New systemic therapies in HCC

BSMO-BORDET meeting, 23-24/11/2018

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Systemic treatment of HCC

10 years	2 years
One drug	6 drugs!
2007 – 2017	2016 - 2018

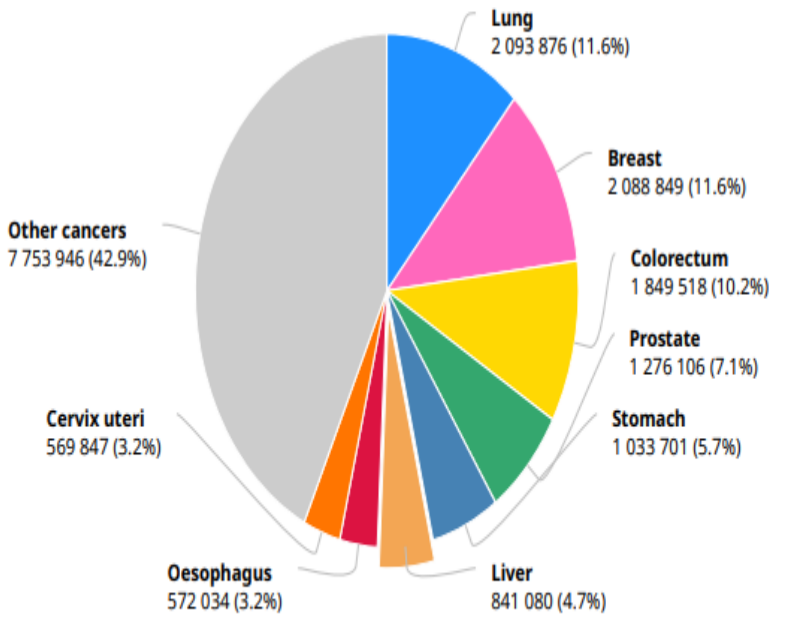
International Agency for Research on Cancer

World Health Organization

Liver

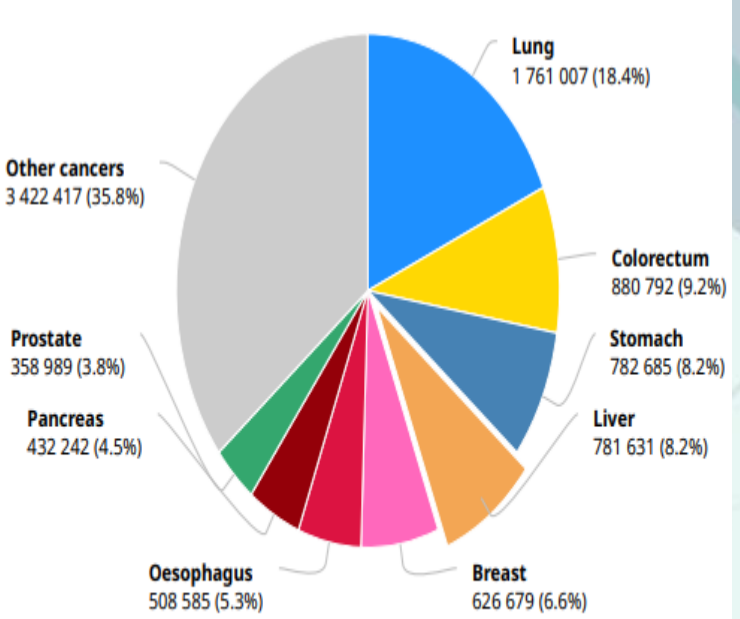
Source: Globocan 2018

Number of new cases in 2018, both sexes, all ages



Total: 18 078 957 cases

Number of deaths in 2018, both sexes, all ages



Total: 9 555 027 deaths

J Hepatol. 2010 Aug;53(2):348-56. doi: 10.1016/j.jhep.2010.02.035. Epub 2010 Apr 27.

Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review.

Papatheodoridis GV[1], Lampertico P, Manolakopoulos S, Lok A.

Author information

Abstract

BACKGROUND & AIMS: Chronic hepatitis B patients are at increased risk for hepatocellular carcinoma (HCC). The effect of medium-term nucleos(t)ide analogue therapy on HCC incidence is unclear; therefore, we systematically reviewed all the data on HCC incidence from studies in chronic hepatitis B patients treated with nucleos(t)ide analogues.

METHODS: We performed a literature search to identify studies with chronic hepatitis B patients treated with nucleos(t)ide analogues for> or = 24 months.

RESULTS: Twenty-one studies including 3881 treated and 534 untreated patients met our inclusion criteria. HCC was diagnosed in 2.8% and 6.4% of treated and untreated patients, respectively, during a 46 (32-108) month period (p=0.003), in 10.8% and 0.5% of nucleos(t)ide naive patients with and without cirrhosis (p<0.001) and in 17.6% and 0% of lamivudine resistance patients with and without cirrhosis (p<0.001). HCC developed less frequently in nucleos(t)ide naive patients compared to those without virological remission (2.3% vs 7.5%, p<0.001), but there was no difference between lamivudine resistance patients with or without virological response to rescue therapy (5.9% vs 8.8%, p=0.466).

