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EXPERTS KNOWLEDGE SHARE

APPROPRIATE SELECTION OF PATIENTS FOR 1ST LINE MONOTHERAPY IN ADVANCED OR UNRESECTABLE HCC AND TREATMENT MANAGEMENT IN RELATION WITH AEs

Prof. Richard Finn (USA)
Dr. Mohamed Bouattour (France)
Prof. James J. Harding (USA)
Dr. Su Pin Choo (Singapore)

Friday January 28th 2022

INTRODUCING THE SCIENTIFIC COMMITTEE

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Prof. Richard S Finn

Geffen School of Medicine at UCLA, Department of Medicine, Division of Hematology/Oncology, USA

Prof. James J. Harding

Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, USA

Dr. Mohamed Bouattour

The University Beaujon Hospital Clichy, Beaujon, France

Dr. Su Pin Choo

Curie Oncology and National Cancer Center Singapore

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EXPERTS KNOWLEDGE SHARE EDUCATIONAL OBJECTIVES

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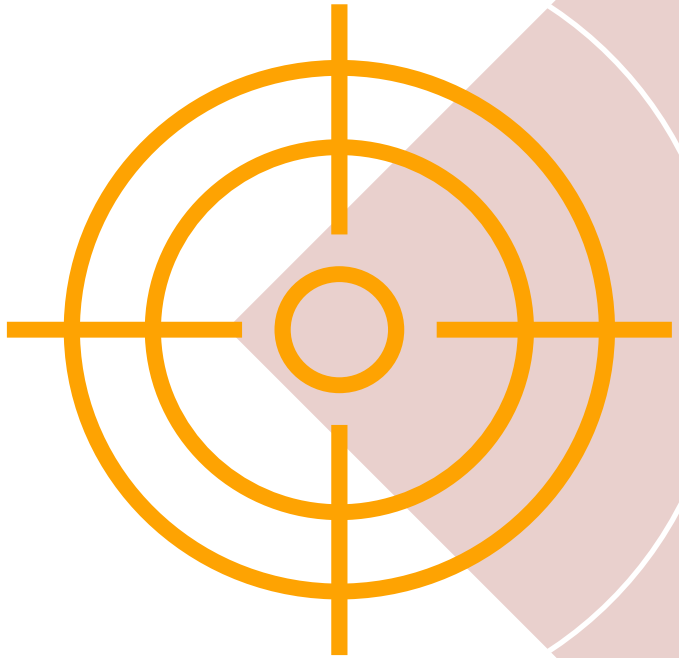

- Explore the patient-profile who could benefit from VEGFR-TKI monotherapy 1st line in advanced or unresectable HCC
- Interpret the real-world data and understand the implications for clinical practice
- Understand the safety profile of the monotherapies, be able to recognise the cause of toxicities and know the appropriate dosing strategies to manage side effects
- A look into the future, the potential of combination therapies in the treatment of HCC

EXPERTS KNOWLEDGE SHARE AGENDA

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Appropriate selection of patients for 1st line monotherapy in advanced or unresectable HCC and treatment management in relation with AEs

Topic	Facilitator
Welcome and introductions	COR2ED
Who can benefit from VEGFR-TKIs monotherapy today?	Richard Finn
Treating patients with VEGFR-TKIs monotherapy: What are the treatment related adverse events and how to manage them?	James Harding
What did we learn from the real-world data? What can we translate into clinical practice?	Mohamed Bouattour
A review of relevant data presented at ASCO GI and a look to future treatments	Su Pin Choo
A look to future treatments and closing remarks	Richard Finn
Discussion and Question and Answers Session	All
Close	COR2ED

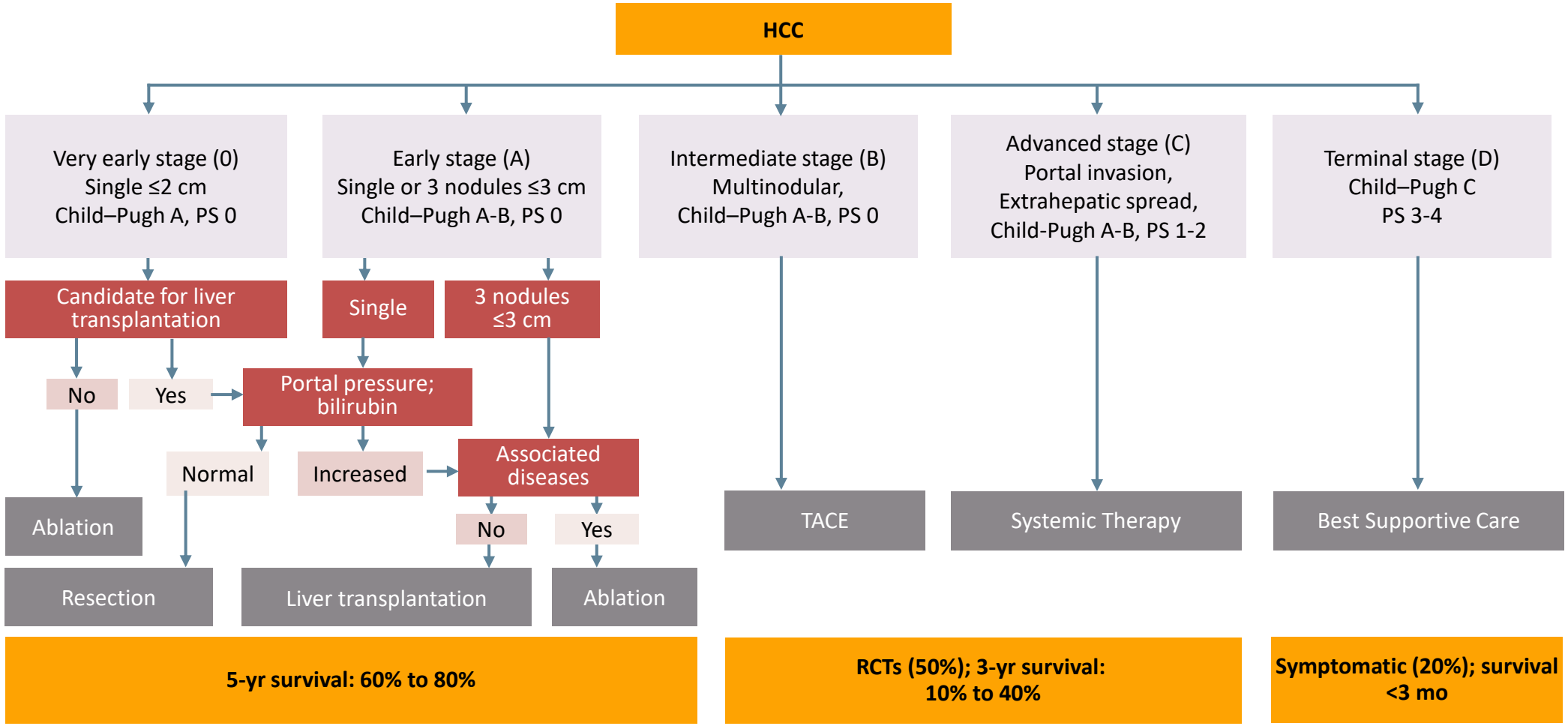
WHO CAN BENEFIT FROM VEGFR-TKI MONOTHERAPY TODAY?

Richard S. Finn, MD
Professor of Clinical Medicine
Division of Hematology/Oncology
Director, Signal Transduction and Therapeutics Program
Jonsson Comprehensive Cancer Center
Geffen School of Medicine at UCLA, California, USA

DISCLOSURES

- Consultant: AstraZeneca, CStone Pharmaceuticals, Bayer, Bristol Myers Squibb, Eisai, Eli Lilly, Exelixis, Merck, Novartis, Pfizer, Roche/Genentech

BARCELONA CLINIC LIVER CANCER (BCLC) STAGING AND TREATMENT STRATEGY[1]



HCC, hepatocellular carcinoma; mo, months; PS, performance status; RCT, randomised controlled trial; TACE, transarterial chemoembolisation; yr, year

Bruix J, et al. Gastroenterology. 2016;150:835-53

PIVOTAL TRIALS DEMONSTRATED OS BENEFIT WITH SORAFENIB IN HCC

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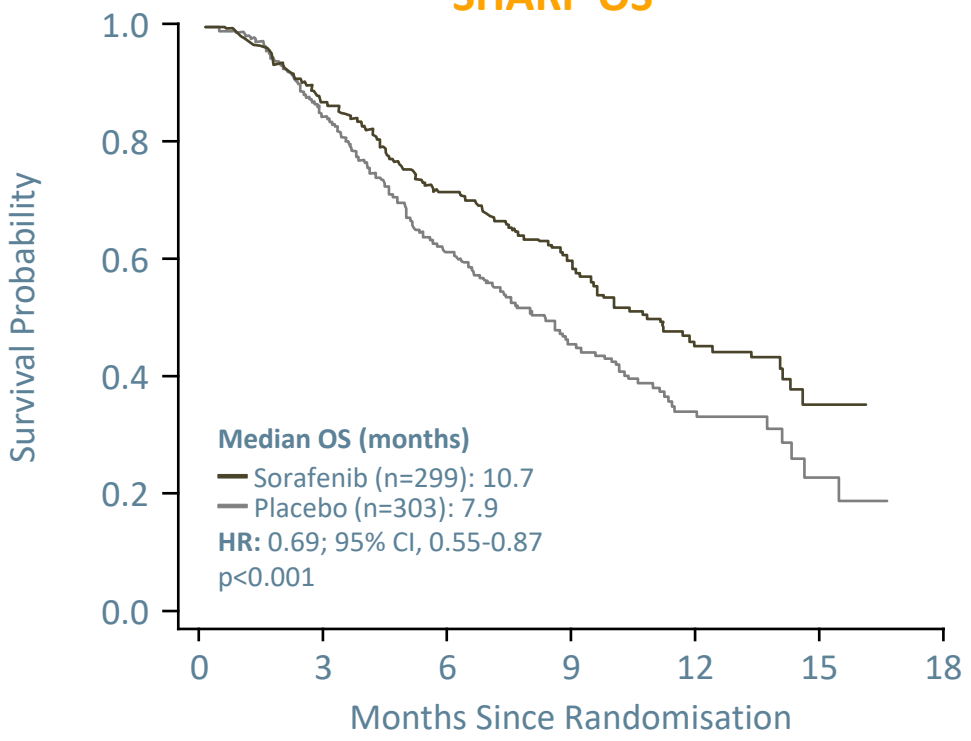
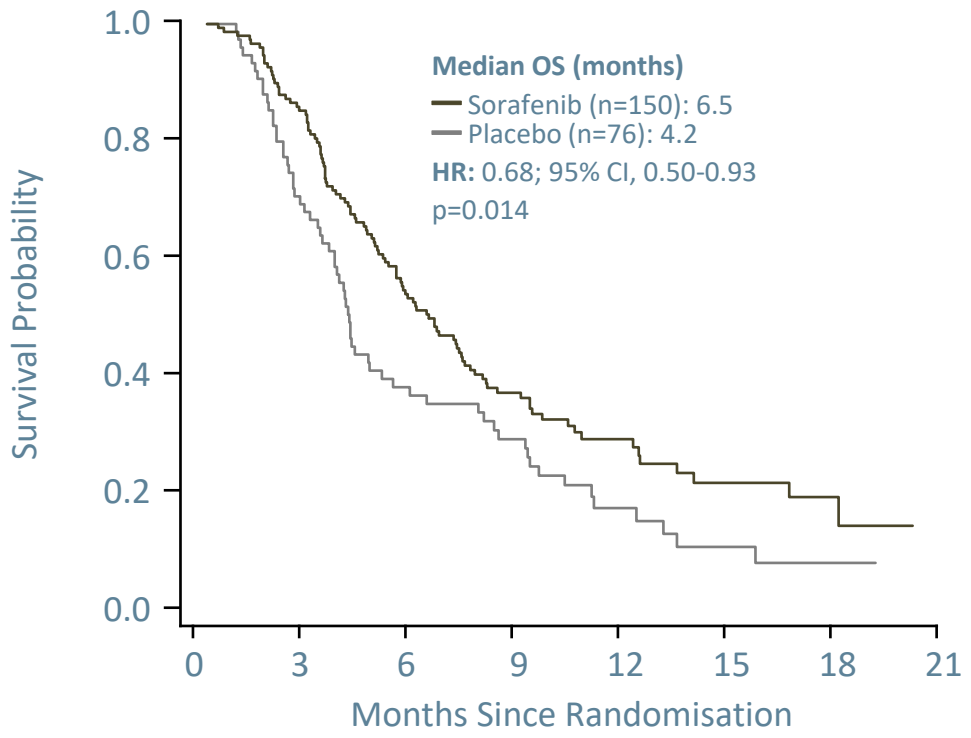
Sorafenib consistently increased OS in different patient populations across geographic regions

SHARP OS[1]



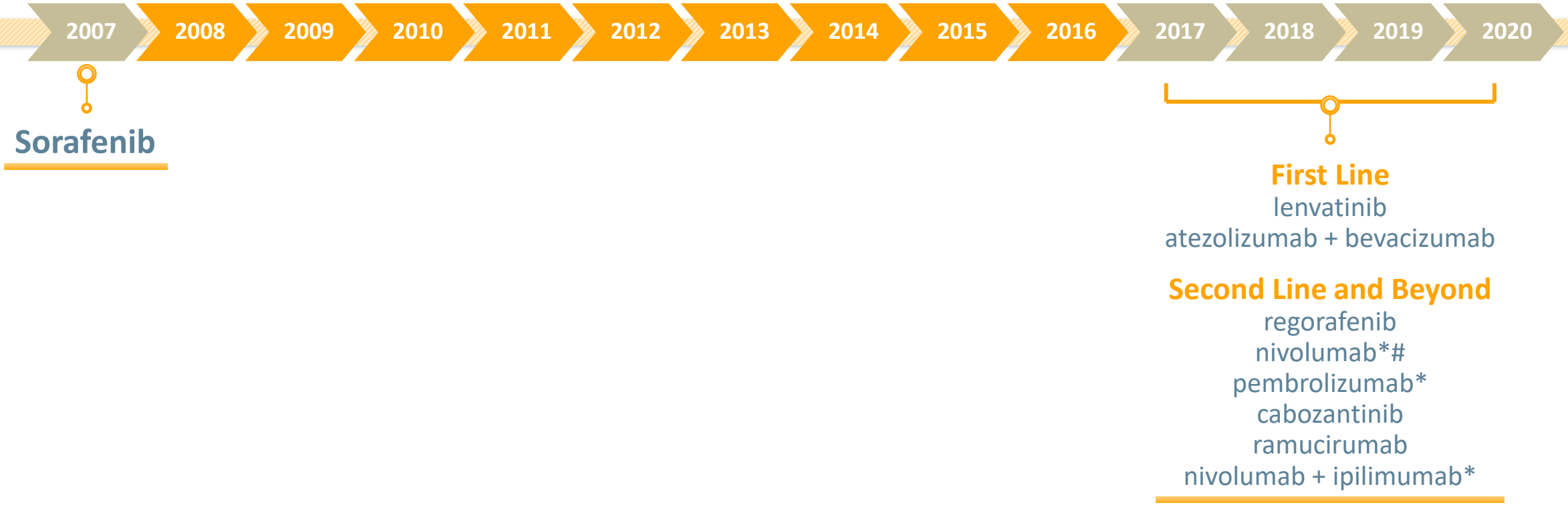
ASIA-PACIFIC OS[2]



CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; SHARP, Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol

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

FDA-APPROVED SYSTEMIC THERAPY FOR ADVANCED HCC



*Accelerated approval, #Accelerated approval withdrawn

FDA, Food and Drug Administration; HCC, hepatocellular carcinoma

LENVATINIB: REFLECT STUDY

- lenvatinib is an oral multikinase inhibitor that targets VEGFR[1–3], FGFR[1–4], PDGFRα[1,3-4], RET[3-4], and KIT[1–4]
- There have been 4 failed phase 3 trials in front-line HCC in the past 10 years[5–8]
- In a global, randomised, open-label phase 3 non-inferiority study, lenvatinib was non-inferior to sorafenib for OS, and significantly improved PFS, TTP, and ORR in patients with untreated advanced HCC[9]

Comparison of kinase inhibitory effect on targeted molecule between lenvatinib and sorafenib[10]

IC_{50} (nmol/L)	lenvatinib	sorafenib
VEGFR1	4.7	21
VEGFR2	3.0	21
VEGFR3	2.3	16
FGFR1	61	340
FGFR2	27	150
FGFR3	52	340
FGFR4	43	3400
RET	6.4	15
KIT	85	140
PDGFRα	29	1.6
PDGFRβ	160	27
BRAF	8700	310
RAF1	1600	46

BRAF, B-Raf proto-oncogene; FGFR, fibroblast growth factor receptor; HCC, hepatocellular carcinoma; IC_{50}, half-maximal inhibitory concentration; ORR, objective response rate; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; TTP, time to progression; VEGFR, vascular endothelial growth factor receptor

1. Matsui J, et al. Int J Cancer. 2008;122:664-71; 2. Matsui J, et al. Clin Cancer Res. 2008;14:5459-65; 3. Tohyama O, et al. J Thyroid Res. 2014;2014:638747; 4. Yamamoto Y, et al. Vasc Cell. 2014;6:18; 5. Cheng A-L, et al. J Clin Oncol. 2013;31:4067-75; 6. Johnson PJ, et al. J Clin Oncol. 2013;31:3517-24; 7. Cainap C, et al. J Clin Oncol. 2015;33:172-9; 8. Zhu AX, et al. J Clin Oncol. 2015;33:559-66; 9. Cheng A-L, et al. J Clin Oncol. 2017:35, no. 15_suppl:4001-4001 (ASCO 2017 poster presentation); 10. Kudo M. Liver Cancer. 2021;10(2):85-93.

REFLECT STUDY- STUDY DESIGN

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Global, randomised, open-label, phase 3 non-inferiority study

Patients with unresectable HCC (N=954)

- No prior systemic therapy for unresectable HCC
- ≥1 Measurable target lesion per mRECIST
- BCLC stage B or C
- Child-Pugh A
- ECOG PS ≤1
- Adequate organ function
- Patients with ≥ 50% liver occupation, clear bile duct invasion, or portal vein invasion at the main portal vein were excluded

Stratification

- Region: (Asia-Pacific or Western)
- MPVI and/or EHS: (yes or no)
- ECOG PS: (0 or 1)
- Body weight: (<60 kg ≥60 kg)

Randomisation 1:1

lenvatinib (n=478)
8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) once daily

sorafenib (n=476)
400 mg twice daily

Primary endpoint:

- OS

Secondary endpoints:

- PFS
- TTP
- ORR
- Quality of life
- PK lenvatinib exposure parameters

Tumour assessments were performed according to mRECIST by the investigator

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 Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic

Kudo M, et al. Lancet. 2018;391:1163-73

REFLECT STUDY- OVERALL SURVIVAL

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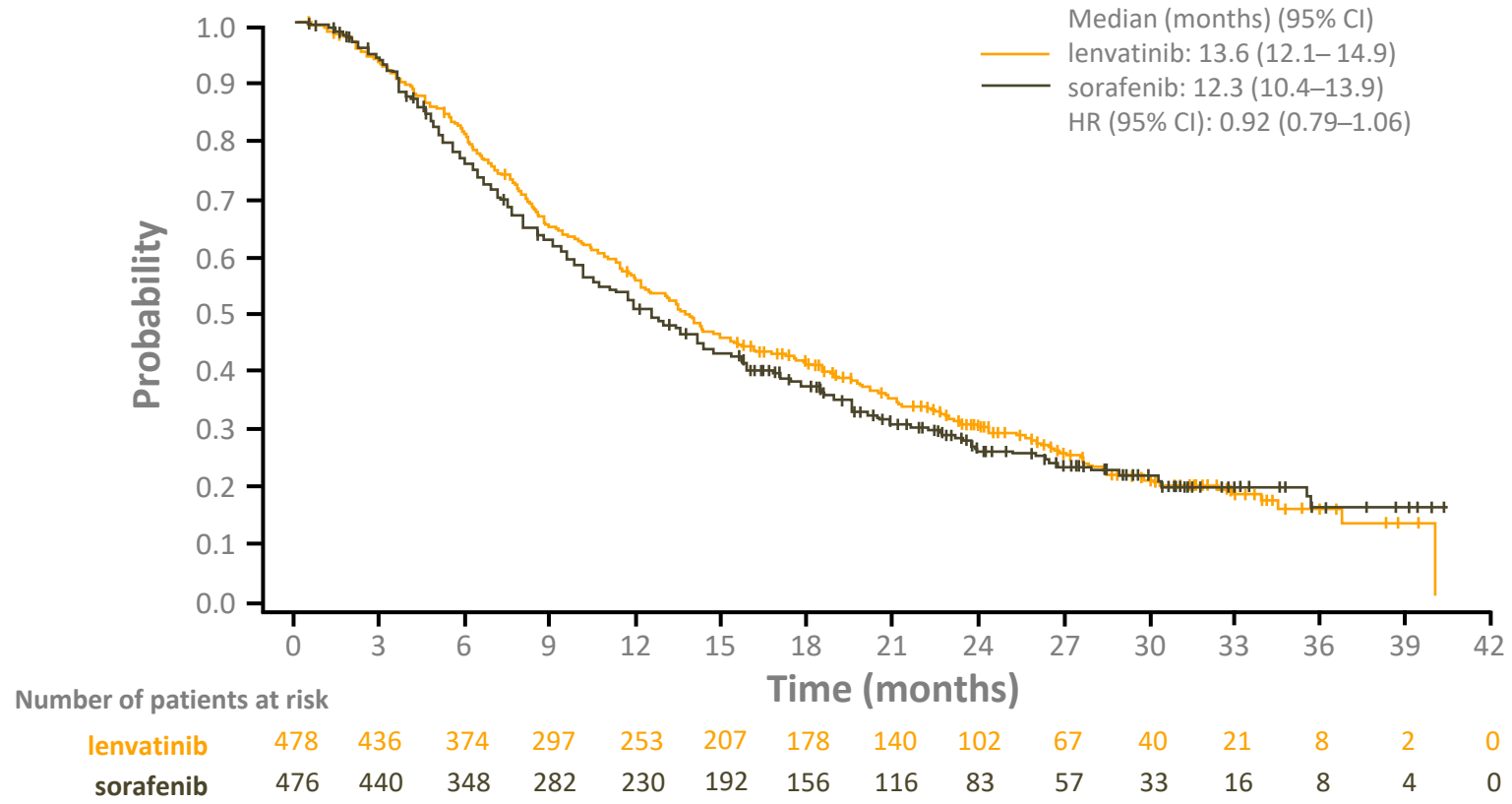
Primary Endpoint: Kaplan-Meier Estimate of OS

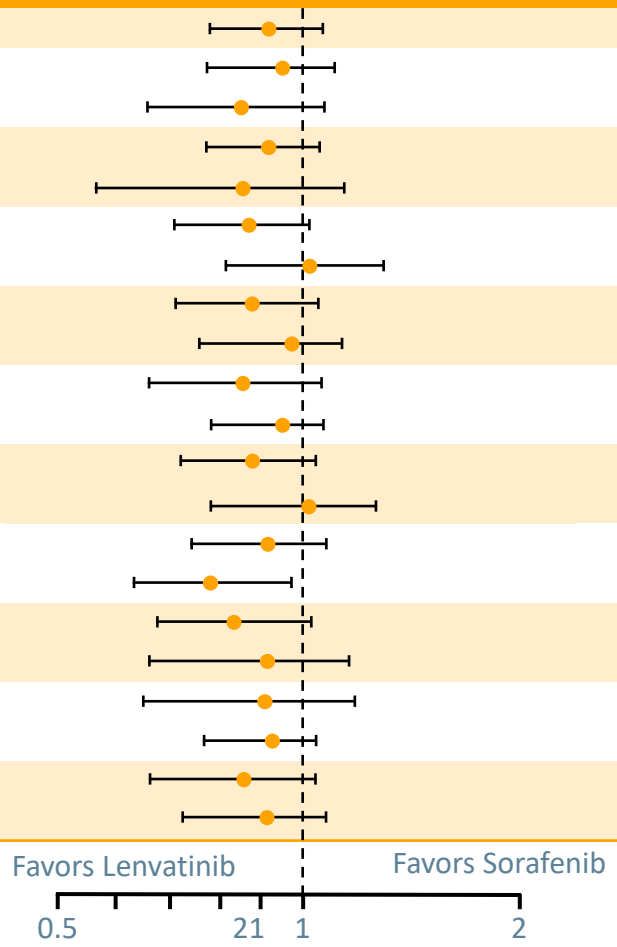


Number of patients at risk															
lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

CI, confidence interval; HR, hazard ratio; OS, overall survival
Kudo M, et al. Lancet. 2018;391:1163-73

REFLECT STUDY- PATIENTS CHARACTERISTICS

Characteristic	Subgroup	Events/Patients		HR (95% CI)	Median (months)	
		Lenvatinib	Sorafenib	Lenvatinib vs Sorafenib	Lenvatinib	Sorafenib
Overall		351/478	350/476	0.92 (0.79–1.06)	13.6	12.3
Age	< 65 y	203/270	204/283	0.94 (0.77–1.15)	12.4	11.4
	≥ 65 y	148/270	146/193	0.84 (0.66–1.07)	14.6	13.4
Sex	Male	293/405	293/401	0.91 (0.77–1.07)	13.4	12.4
	Female	58/73	57/75	0.84 (0.56–1.26)	15.3	11.4
Region	Asia-Pacific	243/321	248/319	0.86 (0.72–1.02)	13.5	11.0
	Western	108/157	102/157	1.08 (0.82–1.42)	13.6	14.2
ECOG-PS	PS = 0	221/304	223/301	0.88 (0.73–1.06)	14.6	12.8
	PS = 1	130/174	127/175	0.97 (0.76–1.25)	10.7	10.3
Body weight	<60 kg	110/153	113/146	0.85 (0.65–1.11)	13.4	10.3
	≥ 60 kg	241/325	237/330	0.95 (0.79–1.14)	13.7	12.5
MVI, EHS, or both	Yes	250/329	259/336	0.87 (0.73–1.04)	11.5	9.8
	No	101/149	91/140	1.05 (0.79–1.40)	18.0	18.0
AFP at baseline	< 200 ng/mL	167/255	193/286	0.91 (0.74–1.12)	19.5	16.3
	≥ 200 ng/mL	183/222	154/187	0.78 (0.63–0.98)	10.4	8.2
Etiology	HBV	196/259	186/244	0.83 (0.68–1.02)	13.4	10.2
	HCV	75/103	97/135	0.91 (0.65–1.28)	15.3	14.1
BCLC staging	Stage B	71/104	65/92	0.91 (0.66–1.26)	18.5	17.3
	Stage C	280/374	285/384	0.92 (0.77–1.08)	11.8	10.3
Posttreatment anticancer therapy	Yes	143/206	175/243	0.84 (0.67–1.06)	19.5	17.0
	No	208/272	175/233	0.91 (0.74–1.11)	10.5	7.9

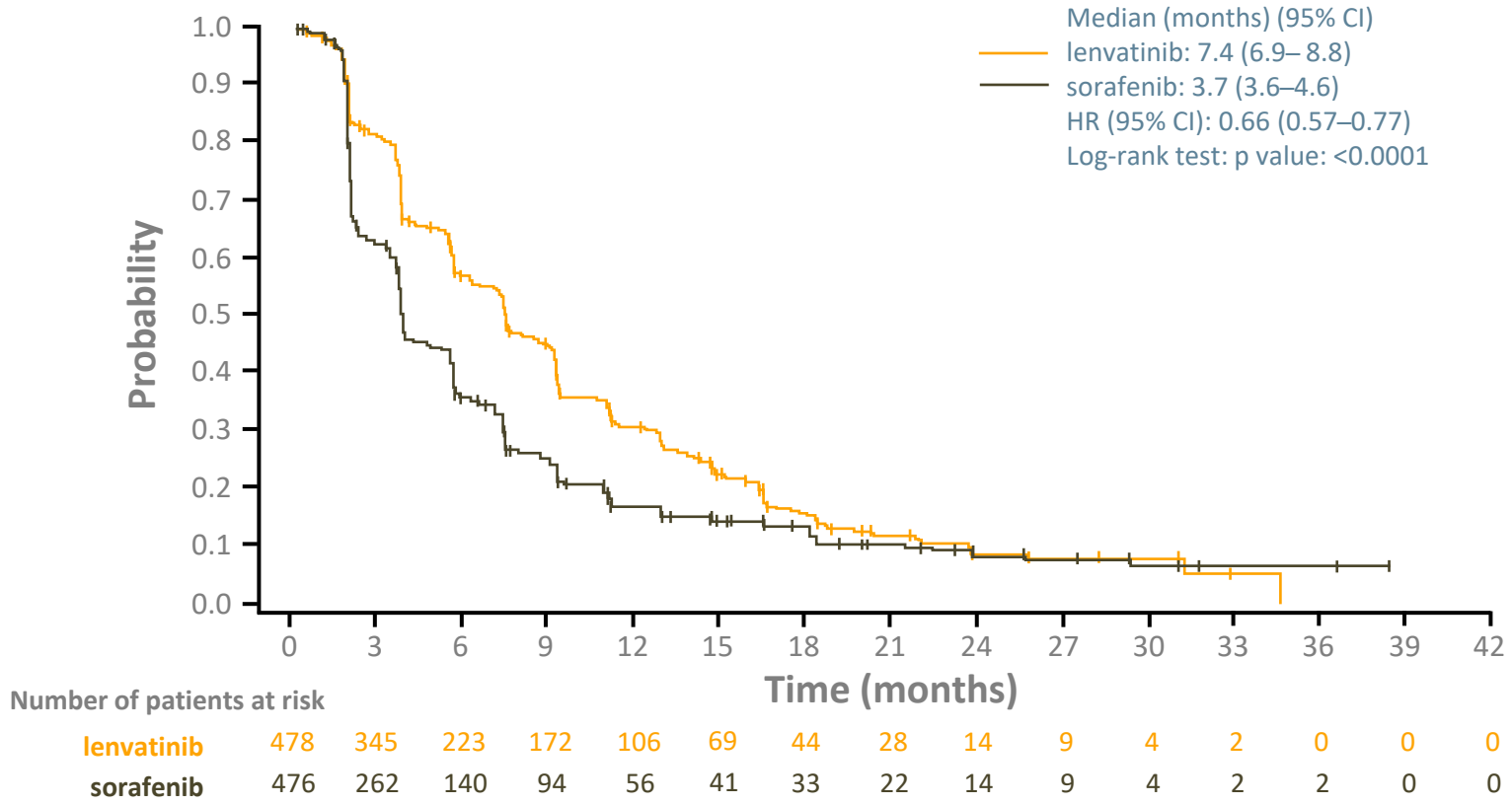


AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macroscopic portal vein invasion; PS, performance status; y, year

