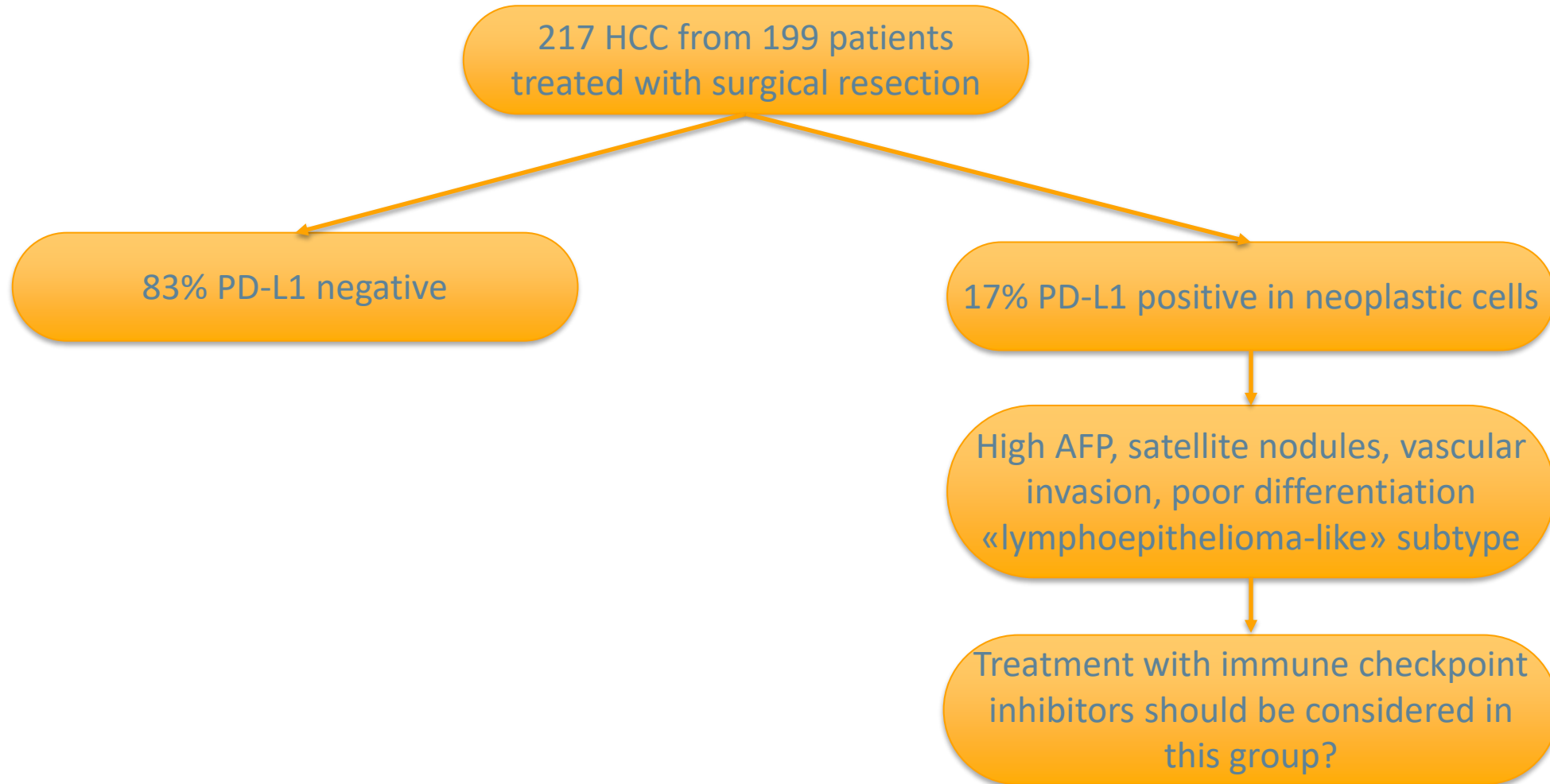
(B) Massive vascular invasion at the tumor margin, with tumoral thrombi within vessel lumens (hematein-eosin-saffron, x 100).

