ADVANCED HEPATOMA
Sequence of therapies

CLINICAL CASE DISCUSSION

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DISCLOSURE

Speaker, consultancy and advisory role:

Roche, Bayer, Sanofi, Bristol-Myers Squibb, Lilly, Novartis, EISAI, AstraZeneca, Merck, Incyte, Medac, Ipsen, Servier, Pierre Fabre, Merck Sharp & Dohme, BTG, Janssen

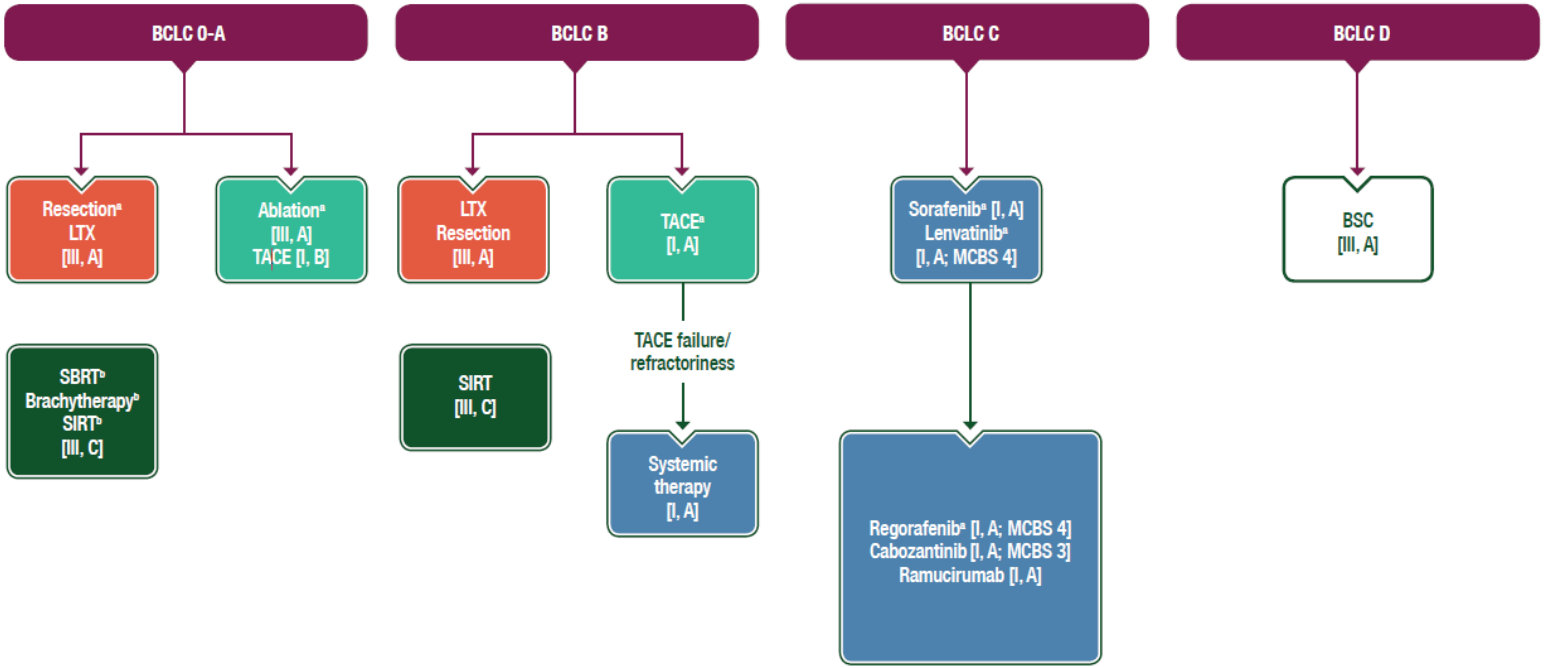
Research funding:

Servier

Commercial medical education provider:

OncLive

Treatment of hepatocellular carcinoma



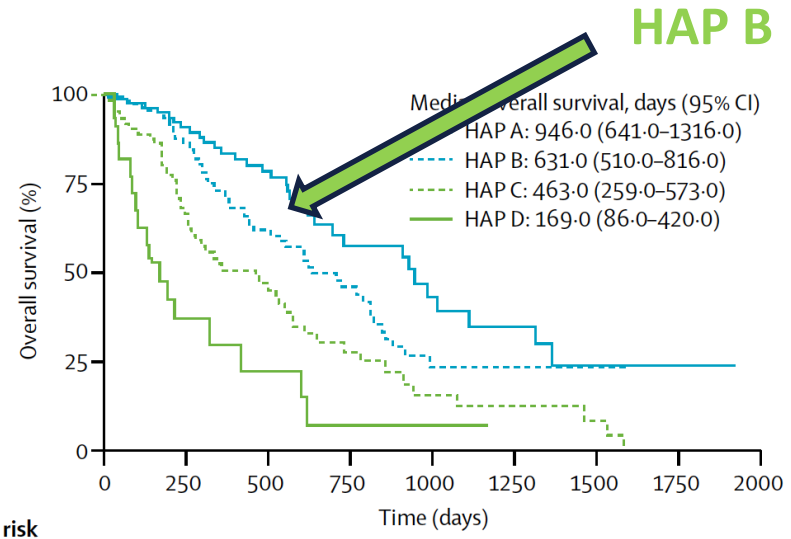
Vogel et al. 2018, Annals of Oncology

BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; LTX, liver transplantation; MCBS, ESMO-Magnitude of Clinical Benefit Scale; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, trans-arterial chemoembolisation

