V Simpósio Internacional de Tumores Gastrointestinais

9 e 10 · agosto · 2019

HOTEL INTERCONTINENTAL SÃO PAULO

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Hepatocarcinoma – Doença metastática: Como escolher a 2a linha?

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Declaração de conflitos de interesse

- Advisory Boards
  - MSD
  - AstraZeneca
  - BMS

- Fees para palestras
  - Amgem
  - AstraZeneca

- Verbas de pesquisa
  - BMS
  - MSD

1. Quais as causas de óbito após 1ª linha?

Table 2 HCC characteristics at diagnosis (initial) and prior to death (final); $n = 237$

Characteristic	Initial	Final
Number of nodules		
0		5 (2.1%)
1	98 (41.3%)	68 (28.7%)
2–5	44 (18.5%)	37 (15.6%)
>5	95 (40%)	129 (54.4%)
Lobar distribution		
Unilobar	99 (41.8%)	65 (27.3%)
Bilobar	138 (58.2%)	172 (72.7%)
Vascular		
Invasion (macro%)	98 (41.4%)	132 (55.7%)
Metastatic disease	85 (35.8%)	154 (65%)
Lymph node	49 (20.7%)	71 (30%)
Distant organ	36 (15.2%)	83 (35%)

Couto, O.F.M. et al – Dig Sis Sci 2017

2. Qual o mecanismo de resistência a sorafenibe?

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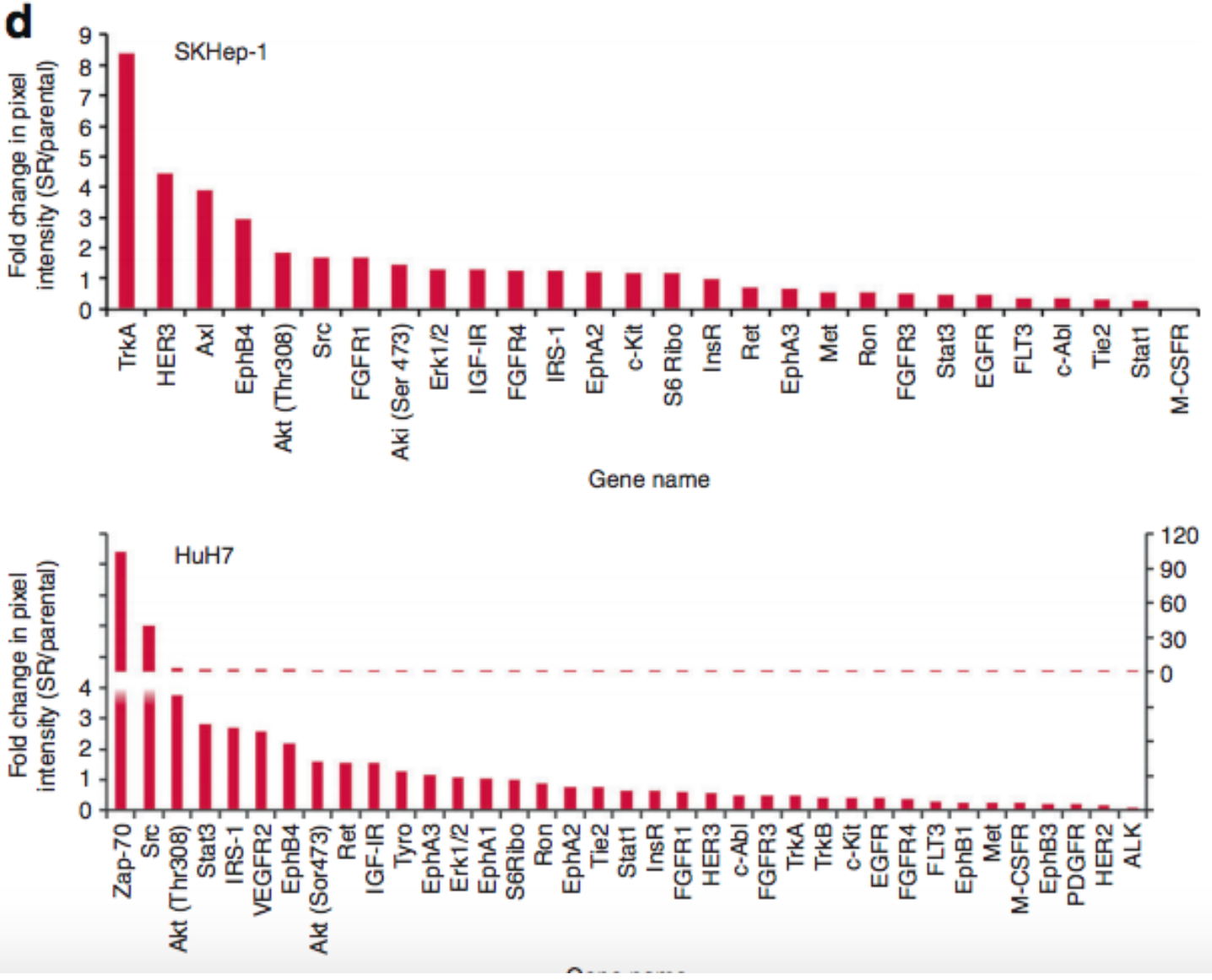