Kudo M, et al. Lancet. 2018;391:1163-73

REFLECT STUDY - PFS

Secondary Endpoint: Kaplan-Meier Estimate of PFS by mRECIST



CI, confidence interval; HR, hazard ratio; mRECIST, modified Response Evaluation Criteria In Solid Tumors; PFS, progression-free survival
Kudo M, et al. Lancet. 2018;391:1163-73

TUMOR ASSESSMENTS: LENVATINIB

Parameter	mRECIST by investigator	mRECIST by independent review	RECIST v1.1 by independent review
	lenvatinib (n=478)		
ORR, n (%)	115 (24.1)	194 (40.6)	90 (18.8)
95% CI	20.2–27.9	36.2–45.0	15.3–22.3
Odds ratio (95%CI)[a]	3.13 (2.15–4.56)	5.01 (3.59–7.01)	3.34 (2.17–5.14)
BOR, n (%)			
Complete response	6 (1)	10 (2)	2 (<1)
Partial response	109 (23)	184 (38)	88 (18)
Stable disease	246 (51)	159 (33)	258 (54)
Durable stable disease[b]	167 (35)	84 (18)	163 (34)
Progressive disease	71 (15)	79 (17)	84 (18)
Not evaluable/unknown	46 (10)	46 (10)	46 (10)

[a]lenvatinib vs sorafenib
[b]Stable disease lasting ≥23 weeks
BOR, best overall response; CI, confidence interval; mRECIST, modified RECIST; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors

Kudo M, et al. Lancet. 2018;391:1163-73

TUMOR ASSESSMENTS: SORAFENIB

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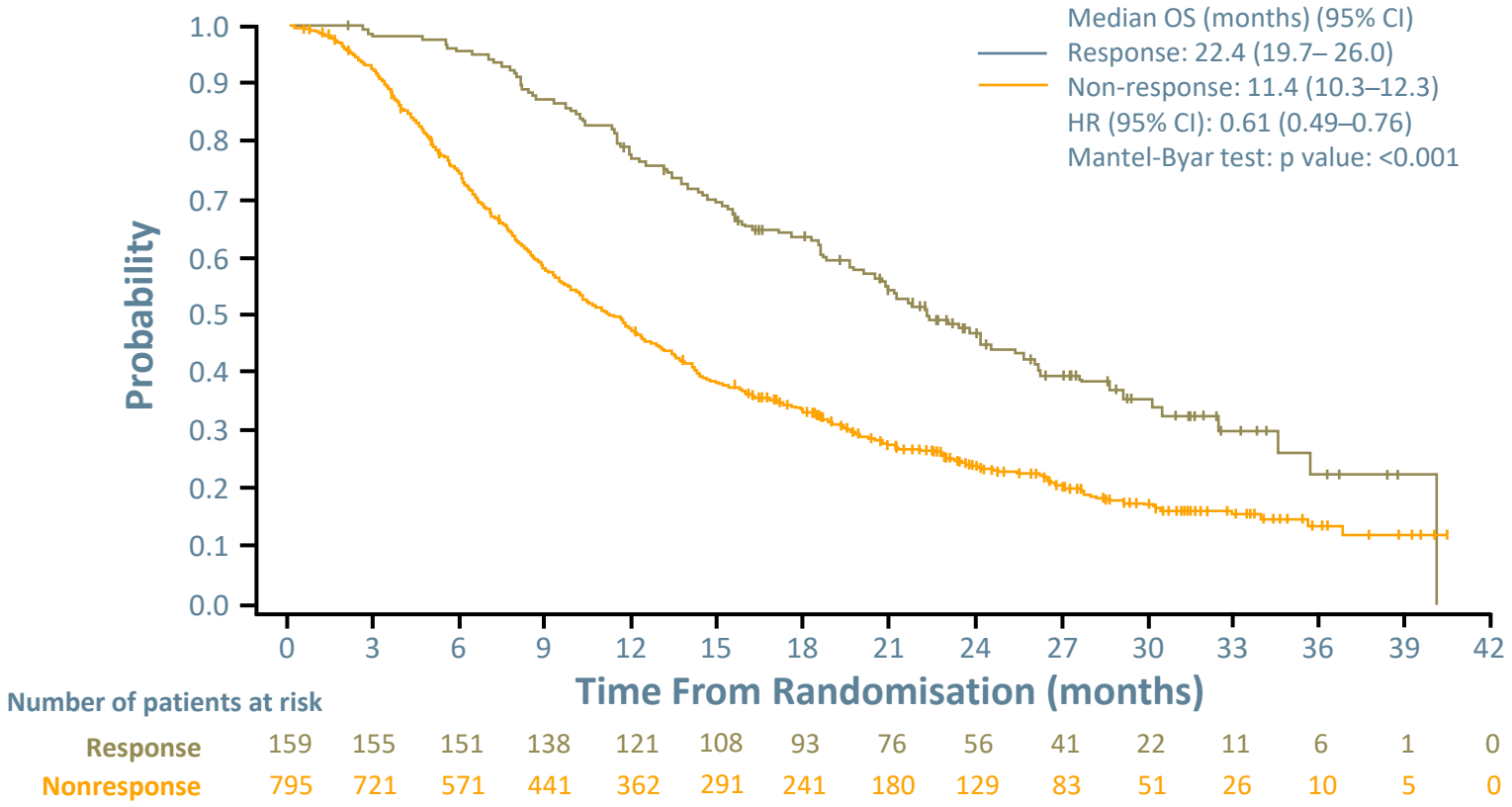
Parameter	mRECIST by investigator	mRECIST by independent review	RECIST v1.1 by independent review
	sorafenib (n=476)		
ORR, n (%)	44 (9.2)	59 (12.4)	31 (6.5)
95% CI	6.6–11.8	9.4–15.4	4.3–8.7
BOR, n (%)			
Complete response	2 (<1)	4 (1)	1 (<1)
Partial response	42 (9)	55 (12)	30 (6)
Stable disease	244 (51)	219 (46)	250 (53)
Durable stable disease[a]	139 (29)	90 (19)	118 (25)
Progressive disease	147 (31)	152 (32)	152 (32)
Not evaluable/unknown	41 (9)	46 (10)	43 (9)

[a]Stable disease lasting ≥23 weeks

BOR, best overall response; CI, confidence interval; mRECIST, modified RECIST; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors

Kudo M, et al. Lancet. 2018;391:1163-73

OS BY OR FOR THE OVERALL REFLECT POPULATION



CI, confidence interval; HR, hazard ratio; OR, objective response; OS, overall survival

Kudo M, et al. J Clin Oncol. 2019;37, no. 4_suppl:186-186 (ASCO 2019 Gastrointestinal Cancers Symposium - poster presentation)

REFLECT STUDY – MOST FREQUENT TEAEs (>15%)

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Adverse event, n (%)	lenvatinib (n=476)		sorafenib (n=475)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hypertension	**201 (42)**	**111 (23)**	**144 (30)**	**68 (14)**
Diarrhea	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 erythrodysesthesia	**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 (0)
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet count	87 (18)	26 (6)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Hypothyroidism	78 (16)	0 (0)	8 (2)	0 (0)
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0 (0)
Elevated aspartate aminotransferase	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0 (0)	76 (16)	2 (0)
Alopecia	14 (3)	0 (0)	119 (25)	0 (0)

TEAE, treatment-emergent adverse event

Kudo M, et al. Lancet. 2018;391:1163-73

REFLECT:
ADVERSE EVENTS AND OUTCOME

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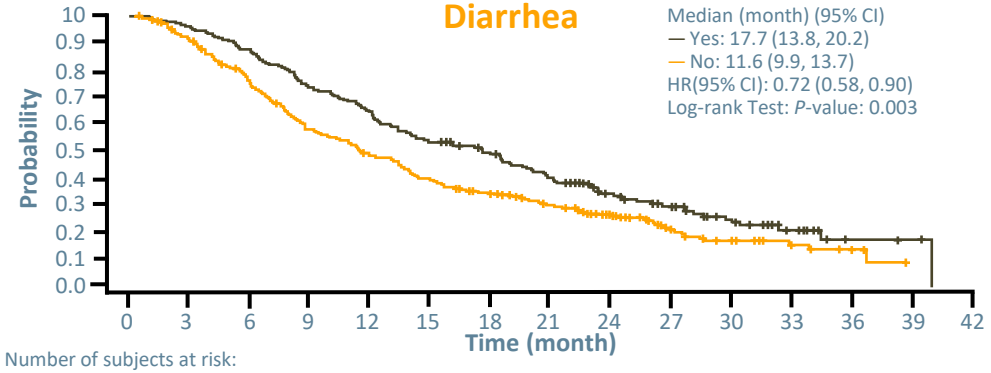
In patients treated with lenvatinib, the occurrence of hypertension, diarrhea, proteinuria, or hypothyroidism was generally associated with longer OS

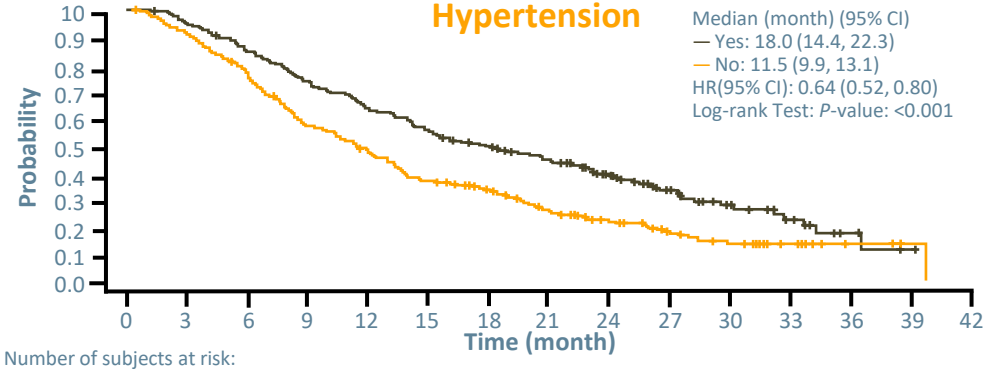
Diarrhea



Number of subjects at risk:

Yes	184	177	161	135	119	98	87	68	48	37	22	11	3	2	0
No	294	259	213	162	134	109	91	72	54	30	18	10	5	0	

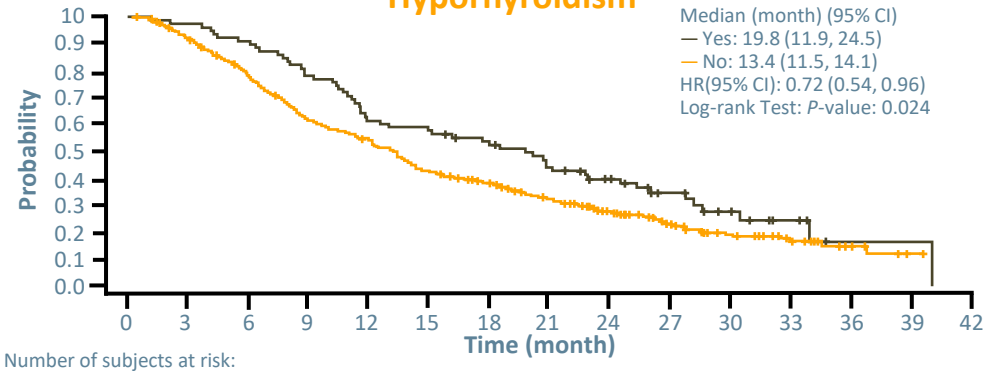
Hypertension



Number of subjects at risk:

Yes	201	190	169	147	127	111	97	81	60	39	23	12	4	1	0
No	277	246	205	150	126	96	81	59	42	28	17	9	4	1	0

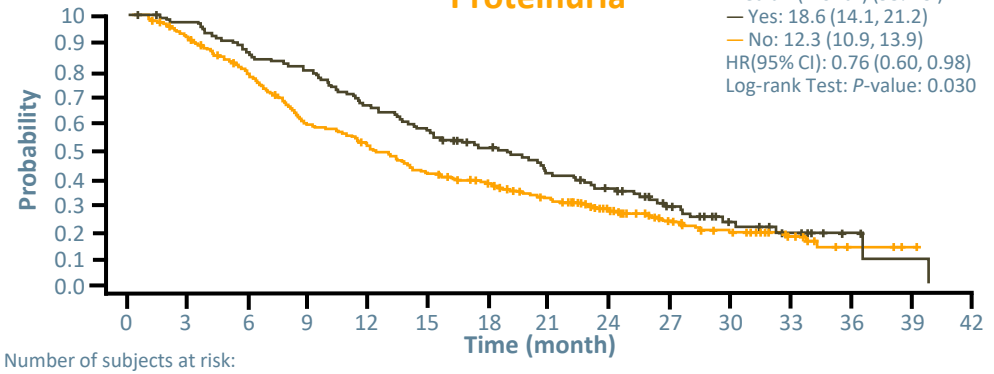
Hyporhyroidism



Number of subjects at risk:

Yes	78	75	71	61	48	45	40	32	25	16	10	5	1	1	0
No	400	360	303	236	205	162	198	108	77	51	30	16	7	1	0

Proteinuria



Number of subjects at risk:

Yes	117	113	100	92	77	66	55	44	36	24	43	8	3	1	0
No	361	323	274	205	176	141	123	96	66	43	27	13	5	1	0

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

Sung MW, et al. J Clin Oncol. 2019;37, no. 4_suppl:317-317 (ASCO 2019 Gastrointestinal Cancers Symposium - poster presentation)

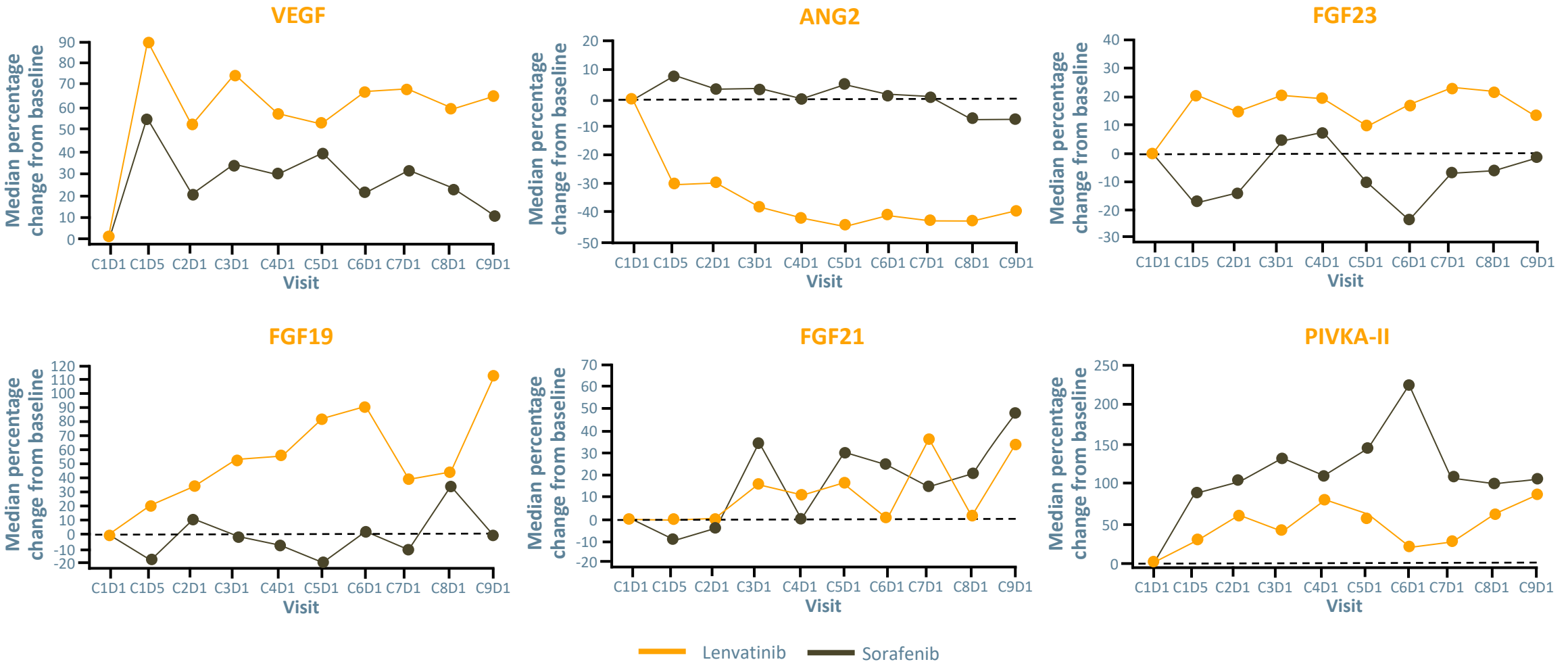
REFLECT: ASSOCIATION BETWEEN AEs OF INTEREST AND OS

Preferred Term	lenvatinib (n=478) n (%)		HR for OS	95% CI	p value
	AEI	No AEI			
Hypertension	201 (42)	277 (58)	0.64	0.52–0.80	0.001
Diarrhea	184 (38)	294 (62)	0.72	0.58–0.90	0.003
Proteinuria	117 (24)	361 (76)	0.76	0.60–0.98	0.030
Dysphonia	113 (24)	365 (76)	0.86	0.68–1.11	0.247
Hypothyroidism	78 (16)	400 (84)	0.72	0.54–0.96	0.024

AEI, adverse event of interest; CI, confidence interval; HR, hazard ratio; OS, overall survival

Sung MW, et al. J Clin Oncol. 2019;37, no. 4_suppl:317-317 (ASCO 2019 Gastrointestinal Cancers Symposium - poster presentation)

REFLECT: PHARMACODYNAMIC SERUM BIOMARKERS

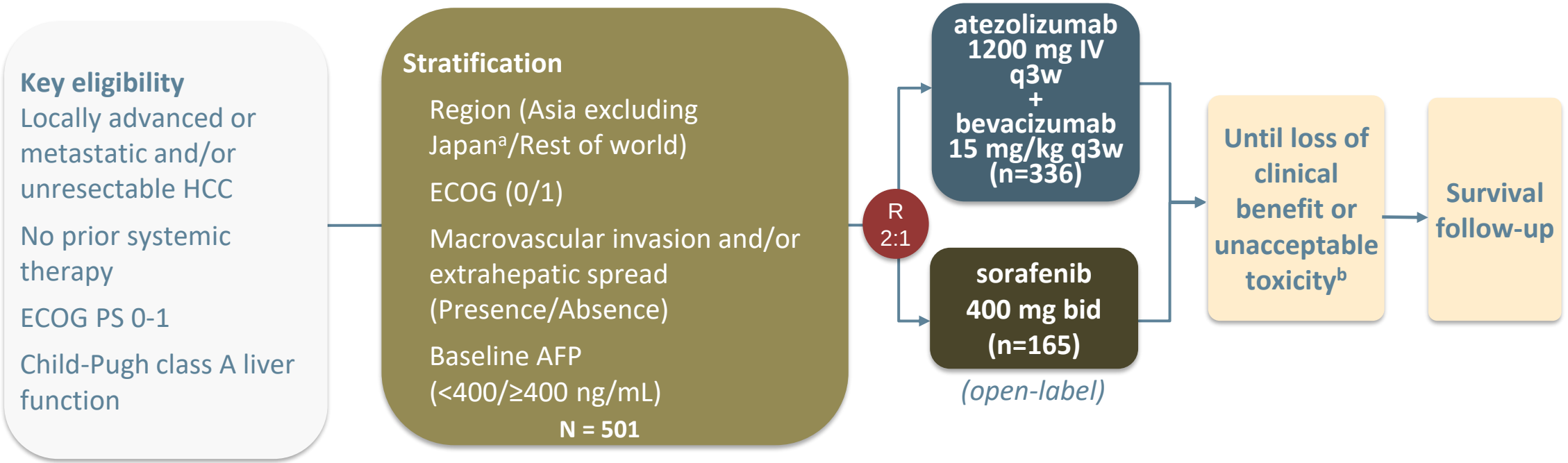


ANG2, angiopoietin-2; C, Cycle; D, Day; FGF, fibroblast growth factor; PIVKA-II, protein induced vitamin K absence/antagonist II; VEGF, vascular endothelial growth factor

Finn RS, et al. Clin Cancer Res. 2021;28:4848-58

IMBRAVE150 - STUDY DESIGN

IMbrave150 (NCT03434379): Randomized phase 3 trial assessing combination therapy with the PD-L1 inhibitor atezolizumab and the VEGF inhibitor bevacizumab versus standard-of-care sorafenib in first line for advanced HCC



Co-primary endpoints

- OS
- IRF-assessed PFS per RECIST 1.1

Secondary endpoints included:

- IRF-assessed ORR, DoR per RECIST 1.1 and HCC mRECIST[b]
- PROs: TTD[c] of QoL, physical and role functioning (EORTC QLQ-C30)
- Safety and tolerability assessed based on the nature, frequency and severity of adverse events per NCI CTCAE version 4.0

a Japan is included in rest of world. b Tumour assessment by computed tomography or magnetic resonance imaging was done at baseline and every 6 weeks until 54 weeks, then every 9 weeks thereafter.
c Time from randomization to first decrease from baseline of ≥10 points maintained for two consecutive assessments, or one assessment followed by death from any cause within 3 weeks

AFP, α-fetoprotein; CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer; HCC, hepatocellular carcinoma; IRF, independent review facility; IV, intravascular; mRECIST, modified RECIST; NCI, National Cancer Institute; PRO, patient-reported outcomes; q3w, every 3 weeks; QoL, quality of life; RECIST, response evaluation criteria in solid tumours; TTD, time to deterioration

Finn RS, et al. N Engl J Med. 2020;382(20):1894-905

IMBRAVE150 - BASELINE PATIENT CHARACTERISTICS (ITT)[a]

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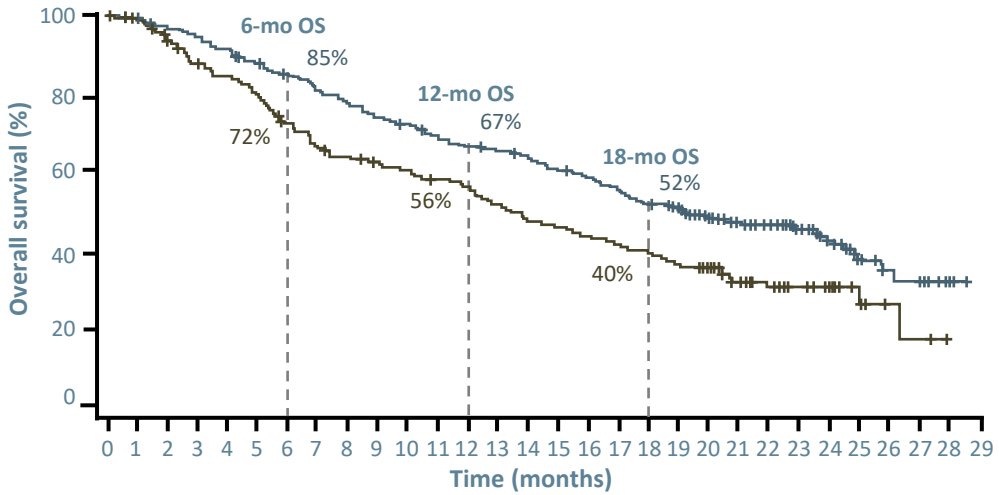
n (%)	atezo + bev (n = 336)	sorafenib (n = 165)
Median age (range), years	64 (56-71)	66 (59-71)
Male	277 (82)	137 (83)
Asia excluding Japan | rest of world[b]	133 (40) | 203 (60)	68 (41) | 97 (59)
ECOG PS 0 | 1	209 (62) | 127 (38)	103 (62) | 62 (38)
Child-Pugh score A5 | A6[c]	239 (72) | 94 (28)	121 (73) | 44 (27)
Barcelona Clinic Liver Cancer stage B | C	52 (15) | 276 (82)	26 (16) | 133 (81)
AFP at baseline ≥ 400 ng/mL	126 (38)	61 (37)
MVI present	129 (38)	71 (43)
EHS present	212 (63)	93 (56)
MVI and/or EHS present	258 (77)	120 (73)
Varices at baseline	88 (26)	43 (26)
Varices treated at baseline	36 (11)	23 (14)
HCC etiology		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Non-viral[d]	100 (30)	53 (32)

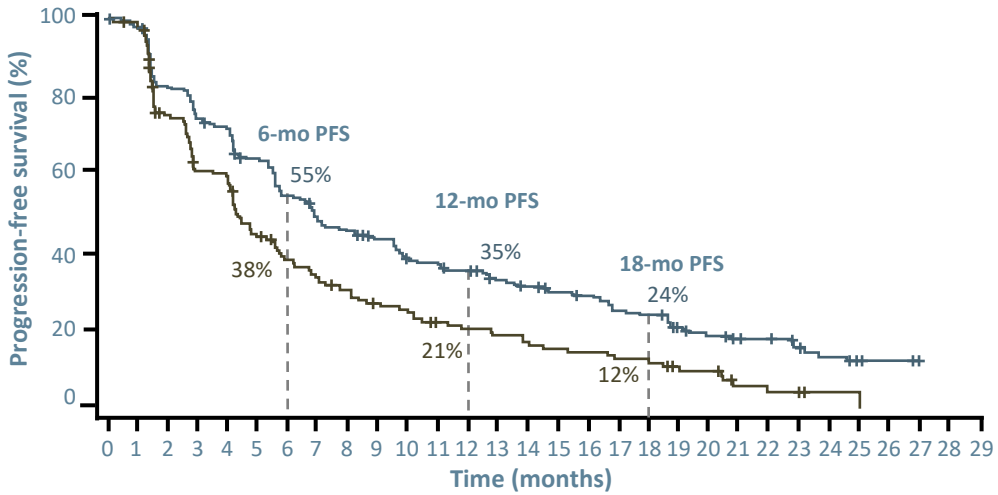
a All randomised patients. b Includes United States, Australia, New Zealand, and Japan. c three patients data not included. d Includes alcohol, other and unknown non–hepatitis B and C causes

AFP, α-fetoprotein; atezo, atezolizumab; bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; ITT, intention to treat; MVI, macrovascular invasion

Finn RS, et al. N Engl J Med. 2020;382(20):1894-905

IMBRAVE150 TRIAL
KEY EFFICACY DATA: UPDATED OS AND PFS





Updated OS	atezo + bev (n = 336)	sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95%CI)	**0.66** (0.52, 0.85) *P* = 0.0009	

- Primary analysis HR (OS): 0.58

Median follow-up: 15.6 mo (vs 8.6 mo in primary analysis)

Updated PFS	atezo + bev (n = 336)	sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95%CI)	**0.65** (0.53, 0.81) *P* = 0.0001	

- Primary analysis HR (PFS): 0.59

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

Finn RS, et al. N Engl J Med. 2020;382(20):1894-905; Finn RS, et al. J Clinical Oncol. 39, no. 3_suppl. 267-267 (presented at ASCO 2021)

UPDATED RESPONSE AND DURATION OF RESPONSE

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	Updated analysis[a]			
	RECIST 1.1		HCC mRECIST	
	atezo + bev (n = 326)	sorafenib (n = 159)	atezo + bev (n = 325)	sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DoR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo

[a] Only patients with measurable disease at baseline were included in the analysis of ORR. [b] Only confirmed responders were included in the analysis of ORR and DoR

atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; HCC, hepatocellular carcinoma; mo, month; mRECIST, modified RECIST; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumours

Finn RS, et al. J Clinical Oncol. 39, no. 3_suppl. 267-267 (presented at ASCO 2021)

ADVERSE EVENTS FROM ANY CAUSE

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- Median duration of treatment:
  - 7.4 months with atezolizumab
  - 6.9 months with bevacizumab
  - 2.8 months with sorafenib
- Mean (±SD) dose intensity and median (range) dose intensities:
  - 95±7% and 98% (54–104%) for atezolizumab
  - 93±10% and 97% (44–104%) for bevacizumab
  - 84±20% and 96% (27–100%) for sorafenib
- No specific events were responsible for the increased SAE rate in the atezolizumab + bevacizumab group
- There were no SAEs with a ≥ 2% difference between treatment groups

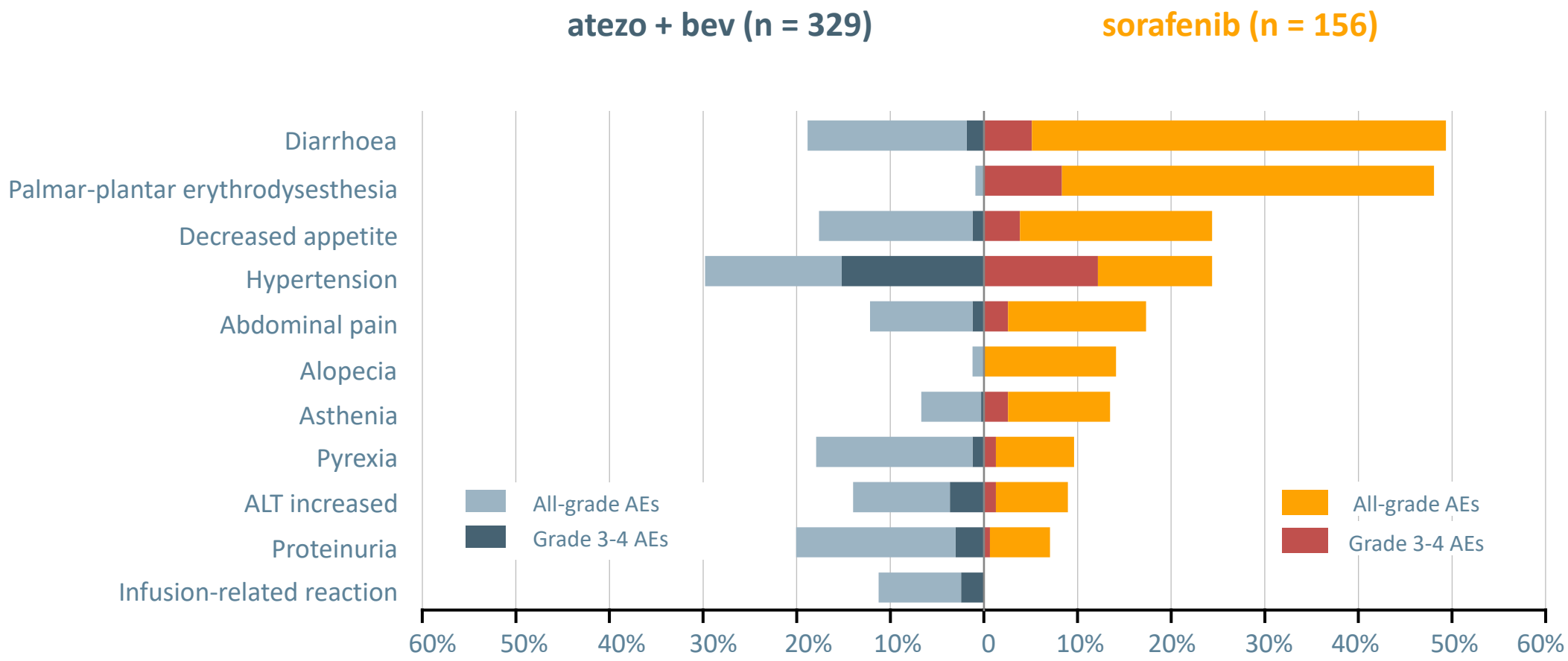
	atezolizumab + bevacizumab (n = 329)[a]	sorafenib (n = 156)[a]
Patients with an adverse event from any cause, n (%)	323 (98.2)	154 (98.7)
Grade 3 or 4 events[b]	186 (56.5)	86 (55.1)
Grade 5 events[c]	15 (4.6)	9 (5.8)
Serious adverse events	125 (38.0)	48 (30.8)
Adverse events leading to withdrawal from any study drug	51 (15.5)	16 (10.3)
Withdrawal from atezolizumab + bevacizumab	23 (7.0)	–
Adverse events leading to dose modification or interruption of any study drug	163 (49.5)	95 (60.9)
Dose interruption of any study treatment	163 (49.5)	64 (41.0)
Dose modification of sorafenib[d]	–	58 (37.2)