Patient selection for TACE: HAP Score
Impact of liver function and tumour burden

Albumin	**< 36 g/dl**
Bilirubin	**> 17 µmol/l**
AFP	**> 400 ng/ml**
Max. tumour	**> 7 cm**

HAP	Points
HAP A	0
HAP B	1
HAP C	2
HAP D	>2

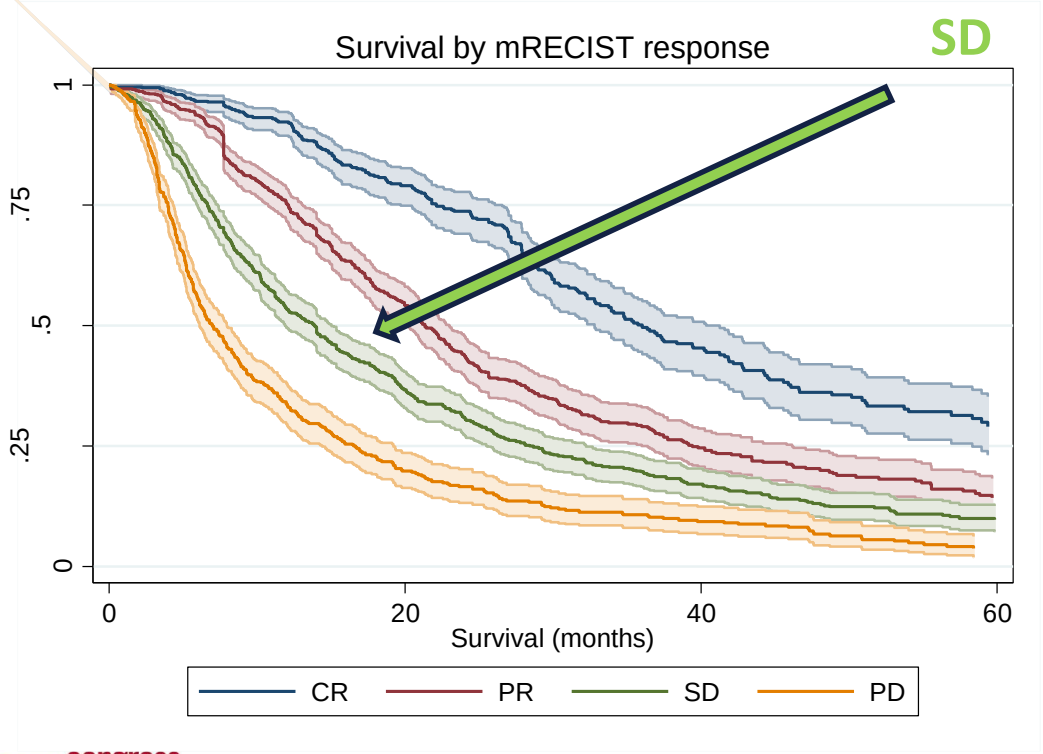


Number at risk (number censored)								
HAP A	87 (16)	64 (28)	44 (43)	20 (48)	11 (50)	7 (51)	4 (53)	2 (55)	0 (55)
HAP B	113 (13)	86 (37)	40 (45)	23 (50)	8 (55)	3 (57)	1 (58)	0 (58)	0 (58)
HAP C	75 (8)	44 (16)	24 (20)	11 (22)	5 (23)	3 (23)	2 (23)	0 (23)	0 (23)
HAP D	24 (5)	6 (6)	3 (6)	1 (6)	1 (7)	0 (7)	0 (7)	0 (7)	0 (7)

Kadalayil et al. Ann Oncol. 2013, Meyer et al. et al. Lancet Gastroenterology & Hepatology 2017

AFP, alpha foetoprotein; HAP, hepatoma arterial-embolisation prognostic; TACE, trans-arterial chemoembolisation

Overall Response matters!
Validated in GO-TREAT HCC cohort



n=508
CR: 36.02
(32.80, 40.33)

n= 653
PR: 21.32
(20.20, 22.96)

n= 674
SD: 13.88
(11.88, 15.00)

n= 504
PD: 6.97
(6.09, 7.93)

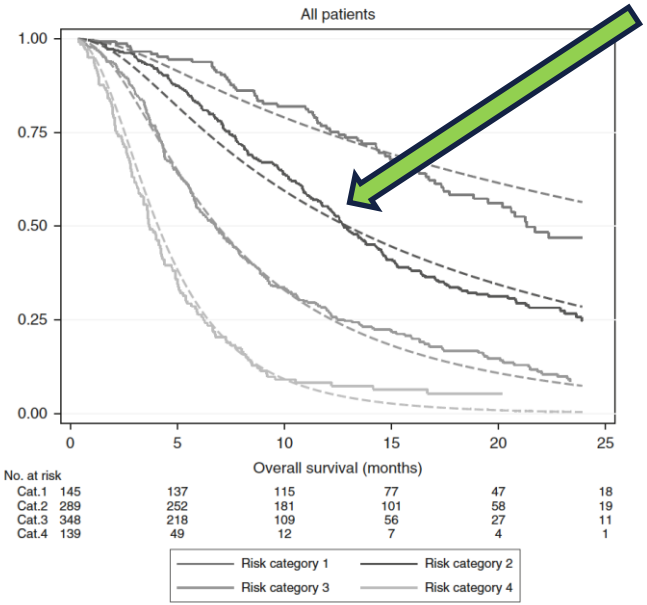
T. Labeur et al. Hepatology, in press

CR, complete response; HCC, hepatocellular carcinoma; PD, progressive disease; PR, partial response; SD, stable disease