Pinato, DJ – BJC 2019

3. Quais os dados de Regorafenibe? (RESORCE)

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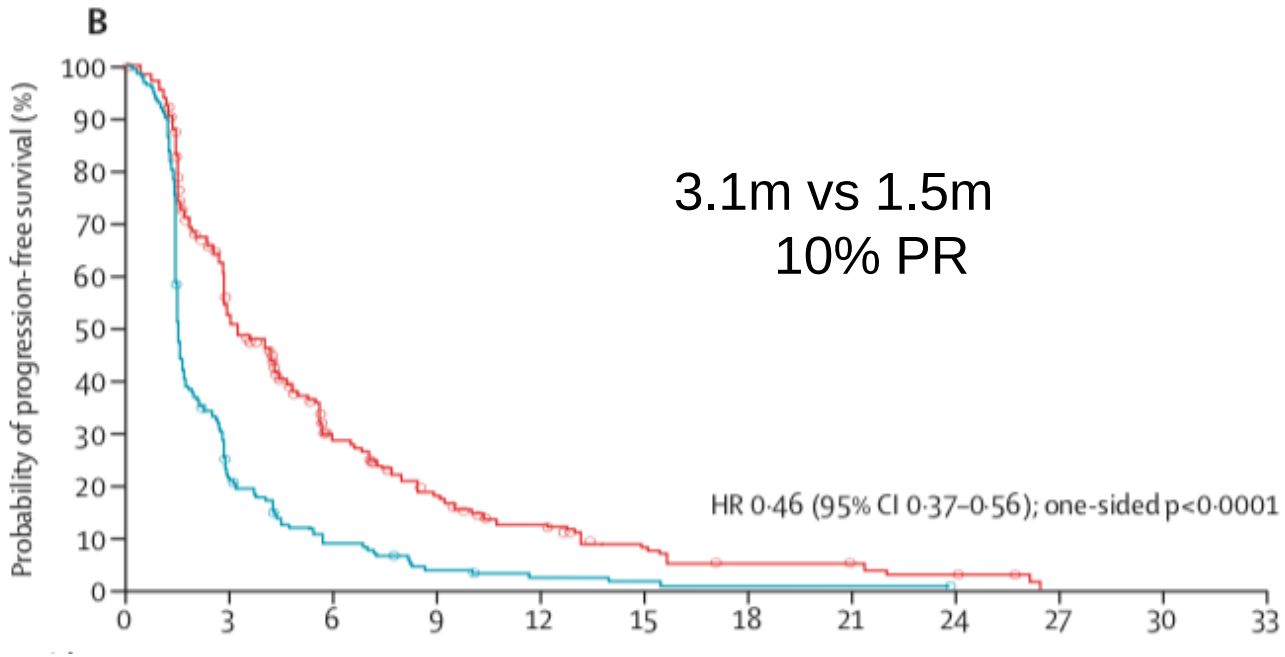
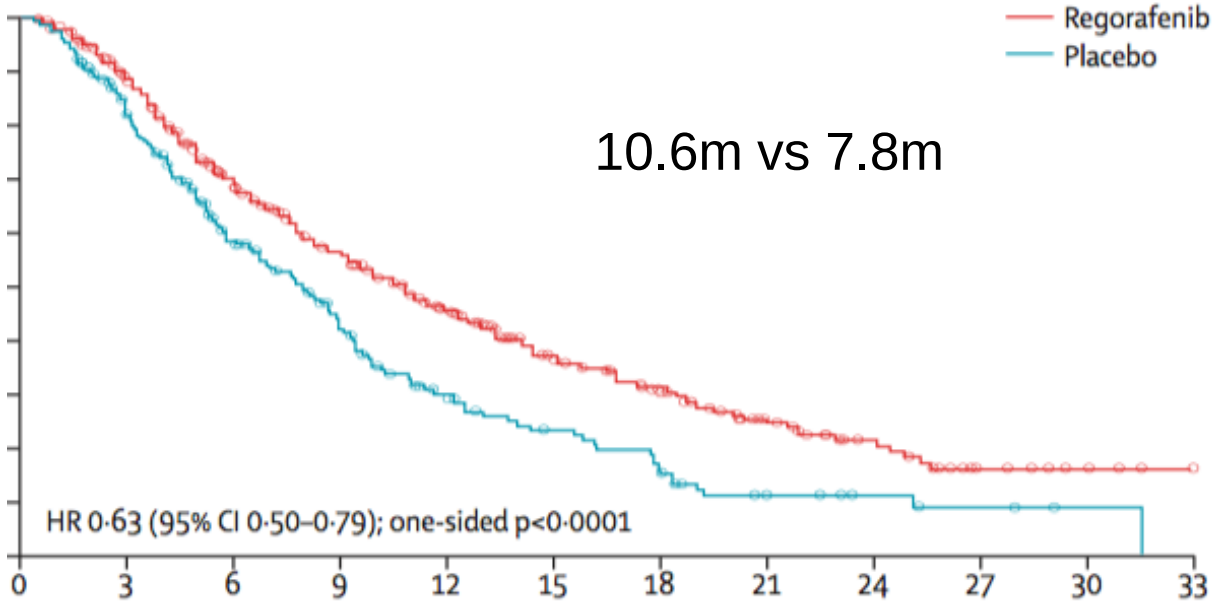