CONCLUSIONS: Chronic hepatitis B patients receiving medium-term nucleos(t)ide analogue therapy had a significantly lower incidence of HCC compared to untreated patients but treatment does not completely eliminate the risk of HCC. Among the treated patients, cirrhosis, HBeAg negative at baseline and failure to remain in virological remission were associated with an increased risk of HCC.

J Hepatol. 2010 May;52(5):652-7. doi: 10.1016/j.jhep.2009.12.028. Epub 2010 Mar 4.

Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis.

Cardoso AC[1], Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, Boyer N, Asselah T, Martinot-Peignoux M, Maylin S, Carvalho-Filho RJ, Valla D, Bedossa P, Marcellin P.

Author information

Abstract

BACKGROUND & AIMS: Hepatocellular carcinoma (HCC) currently represents the major cause of liver-related death in patients with hepatitis C virus (HCV)-related cirrhosis. We assessed the influence of combination therapy on the risk of HCC, liver-related complications (ascites, variceal bleeding), and liver-related death (or liver transplantation).

METHODS: Three hundred seven chronic hepatitis C patients with bridging fibrosis (n=127) or cirrhosis (n=180) were evaluated by Cox regression analysis. Sustained virological response (SVR) was defined as undetectable serum HCV RNA at 24 weeks after treatment.

RESULTS: SVR developed in 33% of patients. The SVR rates were not different between patients with bridging fibrosis (37%) and those with cirrhosis (30%), p=0.186. During a median follow-up of 3.5 years (range 1-18 years) after the last treatment, the incidence rates per 100 person-years of HCC, liver-related complications, and liver-related death, were 1.24, 0.62, and 0.61 among SVR patients, respectively, and 5.85, 4.16, and 3.76 among non-SVR patients, respectively (log-rank test, p<0.001). According to multivariate analysis, non-SVR was an independent predictor of HCC (HR 3.06; 95% CI=1.12-8.39), liver-related complications (HR 4.73; 95% CI: 1.09-20.57), and liver-related death (HR 3.71; 95% CI=1.05-13.05).

CONCLUSIONS: SVR is achieved in one-third of patients with HCV-related cirrhosis treated with peginterferon and ribavirin. SVR has a strong independent positive influence on the incidence of HCC and on the prognosis of these patients.

Clin Liver Dis. 2015 May;19(2):361-79. doi: 10.1016/j.cld.2015.01.012. Epub 2015 Mar 12.

Nonalcoholic Fatty liver disease, diabetes, obesity, and hepatocellular carcinoma.

Noureddin M[1], Rinella ME[2].