[a] Received one dose of study treatment and included in safety population. [b] Represents the highest grades assigned. [c] Gastrointestinal haemorrhage (in 3 patients), pneumonia (in 2 patients), empyema, gastric ulcer perforation, abnormal hepatic function, liver injury, multiple-organ dysfunction syndrome, oesophageal varices haemorrhage, subarachnoid haemorrhage, respiratory distress, sepsis, and cardiac arrest (in 1 patient each) in the atezolizumab + bevacizumab group; and death (in 2 patients), hepatic cirrhosis (in 2 patients), cardiac arrest, cardiac failure, general physical health deterioration, hepatitis E, and peritoneal haemorrhage (in 1 patient each) in the sorafenib group. [d] Dose modification of atezolizumab or bevacizumab was not permitted

SAE, serious adverse event; SD, standard deviation

Finn RS, et al. N Engl J Med. 2020;382(20):1894-905

ALL-CAUSE AEs: ≥ 10% FREQUENCY IN EITHER ARM AND > 5% DIFFERENCE BETWEEN ARMS

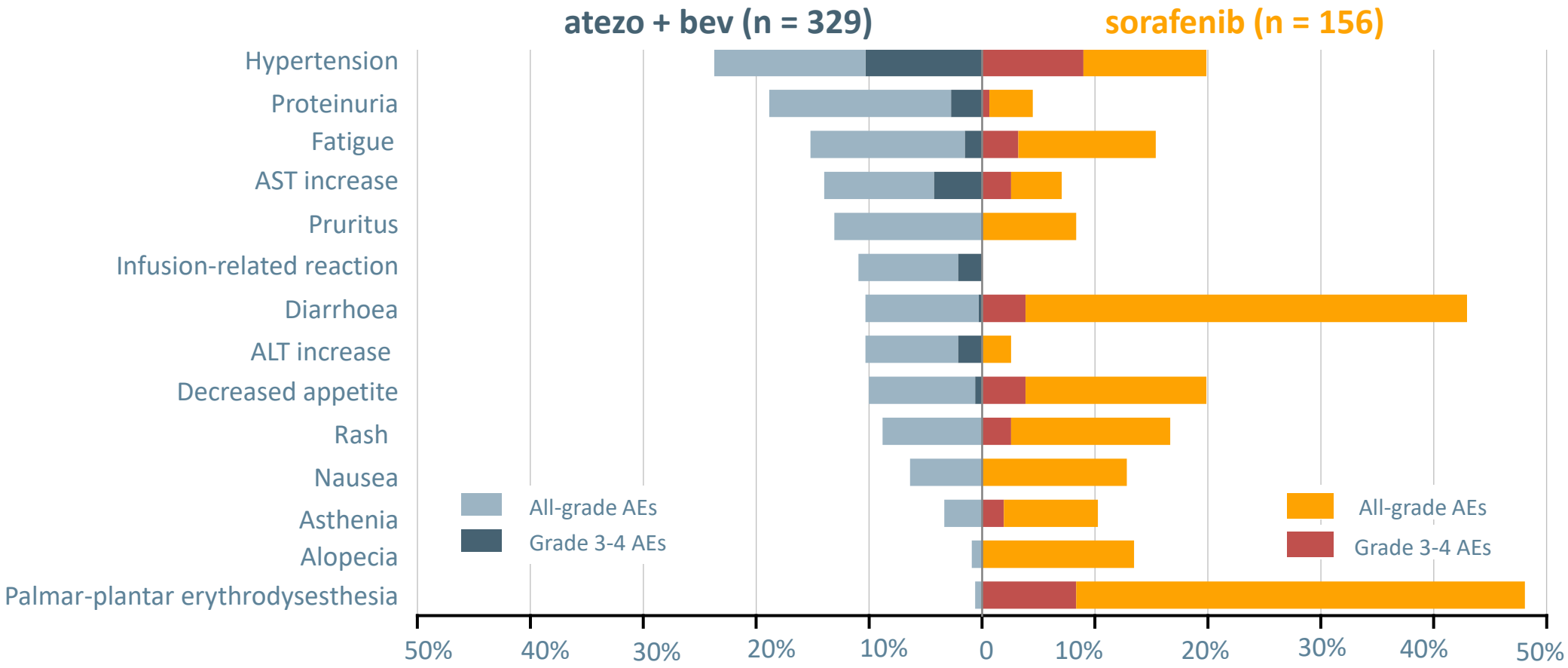


- Other than hypertension, most high-grade AEs were infrequent

AE, adverse event; ALT, alanine aminotransferase; atezo, atezolizumab; bev, bevacizumab

Finn RS, et al. N Engl J Med. 2020;382(20):1894-905

TRAEs: ≥ 10% ANY GRADE IN EITHER ARM



AE, adverse event; atezo, atezolizumab; bev, bevacizumab; TRAE, treatment-related adverse event

Finn RS, et al. N Engl J Med. 2020;382(20):1894-905 (Supplementary Appendix)

SERIOUS AEs ≥ 2% IN EITHER ARM

n (%)	atezo + bev (n = 329)			sorafenib (n = 156)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
Gastrointestinal haemorrhage	8 (2.4)	4 (1.2)	3 (0.9)	3 (1.9)	3 (1.9)	0
Oesophageal varices haemorrhage	8 (2.4)	6 (1.8)	1 (0.3)	1 (0.6)	1 (0.6)	0

atezo, atezolizumab; bev, bevacizumab

Finn RS, et al. N Engl J Med. 2020;382(20):1894-905 (Supplementary Appendix)

BLEEDING EVENTS

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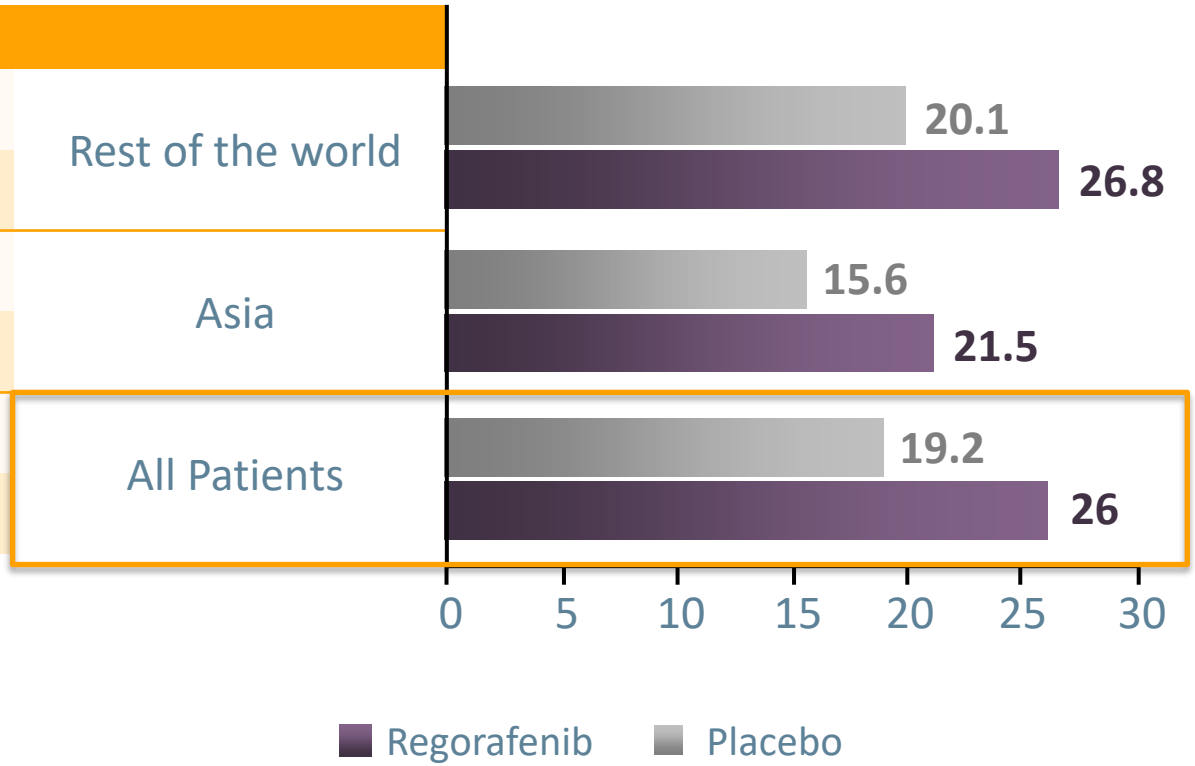
All-cause AESIs by medical concept and preferred term, n (%)[a]	atezolizumab + bevacizumab (n = 329)		sorafenib (n = 156)	
	All grade	Grade 3-4	All grade	Grade 3-4
Bleeding/hemorrhage	83 (25.2)	21 (6.4)	27 (17.3)	9 (5.8)
Bleeding events in > 1% of either group				
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Haematuria	10 (3.0)	1 (0.3)	0	0
Gingival bleeding	9 (2.7)	0	0	0
Oesophageal varices haemorrhage	8 (2.4)	6 (1.8)	1 (0.6)	1 (0.6)
Gastrointestinal haemorrhage	8 (2.4)	4 (1.2)	3 (1.9)	3 (1.9)
Rectal haemorrhage	5 (1.5)	1 (0.3)	3 (1.9)	0
Upper gastrointestinal haemorrhage	4 (1.2)	2 (0.6)	2 (1.3)	2 (1.3)
Haemoptysis	3 (0.9)	0	5 (3.2)	0
Peritoneal haemorrhage	0	0	2 (1.3)	1 (0.6)

a Grouped Medical Dictionary for Regulatory Activities (MedDRA) preferred terms
AESIs, adverse events of special interest;
Finn RS, et al. N Engl J Med. 2020;382(20):1894-905 (Supplementary Appendix)

MEDIAN OS OF 26 MONTHS FROM FIRST SORAFENIB DOSE TO DEATH IN RESORCE STUDY

This analysis examined characteristics and outcomes of patients with HCC who were treated with regorafenib after they had disease progression during sorafenib treatment

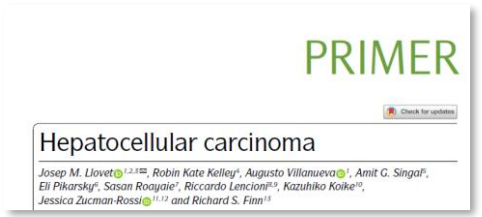
n	(CI)	
120	(17.5 – 25.9)	Rest of the world
231	(23.3 – 29.1)	
73	(12.2 – 24.9)	Asia
143	(19.6 – 27.8)	
193	(16.3 – 22.8)	All Patients
374	(22.6 – 28.1)	

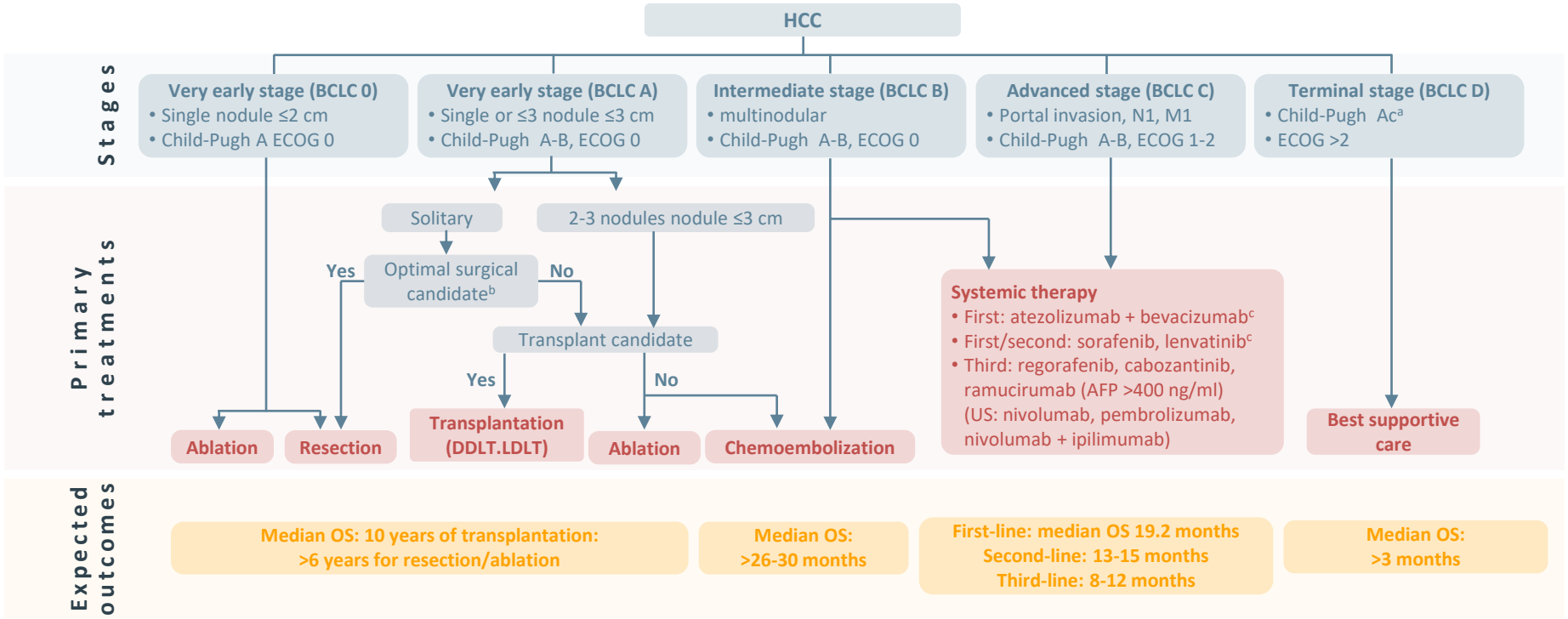


AE, adverse event; atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; HCC, hepatocellular carcinoma; OS, overall survival

Finn RS, et al. J Hepatol. 2018;69:353-58

TREATMENT STRATEGY IN THE MANAGEMENT OF HCC IN 2021





AFP, α- fetoprotein; BCLC, Barcelona Clinic Liver cancer; DDLT, deceased- donor liver transplantation; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; LDLT, living- donor liver transplantation; M1, distant metastasis; N1, lymph node metastasis; OS, overall survival; RCT, randomised controlled trial; TACE, transarterial chemoembolisation

Llovet JM, et al. Nat Rev Dis Primers. 2021;7:6

CONCLUSIONS

- Substantial progress has been made in improving survival in advanced HCC
- Atezolizumab and bevacizumab is the standard of care for most patients in the front-line setting
  - COSMIC-312 recently presented (Kelley ESMO Asia 2021)
    - PFS HR 0.63 (99% CI 0.44–0.91), P=0.0012 (6.8 vs 4.2 mos)
    - OS HR 0.90 (96% CI 0.69–1.18), P=0.438 (15.4 vs 15.5 mos)
    - ORR 11% vs 3.7%
  - Awaiting result of HIMALAYA (press release met primary endpoint)
- For patients with a contraindication to combination therapy, single agent TKIs would be appropriate
  - At progression consider single-agent PD-1 inhibitor
- Ultimately, sequencing active agents in patients with well-preserved liver function will continue to improve overall survival

HCC, hepatocellular carcinoma; PD-1, programmed cell death protein; TKI, tyrosine kinase inhibitor

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- Liver Cancer Research Team: Brandon Brooks, Lia Ethridge, Tierney Olafson, Lillia Gonzalez, Rose Estrada

WHAT DID WE LEARN FROM THE REAL-WORLD DATA? WHAT CAN WE TRANSLATE INTO CLINICAL PRACTICE?

Dr Mohamed Bouattour, MD
Department of Hepatology
Department of Oncology
The University Beaujon Hospital
Clichy, Beaujon, France

DISCLOSURES

- Consultant fees: Bayer, Ipsen, Eisai, Bristol Myers Squibb, Roche/Genentech, Sirtex Medical, MSD
- Advisory Board: Bayer, Ipsen, Eisai, Roche/Genentech, Sirtex Medica, Servier

SYSTEMIC THERAPY FOR ADVANCED HCC: A NEW PARADIGM A NEW FIRST-LINE OF STANDARD OF CARE

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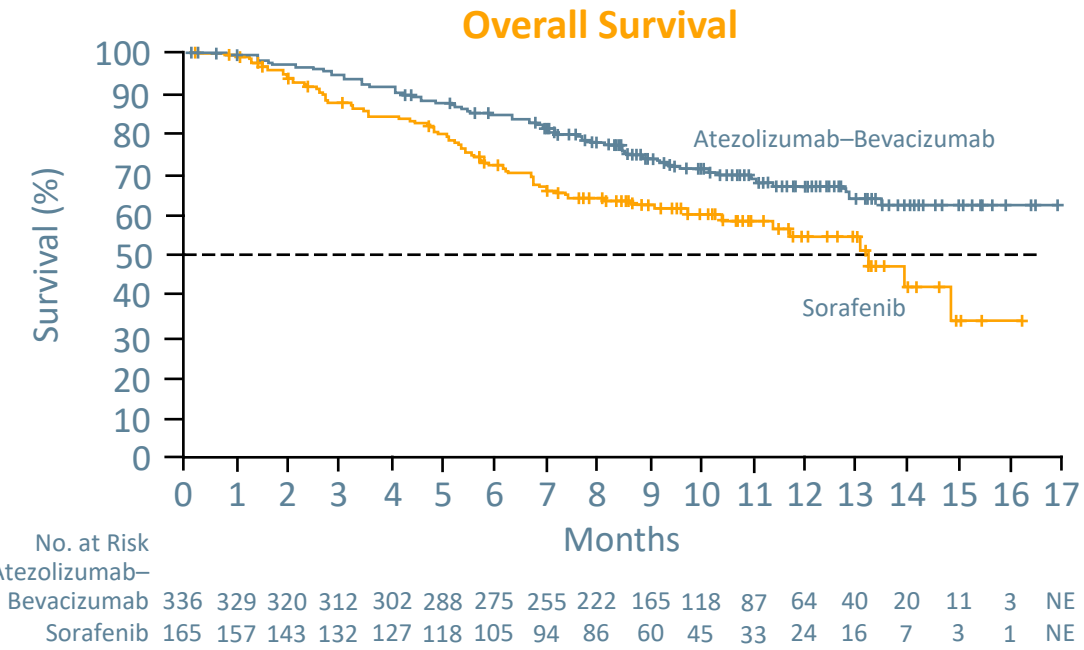
- IMBrave150: Phase 3 trial of first line with Atezolizumab and Bevacizumab[1]



	No of Events/ No of Patients (%)	Median Overall Survival (95% CI) *months*	Overall Survival at 6 months (%)
Atezolizumab–Bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

Stratified hazard ratio for death, 0.58 (95% CI, 0.42–0.79)
P<0.001

Updated OS following additional 12 months of follow-up (2)

Median OS: 19.2 months vs. 13,4 months ; HR = 0,66
Median PFS : 6.9 months vs. 4.3 months ; HR 0,65

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

1.Finn RS, et al. N Engl J Med. 2020;382:1894-905
2.Finn RS, et al. J Clin Oncol. 2021;39(3_suppl):267 267

THE ASCO RECOMMEND TO USE SORAFENIB OR LENVATINIB FOR PATIENTS WHO CANNOT BE TREATED WITH ATEZOLIZUMAB + BEVACIZUMAB[1]

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Recommendations	Type	Evidence quality	Strength of recommendation
First-line therapy			
1.1 Atezolizumab + bevacizumab as first-line therapy for most patients with advanced HCC, Child-Pugh class A, ECOG-PS 0-1, following management of esophageal varices when present	Evidence-based, benefits outweigh harms	Moderate to high	Strong
1.2 With contraindications to atezolizumab and/or bevacizumab, TKIs sorafenib or lenvatinib as first-line therapy of patients with advanced HCC, Child-Pugh class A, and ECOG-PS 0-1	Evidence-based, benefits outweigh harms	Moderate	Strong
Second-line therapy			
2.1 Following first-line treatment with atezolizumab + bevacizumab, second-line therapy with a TKI (sorafenib, lenvatinib, regorafenib, or cabozantinib) may be recommended	Informal consensus, benefits outweigh harms	Low	Weak
2.2 Following first-line therapy with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (AFP ≥ 400 ng/mL), or atezolizumab + bevacizumab may be recommended	Informal consensus, benefits outweigh harms	Low to moderate	Weak
2.3 Following first-line therapy with sorafenib or lenvatinib, pembrolizumab or nivolumab are reasonable options that may be considered for appropriate candidates	Informal consensus, benefits outweigh harms	Low	Weak

HCC: Hepatocellular carcinoma; ECOG-PS: Eastern Cooperative Oncology Group performance status; TKIs: tyrosine kinase inhibitors; AFP: alpl fetoprotein; ASCO: American Society of Clinical Oncology.

Very restrictive criteria for treatment with ICI in clinical trials

Italian Liver Cancer (ITA.LI.CA) database
First-line scenario

When the same Inclusion/Exclusion criteria of RCTs with ICI were applied, less than 30% of patients will be considered potential candidate to treatment with ICI in the real-life clinical practice[2,3]

ICI, immune checkpoint inhibitor; RCT, randomized clinical trial

1. Gordan JD, et al. ASCO Guideline. J Clin Oncol 2020;38:4317-45 2. Giannini EG,et al. Cancers (Basel) 2019;11:1689 3. Tovoli F,et al. Vaccines (Basel) 2020;8:578 Source table: Pelizzaro et al. Hepatoma Res 2021;7:36

TKIs IN THE TREATMENT OF PATIENTS WITH HCC, INCLUDING SORAFENIB AND LENVATINIB, STILL HAVE ROOM IN THE THERAPEUTIC ARSENAL IN PATIENTS WITH ADVANCED HCC

TKIs FOR ADVANCED HCC

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Advanced HCC (vascular invasion and/or extrahepatic spread) Intermediate HCC failed or progressive after loco-regional therapies	
Sorafenib * (SHARP Study) **(Less restrictive criteria)**	**Lenvatinib ** (REFLECT Study)**
OS HR = 0.69 (vs. Placebo)	OS HR = 0.92 (vs. sorafenib)
CHILD A **ECOG-PS ≤ 2**	CHILD A **ECOG-PS ≤ 1**
Region: European + Australasia: 88 % **Cause of disease: Hepatitis B: 19%; hepatitis C : 29%, Alcohol: 26%** **BCLC B/C : 18%/82%[a]** **MVI, extrahepatic spread or both : present 70%**	**Region: Asia-Pacific 67%** **Cause of disease: Hepatitis B : 53%; hepatitis C: 19%; alcohol: 8%** **BCLC B/C : 22%/78%** **No main portal vein invasion** **< 50 % of liver involvement** **MVI, extrahepatic spread or both : present 69%**
Fatigue, **HFS**, Diarrhea, **skin reaction, hypophosphatemia**	Fatigue, HFS, Diarrhea, **hypertension, proteinuria**
Study design **Double-blind, placebo-controlled trial**	Study design **Open-label Trial, Non-inferior study**
FDA and EMA Approval	FDA and EMA Approval
Higher benefit for hepatitis C patients?* **	**Higher benefit for hepatitis B patients?*** **

[a]One patient in the sorafenib group had a BCLC score of D and a Child–Pugh class of C. *Llovet Jel al. N Engl J Med 2008;359:378-90. **Kudo M et al, Lancet 2018;391(10126):1163-1173. ***Bouattour M et al, Liver Cancer 2019;8(5):341-358

LEARNING FROM SEVERAL YEARS OF EXPERIENCE WITH SORAFENIB IN ADVANCED HCC

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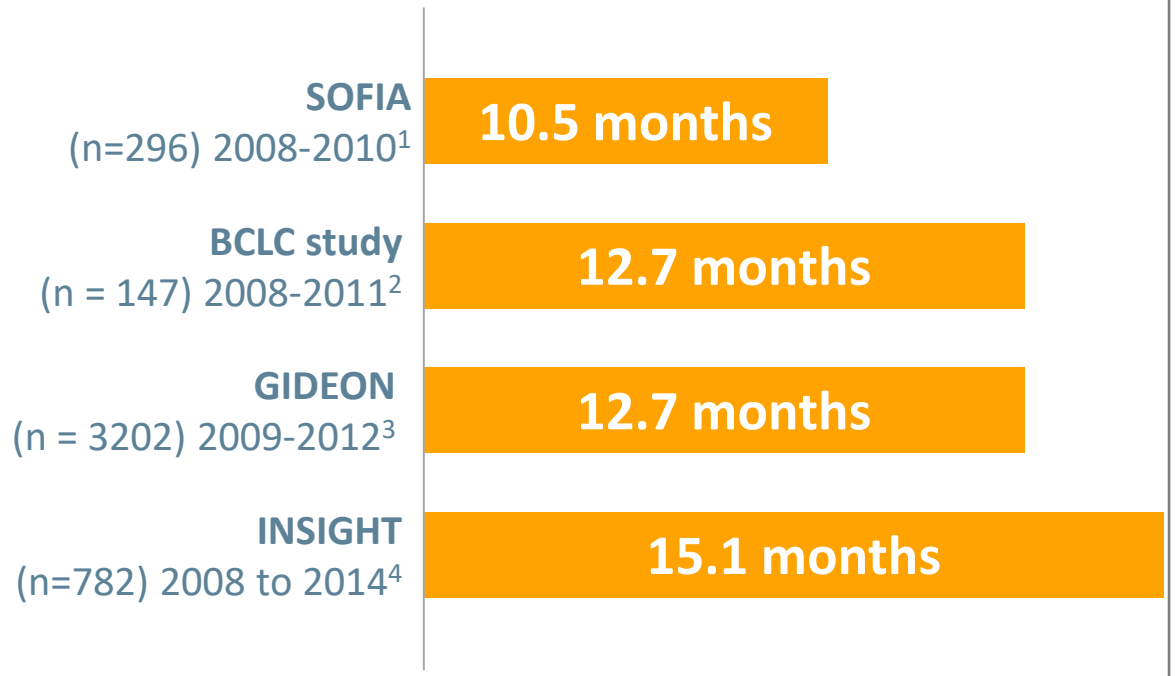
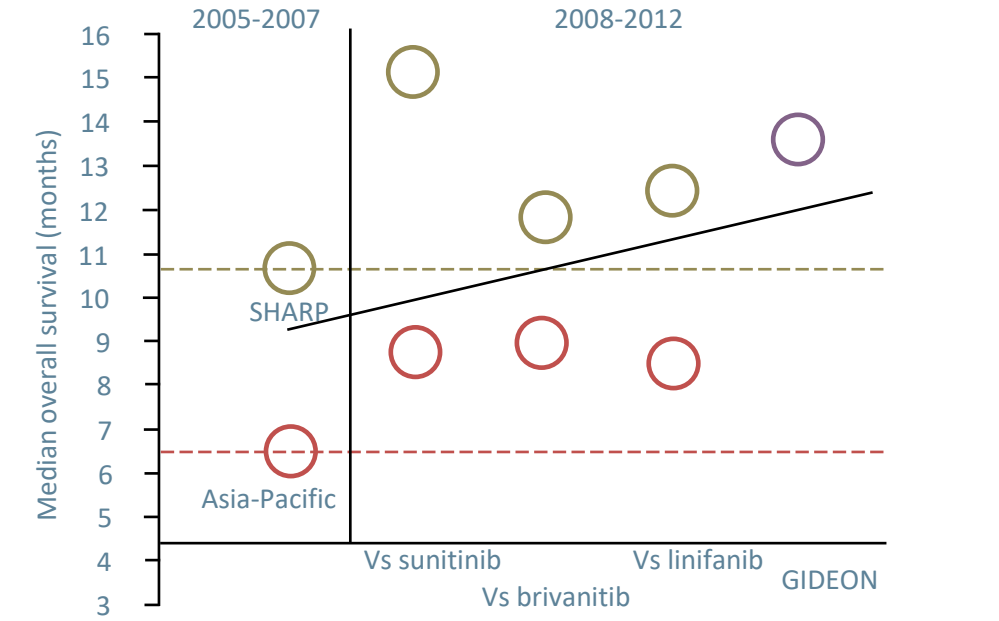
Overall Survival (OS)



Learning from 7 years of experience with sorafenib in advanced HCC : Improved median OS in clinical trials over time[5]



1. Iavarone M, et al. Hepatology 2011;54(6):2055-63 - 2. Reig M, et al. J Hepatol. 2014;61(2):318-24 - 3. Geschwind J-F, et al. Radiology 2016;279(2):630-40
4. Ganten TM, et al. Clin Cancer Res 2017;23(19):5720-5728 - 5. Faivre S, Target Oncol 2016;11(4):565-7