3.1m vs 1.5m
10% PR



10.6m vs 7.8m

RESORCE - Bruix – Lancet 2016

4. Quais os dados de Ramucirumabe? (REACH1/2)

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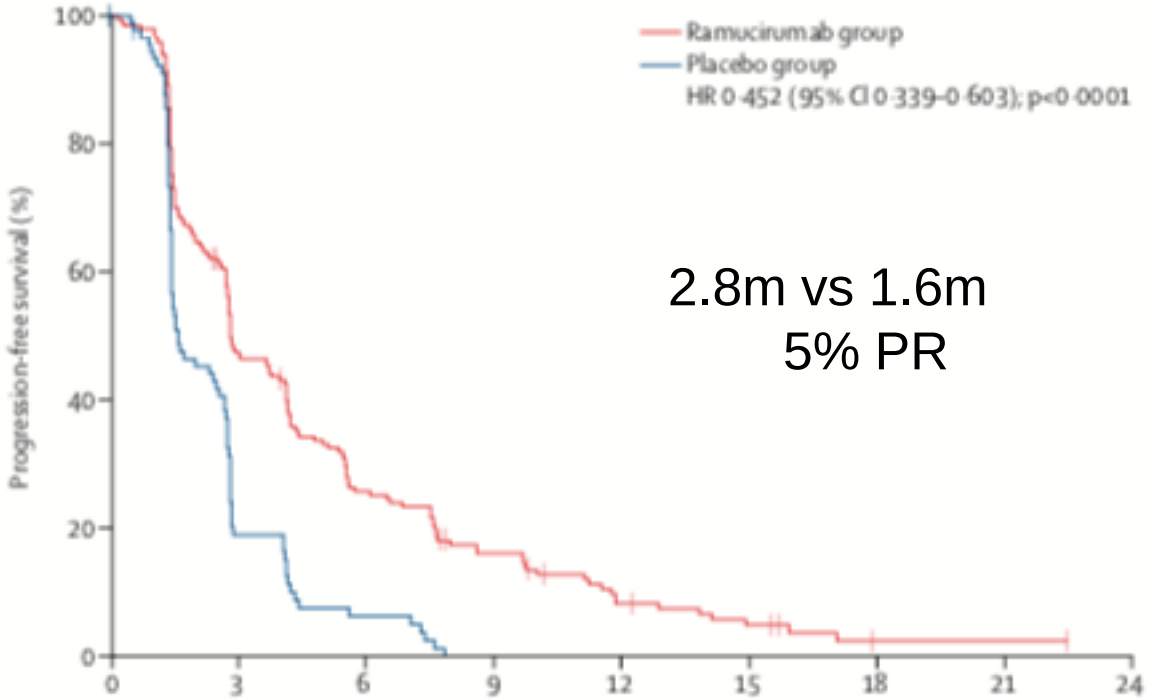
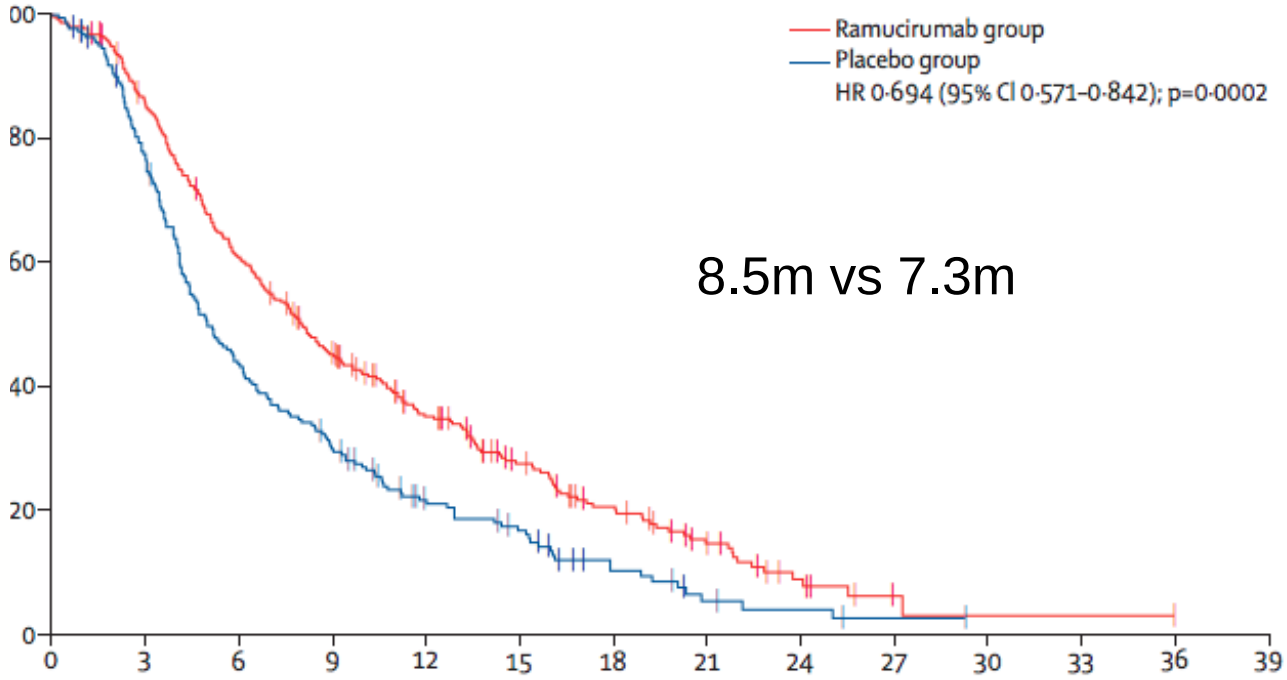