Patient selection for sorafenib: PROSASH Score

PRediction Of Survival in Advanced Sorafenib-treated HCC

1130 patienten from 2 phase-III (Brivanib and Sunitinib)



https://jscalc.io/calc/oGSDLHDsDg9g2XBF

Linear Predictor:

3.399

Risk group:

intermediate low risk

Survival Probabilities

6 months	12 months	24 months	36 months
75.2%	49.9%	24.9%	13.4%

Berhane et al. BJC 2019

Linear predictor; n = (0.327 * **vascular invasion**) + (-0.0231 * (**Age** – 60)) + (0-0303 * ((**Age** – 60) x **vascular invasion**)) + (0.455 * **ECOG**) + (0.0831 * ln(**AFP**)) + (-0.0553 * **albumin**) + (0.709 x ln(**creatinine**)) + (0.349 * ln(**AST**) + 0.298 x **extra-hepatic spread**) + (0.526 * **HBV**) + (0.507 * **other aetiology** if not HCV/HBV)

AFP, alpha foetoprotein; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; Group; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

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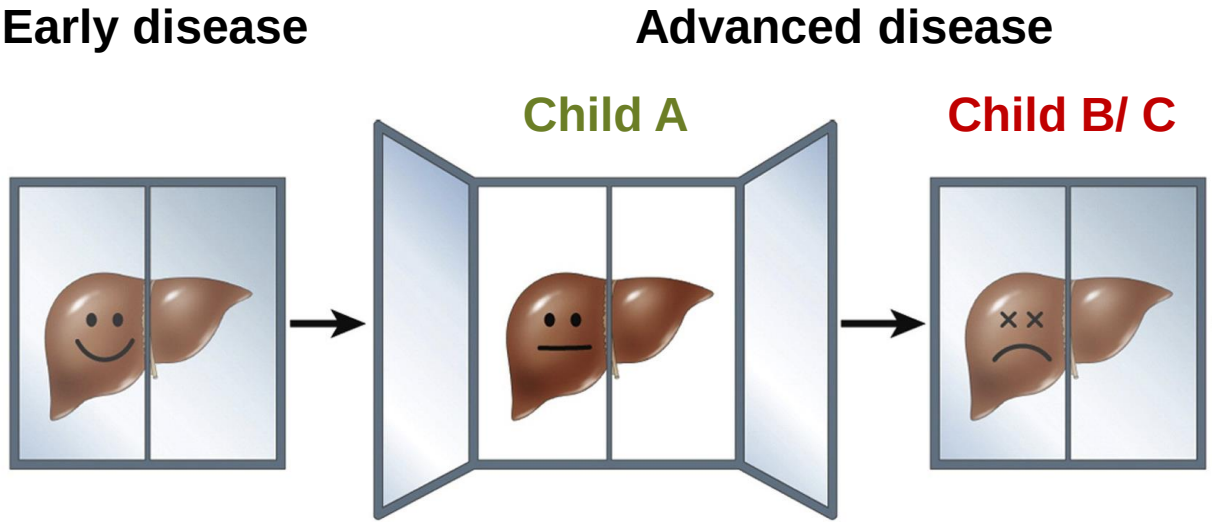
What do we need to consider in HCC?

