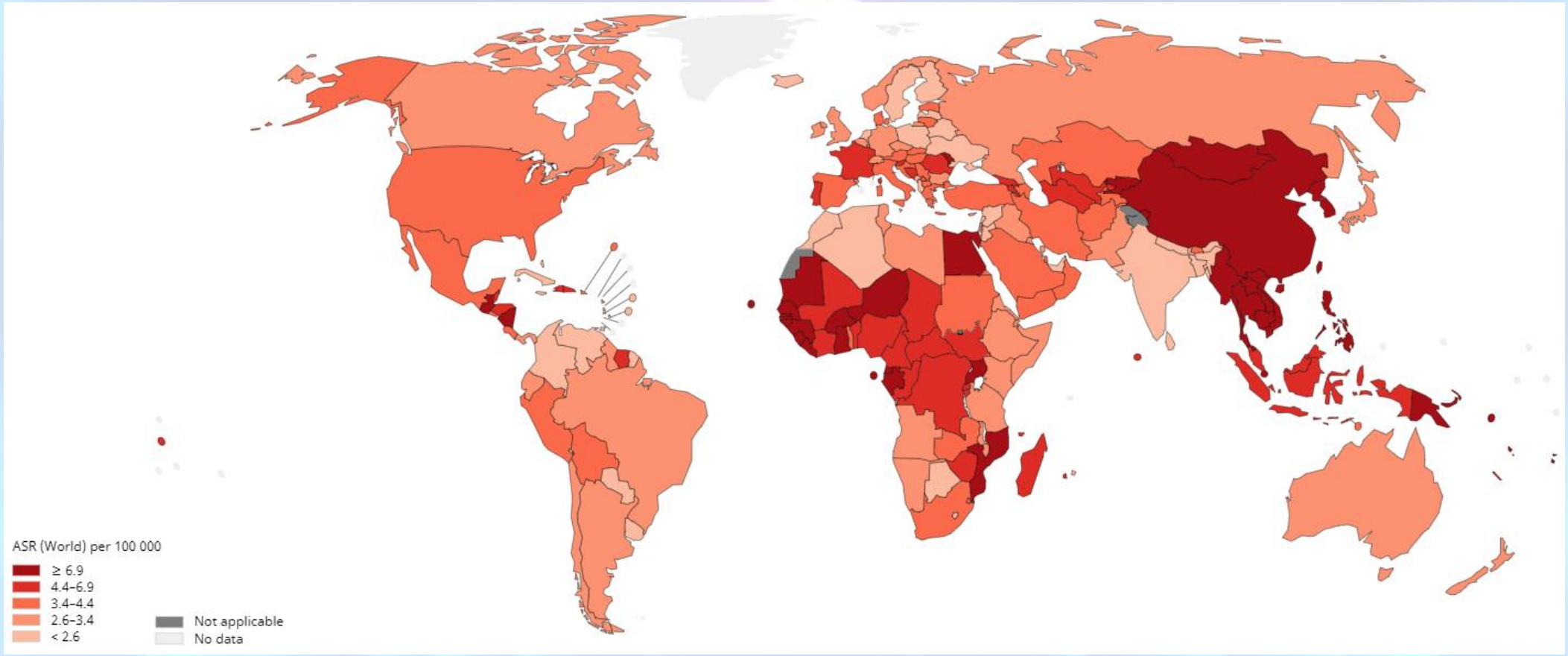
Managing Patients With Advanced HCC

د.نورس نبيل جعفر

أخصائية في علم الأورام

رئيس دائرة التحكم بالسرطان في وزارة الصحة

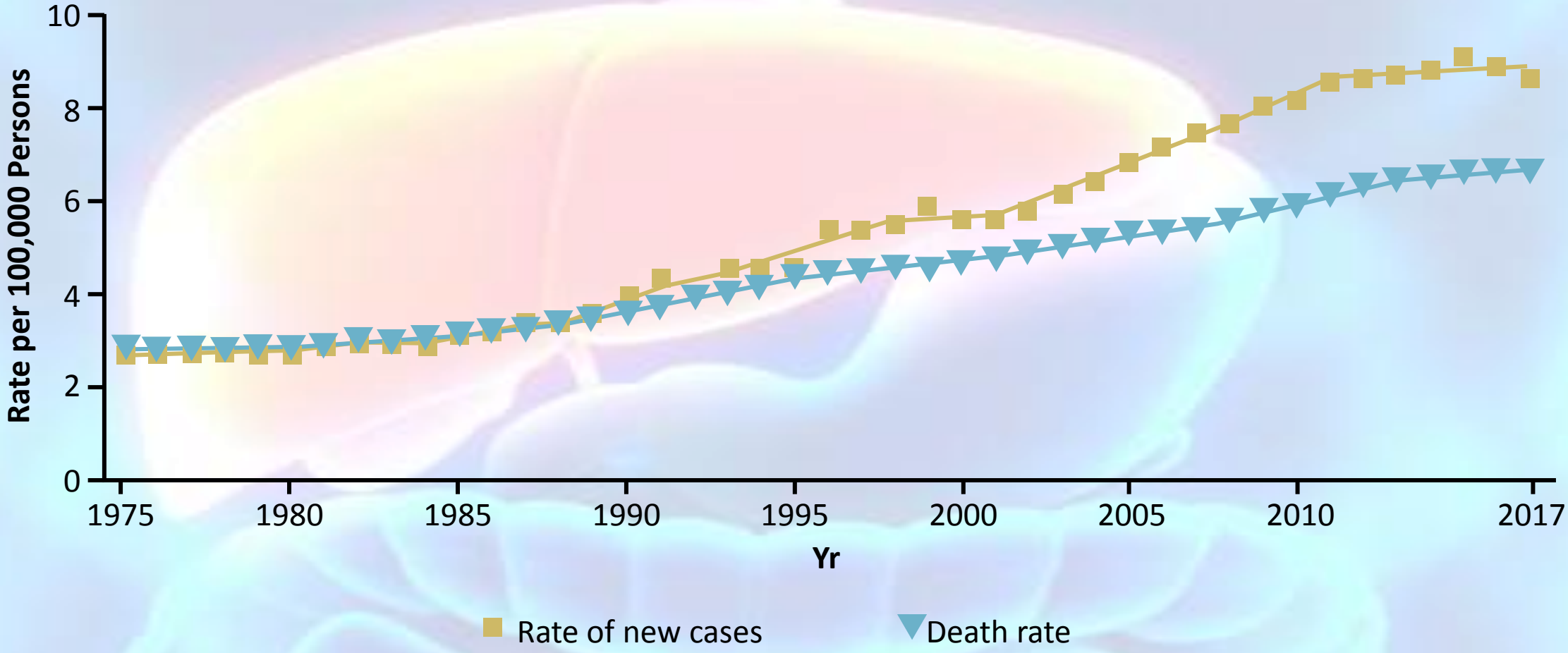
HCC Is the Third Leading Cause of Cancer-Related Death Worldwide



2021 US liver cancer estimates: 42,230 new diagnoses (~75% HCC) and 30,230 deaths

IARC/WHO. Accessed at gco.iarc.fr. American Cancer Society. Cancer Facts & Figures 2021.

Liver Cancer Mortality in the US is Increasing



SEER Database.

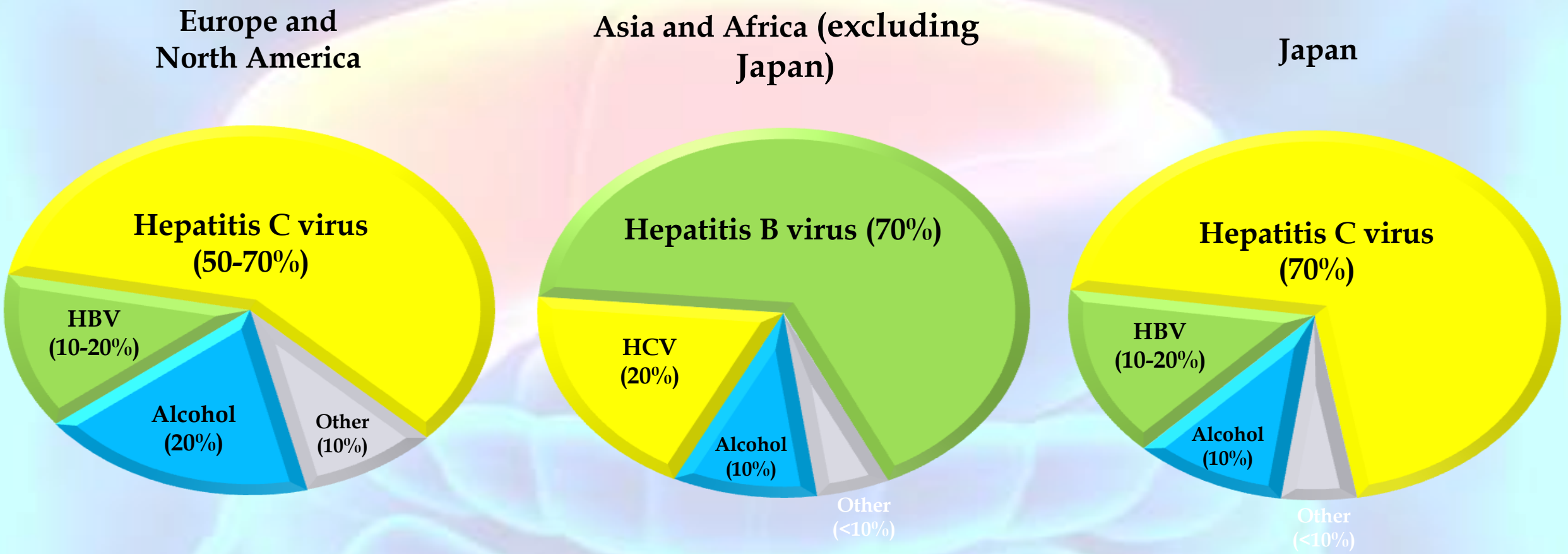
2016 Estimated US Cancer Deaths

Men 314,290	
Lung & bronchus	27%
Prostate	8%
Colon & rectum	8%
Pancreas	7%
Liver & intraheptic bile duct	6%
Leukemia	4%
Esophagus	4%
Urinary bladder	4%
Non-Hodgkin's lymphoma	4%
Brain/other nervous system	3%
All other sites	25%