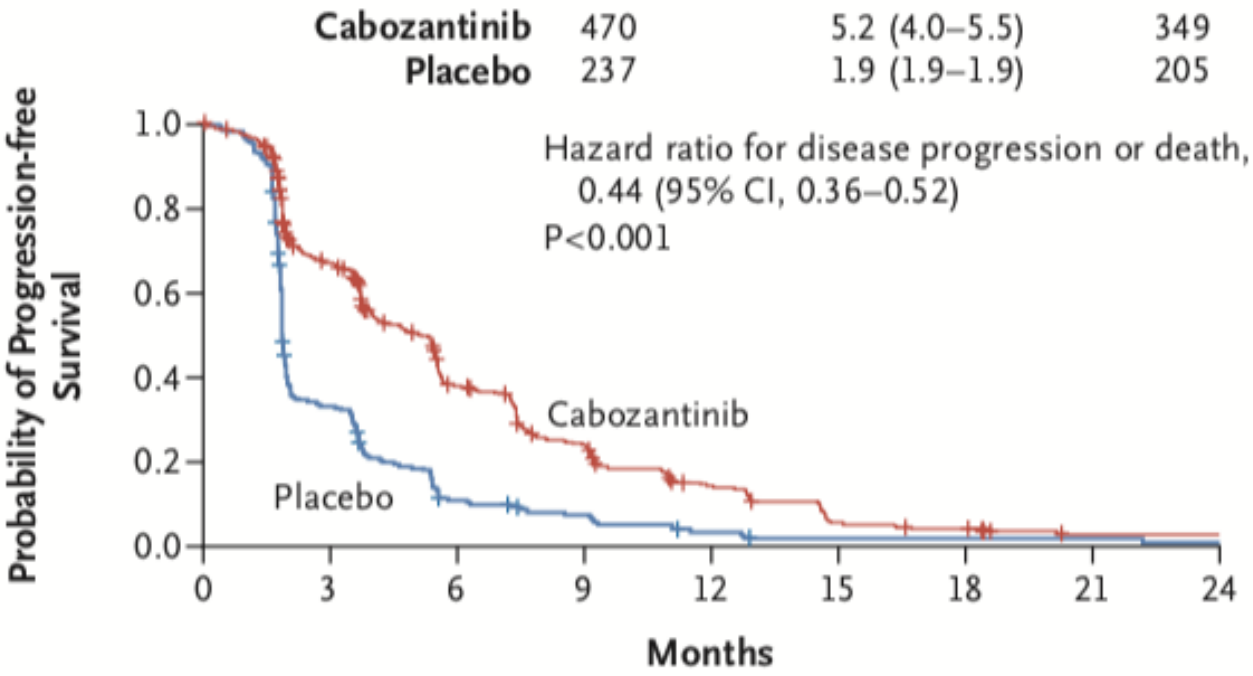
2.8m vs 1.6m
5% PR

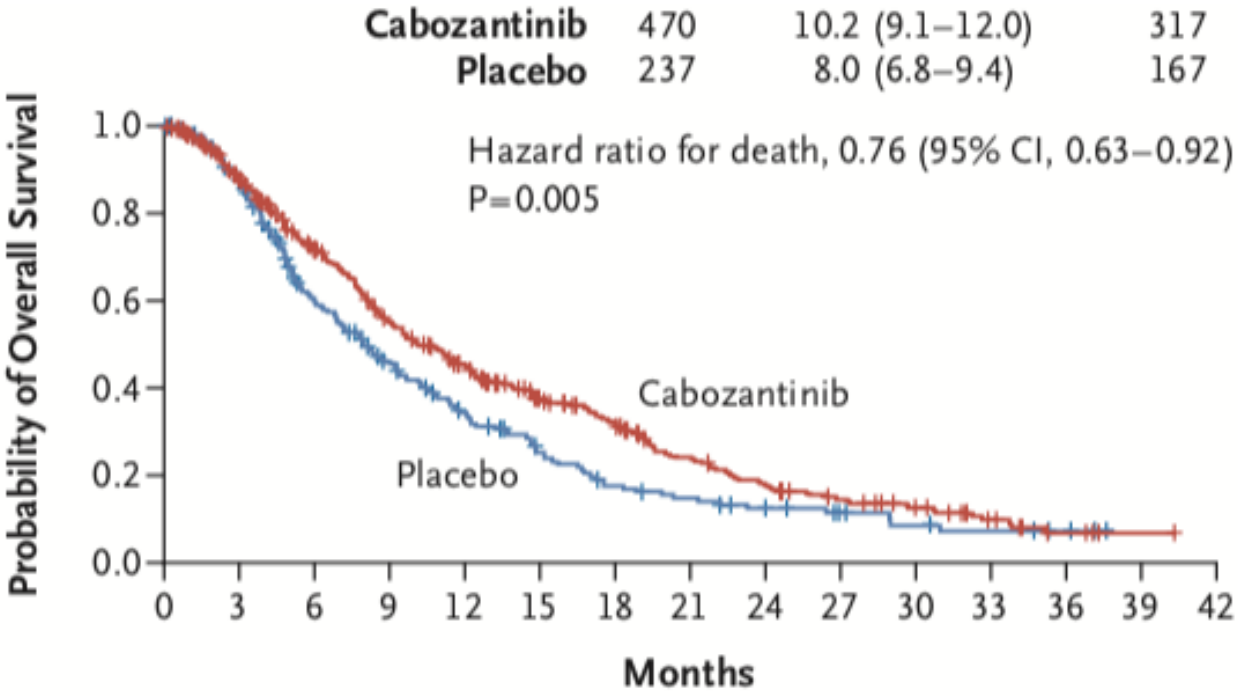


8.5m vs 7.3m

REACH 1/ 2 – Zhu – Lancet 2019

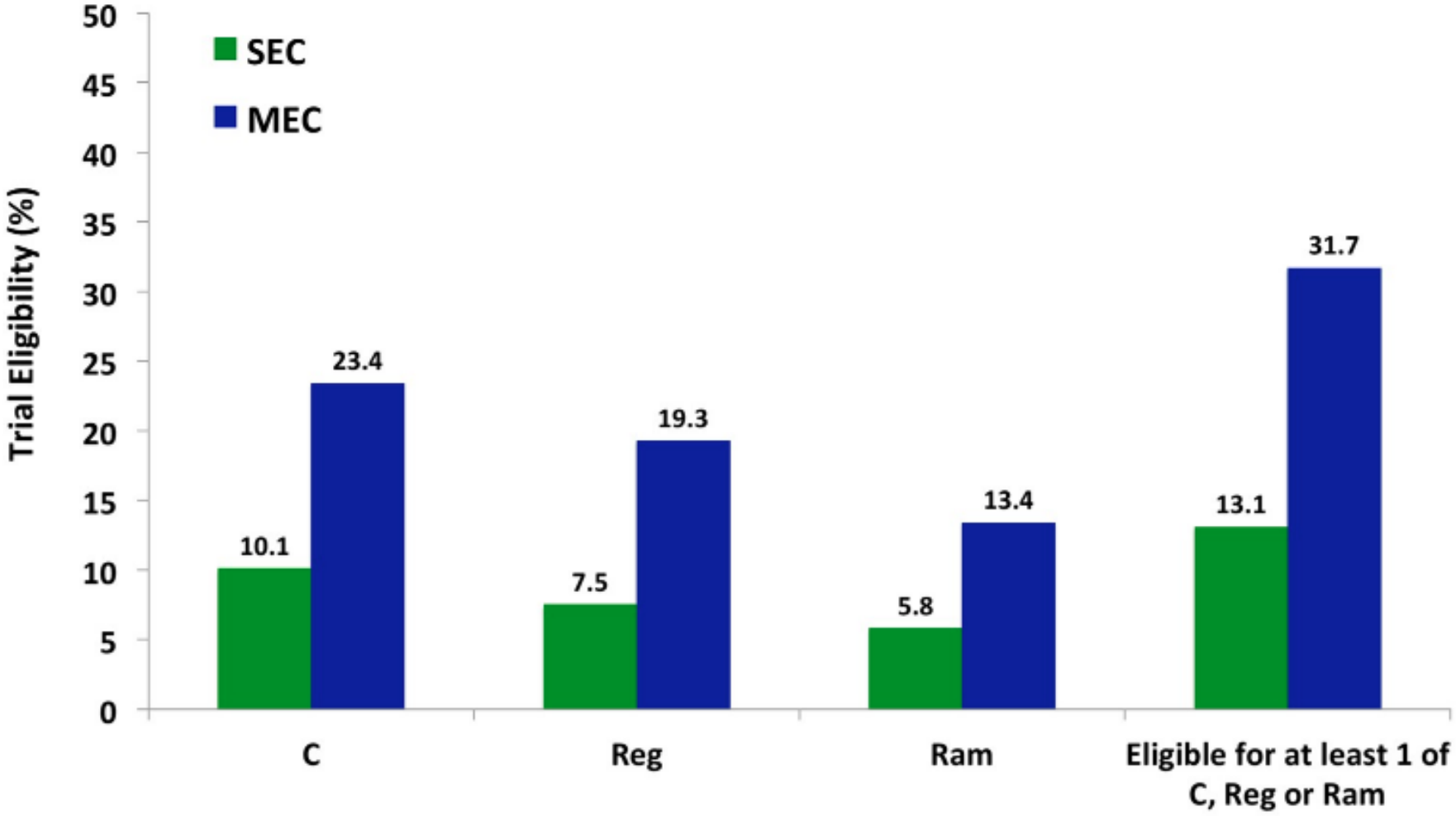
5. Quais os dados de Cabozantinibe? (CELESTIAL)