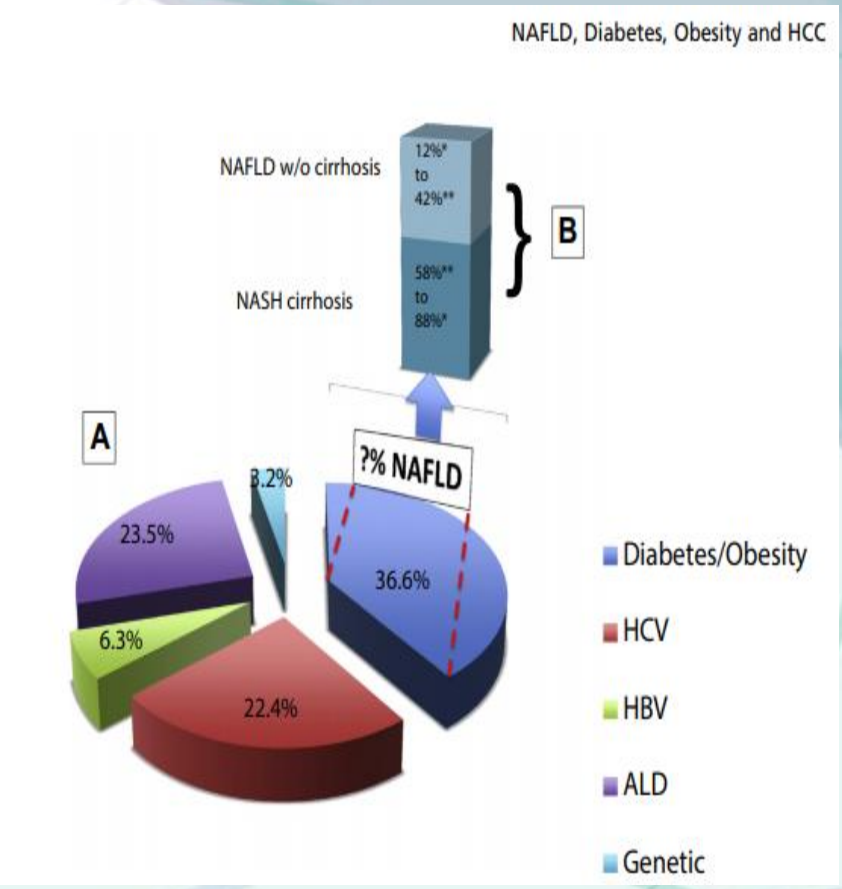
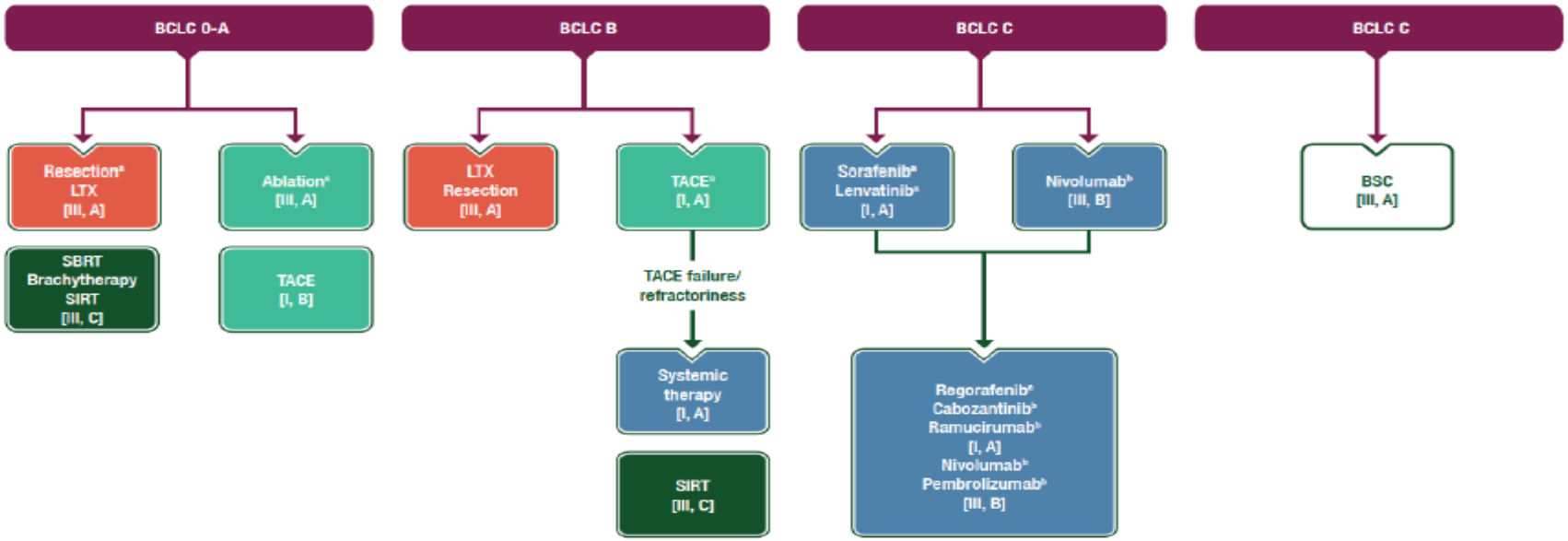


Table 1 – The Barcelona Clinic Liver Cancer (BCLC) classification of hepatocellular carcinoma

BCLC stage	Tumour status	Liver function reserve (Child–Pugh)	Performance status
Very early	Single / ≤2cm	A	0
Early	Single / ≤5cm or ≤3 tumours / each≤3cm	A or B	0
Intermediate	Multiple / Large	A or B	0
Advanced	Vascular invasion or extrahepatic spread	A or B	1–2
Terminal	Any	C	3–4

