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EXPERTS KNOWLEDGE SHARE:

TREATMENT SEQUENCING IN ADVANCED HCC

Prof. Peter Galle, Dr. Ruth He,
Dr. Kirti Shetty and Dr. David Kleiner

Monday November 11th 2019

Boston, USA

HCC, hepatocellular carcinoma

EXPERTS KNOWLEDGE SHARE OBJECTIVES

TREATMENT SEQUENCING IN ADVANCED HCC

- **Objectives:**
  - Provide an overview of the systemic treatment landscape in HCC
    - *Including TKIs and immune therapies*
  - Discuss immune-related hepatotoxicity
  - Explore the future role of tissue-based biomarkers in HCC

HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor

DISCLAIMER

Please note:

The views expressed within this presentation are the personal opinions of the authors. They do not necessarily represent the views of the author's academic institution or the rest of the HCC CONNECT group.

This meeting is supported by an Independent Educational Grant from Bayer.

OVERVIEW OF THE SYSTEMIC TREATMENT LANDSCAPE IN HCC

Peter R. Galle
University of Mainz, Germany

HCC, hepatocellular carcinoma

HISTORY OF THE TREATMENT LANDSCAPE FOR HCC

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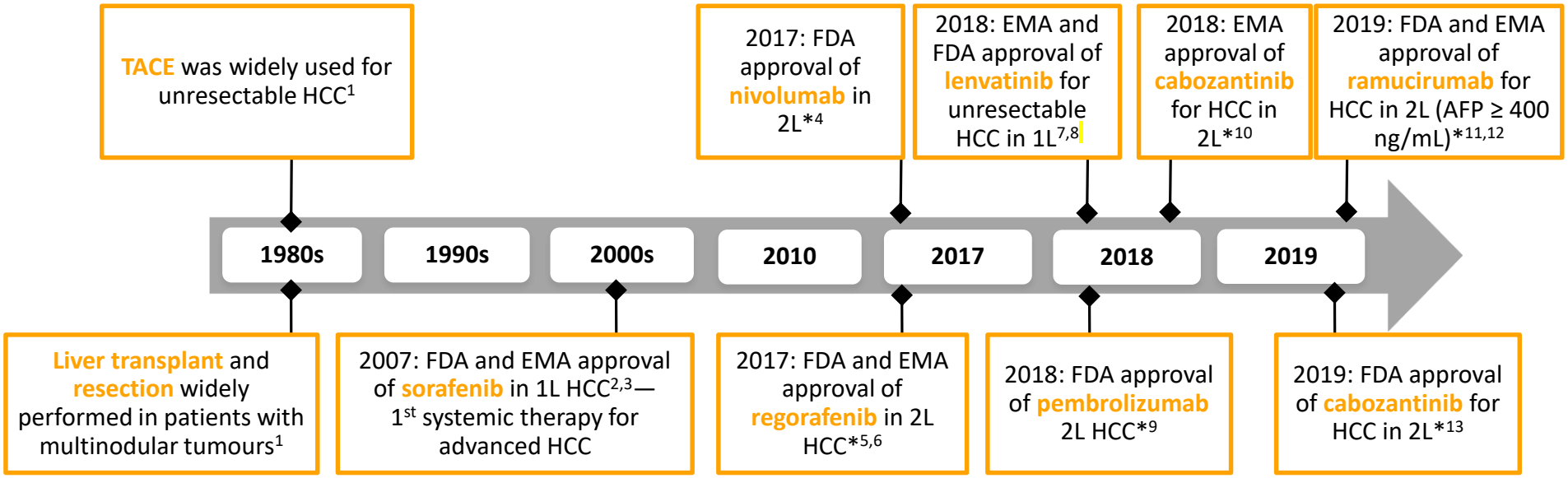
TREATMENT OPTIONS WERE LIMITED FOR UNRESECTABLE HCC

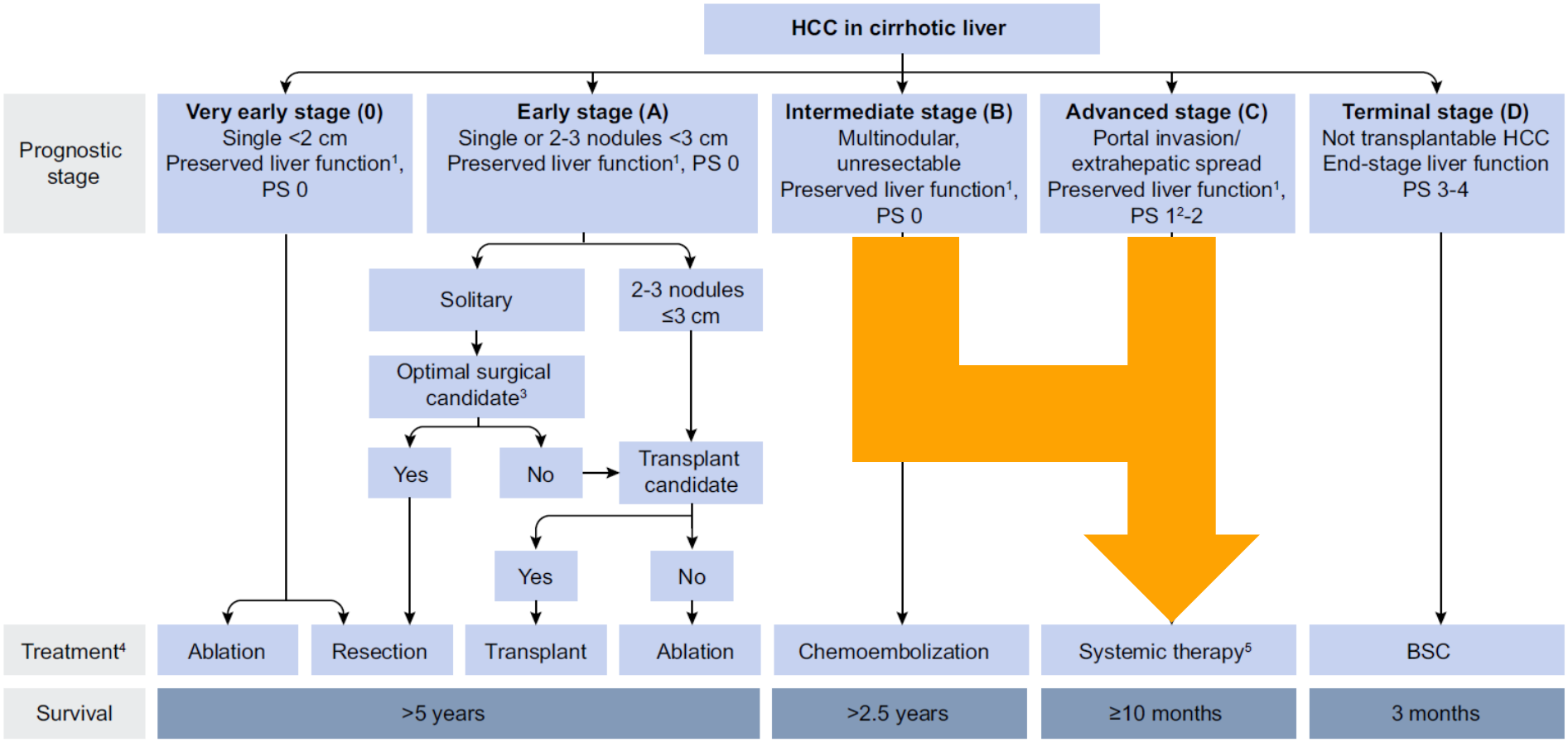


7 (FDA) or 5 (EMA) systemic agents have been approved for use in HCC

*after treatment with sorafenib.

1L, first line; 2L, second line; AFP, alpha fetoprotein; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolisation

1. Tang ZY. 2001. Available from: www.ncbi.nlm.nih.gov/books/NBK6903. 2. FDA PI Nexavar. 3. SmPC Nexavar. 4. FDA PI Opdivo. 5. FDA PI Stivarga. 6. FDA PI Stivarga. 7. SmPC Lenvima. 8. FDA PI Lenvima. 9. FDA PI Keytruda. 10. SmPC Cabometyx. 11. FDA PI Cyramza. 12. SmPC Cyramza. 13. FDA PI Cabometyx.



BSC, best-supportive care; HCC, hepatocellular carcinoma; PS, performance status
EASL. J Hepatol 2018;69:182-236

PHASE 3 CLINICAL TRIALS TESTING MOLECULAR TARGETED THERAPIES AND DEVICES IN ADVANCED HCC

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FIRST LINE[1]

	Drugs	N = 5966	Median OS (months)	HR (95% CI)	p-value
SHARP	sorafenib	299	10.7	0.69 (0.55-0.87)	<0.001
	placebo	303	7.9		
Asia-Pacific	sorafenib	150	6.5	0.68 (0.5 0.93)	0.01
	placebo	76	4.2		
SUN1170	sunitinib	530	7.9	1.3 (1.13-1.5)	0.001
	sorafenib	544	10.2		
BRISK-FL	brivanib	577	9.5	1.07 (0.94-1.23)	0.31
	sorafenib	578	9.9		
LIGHT	linifanib	514	9.1	1.046 (0.896-1.221)	
	sorafenib	521	9.8		
SEARCH	sorafenib + erlotinib	362	9.5	0.92 (0.781 - 1.106)	0.2
	sorafenib	358	8.5		
Study 304/ REFLECT	lenvatinib	478	13.6	0.92 (0.79-1.06)	<0.05
	sorafenib	476	12.3		
ALLIANCE	sorafenib+doxo	173	9.3	1.06 (0.8-1.4)	NS
	sorafenib	173	10.5		
SILIUS	sorafenib + HIAC	88	11.8	1 (0.7-1.4)	NS
	sorafenib	102	11.8		
SARAH	SIRT (Y-90)	Total	8	1.15 (0.94-1.41)	NS
	sorafenib	459	9.9		
SIRveNIB	SIRT (Y-90)	182	8.8	1.12 (0.88-1.42)	NS
	sorafenib	178	10		

SECOND LINE[1]

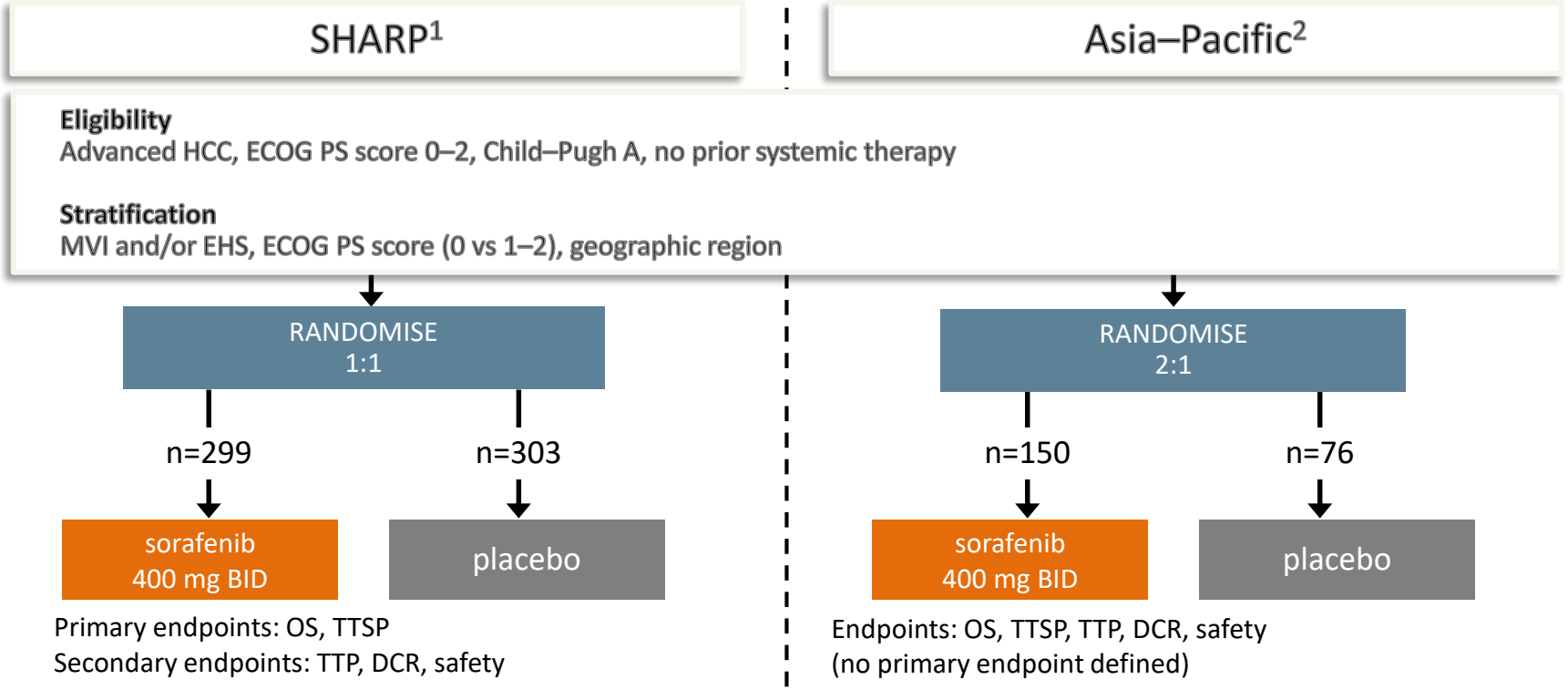
	Drugs	N = 3123	Median OS (months)	HR (95% CI)	p-value
BRISK-PS	brivanib	263	9.4	0.89 (0.69-1.15)	0.33
	placebo	132	8.2		
EVOLVE-1	everolimus	362	7.6	1.05 (0.86-1.27)	0.68
	placebo	184	7.3		
REACH	ramucirumab	283	9.2	0.86 (0.72-1.05)	0.13
	placebo	282	7.6		
RESORCE	regorafenib	379	10.6	0.63 (0.50-0.79)	<0.001
	placebo	194	7.8		
METIV-HCC	tivantinib	226	8.4	0.97 (0.75-1.25)	NS
	placebo	114	9.1		
CELESTIAL	cabozantinib	467	10.2	0.76 (0.63-0.92)	0.0049
	placebo	237	8.0		
REACH-2[2]	ramucirumab	197	8.5	0.71 (0.531-0.949)	0.0199
	placebo	95	7.3		

N=9,381

CI, confidence interval; doxo, doxorubicin; HIAC, hepatic intra-arterial chemotherapy; HR, hazard ratio; OS, overall survival; SIRT, selective internal radiation therapy

1. EASL. J Hepatol 2018;69:182-236. 2. Zhu AX, et al. Lancet Oncol 2019;20:282-96

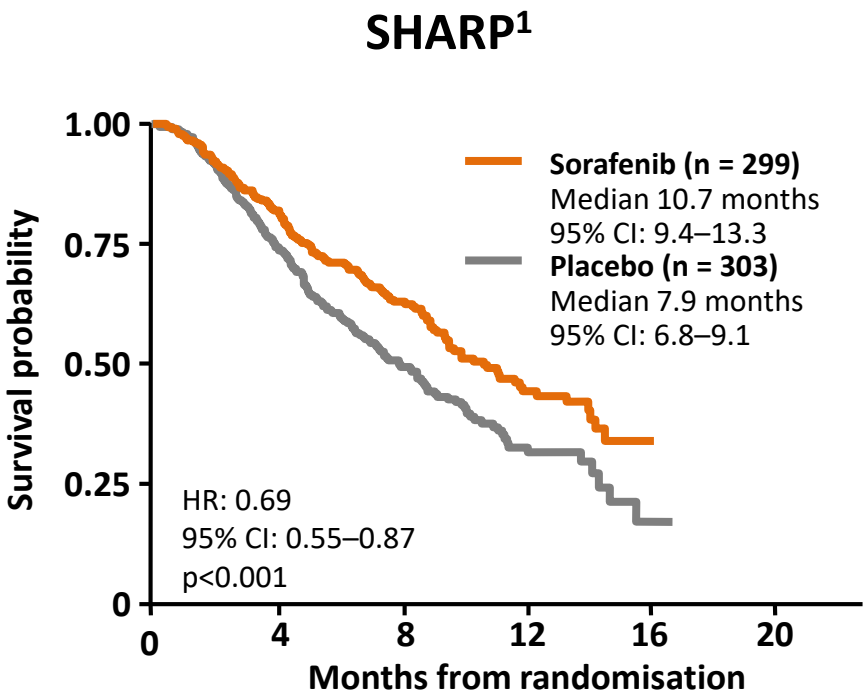
PHASE 3 SHARP AND ASIA-PACIFIC TRIALS

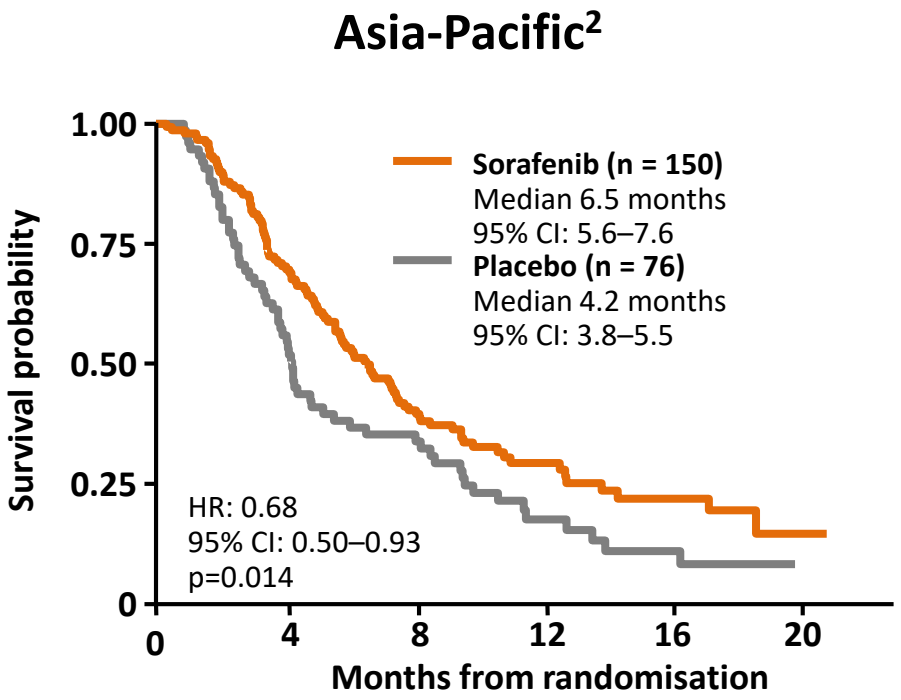


BID, twice daily; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; MVI, macroscopic vascular invasion; OS, overall survival; TTP, time to progression; TTSP, time to symptomatic progression.

1. Llovet JM, et al. N Engl J Med 2008;359:378-90. 2. Cheng AL, et al. Lancet Oncol 2009;10:25-34

SHARP AND ASIA-PACIFIC TRIALS: OS





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

1. Llovet JM, et al. N Engl J Med 2008;359:378-90. 2. Cheng AL, et al. Lancet Oncol 2009;10:25-34

PHASE 3 SHARP TRIAL: BEST RESPONSE BY RECIST

(INDEPENDENT REVIEW)

	Sorafenib n=299 %	Placebo n=303 %
Overall response*		
Complete response	0	0
Partial response	2	1
Stable disease	71	67
Progressive disease	18	24
Progression-free rate at 4 months	62	42

*Not assessable: sorafenib (8.7%), placebo (8.3%)
RECIST, Response Evaluation Criteria in Solid Tumours
Llovet JM, et al. N Engl J Med 2008;359:378-90

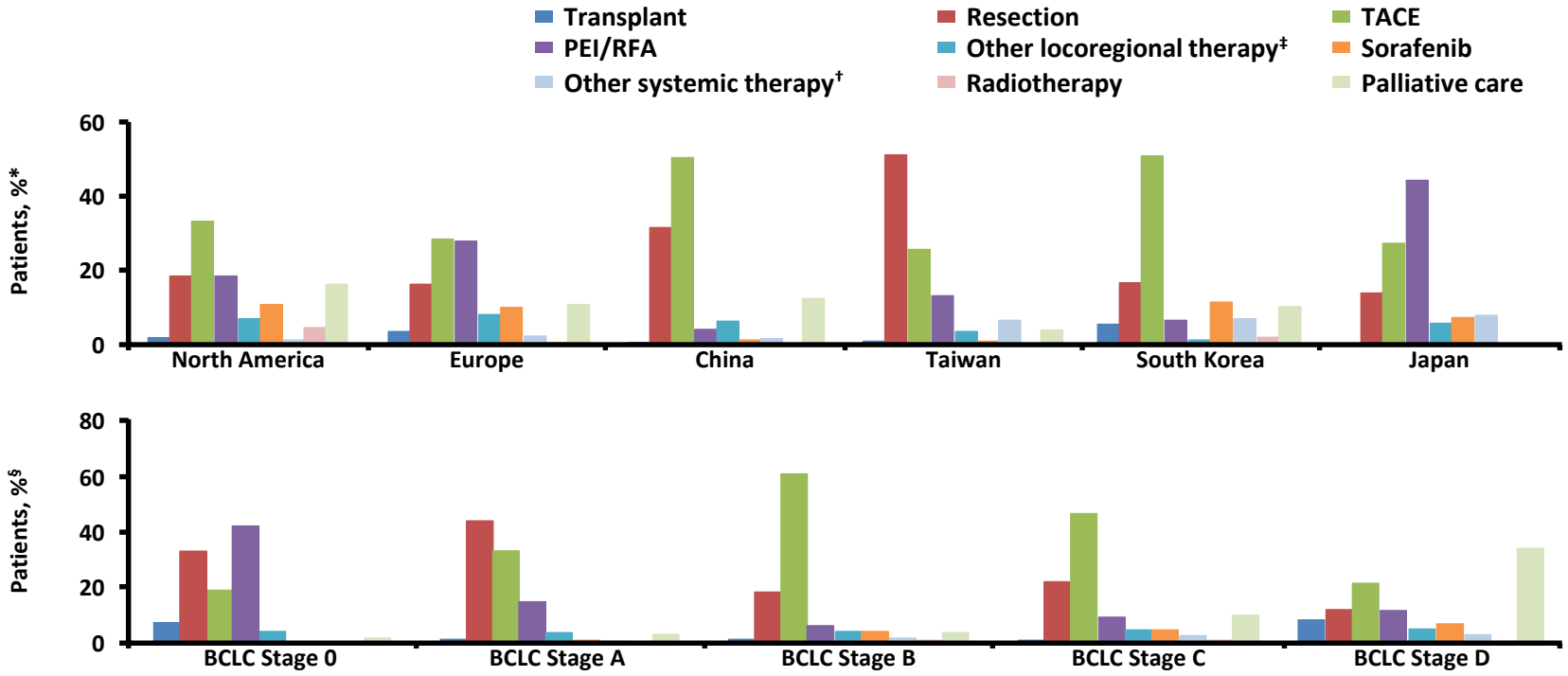
PHASE 3 SHARP TRIAL: TOXICITY

	Sorafenib n=297		Placebo n=302	
Toxicity (%)	**All**	**Grade 3/4**	**All**	**Grade 3/4**
Anorexia	14	<1	3	1
Weight loss	9	2	1	0
Alopecia	14	0	2	0
Hand-foot skin reaction	21	8	3	<1
Pain (abdominal)	8	2	3	1
Nausea	11	<1	8	1
Vomiting	5	1	3	1
Diarrhoea	39	8	11	2
Liver dysfunction	<1	<1	0	0
Bleeding	7	1	4	1

Adapted from Llovet JM, et al. N Engl J Med 2008;359:378-90

BRIDGE STUDY

FIRST RECORDED HCC TREATMENT BY COUNTRY/REGION AND BCLC STAGE



% based on percentage of population with known values
† Other than sorafenib
‡ Other than PEI/RFA or TACE
§ % based on number of patients with data available; total may add up to >100% if more than one treatment was started concurrently

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolisation

Park JW, et al. Liver Int 2015 35:2155-66

OTHER PHASE 3 TRIALS ….

FIRST-LINE PHASE 3 TRIALS TESTING MOLECULAR TARGETED THERAPIES AND DEVICES IN ADVANCED HCC

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EASL. J Hepatol 2018;69:182-236

REFLECT STUDY
STUDY SCHEMA

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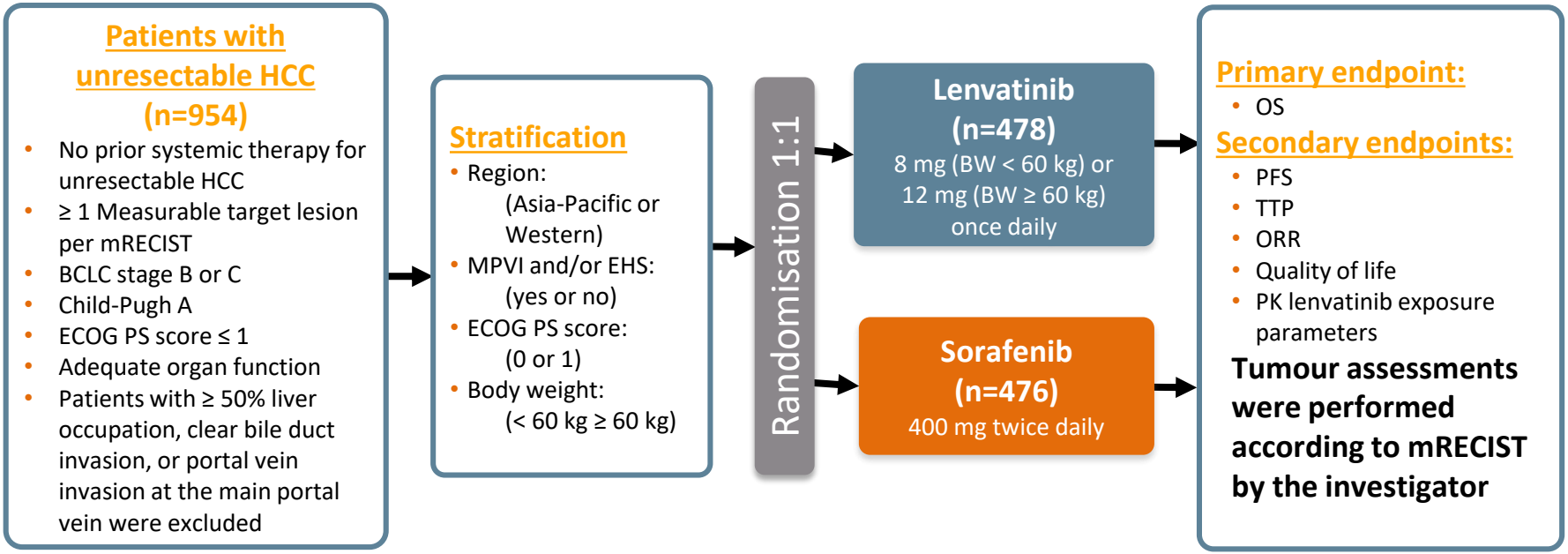
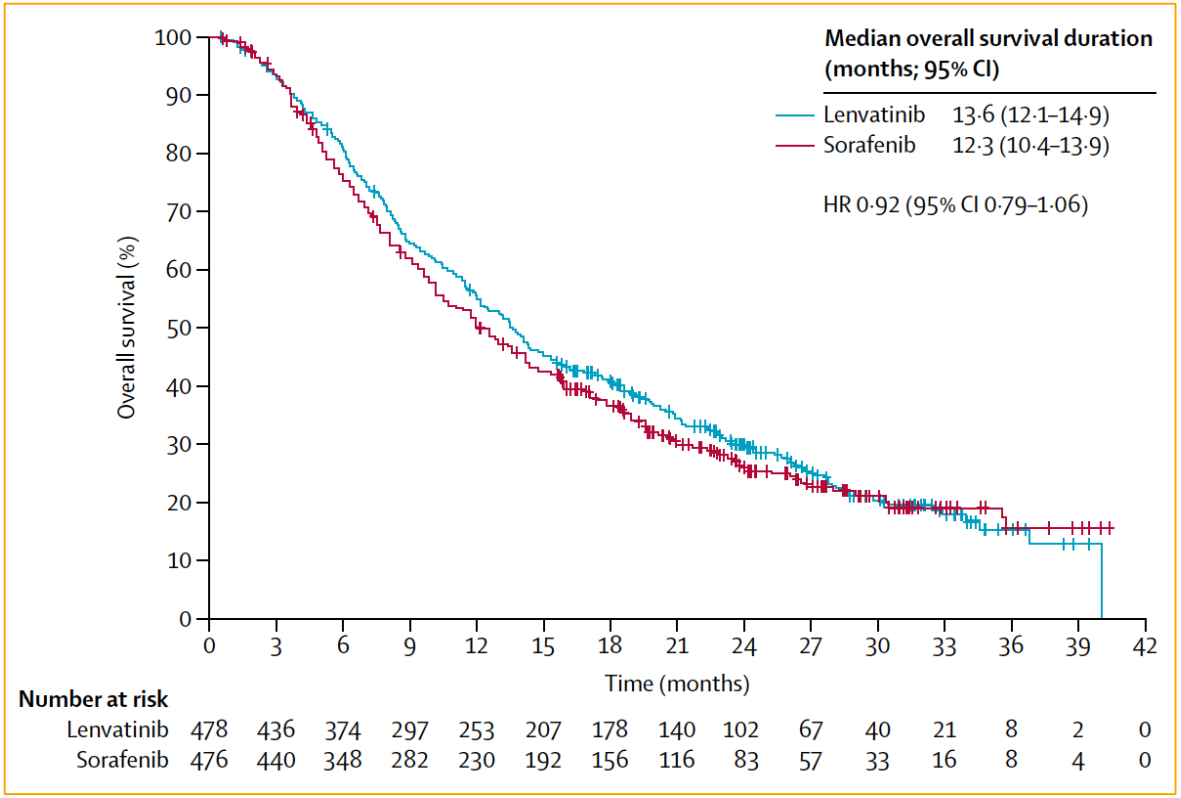
GLOBAL, RANDOMISED, OPEN-LABEL, PHASE 3 NONINFERIORITY STUDY



BCLC, Barcelona Clinic Liver Cancer; BW; body weight; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; MPVI, macroscopic portal vein invasion; mRECIST, modified Response Evaluation Criteria In Solid Tumours; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumours; TTP, time to progression

Kudo M, et al. Lancet. 2018;391:1163-1173

FRONTLINE LENVATINIB VS SORAFENIB IN UNRESECTABLE HCC: RESULTS



Patient selection:
Patients with 50% or higher liver occupation, obvious invasion of the bile duct, or invasion at the main portal vein were excluded from the study

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio
Kudo M, et al. Lancet. 2018;391:1163-1173