CELESTIAL –Zhu, AX et al - Lancet Oncol 2019

6. Drogas-alvo no mundo real

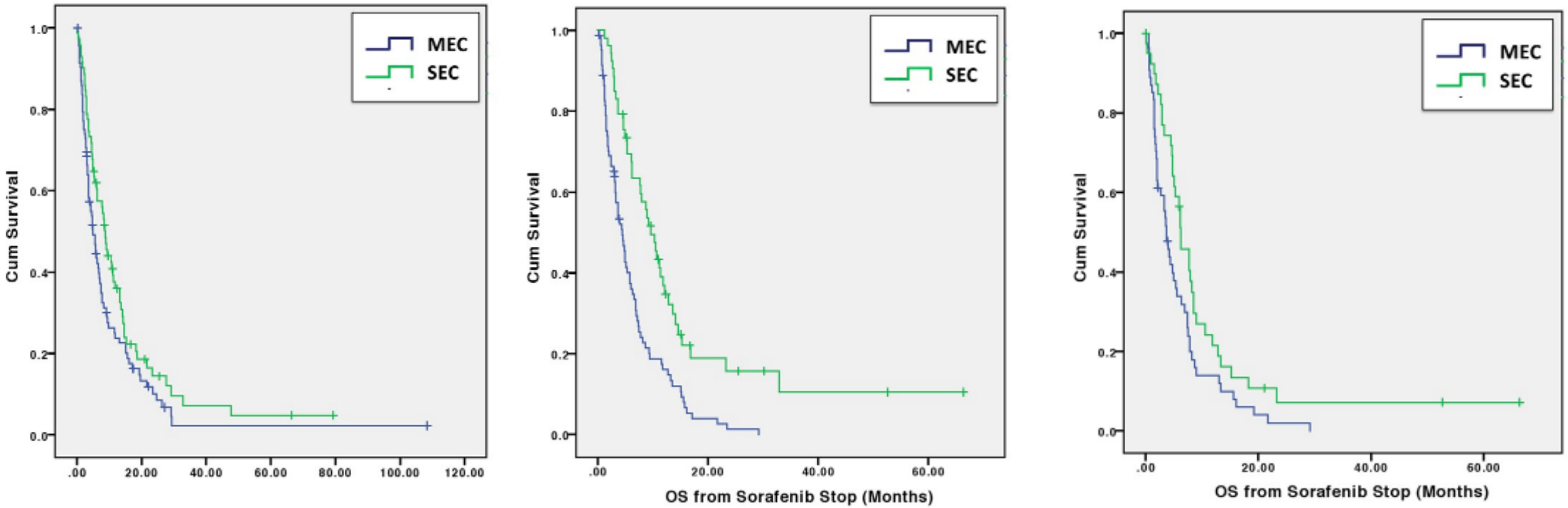


Fung, AS et al – 2019 ASCO Gastrointestinal Symposium

6. Drogas-alvo no mundo real

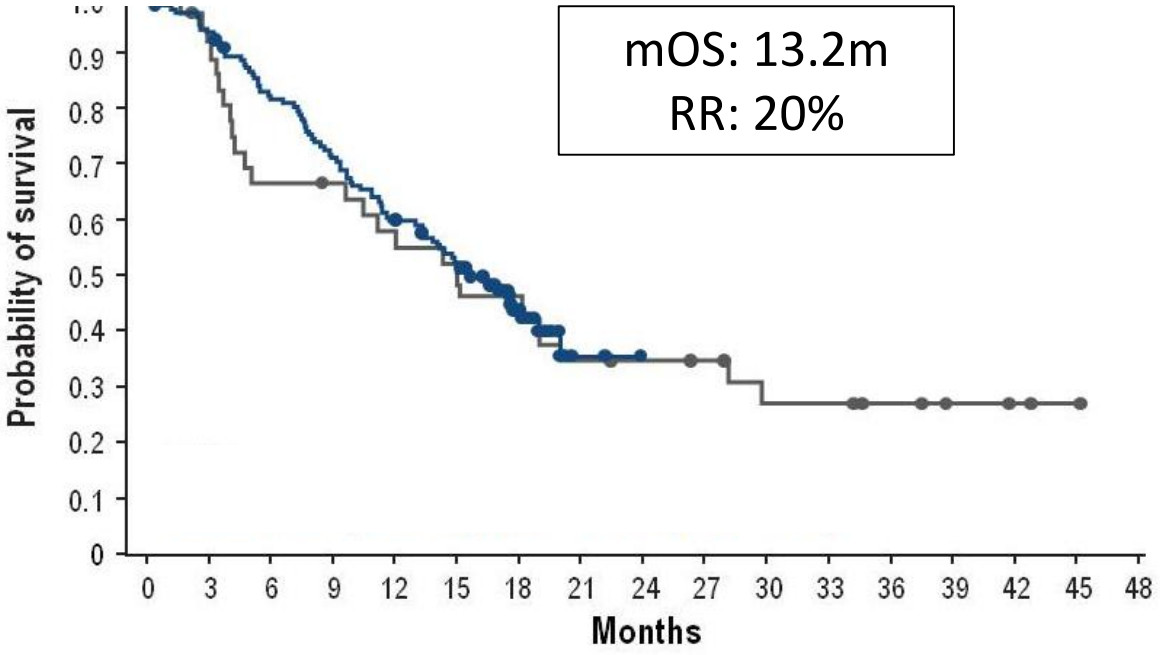
Figure 4. Overall survival based on strict eligibility criteria (SEC) and modified eligibility criteria (MEC) for A) cabozantinib (8.8 vs. 6.2 months, P=0.048), B) regorafenib (9.7 vs. 6.0 months, P<0.001), and C) ramucirumab (6.2 vs. 4.9 months, P=0.025).