✓ **Maintenance of liver function and the "window of opportunity"!**

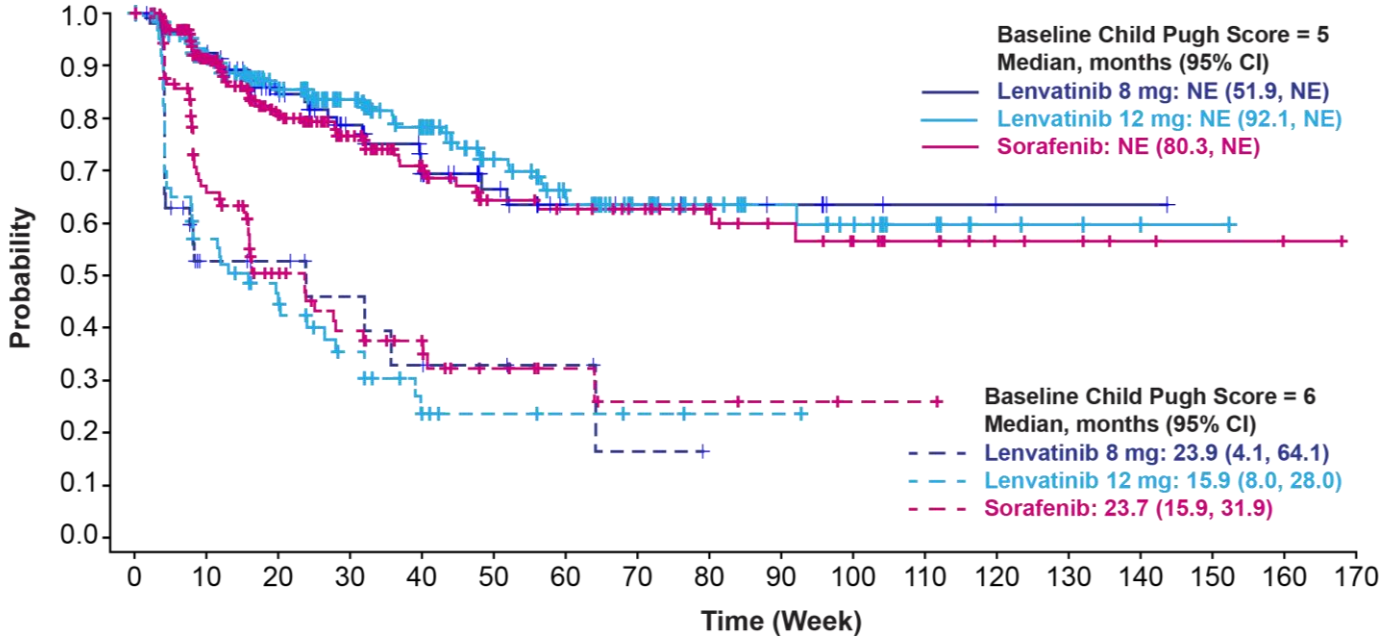


Modified form Ge et al. Gastroenterology 2014

HCC, hepatocellular carcinoma

The “Window of Opportunity” in 1st line

Decline of liver function during systemic treatment

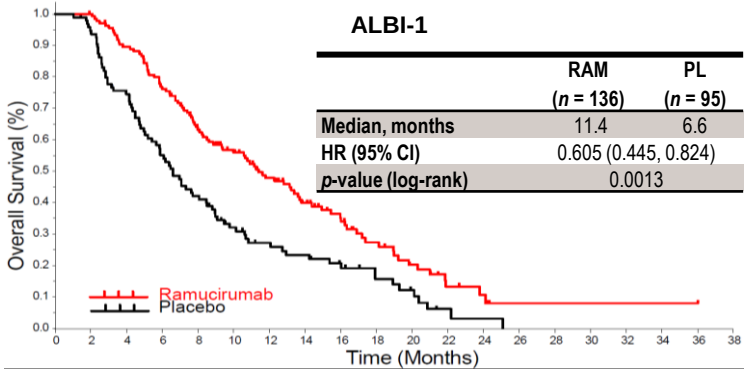


Time to deterioration to Child-Pugh Score ≥ 7 in the REFLECT study

CI, confidence interval; NE, not estimable

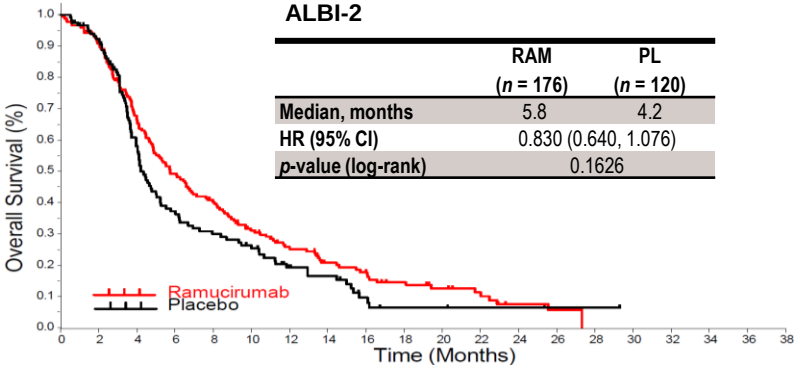
The “Window of Opportunity”
Liver function: Prognostic and Predictive

Ramucirumab mOS benefit in REACH-2/REACH



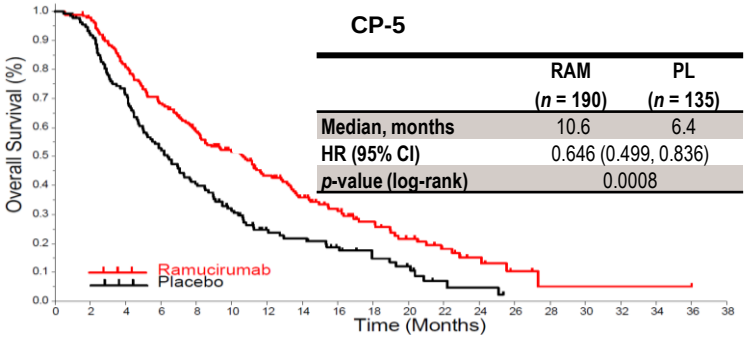
ALBI-1

	RAM (*n* = 136)	PL (*n* = 95)
Median, months	11.4	6.6
HR (95% CI)	0.605 (0.445, 0.824)	
p-value (log-rank)	0.0013	



