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INSIGHTS INTO TRIAL DESIGNS IN ADVANCED HEPATOCELLULAR CARCINOMA

Dr. Leonardo da Fonseca
Instituto do Cancer do Estado de São Paulo,
São Paulo, Brazil

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CURRENT TREATMENT LANDSCAPE FOR ADVANCED HCC

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Sorafenib	Lenvatinib
2008	2018
Phase 3 placebo-controlled[1]	Phase 3 non-inferiority vs sorafenib[2]
Overall survival HR=0.69 (95% CI 0.55-0.87)	Overall survival HR=0.92 (95% CI 0.79-1.06)

Regorafenib	Cabozantinib	Ramucirumab	Nivolumab	Pembrolizumab
2016[a]	2018[a]	2019[a]	2017[a,b]	2018[a,b]
Phase 3 placebo-controlled[3]	Phase 3 placebo-controlled[4]	Phase 3 placebo-controlled[5]	Phase 1/2 single-arm[6]	Phase 2 single-arm[8]
Overall survival HR=0.63 (95% CI 0.50-0.79)	Overall survival HR=0.76 (95% CI 0.63-0.92)	Overall survival HR=0.71 (95% CI 0.53-0.95)	Response rate 15-20%	Response rate 17%
			Negative phase 3 trial in 1st line vs sorafenib[7]	Negative phase 3 trial in 2nd line vs placebo[9]

[a] after treatment with sorafenib
[b] FDA approval only

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio

1. Llovet JM, et al. N Engl J Med. 2008;359:378-390; 2. Kudo M, et al. Lancet. 2018;391:1163-1173; 3. Bruix J, et al. Lancet. 2017;389:56-66; 4. Abou-Alfa GK, et al. N Engl J Med. 2018;379:54-63; 5. Zhu AX, et al. Lancet Oncol. 2019;20:282-296; 6. El-Khoueiry AB, et al. Lancet. 2017;389:2492-2502; 7. Yau, et al. ESMO 2019 Abstract #LBA38; 8. Zhu AX, et al. Lancet Oncol. 2018;19:940-952. 9. Finn R, et al. ASCO 2019. Abstract #4004

ENDPOINTS IN CLINICAL TRIALS

- Overall survival is the most robust endpoint in advanced HCC
- However, overall survival can be affected by sequential therapies received after trial discontinuation
- Increasing number of available treatments underscore the need for surrogate endpoints in HCC trials

HCC, hepatocellular carcinoma
Llovet JM, et al. J Hepatol. 2019;70:1262-1277

ENDPOINTS IN CLINICAL TRIALS

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Patient-centered endpoints

- Overall survival
- Health-related quality of life

Tumour-centered endpoints

- Progression-free survival
- Time-to-progression
- Disease-free survival
- Response rate

IMPACT OF MEASURING PROGRESSION

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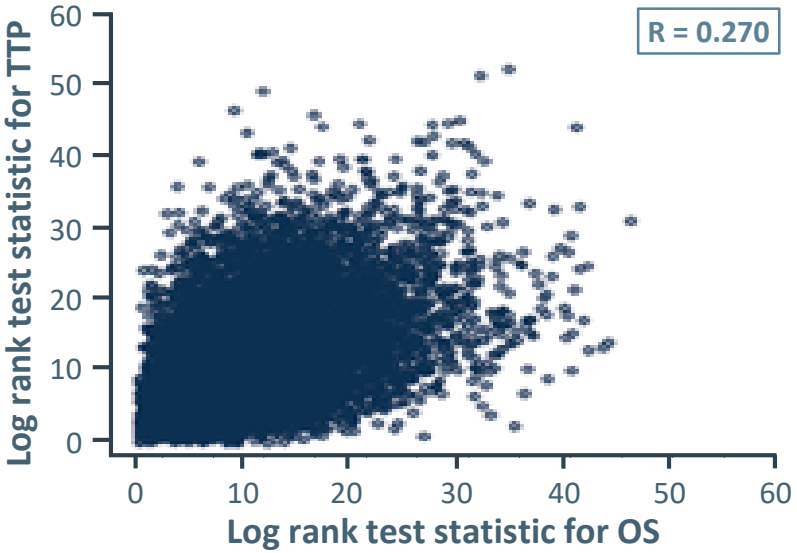
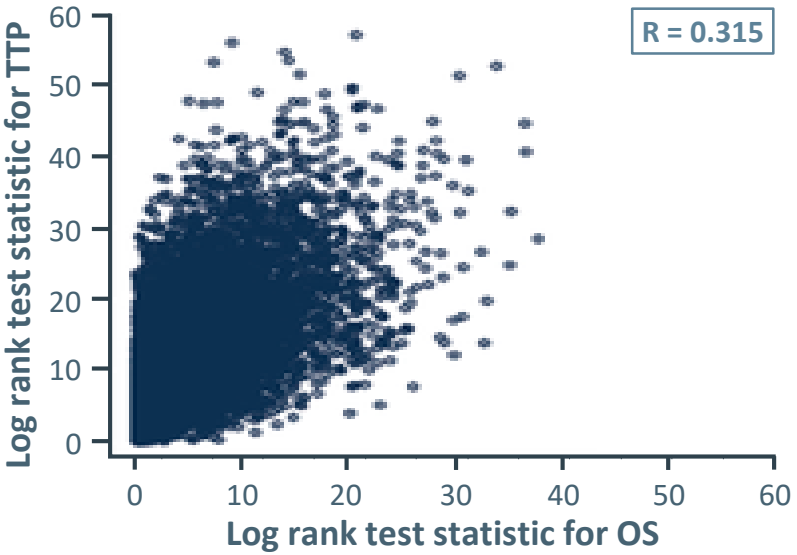
WEAK CORRELATION BETWEEN TTP AND OS