A.



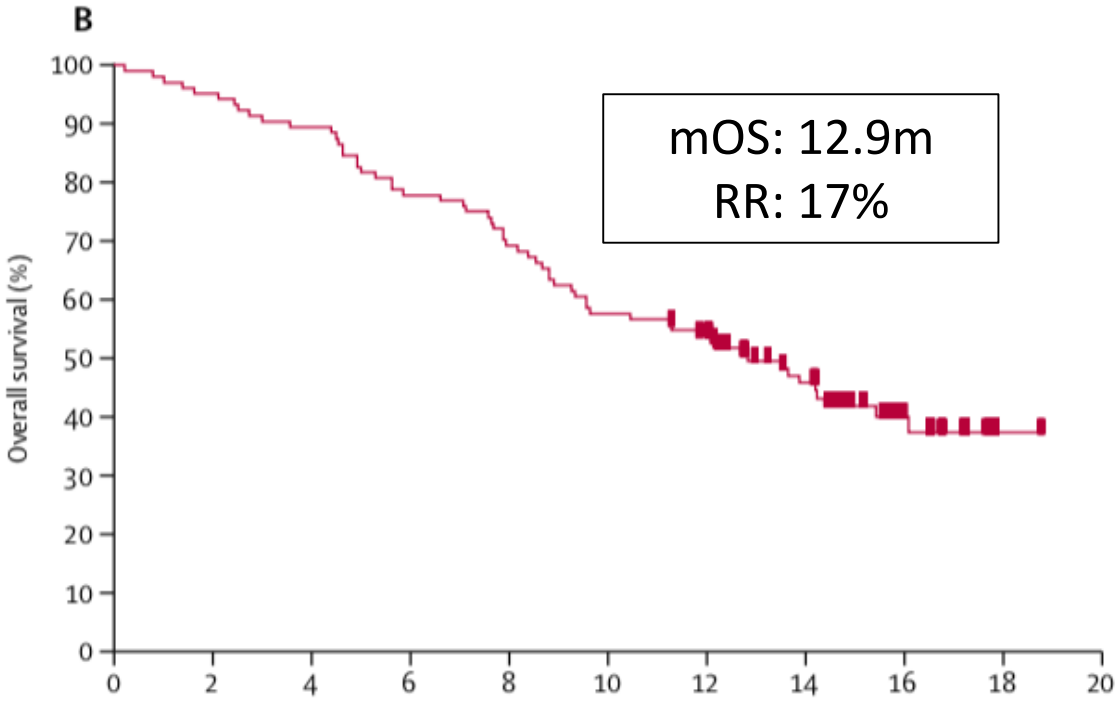
Fung, AS et al – 2019 ASCO Gastrointestinal Symposium