FRONTLINE LENVATINIB VS SORAFENIB IN UNRESECTABLE HCC: RESULTS

Outcome (investigator review according to mRECIST)	Lenvatinib n=478	Sorafenib n=476	HR
Median OS, months (95% CI)	**13.6 (12.1-14.9)**	**12.3 (10.4-13.9)**	**0.92**
Median PFS, months (95% CI)*	7.4 (6.9-8.8)	3.7 (3.6-4.6)	0.66
Median TTP, months (95% CI)*	8.9 (7.4-9.2)	3.7 (3.6-5.4)	0.63
ORR, n (%)*	115 (24)	44 (9)	

*P<.00001

- **Conclusion:** Lenvatinib was non-inferior to sorafenib in OS in first-line setting for unresectable HCC
  - Statistically significant improvements in PFS, TTP and ORR for lenvatinib vs sorafenib

CI, confidence interval; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria In Solid Tumours; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression

Kudo M, et al. Lancet. 2018;391:1163-1173

REFLECT STUDY
MOST FREQUENT TEAEs (≥ 15%)

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Adverse event, n (%)	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhoea	184 (39)	20 (4)	220 (46)	20 (4)
Decreased appetite	162 (34)	22 (5)	127 (27)	6 (1)
Decreased weight	147 (31)	36 (8)	106 (22)	14 (3)
Fatigue	141 (30)	18 (4)	119 (25)	17 (4)
Palmar-plantar erythrodysaesthesia	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (<1)	57 (12)	0
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet count	87 (18)	26 (5)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Hypothyroidism	78 (16)	0	8 (2)	0
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0
Elevated ASAT	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0	76 (16)	2 (<1)
Alopecia	14 (3)	0	119 (25)	0
Increased blood bilirubin	71(15)	31 (7)	63 (13)	23 (5)

ASAT, aspartate aminotransferase; TEAEs, treatment-emergent adverse events
Adapted from: Kudo M, et al. Lancet. 2018;391:1163-1173

SECOND-LINE PHASE 3 TRIALS TESTING MOLECULAR TARGETED THERAPIES AND DEVICES IN ADVANCED HCC

	Drugs	N = 3123	Median OS (months)	HR (95% CI)	p-value
BRISK-PS[1]	brivanib	263	9.4	0.89 (0.69-1.15)	0.33
	placebo	132	8.2		
EVOLVE-1[1]	everolimus	362	7.6	1.05 (0.86-1.27)	0.68
	placebo	184	7.3		
REACH[1]	ramucirumab	283	9.2	0.86 (0.72-1.05)	0.13
	placebo	282	7.6		
RESORCE[1]	regorafenib	379	10.6	0.63 (0.50-0.79)	<0.001
	placebo	194	7.8		
METIV-HCC[1]	tivantinib	226	8.4	0.97 (0.75-1.25)	NS
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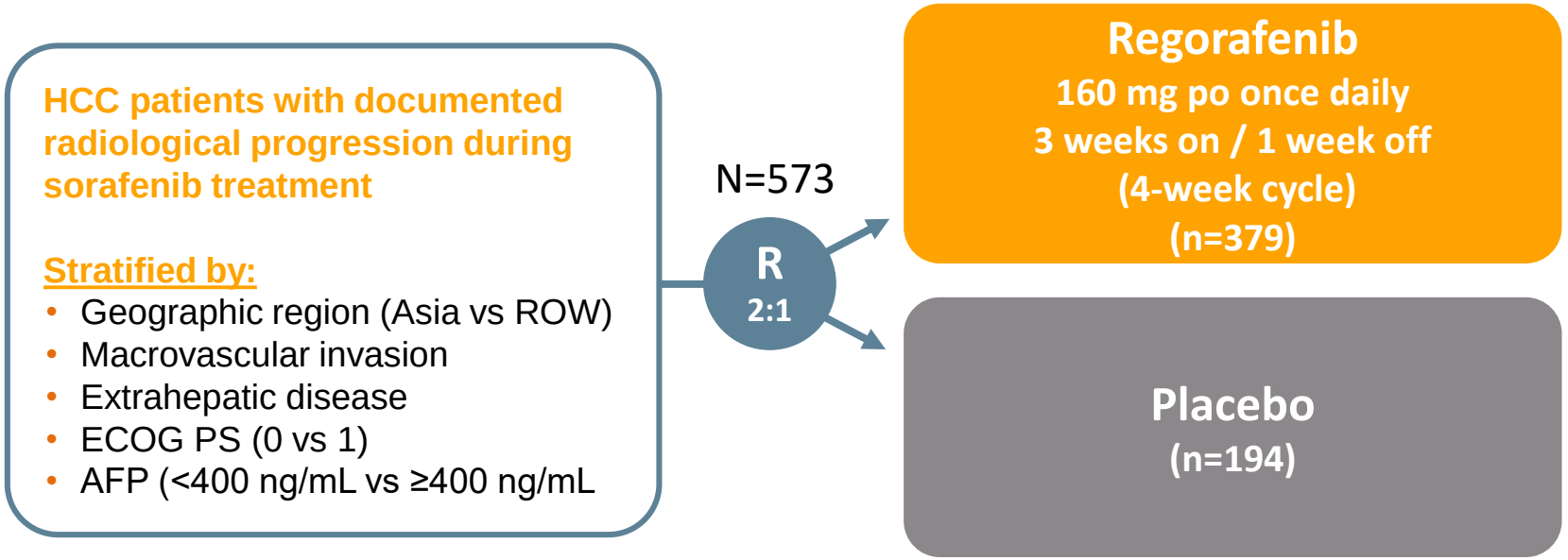
CELESTIAL[1]	cabozantinib	467	10.2	0.76 (0.63-0.92)	0.0049
	placebo	237	8.0		
REACH-2[2]	ramucirumab	197	8.5	0.71 (0.531-0.949)	0.0199
	placebo	95	7.3		

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

1. EASL. J Hepatol 2018;69:182-236. 2. Zhu AX, et al. Lancet Oncol 2019;20:282-96

RESORCE TRIAL DESIGN

CLINICALTRIALS.GOV NCT01774344



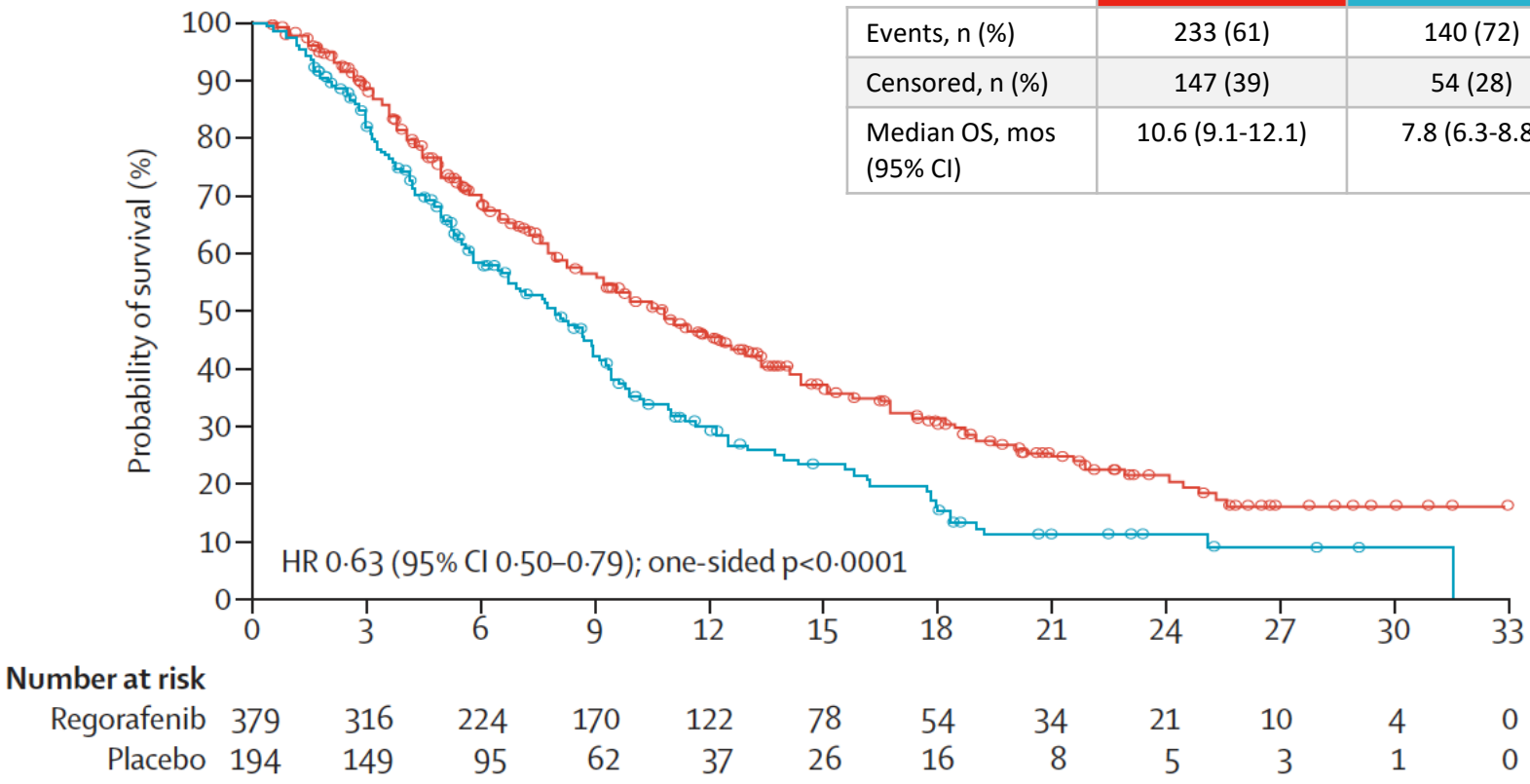
- 152 centres in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity or withdrawal

AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; po, oral; ROW, rest of the world

Bruix J, et al. The Lancet 2017;389:56-66

RESORCE
OS

	Regorafenib (n = 379)	Placebo (n = 194)
Events, n (%)	233 (61)	140 (72)
Censored, n (%)	147 (39)	54 (28)
Median OS, mos (95% CI)	10.6 (9.1-12.1)	7.8 (6.3-8.8)



CI, confidence interval; HR, hazard ratio; OS, overall survival
Bruix J, et al. The Lancet 2017;389:56-66

BEST OVERALL TUMOUR RESPONSE

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	mRECIST		RECIST 1.1	
	Regorafenib n=379	**Placebo** n=194	**Regorafenib** n=379	**Placebo** n=194
ORR	10.6%	4.1%	6.6%	2.6%
	P=0.01 (2-sided)		*P*=0.04 (2-sided)	
DCR	**65.2%**	**36.1%**	**65.7%**	**34.5%**
	P<0.001 (2-sided)		*P*<0.001 (2-sided)	
CR	0.5%	0	0	0
PR	10.0%	4.1%	6.6%	2.6%
SD	**54.4%**	**32.0%**	**58.8%**	**32.0%**
Non CR/Non PD	0.3%	0	0.3%	0
PD	22.7%	55.7%	22.4%	57.2%
Not evaluable	5.0%	4.1%	5.0%	4.6%
Not assessed	7.1%	4.1%	6.9%	3.6%
Clinical progression*	22.7%	20.6%	22.7%	20.6%

*Worsening of ECOG PS≥3 or symptomatic deterioration including increase in liver function tests

CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; mRECIST, modified Response Evaluation Criteria In Solid Tumours; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours; SD, stable disease

Bruix J, et al. The Lancet 2017;389:56-66

MEDIAN OS OF 26 MONTHS FROM FIRST SORAFENIB DOSE TO DEATH ON REGORAFENIB

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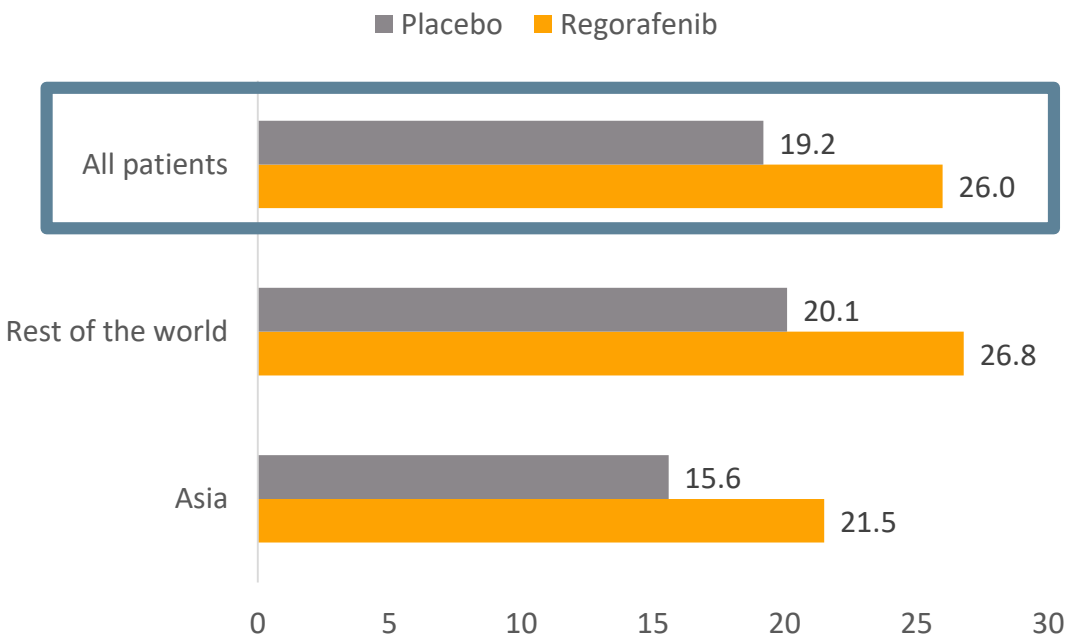
Survival rates from the start of sorafenib treatment

	Sorafenib–Regorafenib (n=379)	Sorafenib–Placebo (n=194)
n*	374	193
6 months	97%	97%
12 months	82%	76%
24 months	53%	42%
36 months	31%	20%
48 months	19%	12%
60 months	16%	3%
72 months	10%	3%

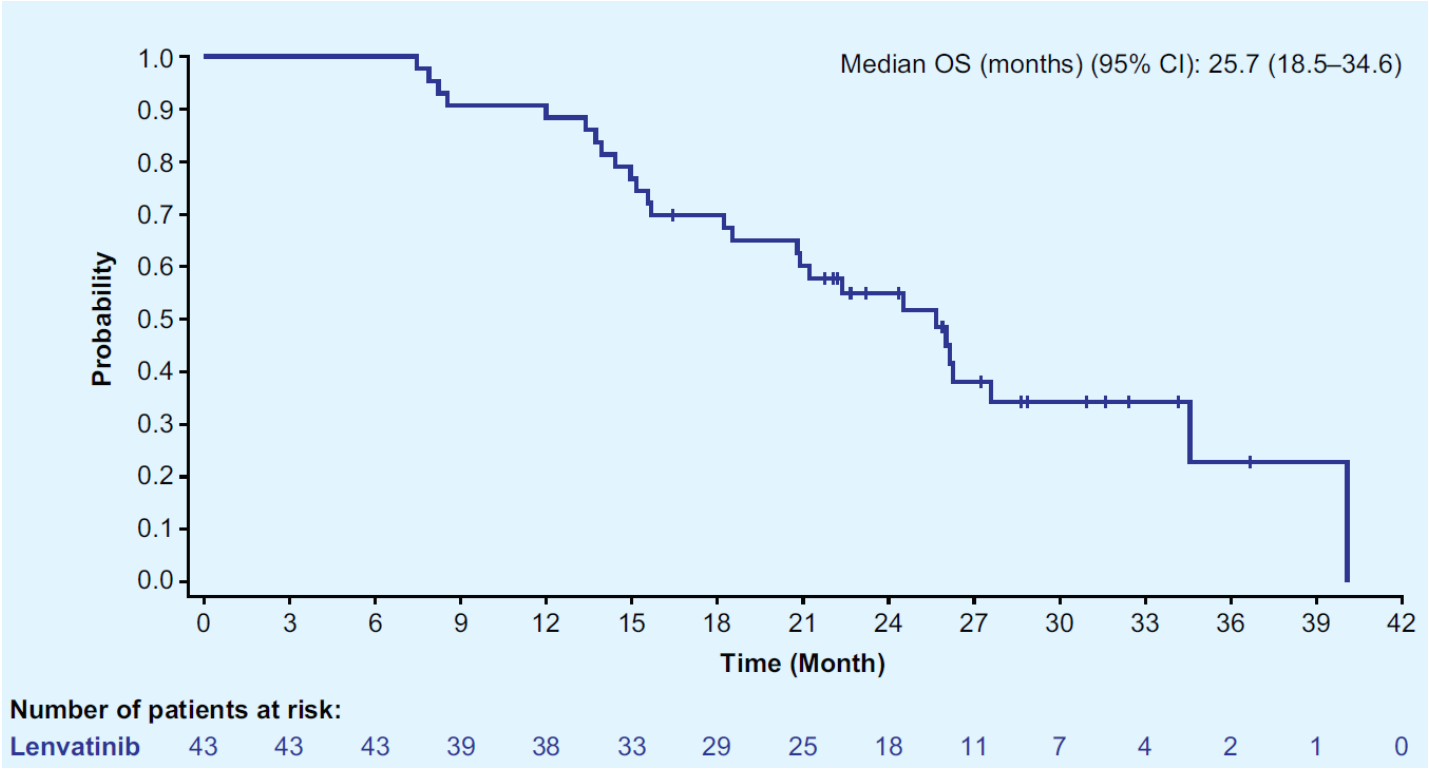
Time from start of prior sorafenib treatment to death on RESORCE study drug (months)



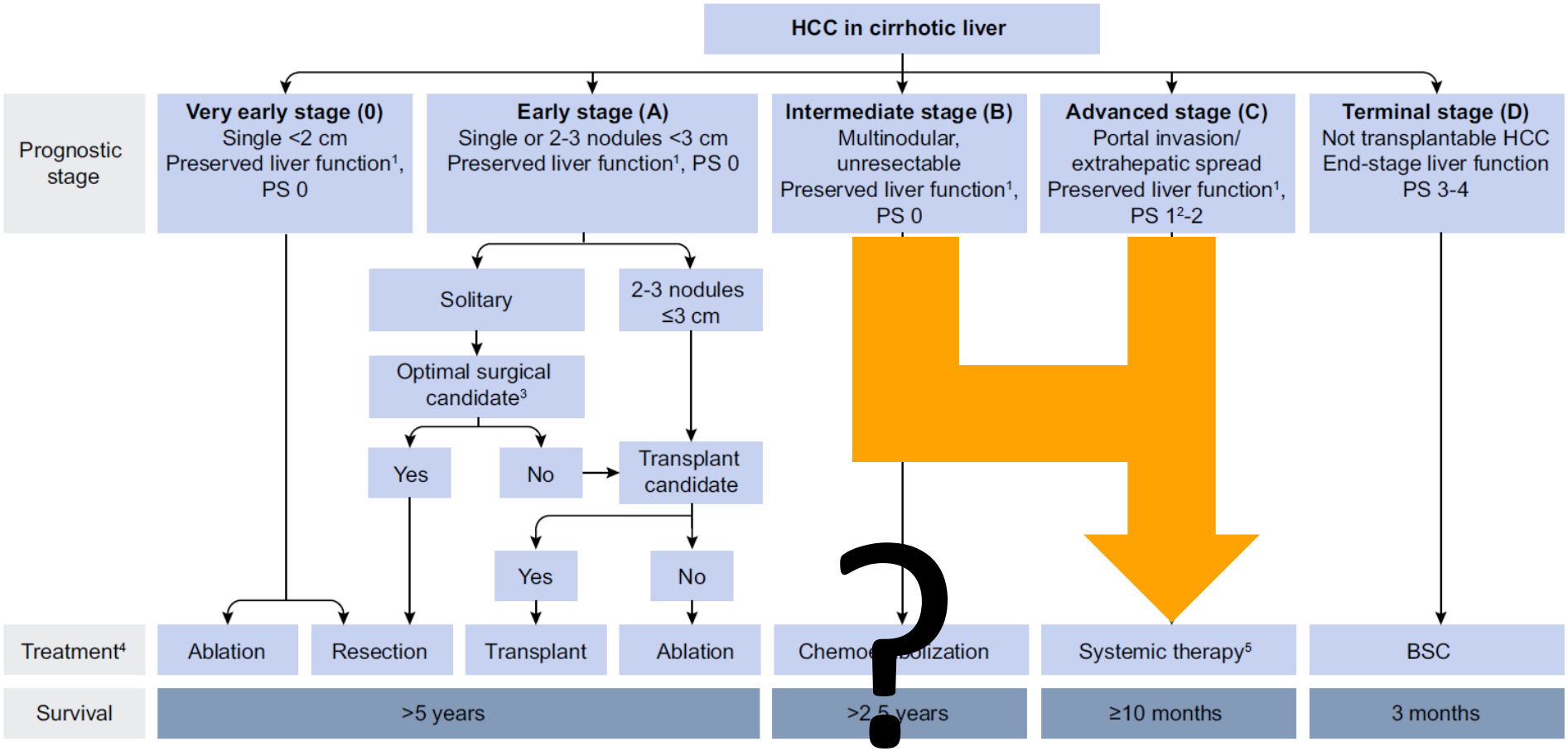
* n = treated patients

Finn RS, et al. J Hepat 2018;69:353-8

KAPLAN-MEIER ESTIMATE OF OS FOR LENVATINIB RESPONDERS WHO RECEIVED ANY POSTSTUDY ANTICANCER MEDICATION



Alsina A, et al. ASCO-GI 2019. Abstract #371

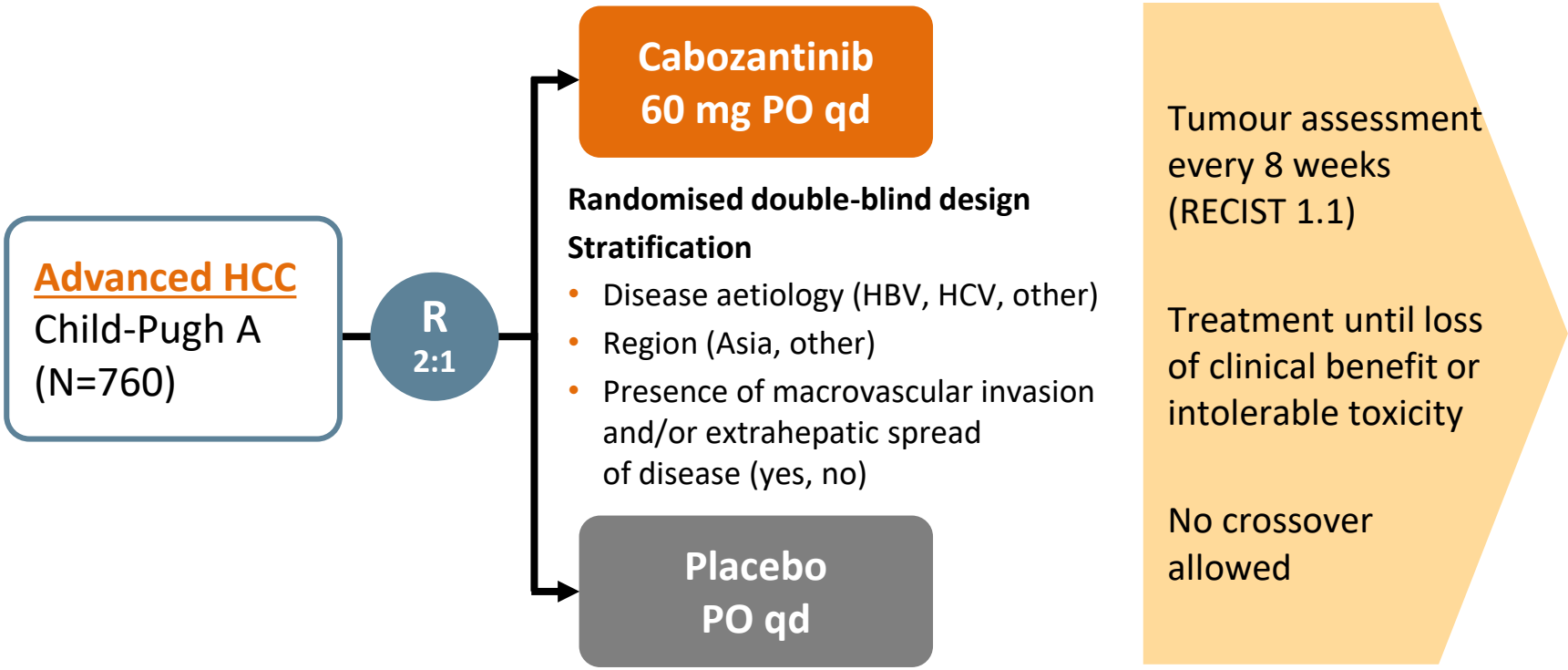


BSC, best-supportive care; HCC, hepatocellular carcinoma; PS, performance status
EASL. J Hepatol 2018;69:182-236

CABOZANTINIB VERSUS PLACEBO IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA WHO HAVE RECEIVED PRIOR SORAFENIB: RESULTS FROM THE RANDOMIZED PHASE 3 CELESTIAL TRIAL

Abou-Alfa GK, Meyer T, Cheng AI, El-Khoueiry A, Rimassa L, Ryoo BY, Cicin I, Merle P, Chen Y, Park JW, Blanc JF, Bolondi L, Klümpen HJ, Chan SL, Dadduzio V, Hessel C, Borgman-Hagey A, Schwab G, Kelley RK
on behalf of the CELESTIAL Investigators

CELESTIAL STUDY: DESIGN

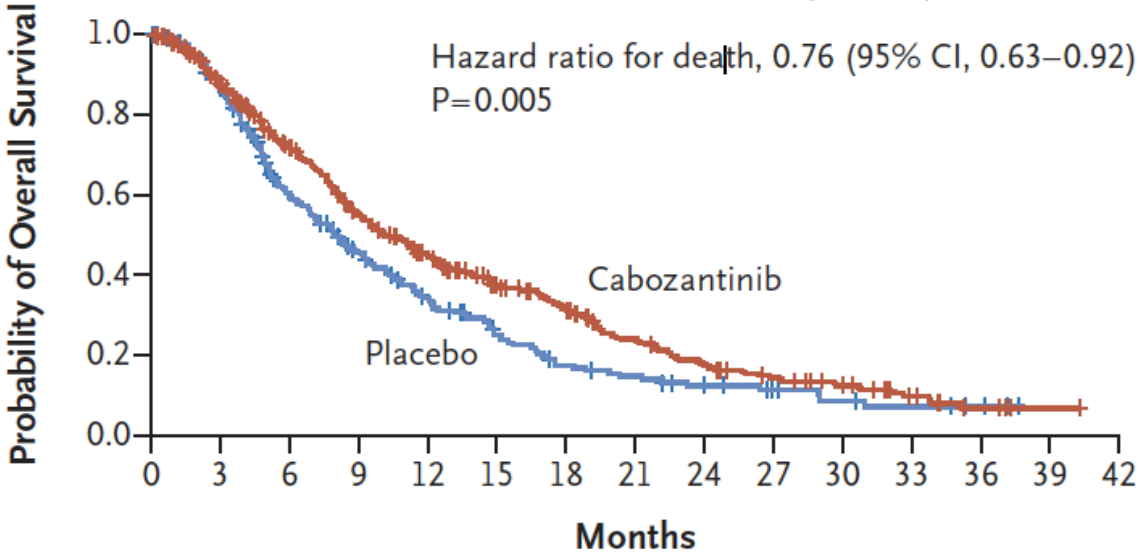


HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PO, oral; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumours

Abou-Alfa GK, et al. N Engl J Med 2018;379:54-63

CELESTIAL STUDY: OVERALL SURVIVAL

	No. of Patients	Median Overall Survival *mo (95% CI)*	No. of Events
Cabozantinib	470	10.2 (9.1–12.0)	317
Placebo	237	8.0 (6.8–9.4)	167



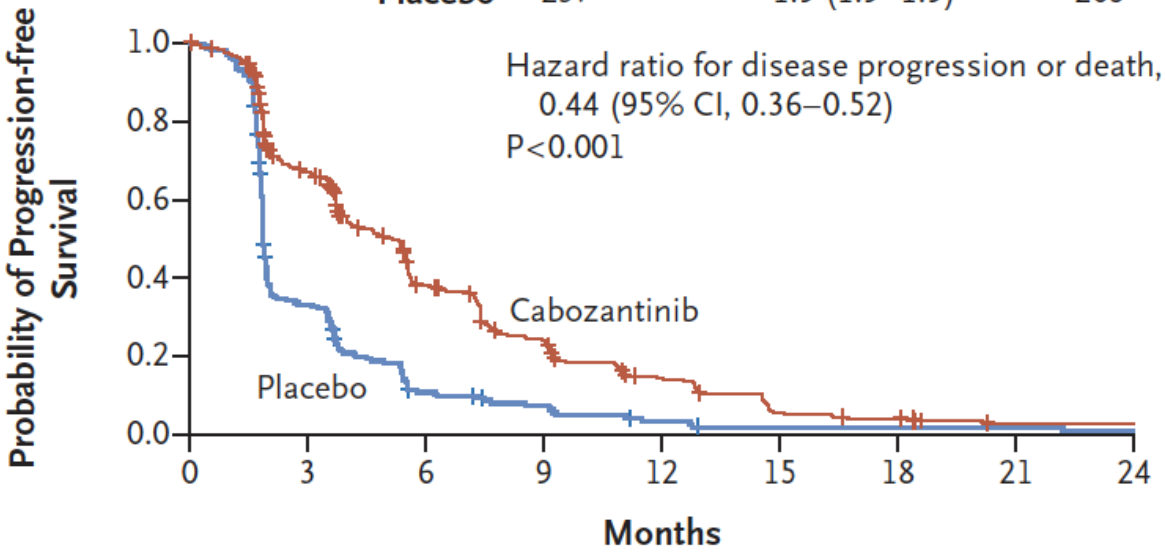
No. at Risk

Cabozantinib	470	328	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

*Critical p-value ≤0.021 for second interim analysis
CI, confidence interval
Abou-Alfa GK, et al. N Engl J Med 2018;379:54-63

CELESTIAL STUDY: PROGRESSION-FREE SURVIVAL

	No. of Patients	Median Progression-free Survival	No. of Events
		mo (95% CI)	
Cabozantinib	470	5.2 (4.0–5.5)	349
Placebo	237	1.9 (1.9–1.9)	205



No. at Risk									
Cabozantinib	470	266	131	80	39	15	10	3	3
Placebo	237	70	21	13	5	2	2	2	1

Progression-free survival assessed per RECIST 1.1
CI, confidence interval
Abou-Alfa GK, et al. N Engl J Med 2018;379:54-63