SHARP



Asia-Pacific



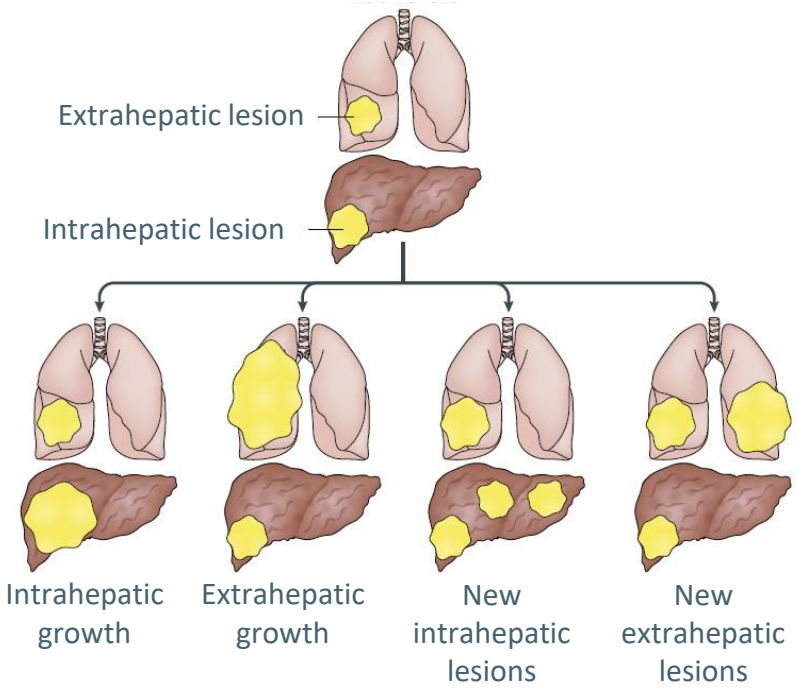
Analysis of patient-level data from the SHARP and AP trials in patients with advanced HCC randomised to sorafenib.

AP, Asia-Pacific; HCC, hepatocellular carcinoma; OS, overall survival; R, Pearson correlation coefficient; TTP, time-to-progression