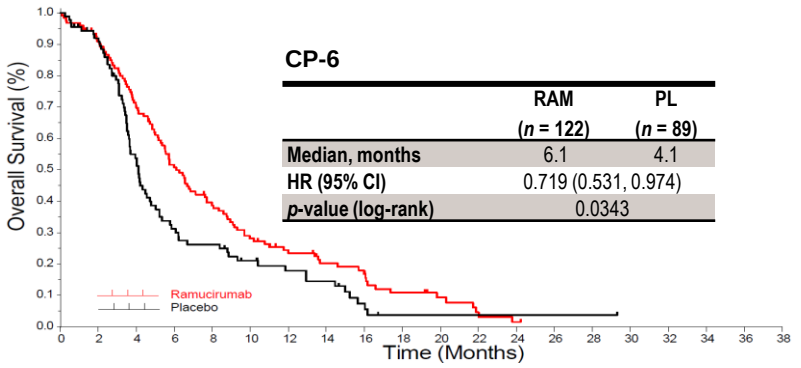
ALBI-2

	RAM (*n* = 176)	PL (*n* = 120)
Median, months	5.8	4.2
HR (95% CI)	0.830 (0.640, 1.076)	
p-value (log-rank)	0.1626	



CP-5

	RAM (*n* = 190)	PL (*n* = 135)
Median, months	10.6	6.4
HR (95% CI)	0.646 (0.499, 0.836)	
p-value (log-rank)	0.0008	



CP-6

	RAM (*n* = 122)	PL (*n* = 89)
Median, months	6.1	4.1
HR (95% CI)	0.719 (0.531, 0.974)	
p-value (log-rank)	0.0343	

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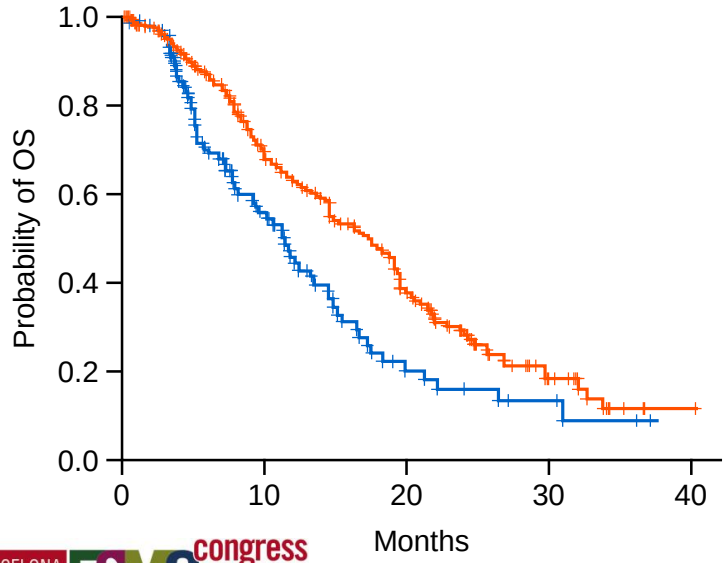
Brandi et al. EASL HCC Summit 2019

The “Window of Opportunity”/ CELESTIAL

ALBI Grade 1

	Median OS months	No. of Deaths (%)
Cabozantinib (N=186)	17.5	106 (57)
Placebo (N=102)	11.4	62 (61)

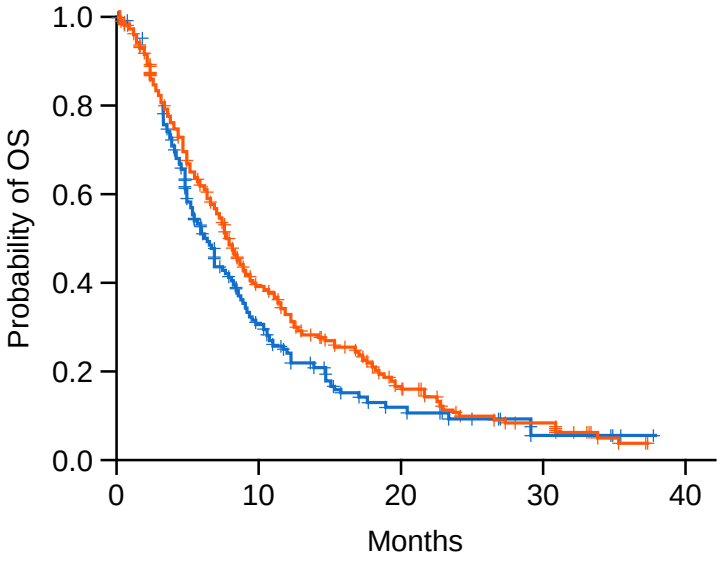
Hazard ratio = 0.62 (95% CI 0.44-0.88)



ALBI Grade 2

	Median OS months	No. of Deaths (%)
Cabozantinib (N=282)	8.0	209 (74)
Placebo (N=133)	6.4	103 (77)

Hazard ratio = 0.79 (95% CI 0.62-1.06)