CELESTIAL STUDY: ALL-CAUSALITY GRADE 3 OR 4 AEs

Preferred term, %	Cabozantinib (N=467)	Placebo (N=237)
Any grade 3 or 4 AE	68	36
Palmar-plantar erythrodysaesthesia	17	0
Hypertension	16	2
ASAT increased	12	7
Fatigue	11	4
Diarrhoea	10	2
Asthenia	7	2
Decreased appetite	6	<1
Anaemia	4	5

Treatment-related grade 5 AEs:

Cabozantinib (6 patients)	hepatic failure, oesophagobronchial fistula, portal vein thrombosis, upper gastrointestinal haemorrhage, pulmonary embolism, hepatorenal syndrome
Placebo (1 patient)	hepatic failure

Grade 3/4 AEs reported in at least 5% of patients in either treatment group
AE, adverse event; ASAT, aspartate aminotransferase
Abou-Alfa GK, et al. N Engl J Med 2018;379:54-63

BIOMARKER-DRIVEN PHASE 3 REACH TRIAL: SECOND-LINE TREATMENT WITH VEGFR2 INHIBITOR RAMUCIRUMAB

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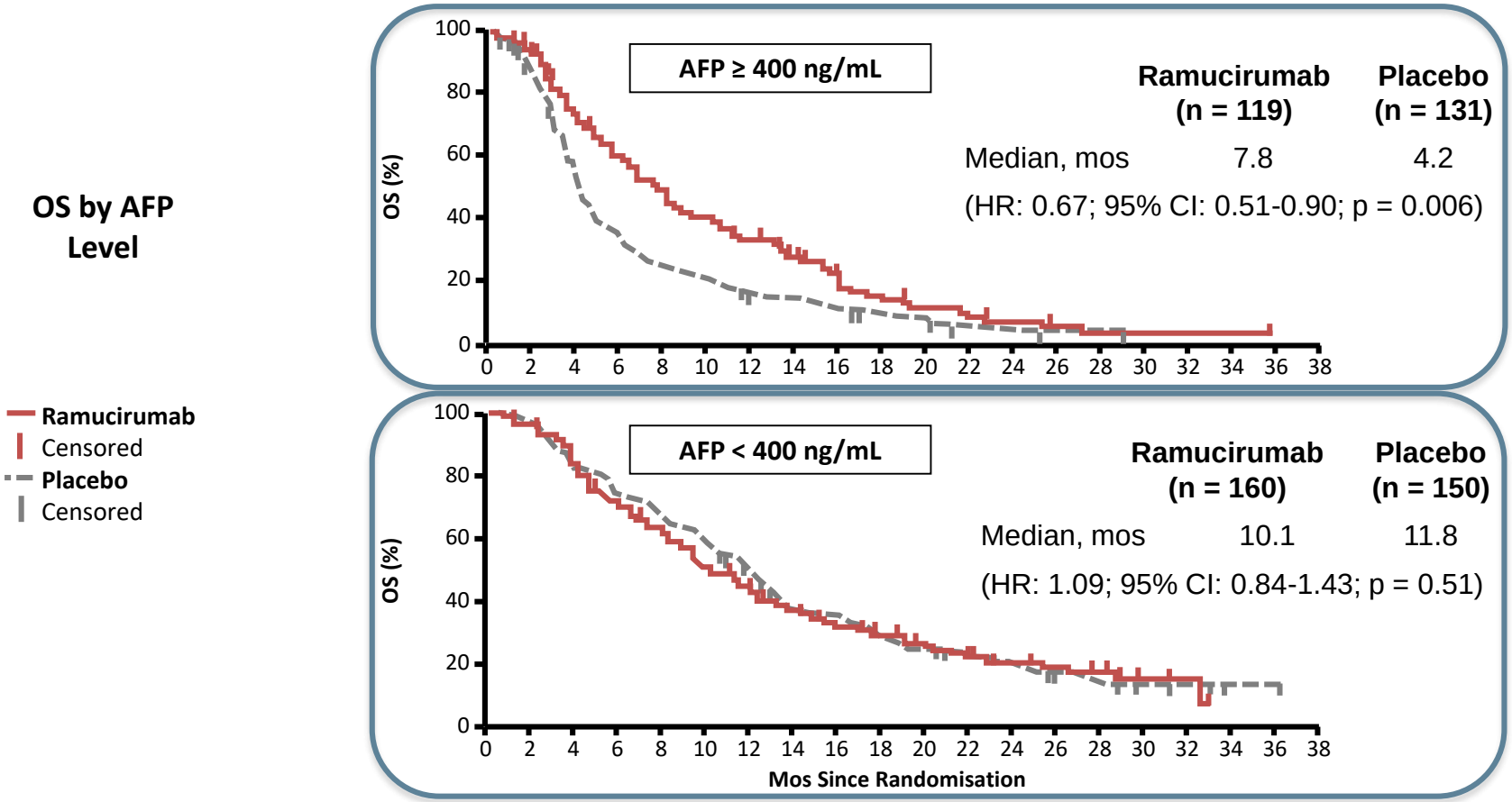
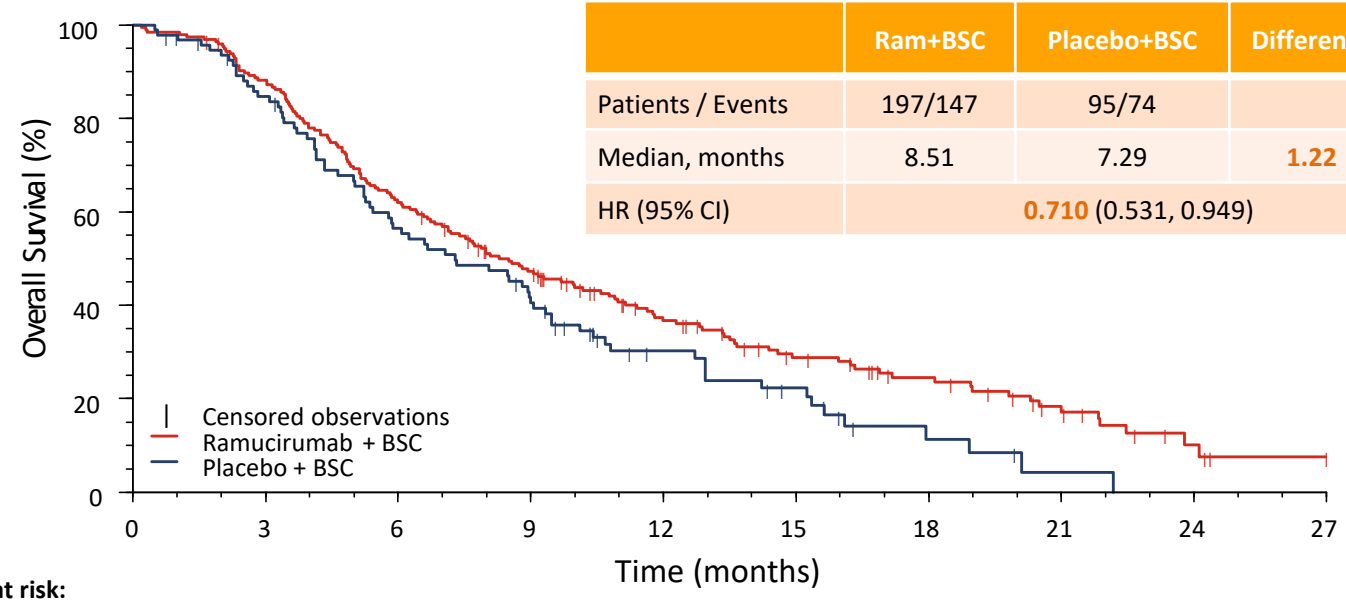
OS by AFP Level



AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio; OS, overall survival; VEGFR2, vascular endothelial growth factor receptor 2

Zhu AX, et al. Lancet Oncol 2015;16:859-70

REACH-2: OVERALL SURVIVAL



	Ram+BSC	Placebo+BSC	Difference	P-value
Patients / Events	197/147	95/74		
Median, months	8.51	7.29	**1.22**	
HR (95% CI)	**0.710** (0.531, 0.949)			**0.0199**

Patients at risk:

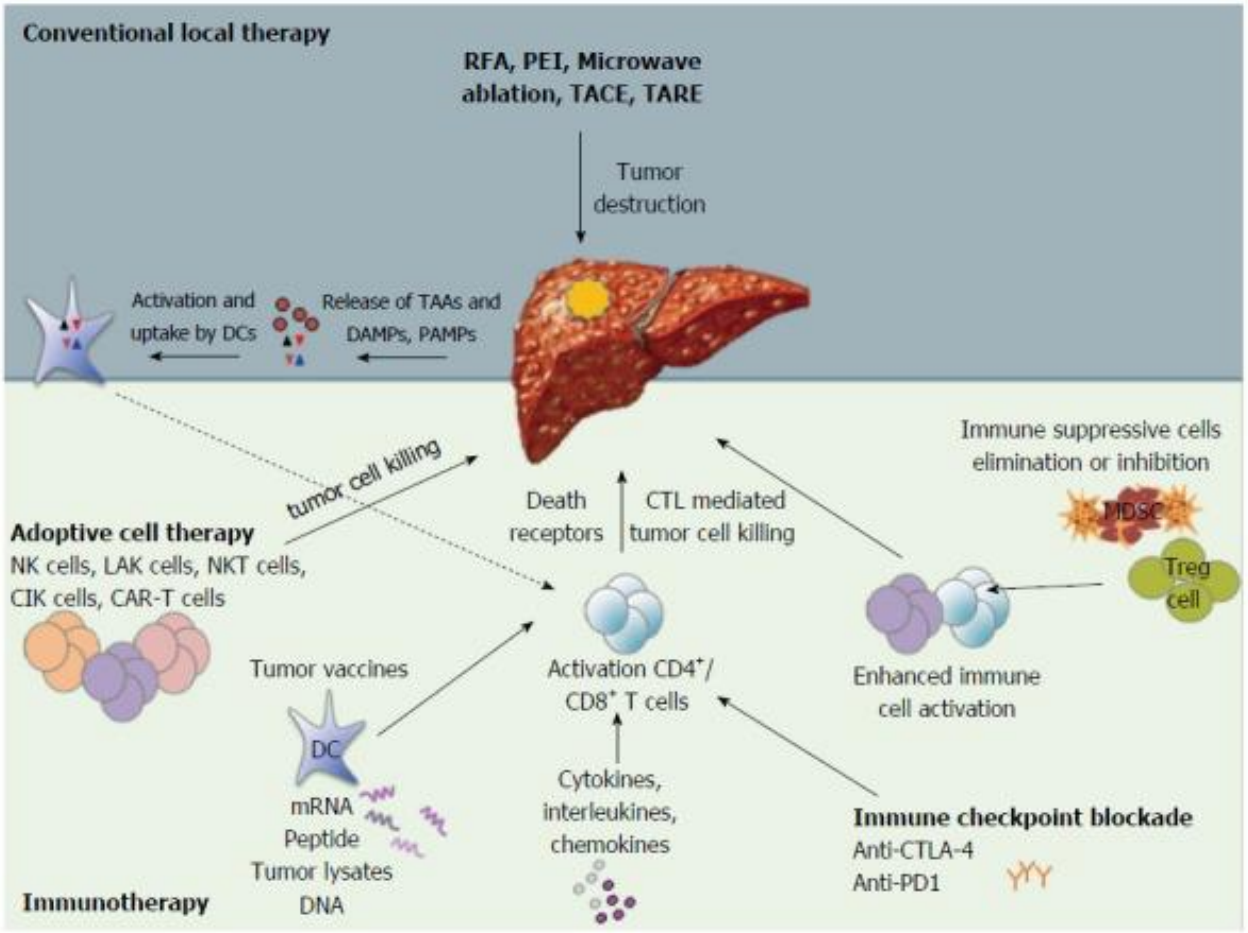
Ram + BSC	197	172	121	87	56	37	26	14	4	0
Placebo + BSC	95	76	50	36	19	12	4	1	0	0

BSC, best-supportive care; CI, confidence interval; HR, hazard ratio; Ram, ramucirumab

Zhu AX, et al. Lancet Oncol 2019;20:282-96

INTRODUCTION TO IMMUNOTHERAPY STRATEGIES IN HCC

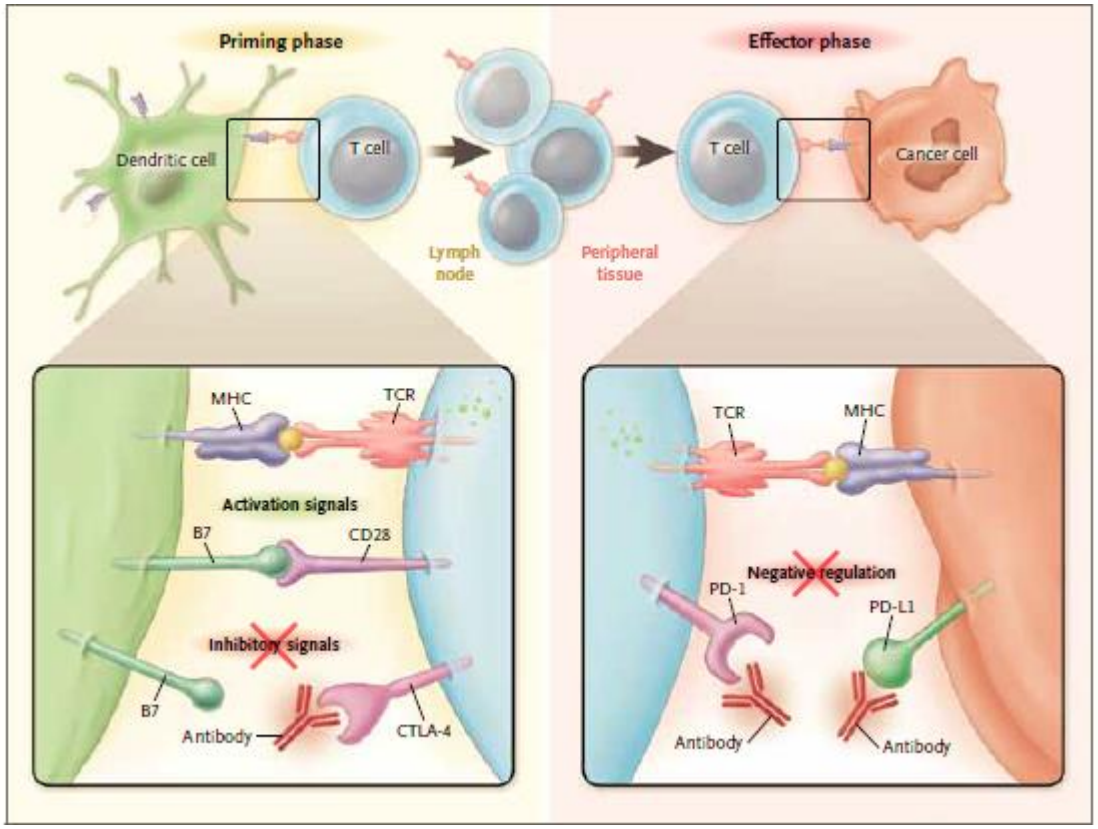
IMMUNOTHERAPY STRATEGIES IN HCC



Aerts M, et al. World J Gastroenterol 2016;22:253-61.

BLOCKADE OF PD-1 OR CTLA-4 SIGNALLING IN TUMOUR IMMUNOTHERAPY

Anti-CTLA-4
Ipilimumab
(BMS)



Anti-PD-1
Nivolumab (BMS)
Pembrolizumab
(Merck)

Anti-PD-L1
Durvalumab
(AstraZeneca)

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; MHC, major histocompatibility complex; PD-1, programmed death 1; PD-L1, programmed-death ligand 1; TCR, T-cell receptor

Ribas A. N Engl J Med 2012;366:2517-9

DURABLE PARTIAL RESPONSE TO NIVOLUMAB

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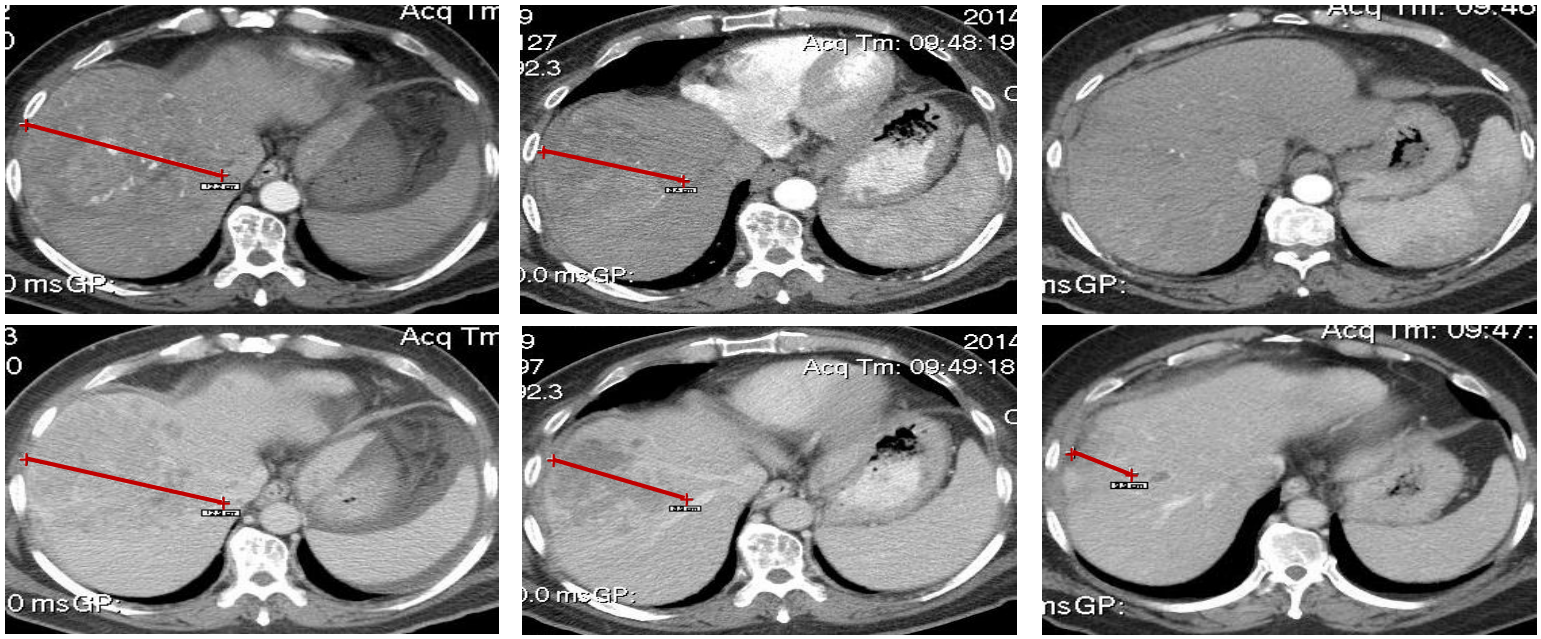

- 58-year old white male with HCV-infected HCC, ECOG PS score 0, Child-Pugh A5
- Progressed on sorafenib

ECOG PS, Eastern Cooperative Oncology Group performance status; HCV, hepatitis C virus; HCC, hepatocellular carcinoma

IMMUNOTHERAPY FOR HCC

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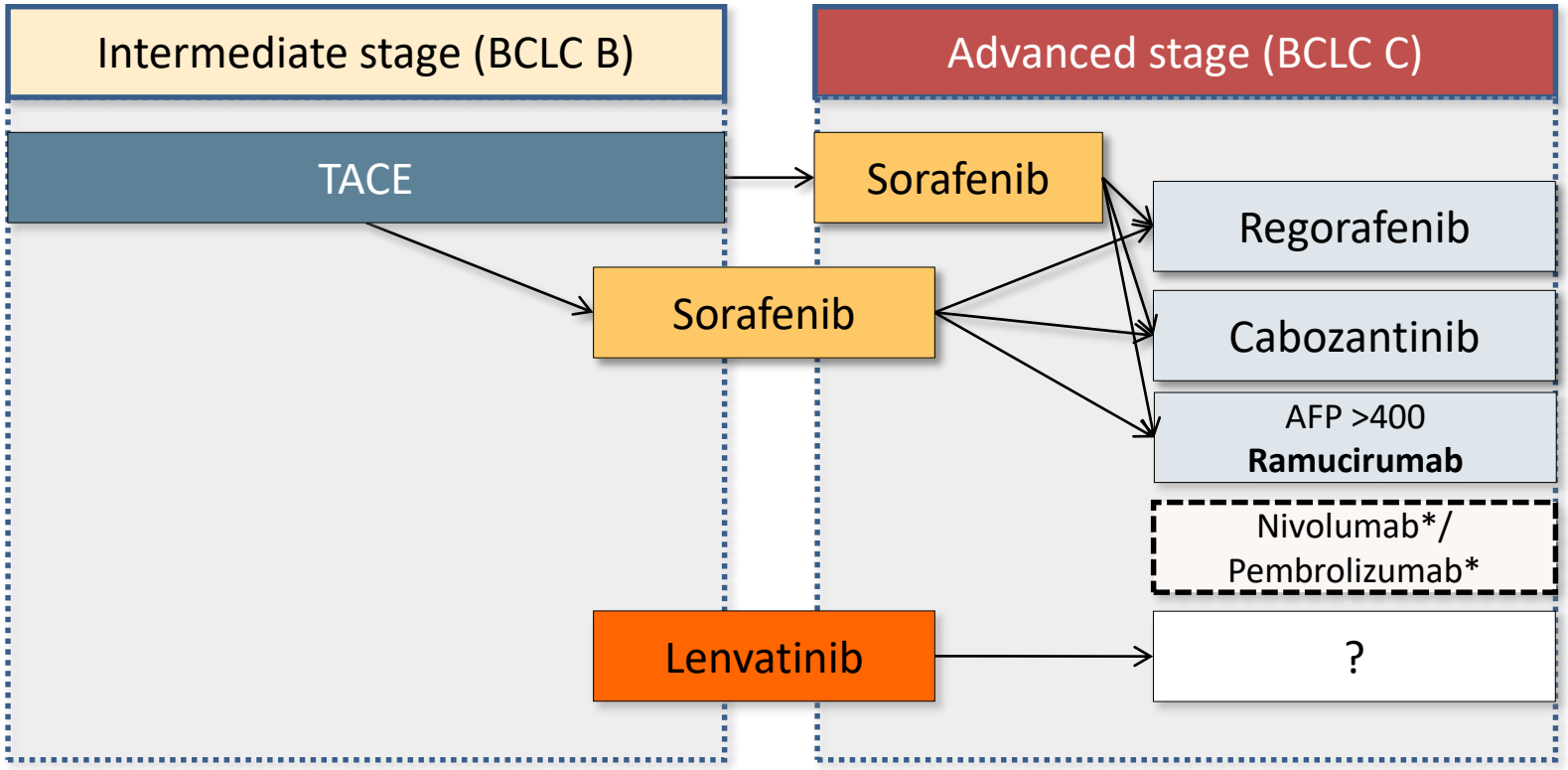
Study	Treatment (target)	N	Response rate (%)	PFS, months (95% CI)	OS, months (95% CI)	NCT number
CHECKMATE 040 Phase 1/2[1]	Nivolumab (PD-1)	214	20	4.0 (2.9-5.4)	NR	NCT01658878
CHECKMATE 459 Phase 3[2]	Nivolumab (PD-1) vs sorafenib	371 vs 372	15 vs 7	3.7 (3.1-3.9) vs 3.8 (3.7-4.5)	16.4 (13.9-18.4) vs 14.7 (11.9-17.2)	NCT02576509
KEYNOTE 224, Phase 2[3]	Pembrolizumab (PD-1)	169	18	4.9 (3.4-7.2)	12.9 (9.7-15.5)	NCT02702414
KEYNOTE 240, Phase 3[4]	Pembrolizumab (PD-1) vs placebo	278 vs 135	18.3 vs 4.4	3.0 mo (2.8-4.1) vs 2.8 mo (2.5-4.1)	13.9 (11.6-16.0) vs 10.6 (8.3-13.5)	NCT02702401
IMbrave150, Phase 3[5]	Atezolizumab (PD-L1) + bevacizumab vs sorafenib	336 vs 165	27 vs 12	6.8 (5.7-8.3) vs 4.3 (4.0-5.6)	NE vs 13.2 (10.4-NE)	NCT03434379
Phase 1/2[6]	Durvalumab (PD-L1)	40	10	2.7 (1.4-5.3)	13.2 (6.3-21.1)	NCT01693562
Phase 1b[7]	BGB-A317 (PD-1)	27	11.1*	NR	NR	NCT02407990
Phase 2[8]	Tremelimumab (CTLA-4)	17	17.6	6.48 (4.0-9.1)	8.2 (4.6-21.3)	NCT01008358

* Confirmed + unconfirmed responses

CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; NE, not estimable; NR, not reported; PD-1, programmed death 1; PD-L1, programmed-death ligand 1

1. El Kouheiry AB, et al. Lancet 2017;389:2492-502. 2. Yau, et al. ESMO 2019 Abstract #LBA38. 3. Zhu AX, et al. Lancet Oncol. 2018;19:940-52. 4. Finn R, et al. ASCO 2019. Abstract #4004. 5. Cheng A-L, et al. ESMO Asia 2019 Abstract #LBA3. 6. Wainberg ZA, et al. ASCO 2017. Abstract #4071. 7. Yen CJ, et al. WCGIC 2017. Abstract #P-140. 8. Sangro B, et al. J Hepatol 2013;59:81-8.

SYSTEMIC THERAPY IN uHCC IN 2019



*FDA approval only

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; uHCC, unresectable hepatocellular carcinoma

CONCLUSIONS

- After nearly a decade, we have had **4 positive phase 3 studies** of new targeted drugs in HCC that improve survival
  - **Lenvatinib** - non-inferior to sorafenib, HR 0.92[1]
  - **Regorafenib** vs placebo - 2nd line, HR 0.63[2]
  - **Cabozantinib** vs placebo - 2nd and 3rd line (HR 0.76 prior sorafenib)[3]
  - **Ramucirumab** vs placebo – 2nd line, AFP high, HR 0.71[4]
- **Nivolumab** and **pembrolizumab** FDA approved as second-line treatment in the US based on single-arm phase 2 studies
  - Nivolumab: RR 15%, 4% CR – CheckMate 459 phase 3 study negative[5]
  - Pembrolizumab: KeyNote 240 phase 3 study negative[6]
- Based on the recently presented data from the IMbrave150 study, **atezolizumab + bevacizumab** may become a new 1st line standard of care[7]

CR, complete response; HCC, hepatocellular carcinoma; HR, hazard ratio; RR, response rate

1. Kudo M, et al. Lancet. 2018;391:1163-1173. 2. Bruix J, et al. The Lancet 2017;389:56-66. 3. Abou-Alfa GK, et al. N Engl J Med 2018;379:54-63. 4. Zhu AX, et al. Lancet Oncol 2019;20:282-96. 5. Yau, et al. ESMO 2019 Abstract #LBA38. 6. Finn R, et al. ASCO 2019. Abstract #4004. 7. Cheng A-L, et al. ESMO Asia 2019 Abstract #LBA3

UNMET NEEDS IN HCC

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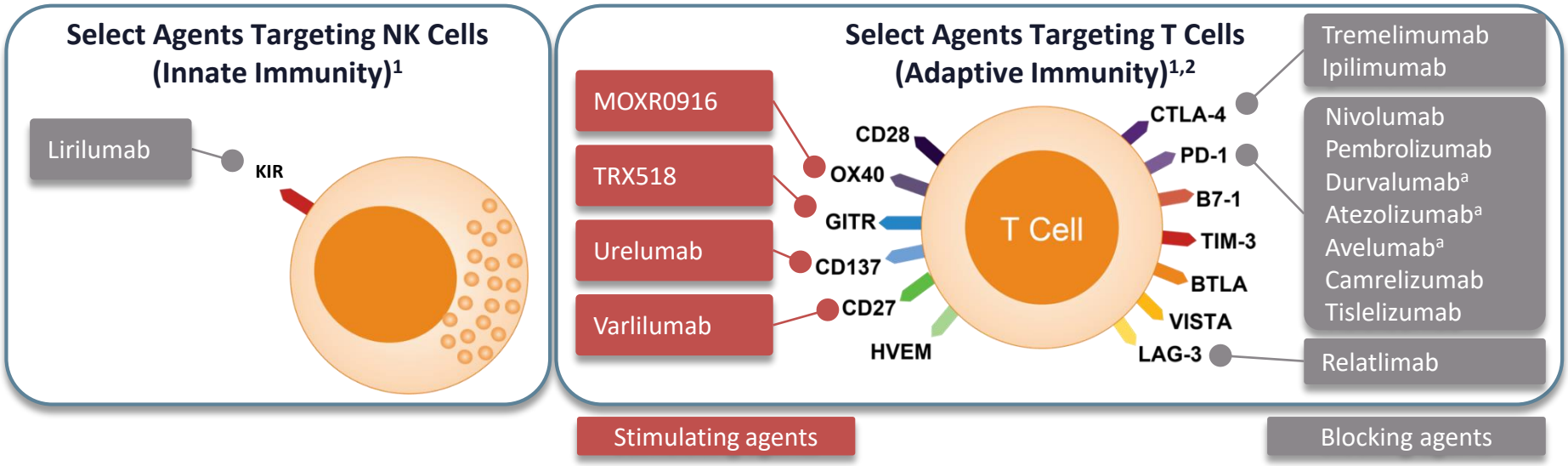
- **Better therapies in earlier settings**
  - Adjuvant and neo-adjuvant settings
  - Combination/sequencing therapies with TACE or other locoregional therapies
- **Approach to sequencing treatments in the second-line setting and beyond**
- **Improved strategies for patient selection**
  - Biomarkers, viral aetiologies, liver function
- **Definition of surrogate markers for OS**
- **Few treatment options exist for patients in Child-Pugh B (C)**

HCC, hepatocellular carcinoma; OS, overall survival; TACE, transarterial chemoembolisation

IMMUNE-CHECKPOINT INHIBITORS IN HCC

Ruth He
Georgetown University Hospital, USA

TARGETING CHECKPOINTS AS AN APPROACH TO CANCER THERAPY



Not a complete list; several checkpoint-targeted agents are under investigation in the cancer setting[3]

[a] These agents target PD-L1.

CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; KIR, killer cell immunoglobulin-like receptor; NK, natural killer; PD-1, programmed death 1; PD-L1, programmed-death ligand 1

1. Adapted from Pardoll DM. Nat Rev Cancer. 2012;12:252-64. 2. Adapted from Mellman I, et al. Nature. 2011;480:480-9.
3. http://www.clinicaltrials.gov. Accessed November 4, 2019.