7. Imunoterapia na 2ª linha



mOS: 13.2m
RR: 20%

CheckMate40 – El – Khoueiry – Lancet 2017



mOS: 12.9m
RR: 17%

Keynote-224 – Zhu – Lancet Oncol 2018

8. Comparações indiretas na 2a linha

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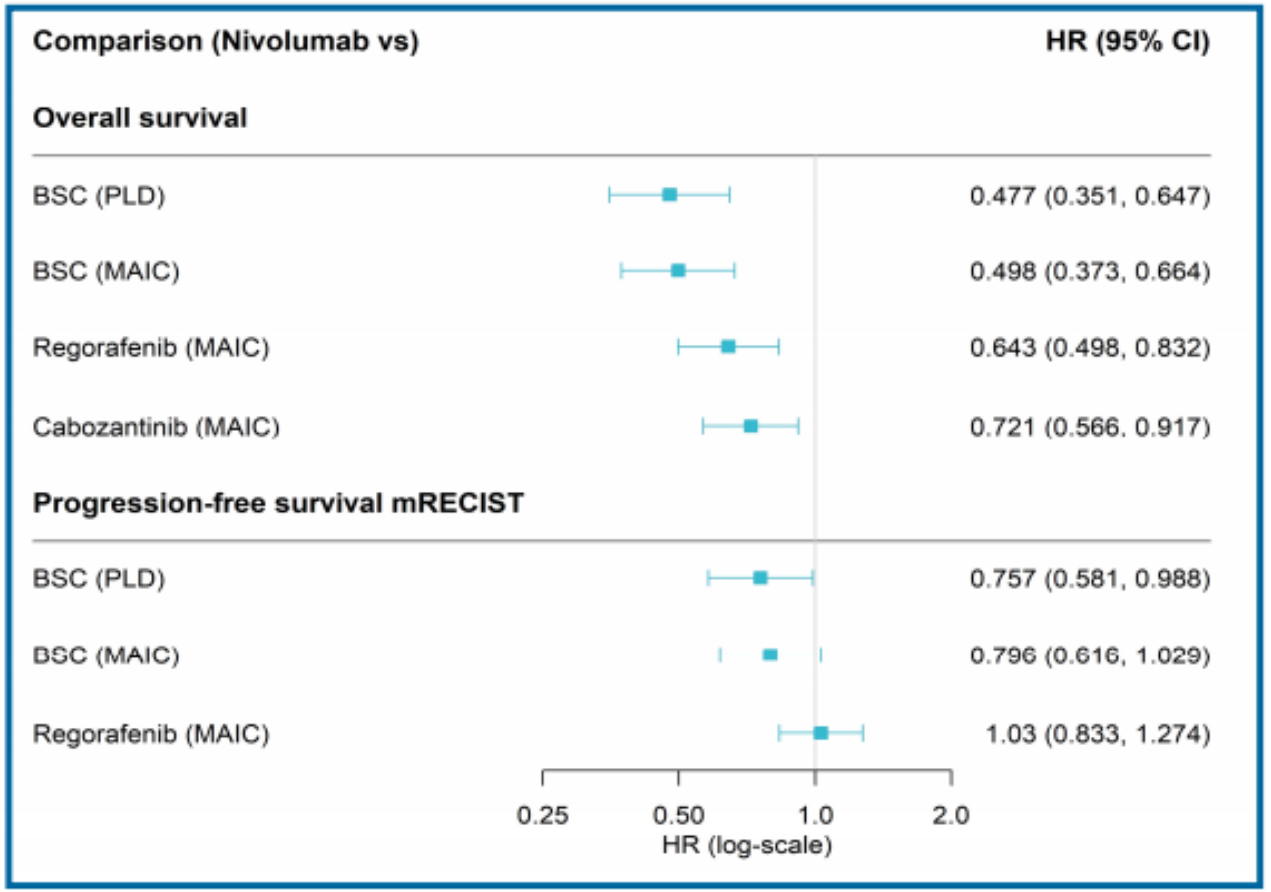
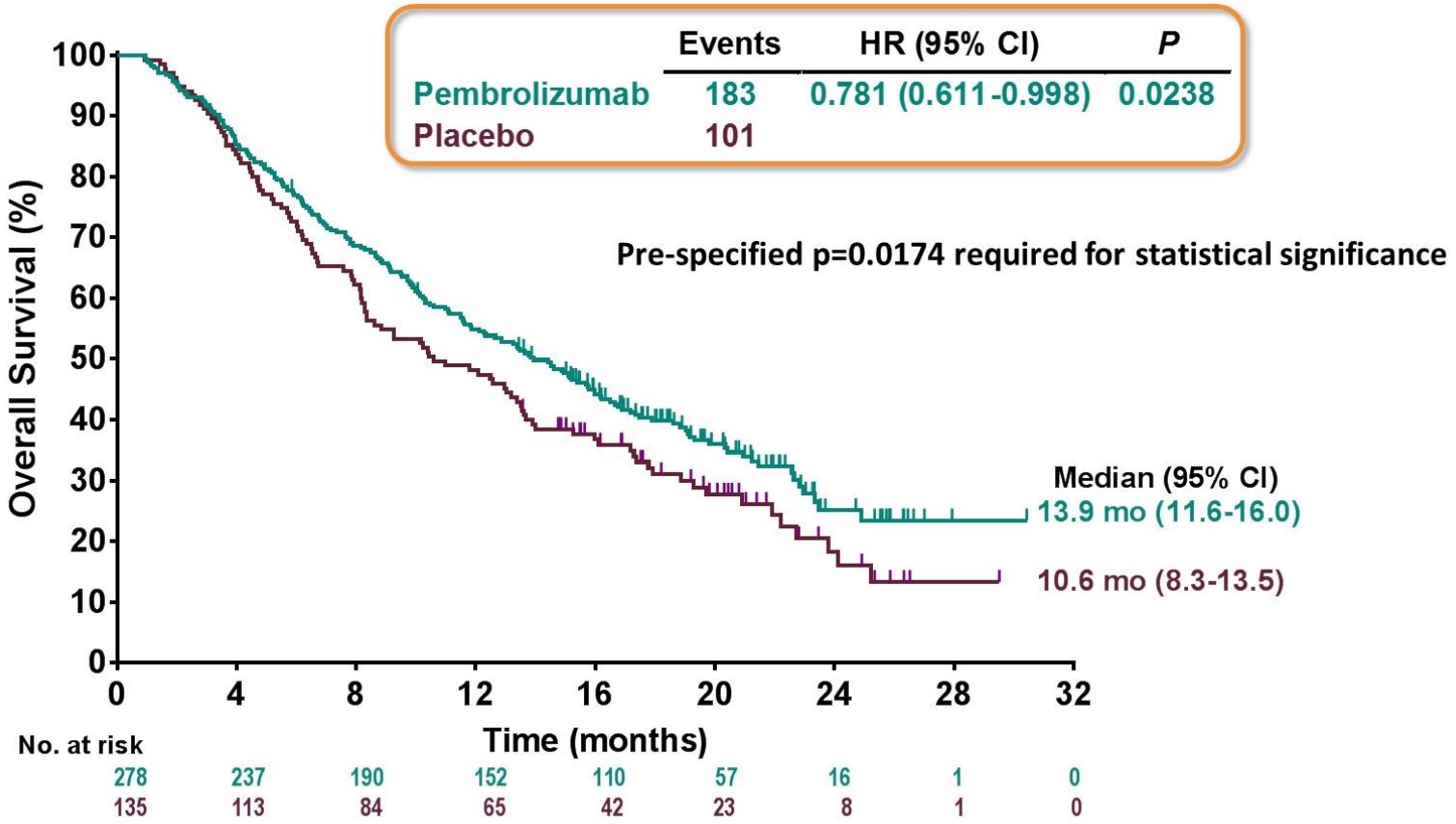
Characteristics	CM040[1] Nivolumab	BRISK-PS[2] Placebo	RESORCE[3] Regorafenib	CELESTIAL[4] Cabozantinib
N	145	132	379	470
Male, n (%)	112 (77)	113 (86)	333 (88)	NR (81)
Age years				
Mean, median	61.4, 63.0	61.1, 62.5	NR, 64.0	NR, 64.0
(range)	(19–81)	(19–87)	(19–85)	(22-86)
Region n (%)				
Asia	71 (49)	50 (38)	143 (38)	NR (25)
Non-Asia	74 (51)	82 (62)	236 (62)	NR (75)
Etiology of HCC n (%)				
Hepatitis B	49 (34)	45 (34)	143 (38)	NR (38)
Hepatitis C	43 (30)	35 (27)	78 (21)	NR (22)
ECOG PS, n (%)				
0	93 (64)	81 (62)	247 (65)	NR (52)
1/2	52 (36)	51 (38)	132 (35)	NR (48)
Child–Pugh class, n (%)				
A	143 (99)	120 (91)	373 (98)	470 (100)
B/C	2 (1)	12 (9)	5 (1)	0 (0)
Macrovascular invasion, n (%)	41 (28)	24 (18)	110 (29)	NR (27)
Extrahepatic disease, n (%)	103 (71)	NR (74)	265 (70)	NR (79)
AFP ≥400 ng/mL n (%)	55 (38)	128 (41)	162 (43)	NR (41)

AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; N, number of patients; NR, not reported