REAL WORLD DATA OF SORAFENIB: THE INTERNATIONAL PROSPECTIVE PHASE IV TRIAL GIDEON

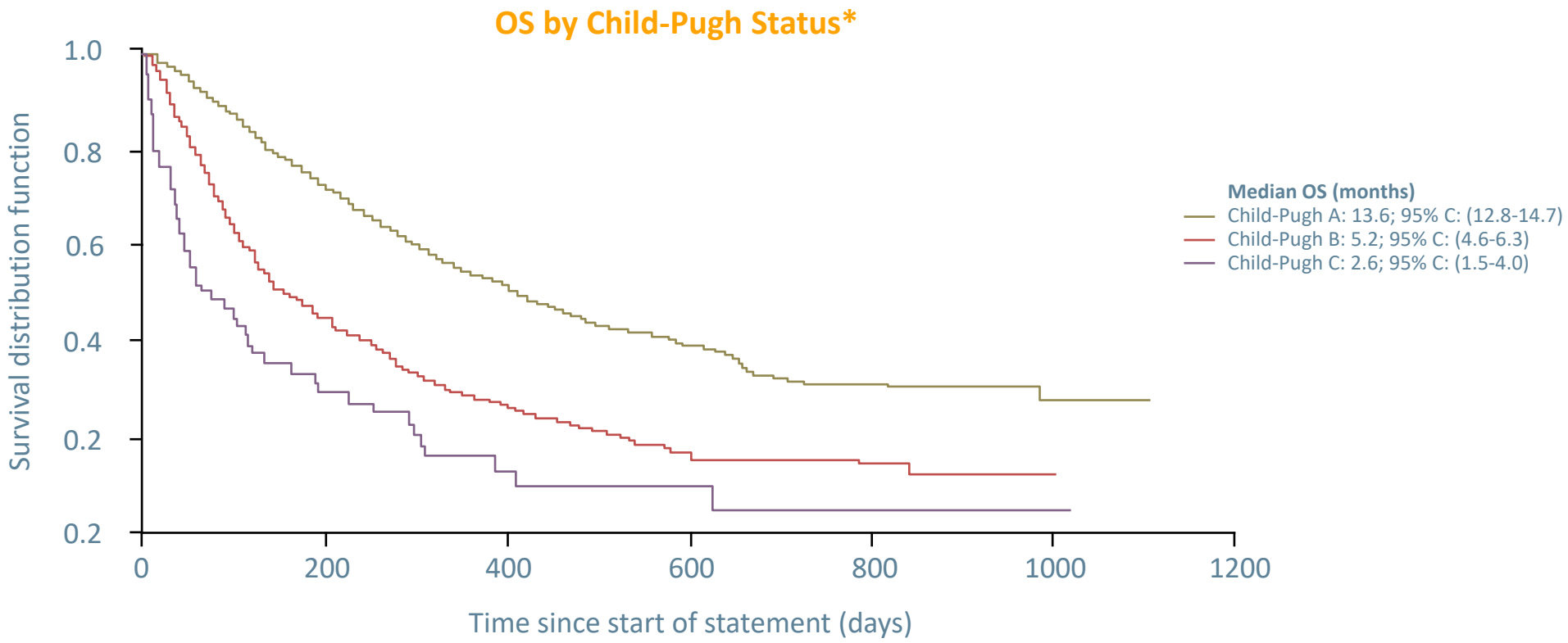
HCC connect® POWERED BY COR2ED

	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 400 mg	 1,415 (72) 482 (25)	 464 (70) 173 (26)	 46 (62) 21 (28)
Dose reduction rate, n (%)	**784 (40)**	**194 (29)**	**19 (26)**
AEs (All grades), n (%)	1,653 (84)	590 (89)	68 (92)
All grade 3 or 4 AEs, n (%)	**638 (33)**	**210 (32)**	**13 (18)**

Patients enrolled in Gideon trial (N =3371)
Safety population, n = 3202
Patients with known Child-Pugh, n = 2708

AEs, adverse events
Marrero J et al. J Hepatol. 2016;65(6):1140-1147

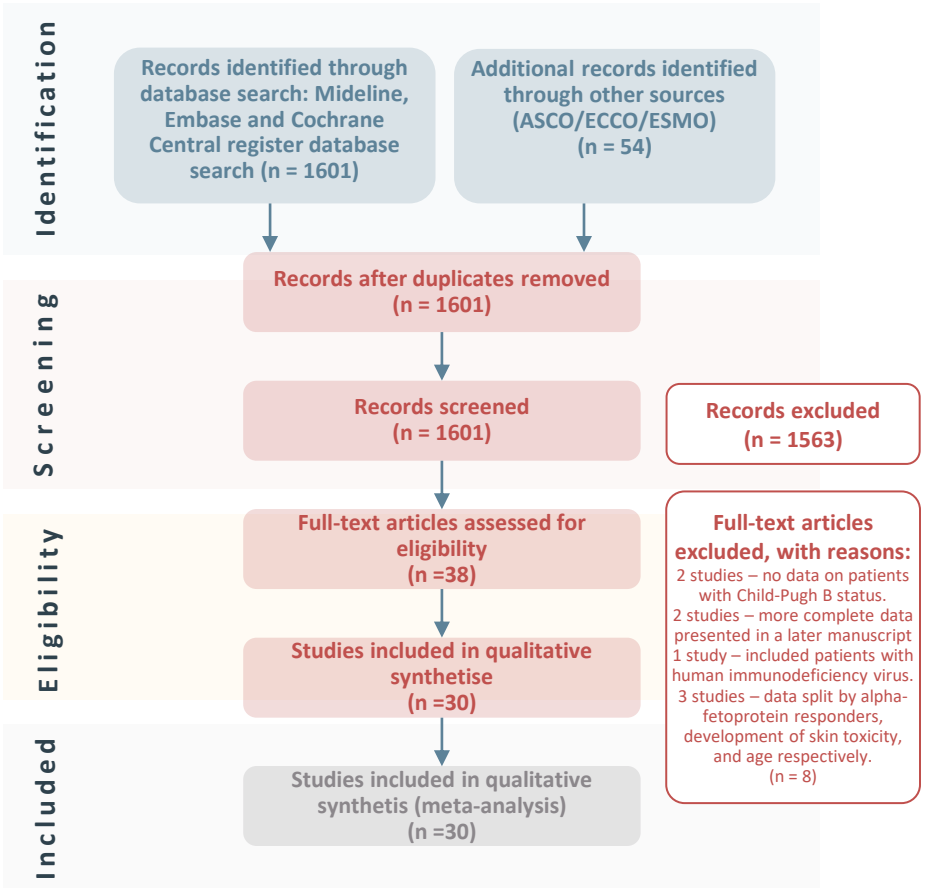
SORAFENIB RESULTS ACCORDING TO THE CHILD-PUGH SCORES: DATA FROM THE GIDEON STUDY



*Child-Pugh A: n=1975; Child-Pugh B: n=669; Child-Pugh C: n=73
OS, overall survival
Marrero J et al. J Hepatol. 2016;65(6):1140-1147

SORAFENIB AS FIRST-LINE IN CHILD-PUGH B – HCC PATIENTS: META-ANALYSIS RESULTS

HCC connect® POWERED BY COR2ED



Major pronostic factor, no added toxicities

Median OS under sorafenib In Child-B patients: 4.6 months

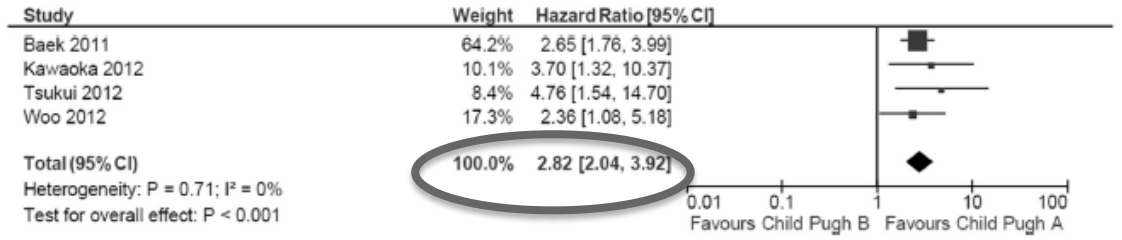


Table 3
Meta-regression for overall survival (all patients; univariable and multivariable analysis).

Variable	Univariable β (*P*)	Multivariable β (*P*)
Age	0.705 (0.001)	0.062 (0.78)
Proportion, male	−0.162 (0.52)	–
Proportion, hepatitis B	−0.687 (0.005)	−0.449 (0.08)
Proportion, hepatitis C	0.418 (0.12)	–
Proportion, ECOG PS2	−0.466 (0.08)	−0.382 (0.04)
Proportion, Child Pugh B	−0.731 (<0.001)	−0.705 (0.001)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 4
Meta-regression for treatment discontinuation and treatment-related death (all patients).

Variable	Treatment discontinuation β (*P*)	Treatment-related death β (*P*)
Age	−0.110 (0.71)	0.227 (0.67)
Proportion, male	0.135 (0.63)	0.559 (0.19)
Proportion, hepatitis B	0.186 (0.54)	−0.470 (0.42)
Proportion, hepatitis C	−0.466 (0.11)	−0.026 (0.97)
Proportion, ECOG PS2	−0.275 (0.39)	0.027 (0.96)
Proportion, Child Pugh B	−0.282 (0.31)	0.036 (0.94)

ECOG PS, Eastern Cooperative Oncology Group performance status.

McNamara, Eur J Cancer 2018;105:1-9

REAL-WORLD EFFECTIVENESS OF FIRST-LINE LENVATINIB FOR ADVANCED HCC

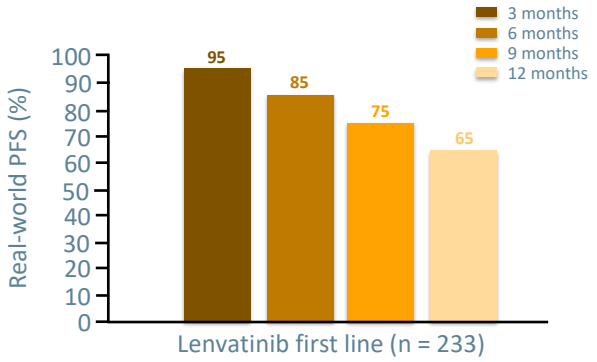
HCC connect® POWERED BY COR2ED

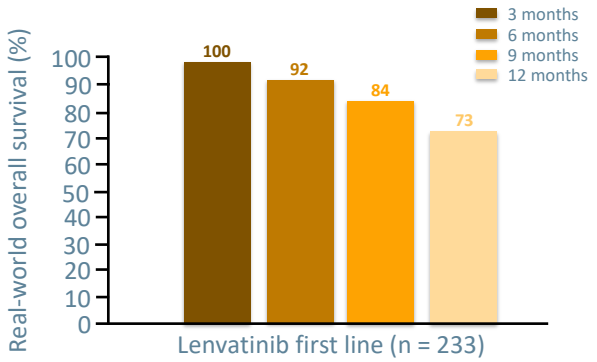
- Retrospective real-world study, 233 patients, median follow-up (9.1 months)

Patients characteristics	%
Race	
White	52.4
ECOG score, 1	63.1
BCLC stage	
A	11.2
B	28.8
C	43.8
D	8.2
Unknown	8.2
Child-Pugh class	
A	**44.6**
B	**39.1**
Etiology	
Hepatitis C	**36.1**
Alcohol related	**28.3**
Presence of portal thrombosis: VP4	**7.0**

Lenvatinib treatment characteristics	All patients (n = 233)	Child-Pugh A (n = 104)	Child-Pugh B (n = 91)
Dose reduction, %	9	7.7	8.8
Median duration of treatment, months	6.7	6.6	7.3
Subsequent lines, %	13.7	16.4	9.9
Complete or partial response, %			
	69.6*	**58.7**	**70.3**

* RECIST 1.1 available for 125 patients





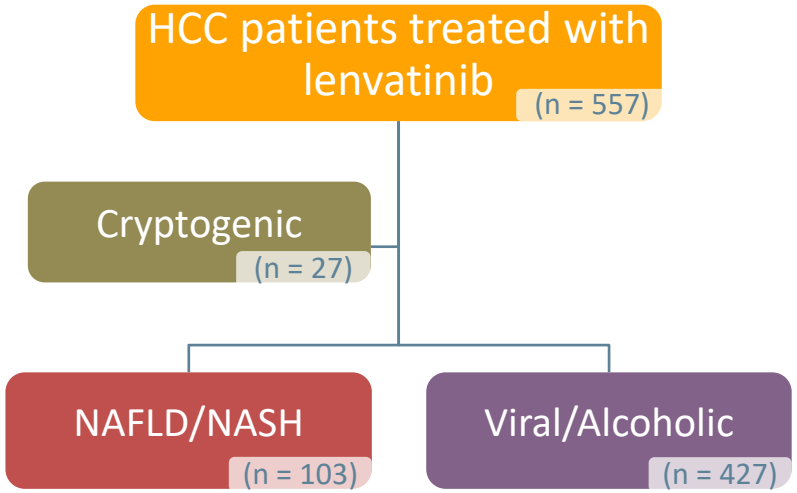
ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours; VP, grade of portal vein thrombosis

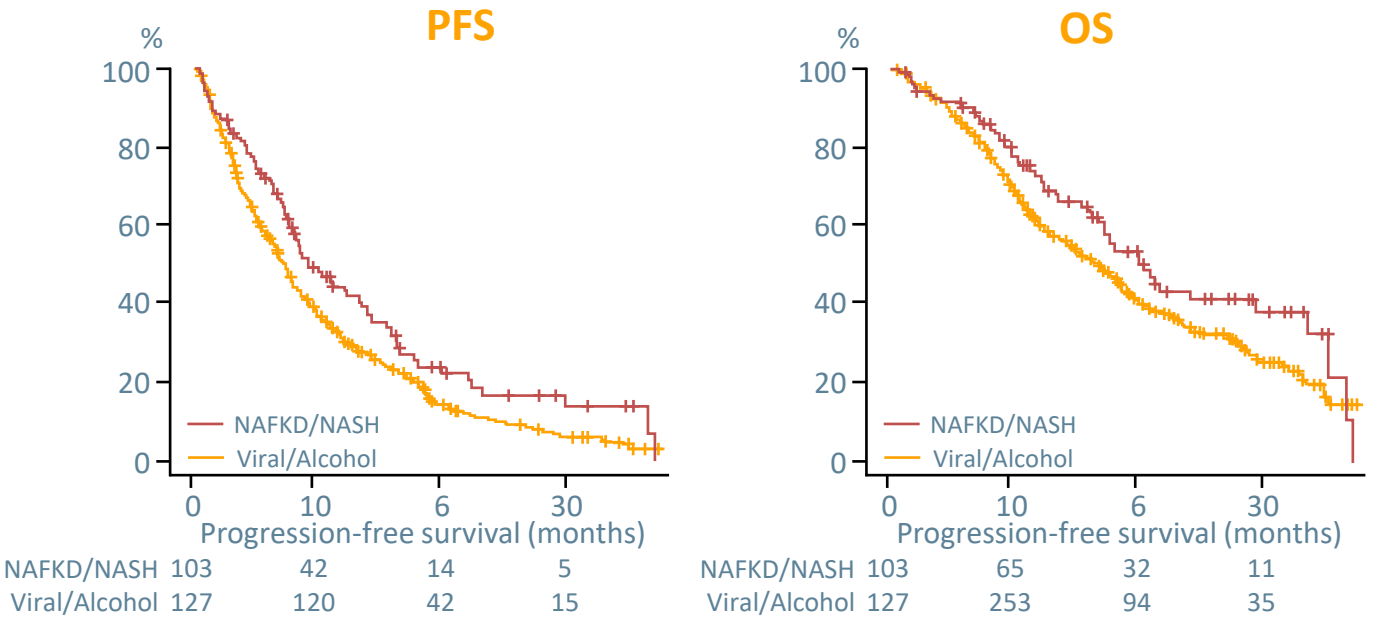
Singal A, et al. Future Oncol 2021; 17: 2759–68

THE REAL-LIFE PRACTICE EXPERTS FOR HCC (RELPEC) STUDY GROUP AND HCC: LENVATINB IN JAPANESE PATIENTS

HCC connect® POWERED BY COR2ED

- Efficacy of lenvatinib in patients with NAFLD/NASH-related unresectable-HCC





PFS : Progression-free survival, OS : overall survival

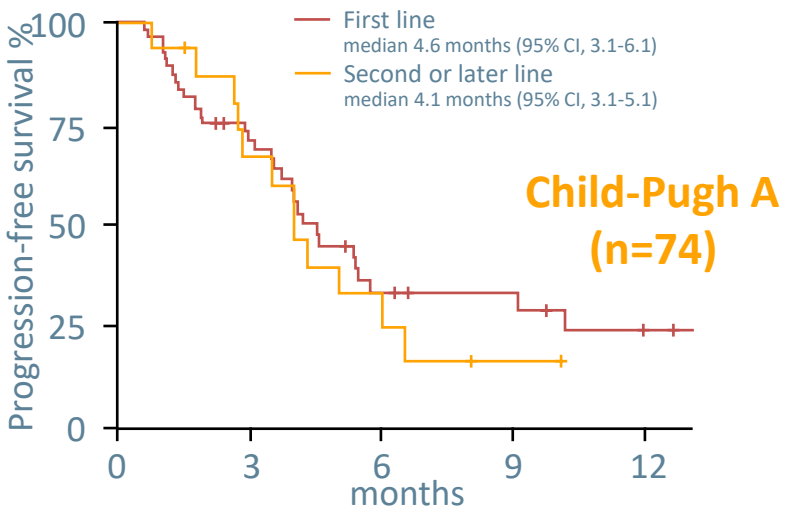
	NAFLD/NASH	Viral/Alcoholic	*p*
Median PFS	9.3 months, 95% CI 7.8–13.5	7.5 months, 95% CI 6.8–8.0	0.012
Median OS	20.5 months, 95% CI 16.8–29.5	16.9 months, 95% CI 14.5–18.6	0.057

Hiraoka A el al. Scientific Reports 2021;11(1):14474

REAL-WORLD EFFECTIVENESS OF LENVATINIB IN PATIENTS WITH ADVANCED HCC IN KOREAN PATIENTS

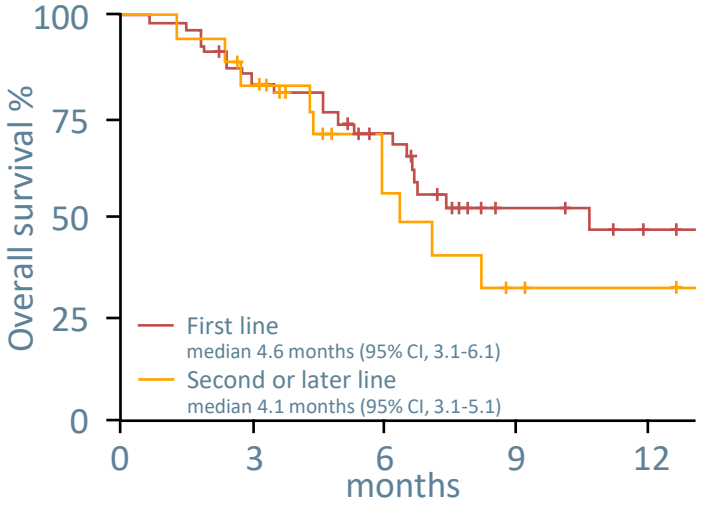
HCC connect® POWERED BY COR2ED

- 92 patients with advanced HCC treated with lenvatinib



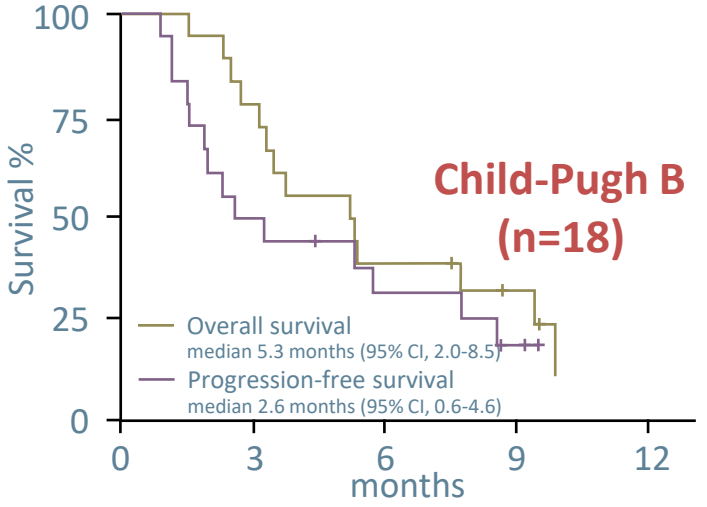
First line
median 4.6 months (95% CI, 3.1–6.1)

Second or later lines
median 4.1 months (95% CI, 3.1–5.1)



First line
median 10.7 months (95% CI, 4.8–16.5)

Second or later lines
median 6.4 months (95% CI, 5.1–7.7)



Overall survival
median 5.3 months (95% CI, 2.0–8.5)

Progression-free survival
median 2.6 months (95% CI, 0.6–4.6)

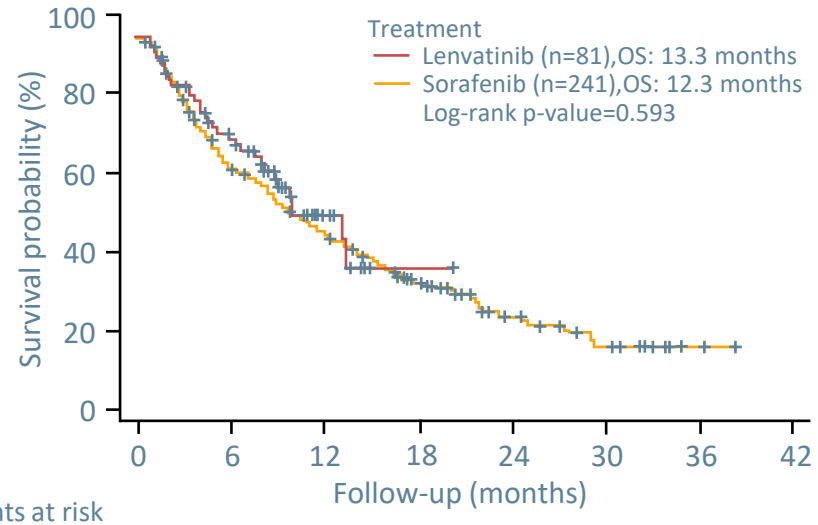
Cheon J et al. Liver Cancer 2020;9:613–624

REAL-WORLD LENVATINIB VERSUS SORAFENIB IN PATIENTS WITH ADVANCED HCC – OVERALL SURVIVAL

HCC connect® POWERED BY COR2ED

- 210 patients : (70 treated with Lenvatinib - 140 patients treated with Sorafenib)
- Propensity Score Matching Analysis

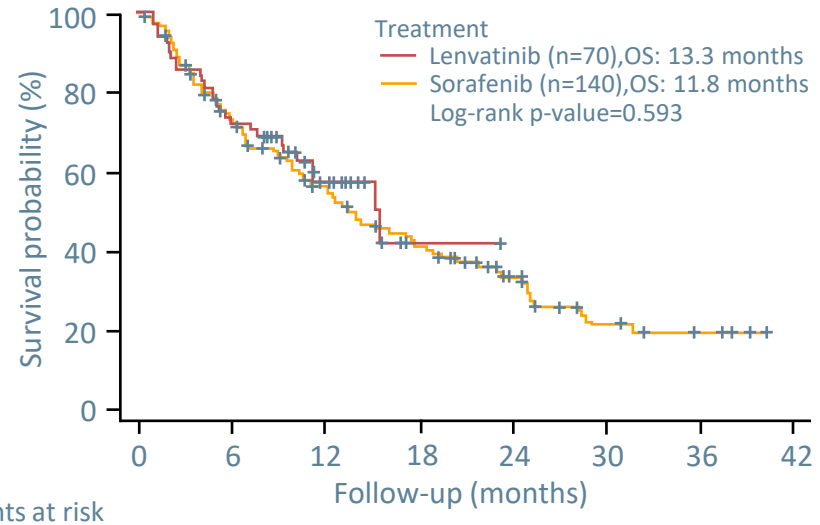
Before Propensity Score -matched



Patients at risk

Lenvatinib	81	53	12	1	-	-	-	-
Sorafenib	241	150	103	66	25	12	2	-

After Propensity Score-matched



Patients at risk

Lenvatinib	81	53	12	1	-	-	-	-
Sorafenib	241	150	103	66	25	12	2	-

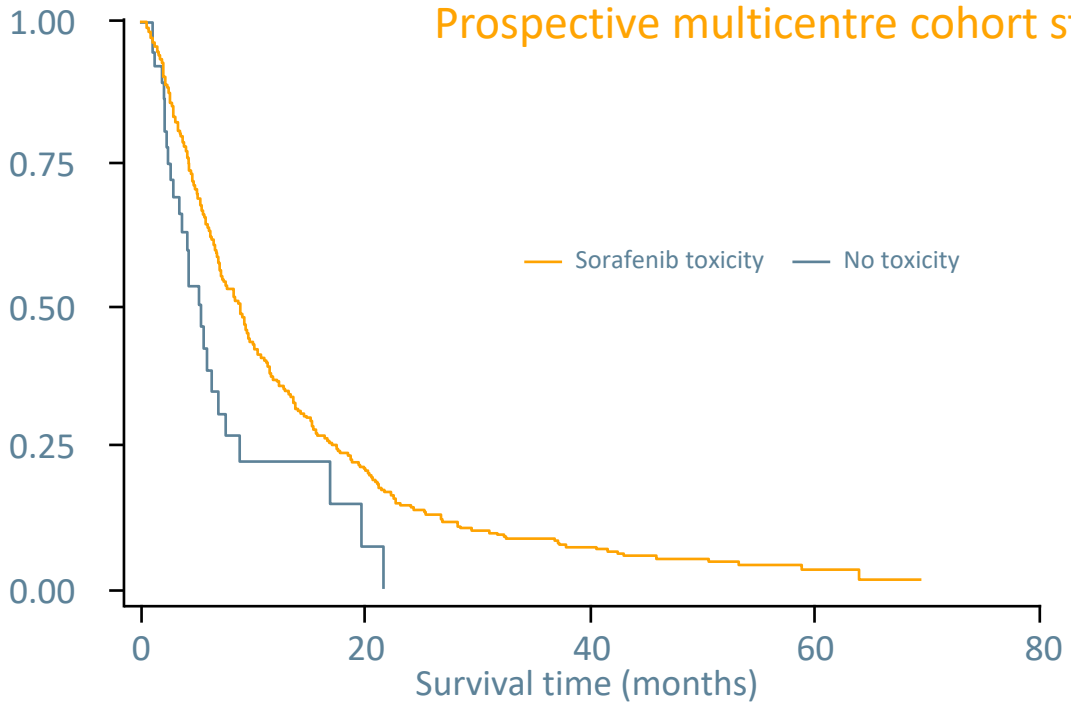
The Lenvatinib group had similar OS to the Sorafenib group, no matter for either before or after PS matching analysis

Kuo YH el al. Front. Oncol 2021;11:737767

EFFECT OF TOXICITY ON PROGNOSIS IN PATIENTS TREATED WITH SORAFENIB

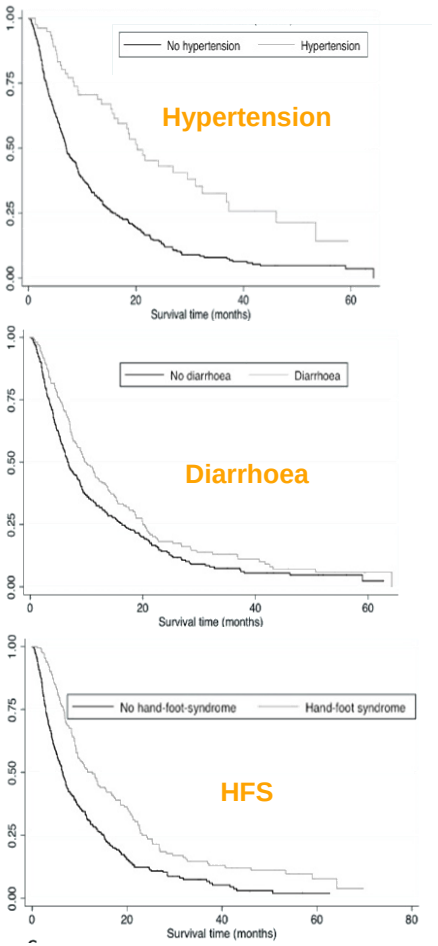
HCC connect® POWERED BY COR2ED

Prospective multicentre cohort study (n = 634)



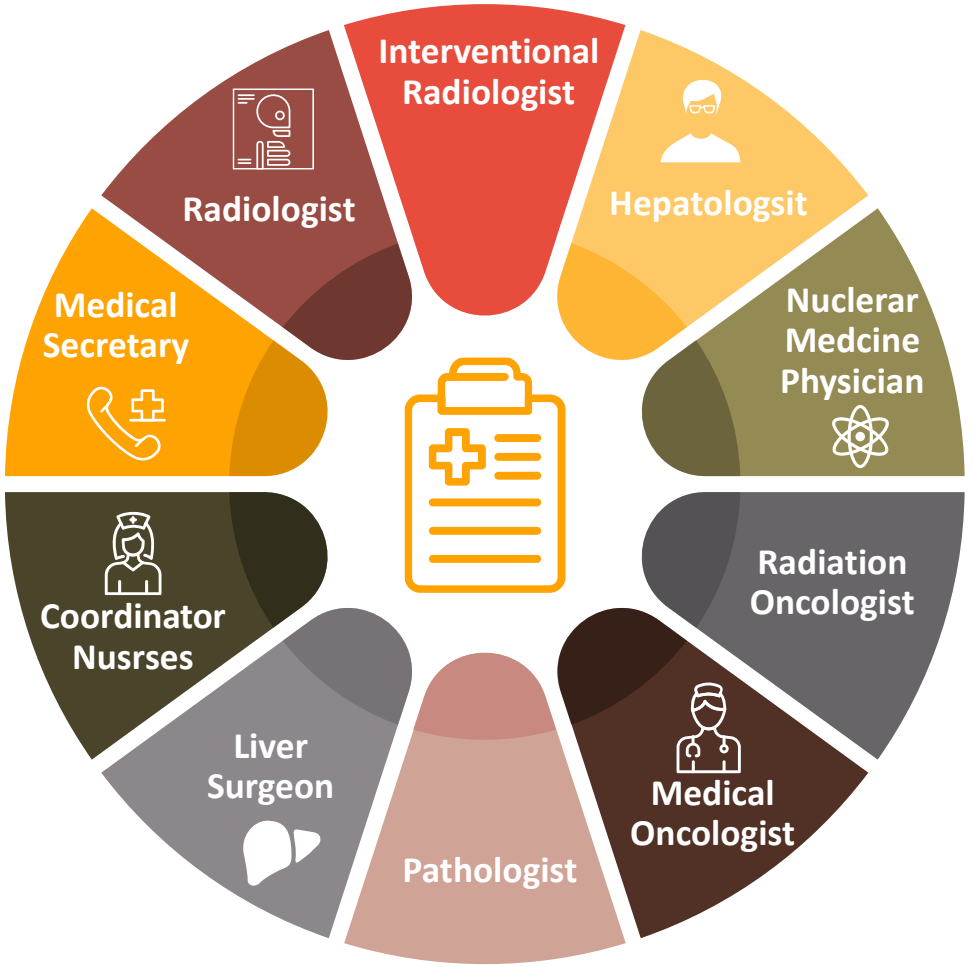
Survival between pts who developed sorafenib toxicity (any severity), compared with pts who did not develop sorafenib toxicity (8.8 months vs. 5.4 months)

Survival between pts who developed toxicity and pts who did not:
- hypertension (20.3 vs 7.0 months)
- diarrhoea (9.7 vs 6.7 months)
- and HFS (12.7 vs 6.4 months)



Howell J et al. Aliment Pharmacol Ther. 2017;45:1146–1155

MULTIDISCIPLINARY TUMOR BOARD



Multidisciplinary decision for individualized treatment decision and strategies

CONCLUSIONS

- Sorafenib and lenvatinib in the treatment of HCC patients, still have room in the therapeutic arsenal in patients with advanced hepatocellular carcinoma
  - Contraindications to atezolizumab and bevacizumab
  - Recurrence after liver transplantation
  - Patients preference (oral versus intravenous administration)
- Sorafenib and lenvatinib should be used in patients with well conserved liver function and preserved performance status
- Caution for patients Child Pugh B patients
- When, they are well selected, patients treated in the Real-world setting, benefit from sorafenib/lenvatinib as well as those treated in clinical trials
- Sides effects may reflect an appropriate dose-intensity, should be adequately managed, since they are frequently associated with better outcome
- Unmet need : to identify patients who are more likely to benefit from TKI rather than ICI in first line

TREATING PATIENTS WITH VEGFR-TKI MONOTHERAPY: WHAT ARE THE TREATMENT RELATED AEs AND HOW TO MANAGE THEM?