Women 281,400	
26%	Lung & bronchus
14%	Breast
8%	Colon & rectum
7%	Pancreas
5%	Ovary
4%	Uterine corpus
4%	Leukemia
3%	Liver & intrahepatic bile duct
3%	Non-Hodgkin's lymphoma
2%	Brain/other nervous system
24%	All other sites

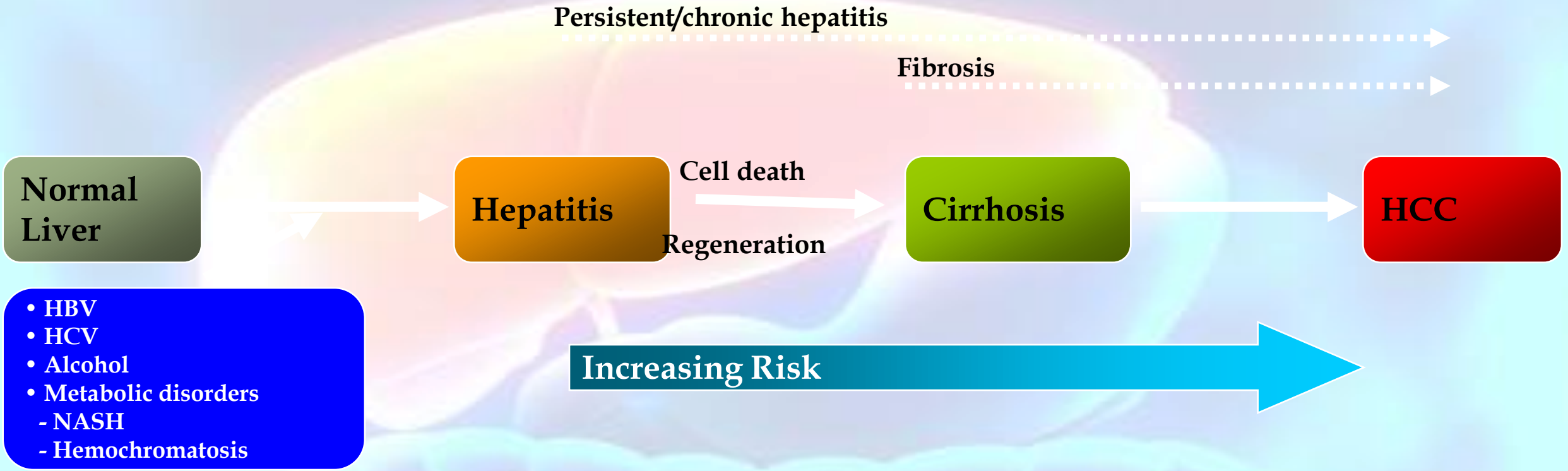
Siegel R, et al. CA Cancer J Clin. 2016;66:7-30.

HCC Risk Factors Are Well Defined and Show Geographical Variation



Adapted from Llovet JM, et al. *Lancet*. 2003;362:1907-1917.

Multifactorial Pathogenesis of HCC[1-5]



HBV = hepatitis B virus; HCV = hepatitis C virus; NASH = nonalcoholic steatohepatitis.

1. Adapted from Rivenbark AG, et al. *Clin Cancer Res*. 2007;13:2309-2312; 2. Marotta F, et al. *Clin Ther*. 2004;155:187-199;
3. Thorgeirsson S, et al. *Nat Genet*. 2002;31:339-346; 4. Wang XW, et al. *Toxicology*. 2002;181-182:43-47;
5. Koike K. *Hepatol Res*. 2005;33:145-150.

Mangement Of HCC

AJCC/UICC Classification System

Classification Parameter	Definition
Primary tumor	
TX	Cannot be assessed
T0	No evidence of tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors with diameter $\leq$ 5 cm
T3	Multiple tumors with diameter $>$ 5 cm or solitary tumor involving a major branch of the portal and/or hepatic vein
T4	Tumor or tumors directly invading adjacent organs other than gallbladder or causing perforation of visceral peritoneum
Regional lymph nodes	
NX	Cannot be assessed
N0	No metastasis to regional lymph nodes
N1	Regional lymph node metastasis
Distant metastasis	
MX	Cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage	
I	T1, N0, M0
II	T2, N0, M0
IIIA	T3, N0, M0
IIIB	T4, N0, M0
IIIC	Any T, N1, M0
IV	Any T, any N, M1
Histologic grade	
GX	Cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated
Fibrosis	
F0	Fibrosis score of 0–4 (no fibrosis to moderate fibrosis)
F1	Fibrosis score of 5–6 (severe fibrosis to cirrhosis)

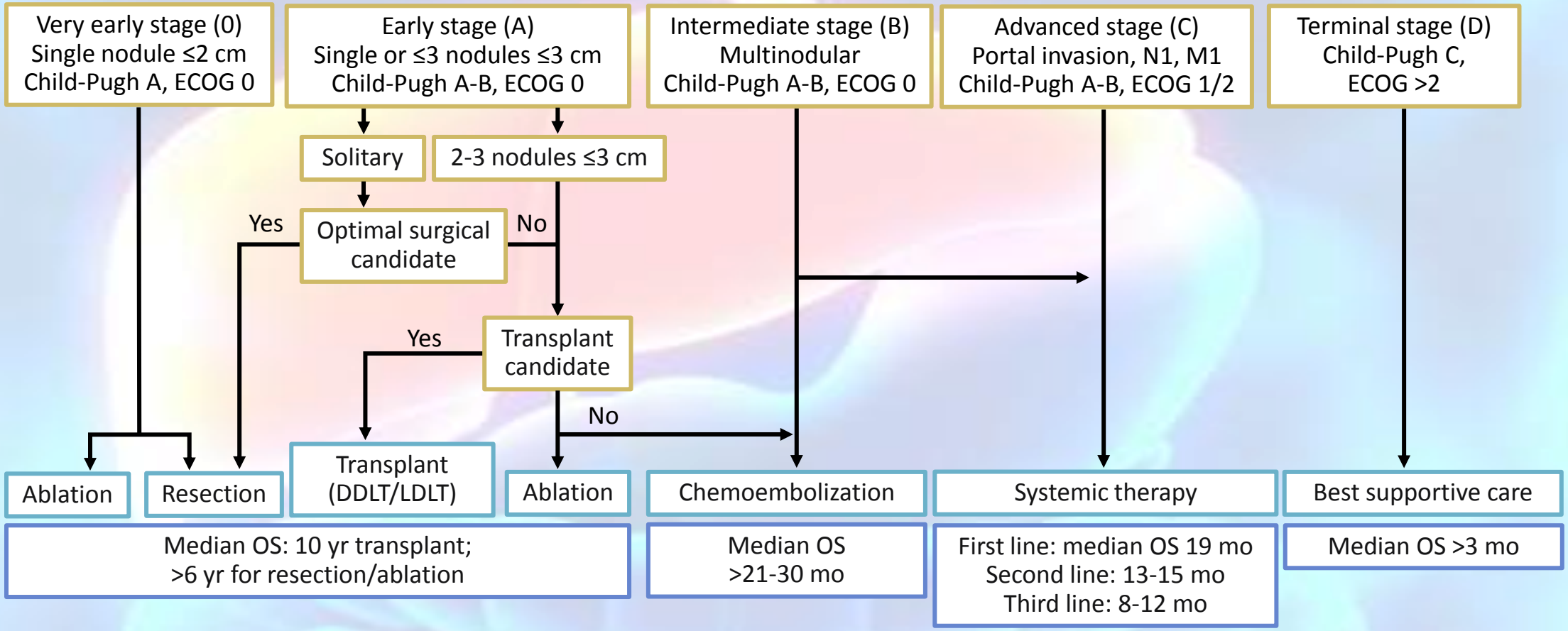
Child-Pugh Classification of Severity of Liver Cirrhosis and functions

Measure	1 Point	2 Points	3 Points
Bilirubin, mg/dL	< 2.0	2.0-3.0	> 3.0
Albumin, g/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin time, sec	< 4.0	4.0-6.0	➢6.0
INR	<1.7	1.7-2.3	➢2.3
Ascites	None	Slight	Moderate
Encephalopathy, grade	None	I-II	III-IV

Grade	Total Points	Surgical Risk	2-Yr Survival, %
A (well-compensated disease)	1-6	Good	85
B (significant functional compromise)	7-9	Moderate	60
C (decompensated disease)	10-15	Poor	35

Pugh RN, et al. Br J Surg. 1973;60:646-649. Lucey MR, et al. Liver Transpl Surg. 1997;3:628-637.

Curative Options Exist for Early-Stage HCC



Llovet. Hepatology. 2021;73(Suppl 1):158.

FDA-Approved Systemic Therapy for Advanced HCC

Sorafenib

First Line
Lenvatinib
Atezolizumab + bevacizumab

Second Line and Beyond
Regorafenib
Nivolumab*
Pembrolizumab*
Cabozantinib
Ramucirumab
Nivolumab + ipilimumab*

*Accelerated approval.