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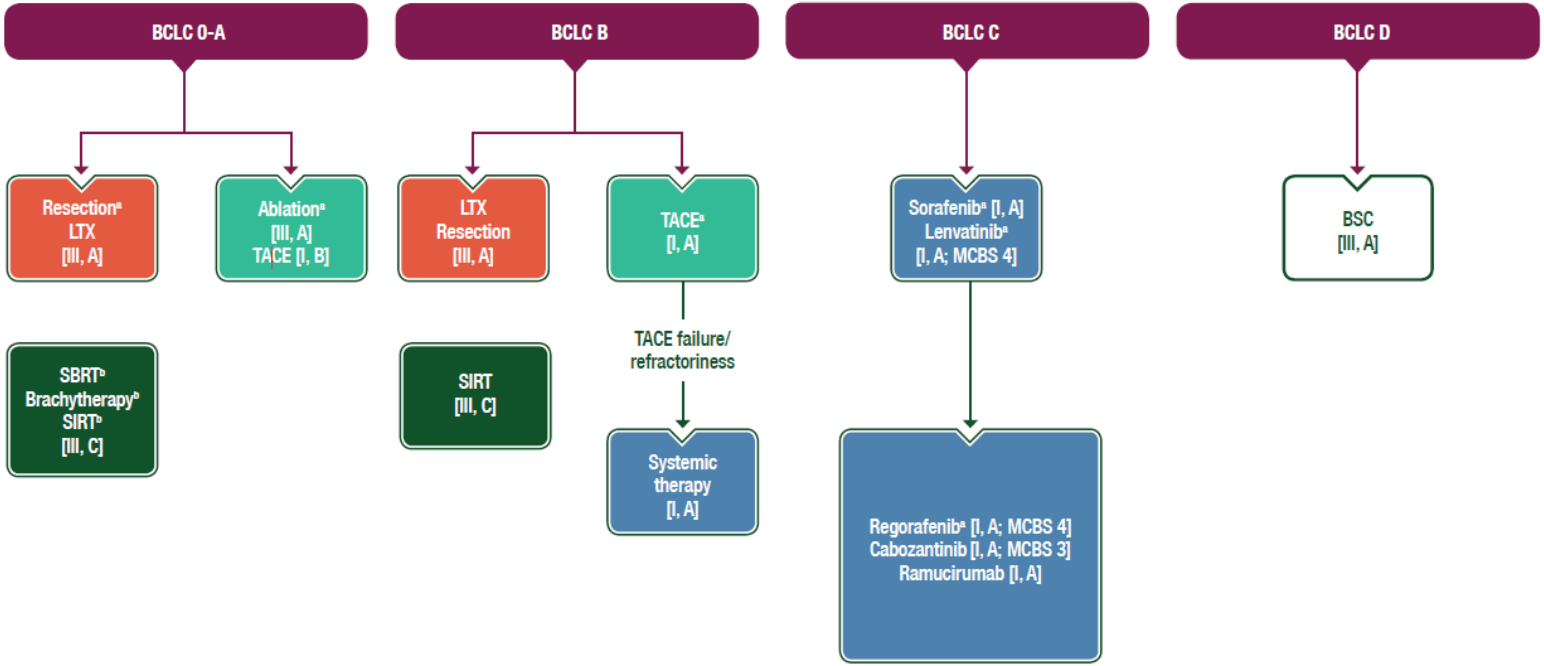
OS, overall survival

Miksad et al. WCGI 2019

Treatment of hepatocellular carcinoma



Vogel et al. 2018, Annals of Oncology

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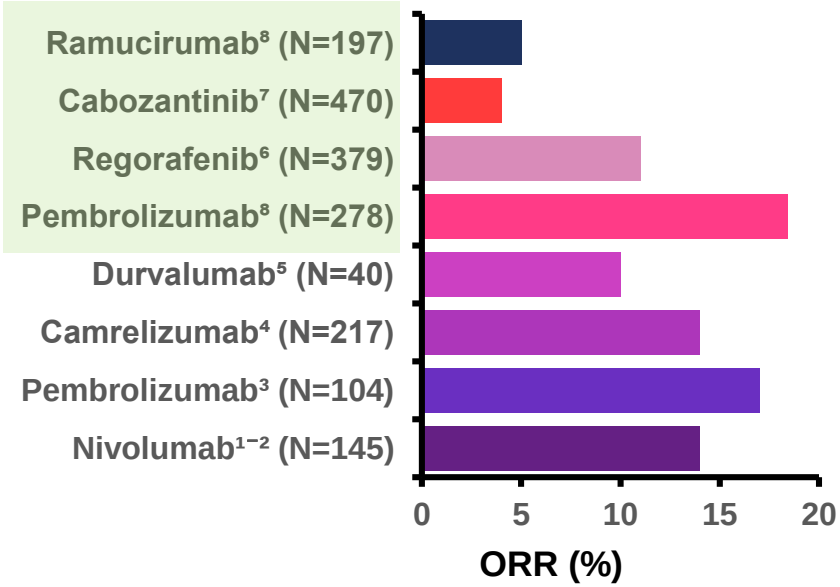
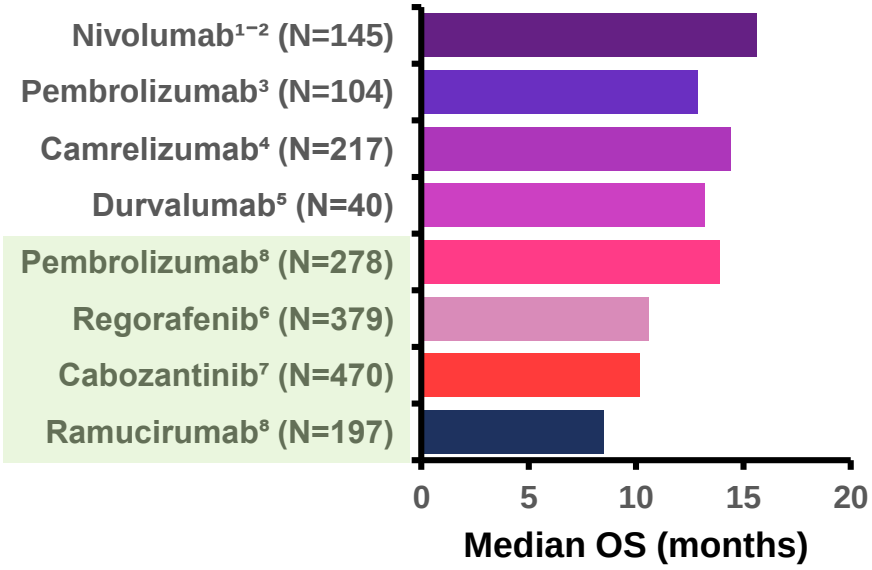
Options in second line
Response rate and survival