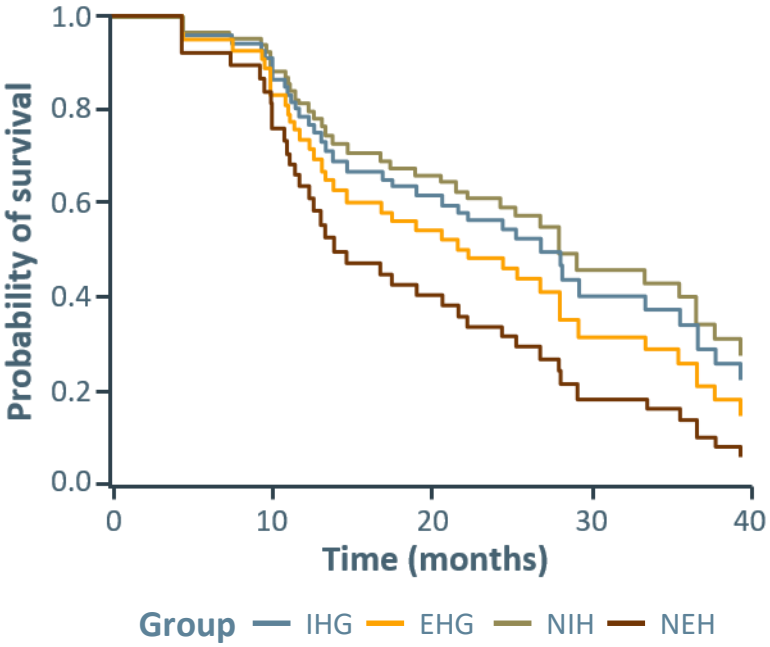
1. Huang L, et al. ASCO 2017. Abstract #233. 2. Huang L, et al. ESMO 2017. Abstract #702P

NOT ALL PROGRESSIONS ARE THE SAME

Patterns of progression[1]



Post-progression survival (PPS) of sorafenib-treated patients with advanced HCC who were candidates for second-line trials[2]



New extrahepatic lesions/vascular invasion: PPS 7.1 months

No extrahepatic growth: PPS 14.9 months

BCLC, Barcelona Clinic Liver Cancer; EHG, extrahepatic increase ≥20% of the tumour size in lesion previously documented; HCC, hepatocellular carcinoma; IHG, intrahepatic increase ≥20% of the tumour size in lesion previously documented; NEH, new extrahepatic lesion and/or vascular invasion; NIH, new intrahepatic lesion; PPS, post-progression survival

1. Bruix J, et al. Nat Rev Gastroenterol Hepatol. 2019;16:617-630; 2. Reig M, et al. Hepatology. 2013;58:2023-20311

IMMUNE-CHECKPOINT INHIBITORS IN HCC

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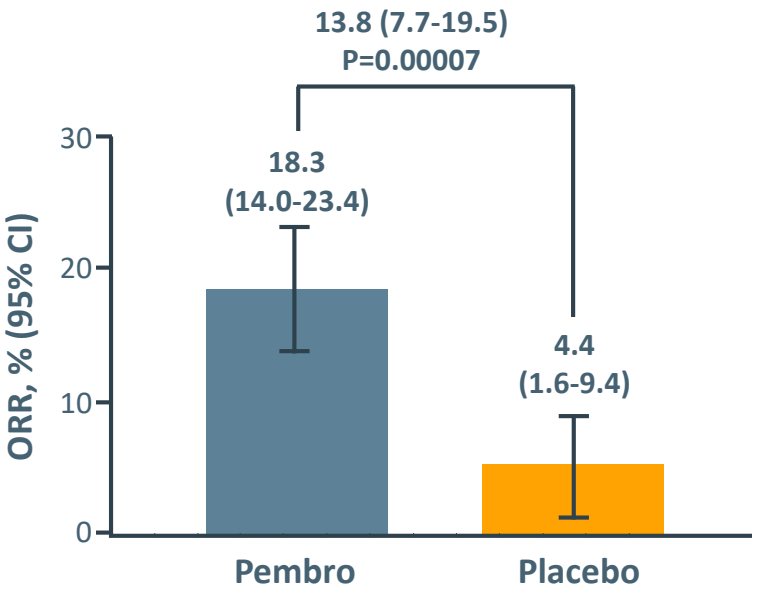
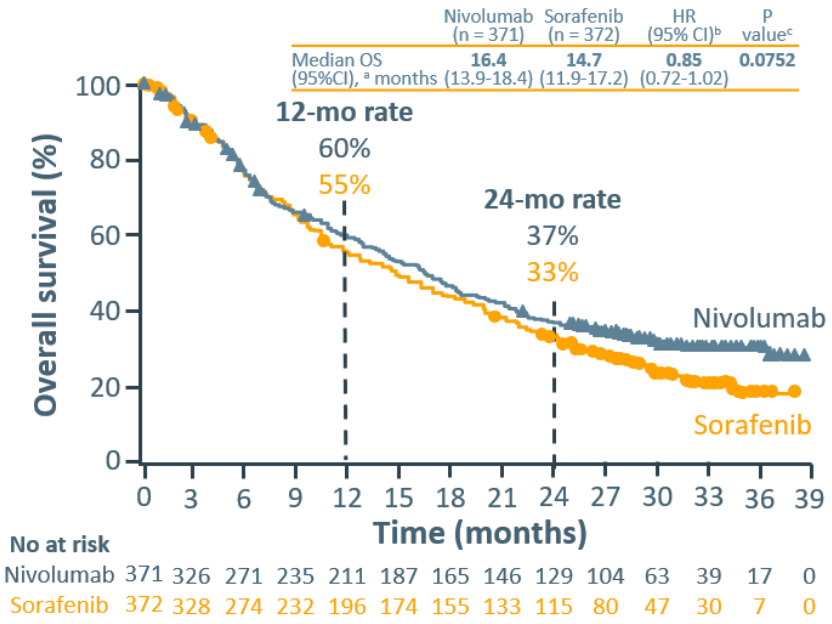
Pembrolizumab[1]