Sorafenib

Phase III SHARP Study: Sorafenib vs Placebo in Advanced HCC

Patients with advanced HCC, Child-Pugh A,

ECOG PS ≤ 2, no previous systemic treatment
(N = 602)

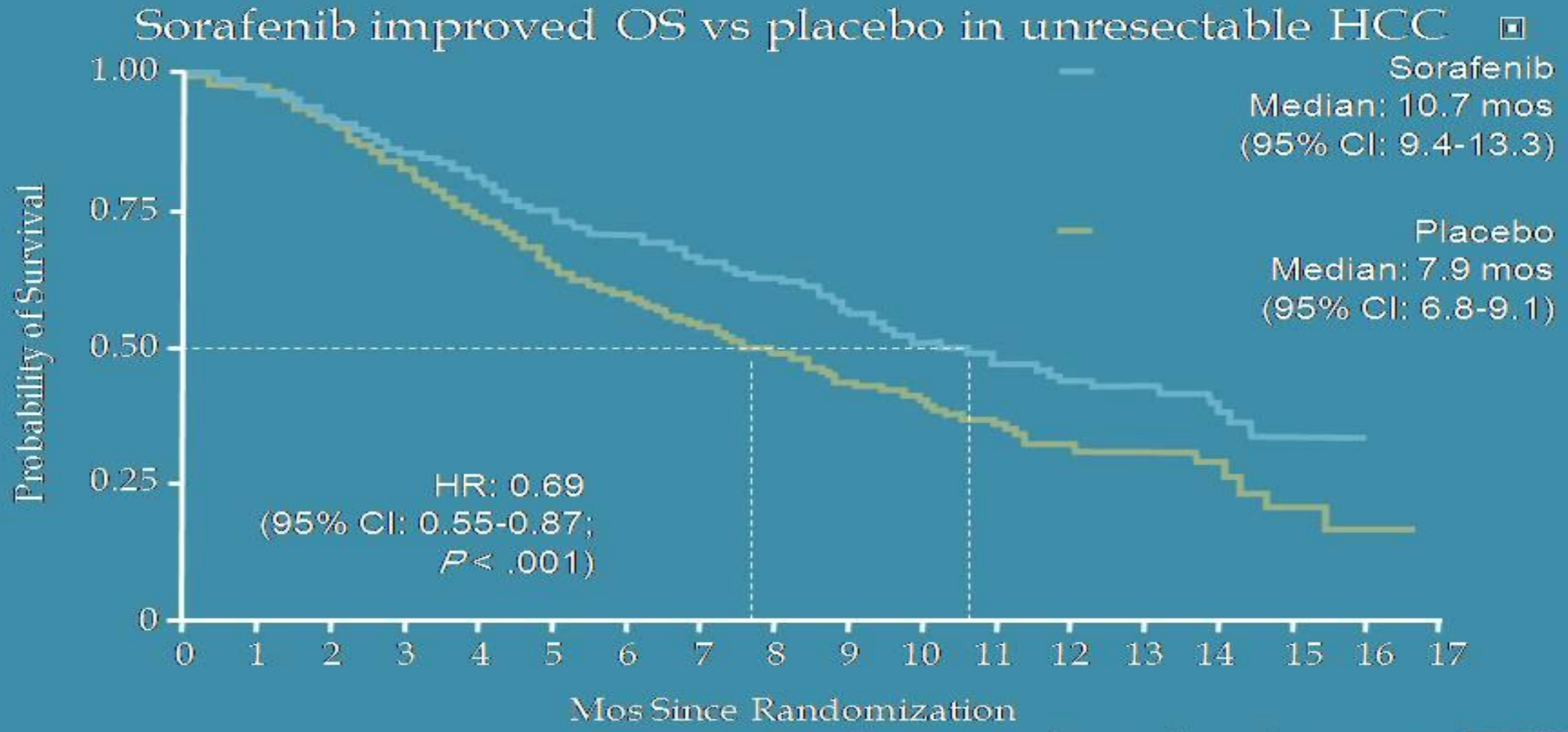
Sorafenib
400 mg PO BID, continuous dosing
(n = 299)

Placebo
2 tablets PO BID, continuous dosing
(n = 303)

- Primary endpoints: OS, time to symptomatic progression
- Secondary endpoint: TTP (independent review), disease control rate, safety

Llovet JM, et al. N Engl J Med. 2008;359:378-390.

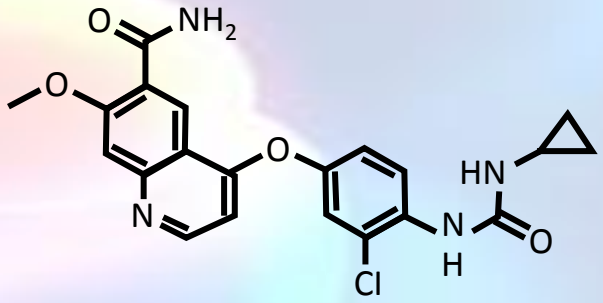
SHARP: Overall Survival



LINVATINIB

Lenvatinib Mechanism of Action

- Lenvatinib is a receptor tyrosine kinase inhibitor that inhibits the activities of the following receptors



Lenvatinib PI. Stepanovic. Biologics. 2014;8:129.

Study Schema

Global, randomized, open-label, phase III noninferiority 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)

Randomization 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

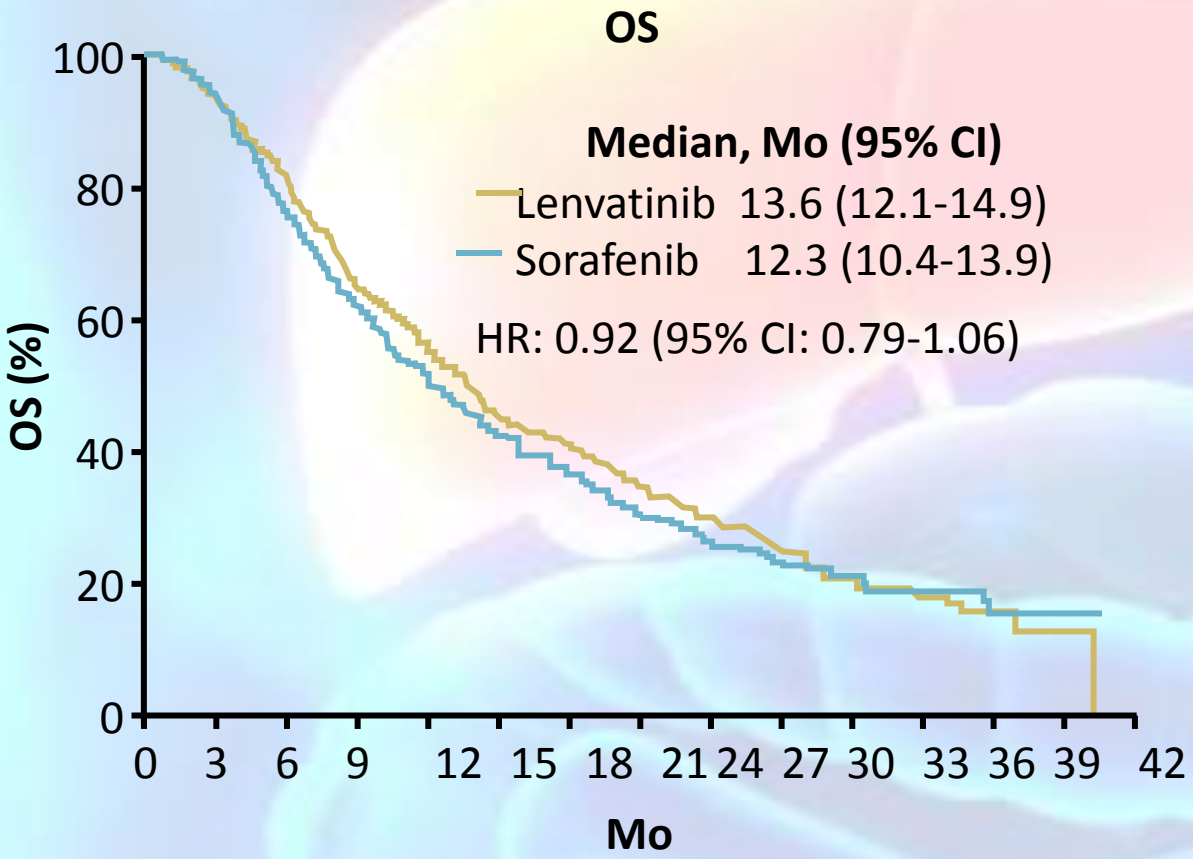
Tumor assessments were performed according to mRECIST by the investigator

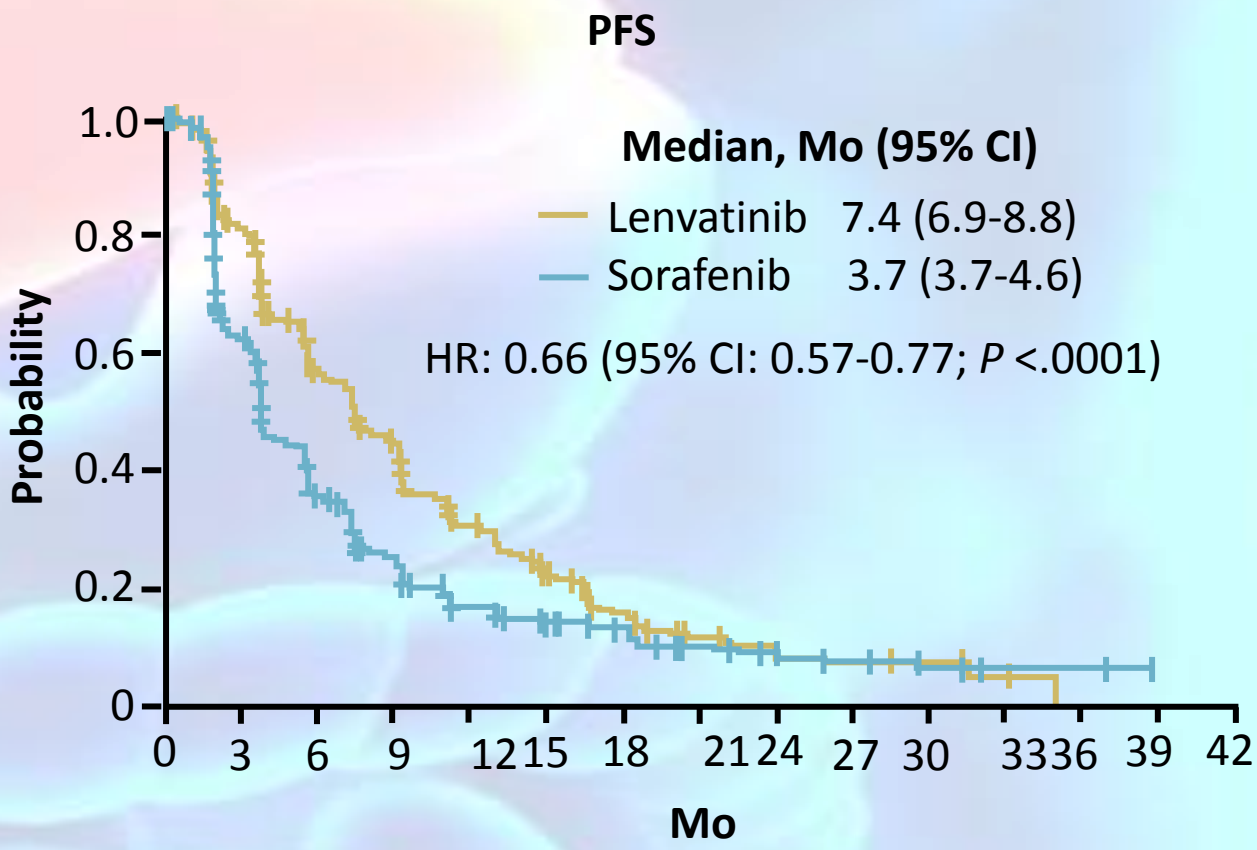
BCLC, Barcelona Clinic Liver Cancer; BW; body weight; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EHS, extrahepatic spread; MPVI, macroscopic portal vein invasion; mRECIST, modified Response Evaluation Criteria In Solid Tumors; ORR, objective response rate; OS, overall survival; PFS,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

Cheng L-A, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 4001.