Objective response rate



Overall survival



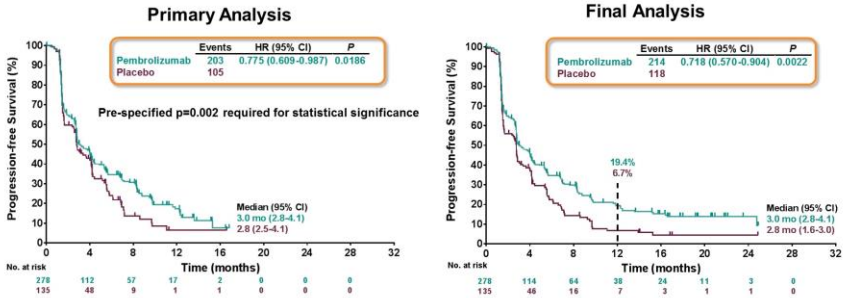
1. El-Khoueiry et al. Lancet 2017; 2. Crocenzi et al. ASCO 2017; 3. Zhu et al. ASCO 2018 4. Qin et al. ESMO 2018; 5. Wainberg et al. ASCO 2017; 6. Bruix et al. Lancet 2017 7. Abou-Alfa et al. N Engl J Med 2018; 8. Zhu et al. Lancet Oncol 2019

ORR, overall response rate; OS, overall survival

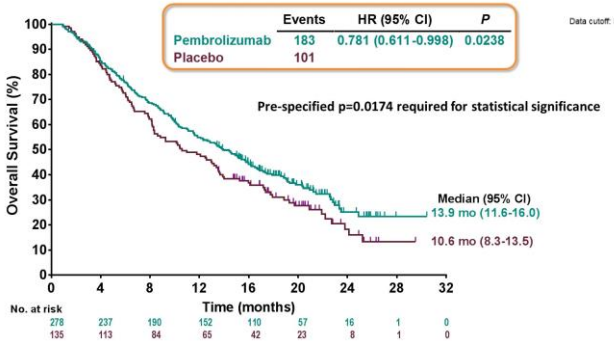
Keynote-240 Phase-III: IO in 2nd line

	Keynote-224 Phase-II	Keynote-240 Phase-III
n	104	278
ORR	17%	18.4%
PFS	4.9 Mo.	3 Mo.
OS	12.9 Mo.	13.9 Mo

Progression-Free Survival



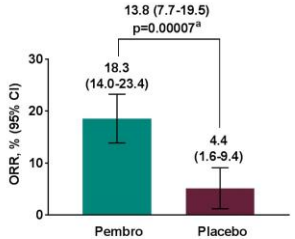
Overall Survival



Data cutoff: Mar 26, 2018 for PFS primar

Data Cutoff: Jan 2, 2019.

Objective Response Rate at Final Analysis (RECIST 1.1, BICR)



Duration of response, median (range)[b,c]:
- Pembrolizumab: 13.8 mo (1.5+ mo − 23.6+ mo)
- Placebo: not reached (2.8 mo−20.4+ mo)