ESMO Clinical Practice Guideline 2018



MUNICH 2018 ESMO congress

Vogel et al. ESMO CPG 2018, Annals of Oncology

1st line setting

The NEW ENGLAND JOURNAL of MEDICINE

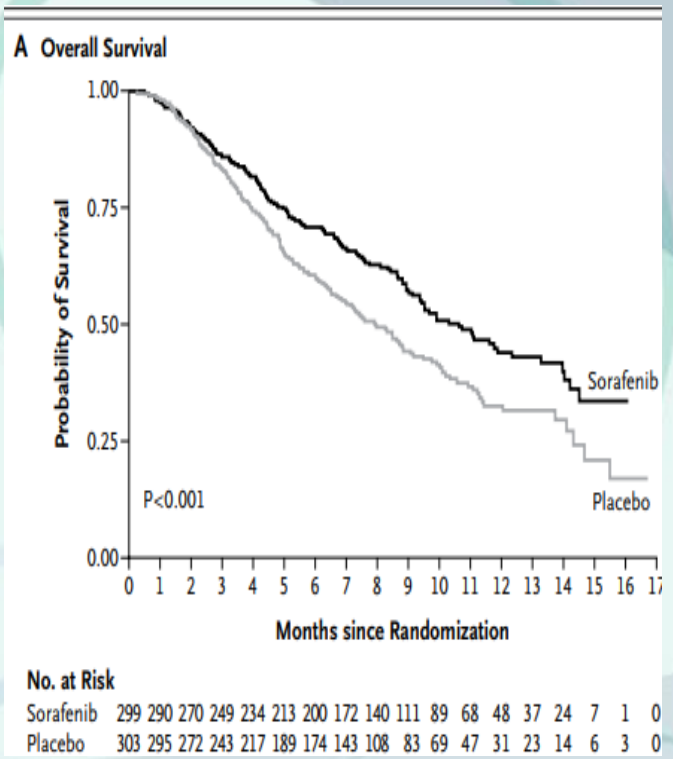
ORIGINAL ARTICLE

Sorafenib in Advanced Hepatocellular Carcinoma

Josep M. Llovet, M.D., Sergio Ricci, M.D., Vincenzo Mazzaferro, M.D., Philip Hilgard, M.D., Edward Gane, M.D., Jean-Frédéric Blanc, M.D., Andre Cosme de Oliveira, M.D., Armando Santoro, M.D., Jean-Luc Raoul, M.D., Alejandro Forner, M.D., Myron Schwartz, M.D., Camillo Porta, M.D., Stefan Zeuzem, M.D., Luigi Bolondi, M.D., Tim F. Greten, M.D., Peter R. Galle, M.D., Jean-François Seitz, M.D., Ivan Borbath, M.D., Dieter Häussinger, M.D., Tom Giannaris, B.Sc., Minghua Shan, Ph.D., Marius Moscovici, M.D., Dimitris Voliotis, M.D., and Jordi Bruix, M.D., for the SHARP Investigators Study Group*

Table 2. Summary of Efficacy Measures.*

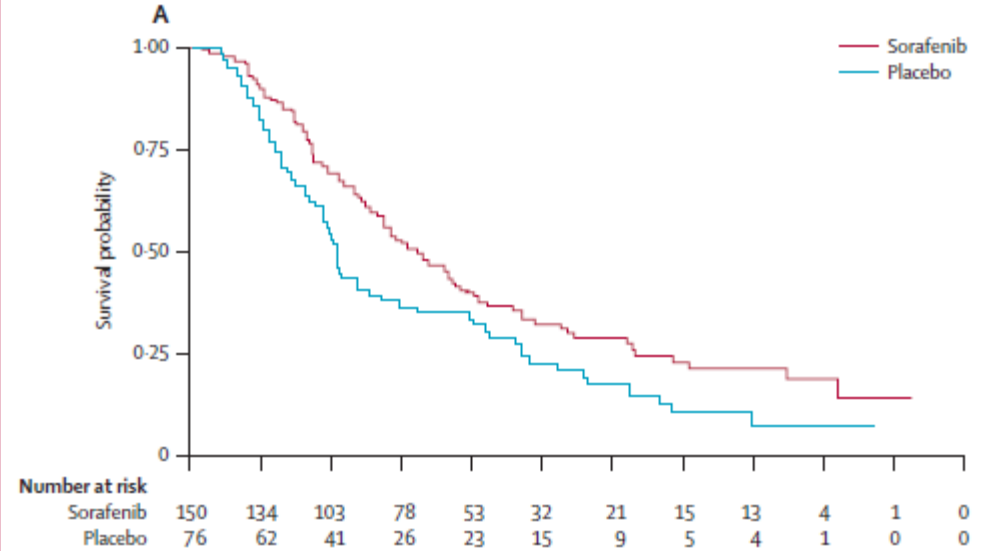
Outcome	Sorafenib (N=299)	Placebo (N=303)	Hazard Ratio (95% CI)	P Value
Overall survival (mo)			0.69 (0.55–0.87)	<0.001
Median	10.7	7.9		
95% CI	9.4–13.3	6.8–9.1		
1-yr survival rate (%)	44	33		0.009
Time to symptomatic progression (mo)†			1.08 (0.88–1.31)	0.77
Median	4.1	4.9		
95% CI	3.5–4.8	4.2–6.3		
Time to radiologic progression (mo)			0.58 (0.45–0.74)	<0.001
Median	5.5	2.8		
95% CI	4.1–6.9	2.7–3.9		
Level of response (%)‡				
Complete	0	0		NA
Partial	2	1		0.05
Stable disease	71	67		0.17
Disease-control rate (%)§	43	32		0.002



N Engl J Med 2008;359:378-90.

Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial

Ann-Lii Cheng, Yoon-Koo Kang, Zhendong Chen, Chao-Jung Tsao, Shukui Qin, Jun Suk Kim, Rongcheng Luo, Jifeng Feng, Shenglong Ye, Tsai-Sheng Yang, Jianming Xu, Yan Sun, Houjie Liang, Jiwei Liu, Jiejun Wang, Won Young Tak, Hongming Pan, Karin Burock, Jessie Zou, Dimitris Voliotis, Zhongzhen Guan



	Sorafenib group (n=150)	Placebo group (n=76)
Complete response	0 (0)	0 (0)
Partial response	5 (3·3)	1 (1·3)
Stable disease	81 (54·0)	21 (27·6)
Progressive disease	46 (30·7)	41 (54·0)
Not assessable	18 (12·0)	13 (17·1)
DCR, n (%; 95% CI)	53 (35·3; 27·7–43·6)	12 (15·8; 8·4–26·0)

DCR=disease control rate, defined as the proportion of patients who had a best response rating of complete response, partial response, or stable disease, which was maintained ≥4 weeks from the first manifestation of that rating.

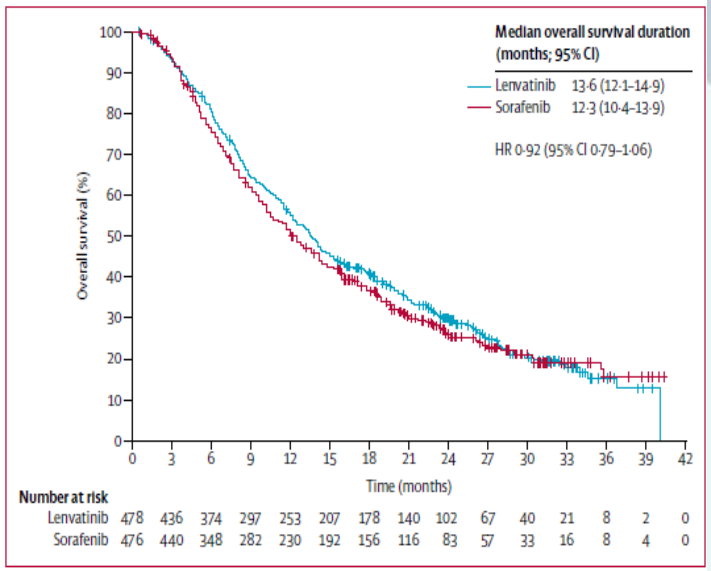
Table 2: **Response rates by Response Evaluation Criteria in Solid Tumors**

Lancet Oncol 2009; 10: 25-34

Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

Masatoshi Kudo, Richard S Finn, Shukui Qin, Kwang-Hyub Han, Kenji Ikeda, Fabio Piscaglia, Ari Baron, Joong-Won Park*, Guohong Han*, Jacek Jassem, Jean Frederic Blanc, Arndt Vogel, Dmitry Komov, T R Jeffry Evans, Carlos Lopez, Corina Dutcus, Matthew Guo, Kenichi Saito, Silvija Kraljevic, Toshiyuki Tamai, Min Ren, Ann-Lii Cheng*

	Lenvatinib (n=478)	Sorafenib (n=476)
Eastern Cooperative Oncology Group performance status		
0	304 (64%)	301 (63%)
1	174 (36%)	175 (37%)
Child-Pugh class		
A	475 (99%)	471 (99%)
B	3 (1%)	5 (1%)
Macroscopic portal vein invasion, extrahepatic spread, or both		
Yes	329 (69%)	336 (71%)
No	149 (31%)	140 (29%)
Barcelona Clinic Liver Cancer stage		
B (intermediate stage)	104 (22%)	92 (19%)
C (advanced stage)	374 (78%)	384 (81%)



PFS: 7.4 s 3.7 m
ORR: 24 vs 9% (mRECIST)

Excluding: main portal vein invasion, bile duct invasion and > 50% of tumour to total liver volume occupancy

Lenv vs soraf: hypertension (42% vs 30%), diarrhoea (39% vs 45%) and hand–foot skin reaction (27% vs 52%), proteinuria (25% vs 11%), hypothyroidism (16 vs2%), dysphonia (24 vs 12%)