CHECKPOINT INHIBITORS TESTED OR BEING TESTED FOR ADVANCED STAGE HCC

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FDA Approved for Subsequent-Line Therapy if Disease Progression after sorafenib[1]

Nivolumab	Pembrolizumab
Child-Pugh A or B7	Child-Pugh A

Emerging Checkpoint-inhibitor Combinations Under Investigation for HCC[2]

	Nivolumab	Durvalumab
Anti-PD-1 + Anti-CTLA4	Targets PD-1 Phase 3: with ipilumumab in first line	Targets PD-L1 Phase 3: With tremelimumab in first line

	Pembrolizumab	Atezolizumab
Anti-PD-1 + Anti-VEGF/TKI	Targets PD-1 Phase 3: with lenvatinib in first line	Targets PD-L1 Phase 3: With cabozantinib in first line Phase 3: With bevacizumab in first line

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HCC, hepatocellular carcinoma; PD-1, programmed death 1; PD-L1, programmed-death ligand 1; TKI, tyrosine-kinase inhibitor

1. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. V3.2019. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed November 4, 2019. 2. http://www.clinicaltrials.gov. Accessed May 13, 2019

CHECKMATE 040: NIVOLUMAB IN HCC

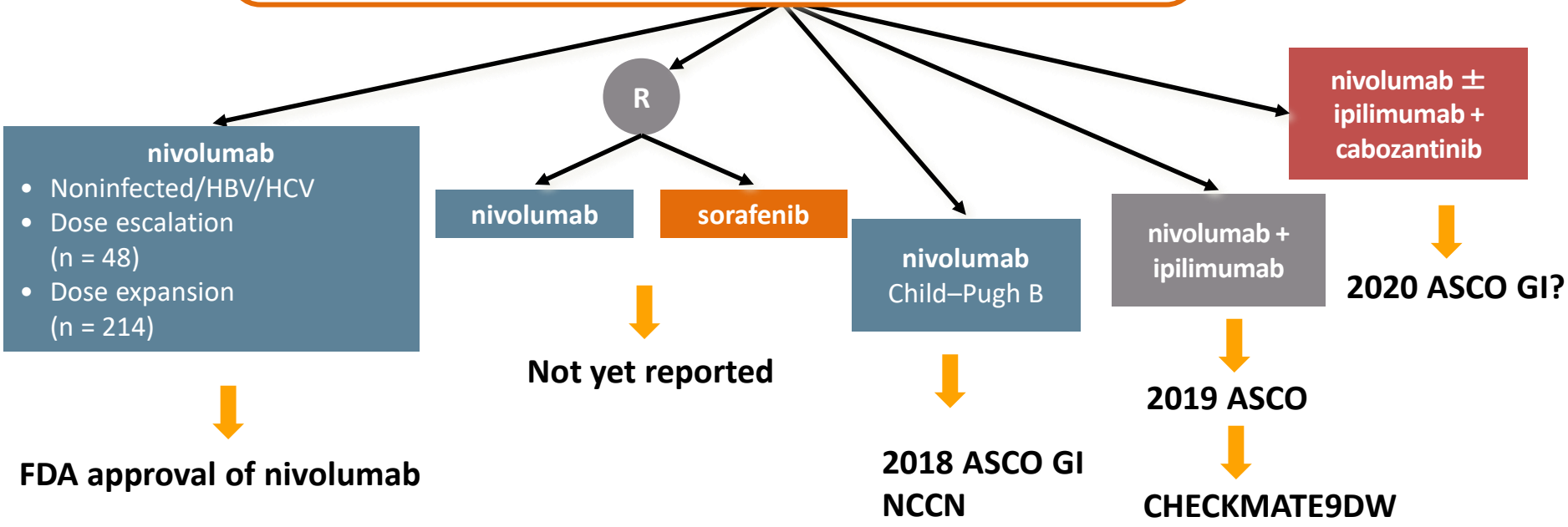
HCC connect
POWERED BY COR2ED

Key eligibility criteria

- HCC not amenable to curative resection
- Child-Pugh ≤6, ≤7 for dose escalation, Child–Pugh B cohort
- Progressed on ≥1 prior line of systemic therapy, intolerant to sorafenib, or refused sorafenib

(N=620)

- **Primary endpoints:** Safety and tolerability, ORR
- **Other endpoints:** CR, DCR, DOR, TTR, TTP, TTP rate, PFS, OS, OS rate, biomarkers, and PK



CR, complete response; DCR, disease-control rate; DOR, duration of response; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, overall response rate; OS, overall survival; PK, pharmacokinetics; TTP, time to progression; TTR, time to response

1. https://clinicaltrials.gov/ct2/show/NCT01658878. Accessed May 9, 2019; 2. El-Khoueiry AB, et al. Lancet. 2017;389:2492-502

CHECKMATE 040 STUDY: OUTCOMES WITH NIVOLUMAB IN HCC

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Investigator assessment using RECIST version 1.1	Uninfected, Untreated, or Intolerant (n=56)	Uninfected Progressor (n=57)	HCV (n=50)	HBV (n=51)	Total (N=214)
ORR, n (%; 95% CI)	13 (23%; 13-26)	12 (21%; 11-34)	10 (20%; 10-34)	7 (14%; 6-26)	42 (20%; 15-26)
CR, n (%)	0	2 (4%)	0	1 (2%)	3 (1%)
PR, n (%)	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
SD, n (%)	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
PD, n (%)	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
NE, n (%)	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
KM median DOR, months (95% CI)	8.4 (8.3-NE)	NR	9.9 (4.5-9.9)	NR	9.9 (8.3-NE)
Ongoing, n/N (%)	8/13 (62%)	7/12 (58%)	8/10 (80%)	5/7 (71%)	28/42 (67%)
Disease control, n (%; 95% CI)	42 (75%; 62-86)	35 (61%; 48-74)	33 (66%; 51-79)	28 (55%; 40-69)	138 (64%; 58-71)
Disease control with SD for ≥6 mo	22 (39%; 27-53)	22 (39%; 26-52)	17 (34; 21-49)	18 (35%; 22-50)	79 (37%; 30-44)

The ORR by RECIST 1.1 in the post-sorafenib population was 14% (n=145)

CR, complete response; DOR, duration of response; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; KM, Kaplan-Meier; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease

El-Khoueiry AB, et al. Lancet. 2017;389:2492-502

NIVOLUMAB CHECKMATE 040 STUDY: RESPONSE AND PD-L1 EXPRESSION

Best Change in Target Lesion From Baseline[a]
Tumour-Cell PD-L1 Expression

Overall, the ORR by RECIST 1.1 in the post-sorafenib population was 14% (n=145)

Sorafenib Naive ESC + EXP

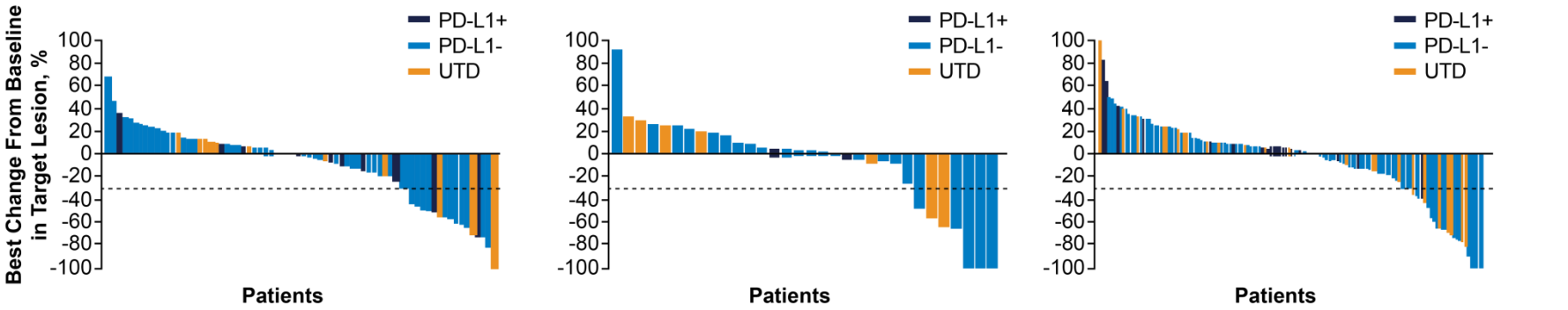
	PD-L1+	PD-L1-	UTD
ORR, n/N (%)	3/11 (27)	11/56 (20)	2/13 (15)

Sorafenib Experienced ESC

	PD-L1+	PD-L1-	UTD
ORR, n/N (%)	2/9 (22)	5/26 (19)	0/2 (0)

Sorafenib Experienced EXP

	PD-L1+	PD-L1-	UTD
ORR, n/N (%)	7/25 (28)	13/102 (13)	1/18 (6)

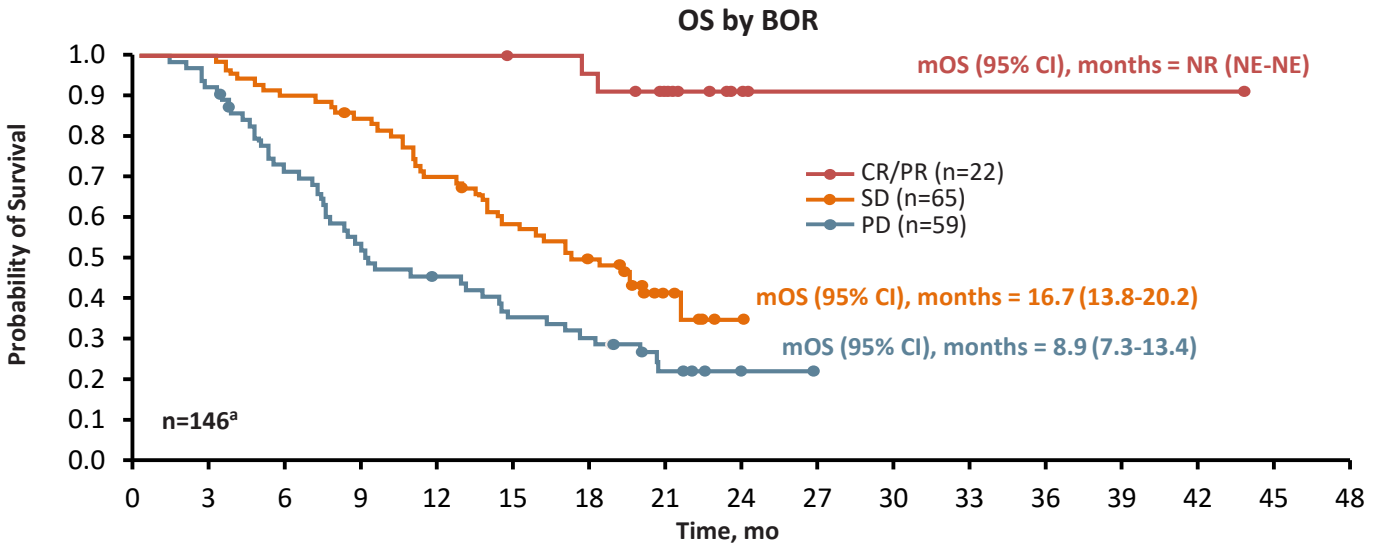


[a]Tumour response assessed by BICR using RECIST v1.1; plots include patients evaluable for tumour response and had ≥1 post-baseline target lesion assessment [sorafenib naive, n=72; sorafenib experienced ESC, n=32; sorafenib experienced EXP, n=135).
PD-L1+: ≥1% tumour cells expressing PD-L1; PD-L1-: <1% tumour cells expressing PD-L1.

ESC, endpoint safety/tolerability; EXP, endpoint overall response rate; HCC, hepatocellular carcinoma; PD-L1, programmed-death ligand 1 RECIST, Response Evaluation Criteria in Solid Tumours; UTD, unable to determine

1. Crocenzi T, et al. 2017 ASCO 2017. Abstract #4013

CHECKMATE 040: OS BY BEST ORR OR CHANGE IN TARGET LESION SIZE



OS Rate, % (95% CI)	CR/PR (n=22)	SD (n=65)	PD (n=59)
12 month	100 (100-100)	67 (55-77)	41 (28-53)
18 month	100 (100-100)	45 (33-57)	26 (15-38)

[a]Best overall response was unable to be determined in 8 patients.

BOR, best overall response; CI, confidence interval; CR, complete response; mOS, median overall survival; NE, not evaluable; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease

1. El-Khoueiry A, et al. ASCO-GI 2018. Abstract #475

CHECKMATE 040 NIVOLUMAB DOSE EXPANSION: TEAEs[1]

TRAEs, n (%)	Uninfected untreated/ intolerant (n=56)		Uninfected progressor (n=57)		HCV infected (n=50)		HBV infected (n=51)		All patients (n=214)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with a TRAE	44 (79)	15 (27)	40 (70)	7 (12)	40 (80)	15 (30)	35 (69)	3 (6)	159 (74)	40 (19)
TRAEs (in ≥5% of all patients)										
Rash	6 (11)	1 (2)	10 (18)	1 (2)	9 (18)	0	8 (16)	0	33 (15)	2 (1)
Pruritus	11 (20)	0	7 (12)	0	14 (28)	1 (2)	13 (25)	0	45 (21)	1 (<1)
Diarrhoea	10 (18)	1 (2)	9 (16)	1 (2)	5 (10)	0	3 (6)	1 (2)	27 (13)	3 (1)
Decreased appetite	4 (7)	0	2 (4)	0	2 (4)	1 (2)	3 (6)	0	11 (5)	1 (<1)
Fatigue	14 (25)	1 (2)	20 (35)	1 (2)	8 (16)	1 (2)	7 (14)	0	49 (23)	3 (1)
Nausea	3 (5)	0	7 (12)	0	6 (12)	0	1 (2)	0	17 (8)	0
Dry mouth	4 (7)	0	5 (9)	0	2 (4)	0	2 (4)	0	13 (6)	0
Laboratory TRAEs (in ≥5% of all patients)										
AST increase	6 (11)	2 (4)	3 (5)	2 (4)	6 (12)	5 (10)	1 (2)	0	16 (7)	9 (4)
ALT increase	4 (7)	0	3 (5)	2 (4)	7 (14)	3 (6)	3 (6)	0	17 (8)	5 (2)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; TRAE, treatment-related adverse event

1. El-Khoueiry AB, et al. Lancet. 2017;389:2492-502.

CHECKMATE 040: CHILD-PUGH B COHORT

Child–Pugh B7-B8 Cohort

Key eligibility criteria

- Advanced HCC

  Sorafenib-naive or -treated intolerant or progressors

→ **Nivolumab** 240 mg flat dose IV for 30 minutes every 2 weeks → Follow-up visit 1 and 2 and survival follow-up → Treat until RECIST v.1.1–defined progression or unacceptable toxicity

Median follow-up: 11.8 months (6.4-18.0 months)

Data from CheckMate 040 cohorts 1 and 2, in which almost all patients (98.5%) had Child-Pugh A status, are presented for comparison*

- **Primary endpoint:** ORR based on investigator assessment using RECIST v1.1
- **Secondary endpoints:** DCR, DOR, TTR, TTP, PFS, and OS
- **Other:** BOR and ORR based on BIRC-assessed tumour response by mRECIST, safety using NCI CTCAE v4.0

*Direct comparisons between cohorts cannot be made.

BICR, blinded independent central review; BOR, best overall response; CTCAE, common terminology criteria of adverse events; CR, complete response; DCR, disease-control rate; DOR, duration of response; HCC, hepatocellular carcinoma; IV, intravenous; mRECIST, modified Response Evaluation Criteria In Solid Tumours; NCI, National Cancer Institute; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression; TTR, time to response

1. Kudo M et al. ASCO GI 2019. Abstract #327

CHECKMATE 040: NIVOLUMAB EFFICACY BY CHILD-PUGH STATUS[1]

Outcome	Child-Pugh B (n=49)	Child-Pugh A (n=262)
	Median	Median
TTR, months	2.7	2.7
DOR, months	9.9	12.4

- **TRAEs** were reported in 25 (51%) patients; 4 (8.2%) patients had select hepatic TRAEs
- Investigator **ORR** was 10.2%; DCR was 55.1%
- Median **OS** = 7.6 months in Child-Pugh B

- **NCCN recommendation** as second-line therapy for Child-Pugh Class A or B7[2]

DCR, disease control rate; DOR, duration of response; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; TRAE, treatment-related adverse event; TTR, time to response

1. Kudo M et al. ASCO GI 2019. Abstract 327. 2. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. V3.2019. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed November 4, 2019.

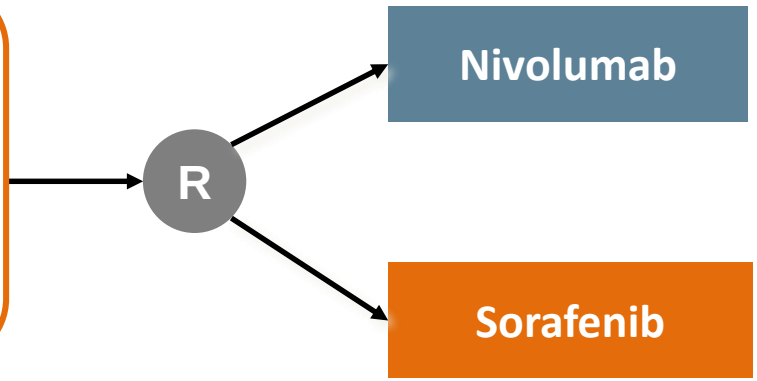
CHECKMATE 459: NIVOLUMAB VERSUS SORAFENIB IN ADVANCED HCC – DID NOT MEET PRIMARY STUDY ENDPOINT

Phase 3

Key eligibility criteria

- Advanced HCC not eligible for or progressive after surgical and/or locoregional treatment
- Child-Pugh A

(N=726)



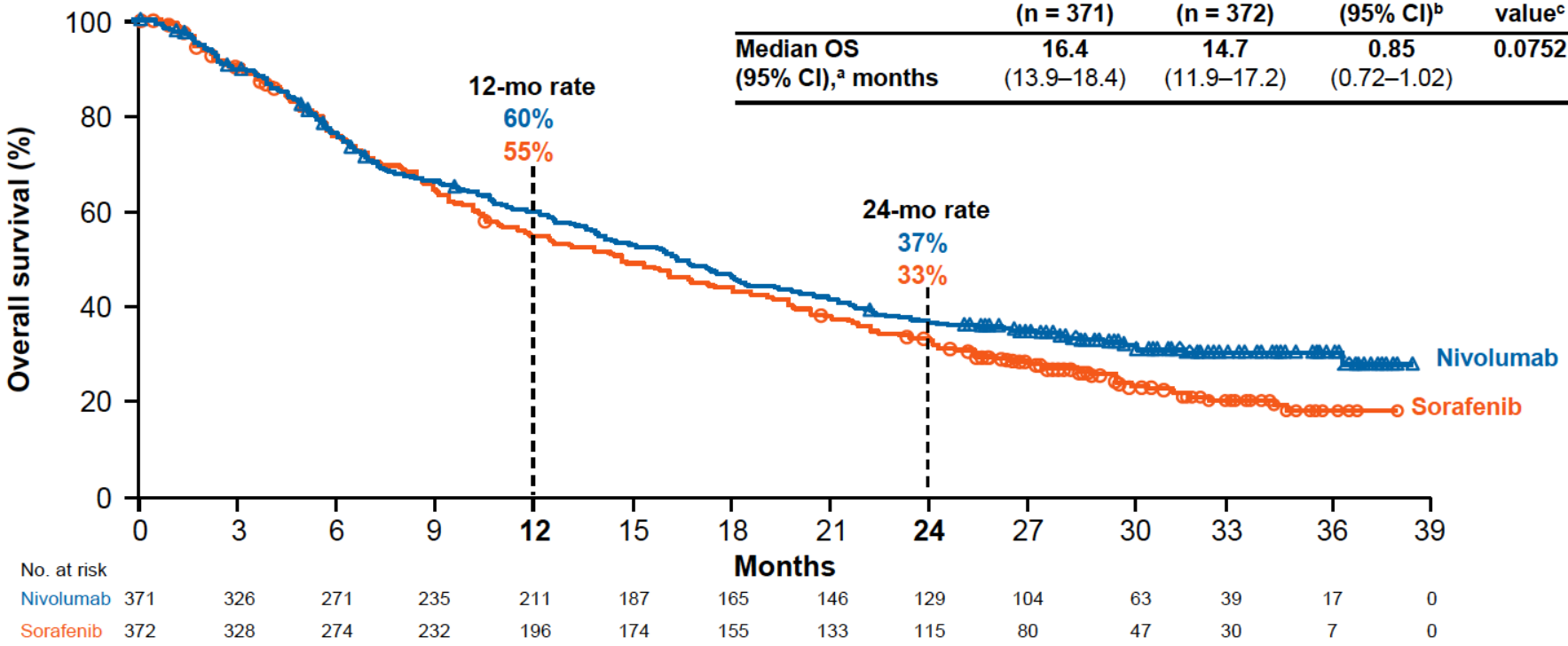
- **Primary endpoint:** OS
- **Other endpoints:** ORR, PFS, and biomarkers

HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

1. https://clinicaltrials.gov/ct2/show/NCT02576509. Accessed May 9, 2019. 2. Yau, et al. ESMO 2019 Abstract #LBA38

CHECKMATE 459: OVERALL SURVIVAL

	Nivolumab (n = 371)	Sorafenib (n = 372)	HR (95% CI)[b]	P value[c]
Median OS (95% CI),[a] months	16.4 (13.9–18.4)	14.7 (11.9–17.2)	0.85 (0.72–1.02)	0.0752



- The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit

[a]Based on Kaplan–Meier estimates; [b]Stratified Cox proportional hazards model. HR is nivolumab over sorafenib; [c]Pvalue from log-rank test
CI, confidence interval; HR, hazard ratio; OS, overall survival
Yau, et al. ESMO 2019 Abstract #LBA38

KEYNOTE 224 STUDY DESIGN

HCC connect
POWERED BY COR2ED

Key eligibility criteria

- ≥18 years
- Pathologically confirmed HCC
- Progression on or intolerance to sorafenib treatment
- Child Pugh class A
- ECOG PS 0-1
- BCLC Stage C or B disease
- Predicted life expectancy >3 months

pembrolizumab
200 mg Q3W
for 2 years or until PD, intolerable toxicity, withdrawal of consent or investigator decision

Survival follow-up

- **Response assessed Q9W**
- **Primary endpoint: ORR** (RECIST v1.1, central review)
- **Secondary endpoint: DOR, DCR, PFS, OS, and safety and tolerability**

BCLC, Barcelona Clinic Liver Cancer; DCR, disease-control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; Q9W, every 9 weeks; RECIST, Response Evaluation Criteria in Solid Tumours

Zhu AX, et al. Lancet Oncol. 2018;19:940-52

KEYNOTE 224: PHASE 2 STUDY OF PEMBROLIZUMAB IN PREVIOUSLY TREATED HCC[1]

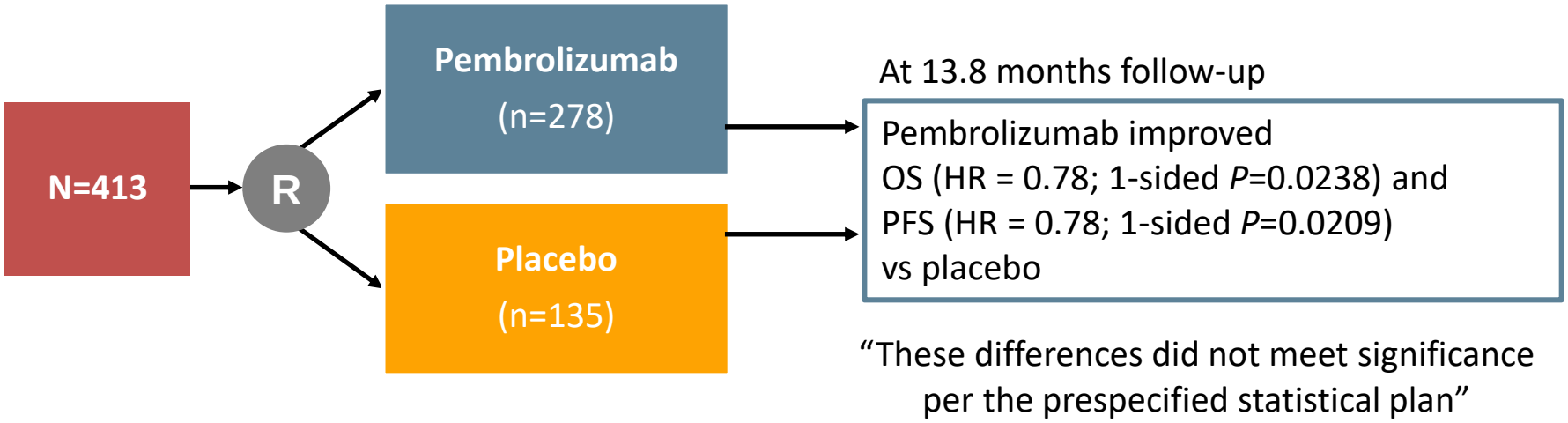
- **KEYNOTE 224:** Non-randomised, multicenter, open-label, phase 2 trial assessing PD-1 inhibitor pembrolizumab 200 mg every 3 weeks
- Patients (N=104) with HCC previously treated with sorafenib who were either intolerant to this treatment or showed radiographic progression after treatment[a]
- The primary endpoint was objective response

Best Response	Patients (n=104)
Objective response	17%
Complete	1%
Partial	16%
Stable disease	44%
Progression	33%

[a]ECOG PS of 0-1; adequate organ function, Child-Pugh class A.
HCC, hepatocellular carcinoma

1. Zhu AX, et al. Lancet Oncol. 2018;19:940-52

KEYNOTE 240: PEMBROLIZUMAB VERSUS BSC AS SECOND-LINE THERAPY DID NOT MEET THE PRIMARY ENDPOINT



Pembrolizumab reduced the risk of death by 22% and improved PFS over placebo
but did not meet predefined HR

BSC, best supportive care; HR, hazard ratio; OS, overall survival; PFS, progression-free survival;

1. Finn RS, et al. ASCO 2019. Abstract #4004.

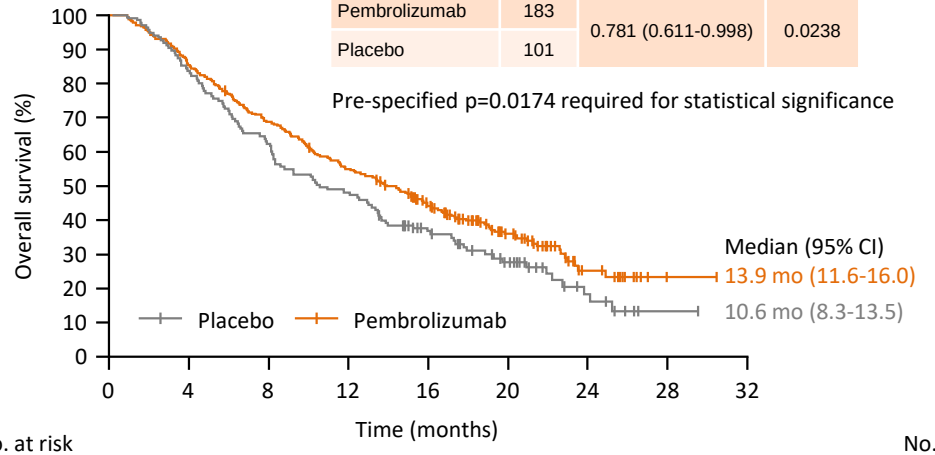
KEYNOTE 240: OS/PFS UPDATE FROM ASCO 2019

HCC connect
POWERED BY COR2ED

OS

	Events	HR (95% CI)	P
Pembrolizumab	183	0.781 (0.611-0.998)	0.0238
Placebo	101		

Pre-specified p=0.0174 required for statistical significance

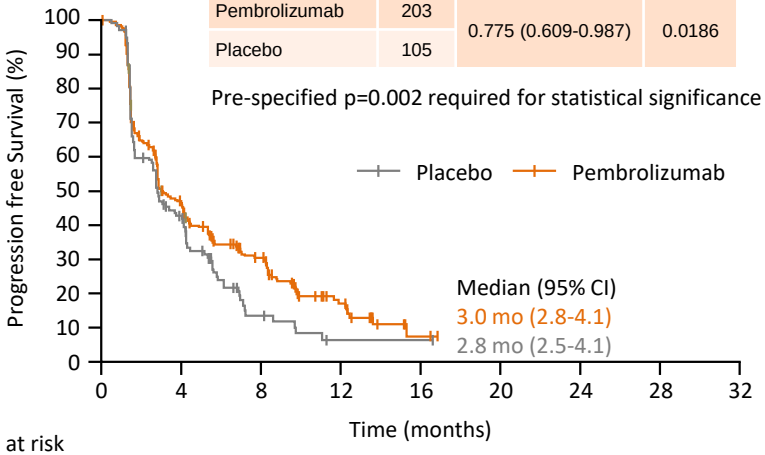


No. at risk									
Pembrolizumab	278	237	190	152	110	57	16	1	0
Placebo	135	113	84	65	42	23	8	1	0

PFS

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

Pre-specified p=0.002 required for statistical significance



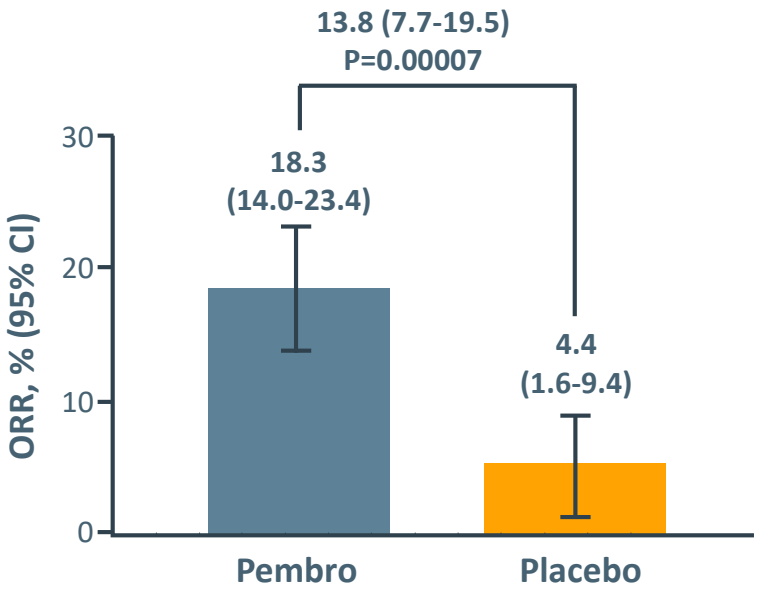
No. at risk									
Pembrolizumab	278	112	57	17	2	0	0	0	
Placebo	135	48	9	1	1	0	0	0	