Roskell, N et al – ISPOR 2018

9. Imunoterapia na 1a linha?

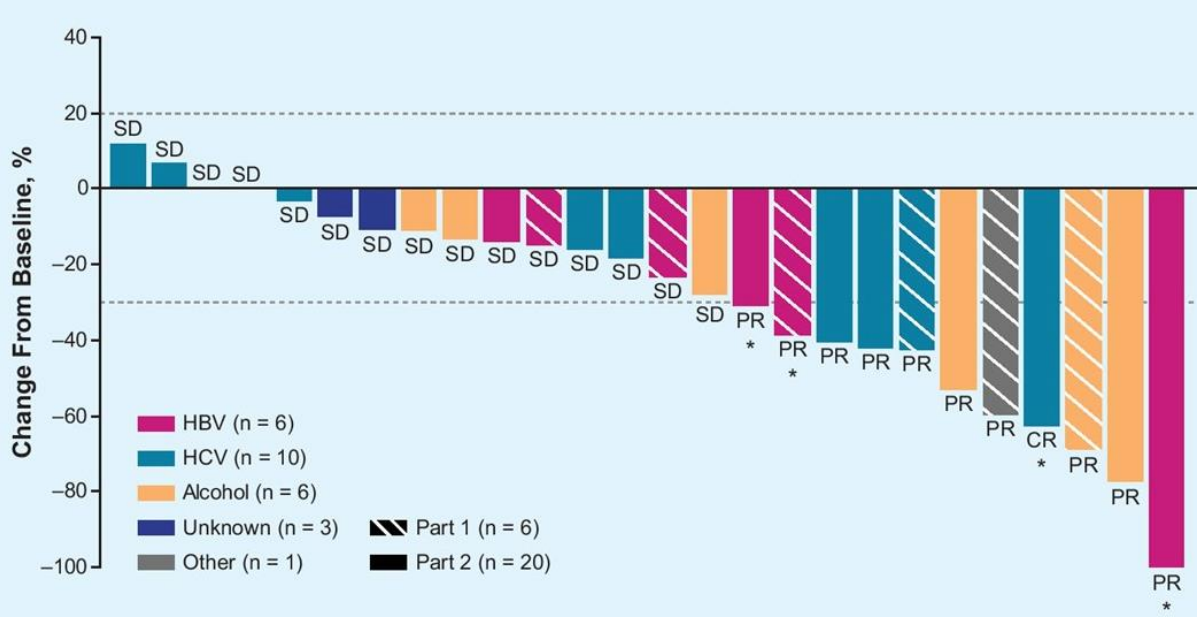


Topline results from the phase III CheckMate 459 trial (NCT02576509) revealed that the trial did not meet its primary endpoint of improved overall survival (OS) with nivolumab (Opdivo) as compared with sorafenib (Nexavar) for the treatment of patients with newly diagnosed, unresectable hepatocellular carcinoma (HCC).

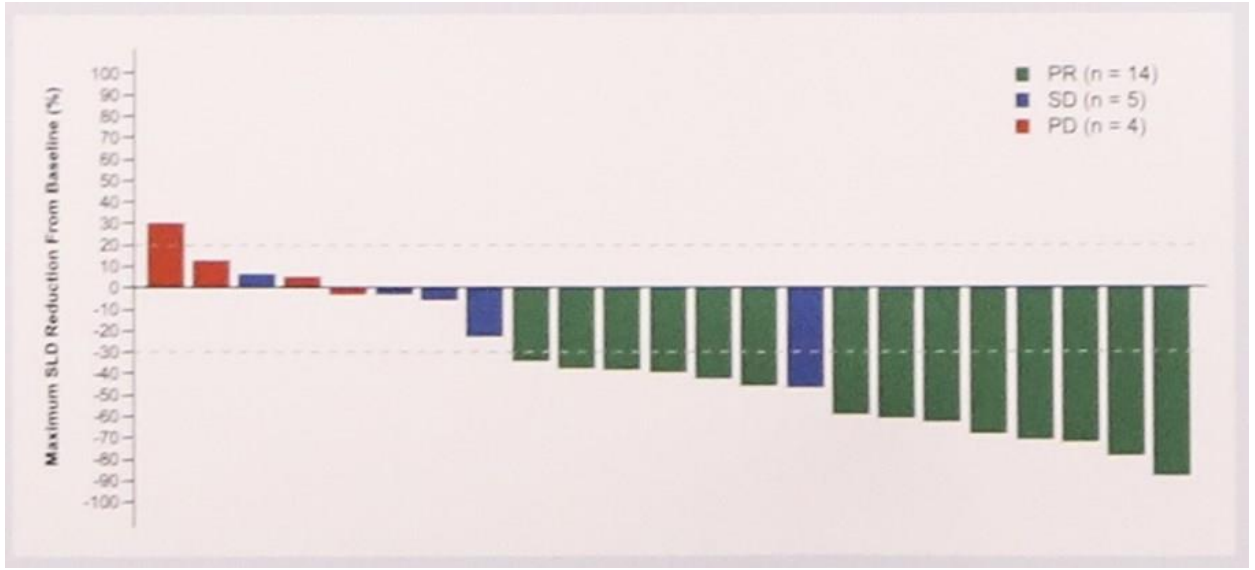
Although it did not meet statistical significance (HR, 0.85; 95% CI, 0.72-1.02; *P* = .0752),

Keynote-240 – Finn, RS et al – ASCO 2019

9. Imunoterapia na 1a linha?



Pembrolizumab - Lenvatinib
Ikeda – ASCO 2018



Atezolizumab-Bevacizumab
Stein – ASCO 2018

10. Conclusões

- O resultado do tratamento de 2ª linha é influenciado pelas complicações da hepatopatia de base.
- Apenas 13% dos pacientes do mundo real atendem aos critérios dos estudos clinicos
- Pacientes com função hepática mais limitrofe (Child B7) têm piores desfechos com as drogas-alvo atuais.
- Priorizar troca precoce para a segunda linha (e talvez terceira)
- Não há biomarcadores ou subgrupos específicos que auxiliem a selecionar a melhor droga na 2ª linha. Na minha prática:
  - Boa tolerância, algum controle de doença e oligo-progressão após sorafenibe -> regorafenibe
  - Restante (se acesso) -> Imunoterapia
- Dados encorajadores de imunoterapia + drogas anti-angiogênicas na primeira linha

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