Pre-specified efficacy boundaries not reached for OS and PFS (co-primary endpoints) vs placebo.

Nivolumab[2]



The primary endpoint of OS did not achieve statistical significance vs sorafenib.

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

1. Finn R, et al. ASCO 2019. Abstract #4004. 2. Yau, et al. ESMO 2019 Abstract #LBA38.

NON-CONVENTIONAL BENEFIT WITH IMMUNOTHERAPY

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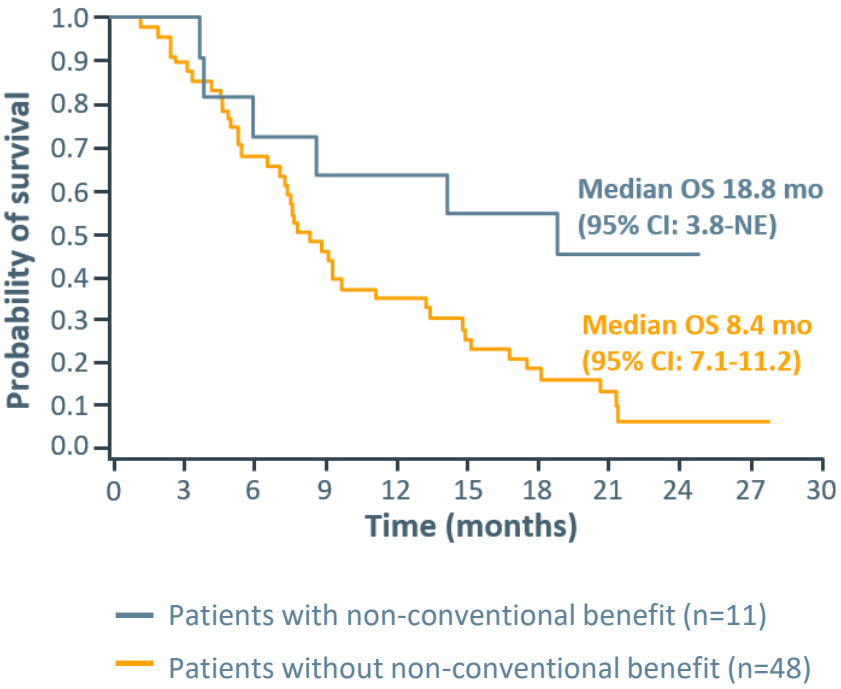
Survival with nivolumab in sorafenib-experienced patients with advanced HCC



Non-conventional benefit:

- PD with new lesions followed by decrease in target lesion ≥ 10%;
- PD of target lesions followed by decrease in target lesion ≥ 30%;
- PD of target lesions or new lesions followed by stabilisation

CI, confidence interval; HCC, hepatocellular carcinoma; NE, not evaluable; OS, overall survival; PD, progressive disease
El Khoueiry AB, et al. ASCO-GI 2018. Abstract #475

CONCLUSIONS: CHALLENGES IN HCC TRIAL DESIGN

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Stratification factors

- Pattern of progression is important in second- and third-line trials[1]

Surrogate endpoints – an unmet need

- Refine definition of treatment failure and disease progression
- Pattern of spread, growth rate and occupation of functional liver parenchyma (BCLC-dismal progression-free survival)

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma

1. Bruix J, et al. Nat Rev Gastroenterol Hepatol. 2019;16:617-630

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Email
froukje.sosef@cor2ed.com

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HCC CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com