James J. Harding MD

Assistant Attending

Gastrointestinal Oncology Service

Early Drug Development Service

Department Of Medicine

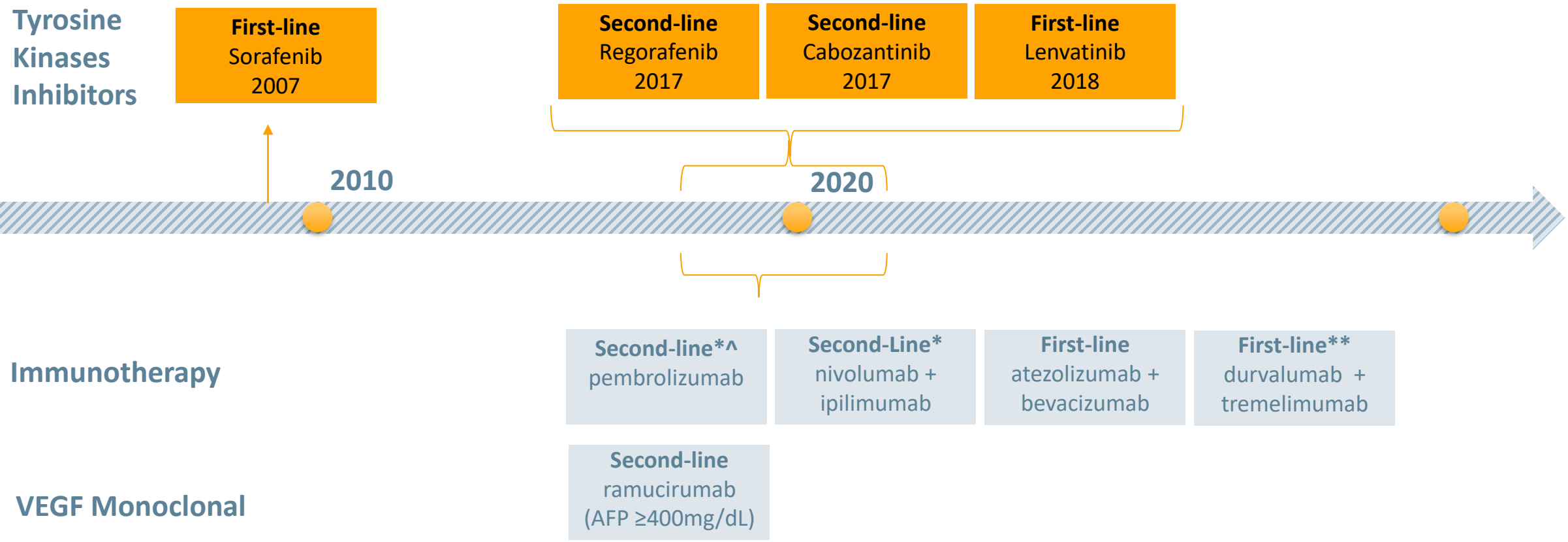
Memorial Sloan Kettering Cancer Centre, New York, USA

DISCLOSURES

- Research Support: Bristol Myers Squibb, Boehringer Ingelheim, Calithera, CytomX, Genoscience, Eli Lilly, Loxo Oncology, Novartis, Pfizer, Yiviva, Zymeworks
- Consulting Fees: Adaptiimune, Bristol Myers Squibb, CytomX, Eisai, Exelexis, Merck, QED, Zymeworks

RAPIDLY EVOLVING TREATMENT LANDSCAPE FOR ADVANCED HCC

HCC connect® POWERED BY COR2ED



FDA approval based on single arm Phase 2 with durable ORR; ^ 1 subsequent confirmatory Phase 3 NEGATIVE, 2nd confirmatory Phase 3 study POSITIVE; ** Top line positive

AFP, alpha-fetoprotein; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; ORR, objective response rate; VEGF, vascular endothelial growth factor

AVAILABLE TKI/ANTIANGIOGENICS FOR ADVANCED HCC PATIENTS

HCC connect® POWERED BY COR2ED

Treatment-naïve study population	sorafenib experienced study population
sorafenib SHARP // ASIA-PACIFIC[1]	regorafenib RESORCE[3]
lenvatinib REFLECT[2]	cabozantinib CELESTIAL[4]
Donafenib[6*]	ramucirumab REACH 1 and REACH 2[5] AFP ≥400 ng/dL

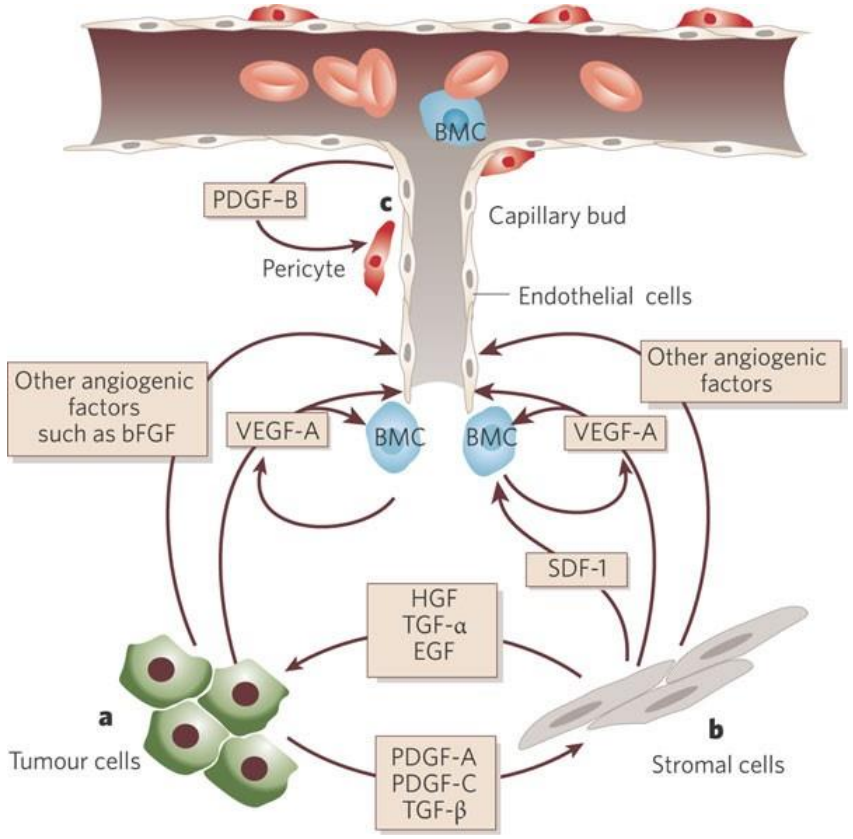
TKI, tyrosine kinase inhibitor

1. Lovett JM, et al. N Eng J Med. 2007;359:378-90; 2. Kudo M, et al. Lancet. 2018;391:1163-73; 3. Bruix J, et al. Lancet. 2017;389:56-66; 4. Abou-Alfa GK, et al. N Eng J Med. 2018;379:54-63; 5. Zhu AX, et al. Lancet. 2019;20:282-96; Qin et al. JCO; 2021; 39: 3002-3011.* Studied and approved in China, Apatinib has also demonstrated improve OS over BSC in second-line.

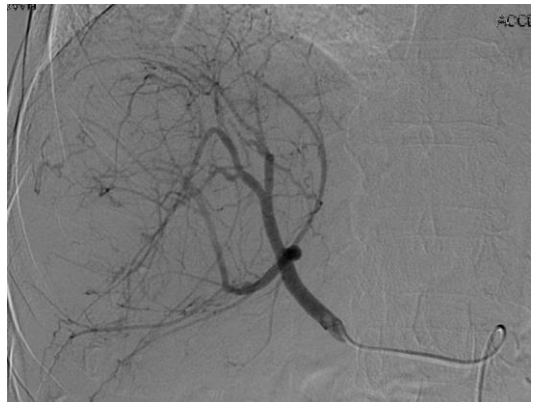
ANGIOGENESIS AS A THERAPEUTIC TARGET IN HCC

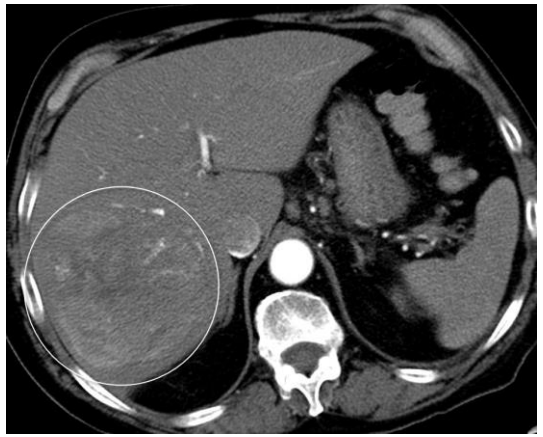
HCC connect® POWERED BY COR2ED

Neoangiogenesis is a hallmark of cancer



HCC is dependent on VEGF/VEGFR axis





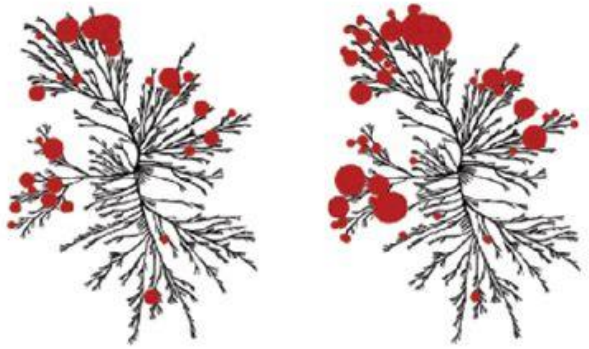
bFGF, basic fibroblast growth factor; BMC, bone marrow-derived angiogenic cells; EGF, epidermal growth factor; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; TGF-α, transforming growth factor alpha; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor

Adapted from Ferrara N and Kerbel RS. Nature. 2005;438:967-74

DRUG CLASS ADVERSE EFFECTS

- Dermatologic
- Cardiovascular
- Digestive
- Renal
- Haemorrhage

Variable frequency of adverse events given differential inhibition of various receptor tyrosine kinases inhibitors



Lovett JM, et al. N Eng J Med. 2007;359:378-90; Bruix J, et al. Lancet. 2017;389:56-66;

COMMON AEs OF ANTIANGIOGENIC TREATMENT IN HCC

HCC connect® POWERED BY COR2ED

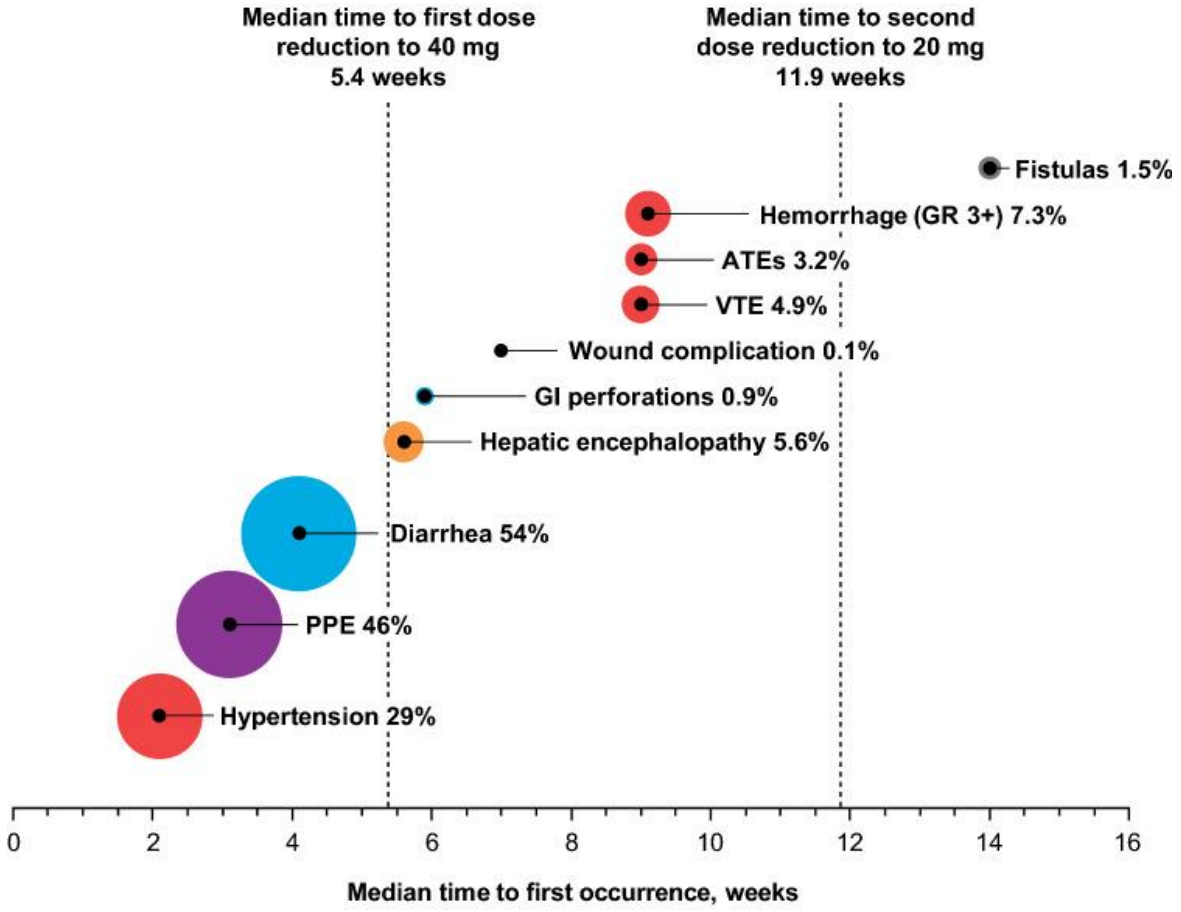
	Treatment Related Event	REFLECT[1] N = 475 (%)	REFLECT[1] N = 476 (%)	RESORCE[2] N = 374 (%)	CELESTIAL[3] N = 467 (%)	REACH-2[4] N = 197 (%)
		sorafenib	lenvatinib	regorafenib	cabozantinib	ramucirumab
	Any Grade	95	94	93	99	NR
	Grade ≥3	49	57	NR	68	NR
	Fatigue	25	30	29	45	14
	Weight Loss	22	31	7	17	NR
Dermatologic	Alopecia	25	3	NR	NR	NR
Dermatologic	Hand-Foot	52	27	52	46	NR
Dermatologic	Rash	16	10	NR	12	NR
GI	Anorexia	27	34	24	48	11
GI	Diarrhea	46	39	33	54	7
Vascular	HTN	30	42	23	29	16
	Proteinuria	11	25	NR	NR	14

GI, gastrointestinal; HCC, hepatocellular growth factor; HTN, hypertension

1. Kudo M, et al. Lancet. 2018;391:1163-73; 2. Bruix J, et al. Lancet. 2017;389:56-66; 3. Abou-Alfa GK, et al. N Eng J Med. 2018;379:54-63; 4. Zhu AX, et al. Lancet. 2019;20:282-96

TIME COURSE OF TKI ASSOCIATED AEs

cabozantinib



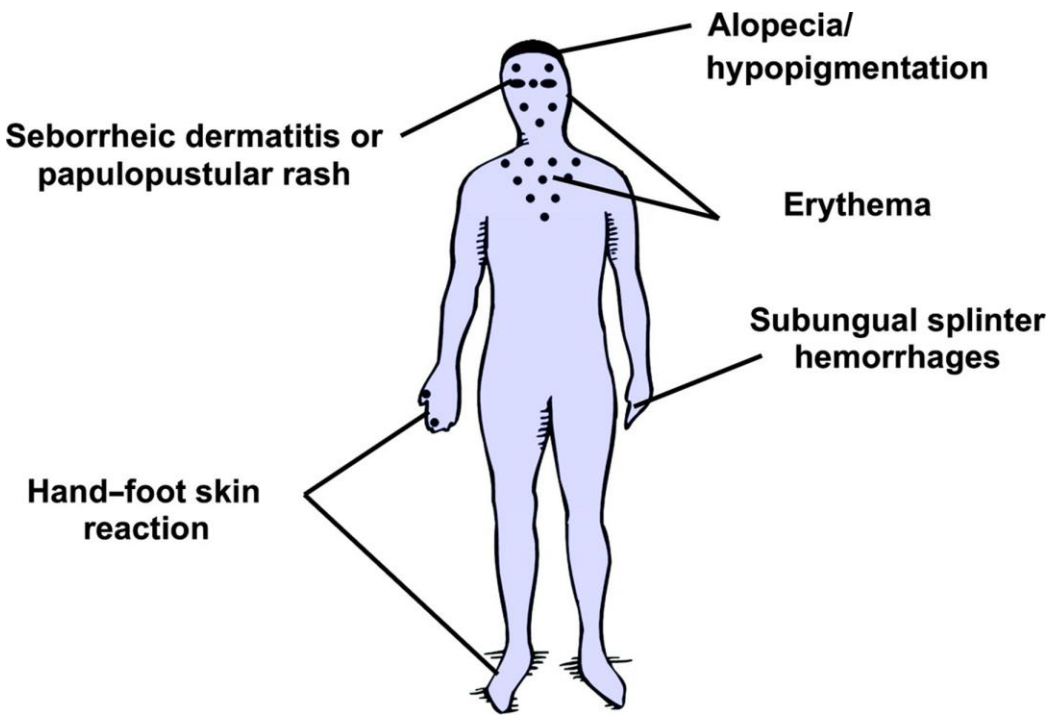
AE, adverse event; ATE, arterial thrombotic event; GI, gastrointestinal; GR, grade; HCC, hepatocellular carcinoma; PPE, palmar-plantar erythrodysesthesia; TKI, tyrosine kinase inhibitor; VTE, venous thrombotic event

Schwartz G, et al. Target Oncol. 2020;15:549-65

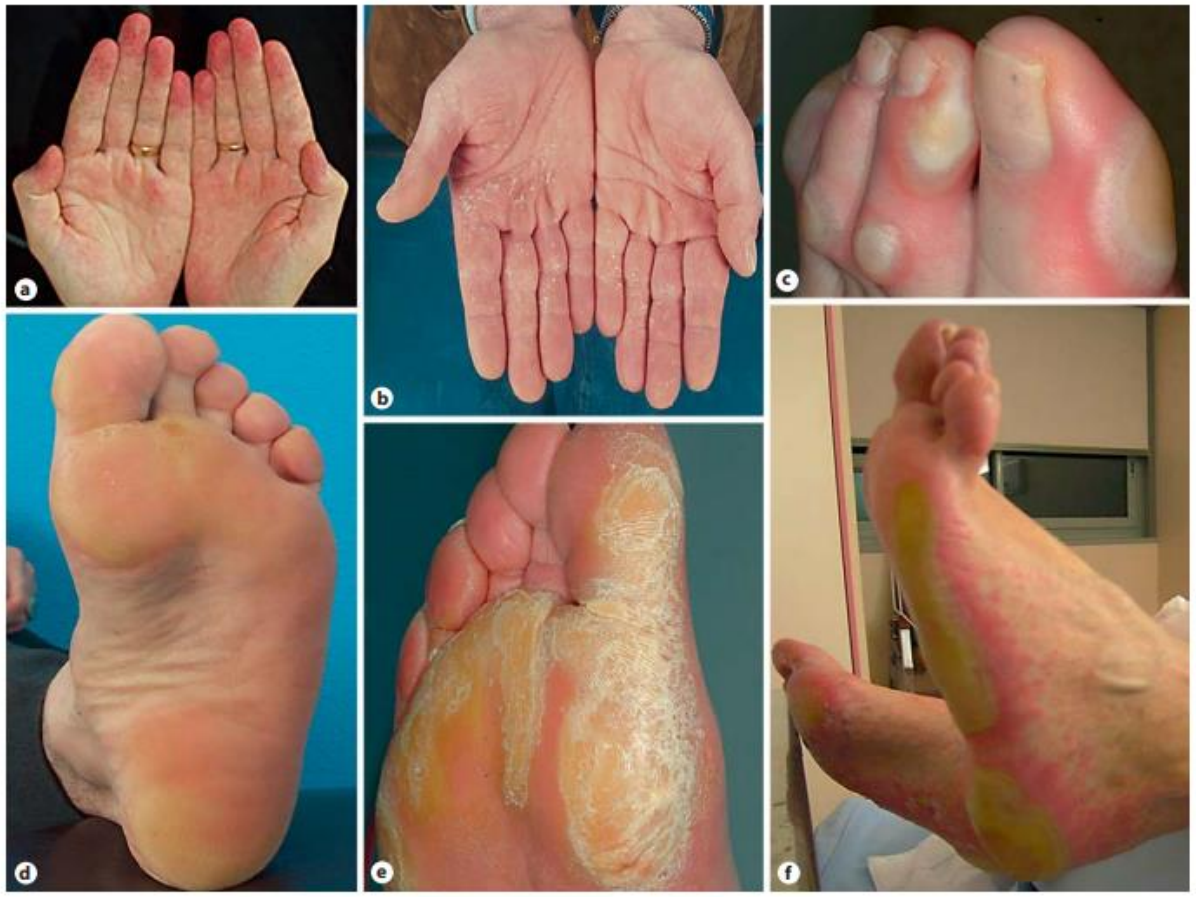
TKI-ASSOCIATED DERMATOLOGIC TOXICITY

HCC connect® POWERED BY COR2ED

Common dermatological toxicitities associated with TKIs[1]



Hand Foot Skin Reaction[2]



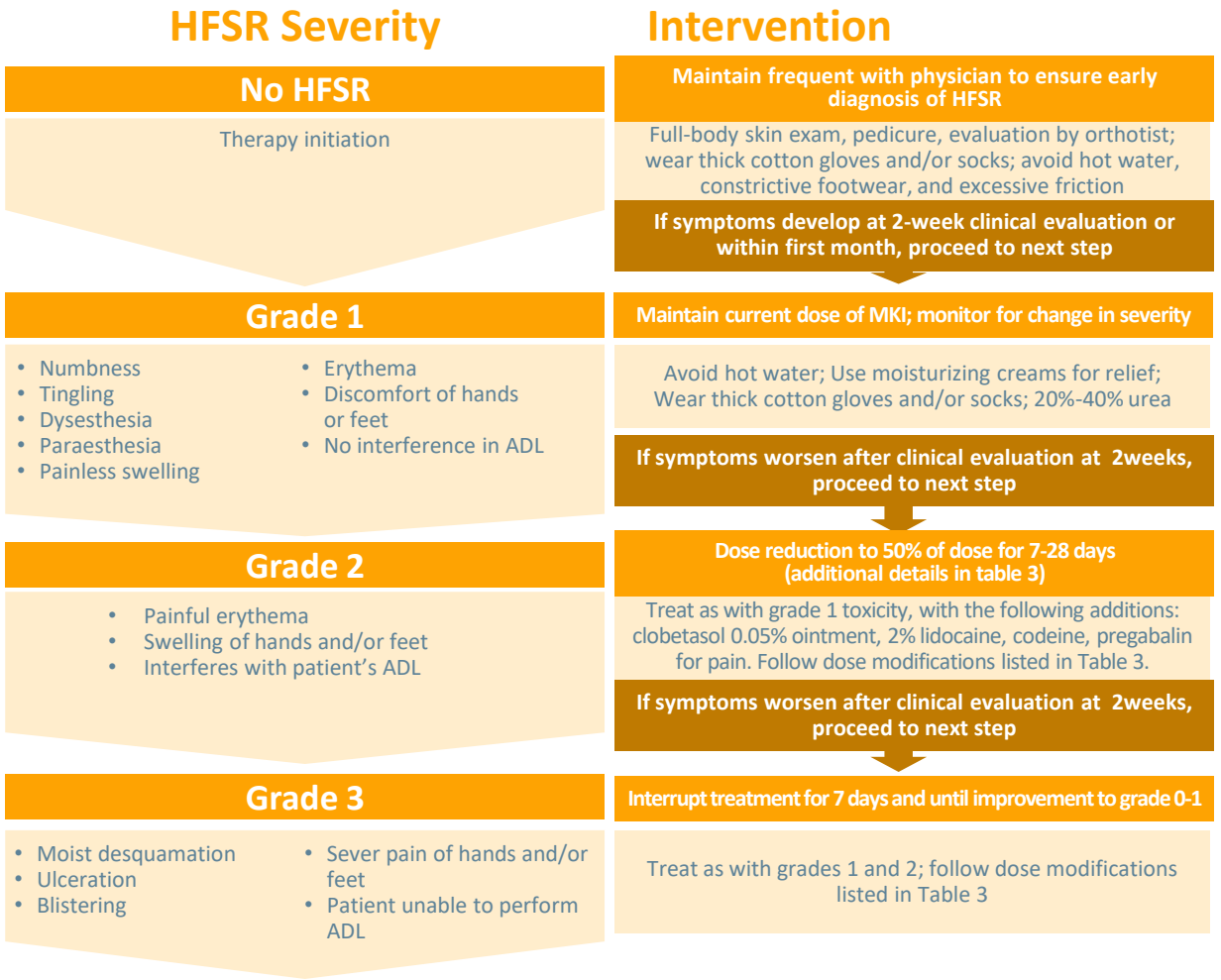
Time to onset: 2-4 weeks

TKI, tyrosine kinase inhibitor

1. Lacouture ME, et al. Oncologist. 2008;13:1001-11; 2. Lipworth AD, et al. Oncology. 2009;77:257-71

KEY MANAGEMENT OPTIONS

- Prophylaxis
- Lifestyle Modification
- Keratolytic Agents
- Corticosteroids
- Topical Analgesia
- Systemic Analgesia
- Dose Reduction



ADL, activities of daily living; HFSR, hand-foot skin reaction; NSAID, non-steroidal anti-inflammatory drug

1. Lacouture ME, et al. Oncologist. 2008;13:1001-11

PROPHYLACTIC EFFECT OF UREA-BASED CREAM ON SORAFENIB-ASSOCIATED HFSR

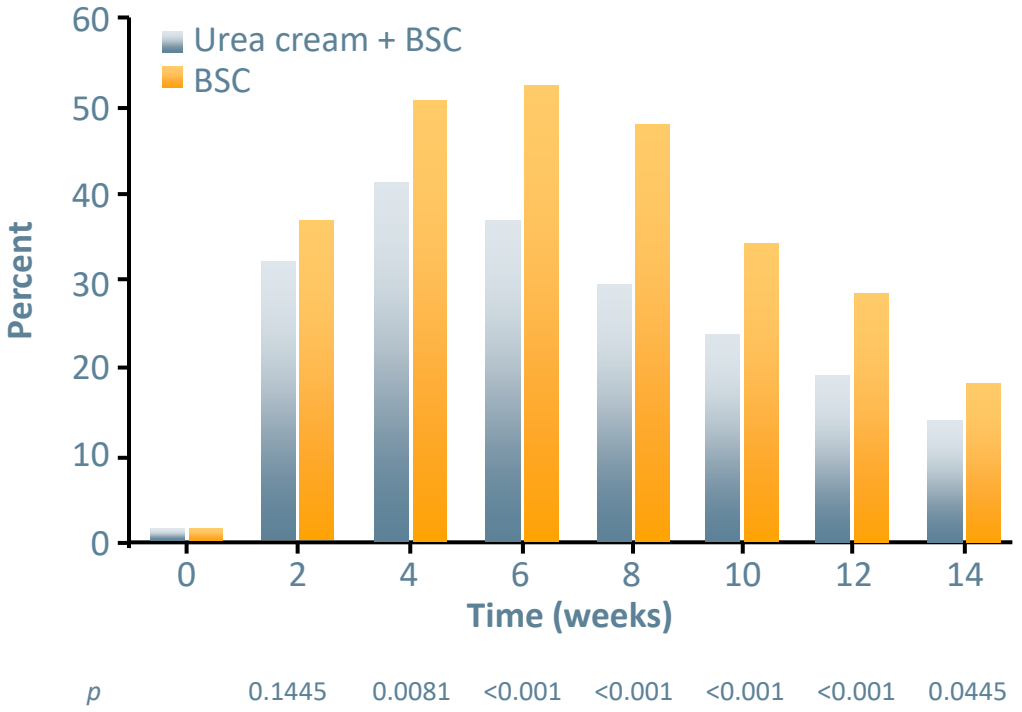
HCC connect® POWERED BY COR2ED

Randomized Controlled Trial of the Prophylactic Effect of Urea-Based Cream on Sorafenib-Associated Hand-Foot Skin Reactions in Patients With Advanced Hepatocellular Carcinoma