KEYNOTE 240 did not meet the statistical criteria for either of the dual primary endpoints

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

Finn R, et al. ASCO 2019. Abstract #4004

OBJECTIVE RESPONSE RATE AT FINAL ANALYSIS (RECIST 1.1, BICR)



Response n (%)	Pembrolizumab N=278	Placebo N=135
Best Overall Response		
CR	6 (2.2)	0 (0.0)
PR	45 (16.2)	6 (4.4)
SD	122 (43.9)	66 (48.9)
SD ≥23 wks	37 (18.3)	20 (14.8)
Progressive Disease	90 (32.4)	57 (42.2)
Disease Control Rate (CR+PR+SD)	173 (62.2)	72 (53.3)

Duration of response, median (range)[b,c]:

- Pembrolizumab: 13.8 mo (1.5+ mo − 23.6+ mo)
- Placebo: not reached (2.8 mo−20.4+ mo)

BICR, blinded independent central review; CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease

Finn R, et al. ASCO 2019. Abstract #4004

COMBINING CTLA-4 AND PD-1/PD-L1 INHIBITORS IN HCC

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HCC, hepatocellular carcinoma; PD-1, programmed death 1; PD-L1, programmed-death ligand 1

CHECKMATE 040: NIVOLUMAB PLUS IPILIMUMAB

- **148 sorafenib-treated patients** were randomised
  - 88% had vascular invasion or EHS
  - 91% had BCLC stage C
  - 84% discontinued sorafenib due to disease progression
  - 14% discontinued due to toxicity
- **3 treatment arms**

nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg every 2 weeks	**nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks**	**nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks**

BCLC, Barcelona Clinic Liver Cancer; EHS, extrahepatic spread
Yau T, et al. ASCO 2019. Abstract #4012

CHECKMATE 040: NIVOLUMAB PLUS IPILIMUMAB (CONT'D)

	nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (n=50)	nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (n=49)	nivolumab 3 mg/kg Every 2 Weeks + ipilimumab 1 mg/kg Q6W (n=49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
CR	4 (8)	3 (6)	0
PR	12 (24)	12 (24)	15 (31)
SD	9 (18)	5 (10)	9 (18)
PD	20 (40)	24 (49)	21 (43)
DCR, % (95% CI)	54 (39-68)	43 (29-58)	49 (34-64)
Median OS, mo (95% CI)	23 (9-NA)	12 (8-15)	13 (7-33)
12-mo OS rate, % (95% CI)	61 (46-73)	56 (41-69)	51 (36-64)
24-mo OS rate, % (95% CI)	48 (34-61)	30 (18-44)	42 (28-56)

37% of patients had a grade 3-4 TRAE
Most common: pruritus and rash

Nivolumab plus ipilimumab led to meaningful responses with an ORR twice that of nivolumab monotherapy

CR, complete response; DCR, disease control rate; NA, not available; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response; QxW, every x weeks; SD, stable disease; TRAE, treatment-related adverse event
Yau T, et al. ASCO 2019. Abstract #4012

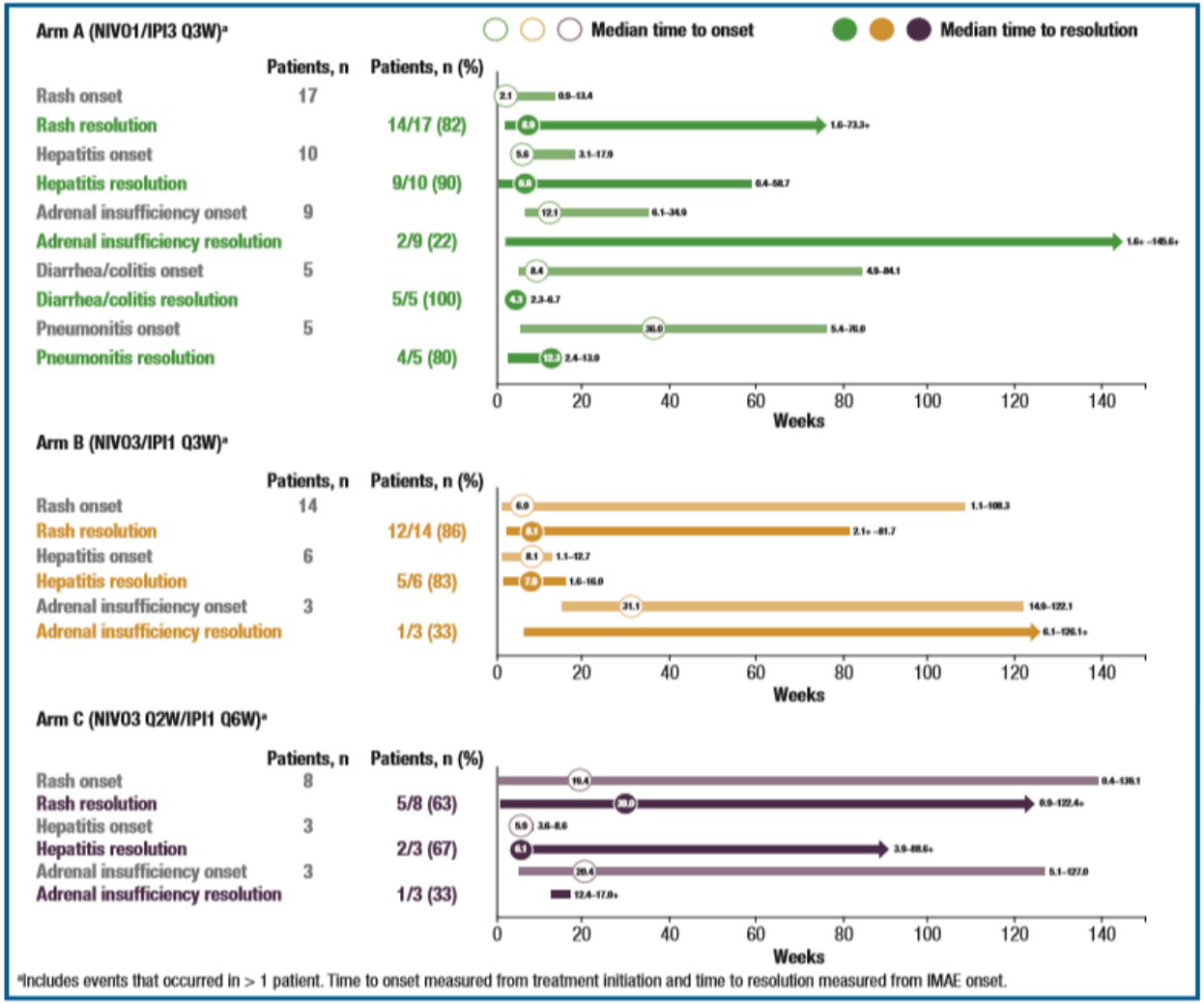
SUMMARY OF IMAEs

N (%)	nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (n=49)		nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (n=49)		nivolumab 3 mg/kg Every 2 Weeks + ipilimumab 1 mg/kg Q6W (n=48)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Rash	17 (35)	3 (6)	14 (29)	2 (4)	8 (17)	0
Hepatitis	10 (20)	10 (20)	6 (12)	5 (10)	3 (6)	3 (6)
Adrenal insufficiency	9 (18)	2 (4)	3 (6)	0	3 (6)	0
Diarrhoea/colitis	5 (10)	3 (6)	1 (2)	1 (2)	1 (2)	1 (2)
Pneumonitis*	5 (10)	3 (6)	0	0	0	0
Nephritis/renal dysfunction	0	0	1 (2)	0	1 (2)	1 (2)
Hypersensitivity	0	0	1 (2)	1 (2)	1 (2)	0
Hypophysitis	1 (2)	0	0	0	1 (2)	1 (2)
Hyperthyroidism	0	0	1 (2)	0	1 (2)	0
Hypothyroidism/thyroiditis	0	0	0	0	1 (2)	0
Diabetes mellitus	0	0	0	0	0	0

IMAEs are specific events considered as potential immune-mediated events by investigator occurring <100 days of last dose, regardless of casualty, treated with immune-modulating medication.

*Within 100 days after the final dose of study drug, 1 patient from Arm A died of a serious TRAE (grade 5 pneumonitis).
IMAE, immune-mediated adverse event; QxW, every x weeks; TRAE, treatment-related adverse event
Yau T, et al. ASCO 2019. Abstract #4012

TIME TO ONSET AND TIME TO RESOLUTION OF MOST COMMON ANY GRADE IMAEs



IMAE, immune-mediated adverse event

Yau T, et al. ASCO 2019. Abstract #4012

CHECKMATE 9DW

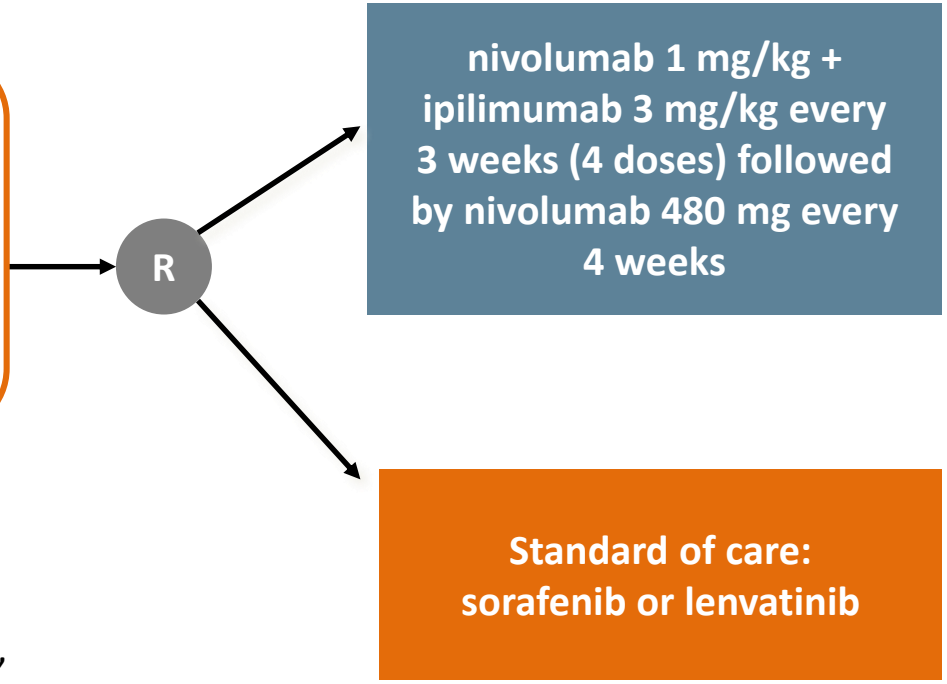
Phase 3

Key eligibility criteria

- Unresectable HCC not eligible for locoregional therapies
- HCC with histological confirmation
- Child-Pugh A (5 or 6)
- No prior systemic therapy

(N=~1,084)

- **Primary endpoint:** OS
- **Other endpoints:** ORR, DOR, and TTSD



DOR, duration of response; HCC, hepatocellular carcinoma; OS, overall survival; ORR, overall response rate; TTSD, time to symptom deterioration

https://clinicaltrials.gov/ct2/show/NCT04039607. Accessed Oct 31, 2019.

PHASE 1/2 STUDY: DURVALUMAB PLUS TREMELIMUMAB

HCC connect
POWERED BY COR2ED

Key eligibility criteria

- Advanced HCC progression on or intolerant of sorafenib
- Adequate liver function
- ECOG PS 0-1
- ≥1 measurable lesion

Safety run-in and efficacy gating

R

- durvalumab + tremelimumab — Arm A
- durvalumab — Arm B
- tremelimumab — Arm C

- **Primary endpoints:** AEs, SAEs, and dose-limiting toxicities
- **Secondary endpoints:** ORR, DOR, OS, PD-L1 expression, TTP, PFS, DCR, and TTR

Each arm to include an equal number of:

- Uninfected patients
- Patients with HBV
- Patients with HCV

AE, adverse event; DCR, disease-control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OS, overall survival; ORR, overall response rate; PD-L1, programmed-death ligand 1; PFS, progression-free survival; SAE, serious adverse event; TTP, time to progression; TTR, time to response

https://clinicaltrials.gov/show/NCT02519348. Accessed November 4, 2019.

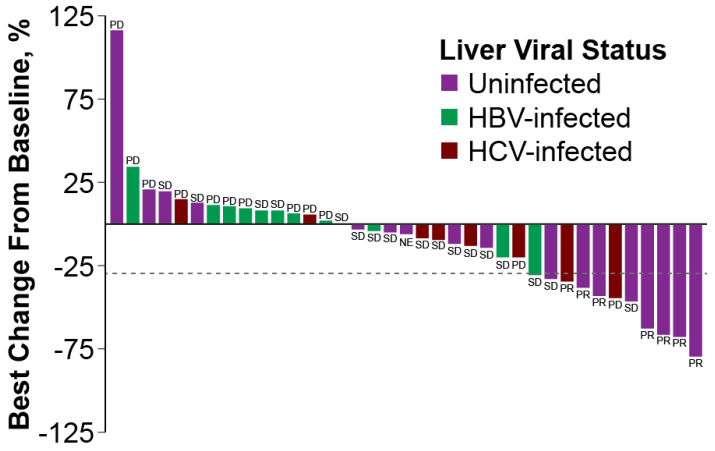
DURVALUMAB PLUS TREMELIMUMAB: EFFICACY AND SAFETY DATA

HCC connect
POWERED BY COR2ED

Investigator-Assessed Response

	HBV+ (n=11)	HCV+ (n=9)	Uninfected (n=20)	All (N=40)
Confirmed ORR, % (95% CI)	0 (0.0-28.5)	11.1 (0.3-48.2)	30.0 (11.9-54.3)	17.5 (7.3-32.8)
CR + PR, (confirmed + unconfirmed), % (95% CI)	9.1 (0.2-41.3)	11.1 (0.3-48.2)	40.0 (19.1-63.9)	25.0 (12.7-41.2)
DCR at week 16, % (95% CI)	45.5 (16.7-76.6)	44.4 (13.7-78.8)	70.0 (45.7-88.1)	57.5 (40.9-73.0)

Antitumour Activity



Most common AEs were fatigue, pruritus, and elevated liver enzymes

AE, adverse event; CI, confidence interval; CR, complete response; DCR, disease-control rate; HBV, hepatitis B virus; HCV, hepatitis C virus; ORR, overall response rate; PR, partial response

Kelley RK, et al. ASCO 2017. Abstract #4073.

DURVALUMAB PLUS TREMELIMUMAB: EFFICACY AND SAFETY DATA (CONT'D)

Preferred Term	HBV+ (n=11)	HCV+ (n=9)	Uninfected (n=20)	Total (N=40)	
				Any	Grade 3/4
Pruritus	3 (27.3)	3 (33.3)	3 (15.0)	9 (22.5)	0
Elevated ALT	3 (27.3)	3 (33.3)	2 (10.0)	8 (20.0)	2 (5.0)
Elevated AST	3 (27.3)	2 (22.2)	2 (10.0)	7 (17.5)	4 (10.0)
Elevated lipase	2 (18.2)	1 (11.1)	3 (15.0)	6 (15.0)	4 (10.0)
Rash	2 (18.2)	1 (11.1)	2 (10.0)	5 (12.5)	0
Diarrhoea	3 (27.3)	2 (22.2)	0	5 (12.5)	1 (2.5)
Elevated amylase	2 (18.2)	0	1 (5.0)	3 (7.5)	1 (2.5)
Colitis	0	2 (22.2)	0	1 (2.5)	1 (2.5)
Pneumonitis	1 (9.1)	0	0	1 (2.5)	1 (2.5)
Pancreatitis	0	1 (11.1)	0	1 (2.5)	1 (2.5)
Hypertransaminasaemia	0	1 (11.1)	0	1 (2.5)	1 (2.5)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus

Kelley RK, et al. ASCO 2017. Abstract #4073.

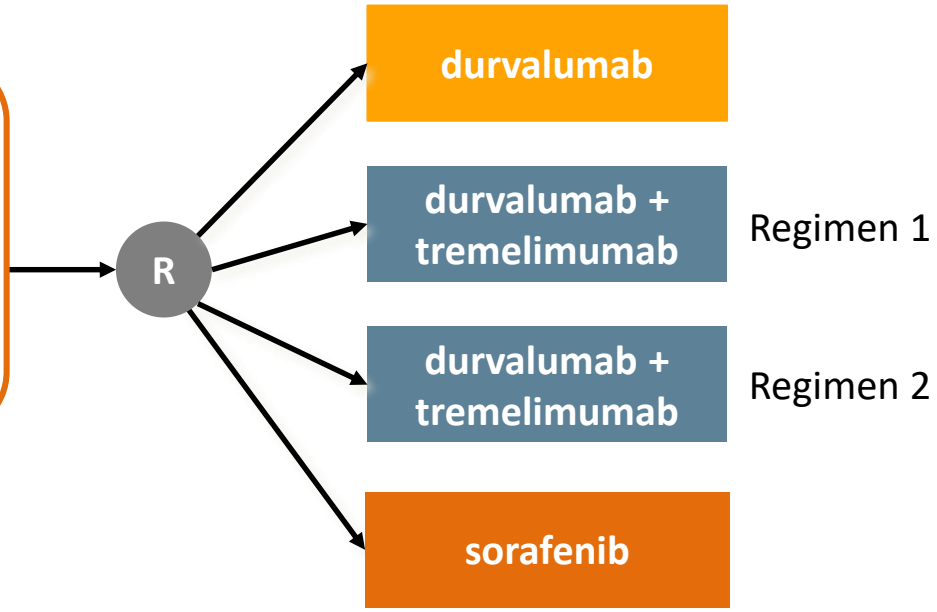
HIMALAYA: DURVALUMAB PLUS TREMELIMUMAB VERSUS SORAFENIB

Phase 3

Key eligibility criteria

- Unresectable HCC not eligible for locoregional therapies
- BCLC stage B or C
- Child-Pugh A
- No prior systemic therapy

(N=~1,310)



- **Primary endpoint:** OS
- **Other endpoints:** TTP, PFS, ORR, DCR, DOR, and QoL

BCLC, Barcelona Clinic Liver Cancer; DCR, disease-control rate; DOR, duration of response; HCC, hepatocellular carcinoma; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; QoL, quality of life; TTP, time to progression

https://clinicaltrials.gov/ct2/show/NCT03298451. Accessed November 4, 2019.

COMBINING IMMUNE-CHECKPOINT INHIBITORS AND ANGIOGENESIS INHIBITORS IN HCC

RATIONALE BEHIND COMBINING ANGIOGENESIS INHIBITORS AND IMMUNE CHECKPOINT INHIBITORS

HCC connect
POWERED BY COR2ED

Systemic Therapy
(anti angiogenic, multi targeted)

+ Immune checkpoint inhibitors

Systemic Therapy
(anti angiogenic, multi targeted)
induces:

- Hypoxia
- Treg population
- ↑ PD-L1 expression

↓

Synergistic Antitumour Response

PD-L1, programmed-death ligand 1; Treg, regulatory T cells

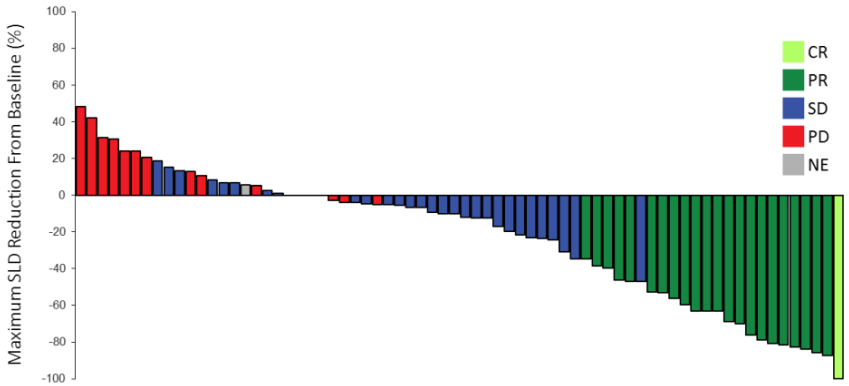
1. Chen Y, et al. Hepatology. 2015;61:1591-602. 2. Greten TF, et al. Rev Recent Clin Trials. 2008;3:31-9

ATEZOLIZUMAB PLUS BEVACIZUMAB IN ADVANCED HCC: RESPONSE

HCC connect
POWERED BY COR2ED

ORR	
Overall, n (%)[a]	23/73 (32)
CR	1/73 (1)
PR	22/73 (30)
SD	33/73 (45)
PD	13/73 (18)
By region, n/n (%)[b]	
Asia excluding Japan	12/41 (29)
Japan/USA	10/31 (32)
By etiology, n/n (%)	
HBV	11/36 (31)
HCV	10/23 (43)
Nonviral	2/14 (14)
By baseline AFP, n/n (%)[c]	
<400 ng/mL	12/41 (29)
≥400 ng/mL	11/27 (41)
By EHS/MVI, n/n (%)[d]	
EHS and/or MVI	18/64 (28)
MVI negative	13/32 (41)
EHS negative	9/22 (41)
Neither EHS nor MVI	5/8 (63)

PHASE 1B STUDY



[a]Four patients were unevaluable. [b]Region data from one patient are missing. [c]Baseline AFP data from five patients are missing. [d]EHS and MVI baseline data from two patients are missing.

AFP, alpha-fetoprotein; CR, complete response; EHS, extra-hepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macroscopic vascular invasion; NE, not evaluable or missing; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameter

Pishvaian MJ, et al. ESMO 2018. Abstract #LBA26.

ATEZOLIZUMAB PLUS BEVACIZUMAB IN ADVANCED HCC: SAFETY

Most common AEs (≥20% of patients); n=103	n (%)
Decreased appetite	29 (28)
Fatigue	21 (20)
Rash	21 (20)
Pyrexia	21 (20)

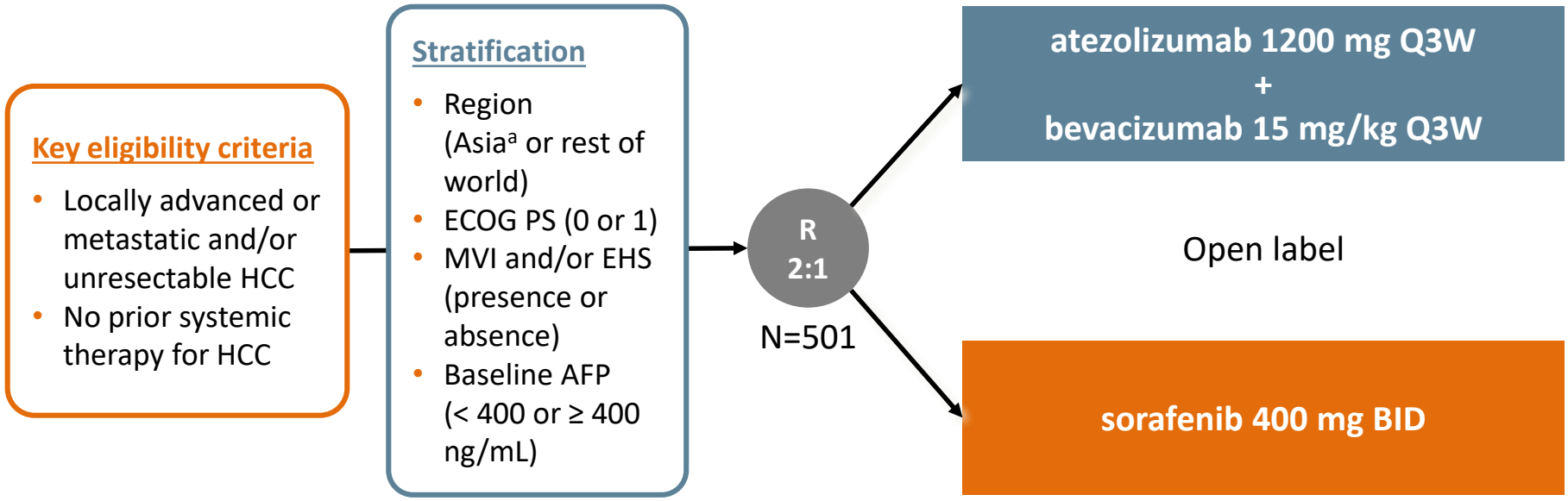
Grade 3/4 TRAEs (≥5% of patients); n=103	n (%)
Hypertension	10 (10)

Grade ≥3 atezolizumab AESIs requiring systemic corticosteroids	n (%)
Pneumonitis	2 (2)
Encephalitis autoimmune	1 (1)
Drug-induced liver injury	1 (1)
Colitis	1 (1)
AST increased	1 (1)
Gamma-glutamyltransferase increased	1 (1)
Diabetes mellitus	1 (1)
Pancreatitis	1 (1)

AE, adverse event; AESI, adverse event of special interest; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; TRAE, treatment-related adverse event

Pishvaian MJ, et al. ESMO 2018. Abstract LBA26.

PHASE 3 IMbrave150 STUDY: ATEZOLIZUMAB + BEVACIZUMAB VS SORAFENIB IN UNTREATED PATIENTS



Primary endpoints: OS and PFS (IRF-assessed per RECIST 1.1)
Patients were treated until loss of clinical benefit or unacceptable toxicity

[a] excluding Japan

AFP, alpha-fetoprotein; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; IRF, independent review facility; MVI, macroscopic vascular invasion; OS, overall survival; PFS, progression-free survival; QxW, every x weeks; RECIST, Response Evaluation Criteria in Solid Tumours

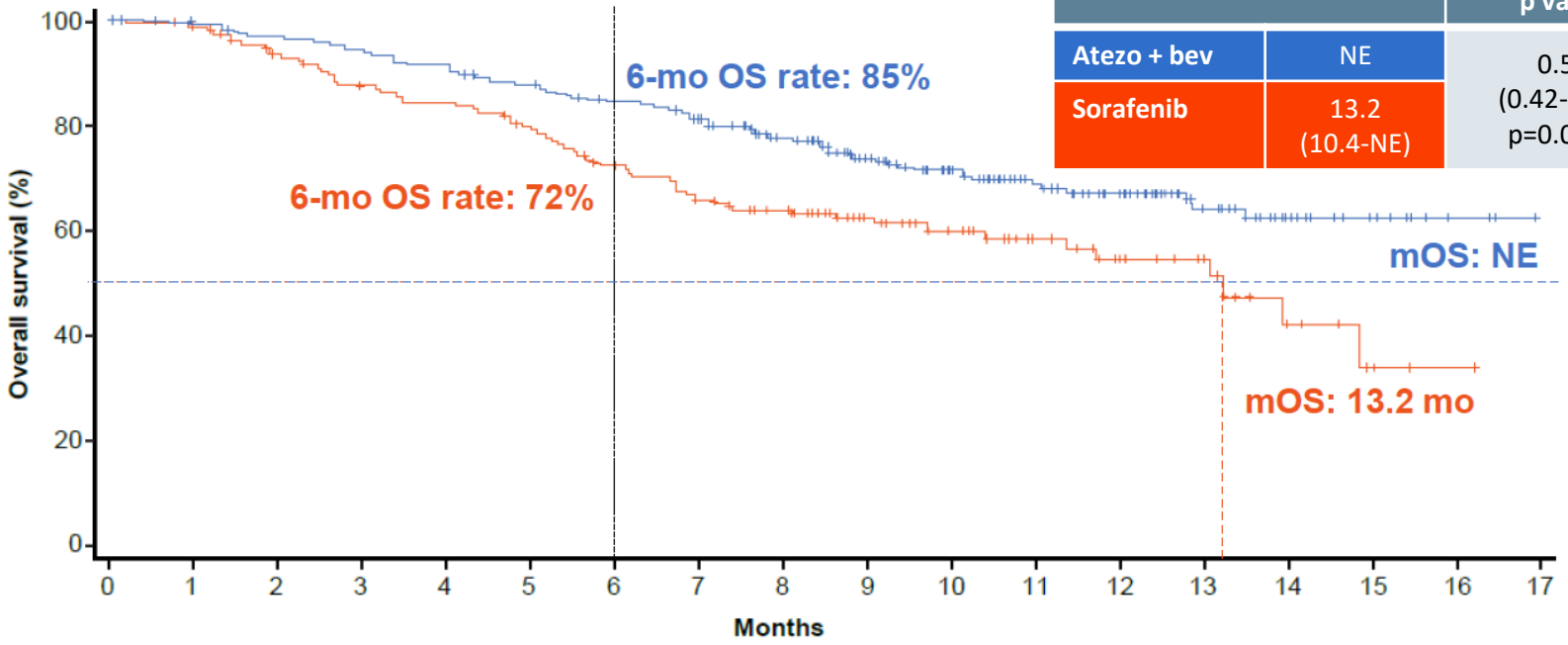
1. Cheng A-L, et al. ESMO Asia 2019 Abstract #LBA3. 2. https://clinicaltrials.gov/ct2/show/NCT03434379. Accessed November 4, 2019.