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

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



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





# 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

**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

## Cancer immunotherapy combinations with anti-VEGF or a TKI

Anti-PDL1	<b>Atezolizumab + cabozantinib</b> (COSMIC-312; phase III) <i>Anti-PD-L1 + TKI</i>	<b>Avelumab + axitinib</b> (VEGF Liver 100; phase Ib) <i>Anti-PD-L1 + TKI</i>	<b>Durvalumab + tivozanib</b> (DEDUCTIVE; phase Ib/II) <i>Anti-PD-L1 + VEGFR TKI</i>	<b>Durvalumab + lenvatinib*</b> (Dulect2020-1; N/A) <i>Anti-PD-L1 + TKI</i>		
	<b>Pembrolizumab + lenvatinib</b> (LEAP-002; phase III) <i>Anti-PD-1 + TKI</i>	<b>Pembrolizumab + regorafenib</b> (KEYNOTE-743; phase Ib) <i>Anti-PD-1 + TKI</i>	<b>Penpulimab + anlotinib*</b> (phase III) <i>Anti-PD-1 + TKI</i>	<b>CS1003 + lenvatinib*</b> (phase III) <i>Anti-PD-1 + TKI</i>	<b>Camrelizumab + apatinib*</b> (phase III) <i>Anti-PD-1 + TKI</i>	
Anti-PD1	<b>Nivolumab + lenvatinib</b> (IMMUNIB; phase II) <i>Anti-PD-1 + TKI</i>	<b>Sintilimab + bev-biosimilar*</b> (ORIENT-32; <sup>‡</sup> phase II/III) <i>Anti-PD-1 + anti-VEGF</i>	<b>Nivolumab + lenvatinib</b> (Study 117; phase Ib) <i>Anti-PD-1 + TKI</i>	<b>Toripalimab + lenvatinib*</b> (phase III) <i>Anti-PD-1 + TKI</i>		
	<b>SCT-I10A + bev-biosimilar*</b> (phase II/III) <i>Anti-PD-1 + anti-VEGF</i>	<b>Toripalimab + bevacizumab*</b> (phase II) <i>Anti-PD-1 + anti-VEGF</i>	<b>Nivolumab + regorafenib</b> (RENOBATE; phase II) <i>Anti-PD-1 + TKI</i>	<b>Nivolumab + sorafenib</b> (phase II) <i>Anti-PD-1 + TKI</i>		
	<b>Camrelizumab + lenvatinib*</b> (phase I/II) <i>Anti-PD-1 + TKI</i>	<b>Toripalimab + sorafenib*</b> (phase I/II) <i>Anti-PD-1 + TKI</i>	<b>Spartalizumab + sorafenib</b> (phase Ib) <i>Anti-PD-1 + TKI</i>			
				<ul style="list-style-type: none"> <li>■ Phase Ib/II data available</li> <li>■ No data available</li> <li>□ Ongoing global phase III trials</li> </ul>		