REFLECT: Frontline Lenvatinib vs Sorafenib in Unresectable HCC

- Randomized, open-label, noninferiority phase III trial of lenvatinib vs sorafenib for patients with unresectable HCC, no prior systemic therapy, Child-Pugh A, BCLC stage B or C (N = 954)





Kudo. Lancet. 2018;391:1163.

REFLECT: Tumor Assessments

Parameter	mRECIST by Investigator		mRECIST by Independent Review		RECIST v1.1 by Independent Review	
	Lenvatinib (n = 478)	Sorafenib (n = 476)	Lenvatinib (n = 478)	Sorafenib (n = 476)	Lenvatinib (n = 478)	Sorafenib (n = 476)
ORR, n(%)	115 (24.1)	(9.2) 44	(40.6) 194	(12.4) 59	(18.8) 90	(6.5) 31
%95CI	20.2-27.9	6.6-11.8	36.2-45.0	9.4-15.4	15.3-22.3	4.3-8.7
Odds ratio %95) CI(*	3.13 (2.15-4.56)		3.59) 5.01-(7.01		2.17) 3.34-(5.14	
BOR, n(%)						
CR	6 (1)	(1>) 2	(2) 10	(1) 4	(1>) 2	(1>) 1
PR	109 (23)	(9) 42	(38) 184	(12) 55	(18) 88	(6) 30
SD	246 (51)	(51) 244	(33) 159	(46) 219	(54) 258	(53) 250
Durable SD†	167 (35)	(29) 139	(18) 84	(19) 90	(34) 163	(25) 118
PD	71 (15)	(31) 147	(17) 79	(32) 152	(18) 84	(32) 152
NE/unknown	46 (10)	(9) 41	(10) 46	(10) 46	(10) 46	(9) 43

*Lenvatinib vs sorafenib. †SD lasting ≥23 wk.

Kudo. Lancet. 2018;391:1163.

REFLECT: Select Treatment-Emergent AEs

AE, %	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Total	99	75	99	67
HFSR	**27**	**3**	**52**	**11**
Hypertension	**42**	**23**	**30**	**14**
Diarrhea	39	4	46	4
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Fatigue	30	4	25	4
Alopecia	3	0	25	0
Proteinuria	25	6	11	2
Dysphonia	24	<1	12	2
Nausea	20	1	14	1

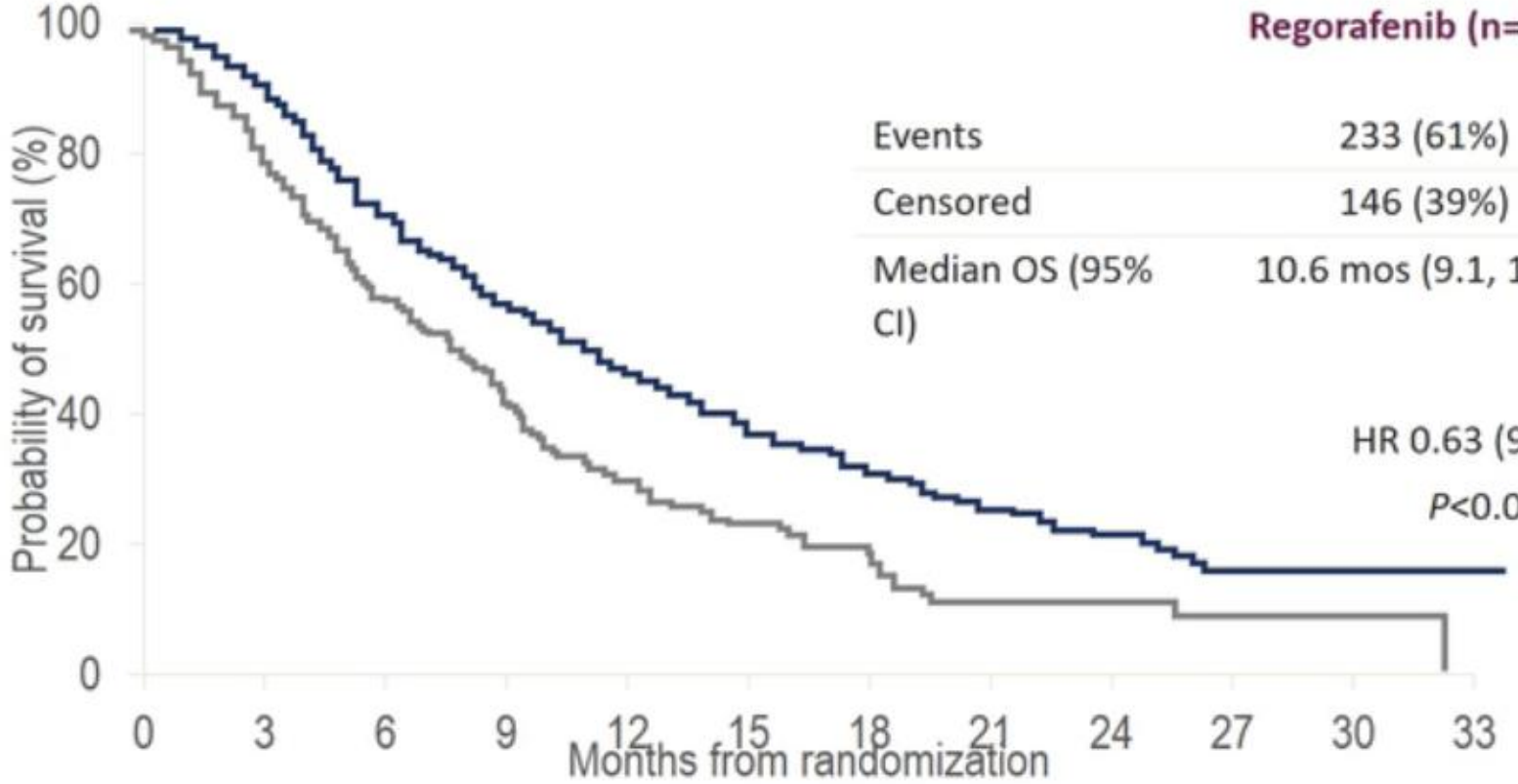
Kudo. Lancet. 2018;391:1163.

Positive Second Line Trials in HCC

Trial	Drug	N	PFS benefit (months)	OS benefit (months)	RR
RESORCE	Regorafenib vs Placebo	573	+1.6	+2.8	11%
CELESTIAL	Cabozantinib vs Placebo	707	+3.2	+2.2	4%
REACH 2*	Ramucirumab vs Placebo	292	+1.2	+1.2	4.6%

*Only patients with AFP ≥ 400 ng/ml

RESORCE: OS



	Regorafenib (n=379)	Placebo (n=194)
Events	233 (61%)	140 (72%)
Censored	146 (39%)	54 (28%)
Median OS (95% CI)	10.6 mos (9.1, 12.1)	7.8 mos (6.3, 8.8)

HR 0.63 (95% CI: 0.50, 0.79)

P<0.0001 (1-sided)

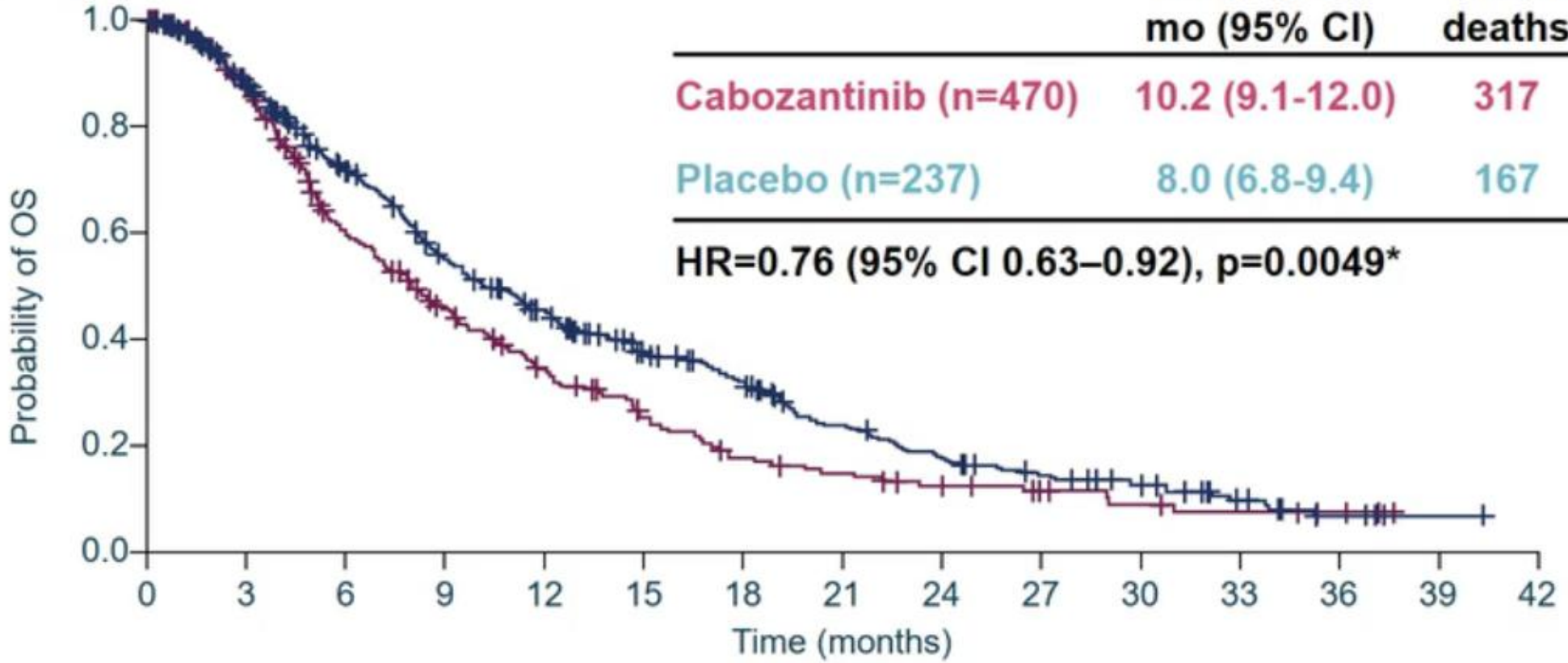
—Regorafenib n=	379	316	224	170	122	78	54	34	21	10	4	0
—Placebo n=	194	149	95	62	37	26	16	8	5	3	1	0