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

Finn et al. @ 2019 ASCO

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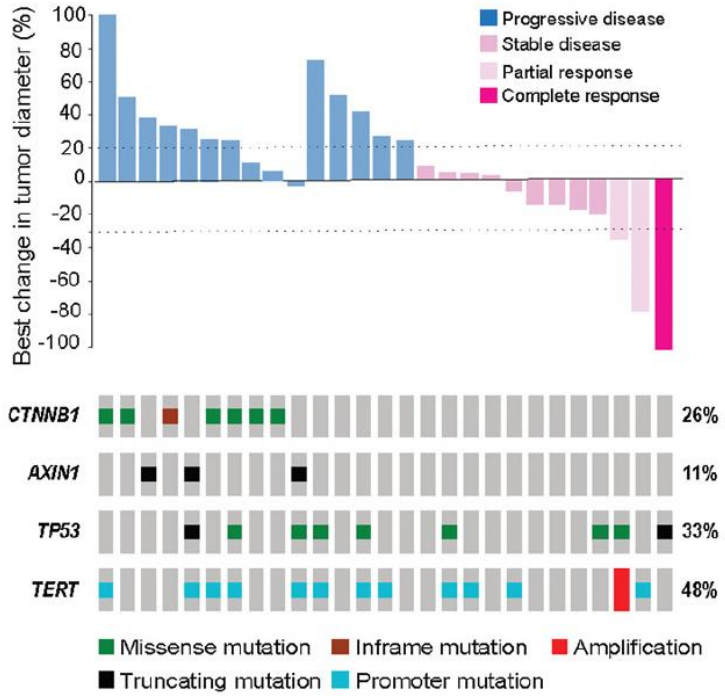
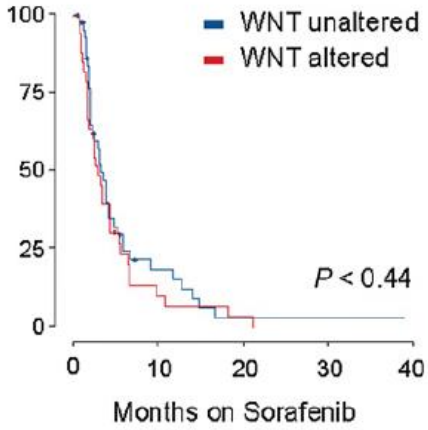
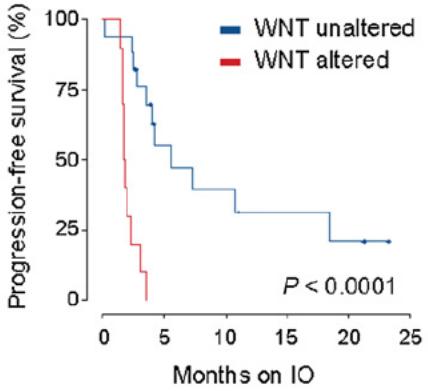
CI, confidence interval; CR, complete response; HR, high risk;IO, immuno-oncology; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease

IO Resistance mechanism in HCC
Immune Exclusion-Wnt/CTNNB1 class







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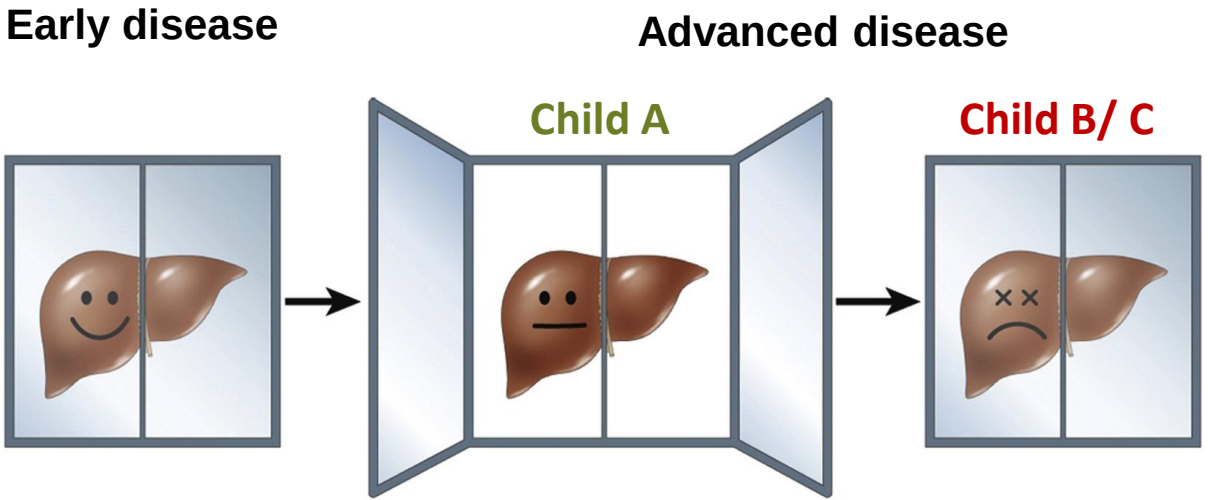
HCC, hepatocellular carcinoma; IO,immuno-oncology

Harding et al. Clin Cancer Res 2019

My take home...

- ✓ **Multidisciplinary evaluation is mandatary**
- ✓ Patients for **local therapies** need to be identified
- ✓ We have a *small* **"Window of Opportunity"** for systemic therapies



My take home continued...

- ✓ **Multidisciplinary evaluation is mandatary**
- ✓ Patients for **local therapies** need to be identified
- ✓ We have a (small) **“Window of Opportunity”** for systemic therapies
- ✓ **Survival, side effects, QoL and liver function** need to be considered
- ✓ Around 50% and 30% of patients can receive **subsequent therapies** after 1st and 2nd line
- So far no positive phase-III for IO, but negative ≠ negative trials
- ✓ Significant benefit for the responders, moderate side effect profile and minor liver toxicity: I still consider **IO as a part of the “HCC sequence”** and there many ongoing studies to include patients
- ✓ We need **biomarkers**!

HCC, hepatocellular carcinoma; IO, Immuno-Oncology; QoL, quality of life