## Cancer immunotherapy combinations with two CPIs

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

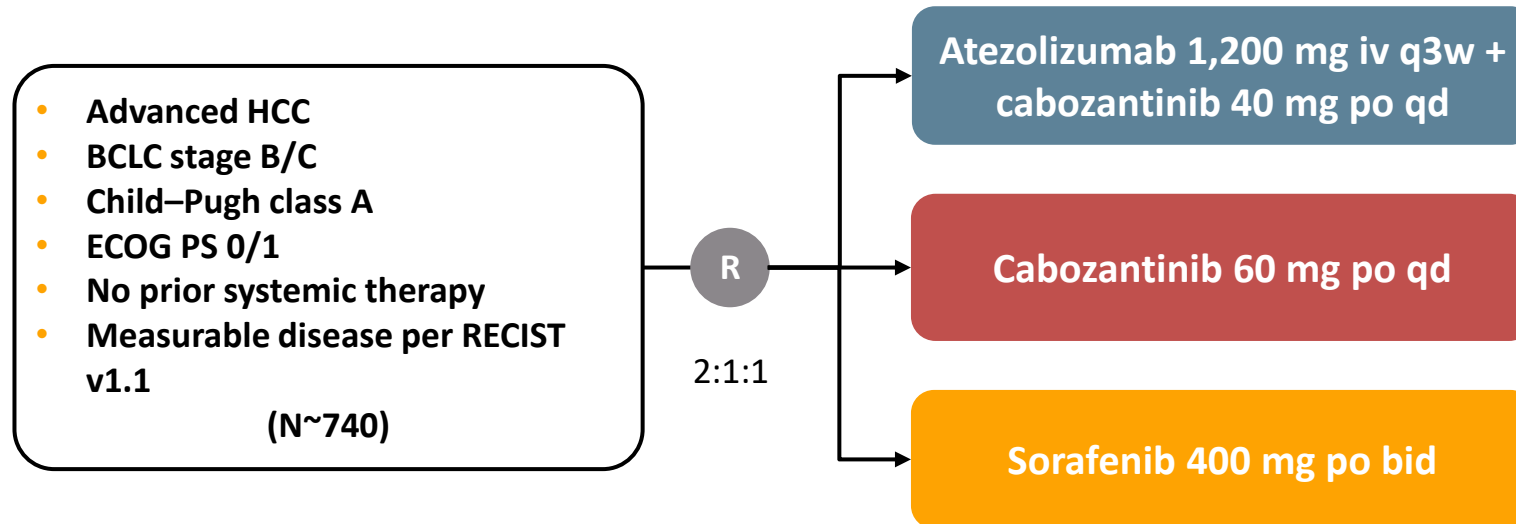
## Bispecific antibody combinations

<b>XmAb22841 ± pembrolizumab</b> (DUET-4; phase I) <i>Anti-CTLA-4 × anti-LAG3 ± anti-PD-1</i>	<b>AK104 + lenvatinib*</b> (phase I/II) <i>Anti-PD-1 × anti-CTLA-4 + TKI</i>
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\*China only; <sup>‡</sup>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



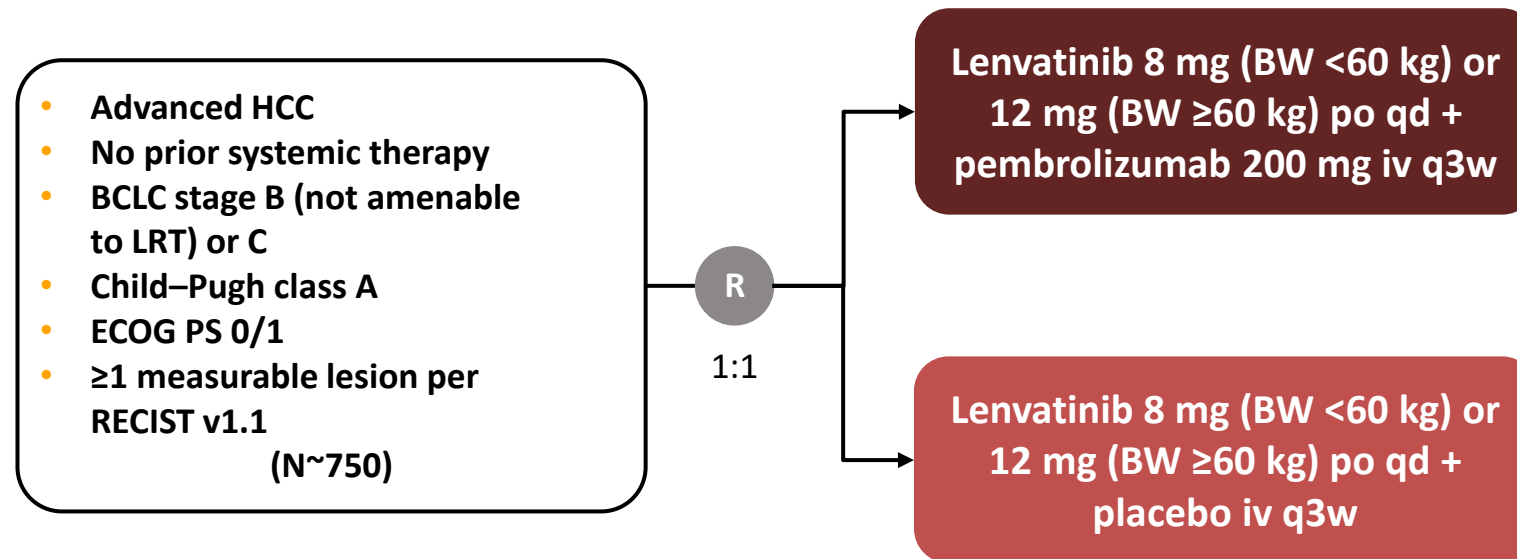
- **Co-primary endpoints:** PFS by BIRC RECIST v1.1 and OS for atezolizumab + cabozantinib vs sorafenib
- **Secondary endpoint:** Duration of PFS by BIRC RECIST v1.1 for cabozantinib vs sorafenib