ZhengGang Ren, KangShun Zhu, HaiYan Kang, MinQiang Lu, ZengQiang Qu, LiGong Lu, TianQiang Song, WeiPing Zhou, Hui Wang, WeiZhu Yang, Xuan Wang, YongPing Yang, LeHua Shi, YuXian Bai, XiaoFeng Guo, and Sheng-Long Ye

Randomized, **open-label**
N = 871 patients with advanced HCC treated with sorafenib
10% Urea cream TID + BSC (BSC; n = 439)
BSC alone excluding all creams (n = 432),

Prevalence of any-grade hand-foot skin reaction



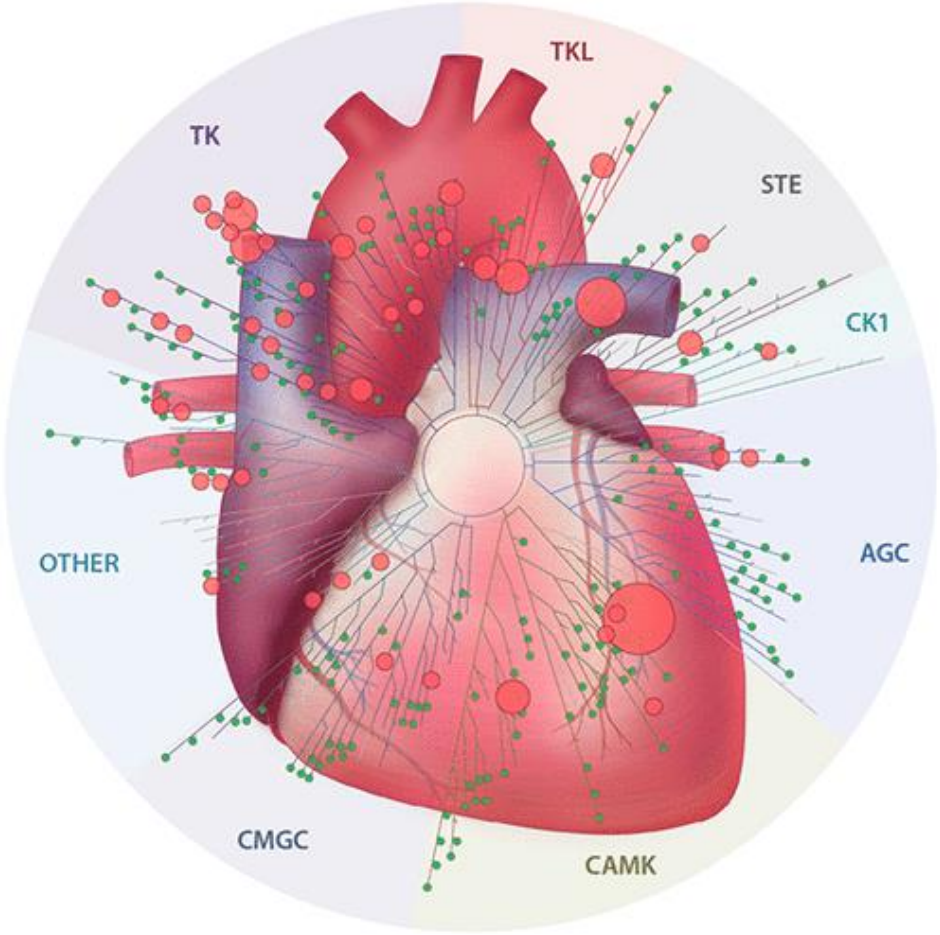
BSC, best supportive care; HCC, hepatocellular carcinoma; HFSR, hand-foot skin reaction; TID, three times per day

Ren Z, et al. J Clin Oncol. 2015;33:894-900

TKI ASSOCIATED CARDIOVASCULAR COMPLICATIONS

HCC connect® POWERED BY COR2ED

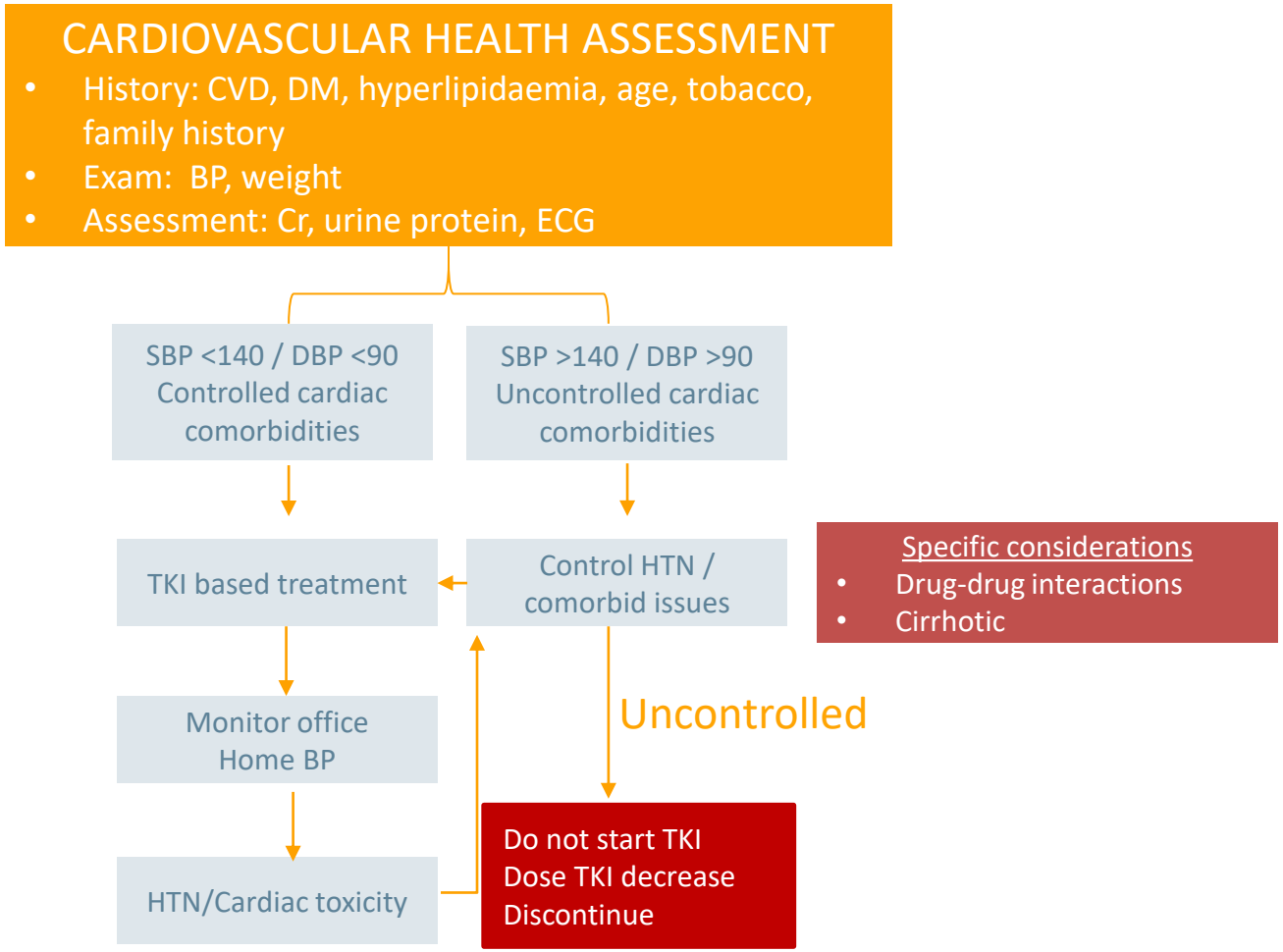
- **Hypertension**
- QTc prolongation
- Arrhythmia
- Myocardial infarction/ischaemia
- Cardiomyopathy/LV dysfunction
- CVA
- PRES



AGC, PKA, PKG, and PKC kinases; CAMK, Ca2+/calmodulin-dependent protein kinase; CK1, casein kinase 1; CMGC, containing CDK, MAPK, GSK3, CLK families; CVA, cerebrovascular accident; LV, left ventricle; PRES, posterior reversible encephalopathy syndrome; QTc, corrected QT; STE, serine-threonine kinase; TK, tyrosine kinase; TKI, tyrosine kinase inhibitor; TKL, tyrosine kinase-like

Lamore SD, et al. Chem Res Toxicol. 2020;33:125-36; Force T, et al. Nat Rev Cancer. 2007;7:332-44

MANAGEMENT CONSIDERATIONS



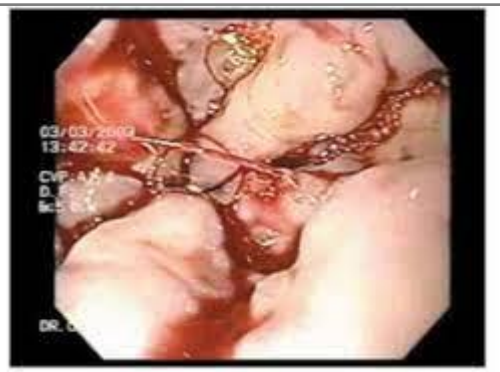
BP, blood pressure; Cr, creatinine; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiogram; DM, diabetes mellitus; HTN, hypertension; SBP, systolic blood pressure; TKI, tyrosine kinase inhibitor

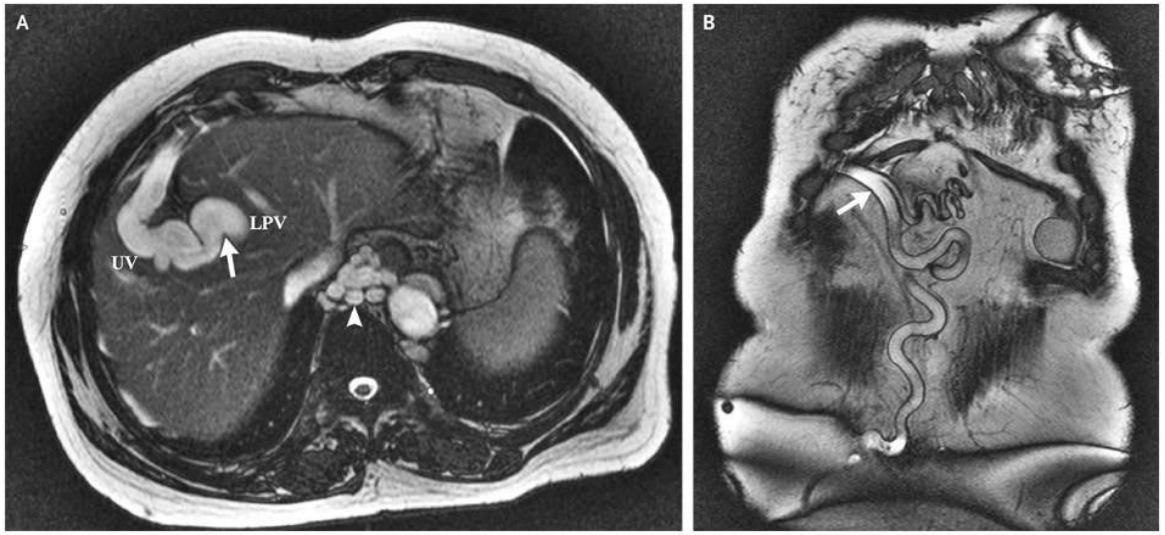
Adapted from Agarwal et al. Curr. Oncol. Rep. 2018 Jun 21;20(8):65

TREATMENT-EMERGENT BLEEDING WITH TKIs

	Grade ≥3*
lenvatinib	2-5%
cabozantinib	5%
sorafenib	1-2.4%
regorafenib	3%
ramucirumab	2-5%

HCC patients may be at risk for bleeding





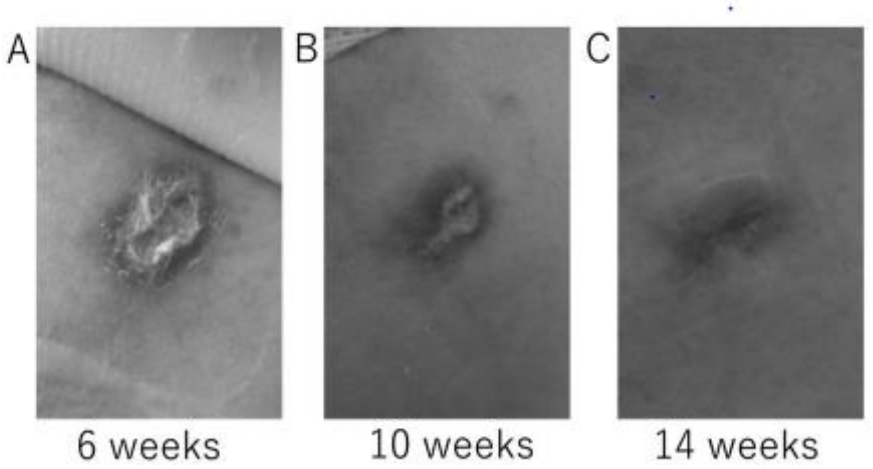
HCC, hepatocellular carcinoma

*Rates FDA Package Insert for each agent. Grade ≥ 3 haemorrhagic events across cancer types.
Images sources: Torrazza-Perez et al. N Engl J Med. 2010;362(5):e13; Young et al. N Engl J Med 2007; 357:e17

DELAYED WOUND HEALING, PERFORATION, OR FISTULA

Drug	Activity	Half-life
regorafenib	VEGFR1-3, KIT, PDGFR, FGFR, RAF, RAS, RET	~24 hours
sorafenib	VEGFR1-3, KIT, PDGFR, RAF, RAS	~28 hours
lenvatinib	VEGFR1-3, PDGFRα, FGFR, KIT, RET	~35 hours
cabozanentib	MET, VEGFR-1-3, AXL	~4 days
ramucirumab	VEGFR-2	8 days
bevacizumab	VEGF-A	20 days

Delayed wound healing in a patient with a thoracic drain placed for pneumothorax*



*Extent of healing at 6, 10 and 14 weeks after removal of the catheter

PIGF, placenta growth factor; VEGF, vascular growth factor; VEGFR, vascular growth factor receptor

Adapted from Toda S, et al. Mol Clin Oncol. 2021;14:81,

GASTROINTESTINAL TOXICITY WITH TKI

HCC connect® POWERED BY COR2ED

- Dysgeusia
- Stomatitis
- Anorexia
- Weight loss
- Nausea/Vomiting
- Diarrhea
- Hepatic dysfunction

Agent	Diarrhea	
	Any Grade	Grade ≥3
lenvatinib[1]	49%	6%
cabozantinib[2]	62%	10%
sorafenib[3]	55%	10%
regorafenib[4]	41%	3%
ramucirumab[5]	15%	1%

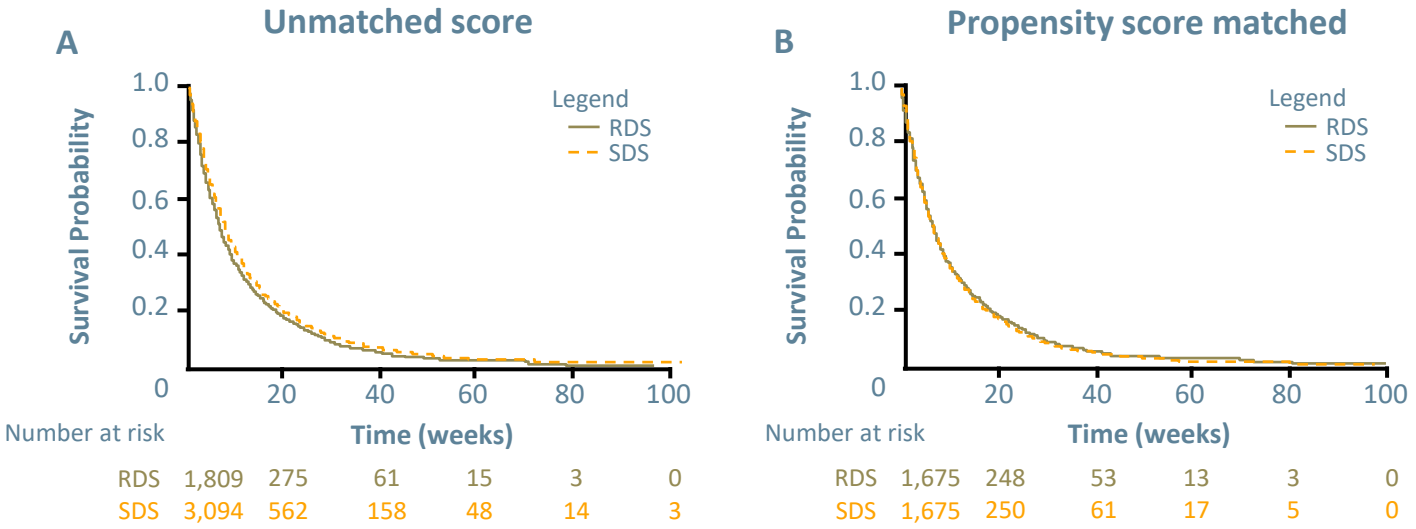
1. Kudo M, et al. Lancet. 2018;391:1163-73; 2. Abou-Alfa GK, et al. N Eng J Med. 2018;379:54-63; 3. Lovett JM, et al. N Eng J Med. 2007;359:378-90; 4. Bruix J, et al. Lancet. 2017;389:56-66; 5. Zhu AX, et al. Lancet. 2019;20:282-96;

INVESTIGATIONAL DOSE TITRATIONS OR DOSE ATTENUATION STRATEGIES

HCC connect® POWERED BY COR2ED

Starting Dose of Sorafenib for the Treatment of Hepatocellular Carcinoma: A Retrospective, Multi-Institutional Study

Kim A. Reiss, Shun Yu, Ronac Mamtani, Rajni Mehta, Kathryn D'Addeo, E. Paul Wileyto, Tamar H. Taddei, and David E. Kaplan



Reasons for sorafenib cessation after propensity score matching

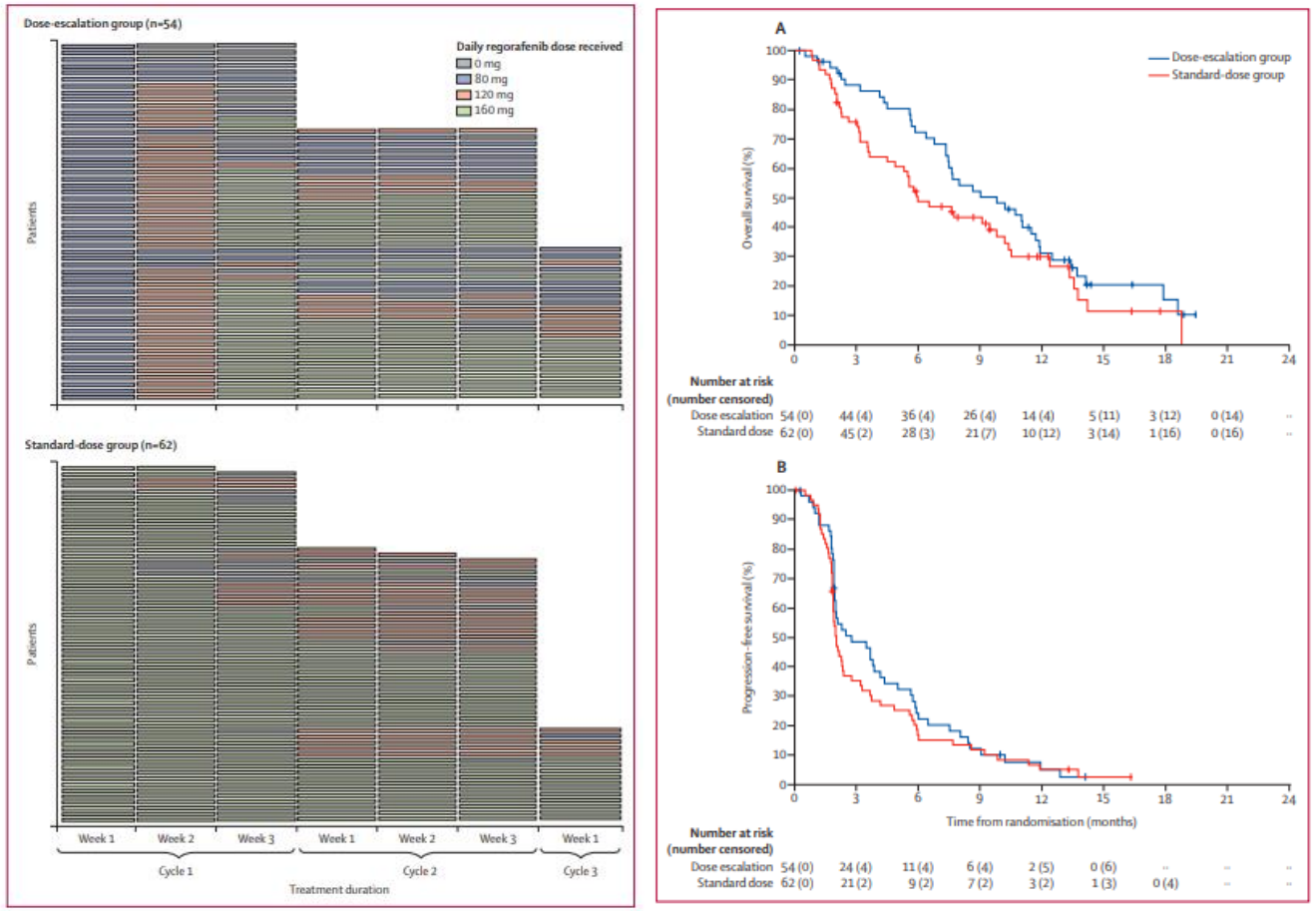
Reason for sorafenib cessation	SDS (n = 1,675)	RDS (n = 1,675)	*p*
Any adverse event	375 (22.4)	329 (19.6)	0.056
GI adverse effects	180 (10.75)	145 (8.66)	0.047
Hand-foot skin reaction	75 (4.48)	55 (3.28)	0.088
Fatigue	83 (4.96)	102 (6.09)	0.172

NOTE: Data are presented as No. (%)

GI, gastrointestinal; RDS, reduced starting dose; SDS, standard starting dose

Reiss KA, et al. J Clin Oncol. 2017;35:3575-81

EXAMPLE OF PROSPECTIVE DOSE TITRATION STRATEGY IN COLORECTAL CANCER WITH REGORAFENIB



Bekaii-Saab et al. Lancet Oncology 2019

CONCLUSIONS

- Multiple antiangiogenic treatments extend overall survival in the first and second-line for patients with advanced HCC
- Spectrum of adverse events for VEGFR TKI based treatment is well characterized
- Common class effect adverse events include fatigue, weight loss, diarrhoea, hand foot syndrome, hypertension
- Multiple management guidelines are in place to prevent or mitigate toxicity
- Dose titration strategies and up front dose attenuation remain investigational in nature in advanced HCC population

HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

LATEST UPDATES IN HCC FROM ASCO GI 2022

- HIMALAYA STUDY

- KN 394 TRIAL

- LAUNCH STUDY

Dr. Su Pin Choo

Medical Oncologist, Curie Oncology Singapore,
National Cancer Centre Singapore

HIMALAYA STUDY DESIGN

HCC connect® POWERED BY COR2ED

HIMALAYA was an open-label, multicenter, global, Phase 3 trial

Single priming dose of Tremelimumab

Study population

- Patients aged ≥18 years with uHCC
- BC:C stage B (not eligible for locoregional therapy) and stage C
- No prior systemic therapy
- ECOG PS –1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

R

N=1,324

STRIDE (n=393)
Tremelimumab 300 mg x 1 dose + durvalumab 1500 mg Q4W*

durvalumab (n=389)
Durvalumab monotherapy 1500 mg Q4W*

sorafenib (n=476)
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

T75+D (n=153): *arm closed*†
Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

Stratification factors

- Macrovascular invasion: yes vs no
- Etiology of liver disease: HBV vs HCV vs others
- Performance status: ECOG 0 vs 1

* Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease continue treatment. † The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation. BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks; STRIDE, Single Tremelimumab Regular Intervl Durvalumab

HIMALAYA OBJECTIVES AND STATISTICAL DESIGN

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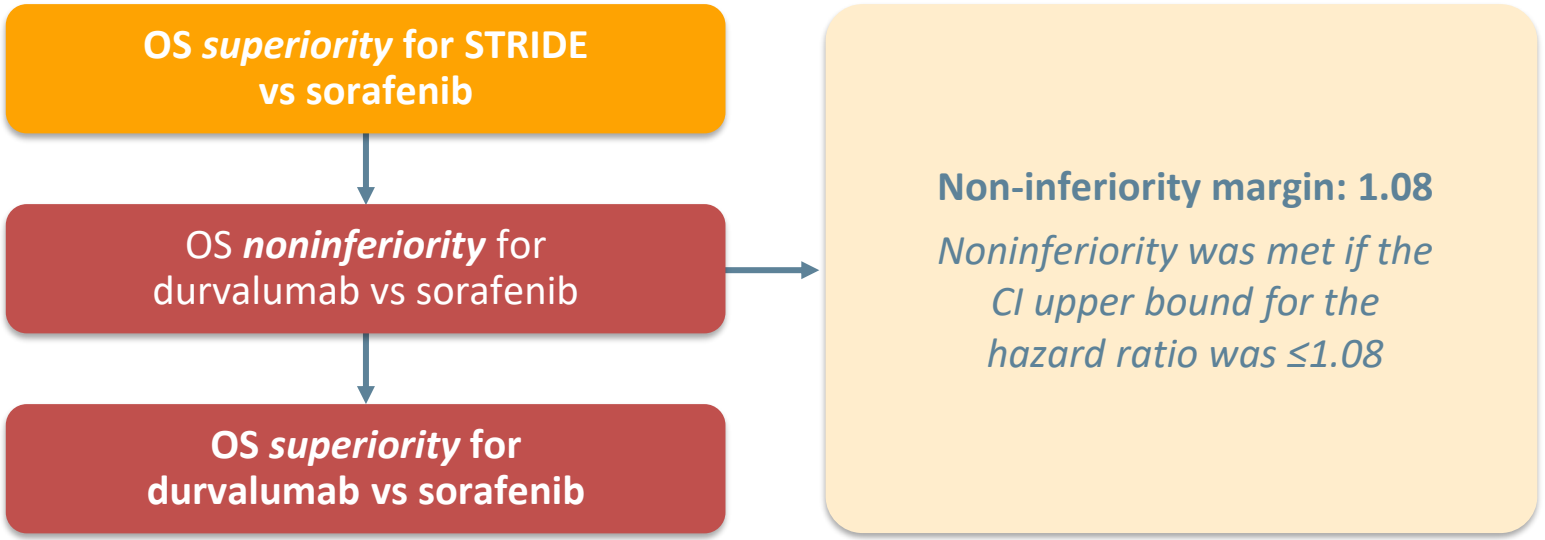
Multiple testing procedure

Primary objective
- OS for STRIDE vs sorafenib

Key secondary objective
- OS for durvalumab vs sorafenib

Additional secondary objectives
- PFS, ORR and DoR as assessed by investigator per RECIST v1.1
- Safety



CI, confidence interval; DoR, duration of response; ORR, objective response rate; OR, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; STRIDE, Single Tremelimumab Regular Interval Durvalumab

BASELINE CHARACTERISTICS

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Characteristic	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Male sex, n (%)	327 (83.2)	323 (83.0)	337 (86.6)
Median age (range), years	65.0 (22-86)	64.0 (20-86)	64.0 (18-88)
Region, n (%)			
Asia (excluding Japan)	156 (39.7)	167 (42.9)	156 (40.1)
Rest of world (including Japan)	237 (60.3)	222 (57.1)	233 (59.9)
Viral etiology,*,† n (%)			
HBV	122 (31.0)	119 (30.6)	119 (30.6)
HCV	110 (28.0)	107 (27.5)	104 (26.7)
Nonviral	161 (41.0)	163 (41.9)	166 (42.7)
ECOG PS, n (%)			
0	244 (62.1)	237 (60.9)	241 (62.0)
1	148 (37.7)	150 (38.6)	147 (37.8)
MVI,† n (%)	103 (26.2)	94 (24.2)	100 (25.7)
EHS,† n (%)	209 (53.2)	212 (54.5)	203 (52.5)
PD-L1 positive, n (%)	148 (37.7)	154 (39.6)	148 (38.0)
AFP ≥400 ng/ml,† n (%)	145 (36.9)	137 (35.2)	124 (31.6)

Biomarker evaluable samples were collected for all but 20 patients across all treatment arms

* HBV: patients who tested positive for HBsAg or anti-HBc with detectable HBV DNA; HCV: patients who tested positive for HCV or had history of HCV infection; Nonviral: no active viral hepatitis identified.
† Determined at screening

AFP, alfa-fetoprotein; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI macrovascular invasion; PD-L1, programmed cell death ligand-1; PS, performance status; STRIDE, Single Tremelimumab Regular Interval Duravalumab