IMbrave150: OS

STATISTICALLY SIGNIFICANT AND CLINICALLY MEANINGFUL IMPROVEMENT IN OS

Median survival follow up was 8.6 months

Median OS, months (95% CI)		HR (95% CI), p value
Atezo + bev	NE	0.58 (0.42-0.79) p=0.0006
Sorafenib	13.2 (10.4-NE)	



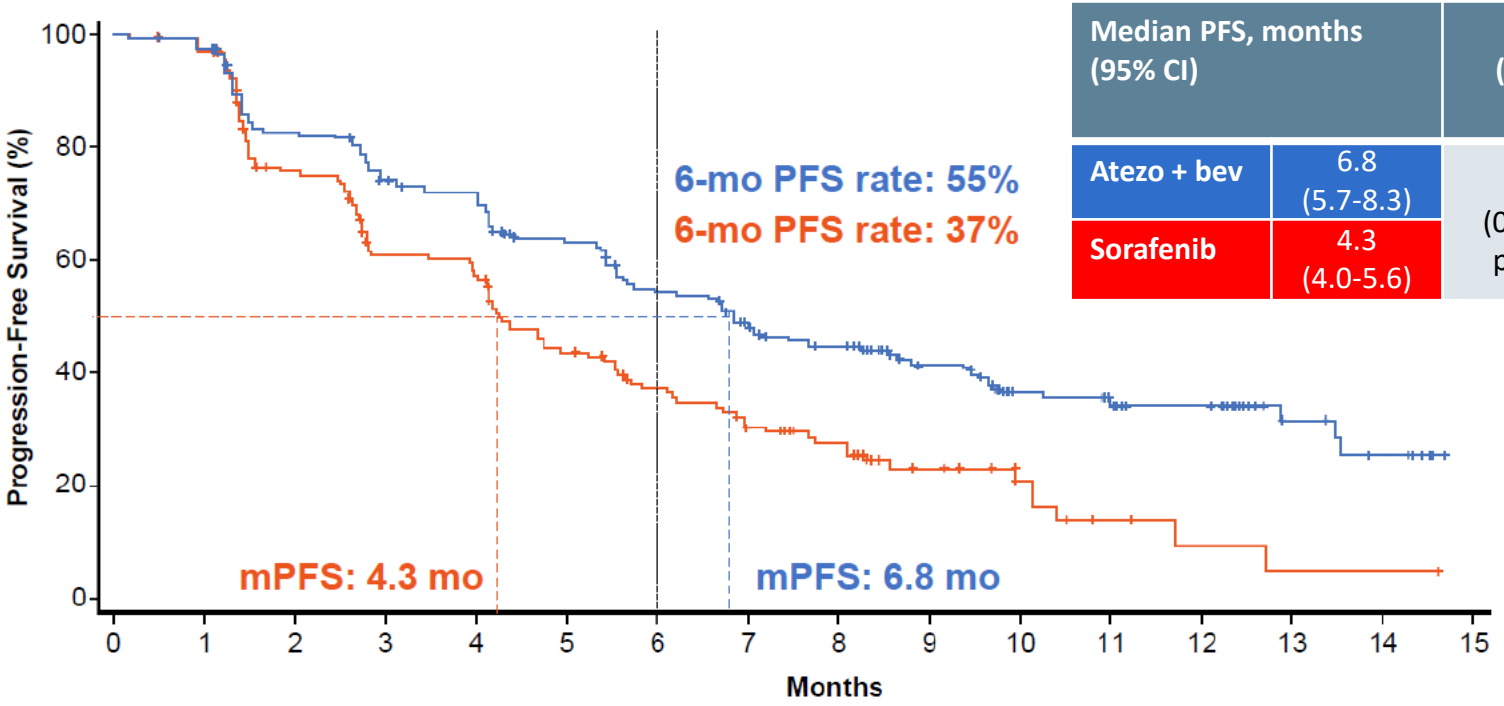
No. at risk																	
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival

Cheng A-L, et al. ESMO Asia 2019 Abstract #LBA3

IMbrave150: PFS

STATISTICALLY SIGNIFICANT AND CLINICALLY MEANINGFUL IMPROVEMENT IN IRF-ASSESSED PFS PER RECIST 1.1



Median PFS, months (95% CI)		HR (95% CI), p value
Atezo + bev	6.8 (5.7-8.3)	0.59 (0.47-0.76) p<0.0001
Sorafenib	4.3 (4.0-5.6)	

No. at risk															
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; HR, hazard ratio; IRF, independent review facility; NE, not estimable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

Cheng A-L, et al. ESMO Asia 2019 Abstract #LBA3

IMbrave150: RESPONSE

STATISTICALLY SIGNIFICANT, CLINICALLY MEANINGFUL IMPROVEMENTS IN ORR DURABLE RESPONSE

Response, n (%)	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + bev (n = 326)	Sorafenib (n = 159)	Atezo + bev (n = 325)[b]	Sorafenib (n = 158)
Confirmed ORR[a]	89 (27)	19 (12)	108 (33)	21 (13)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
SD	151 (46)	69 (43)	127 (39)	66 (42)
PD	64 (20)	39 (25)	66 (20)	40 (25)
DCR	240 (74)	88(55)	235 (72)	87 (55)
Ongoing response, n/N (%)	77/89 (87)	13/19 (68)	84/108 (78)	13/21 (62)
Median DoR, months (95% CI)	NE	6.3 (4.7-NE)	NE	6.3 (4.9-NE)

[a] p<0.0001

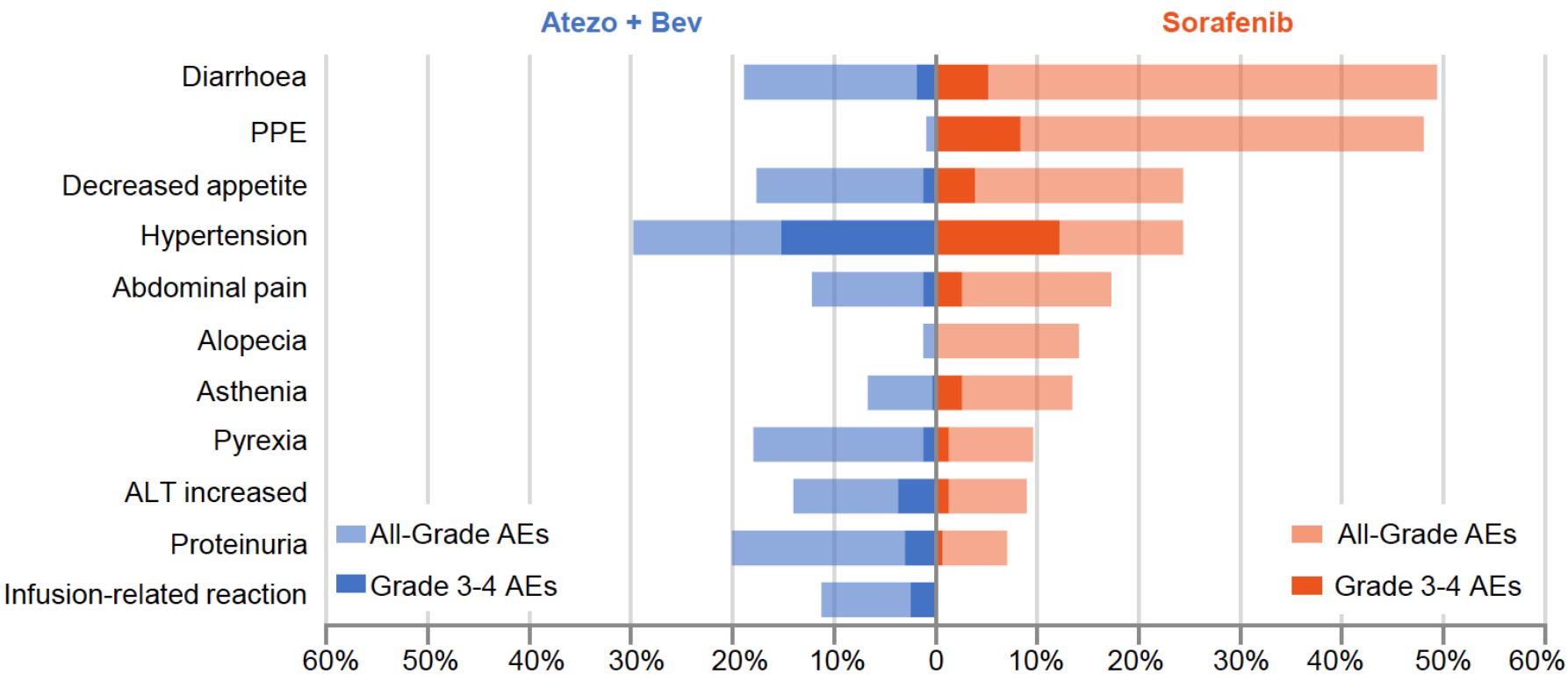
[b] IRF HCC mRECIST-evaluable population was based on patients who presented with measurable disease at baseline per HCC mRECIST criteria

atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IRF, independent review facility; mRECIST, RECIST, Response Evaluation Criteria in Solid Tumours; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease

Cheng A-L, et al. ESMO Asia 2019 Abstract #LBA3

IMbrave150: SAFETY

AEs OCCURRING IN ≥10% OF PATIENTS IN EITHER ARM AND WITH A >5% DIFFERENCE BETWEEN ARMS



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

Cheng A-L, et al. ESMO Asia 2019 Abstract #LBA3

PHASE 1b STUDY: LENVATINIB PLUS PEMBROLIZUMAB IN UNRESECTABLE HCC

HCC connect
POWERED BY COR2ED

Summary of TEAEs: Safety Analysis Set

Parameter, n (%)	lenvatinib + pembrolizumab		
	Part 1 (n=6)	Part 2 (n=24)	Overall (N=30)
TEAEs	6 (100.0)	24 (100.0)	30 (100.0)
Treatment-related TEAEs	6 (100.0)	22 (91.7)	28 (93.3)
TEAEs ≥ grade 3	5 (83.3)	13 (54.2)	18 (60.0)
Serious AEs	2 (33.3)	6 (25.0)	8 (26.7)
Fatal AEs[a]	0	3 (12.5)	3 (10.0)
Dose modifications			
LEN or PEM dose interruptions due to TEAEs	5 (83.3)	13 (54.2)	18 (60.0)
LEN dose reductions due to TEAEs	5 (83.3)	13 (54.2)	18 (60.0)
Discontinuation of LEN or PEM due to TEAE(s)[b]	0	5 (20.8)	5 (16.7)

Summary of Tumour Response: Investigator Assessment by mRECIST; Efficacy Analysis Set[c]

Parameter, n (%)	lenvatinib + pembrolizumab		
	Part 1 (n=6)	Part 2 (n=24)	Overall (N=30)
BOR			
CR[d]	0	1 (5.0)	1 (3.8)
PR[e]	4 (66.7)	6 (30.0)	10 (38.5)
SD	2 (33.3)	13 (65.0)	15 (57.7)
PD	0	0	0
ORR (incl. unconfirmed responses)	4 (66.7)	7 (35.0)	11 (42.3)
95% CI	22.3-95.7	15.4-59.4	23.4-63.1
ORR (excl. unconfirmed responses)	3 (50.0)	4 (20.0)	7 (26.9)
95% CI	11.8-88.2	5.7-43.7	11.6-47.8

[a]Acute respiratory distress syndrome (n=1); intestinal perforation (n=1); bacterial peritonitis (n=1). [b]Two TEAEs leading to discontinuation (acute respiratory distress syndrome and acute respiratory failure) were reported in the same patient. [c]Patients with post-evaluable tumour assessment. [d]Zero CR confirmed. [e]Seven PR confirmed.

AE, adverse event; CI, confidence interval; CR, complete response; LEN, lenvatinib; mRECIST, modified Response Evaluation Criteria In Solid Tumours; ORR, overall response rate; PEM, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease; TRAE, treatment-related adverse event

Ikeda M, et al. ASCO 2018. Abstract #4076

LEAP-002: 1ST-LINE LENVATINIB PLUS PEMBROLIZUMAB VERSUS LENVATINIB PLUS PLACEBO IN ADVANCED HCC

HCC connect
POWERED BY COR2ED

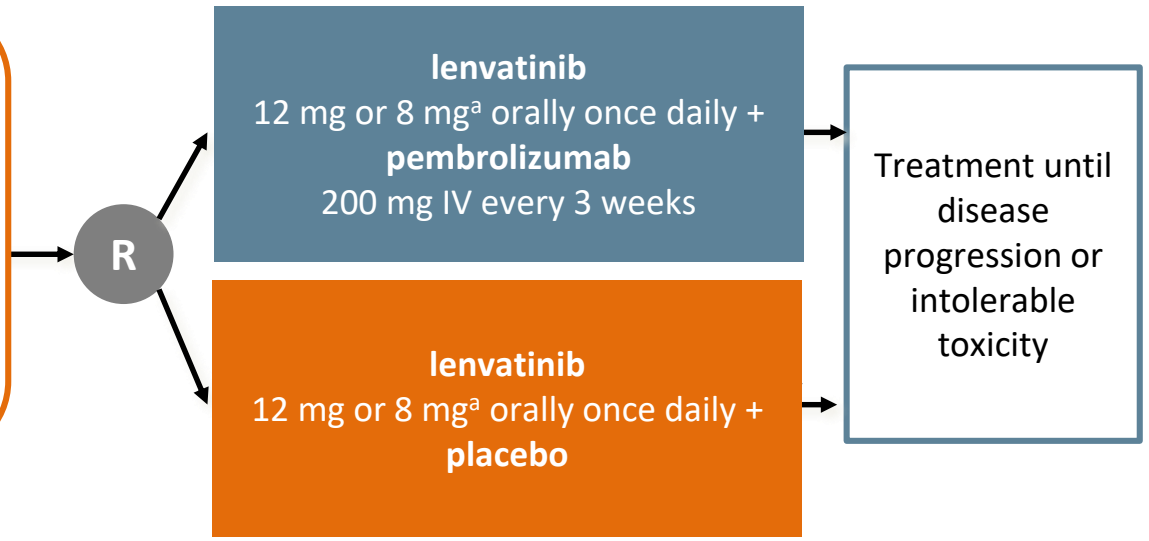
Phase 3

Key eligibility criteria

- BCLC stage C or B disease not amenable to locoregional therapy or refractory to locoregional therapy and not amenable to a curative treatment approach
- Child-Pugh A
- ECOG PS 0 or 1

(N=750)

- **Primary endpoints:** OS and PFS
- **Secondary endpoints:** ORR, DOR, DCR, and safety



[a]12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg).

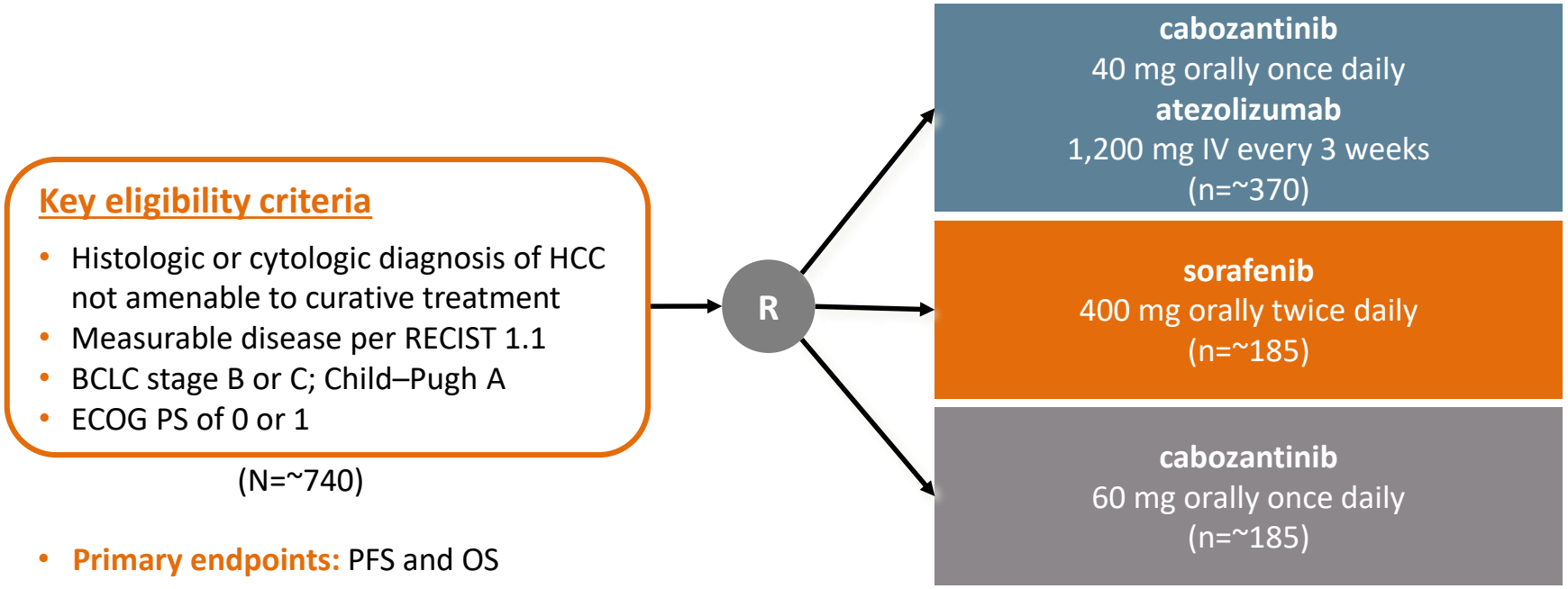
BCLC, Barcelona Clinic Liver Cancer; DCR, disease-control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IV, intravenous; OS, overall survival; ORR, overall response rate; PFS, progression-free survival

https://clinicaltrials.gov/ct2/show/NCT03713593. Accessed November 4, 2019.

PHASE 3 COSMIC-312 STUDY: CABOZANTINIB ± ATEZOLIZUMAB VS SORAFENIB IN ADVANCED HCC

HCC connect
POWERED BY COR2ED

Study in adults with advanced HCC who have not received prior systemic anticancer therapy in the advanced setting



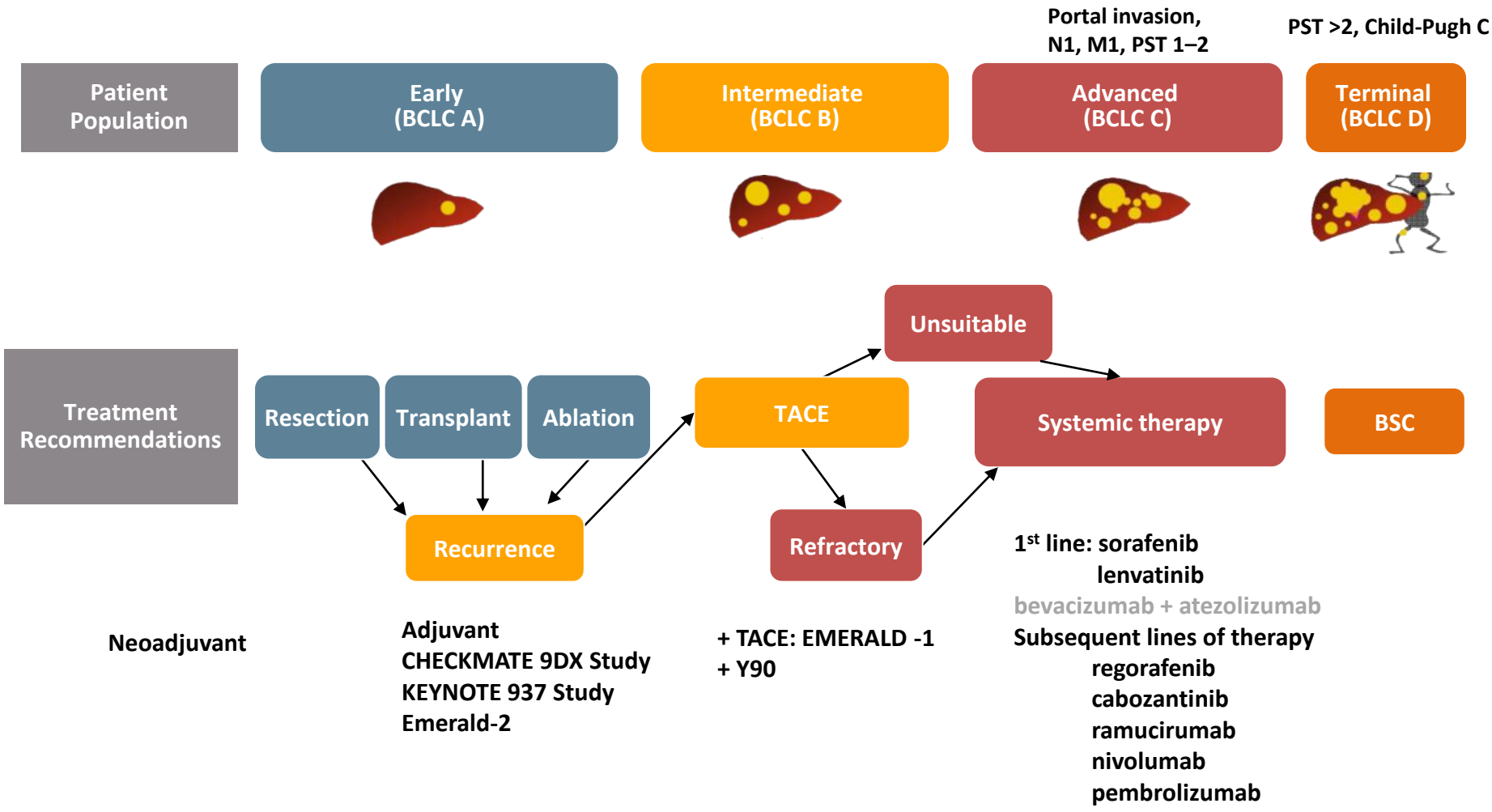
- **Primary endpoints:** PFS and OS

BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IV, intravenous; OS, overall survival; PFS, progression-free survival

https://clinicaltrials.gov/ct2/show/NCT03755791. Accessed November 4, 2019.

EXPANDING IO THERAPIES TO EARLIER STAGES OF HCC

HCC connect
POWERED BY COR2ED



BCLC, Barcelona Clinic Liver Cancer; BSC, best-supportive care; HCC, hepatocellular carcinoma; IO, immuno-oncology; PST, Performance Status Test; TACE, transarterial chemoembolisation

CONCLUSIONS

- The **systemic therapy** for advanced-stage HCC is **expanding**
  - Seven FDA approved treatments will likely result extended survival in patients who can be exposed to all these treatment options
- The landscape of treatment of HCC is **changing** with more systemic therapy options

The combination of bevacizumab and atezolizumab showed improved PFS and OS over sorafenib in the phase 3 IMbrave 150 study. This may become a first-line systemic treatment for advanced stage HCC.

HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival

A PEEK INTO THE FUTURE OF THE SYSTEMIC TREATMENT OF HCC

HCC connect
POWERED BY COR2ED

Combination therapy may replace single-agent treatment

The optimal **treatment sequence** over various lines of therapy will be determined

Exposure the one type of therapy could potentially make HCC more sensitive or resistant to another type of therapy given the complex effect of TKIs and IO on the tumour microenvironment

Systemic therapy will be moved to the **earlier stages** of HCC

To extend the life of HCC patients by improving the efficacy of current therapy (surgery, transplant, RFA, TACE etc.) and preserving liver function

Biomarkers may be discovered to prioritise treatment for HCC patients

HCC, hepatocellular carcinoma; IO, immuno-oncology; RFA, radiofrequency ablation; TKI, tyrosine-kinase inhibitor

MANAGEMENT OF TOXICITIES

TARGETED THERAPY: COMMON AEs

HCC connect
POWERED BY COR2ED

Sorafenib[1]

Most common (≥20%)

- Diarrhoea
- Fatigue
- Infection
- Alopecia
- Dermatologic AEs (e.g. HFSR, rash)
- Weight loss
- GI AEs (e.g. decreased appetite, nausea, pains
- Hypertension
- Haemorrhage

Other AEs

- Cardiac AEs
- QT/QTc interval prolongation
- Cases of increased bilirubin/INR

Lenvatinib[2]

Most common (≥20%)

- Hypertension
- Fatigue
- GI AEs (diarrhoea nausea, decreased appetite, pain)
- Arthralgia/myalgia
- Decreased weight
- Dermatologic AEs (HFSR)
- Proteinuria
- Dysphonia
- Haemorrhagic AEs
- Hypothyroidism

Other AEs

- Elevated TSH
- Cardiac AEs
- QT/QTc interval prolongation
- Hepatotoxicity

Regorafenib[3]

Most common (≥20%)

- Pain
- Dermatologic AEs (HFSR, rash)
- Asthenia/fatigue
- GI AEs (diarrhoea, decreased appetite, pain, nausea)
- Hypertension
- Infection
- Dysphonia
- Hyperbilirubinemia
- Fever
- Mucositis
- Weight loss

Other AEs

- Haemorrhage
- Hepatotoxicity
- Cardiac ischemia
- RPLS

Cabozantinib[4]

Most common (≥25%)

- Diarrhoea
- Fatigue
- GI AEs (decreased appetite, nausea, vomiting
- Dermatologic AEs (HFSR)
- Hypertension

Other AEs

- VTE
- RPLS
- Proteinuria
- Haemorrhage
- Jaw osteonecrosis

Ramucirumab[5]

Most common (≥15% and ≥2% vs placebo)

- Fatigue
- Peripheral oedema
- Hypertension
- GI AEs (abdominal pain, decreased appetite, nausea)
- Proteinuria
- Ascites
- Thrombocytopenia
- Hypoalbuminemia
- Hyponatremia

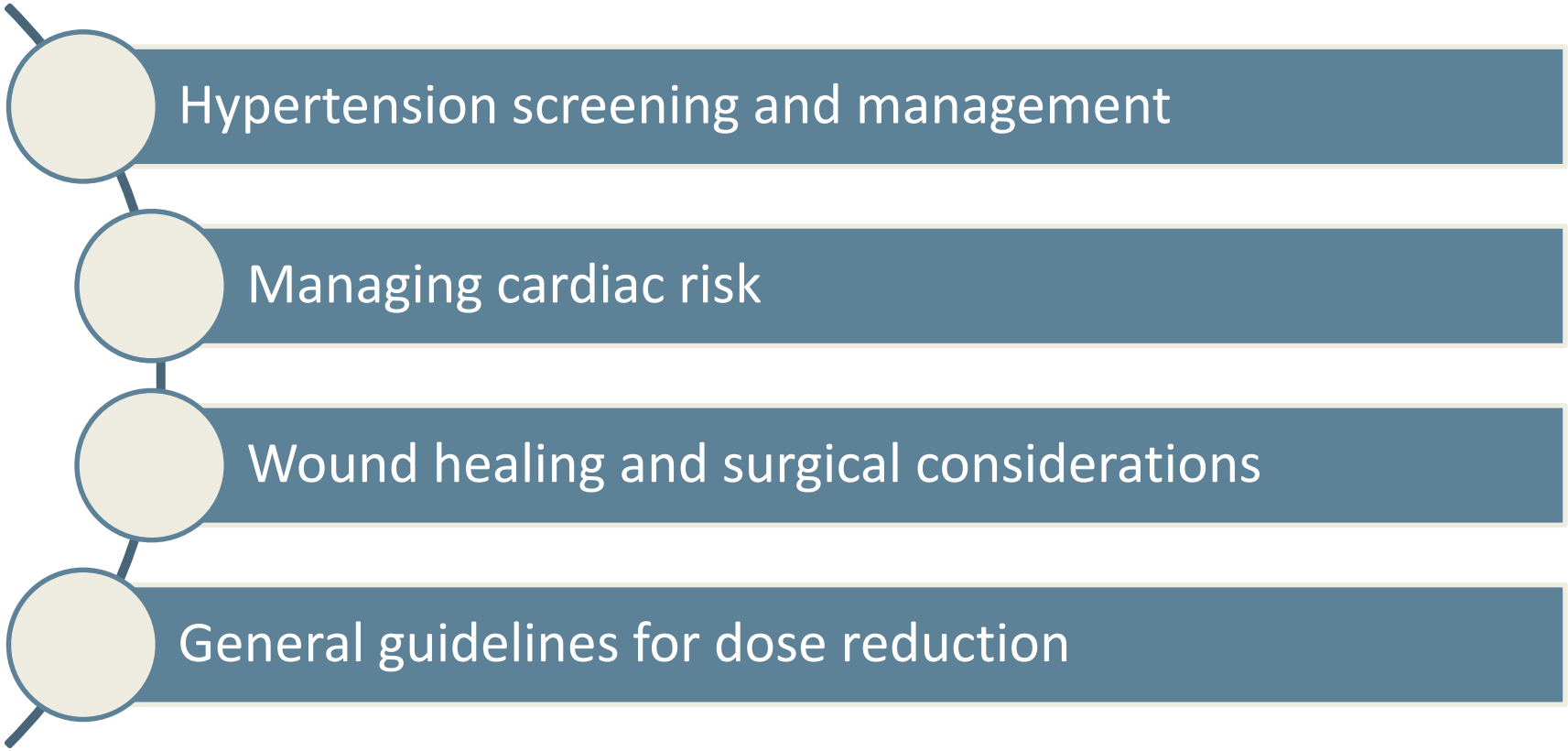
Other AEs

- Gastrointestinal perforation
- Haemorrhage
- RPLS
- VTE

AE, adverse event; GI, gastrointestinal; HFSR, hand-foot skin reaction; INR, international normalized ratio; RPLS, reversible posterior leukoencephalopathy syndrome; TSH, thyroid stimulating hormone; VTE, venous thromboembolism

1. Nexavar Package Insert. 2. Lenvima Package Insert. 3. Stivarga Package Insert. 4. Cabometyx Package Insert. 5. Cyramza Package Insert.

TARGETED THERAPY: AE MANAGEMENT



AE, adverse event

National Comprehensive Cancer Network. Hepatobiliary Cancers. V3.2019.

IMMUNOTHERAPY: COMMON AEs

HCC connect
POWERED BY COR2ED

Nivolumab (CheckMate 040)[1]

- 19% of 262 patients experienced grade 3/4 TRAEs
- Serious TRAEs included pemphigoid, adrenal insufficiency, and liver disorders
- No new safety signals were noted

Pembrolizumab (KeyNote 224)[2]

- 24% of 104 patients experienced grade 3 TRAEs
- Increased AST (7%)
- Increased ALT (4%)
- Fatigue (4%)
- Immune-mediated hepatitis occurred in 3% of patients

Atezolizumab + bevacizumab (IMbrave150)[3]

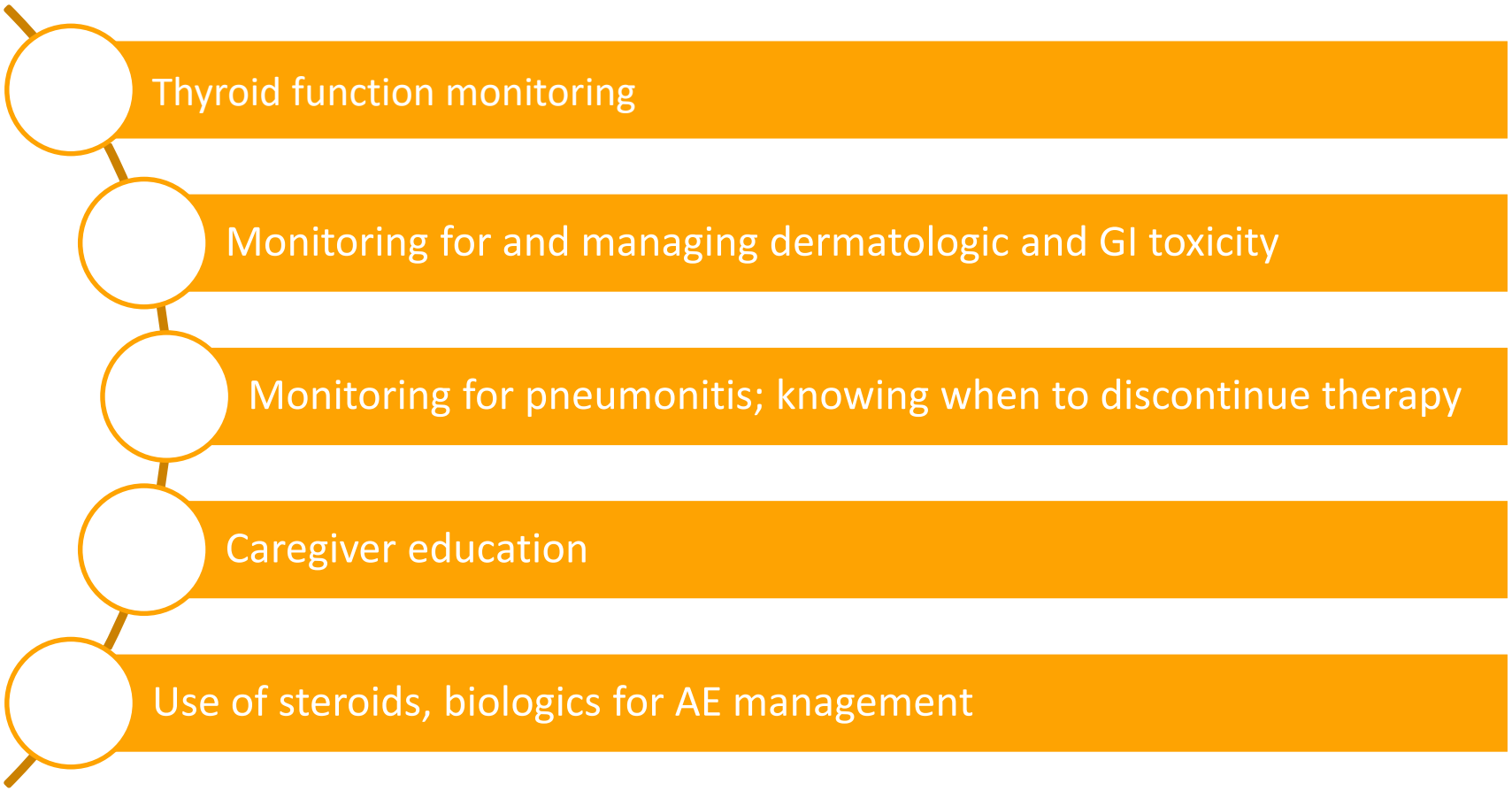
- 36% of 329 patients experienced grade 3-4 TRAEs
- Common AEs (>10%) included
  - Hypertension
  - Proteinuria
  - Diarrhoea
  - Decreased appetite
  - Pyrexia
  - ALT increased
  - Abdominal pain
  - Infusion-related reactions

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event

1. El-Khoueiry AB, et al. Lancet. 2017;389:2492-2502. 2. Zhu AX, et al. Lancet Oncol. 2018;19:940–52. 3. Cheng A-L, et al. ESMO Asia 2019 Abstract #LBA3

IMMUNOTHERAPY: AE MANAGEMENT

HCC connect
POWERED BY COR2ED



AE, adverse event; GI, gastrointestinal

National Comprehensive Cancer Network. Hepatobiliary Cancers. V3.2019.