EMA

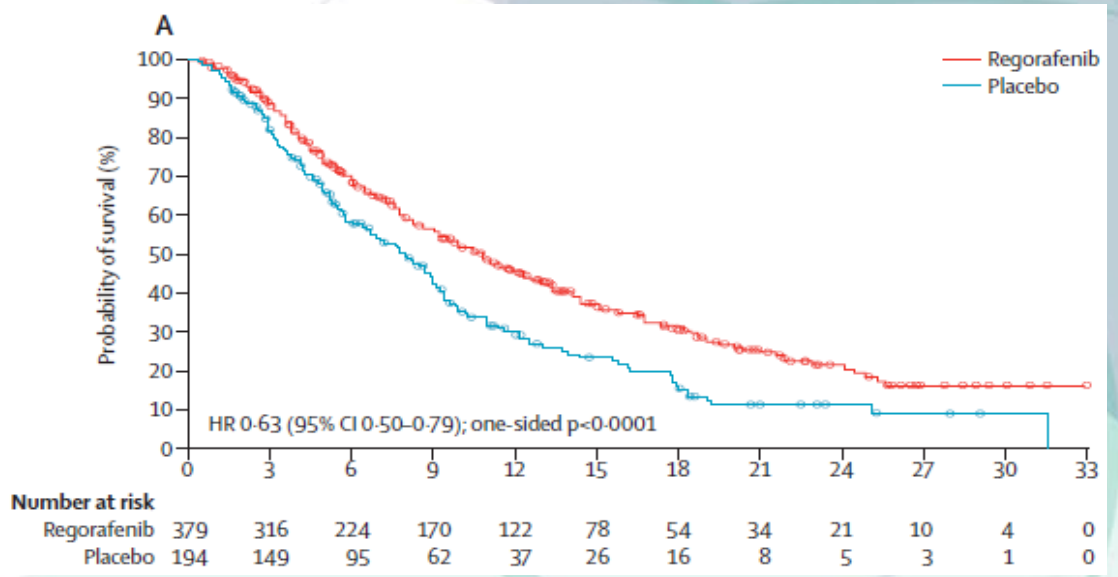
Lancet 2018; 391: 1163–73

Beyond 1st line setting

Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial

*Jordi Bruix, Shukui Qin, Philippe Merle, Alessandro Granito, Yi-Hsiang Huang, György Bodoky, Marc Pracht, Osamu Yokosuka, Olivier Rosmorduc, Valeriy Breder, René Gerolami, Gianluca Masi, Paul J Ross, Tianqiang Song, Jean-Pierre Bronowicki, Isabelle Ollivier-Hourmand, Masatoshi Kudo, Ann-Lii Cheng, Josep M Llovet, Richard S Finn, Marie-Aude LeBerre, Annette Baumhauer, Gerold Meinhardt, Guohong Han, on behalf of the RESORCE Investigators**

	Regorafenib (n=379)	Placebo (n=194)
ECOG performance status		
0	247 (65%)	130 (67%)
1	132 (35%)	64 (33%)
Macrovascular invasion	110 (29%)	54 (28%)
Extrahepatic disease	265 (70%)	147 (76%)
Macrovascular invasion and/or extrahepatic disease	304 (80%)	162 (84%)
Child-Pugh class‡		
A	373 (98%)	188 (97%)
B	5 (1%)	6 (3%)
BCLC stage		
A (early)	1 (<1%)	0
B (intermediate)	53 (14%)	22 (11%)
C (advanced)	325 (86%)	172 (89%)



mOS: 10.6 vs 7.8 m
ORR: 11% vs 4%
DCR: 65% vs 36%
mRECIST

G3/4: HTN (15%), HFS (13%), fatigue (9%), diarrhoea (3%)

EMA

www.thelancet.com Published online December 5, 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

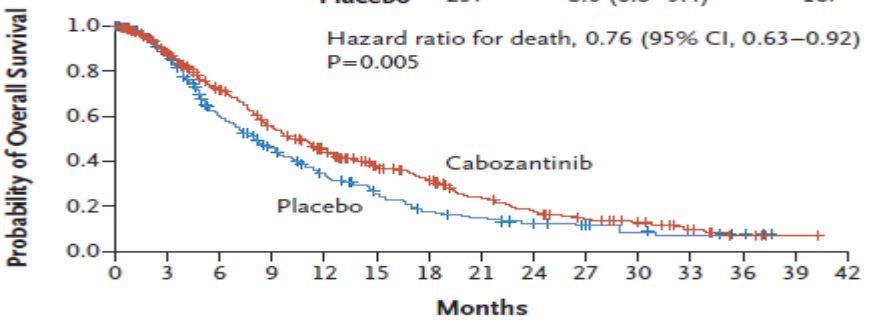
Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma

G.K. Abou-Alfa, T. Meyer, A.-L. Cheng, A.B. El-Khoueiry, L. Rimassa, B.-Y. Ryoo, I. Cicin, P. Merle, Y.H. Chen, J.-W. Park, J.-F. Blanc, L. Bolondi, H.-J. Klümpen, S.L. Chan, V. Zagonel, T. Pressiani, M.-H. Ryu, A.P. Venook, C. Hessel, A.E. Borgman-Hagey, G. Schwab, and R.K. Kelley

	Cabozantinib (N=470)	Placebo (N=237)
ECOG performance-status score — no. (%)‡		
0	245 (52)	131 (55)
1	224 (48)	106 (45)
2	1 (<1)	0
Etiologic factor — no. (%)§		
HBV	178 (38)	89 (38)
HCV	113 (24)	55 (23)
Dual HBV and HCV infection	8 (2)	4 (2)
Alcohol use	112 (24)	39 (16)
Nonalcoholic steatohepatitis	43 (9)	23 (10)
Other	24 (5)	16 (7)
Unknown	75 (16)	47 (20)
Extrahepatic spread of disease — no. (%)	369 (79)	182 (77)
Macrovascular invasion — no. (%)	129 (27)	81 (34)
Extrahepatic spread of disease, macrovascular invasion, or both — no. (%)	398 (85)	200 (84)