MUNICH 2018 ESMO congress

Bruix J *et al. Lancet* 2017;389:56–66

Ospedale del mare

CELESTIAL: OS



	Median OS mo (95% CI)	No. of deaths
Cabozantinib (n=470)	10.2 (9.1-12.0)	317
Placebo (n=237)	8.0 (6.8-9.4)	167

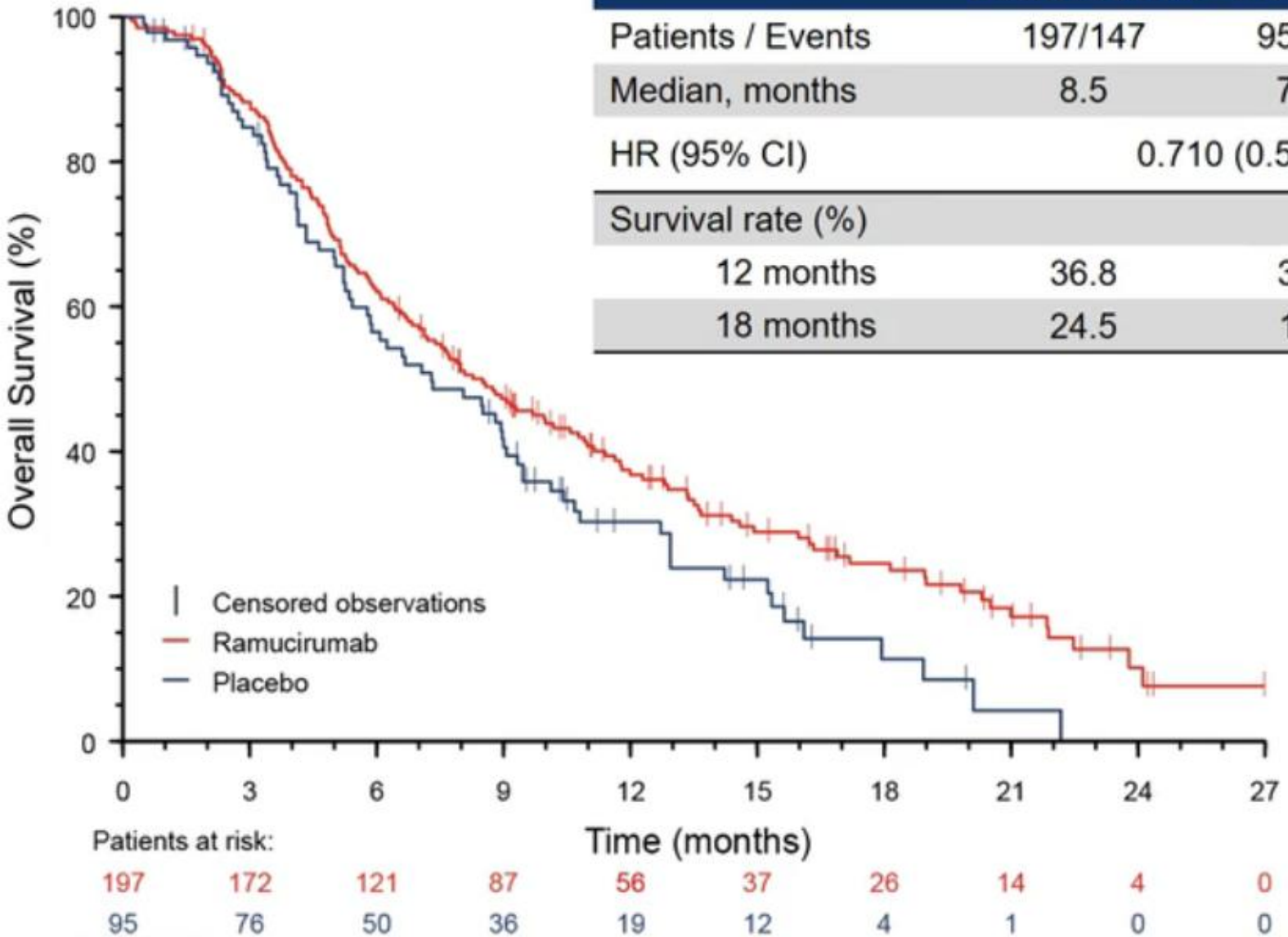
HR=0.76 (95% CI 0.63–0.92), p=0.0049*

No. at Risk

Cabozantinib	470	382	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

REACH-2: OS

	Ramucirumab	Placebo	Difference	P-value
Patients / Events	197/147	95/74		
Median, months	8.5	7.3	1.2	
HR (95% CI)	0.710 (0.531, 0.949)			0.0199
Survival rate (%)				
12 months	36.8	30.3	6.5	0.2930
18 months	24.5	11.3	13.2	0.0187



Zhu AX et al; *ASCO* 2018

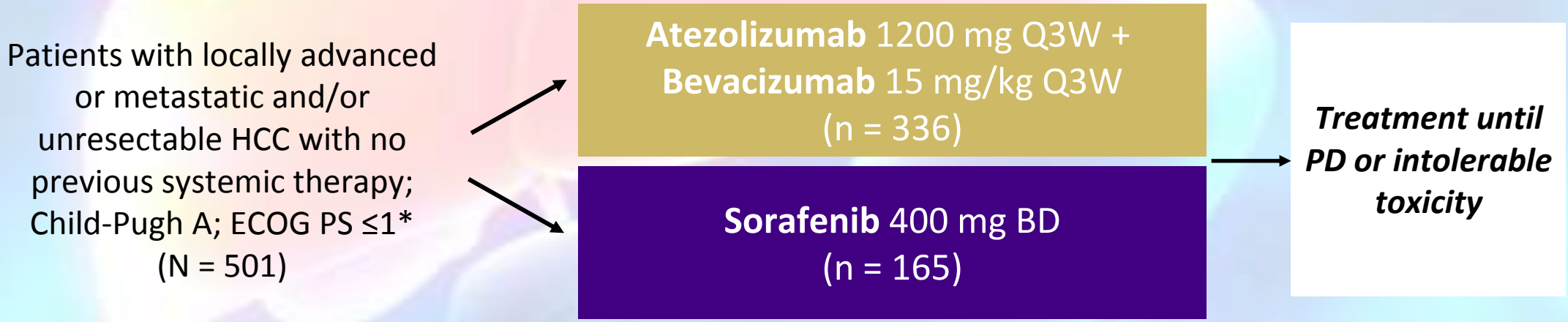
RESORCE, CELESTIAL & REACH-2 TRIALS: AEs

AE (%)	REGORAFENIB	CABOZANTINIB	RAMUCIRUMAB
Diarrhea	41	54	16
HFSR	53	46	NR
Fatigue	40	45	27
Hypertension	31	29	24
Ascites	16	12	18
Weight Loss	14	17	NR
Abdominal Pain	28	18	20
Proteinuria	NR	NR	20
Bleeding	NR	NR	24

Setting New Standards in Advanced Liver Cancer: Frontline Therapy

IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib for First-line Treatment of Advanced HCC

- Multicenter, randomized, open-label phase III trial[1]
  - GO30140: randomized phase Ib study showed potential benefit of atezolizumab + bevacizumab for patients with advanced HCC (ORR 36%)[2]



- Coprimary endpoints: OS and PFS

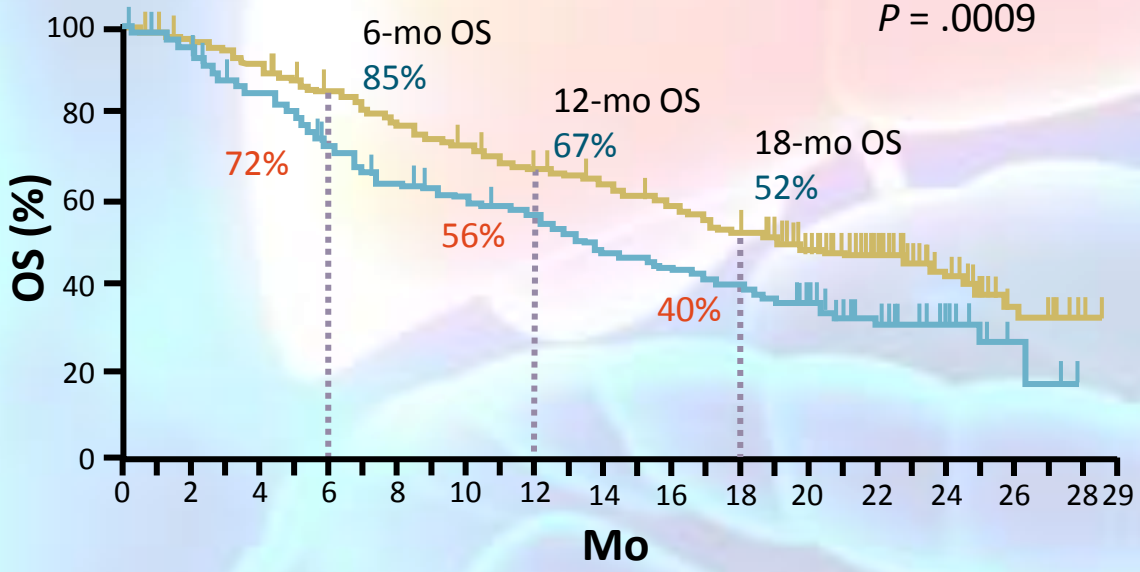
*Trial included subgroups of high-risk patients excluded from other contemporary phase III trials: ≈ 40% had macrovascular invasion; specifically included patients with 50% hepatic involvement or main portal vein invasion or invasion of the portal vein branch contralateral to the primarily involved lobe.