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



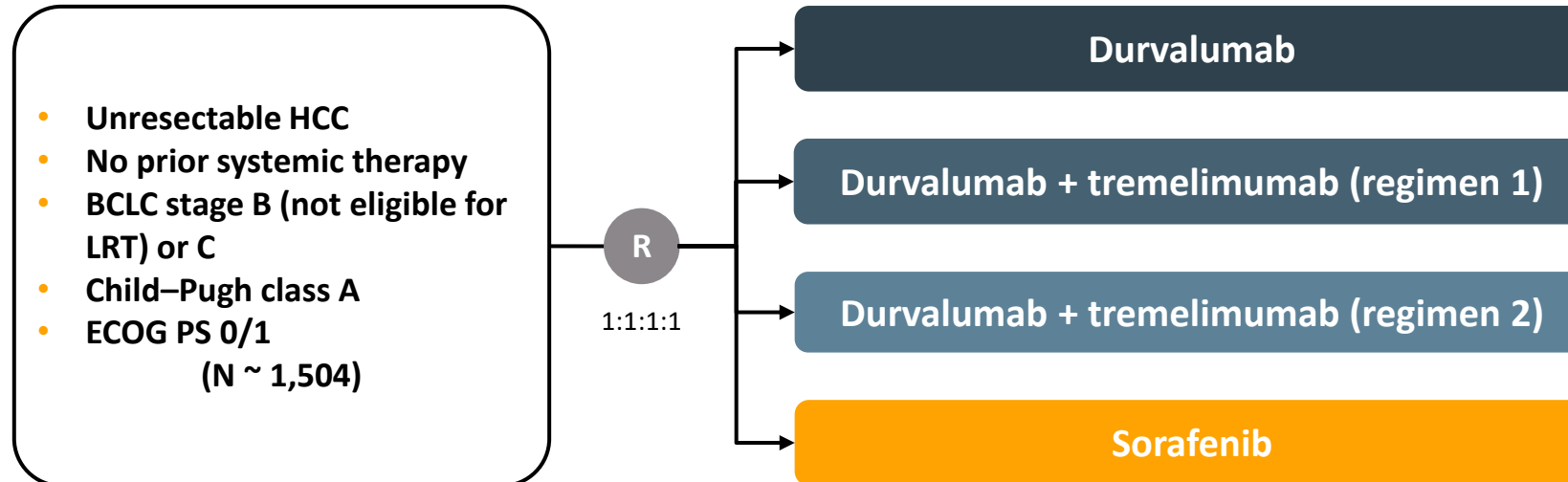
- **Co-primary endpoints:** PFS BICR assessed by RECIST v1.1, OS
- **Secondary/exploratory endpoints includes:** ORR,\* DoR,\* DCR,\* TTP,\* PFS,‡ safety, PK

\*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

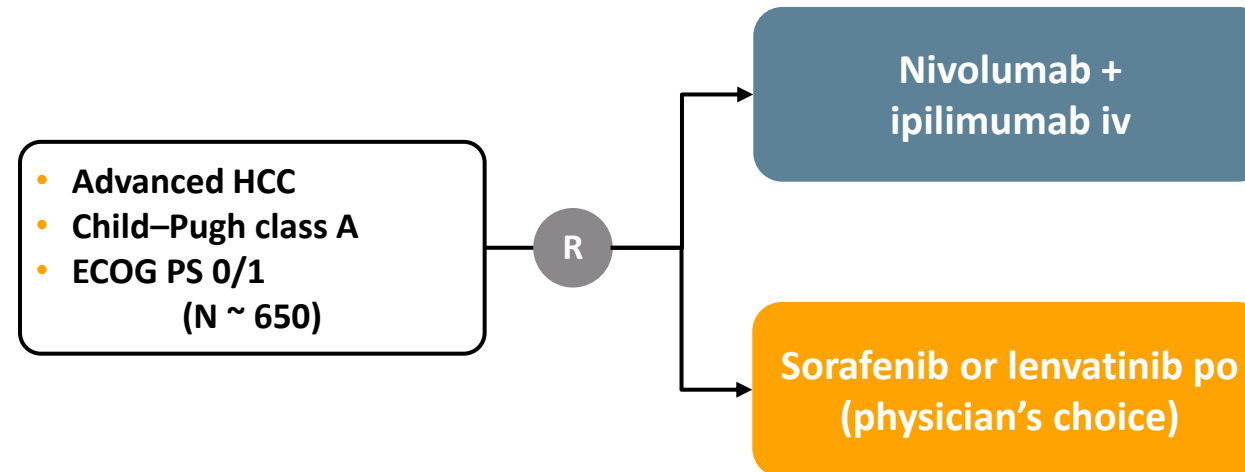
Source: <https://clinicaltrials.gov/ct2/show/NCT03713593>