SUBSEQUENT ANTICANCER THERAPIES

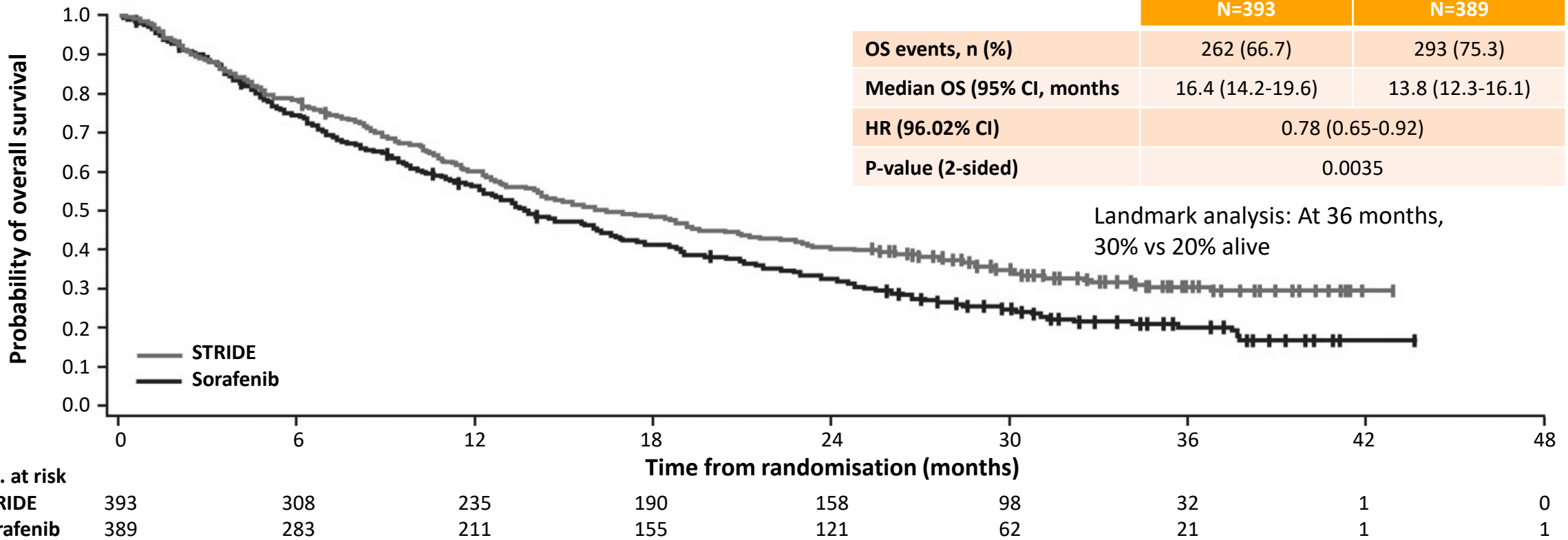
Subsequent therapy type,* n (%)	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Any therapy	160 (40.7)	168 (43.2)	175 (45.0)
Immunotherapy	15 (3.8)	20 (5.1)	89 (22.9)
Cytotoxic chemotherapy	20 (5.1)	18 (4.6)	25 (6.4)
Targeted therapy	147 (37.4)	155 (39.8)	108 (27.8)
Antiangiogenic therapy	11 (2.8)	20 (5.1)	19 (4.9)
Homeopathic therapy	0	1 (0.3)	2 (0.5)
Other	3 (0.8)	1 (0.3)	9 (2.3)

* Includes anticancer therapies received post discontinuation of study treatment. Patients may have taken ≥1 subsequent therapy

STRIDE, Single Tremelimumab Regular Interval Duravalumab

PRIMARY OBJECTIVE: OVERALL SURVIVAL FOR STRIDE VS SORAFENIB

	STRIDE N=393	Sorafenib N=389
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI, months	16.4 (14.2-19.6)	13.8 (12.3-16.1)
HR (96.02% CI)	0.78 (0.65-0.92)	
P-value (2-sided)	0.0035	

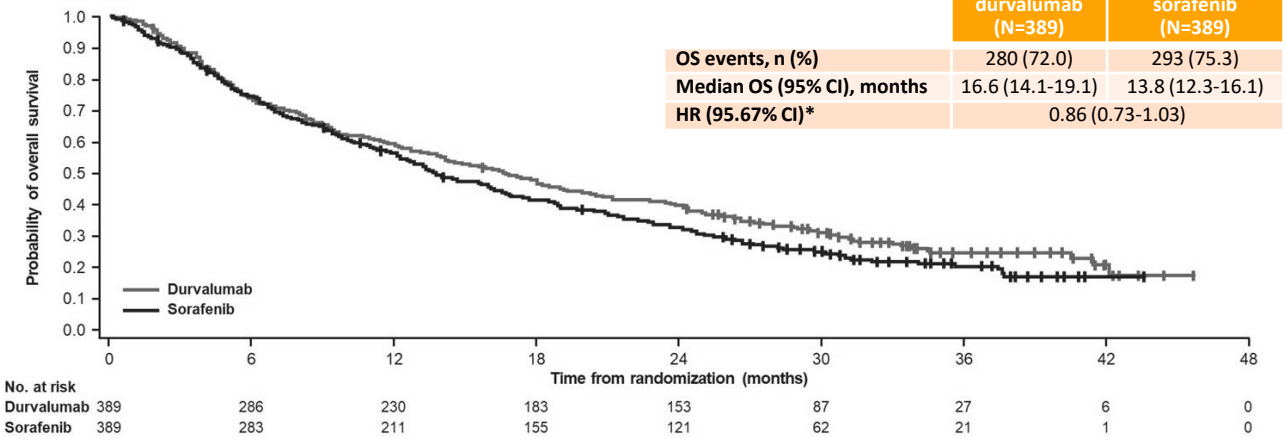


No. at risk								
STRIDE	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	1

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74-34.53) months for STRIDE and 32.23 (95% CI, 30.42-33.71) months for sorafenib

CI, confidence interval; HR, hazard ratio; OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab

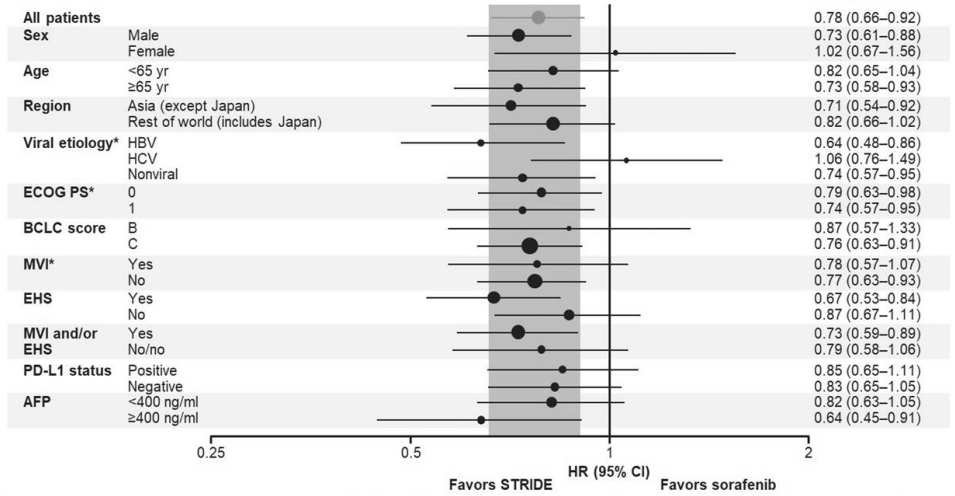
Secondary objective: overall survival for durvalumab vs sorafenib



	durvalumab (N=389)	sorafenib (N=389)
OS events, n (%)	280 (72.0)	293 (75.3)
Median OS (95% CI), months	16.6 (14.1-19.1)	13.8 (12.3-16.1)
HR (95.67% CI)*	0.86 (0.73-1.03)	

Data cut-off: August 27, 2021. Median duration of follow-up was 32.56 (95% CI, 31.57–33.71) months for durvalumab and 32.23 (95% CI, 30.42–33.71) months for sorafenib. *NI margin=1.08.
CI, confidence interval; HR, hazard ratio; NI, noninferiority; OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

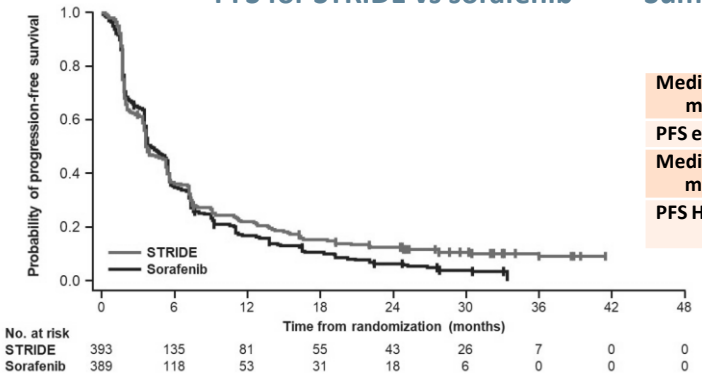
OS for STRIDE vs sorafenib in patient subgroups



lification factor.

Progression-free survival

PFS for STRIDE vs sorafenib



*Versus sorafenib.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTP, time to progression.

Summary of PFS

	STRIDE (N=393)	Durvalumab (N=389)	Sorafenib (N=389)
Median TTP (95% CI), months	4.52 (3.81-5.62)	3.75 (3.68-5.42)	5.55 (5.13-5.75)
PFS events, n (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68-5.32)	3.65 (3.19-3.75)	4.07 (3.75-5.49)
PFS HR* (95% CI)	0.90 (0.77-1.05)	1.02 (0.88-1.19)	–

Tumour response

	STRIDE (N=393)	Durvalumab (N=389)	Sorafenib (N=389)
ORR,* %	20.1	17.0	5.1
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months	22.34	16.82	18.43
25th percentile	8.54	7.43	6.51
75th percentile	NR	NR	25.99
Median TTR (95% CI), months	2.17 (1.84-3.98)	2.09 (1.87-3.98)	3.78 (1.89-8.44)
Remaining in response,‡ %			
6 months	82.3	81.8	78.9
12 months	65.8	57.8	63.2

*By investigator assessment according to RECIST v1.1. Responses are confirmed. †Defined as neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD. ‡Calculated using Kaplan-Meier technique.
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTR, time to response.

SAFETY AND TOLERABILITY

Event, n (%)	STRIDE (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE*	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
Any TRAE leading to death	9 (2.3)[†]	0	3 (0.8)[‡]
Any TRAE leading to discontinuation	32 (8.2)	16 (14.1)	41 (11.0)
Any grade 3/4 hepatic SMQ TRAE	23 (5.9)	20 (5.2)	17 (4.5)
Any grade 3/4 hemorrhage SMQ TRAE	2 (0.5)	0	4 (1.1)
Any grade 3/4 immune-mediated TRAE	49 (12.6)	24 (6.2)	9 (2.4)
Any immune-mediated AE requiring treatment with high-dose steroids	78 (20.1)	37 (9.5)	7 (1.9)
Any immune-mediated AE leading to discontinuation of study treatment	22 (5.7)	10 (2.6)	6 (1.6)

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of the initiation of the first subsequent therapy.

* Treatment-related was assessed by investigator. [†] Nervous system disorder (n=1), acute respiratory distress syndrome (n=1), hepatitis (n=1), myocarditis (n=1), immune-mediated hepatitis (n=2), pneumonitis (n=1), hepatic failure (n=1), myasthenia gravis (n=1), [‡] Hematuria (n=1), cerebral hematoma (n=1), hepatic failure (n=1)

AE, adverse event; SMQ, Standardised MedDRA Query; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TRAE, treatment-related adverse event

TREATMENT-RELATED HEPATIC OR HEMORRHAGE SMQ EVENTS

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Event, n (%)	STRIDE (n=388)		Durvalumab (n=388)		Sorafenib (n=374)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with hepatic SMQ TRAE	66 (17.0)	27 (7.0)	55 (14.2)	20 (5.2)	46 (12.3)	18 (4.8)
Patients with hemorrhage SMQ TRAE	7 (1.8)	2 (0.5)	3 (0.8)	0	18 (4.8)	6 (1.6)
Alanine aminotransferase increased	18 (4.6)	4 (1.0)	22 (5.7)	5 (1.3)	8 (2.1)	3 (0.8)
Aspartate aminotransferase increased	22)5/7)	9 (2/3)	25 (6/4)	9 (2.3)	10 (2.7)	6 (1.6)
Blood bilirubin increased	6 (1.5)	1 (0.3)	6 (1.5)	0	10 (2.7)	2 (0.5)
Ascites	1 (0.3)	0	0	0	2 (0.5)	0
Hepatic encephalopathy	0	0	0	0	2 (0.5)	1 (0.3)
Activated partial thromboplastin time prolonged	1 (0.3)	0	0	0	0	0
International normalized ratio increased	4 (1.0)	1 (0.3)	0	0	0	0
Esophageal varices hemorrhage	0	0	0	0	0	0

Includes adverse events with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Treatment-related was as assessed by investigator

SMQ, Standardised MedDRA Query; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TRAE, treatment-related adverse event

IMMUNE-MEDIATED ADVERSE EVENTS

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Event, n (%)	STRIDE (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypophysitis	4 (1.0)	0	1 (0.3)	0	1 (0.3)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Thyroiditis	6 (1.5)	0	1 (0.3)	0	2 (0.5)	0	0	0
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0

Includes adverse events with onset or increase in severity on or after the date of the first dose through 90 days following the start of the last dose or the date of initiation of the first subsequent therapy. Patients may have had >1 event. Events include those that occurred in ≥1% of patients in either treatment arm.

STRIDE, Single Tremelimumab Regular Interval Durvalumab

CONCLUSIONS

- The HIMALAYA study was a large, Phase 3 study that included a global heterogeneous population of patients with uHCC
- A single priming dose of tremelimumab plus regular interval durvalumab with the STRIDE regimen statistically significantly improved overall survival versus sorafenib
  - STRIDE appeared to provide a long-term survival benefit, with a landmark 36-month overall survival of 30.7% vs 20.2% for sorafenib
- Overall survival for durvalumab monotherapy was noninferior to sorafenib, with a favorable benefit-risk profile
- Both STRIDE and durvalumab monotherapy had manageable safety profiles, with lower rates of grade 3/4 TRAEs leading to discontinuation than sorafenib and no increase in liver toxicity or bleeding risk
- Overall, the STRIDE regimen now represents another first-line treatment option in uHCC

STRIDE, Single Tremelimumab Regular Interval Duravalumab; TRAE, treatment-related adverse event; uHCC, unresectable hepatocellular carcinoma

1ST LINE COMBINATION THERAPIES IN ADVANCED HCC

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	HIMALAYA: T300 + durvalumab	COSMIC 312: Atezolizumab + cabozantinib	IMBRAVE150: Atezolizumab + bevacizumab	ORIENT: Sintilimab + biosimilar bevacizumab	Checkmate 459: Nivolumab
Level of evidence	Phase III vs sorafenib (vs durvalumab)	Phase III vs cabozantinib	Phase III vs sorafenib	Phase III vs sorafenib	Phase III vs sorafenib
Asia-Pacific **Rest of the world**	39.7% 60.3%	28% 72%	40% 60%	Chinese patients only	40% 60%
ECOG 0 **ECOG 1**	62% 38%	64% 36%	62% 38%	48.2% 51.8%	73% 27%
HBV **HCV** **Other**	31% 28% 41%	29% 31% 39%	49% 21% 30%	94% 1.6% -	31% 23% 45%
AFP >400	36.9%	38%	38%	43.4%	335 (>400)
Macrovascular Invasion **Extrahepatic disease**	26.2% 53.2%	31% 54%	38% 63%	73.4%	75%
Stage A **Stage B** **Stage C**	-	0 32 68	2 15 82	0 14.7 85.3	4 14 82
Prior anti-cancer treatment	-	32% (prior TACE)	48% (39% prior TACE)	65.8% (prior TACE)	>50%
Subsequent anti-cancer therapy Including IO	40.7% vs 45% (22.9% IO)	20% vs 37% (17% IO)	36% vs 52% (26% IO)	-	

1ST LINE COMBINATION THERAPIES FOR ADVANCED HCC: OUTCOMES

HCC connect® POWERED BY COR2ED

	HIMALAYA: T300 + durvalumab vs sorafenib (vs durvalumab)	COSMIC 312: Atezolizumab + cabozantinib vs sorafenib (vs cabozantinib)	*Atezolizumab + bevacizumab vs sorafenib	Sintilimab + biosimilar bevacizumab vs sorafenib	Nivolumab (CM459) vs sorafenib
Median OS	16.4m vs 13.8m HR 0.85 , p 0.035	15.4m vs 15.5m HR 0.9, p=.438	**19.2m** vs 13.2m HR 0.66 p0.0009	NR vs 10.4m HR 0.56	16.4 vs 14.7m HR 0.85
Median PFS	3.78m vs 4.07m HR 0.9	6.8m vs 4.2m HR 0.63 p 0.0012	6.9m (vs 4.3m) HR 0.65 p0.0001	4.5m vs 2.8m HR 0.56	3.7m (vs 3.8m)
ORR (RECIST)	20% vs 5.1%	11% v 3.7%	**30%** vs 11%	20.3% vs 4.1	15% vs 7% (RECIST)
DCR	60% vs 60%	78% vs 65%	74 vs 55%	-	55% vs 58%
Median Duration of Rx	22.3m vs 18.4m	10.6m vs 8.8m	**18.1m vs 14.9m**	NR vs 9.8m	23.3m vs 23.4m
G3/4 AE		53.1% vs 31%	43% vs 46%	-	-
G3/4 irAE	irAE only 12.6%	-		-	-
Discontinuation due to toxicities	8.2%	6.1%; 14% withdrew 1 drug	7% : 16% withdrew 1 drug	13.7%; 5.5% dose reduction	9% vs 11%
Use of steroids for irAE	20.1%	7.2%			

1. Llovet J, et al. N Engl J Med. 2008;359:378-90; 2. Cheng A, et al. Lancet Oncol. 2009;10:25-34; 3. Kudo M, et al. Lancet 2018;391:1163-73
4. Finn R, et al. N Engl J Med. 2020;382:1894-905; 5. Cheng A, et al. ESMO Asia 2019 (Abstract LBA3); 6. T Yau Annals Oncol Oct. 2019

MY THOUGHTS

- HIMALAYA is a positive trial
- The STRIDE combination is an alternative option in the 1st line therapy of advanced HCC with improved OS, better ORR with durable responses
- As seen with other IO-IO combinations , expect more irAEs requiring steroids
- The choice for 1st line at this point will have to take toxicities into consideration
- Further biomarkers or clinical markers are needed to help us choose best treatment for the individual patient

PEMBROLIZUMAB PLUS BEST SUPPORTIVE CARE VS PLACEBO PLUS BEST SUPPORTIVE CARE AS 2ND -LINE THERAPY IN PATIENTS IN ASIA WITH ADVANCED HCC: PHASE 3 KEYNOTE-394 STUDY

Shukui Quin, et al.

Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing, China

KEYNOTE-394 STUDY DESIGN (NCT03062358) AND STATISTICAL CONSIDERATIONS

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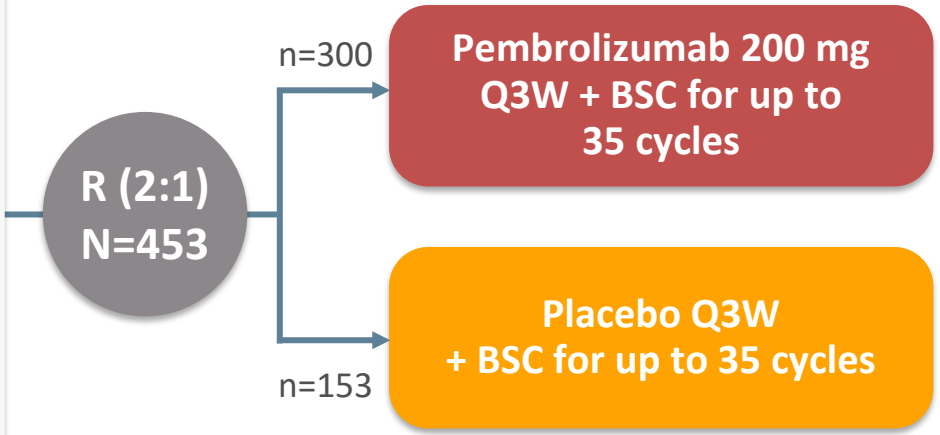
Key Eligibility Criteria

- Confirmed HCC[a]
- Measurable disease per RECIST v1.1[b]
- Progression during or after or intolerance to sorafenib or oxaliplatin-based chemotherapy
- Child-Pugh class A
- BCLC stage C or B not amenable or refractory to locoregional therapy, and not amenable to curative treatment
- ECOG PS 0 or 1

Stratification Factors

- Prior treatment (sorafenib vs chemotherapy)
- Macrovascular invasion (yes vs no)
- HCC etiology (HBV vs other [HCV or non-infection])



End Points

- Primary: OS
- Secondary: PFS, ORR, DoR, DCR, TTP (all assessed by BICR per RECIST v1.1), and safety/tolerability

- Overall Type I error = 0.025 controlled across testing of OS, PFS, and ORR[1]
  - Initial allocation PFS = 0.002; OS = 0.023
  - Re-allocated per multiplicity strategy specified in the protocol among 3 endpoints above
- Per protocol, there were 2 interim and 1 final analysis for OS and 1 interim and 1 final analysis for PFS and ORR
  - Interim analysis for PFS and ORR at the time of OS 1st interim analysis
  - Final analysis at the time of OS 2nd interim analysis
- Efficacy boundaries
  - P=0.0193 for OS (final analysis cutoff, June 30, 2021, based on 350 observed events)
  - P=0.0134 for PFS and P=0.0091 for ORR (at 2nd interim cutoff, June 30, 2020; only if OS criteria met)

[a] Histologically, cytologically, or radiographically confirmed HCC. [b] Based on investigator assessment

1. Maurer W, Bretz F. Stat Biopharm Res. 2013;5(4):311-20; 2. Finn RS, et al. J Clin Oncol. 2020;38:193-202

Median time from randomisation to data cutoff for the final analysis was 33.8 months (range 18.7-49.0) and 21.8 months (range 6.7-37.0) for the 2nd interim analysis

Baseline demographics and clinical characteristics

	pembrolizumab (N=300)	placebo (N=153)
Age, median (range), years	54 (22-82)	54 (22-78)
≥65 years, n (%)	69 (23.0)	29 (19.0)
Male	257 (85.7)	126 (82.4)
Region		
China	255 (85.0)	132 (86.3)
Ex-China	45 (15.0)	21 (13.7)
ECOG PS 1	176 (58.7)	93 (60.8)
Child-Pugh Class A	300 (100.0)	153 (100.0)
α-fetoprotein ≥200 ng/mL	169 (56.3)	78 (51.0)
Extrahepatic spread	232 (77.3)	120 (78.4)
Macrovascular invasion	33 (11.0)	17 (11.1)
BCLC stage C	277 (92.3)	146 (95.4)

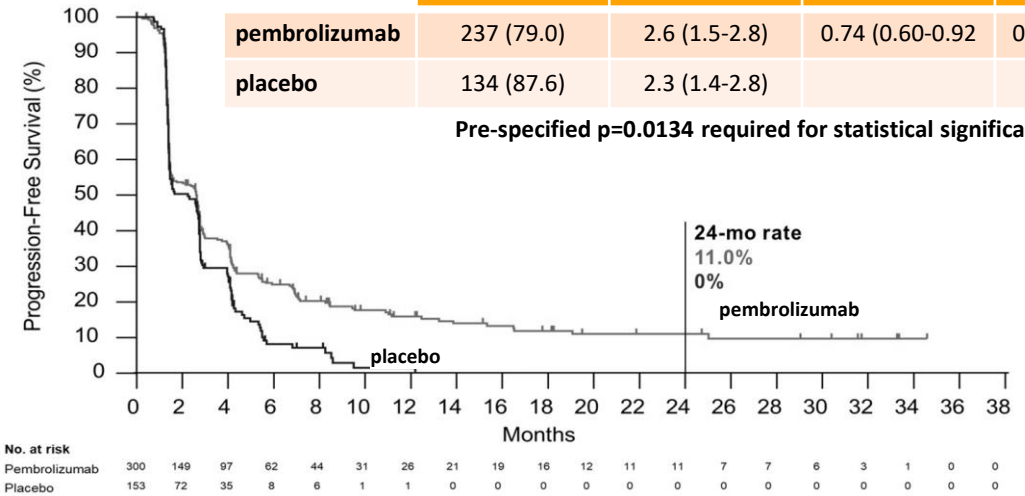
	pembrolizumab (N=300)	placebo (N=153)
Hepatitis B status		
Positiveb	236 (78.7)	124 (81.0)
Hepatitis C status		
Posivivec	5 (1.7)	1 (0.7)
Prior first-line treatment		
Sorafenib	272 (90.7)	139 (90.8)
Oxaliplatin-based chemotherapy	28 (9.3)	14 (9.20

n (%) unless otherwise specified. Percentages may not equal 100 because of rounding. [a] Region for China includes China Mainland, Hong Kong, and Taiwan; region for ex-China includes Republic of Korea and Malaysia. [b] Hepatitis B status was collected from the electronic case report form and positive was defined as hepatitis B surface antigen positive and/or detectable HBV DNA based on investigator assessment. [c] Hepatitis C was collected from the electronic case report form and positive was defined as anti–hepatitis C antibody positive and detectable HCV RNA based on investigator assessment

Progression-free survival

	Events	PFS, median (95% CI), mo	HR (95% CI)	P[a]
pembrolizumab	237 (79.0)	2.6 (1.5-2.8)	0.74 (0.60-0.92	0.0032
placebo	134 (87.6)	2.3 (1.4-2.8)		

Pre-specified p=0.0134 required for statistical significance

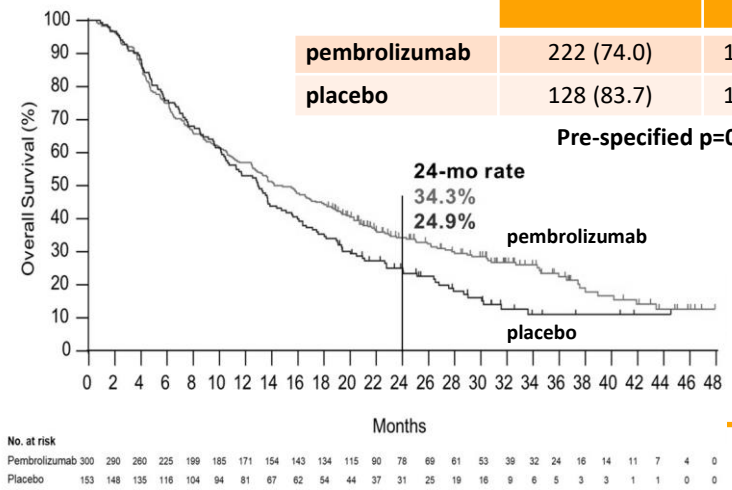


[a] One-sided p for testing difference. Data cutoff: June 30, 2020 (second-interim analysis)

Overall survival

	Events	OS, median (95% CI), mo	HR (95% CI)	P[a]
pembrolizumab	222 (74.0)	14.6 (12.6-18.0)	0.79 (0.63-0.99)	0.0180
placebo	128 (83.7)	13.0 (10.5-15.1)		

Pre-specified p=0.0193 required for statistical significance



Post-study systemic anticancer therapy

	pembrolizumab (N=300)	placebo (N=153)
Any post-study systemic anticancer therapy	152 (50.7)	102 (66.7)
PD-1 inhibitor or PD-L1 inhibitor[b]	62 (20.7)	43 (28.1)

[a] One-sided p for testing difference. Data cutoff: June 30, 2021 (final analysis)
[b] Includes both with/without prior exposure to other post-study systemic anticancer therapies

Objective response

	pembrolizumab (N=300)	placebo (N=153)
ORR (CR + PR), % (95% CI)	12.7 99.1-17.0)	1.3 (0.2-4.6)
Estimated treatment difference, (95% CI; p[a])	11.4 (6.7-16.0); <0.0001	
Best overall response, n (%)		
CR	6 (2.0)	1 (0.7)
PR	32 (10.7)	1 (0.7)
SD	115 (38.3)	70 (45.8)
Sustained SD[b]	26 (8.7)	8 (5.2)
PD	129 (43.0)	72 (47.1)
Not evaluable	10 (3.3)	1 (0.7)
Not assessable[c]	8 (2.7)	8 (5.2)
DoR,[d] median (range), mo	23.9 (2.8 to 32.0+)	5.6 (3.0+ to 5.6)

Pre-specified p=0.0091 required for statistical significance

[a] One-sided p for testing difference. [b] Duration of stable disease ≥23 weeks (stable disease within 24-week scan window or later). [c] Includes patients with a baseline assessment (by investigator or blinded independent central review) but no postbaseline assessment on the data cutoff date, including discontinuation or death before the first postbaseline scan. [d] Assessed in the 38 patients in the pembrolizumab group and 2 patients in the placebo group who had a confirmed complete response or partial response. Data cutoff: June 30, 2020 (second-interim analysis)

OVERALL SURVIVAL BASED ON META-ANALYSIS OF KEYNOTE-394 AND KEYNOTE-240

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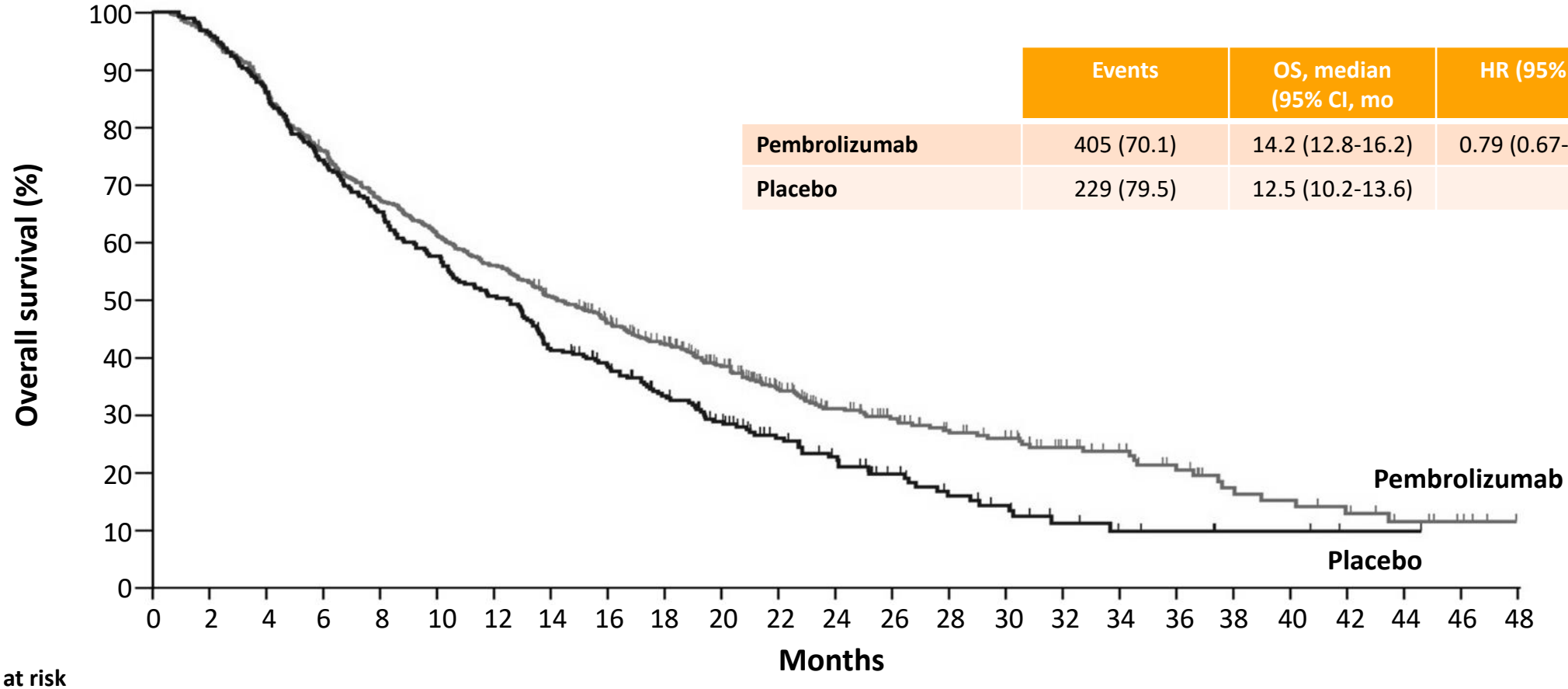
	Events	OS, median (95% CI, mo	HR (95% CI)
Pembrolizumab	405 (70.1)	14.2 (12.8-16.2)	0.79 (0.67-0.93)
Placebo	229 (79.5)	12.5 (10.2-13.6)	