1. Finn. NEJM. 2020;382:1894. 2. Lee. Lancet Oncol. 2020;21:808.

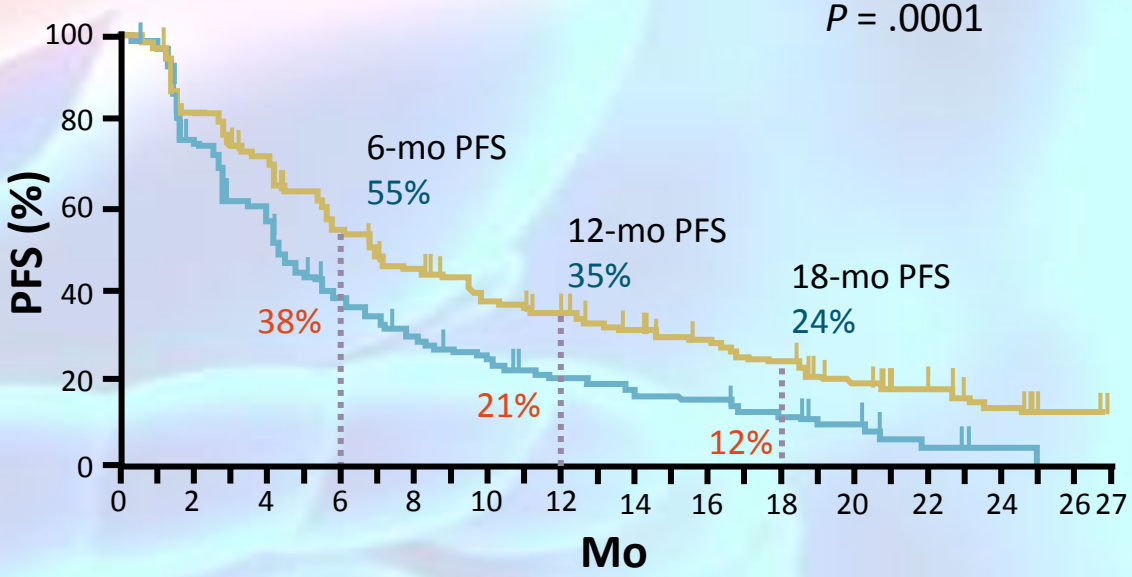
IMbrave150: Updated OS and PFS

- Primary analysis OS/PFS HR: 0.58/0.59 (median f/u 8.6 mo)

	Atezo + Bev (n = 336)	Sorafenib (n = 165)
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 = .0009	



	Atezo + Bev (n = 336)	Sorafenib (n = 165)
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 = .0001	



Median follow-up: 15.6 mo.

Finn. NEJM. 2020;382:1894. Finn. ASCO GI 2021. Abstr 267.

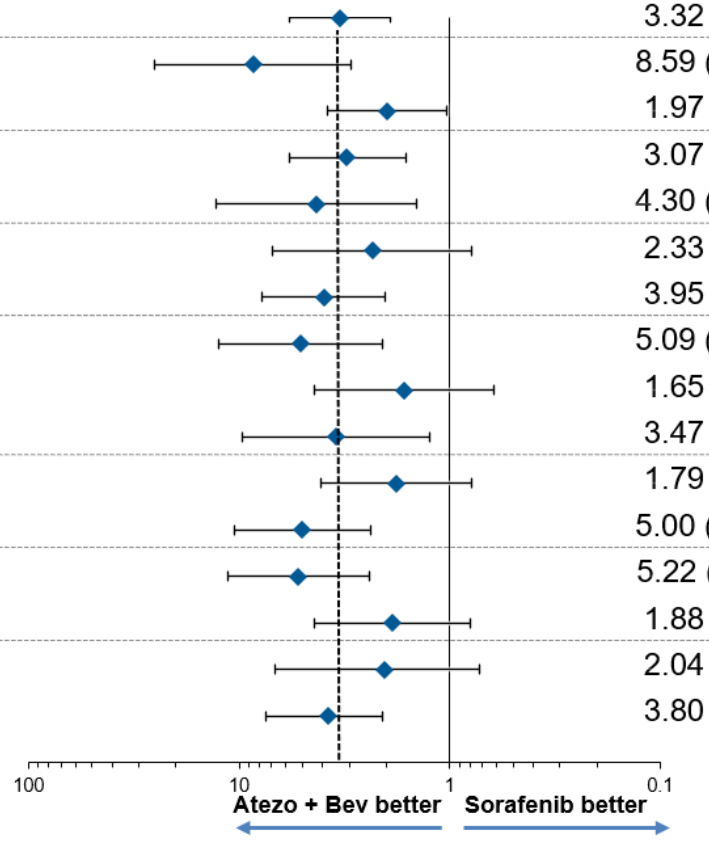
IMbrave150: Updated Response

Outcome	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR,% (95% CI)	**30 (32-35)**	**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, mo (95% CI)	**18.1 (14.6-NE)**	**14.9 (4.9-17.0)**	**16.3 (13.1-21.4)**	**12.6 (6.1-17.7)**

Finn. NEJM. 2020;382:1894. Finn. ASCO GI 2021. Abstr 267.

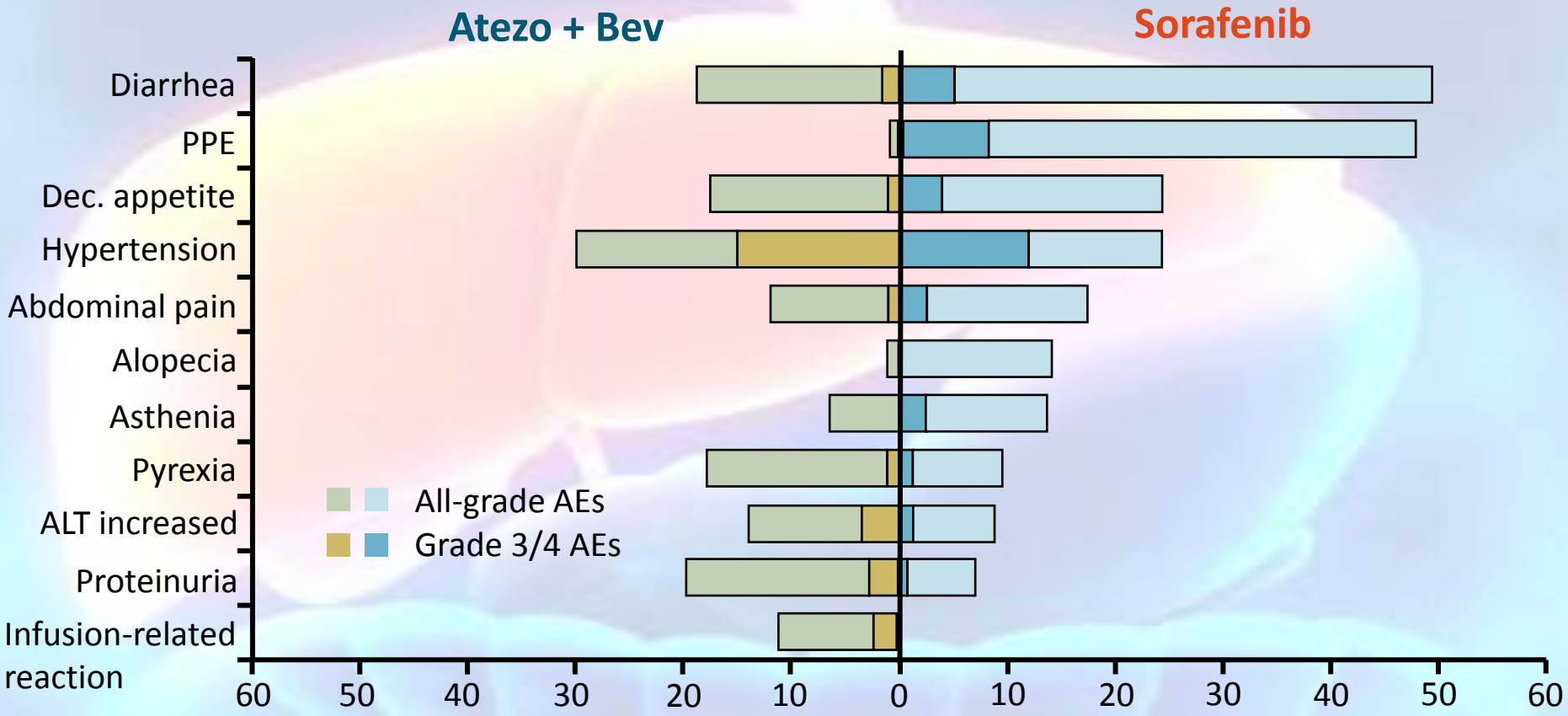
IMbrave150: ORR Subgroup Analysis (IRF RECIST 1.1)

Characteristic (n)	Atezo + Bev ORR, %	Sorafenib ORR, %	OR (95% CI)
All patients (485)	30	11	3.32 (1.92, 5.72)
Asia (excluding Japan[a]) (195)	36	6	8.59 (2.94, 25.13)
Rest of world (290)	26	15	1.97 (1.03, 3.78)
ECOG PS 0 (299)	34	14	3.07 (1.62, 5.80)
ECOG PS 1 (186)	23	7	4.30 (1.44, 12.87)
BCLC stage B (72)[b]	44	25	2.33 (0.79, 6.91)
BCLC stage C (400)[b]	27	9	3.95 (2.02, 7.75)
Hepatitis B virus HCC (230)	32	8	5.09 (2.07, 12.53)
Hepatitis C virus HCC (104)	30	21	1.65 (0.62, 4.39)
Nonviral HCC (151)	27	9	3.47 (1.24, 9.65)
AFP ≥ 400 ng/mL (185)	24	15	1.79 (0.79, 4.06)
AFP < 400 ng/mL (300)	33	9	5.00 (2.37, 10.54)
EHS and/or MVI (368)[c]	28	7	5.22 (2.42, 11.26)
No EHS and MVI (117)[c]	36	23	1.88 (0.80, 4.41)
High risk (98)[d]	25	14	2.04 (0.72, 6.77)
No high risk (387)[d]	31	10	3.80 (2.08, 7.44)



Finn. EASL 2021. Abstr.