IMMUNE-RELATED HEPATOTOXICITY

Kirti Shetty
University of Maryland, Baltimore, USA

IMMUNE-RELATED ADVERSE EVENTS (irAEs)

- Discrete toxicities caused by **non-specific activation of the immune system**
- Can affect almost **any organ system**
  - Common: skin, gut, endocrine, lung, musculoskeletal
  - Uncommon: haematological, renal, neurological, ophthalmological, cardiovascular

Meta-analysis of 6,938 patients

- Grade 3/4 irAEs are **more common with anti-CTLA-4** vs anti-PD1
  - 31% vs 10%
- Colitis, hypophysitis and rash occurred more often with anti-CTLA-4
- Pneumonitis, vitiligo, hypothyroidism, arthralgia were more common with anti-PD-1
- **Melanoma patients** have a higher frequency of GI and skin AEs and a lower frequency of pneumonitis

AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GI, gastrointestinal; irAE, immune related adverse event; PD-1, programmed death 1

Khoja L, et al. Ann Onc 2017;28:2377-85

INCIDENCE OF irAEs

Incidence

- The reported incidence of irAEs is as high as 90% in some studies
- A meta-analysis indicates:
  - <75% with anti-CTLA-4 monotherapy (ipilimumab)
  - <30% with anti-PD-1/PD-L1 agents
- irAEs are a dose-related phenomenon
- Incidence varies in adjuvant vs metastatic disease settings

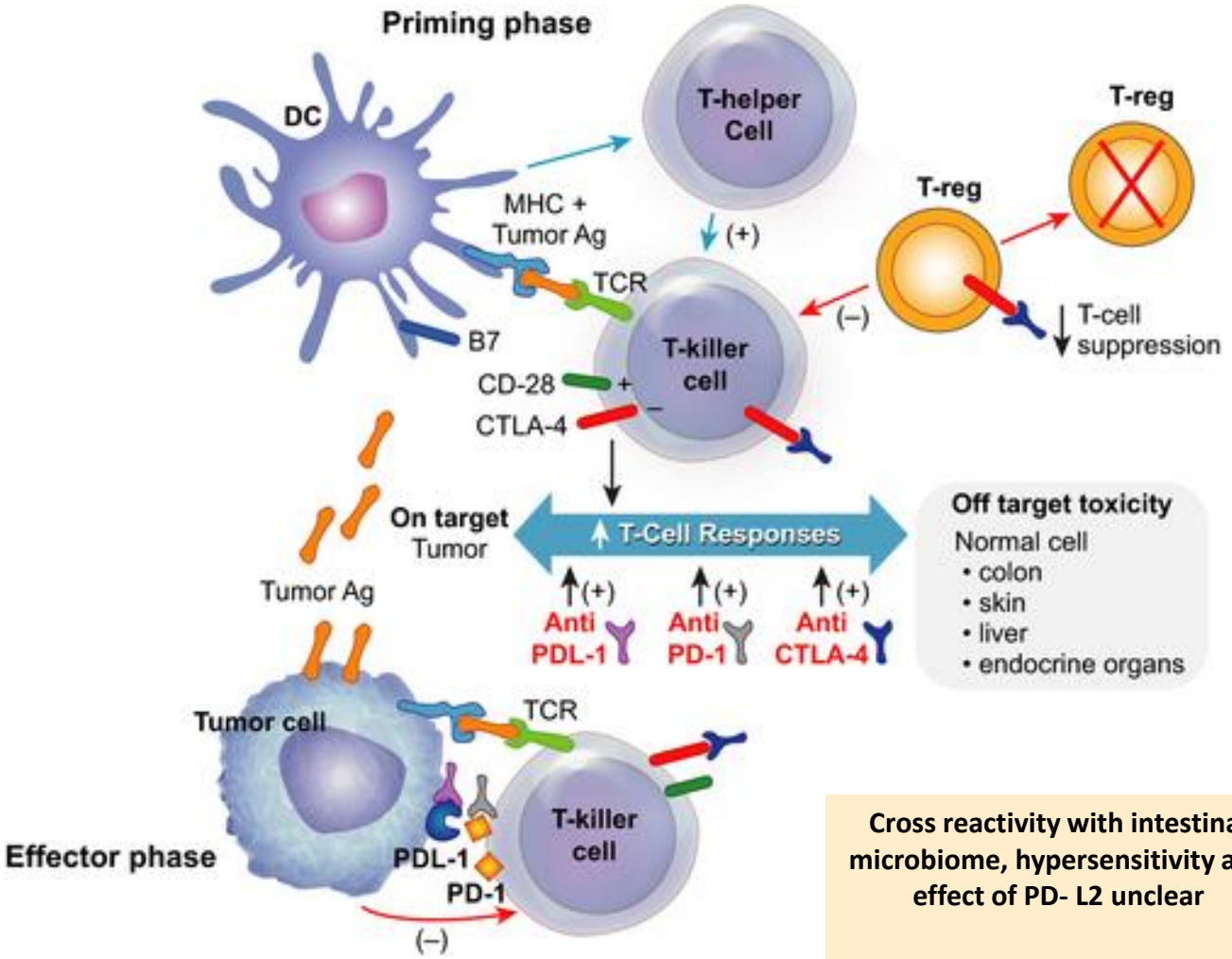
Severity

- The majority of irAEs are mild to moderate in severity
- However, in clinical trials treatment-related deaths occur in up to 2% of patients

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; irAE, immune related adverse event; PD-1, programmed death 1; PD-L1, programmed-death ligand 1

Wang W, et al. Int J Cancer 2017;141:1018-28

PATHOGENESIS OF irAEs



Epitope spreading
- Epitope spreading
- Diversification of T cell repertoire

•Reduced immune tolerance
- Reduced immune tolerance

Inhibition of Tregs | **Activation of Th1 /Th17**

Proinflammatory cytokines (IFN gamma/IL-17)

Cross reactivity with intestinal microbiome, hypersensitivity and effect of PD- L2 unclear

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; irAE, immune related adverse event; PD-1, programmed death 1; PD-L1, programmed-death ligand 1; TCR, T-cell receptor; Treg, regulatory T cell

Suzman DL, et al. Liver Int 2018;38:976-87.

RECOGNISING IMMUNE-RELATED HEPATOTOXICITY

HCC connect
POWERED BY COR2ED

- **No uniform definition**
- Hepatotoxicity ranges from asymptomatic increases in aminotransferases to acute hepatitis
- Minority of patients have **fever**
- Median **time to onset**: 5 weeks (1-49)
  Median of 2 (1-12) doses
- **Dose dependent**
  7% vs 25% with ipilimumab 3 mg vs 10 mg/kg
- **Increased with combination**
  ALT increase in 3.8% (monotherapy) vs 17.6% (nivolumab + ipilimumab)

ALT, alanine aminotransferase;

1. Boutros C, et al. Nat Rev Clin Oncol 2016;13:473-486. 2. Larkin J, et al. N Engl J Med 2015;373:23-34

GRADING HEPATOTOXICITY

UTILISE COMMON TERMINOLOGY CRITERIA OF ADVERSE EVENTS (CTCAE) - NCI

Severity based on peak abnormalities of liver biochemistry

- AST / ALT / ALP / GGT

Higher grades of severity – 3 and 4

INR not included

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalised ratio; NCI, National Cancer Institute

https//ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

INCIDENCE OF IMMUNE-MEDIATED HEPATOTOXICITY

NON-HEPATIC TUMOURS

French study[1]

- 536 patients with non-hepatic tumours treated with anti-PD1/PD-L1 or anti-CTLA-4
  - 3.5% severe hepatitis
  - Outcome universally benign
  - Immunotherapy was reintroduced in 3 patients

Combination of studies / meta-analysis of 17 clinical trials[2]

Odds ratio	All grade	High grade
CTLA-4 inhibitors	1.24 (0.75-2.05)	1.93 (0.84-4.44)
PD-1 inhibitors	1.52(1.24-1.86)	0.48 (0.29-0.80)

- Higher rate of all-grade and high-grade hepatotoxicity with CTLA-4 inhibitors

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed death 1; PD-L1, programmed-death ligand 1

1. De Martin E, et al. J Hepatol 2018;68:1181-90. 2. Wang W, et al. Int J Cancer 2017;141:1018-28

INCIDENCE OF IMMUNE-MEDIATED HEPATOTOXICITY

HEPATIC TUMOURS

- **CheckMate 040** trial (nivolumab)
  - Any grade ALT elevations 7.8%
  - Grade 3-4 elevations 2.6%
- Overall incidence of severe immune-mediated hepatotoxicity
  - **Nivolumab**: 4% of 154 exposed patients
  - **Pembrolizumab**: 3% of 104 exposed patients
  - **Tremelimumab**: 10% of 32 patients

ALT, alanine aminotransferase

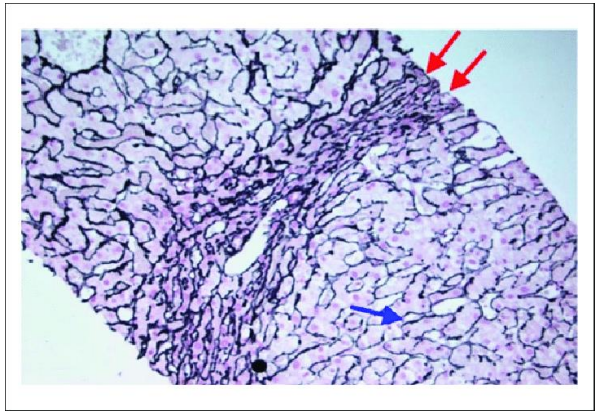
Lleo A, et al. Dig Liver Dis. 2019;51:1074-8

RARE LIVER-RELATED AEs

NODULAR REGENERATIVE HYPERPLASIA[1]

Case Report

- 35-year old male with no history of liver disease, treated for melanoma
- Anasarca / ascites 3 weeks after pembrolizumab initiated
- Transjugular liver biopsy: portosystemic gradient of 7
- Liver biopsy: NRH
- Treatment: drug withdrawal, TIPS



ACUTE LIVER FAILURE[2,3]

- Reported with ipilimumab / nivolumab
- Treatment response reported with ATG and plasma exchange

AE, adverse event; ATG, antithymocyte globulina; NRH, nodular regenerative hyperplasia; TIPS, transjugular intrahepatic portosystemic shunt

1. LoPiccolo J, et al. Hepatology 2018;68:2431-3. 2. Chmiel KD, et al. J Clin Oncol 2011;29:e237-40. 3. Riveiro-Barciela M, et al. J of Hepatology 2019;70:564-6

MANAGEMENT

HCC connect
POWERED BY COR2ED

Before therapy

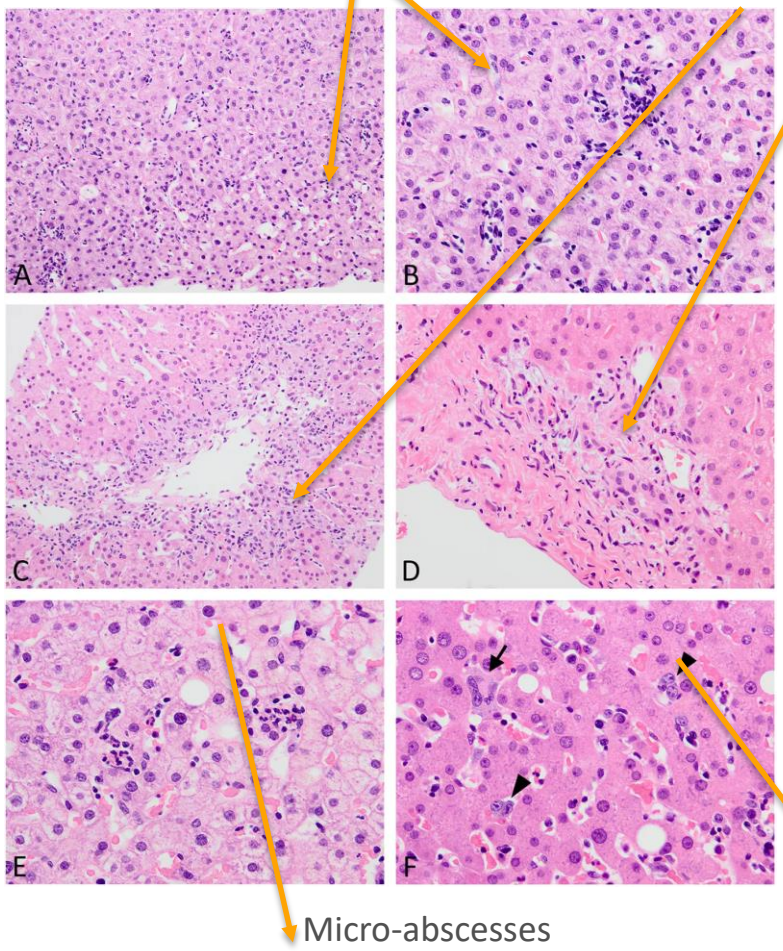
- Assess baseline hepatic synthetic function
- Check for potential pre-existing liver disease, metastatic disease and viral infections
- Rule out underlying autoimmune hepatitis

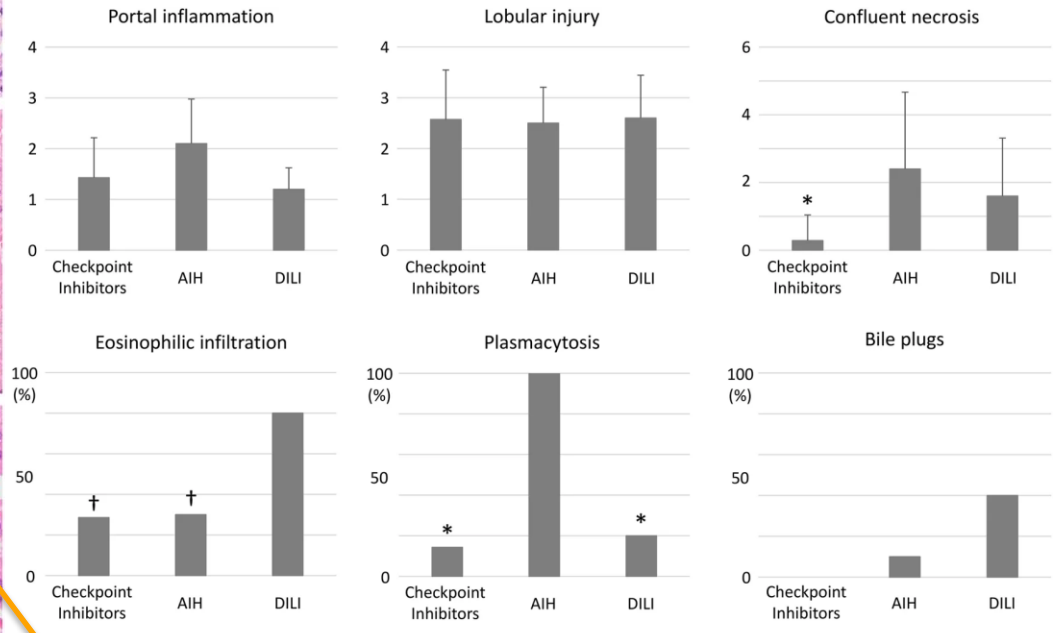
During therapy

- Monitor liver associated enzymes
  - Every 2 weeks for the first 8 – 12 weeks
  - Then every 4 weeks

Lleo A, et al. Dig Liver Dis 2019:51;1074-8

ROLE OF LIVER BIOPSY





Zen Y, et al. Mod Pathol 2018;31:965-73

ROLE OF LIVER BIOPSY

HCC connect
POWERED BY COR2ED

Histologic pattern of hepatitis differs according to drug used

CTLA4 inhibitors

- Granulomatous hepatitis / central vein endotheliitis

PD1 inhibitors

- Lobular hepatitis

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed death 1

MANAGEMENT OF HEPATOTOXICITY

CTCAE GRADE OF SEVERITY	GENERAL RECOMMENDATIONS

• Grade 2
  • AST > 3 – 5 ULN *and/or*
  • ALT > 3 – 5 ULN
• Bilirubin > 1.5 – 3 ULN
	• Corticosteroids
	  • 0.5- 1 mg /kg prednisone
	• Withhold immune-checkpoint inhibitor
	• Monitor labs every 3 days
	• Work up for alternate causes of liver disease

• Grade 3 / 4
  • AST/ ALT > 5 ULN *or*
  • Total bilirubin > 3 times ULN
	• Corticosteroids
	  • 0.5- 1 mg /kg prednisone
	  • Add mycophenolate mofetil if no response
	• Hospital admission
	• Permanent discontinuation of immune-checkpoint inhibitor

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria of Adverse Events; ULN, upper limit of normal

1. EASL. J Hepatol 2018;69:182-236. 2. EASL. J Hepatol 2019;70:1222-61. 3. Lleo A, et al. Dig Liver Dis 2019:51;1074-8.

SUMMARY

- **irAEs are commonly encountered** with immune-checkpoint inhibitors
  - Majority of cases mild and self-limited
  - The incidence of irAEs is determined by the agent, dose and tumour microenvironment

- **Hepatotoxicity** rates are similar in hepatic and non hepatic cancer
  - Important to **exclude other causes** of liver disease
- **Steroids and immunomodulatory agents** are of benefit
- Further studies required to define pathophysiology of hepatotoxicity and develop evidence-based therapies

irAE, immune related adverse event

THE FUTURE ROLE OF TISSUE-BASED BIOMARKERS IN HCC

David Kleiner
National Cancer Institute, Bethesda, USA

BIOMARKERS

- **Diagnostic**
  - Is it hepatocellular? – HepPar, Arginase, pCEA, CD10
  - Is it malignant? – CD34, HSP70, Glypican-3, Glut synthase
- **Prognostic**
  - Histological subtype and grade
  - Molecular subtype
- **Theragnostic**
  - Potential for molecular or immune markers
  - NGS panels (>100 genes) currently available in most academic labs
  - Whole exome, RNA sequencing, Methylation arrays available in some labs with research applications

HepPar, hepatocyte paraffin; NGS, next generation sequencing; pCEA, polyclonal carcinoembryonic antigen; RNA, ribonucleic acid

LIVER BIOPSY

HCC connect
POWERED BY COR2ED

Adequacy

- 1.5 cm, 16 gauge
- Diagnosis can be made on minimal tissue

Risks

- Bleeding[1]
  - Mild: 3-4%
  - Severe: 0.5%
- Tumour seeding (<3%)[2]
  - Seeding has no appreciable impact on survival

Guidelines

- AASLD: neutral on biopsy if imaging adequate[3]
- EASL: concern over complications should not justify abstaining from biopsy[4]
- EASL: biopsy should be performed in clinical trials[5]

Biopsy should be performed:

- Lesions <1.0 cm (biopsy sensitivity >80%)[6]
- Lesions with ambiguous Li-Rads scores
- Lesions in non-cirrhotic livers

1. Rockey DC, et al. Hepatology 2009;49:1017-44. 2. Silva MA, et al. Gut 2008;57:1592-6. 3. Heimbach JK, et al. Hepatology 2018;67:358-80. 4. EASL. J Hepatol 2018;69:182-236. 5. EASL. J Hepatol 2012;56:908-43. 6. Caturelli E, et al. Gut 2004;53:1356-62

PERSONALISED MEDICINE FOR PATIENTS WITH HCC

HCC connect
POWERED BY COR2ED

- Current **approved therapies** for HCC:
  - TKI's: sorafenib, lenvatinib, regorafenib, cabozantinib
  - Checkpoint inhibitors: nivolumab, pembrolizumab
  - VEGFR2 inhibitor: ramucirumab
- **No approved therapies for specific molecular targets** for HCC
- **No confirmed molecular biomarkers** to identify subgroups likely to respond (or not respond) to standard therapies
  - MSI testing, PD-1/PD-L1 IHC not predictive for checkpoint inhibition
- **Liver biopsy opens the door to IHC-based and molecular diagnostics**
  - Current methodology permits evaluation of all currently druggable mutation-based targets from a FFPE biopsy[1]

FFPE, formalin-fixed paraffin-embedded; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; MSI, microsatellite instability testing; PD-1, programmed death 1; PD-L1, programmed-death ligand 1; TKI, tyrosine-kinase inhibitors; VEGFR2, vascular endothelial growth factor receptor 2

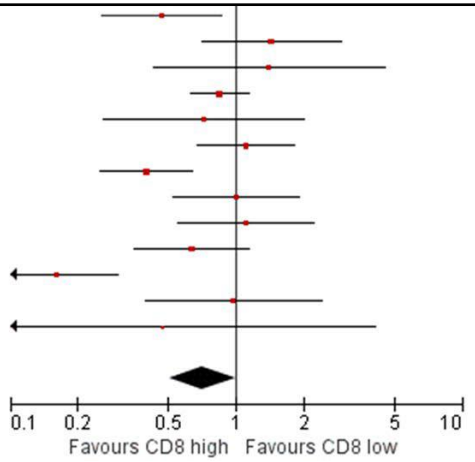
1. Leichsenring J, et al. Genes Chromosomes Cancer 2018;57:70-9

IMMUNOLOGICAL EVALUATION

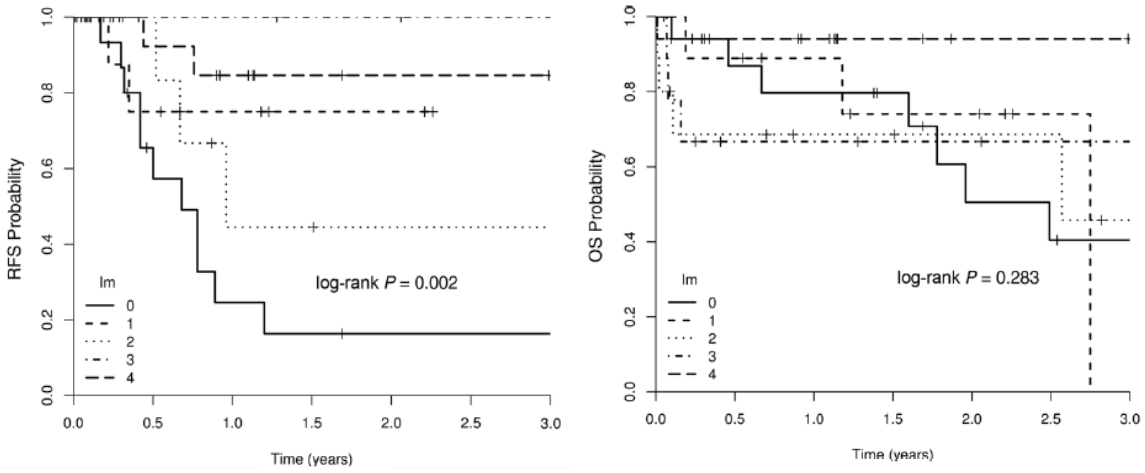
CD8(+) TIL ARE ASSOCIATED WITH OS IN HCC[1]

Study or Subgroup	Log (Hazard Ratio)	SE	Weight	Hazard Ratio IV, Random, 95% CI
Brunner 2015	-0.76	0.31	8.7%	0.47 (0.25, 0.86)
Chen 2012	0.36	0.36	7.9%	1.43 (0.71, 2.90)
Gabrielson 2016	0.34	0.6	4.9%	1.40 (0.43, 4.55)
Gao 2007	-0.17	0.15	11.1%	0.84 (0.63, 1.13)
Ikeguchi 2005	-0.33	0.52	5.7%	0.72 (0.26, 1.99)
Kobayashi 2007	0.1	0.25	9.7%	1.11 (0.68, 1.80)
Li 2011	-0.91	0.24	9.8%	0.40 (0.25, 0.64)
Lin-Training cohort 2013	0	0.33	8.4%	1.00 (0.52, 1.91)
Lin-Validation cohort 2013	0.1	0.35	8.1%	1.11 (0.56, 2.19)
Pang 2009	-0.45	0.3	8.8%	0.64 (0.35, 1.15)
Sun 2015	-1.83	0.32	8.5%	0.16 (0.09, 0.30)
Wang 2012	-0.03	0.46	6.5%	0.97 (0.39, 2.39)
Wang 2016	-0.75	1.11	2.0%	0.47 (0.05, 4.16)
Total (95% CI)			**100.00%**	**0.71 (0.51, 0.99)**

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 41.97$, df = 12 (P<0.0001); $I^2 = 71\%$
Test for overall effect: Z = 2.01 (P=0.04)



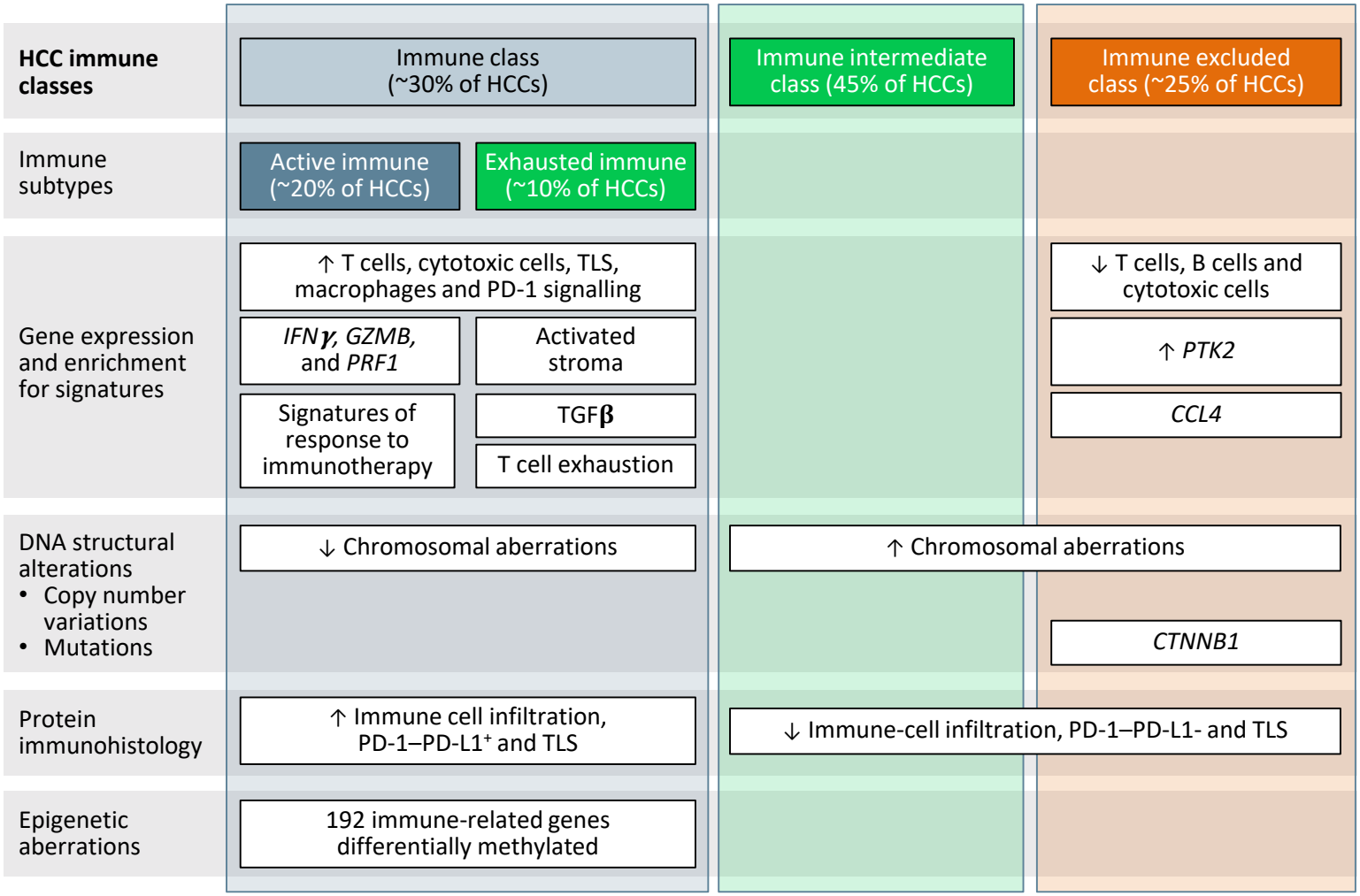
IMMUNOSCORE IS ASSOCIATED WITH RECURRENCE-FREE SURVIVAL BUT NOT OS IN HCC[2]