No. at risk																								
Pembrolizumab	578	555	497	438	389	354	323	289	253	220	172	123	94	76	62	54	39	32	24	16	14	11	7	4	0
Placebo	288	278	248	214	188	166	146	118	104	84	67	50	39	28	20	16	9	6	5	3	3	1	1	0	0

Meta-analysis of pooled OS data from KEYNOTE-240 and KEYNOTE-394 was performed using all the patients receiving pembrolizumab or placebo in the intent-to-treat populations of each study
Data cutoff KEYNOTE-240: January 2, 2019 (final analysis; Finn RS, et al. J Clin Oncold 2020;38:1923-202); KEYNOTE-394: June 30, 2021 (final analysis)

ADVERSE EVENT SUMMARY

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N (%)	Pembrolizumab (N=299)	Placebo (N=153)
All-cause AEs		
Any	283 (94.6)	147 (96.1)
Grade 3-5	157 (52.5)	50 (32.7)
Led to discontinuation	38 (12.7)	12 (7.8)
Led to death	10 (3.3)	2 (1.3)
Treatment-related AEs		
Any	200 (66.9)	76 (49.7)
Grade 3-5[a]	43 (14.4)	9 (5.9)
Led to discontinuation	12 (4.0)	1 (0.7)
Led to death	3 (1.0)	0
Immune-mediated AEs[b]		
Any	54 (18.1)	16 (10.5)
Grade 3-5	9 (3.0)	0
Led to discontinuation	5 (1.7)	0
Led to death[c]	1 (0.3)	0
Immune-mediated hepatitis[c,d]	5 (1.7)	0

[a] 3 treatment-related deaths (as determined by the investigator) occurred in the pembrolizumab group (gastrointestinal hemorrhage, n=1; autoimmune hepatitis [confounded by metastasis to both lungs and lymphatic metastasis with chylous ascites resulting in circulatory failure], n=1; soft tissue infection, n=1). No treatment-related deaths occurred in the placebo group. [b] Includes immune-mediated events and infusion-related reactions of any attribution. [c] (0.3%) patient died from autoimmune hepatitis.
[d] Based on sponsor assessment
Data cutoff: June 30, 2021 (final analysis)

SUMMARY AND CONCLUSIONS

- In KEYNOTE-394, pembrolizumab showed statistically significant and clinically meaningful improvement in OS, PFS, and ORR in patients from Asia with previously treated advanced HCC compared with placebo
  - The use of post-study anticancer therapy at progression may have attenuated the observed treatment effect
- A meta-analysis of KEYNOTE-240 and KEYNOTE-394 showed pembrolizumab therapy provided a consistent treatment effect and clinically meaningful improvement in OS compared to placebo in patients with advanced HCC
- The AE profile of pembrolizumab was manageable and consistent with previous reports in this patient population
- These data reinforce the benefit-risk balance for pembrolizumab observed in globally conducted studies in the second-line treatment of advanced HCC and provide support for the generalizability of the data worldwide

2L IMMUNE CHECKPOINT BLOCKERS IN ADVANCED HCC

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	CheckMate 040: nivolumab + ipilimumab[1,3]	KEYNOTE-240: pembrolizumab[5]	KEYNOTE-394: Pembrolizumab	RESORCE: Regorafenib	CELESTIAL: Cabozantinib	REACH2: Ramucirumab
Phase	**Phase I/II (NIVO1+IPI3)**	**Phase III**	**Phase III**	**Phase III**	**Phase III**	**Phase III**
Asia Pacific **Rest of World**	74% 26%	24.1 % + 14.4 % Japan 61.5%	100% (incl Japan) 0%	41% 59%	25% 75%	27.9% 72.1%
HBV **HCV** **Non-viral**	56% 14% 26%	29.9% 15.5% 54.6%	79% 1.7% 19.3%	41% 38% 21%	38% 22% 40%	36% 24.4% 39.6%
Prior sorafenib	100%	100%	90.7%	100% tolerated sorafenib	Include 28% who had 2 or more prior systemic tx	100% and all AFP >400
OS, months	**22.2**	**13.9**	**14.6**	**10.6**	**10.2**	**8.5**
PFS, months	NA	**3.3**	**2.6**	**3.1**	**5.2**	**2.8**
ORR, %	**32**	18	12.7	11	4	5
Grade ≥3 AEs, %	55[b]	52[b]	14.4	50	68	NA
Median DOR, months	16.5	13.8	**23.9**	**3.6**	**3.8**	**3.5**

2L, second-line; AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; DOR, duration of response; ESC, dose-escalation phase; EXP, dose-expansion phase; HCC hepatocellular carcinoma; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

[a] Treatment related; [b] Grade 3/4

1. El-Khoueiry A, et al. Lancet 2017;389:2492-502. 2. Crocenzi T, et al. ASCO 2017 (Abstract 4013).
3. Yau T, et al. ASCO 2019 (Abstract 4012). 4. Zhu A, et al. Lancet Oncol 2018;19:940-52.
5. Finn R, et al. J Clin Oncol 2020;38:193-202

MY THOUGHTS

- KN394 results in Asian patients are consistent with what has been seen in KN240.
- Pembrolizumab is very manageable toxicity wise
- In the 2nd line setting after TKI, we have many treatment options including pembrolizumab
- However, with combination therapies in the 1st line setting, the role of monotherapy IO in the 2nd line setting is questionable

LENVATINIB PLUS TRANSARTERIAL CHEMOEMBOLIZATION VERSUS LENVATINIB ALONE AS 1ST-LINE TREATMENT FOR PRIMARY ADVANCED HCC: A PHASE 3, MULTICENTER, RANDOMIZED CONTROLLED TRIAL (LAUNCH)

Zhenwei Peng[1], Wenzhe Fan[1], Bowen Zhu[1], Jiping Wang[2], Jiaping Li[1], Ming Kuang[1]

[1] Cancer center, First Affiliated Hospital, Sun Yat-sen University, China
[2] Brigham and Women's Hospital, Harvard Medical School, USA

SCHEMATIC DIAGRAM

- Advanced primary HCC without any previous treatment or initial recurrent advanced HCC after radical resection without any postoperative treatment
- At least one measurable lesion in the liver based on mRECIST criteria
- Single lesion size <10 cm or number of multiple lesions <10, tumour burden <50%

Stratification Factors
- ECOG performance status (0 vs 1)
- Tumour thrombus: yes vs no
- Body weight (<60 vs ≥60 kg
- Trial site

Randomisation 1:1

TACE + lenvatinib (N=168)
TACE starts 1 day after lenvatinib
lenvatinib: 8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) once daily

lenvatinib (N=168)
8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) once daily

Primary study endpoints:
- OS

Secondary study endpoints:
- PFS*
- TTP*
- ORR*
- Quality of life

* Investigaors assess the tumour based on mRECIST

HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; TACE, transarterial chemoembolization; BW, body weight; OS, overall survival; PFS, progression-free survival; TTP, time to progression; ORR, objective response rate;
mRECIST, modified response evaluation criteria in solid tumours

BASELINE CHARACTERISTICS

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- In general, the two groups had balanced baseline characteristic (all p values >0.05)

Characteristics	LEN-TACE Group (N=170)	LEN Group (N=168)
Age (y), median (IQR)	54 (46-64)	56 (48-63)
≤60 (n, %)	113 (66.5)	117 (69.6)
>60 (n, %)	57 (33.5)	51 (30.4)
Sex, n (%)		
Male	139 (81.8)	132 (78.6)
Female	31 (18.2)	36 (21.4)
Bodyweight (kg), n (%)		
<60	60 (35.3)	65 (38.7)
≥60	110 (64.7)	103 (61.3)
Aetiology, n (%)		
Hepatitis B	148 (87.1)	144 (85.7)
Hepatitis C	4 (2.4)	6 (3.6)
Other	18 (10.6)	18 (10.7)
ECOG-PS score, n (%)		
0	89 (52.4)	99 (58.9)
1	81 (47.6)	69 (41.1)

Characteristics	LEN-TACE Group (N=170)	LEN Group (N=168)
Intrahepatic tumours, n (%)		
Single	30 (17.6)	38 (22.6)
Multiple	140 (82.4)	130 (77.4)
Main tumour size (cm), median (IQR)	8.4 (4.5-9.5)	7.4 (4.1-9.7)
<5 cm, n (%)	47 (27.6)	58 (34.5)
≥5 cm, n (%)	123 (72.4)	110 (65.5)
Macroscopic portal vein invasion, n (%)		
Yes	122 (71.8)	117 (69.6)
No	48 (28.2)	51 (30.4)
Extrahepatic spread, n (%)		
Yes	94 (55.3)	95 (56.5)
No	74 (44.7)	73 (43.5)
AFP (ng/mL), mean (SD)	55,979 (224,434)	31,753 (119,316)
<400, n (%)	87 (51.2)	81 (48.2)
≥400, n (%)	83 (48.8)	87 (51.8)
ALBI score, mean (SD)	−2.38 (0.33)	−2.46 (0.40)

LEN, lenvatinib; TACE, transarterial chemoembolization; CI, confidence interval; IQR, interquartile range; ALBI, albumin-bilirubin score

TUMOR RESPONSE

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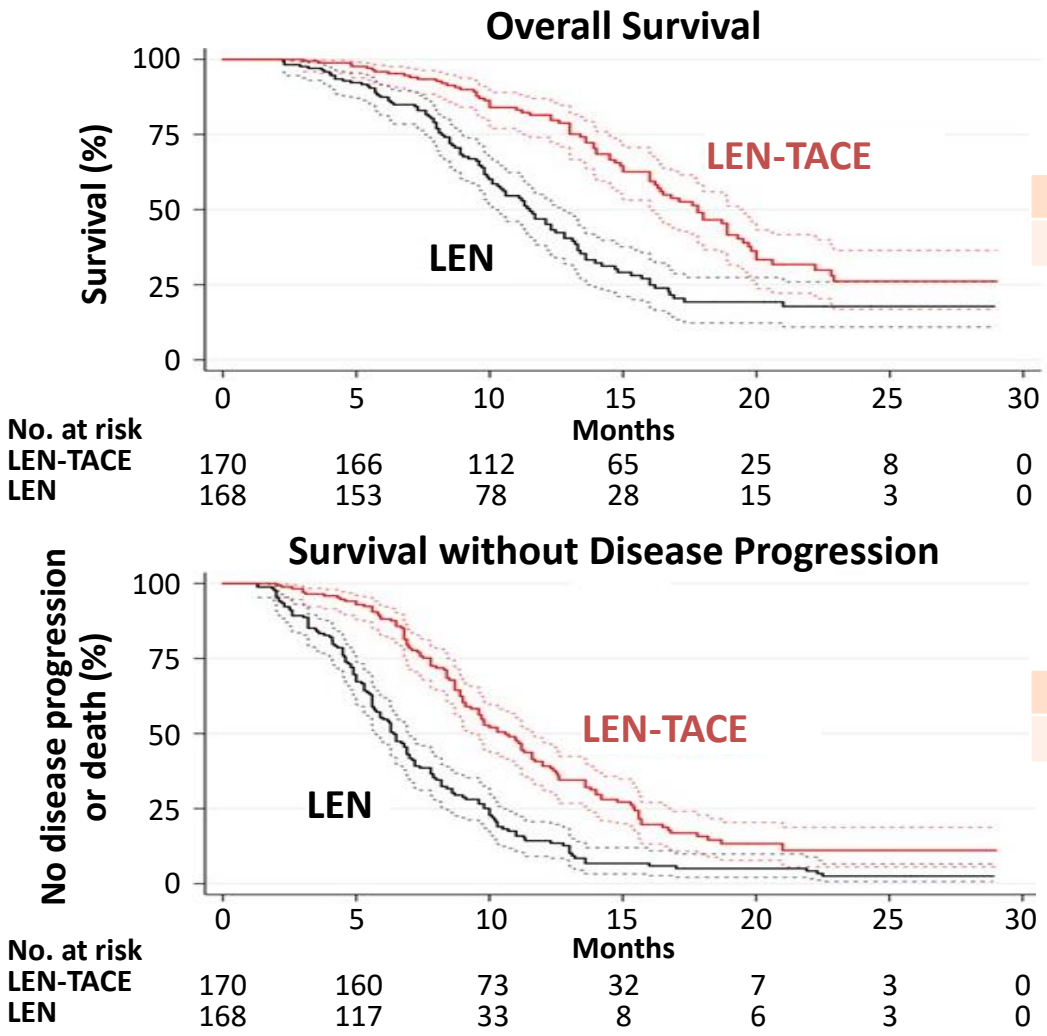
- The ORR and DCR were both higher in LEN-TACE group than in the LEN group

Variable	RECIST 1.1		p value	mRECIST		p value
	Group, No (%)			Group, No (%)		
	LEN-TACE group (N=170)	LEN group (N=168)		LEN-TACE group (N=170)	LEN group (N=168)	
Complete response	1 (0.6)	1 (0.6)	0.993	5 (2.9)	1 (0.6)	0.102
Partial response	77 (45.3)	34 (20.2)	<0.001	87 (51.2)	41 (24.4)	<0.001
Stable disease	79 (46.5)	87 (51.8)	0.328	68 (40.0)	81 (48.2)	0.128
Progressive disease	13 (7.6)	46 (27.4)	<0.001	10 (5.9)	45 (26.8)	<0.001
Objective response rate	78 (45.9)	35 (20.8)	**<0.001**	92 (54.1)	42 (25.0)	**<0.001**
Disease control rate	157 (92.4)	122 (72.6)	**<0.001**	160 (94.1)	123 (73.2)	**<0.001**

LEN, lenvatinib; TACE, transarterial chemoembolization; ORR, objective response rate; DCR, disease control; RECIST, response evaluation criteria in solid tumours, mRECIST, modified RECIST

SURVIVAL OUTCOME



	No. of events/ No. of patients %	Median overall survival (95% CI) mo	Overall survival at 6 mo %	Overall survival at 12 mo %	Overall survival at 24 mo %
LEN-TACE	75/170 (44.1)	17.8 (16.1-19.5)	95.9 (91.5-98.0)	81.5 (74.0-87.0)	26.1 (16.8-36.4)
LEN	104/168 (61.9)	11.5 (10.3-12.7)	87.4 (81.3-91.6)	46.9 (38.2-55.0)	17.8 (11.0-26.0)

Hazard ratio for death, 0.45
(95% CI, 0.33-0.61)
Log-rank p<0.001

- The median OS was 17.8 vs 11.5
- HR = 0.45

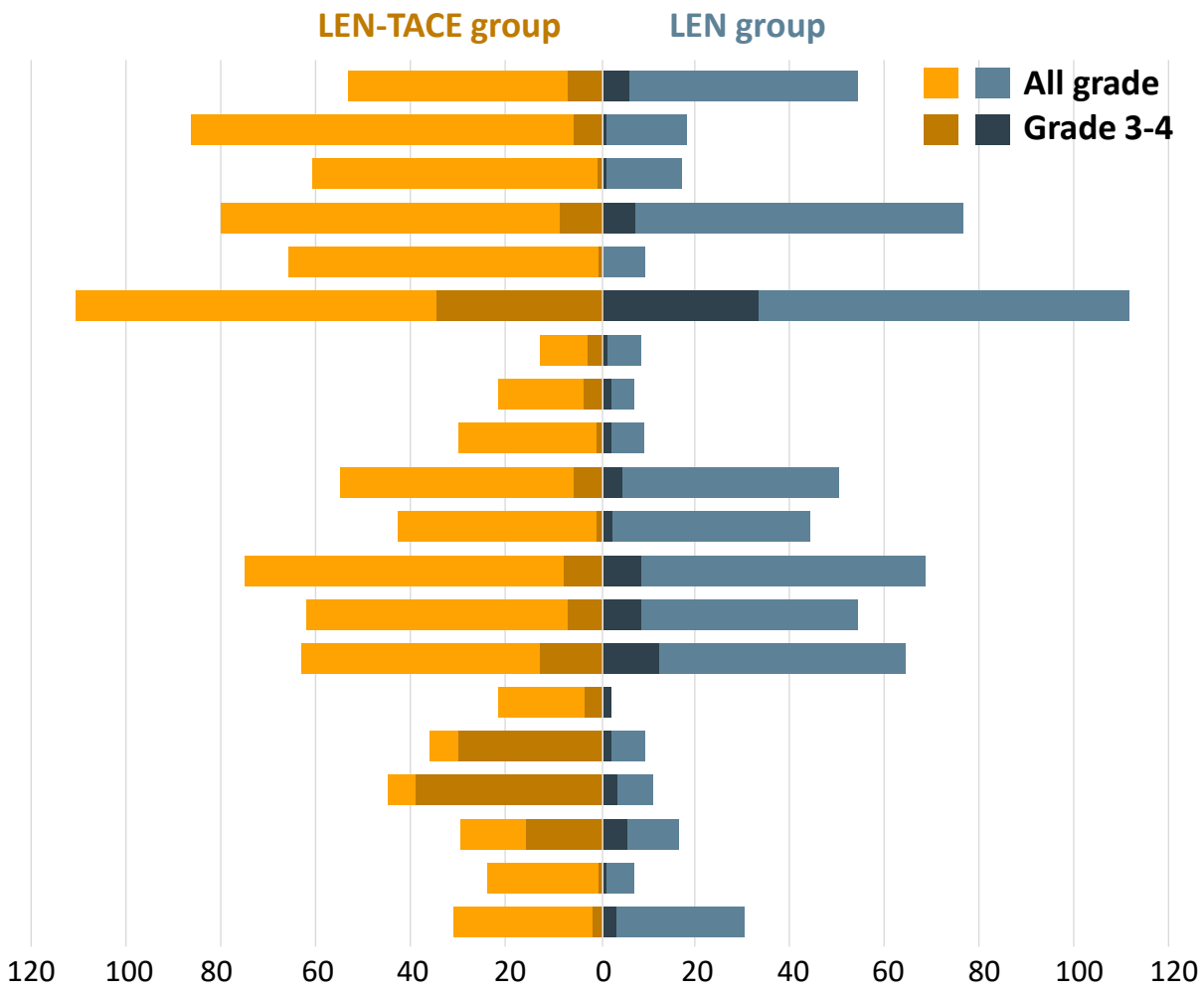
	No. of events/ No. of patients %	Median progression-free survival (95% CI) mo	Progression-free survival at 6 mo %	Overall survival at 12 mo %
LEN-TACE	122/170 (71.8)	10.6 (9.5-11.7)	88.2 (82.3-92.2)	39.2 (31.2-47.0)
LEN	149/168 (88.7)	6.4 (5.8-7.0)	54.8 (46.9-61.9	14.3 (9.1-20.6)

Hazard ratio for progression or death, 0.43
(95% CI, 0.34-0.55)
Log-rank p<0.001

- The median PFS was 10.6 vs 6.4
- HR = 0.43

LEN, lenvatinib; TACE, transarterial chemoembolization; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval

ADVERSE EVENT



Adverse Events	p value	
	All grade	Grade 3-4
Hand-foot skin reaction	0.849	0.749
Abdominal pain	<0.001	0.058
Nausea	<0.001	0.993
Diarrhea	0.737	0.626
Fever	<0.001	0.319
Hypertension	0.792	0.828
Alopecia	0.272	0.320
Ascites	0.004	0.418
Vomiting	<0.001	0.555
Fatigue	0.607	0.533
Dysphonia	0.851	0.555
Decreased appetite	0.498	0.981
Proteinuria	0.402	0.774
Weight decreased	0.844	0.859
Rash	0.966	0.418
ALT increased	<0.001	<0.001
AST increased	<0.001	<0.001
Hyperbilirubinemia	0.029	0.014
Hypoalbuminemia	0.001	0.993
Constipation	0.928	0.643

AE, adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TACE, transarterial chemoembolization

TACE ADMINISTRATION

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- Patients in the LEN-TACE group were treated with a total of 560 times of TACE, and the median TACE session per patient was 3 (ranged 1 to 6)

	DEB-TACE (N=117)	cTACE (N=53)
TACE times	306	254
Mean (SD)	2.6 (0.7)	4.8 (0.9)
Median (IQR)	3 (2-3)	5 (3-5)
Reasons for TACE discontinuation		
Disease progression	78	44
Hepatic resection	17	9
Disappearance of any intratumoral arterial enhancement in all intrahepatic lesion	4	1
Unacceptable AEs	2	2
Other reasons	0	2
TACE delay related to AEs	35	30

LEN, Lenvatinib; TACE, transarterial chemoembolization; IQR, interquartile range; SD, standard deviation; AE, adverse events

MY THOUGHTS

- This study is a positive study
- It emphasizes the safety and tolerability of using TACE after Lenvatinib in advanced HCC
- However, it remains to be seen which are the right patients to be selected for this sequence as these patients are heterogenous

A LOOK TO FUTURE TREATMENTS AND CLOSING REMARKS

Richard S. Finn, MD
Professor of Clinical Medicine
Division of Hematology/Oncology
Director, Signal Transduction and Therapeutics Program
Jonsson Comprehensive Cancer Center
Geffen School of Medicine at UCLA, California, USA

TREATMENT STRATEGY IN THE MANAGEMENT OF HCC 2021 AND BEYOND

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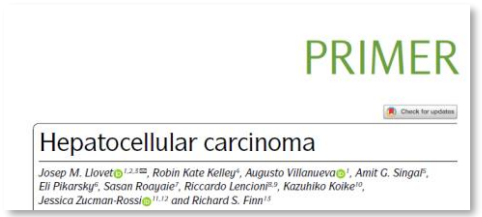
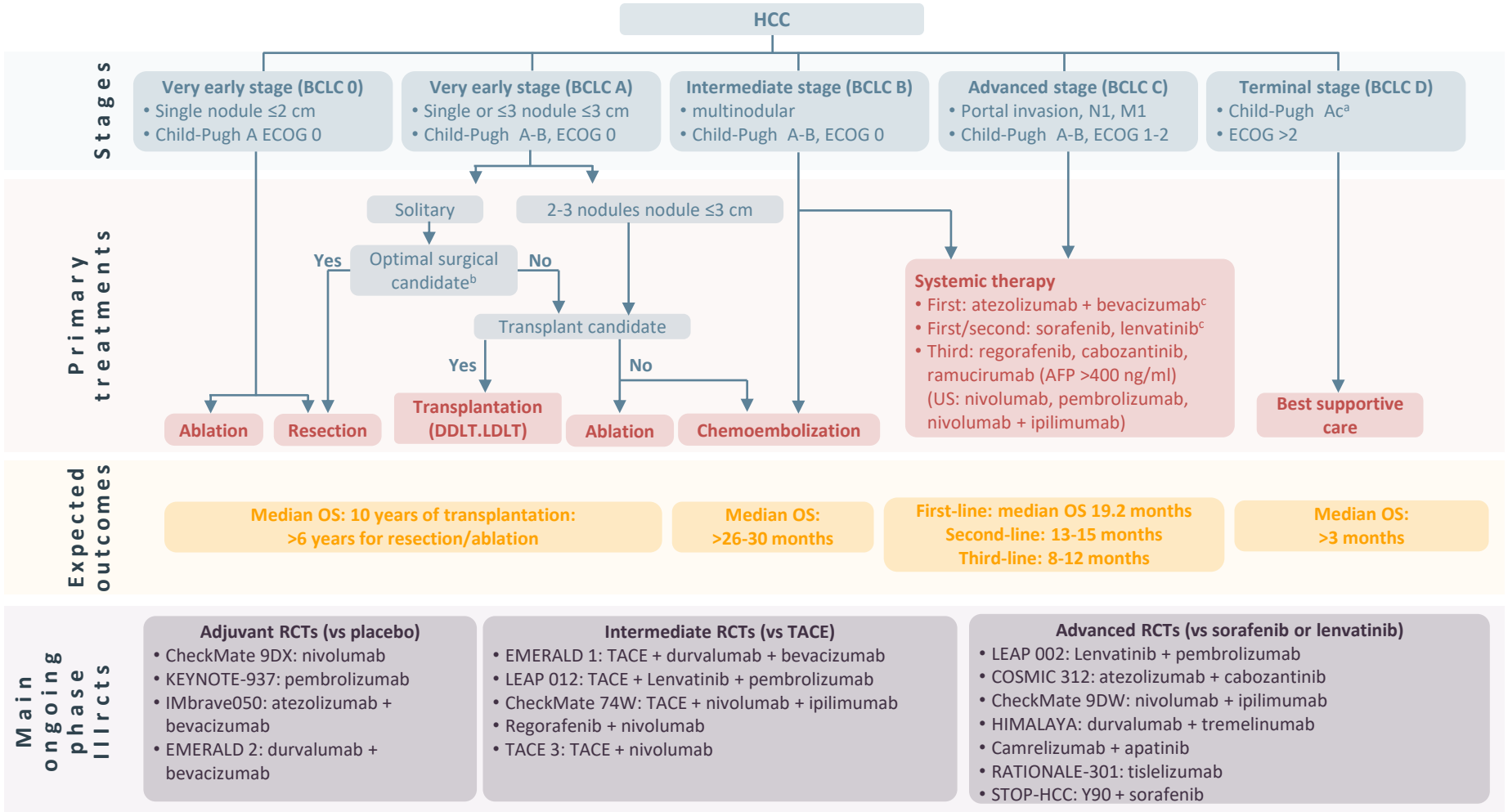

PRIMER

Hepatocellular carcinoma

Josep M. Llovet[1,2,3✉], Robin Kate Kelley[4], Augusto Villanueva[5], Amit G. Singal[6], Eli Pikarsky[6], Sasan Roayaie[7], Riccardo Lencioni[8,9], Kazuhiko Koike[10], Jessica Zucman-Rossi[11,12] and Richard S. Finn[13]



AFP, α- fetoprotein; BCLC, Barcelona Clinic Liver cancer; DDLT, deceased- donor liver transplantation; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; LDLT, living- donor liver transplantation; M1, distant metastasis; N1, lymph node metastasis; OS, overall survival; RCT, randomised controlled trial; TACE, transarterial chemoembolisation

Llovet JM, et al. Nat Rev Dis Primers. 2021;7:6

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froukje.sosef@cor2ed.com

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HCC CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

antoine.lacombe@cor2ed.com

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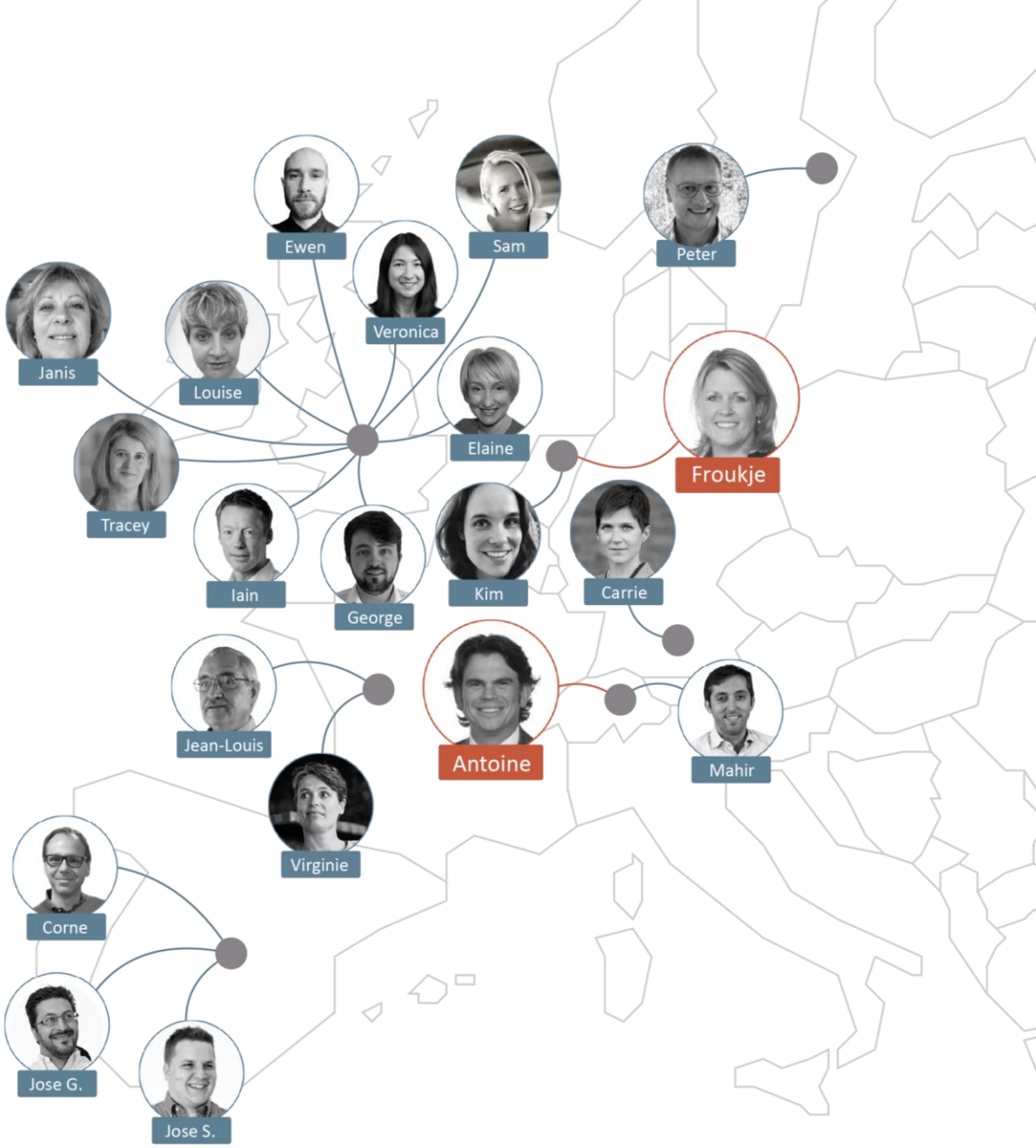

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