IMbrave150: Safety



≥10% frequency in either arm and >5% difference between arms.

Cheng. ESMO Asia 2019. Abstr LBA3. Finn. NEJM. 2020;382:1894.

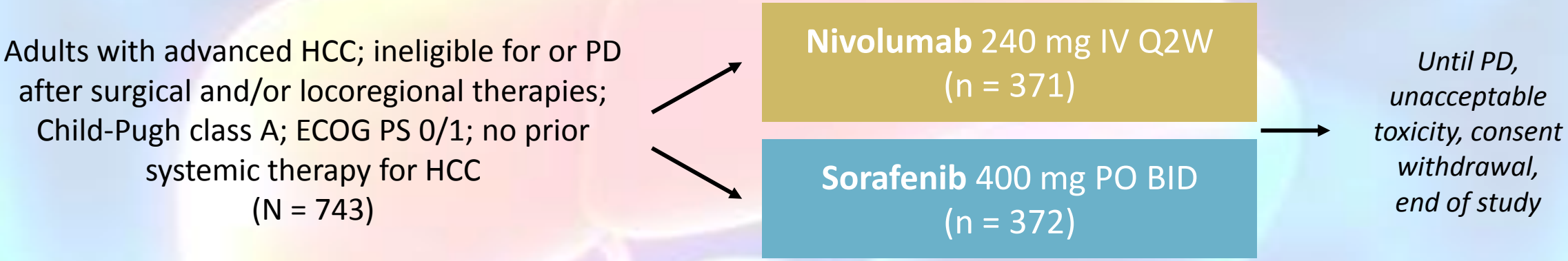
IMbrave150: Bleeding

All-Cause AESI, n (%)	Atezolizumab + Bevacizumab (n = 329)		Sorafenib (n = 156)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Bleeding/hemorrhage	83 (25.2)	21 (6.4)	27 (17.3)	9 (5.8)
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Hematuria	10 (3.0)	1 (0.3)	0	0
Gingival bleeding	9 (2.7)	0	0	0
Esophageal varices hemorrhage	8 (2.4)	6 (1.8)	1 (0.6)	1 (0.6)
Gastrointestinal hemorrhage	8 (2.4)	4 (1.2)	3 (1.9)	3 (1.9)
Rectal hemorrhage	5 (1.5)	1 (0.3)	3 (1.9)	0
Upper gastrointestinal hemorrhage	4 (1.2)	2 (0.6)	2 (1.3)	2 (1.3)
Hemoptysis	3 (0.9)	0	5 (3.2)	0
Peritoneal hemorrhage	0	0	2 (1.3)	1 (0.6)

Finn. NEJM. 2020;382:1894.

CheckMate 459: Nivolumab vs Sorafenib as First-line Therapy for Advanced HCC

International, open-label, randomized phase III trial (minimum follow-up: 22.8 mo)



- Primary endpoint: OS
  - Predefined threshold for statistical significance: HR of 0.84 (*P* = .0419)
- Secondary endpoints: PFS, ORR, association between PD-L1 expression and efficacy

Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

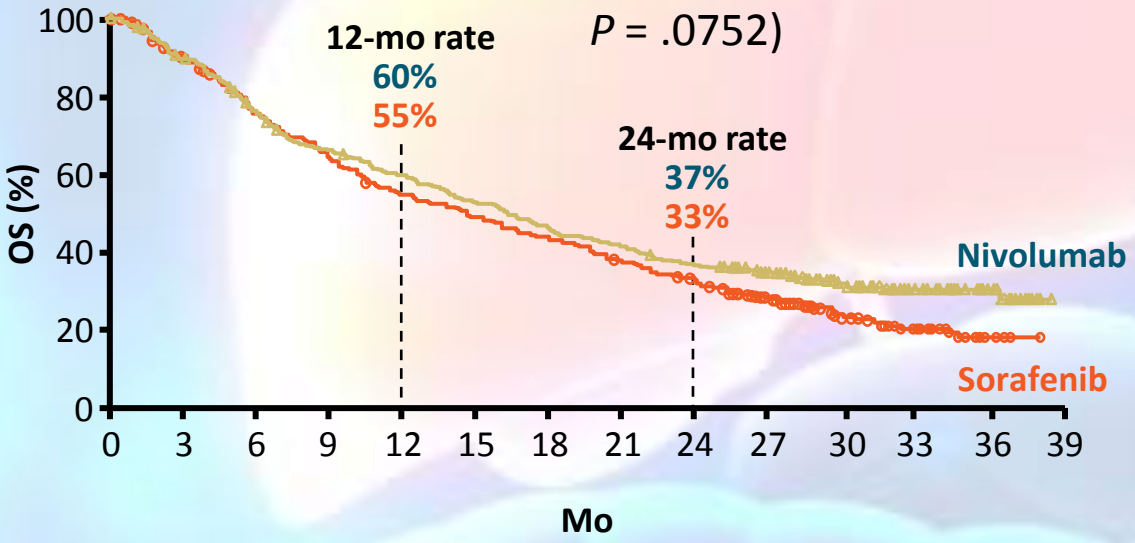
CheckMate 459: OS and PFS

Median OS, Mo (95% CI)

Nivolumab 16.4 (13.9-18.4)

Sorafenib 14.7 (11.9-17.2)

HR: 0.85 (95% CI: 0.72-1.02; *P* = .0752)

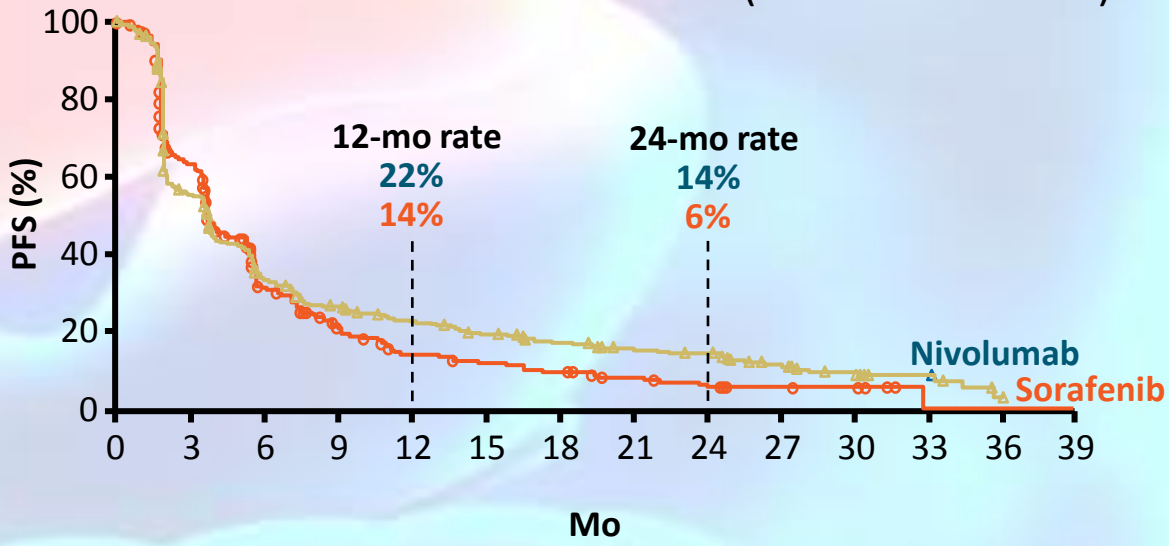


Median PFS, Mo (95% CI)

Nivolumab 3.7 (3.1-3.9)

Sorafenib 3.8 (3.7-4.5)

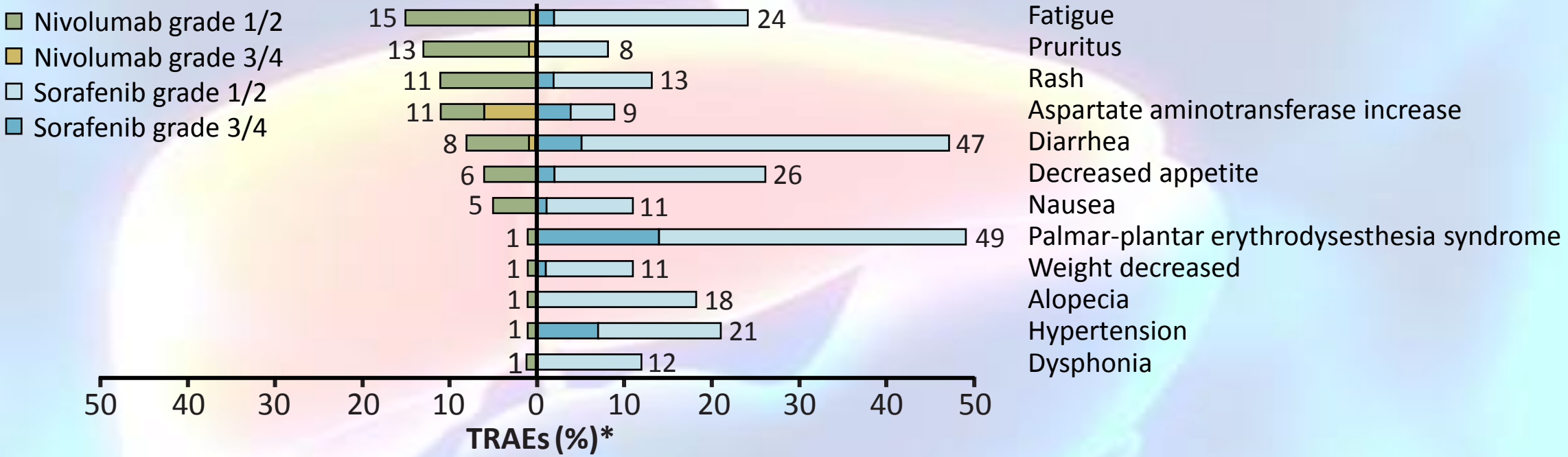
HR: 0.93 (95% CI: 0.79-1.10)



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

Yau. ESMO 2019. Abstr LBA38_PR.