A Overall Survival

	No. of Patients	Median Overall Survival mo (95% CI)	No. of Events
Cabozantinib	470	10.2 (9.1–12.0)	317
Placebo	237	8.0 (6.8–9.4)	167



No. at Risk

Cabozantinib	470	328	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

PFS: 5.2 vs 1.9 m

ORR: 4% vs 1 % (RECIST)

DCR: 64% vs 33%

Allowed patients intolerant to sorafenib and with PD on one (100%) or two (27%) systemic Tx.

G3/4 tox: PPE (22%), diarrhoea (10%), fatigue & HTN (7%), AST (6%)

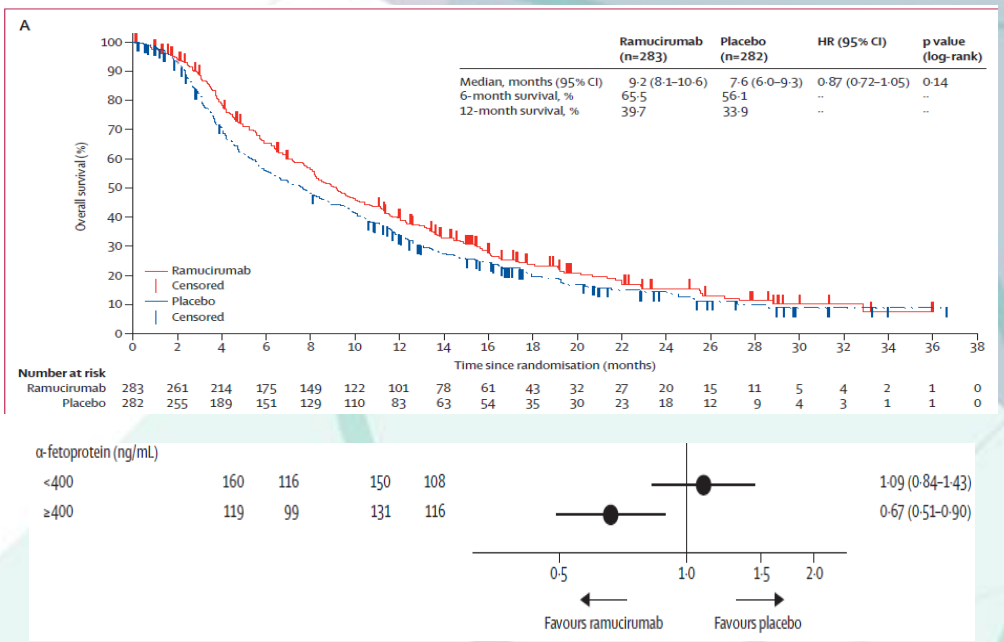
EMA

N Engl J Med 2018;379:54-63.

Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial

Andrew X Zhu, Joon Oh Park, Baek-Yeol Ryoo, Chia-Jui Yen, Ronnie Poon, Davide Pastorelli, Jean-Frederic Blanc, Hyun Cheol Chung, Ari D Baron, Tulio Eduardo Flesch Pfiffer, Takuji Okusaka, Katerina Kubackova, Jorg Trojan, Javier Sastre, Ian Chau, Shao-Chun Chang, Paolo B Abada, Ling Yang, Jonathan D Schwartz, Masatoshi Kudo, for the REACH Trial Investigators*

	Ramucirumab (n=283)	Placebo (n=282)
ECOG performance status†		
0	159 (56%)	153 (54%)
1	124 (44%)	129 (46%)
Baseline Child-Pugh A¶	277 (98%)	276 (98%)
Macrovascular invasion present	82 (29%)	79 (28%)
Extrahepatic spread present	207 (73%)	200 (71%)
Baseline BCLC stage		
Stage B	33 (12%)	34 (12%)
Stage C	250 (88%)	248 (88%)
Previous sorafenib therapy		
Sorafenib only	244 (86%)	253 (90%)
Sorafenib and other systemic therapy	39 (14%)	29 (10%)
α-fetoprotein (ng/mL)		
<400	160 (57%)	150 (53%)
≥400	119 (42%)	131 (46%)



PD on or intolerant of soraf/ Initially included CP B patients

PFS: 2.8 vs 2.1 p sign
ORR: 7 vs < 1%
DCR: 56 vs 46%
RECIST

G3/4 tox: HTN (12%), asthenia (5%), AST (5%), PLT (5%), bilirubin (2%), GI bleed (3%), proteinuria (2%), thrombosis (2%)