# 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

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



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

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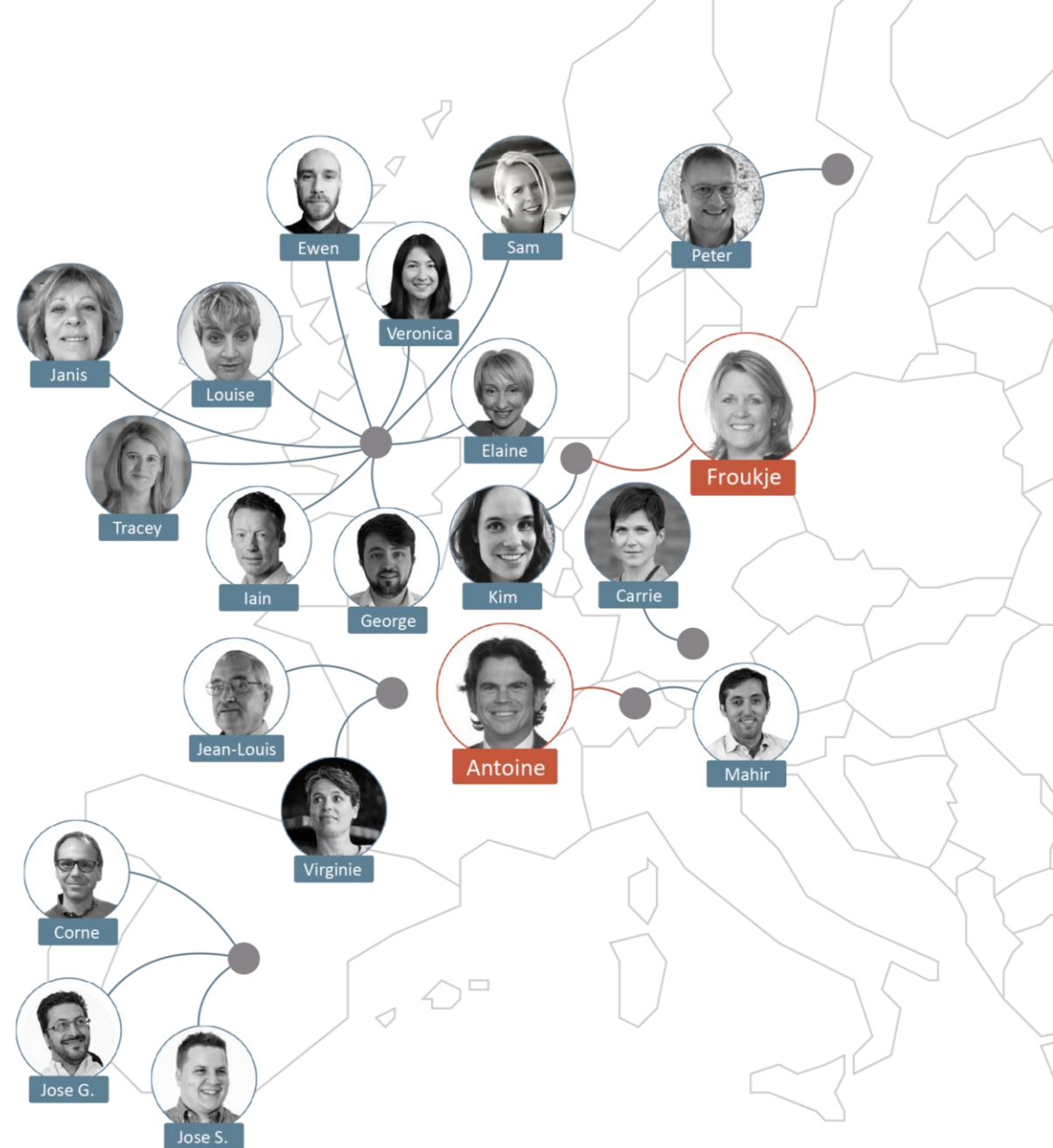
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