CI, confidence interval; HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival; SE, standard error; TIL, tumour infiltrating lymphocytes

1. Yao W, et al. Sci Rep 2017;7:7525. 2. Gabrielson A, et al. Cancer Immunol Res 2016;4:419-30

MICROENVIRONMENT IMMUNE-BASED CLASSIFICATION OF HCC

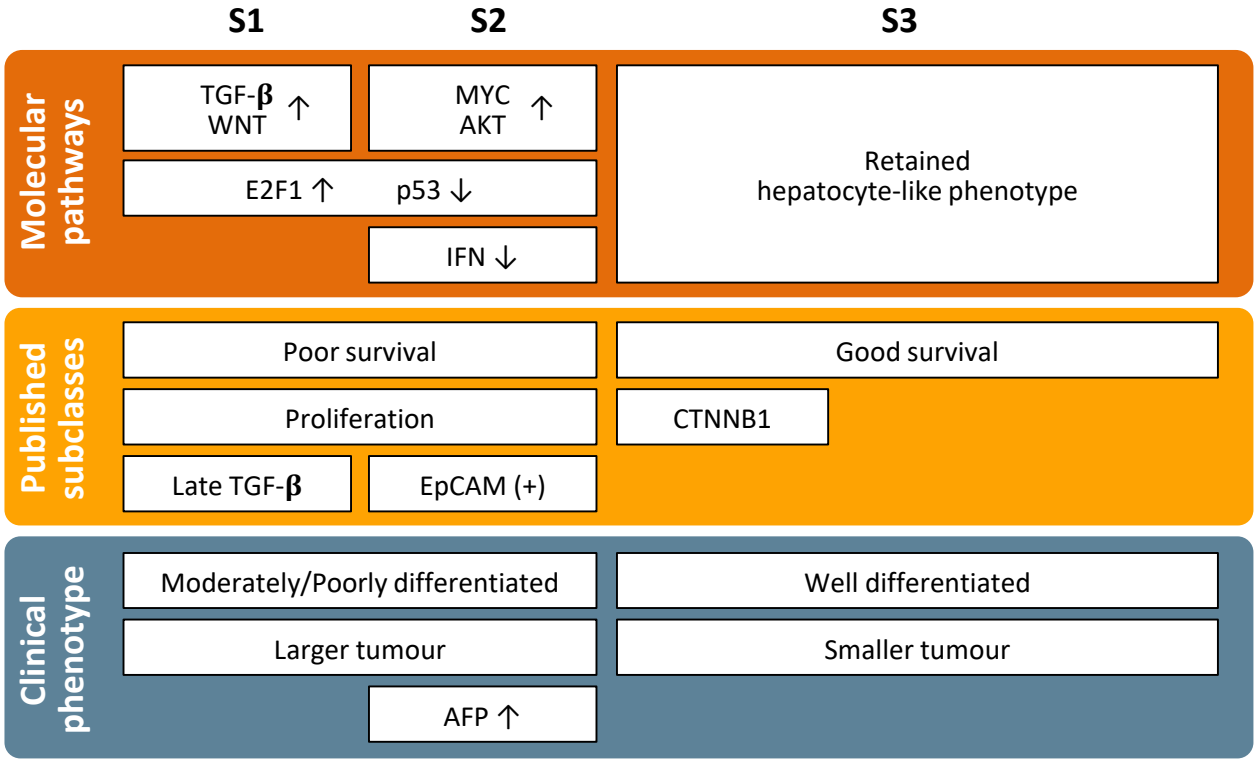


HCC, hepatocellular carcinoma; IFNγ, interferon gamma; PD-1, programmed death 1; PD-L1, programmed-death ligand 1; TGFβ, transforming growth factor beta; TLS, tertiary lymphoid structure

1. Sia D, et al. Gastroenterology 2017;153:812-26. 3. Llovet JM, et al. Nat Rev Clin Oncol 2018;15:599-616

MOLECULAR GENETIC LANDSCAPE

INTEGRATIVE TRANSCRIPTOME ANALYSIS REVEALS COMMON MOLECULAR SUBCLASSES OF HUMAN HCC

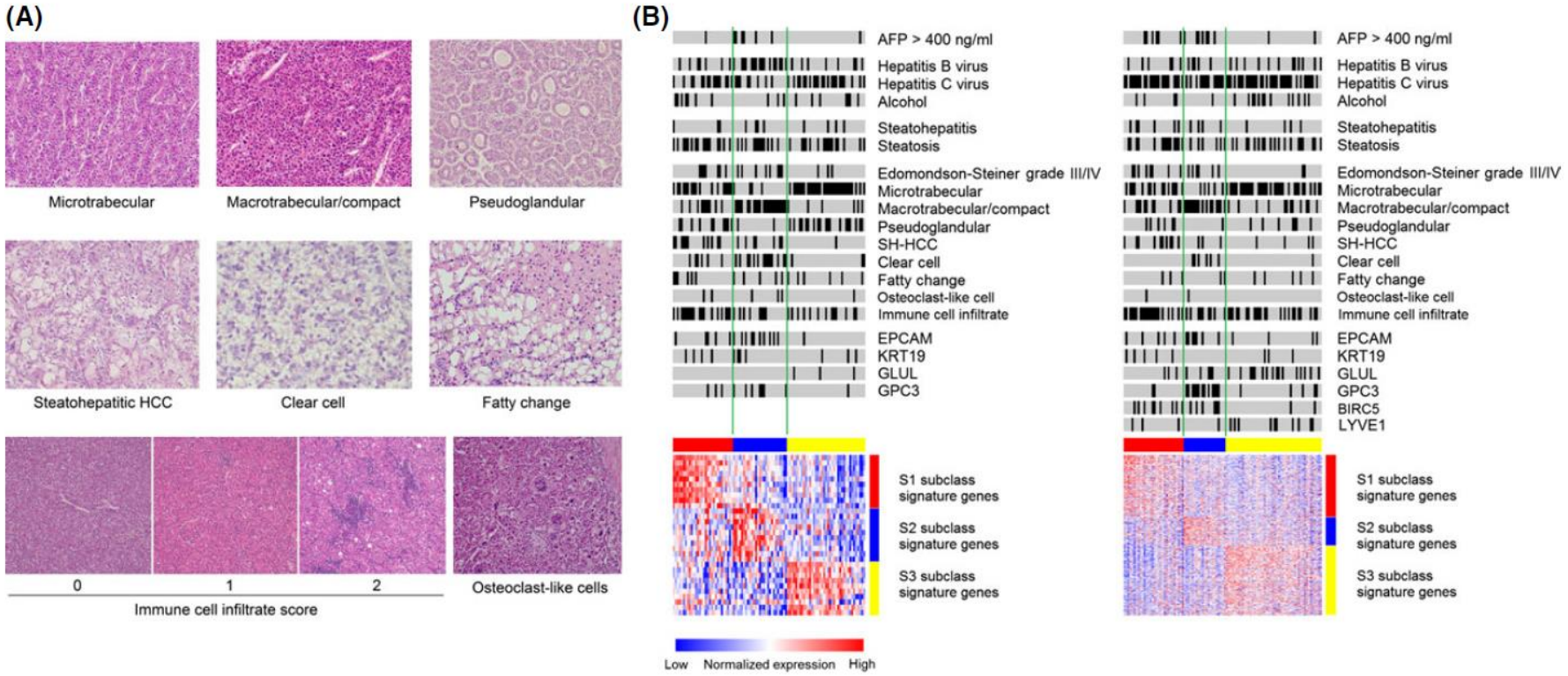


Analysis using gene expression data on ~600 cases of HCC, defined three broad classes of HCC

AFP, alpha-fetoprotein; EpCAM, epithelial cell adhesion molecule; HCC, hepatocellular carcinoma; IFN, interferon; TGFβ, transforming growth factor beta

Hoshida Y, et al. Cancer Res 2009;69:7385-92.

CLINICOPATHOLOGICAL INDICES TO PREDICT HCC MOLECULAR CLASSIFICATION



HCC, hepatocellular carcinoma

Tan PS, et al. Liver Int 2016;36:108-18

TUMOUR-RELATED CLINICOPATHOLOGICAL FEATURES ASSOCIATED WITH HCC MOLECULAR SUBCLASSES*

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Variable	Unvariable analysis			Multivariable analysis	
	No. of HCC tumours (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
S1 subclass	S1: n=30 / Rest: n=66				
SH-HCC	11 (37%) / 8 (12%)	4.20 (1.47–11.97)	0.007	4.25 (1.44–13.20)	0.01
Immune cell infiltrate ≥2	18 (60%) / 21 (32%)	3.21 (1.31–7.87)	0.01	3.25 (1.29–8.53)	0.01
S2 subclass	S2: n=27 / Rest: n=69				
Microtrabecular	4 (15%) / 49 (71%)	0.07 (0.02–0.23)	<0.001		
Macrotrabecular/compact	22 (81%) / 16 (23%)	14.58 (4.75–44.69)	<0.001	11.99 (3.48–41.24)	<0.001
Pseudoglandular	2 (7%) / 29 (42%)	0.11 (0.02–0.50)	0.004	0.22 (0.04–1.16)	0.07
Clear cell	14 (52%) / 9 (13%)	7.18 (2.56–20.11)	<0.001		
Serum AFP >400 ng/ml	6 (22%) / 2 (3%)	9.57 (1.80–51.03)	0.008	10.81 (1.27–91.63)	0.03
S3 subclass	S3: n=39 / Rest: n=57				
Microtrabecular	32 (82%) / 21 (37%)	7.84 (2.94–20.86)	<0.001	3.94 (1.23–12.56)	0.02
Macrotrabecular/compact	6 (15%) / 32 (56%)	0.14 (0.05–0.39)	<0.001		
Pseudoglandular	19 (49%) / 11 (19%)	3.56 (1.46–8.71)	0.005		
SH-HCC	1 (3%) / 18 (32%)	0.06 (0.01–0.45)	0.006	0.05 (0.01–0.44)	0.007
Clear cell	3 (8%) / 20 (35%)	0.15 (0.04–0.56)	0.005	0.20 (0.05–0.91)	0.04
Edmondson-Steiner I or II	36 (92%) / 42 (74%)	4.29 (1.15–16.00)	0.03	3.08 (0.65–14.58)	0.16

- S1 class associated with SH-HCC, immune cell infiltration
- S2 class associated with macrotrabecular/compact morphology, enriched for the oncogene *YAP* and stemness markers (*EPCAM, KRT19*)

* in the training set (logistic regression)
AFP, alpha-fetoprotein; CI, confidence interval; HCC, hepatocellular carcinoma; OR, odds ratio; SH-HCC, steatohepatitic HCC
Tan PS, et al. Liver Int 2016;36:108-18

COMPREHENSIVE AND INTEGRATIVE GENOMIC CHARACTERIZATION OF HCC

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THE CANCER GENOME ATLAS RESEARCH NETWORK

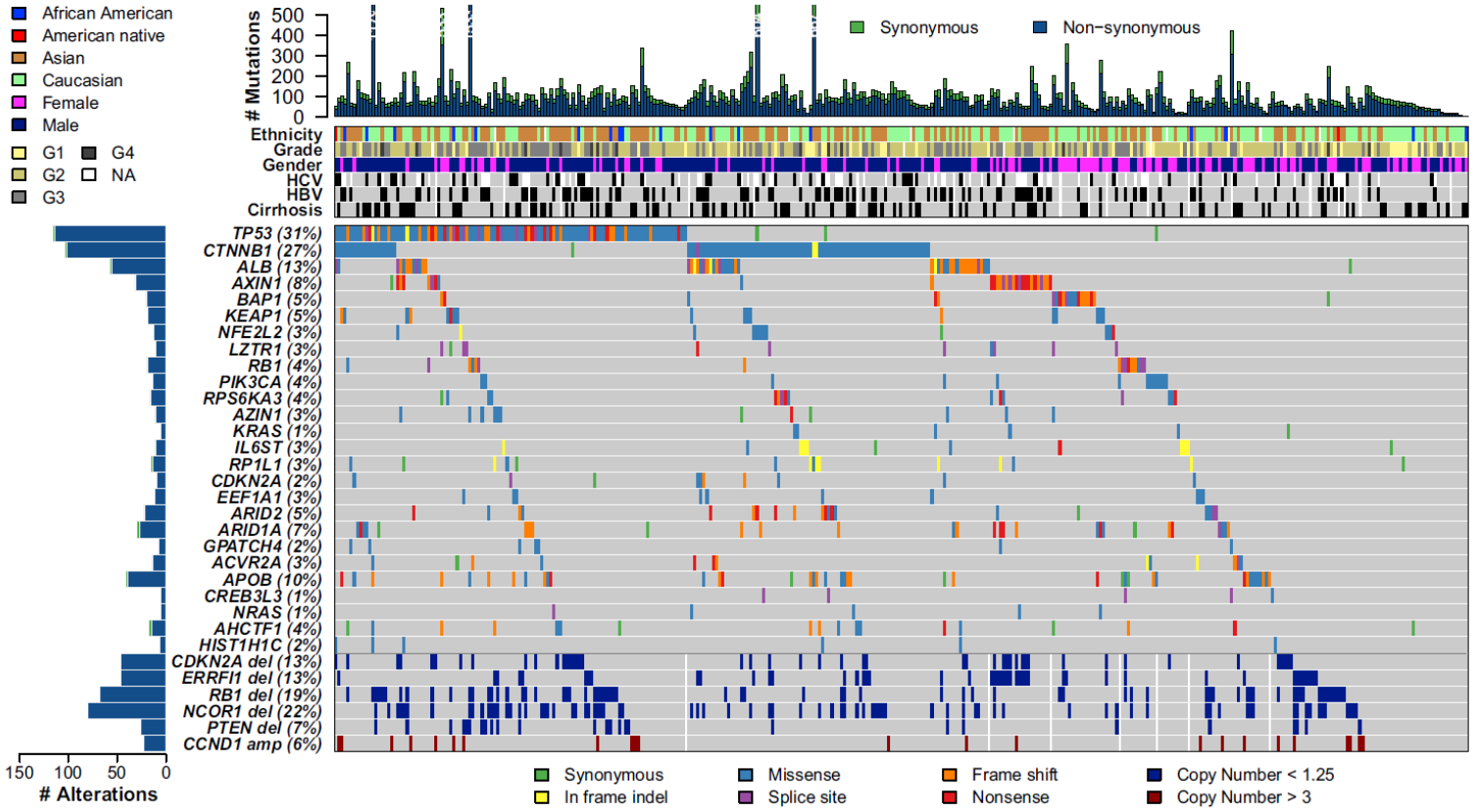

Figure 1. The Genomic Landscape of Liver Hepatocellular Carcinoma and Mutational Signatures

Cancer Genome Atlas Research Network. Cell 2017;169:1327-41
HCC, hepatocellular carcinoma

RECURRENT GENE MUTATIONS IN HCC

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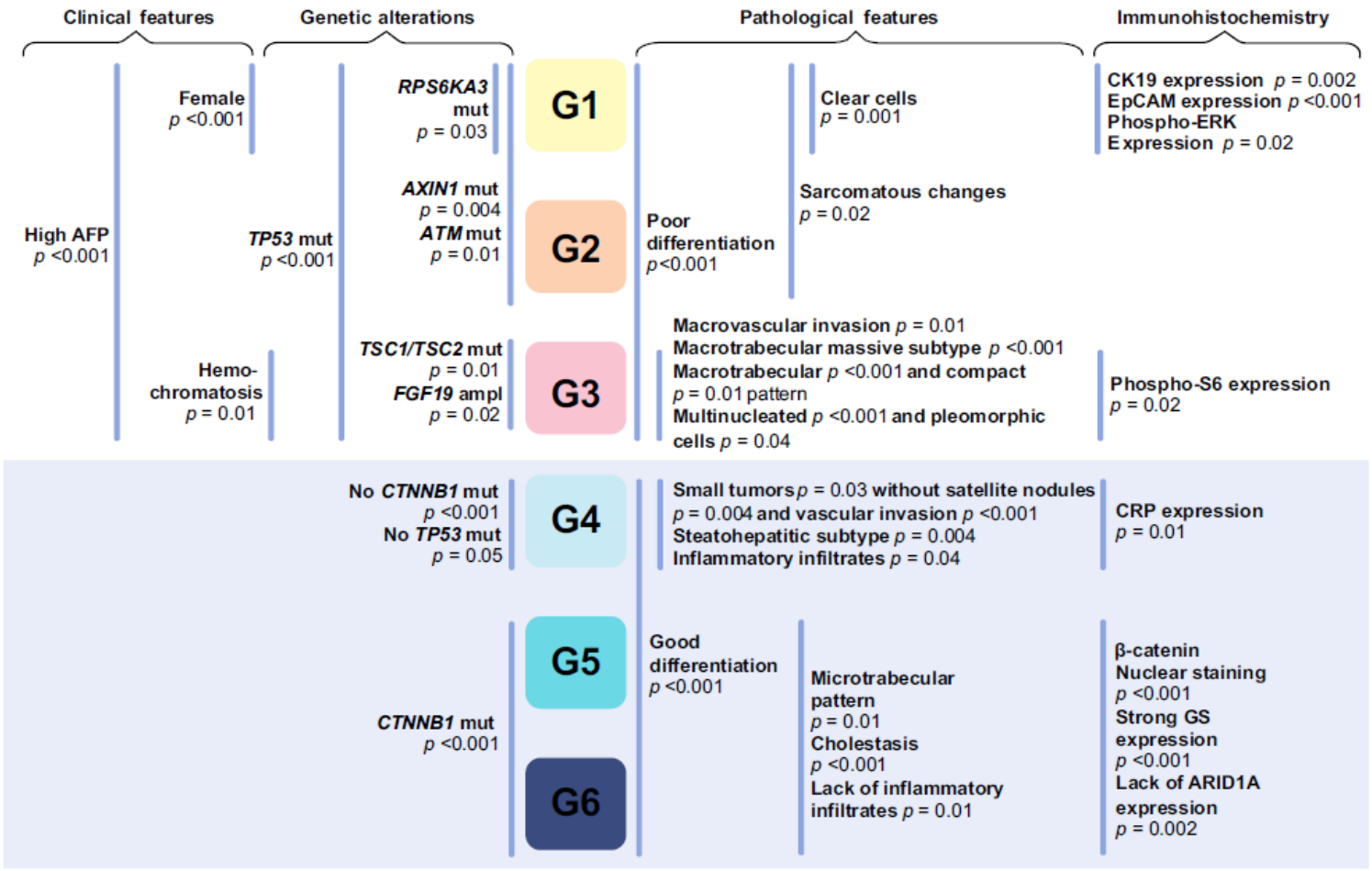
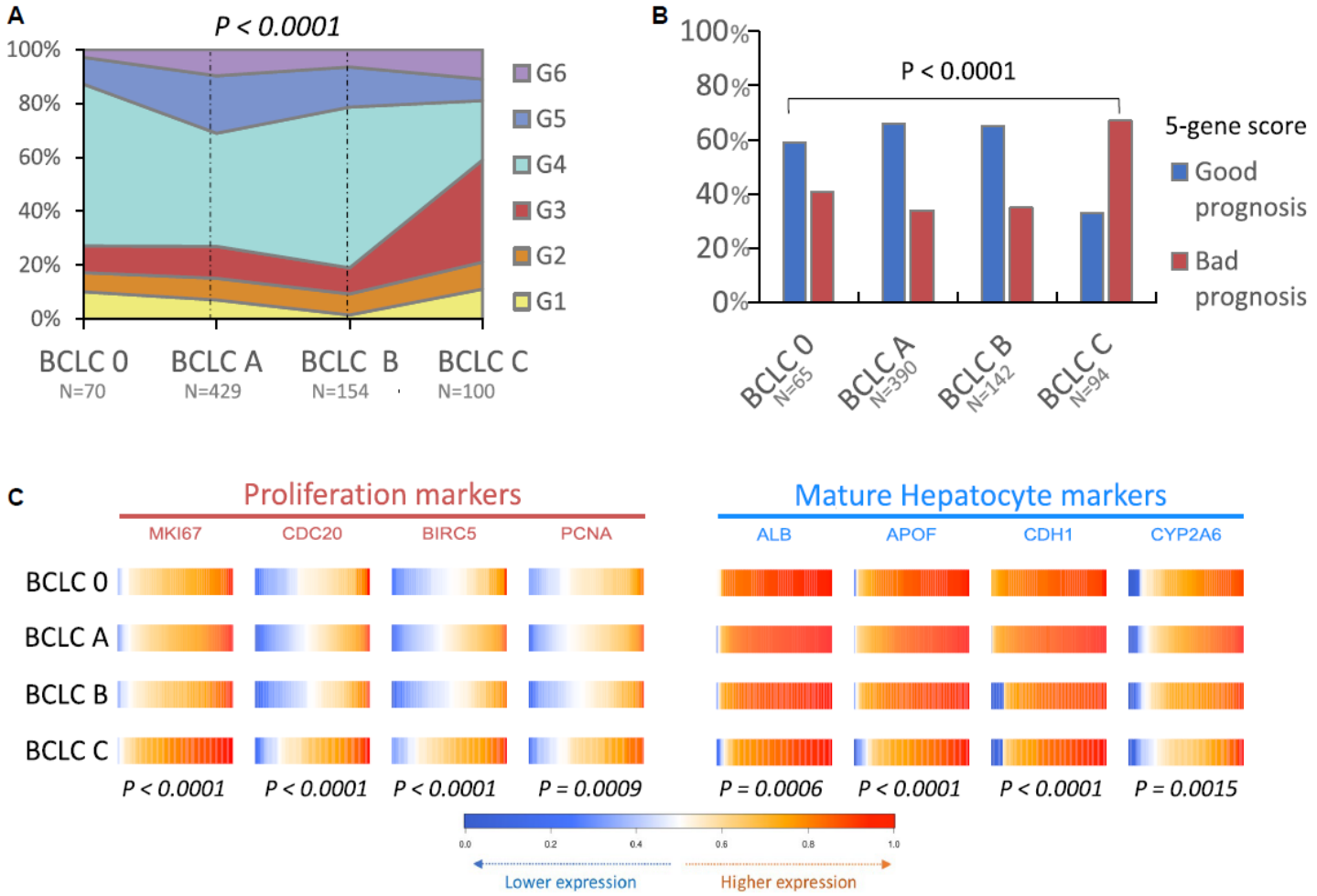
	Frequency of Mutation (%)			
Driver gene	**HBV**	**HCV**	**Non-viral**	**Pathways/Role**
TP53	10-65	24	16	DNA repair and surveillance, high risk with aflatoxin B1
CTNNB1	15	30	39	WNT/β-catenin signaling pathway
AXIN1	12	13	6	
ARID1A	12	2	16	Chromatin remodeling
ARID1B	0	4	2	
ARID2	4	4	7	
NFE2L2	0	9	6	Oxidative stress
KEAP1	4	7	6	
RPS6KA3	4	9	6	Oncogenic MAPK signalling
KMT2A (MLL)	0	4	2	Histone modification
KMT2C (MLL3)	8	0	3	
KMT2D (MLL4)	4	4	2	
CDKN2A	0	4	2	DNA repair and surveillance
RB1	8	4	2	
TERT promoter	50	61	65	Most common mutation in HCC
HBV integration	65-100	N/A	N/A	
FGF19 amplification	5-10			Bile acid synthesis, hepatocyte prolif through FGFR4

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MAPK, mitogen-activated protein kinase
WHO Classification of Tumours, 5th Ed., Digestive System Tumours, p. 231.

HISTOLOGICAL SUBTYPES OF HCC ARE RELATED TO GENE MUTATIONS AND MOLECULAR TUMOUR CLASSIFICATION



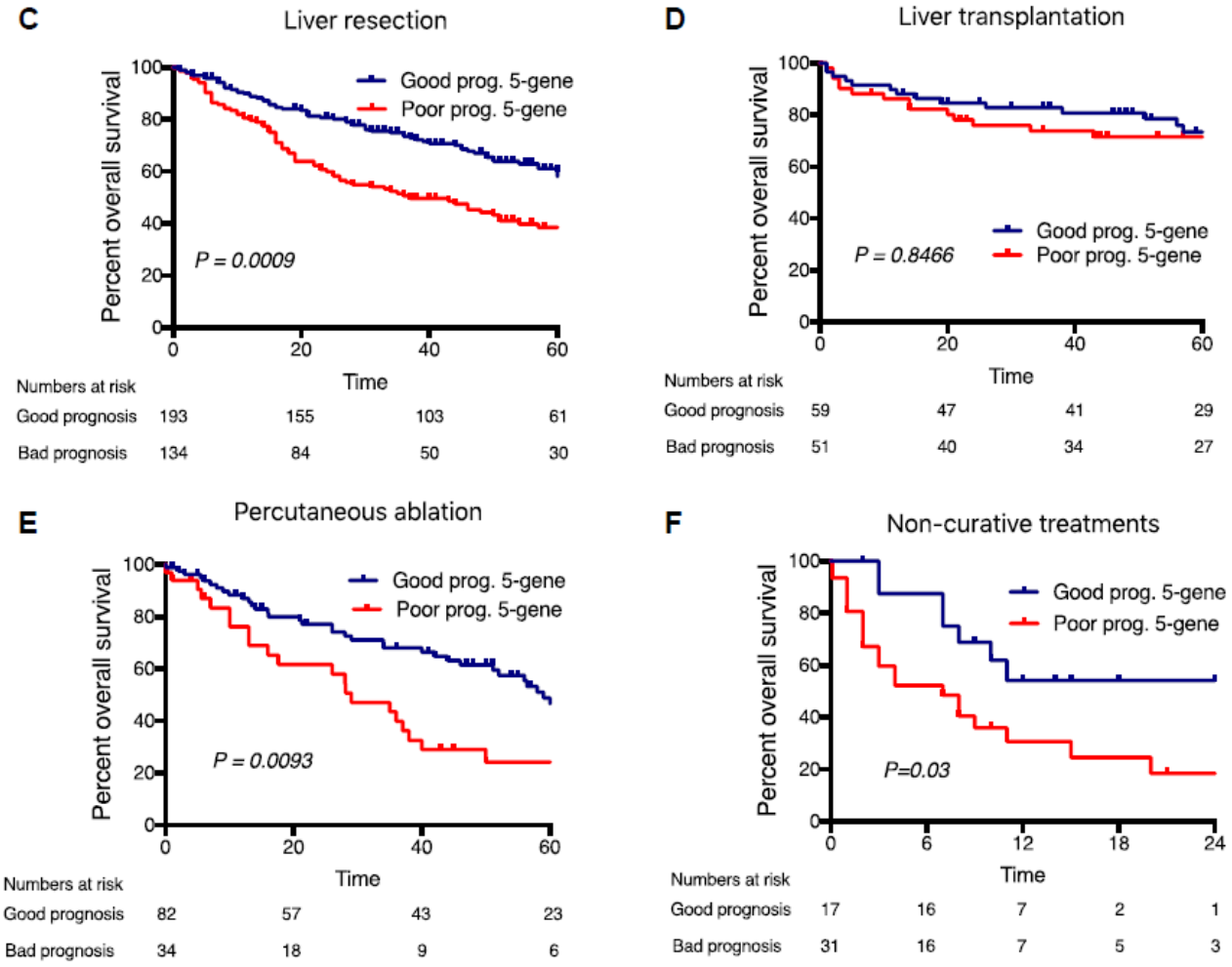
TRANSCRIPTOMIC CLASSIFICATION ACCORDING TO TUMOUR STAGE



BCLC, Barcelona Clinic Liver Cancer

Nault JC, et al. Hepatology 2019. Epub 17 June 2019

5-GENE PANEL PROVIDES PROGNOSTIC INFORMATION[1,2]



The 5-gene score is based on the expression level of 5 genes: *HN1, RAN, RAMP3, KRT19*, and *TAF9*[2]

1. Nault JC, et al. Hepatology 2019. Epub 17 June 2019. 2. Nault JC, et al. Gastroenterology. 2013;145:176-87

ONGOING TRIALS OF TARGETED THERAPIES FOR HCC

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	Drug	Targets	Clinical stage and treatment setting	Enrichment biomarker	Study phase (comparator)	Primary endpoint	ClinicalTrials. gov reference
	Cell cycle inhibitors and anti-proliferative agents						
	Donafenib	RAF	Advanced; first line	None	3 (sorafenib)	OS	NCT02645981
*	Palbociclib	CDK4 and CDK6	Advanced; second line	RB$^+$	2	TTP	NCT01356628
	Milciclib	CDKs	Advanced; second line	None	2	AEs	NCT03109886
*	Ribociclib	CDK4 and CDK6	Intermediate (plus TACE)	RB$^+$	2	PFS	NCT02524119
	Chiauranib	AURKB, VEGFRs, KIT, and PDGFRs	Advanced; second line	None	1	PFS	NCT03245190
*	Capmatinib	MET	Advanced; second line	MET$^+$	2	TTP	NCT01737827
*	MSC2156119J	MET	Advanced; second line	MET$^+$	1-2	DLTs	NCT02115373
	Galunisertib	TGFβR1	Advanced; first line (plus sorafenib)	None	2	OS	NCT02178358
*	BLU-554	FGFR4	Advanced; second line	FGF19$^+$ (by IHC)	1-2	MTD	NCT02508467
*	INCB062079	FGFR4	Advanced; second line	*FGF19* amplification	1-2	AEs	NCT03144661
	H3B-6527	FGFR4	Advanced; second line	None	1	DLTs	NCT02834780
*	Erdafitinib	FGFRs	Advanced; second line	*FGF19* amplification	1	RP2D	NCT02421185
	Sapanisertib	mTOR	Advanced; first line	None	1-2	MTD	NCT02575339
	SF1126	PI3K and mTOR	Advanced; second line	None	1	MTD	NCT03059147

AE, adverse event; AURKB, aurora Kinase B CDK, cyclin-dependent kinase; DLT, dose-limiting toxicity; FGF, fibroblast growth factor; FGFR4, fibroblast growth factor receptor 4 HCC, hepatocellular carcinoma; IHC, immunohistochemistry; MTD, maximum tolerated dose; mTOR, mammalian target of rapamycin ; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PI3K, phosphoinositide 3-kinases; RP2D, recommended phase 2 dose; TGFβR1, transforming growth factor beta receptor 1; TTP, time to progression; VEGFR, vascular endothelial growth factor receptor
Adapted from Llovet JM, et al. Nat Rev Clin Oncol 2018;15:599-616.

SUMMARY

- Although targeted therapies are used for HCC, **biomarkers are not used** to select patients or decide on therapeutic options
- Clinical trials are underway to evaluate therapy directed at particular **driver mutations**
- A **wealth of molecular data** is available from tumour biopsies
- **Biopsies should be performed at least in clinical trials** to evaluate tissue biomarkers for prognostic and theragnostic information

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