CheckMate 459: Summary of TRAEs



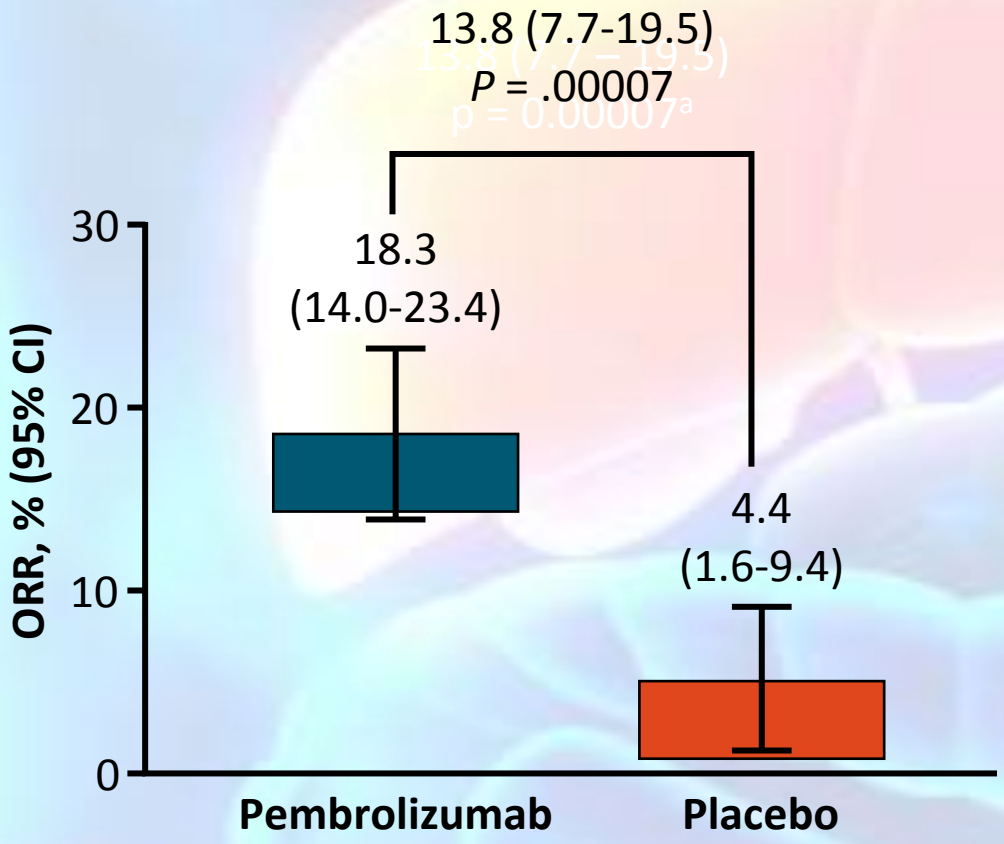
- Nivolumab demonstrated improved safety profile compared with sorafenib, with fewer grade 3/4 TRAEs and TRAEs leading to discontinuation vs sorafenib
  - Grade 3/4 TRAEs: nivolumab, 22%; sorafenib, 49%

*Occurring in >10% of patients in either treatment arm.

Yau. ESMO 2019. Abstr LBA38_PR.

KEYNOTE-240: Pembrolizumab for Patients With Previously Treated HCC

Randomized phase III trial of pembrolizumab or placebo (both plus BSC) for patients with advanced HCC with intolerance to or PD on or after sorafenib; Child-Pugh A; no invasion of main portal vein (N = 413)



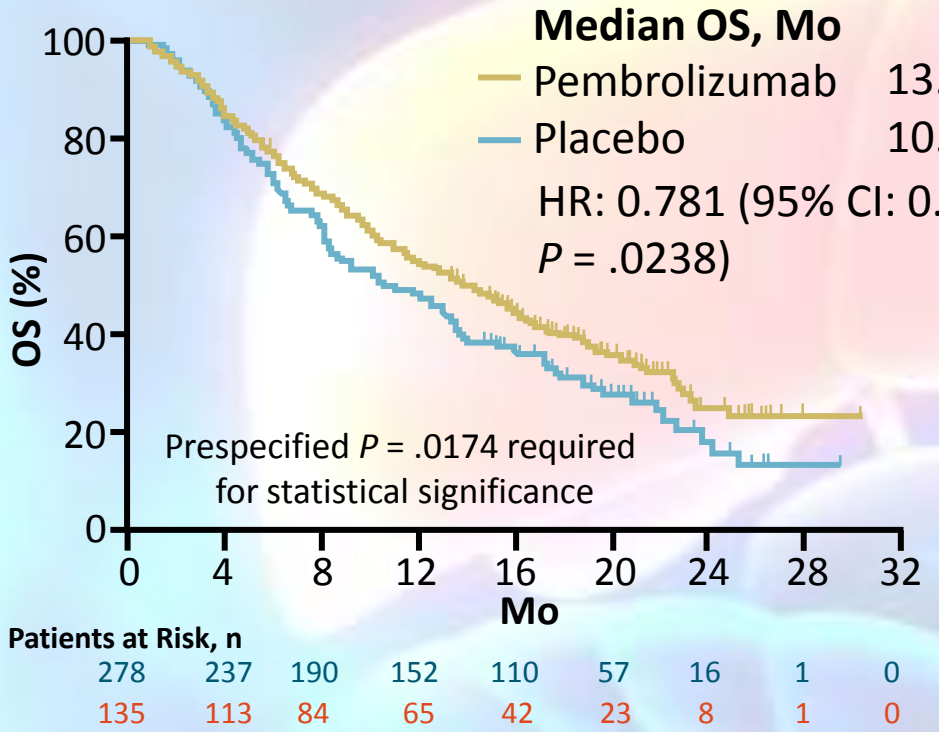
Response n(%)	Pembrolizumab (n = 278)	Placebo (n = 135)
Best overall response		
▪ CR	6 (2.2)	0
▪ PR	45 (16.2)	6 (4.4)
▪ SD	122 (43.9)	66 (48.9)
▪ SD ≥23 wk	37 (13.3)	20 (14.8)
Progressive disease	90 (32.4)	57 (42.2)
Disease control rate (CR + PR + SD)	173 (62.2)	72 (53.3)

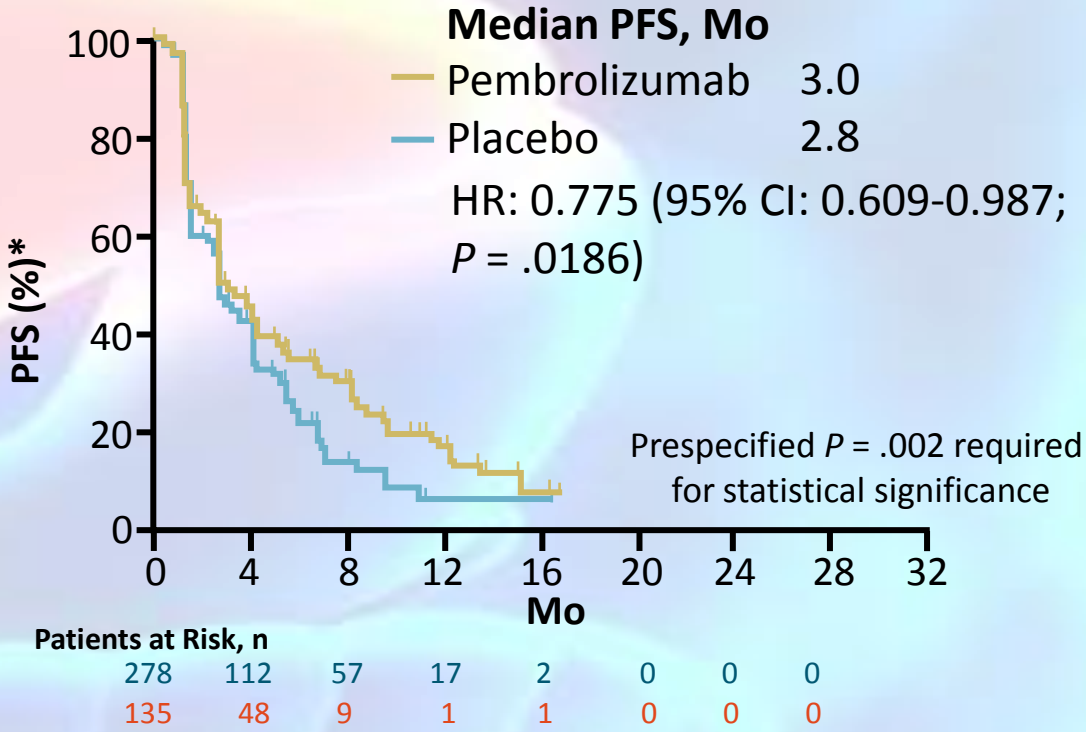
Duration of response, median (range): pembrolizumab, 13.8 mo (1.5+ to 23.6+ mo); placebo, not reached (2.8 to 20.4+ mo)

Finn. JCO. 2020;38:193.

KEYNOTE-240: OS and PFS

Failed to reach prespecified level of statistical significance for OS, PFS





*Primary analysis.

Finn. JCO. 2020;38:193.

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Hepatocellular Carcinoma

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First-Line Systemic Therapy

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1]	• Sorafenib (Child-Pugh Class A) [category 1] or B7)[d,e,2,3] • Lenvatinib (Child-Pugh Class A only)[4,5] (category 1)	• Nivolumab[b,6] (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B) • FOLFOX (category 2B)[f]

Subsequent-Line Therapy[g] if Disease Progression[h]	Other Recommended Regimens	Useful in Certain Circumstances
Options • Regorafenib (Child-Pugh Class A only) (category 1)[i,7] • Cabozantinib (Child-Pugh Class A only) (category 1)[i,8] • Ramucirumab (AFP ≥400 ng/mL only) (category 1)[i,9] • Lenvatinib (Child-Pugh Class A only) • Sorafenib (Child-Pugh Class A or B7)[d,e]	• Nivolumab + ipilimumab (Child-Pugh Class A only)[b,i,13] • Pembrolizumab (Child-Pugh Class A only)[b,j,k,14] (category 2B)	• Nivolumab (Child-Pugh Class B only)[b,j,10-12] (category 2B)


THANK
YOU