Lancet Oncol 2015
Published Online June 19, 2015

REACH-2: Ramucirumab vs Placebo in HCC With Elevated Baseline AFP

- Randomized, double-blind phase III trial

Randomized 2:1

Pts with advanced HCC; Child-Pugh A; BCLC B/C; ECOG PS 0-1; progression on or intolerance to sorafenib; no other systemic therapy; baseline AFP ≥ 400 ng/mL (Planned N = 399)

Ramucirumab + BSC
8 mg/kg IV Q2W

Placebo + BSC
IV Q2W

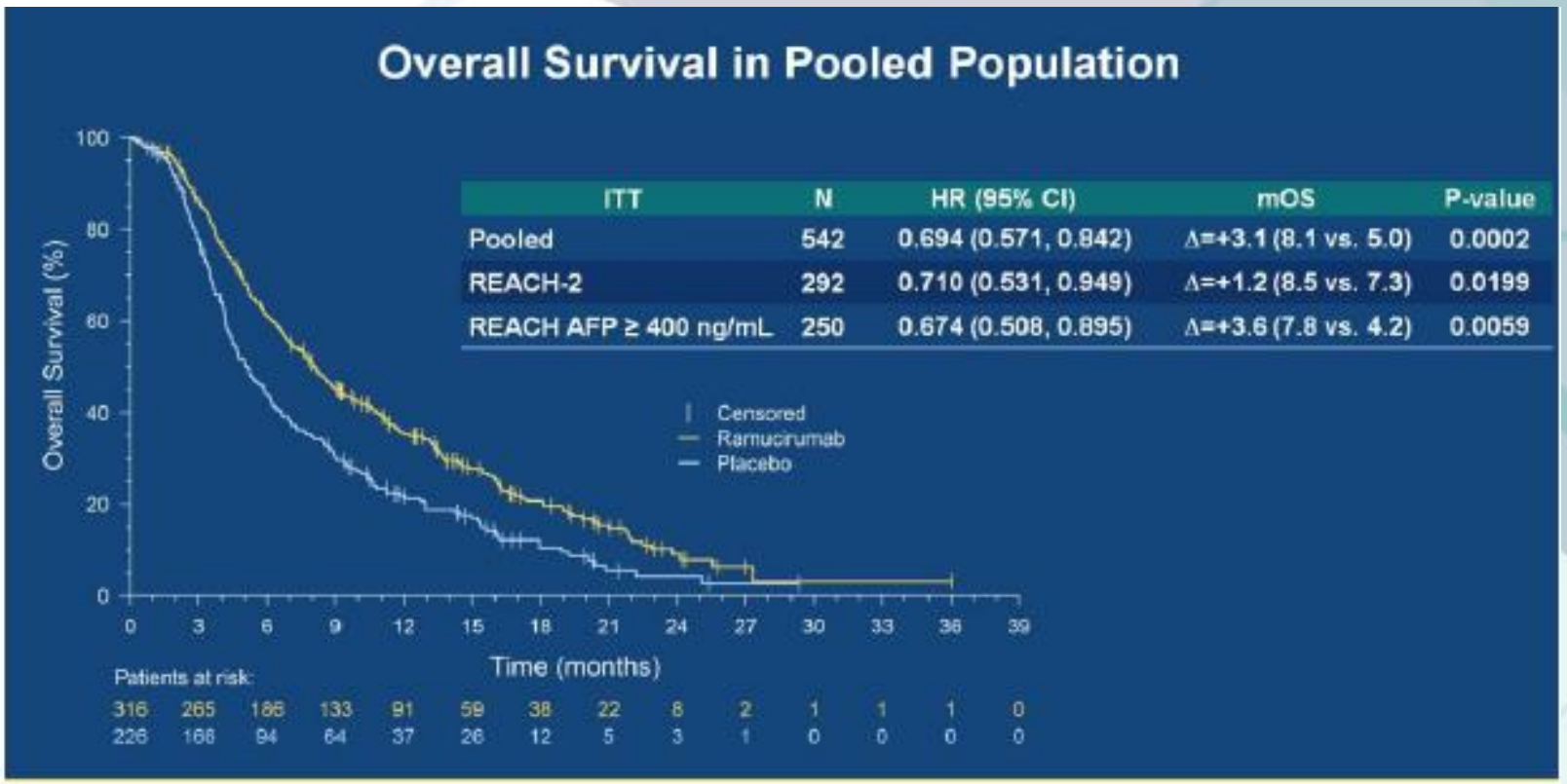
All pts treated until PD, unacceptable toxicity, or withdrawal of consent

Crossover to ramucirumab permitted for pts remaining on treatment at study completion

- Primary endpoint: OS
- Secondary endpoints: PFS, time to radiographic progression, best overall response of CR or PR, PK, anti-ramucirumab antibodies, QoL

ClinicalTrials.gov. NCT02435433.

Slide credit: clinicaloptions.com



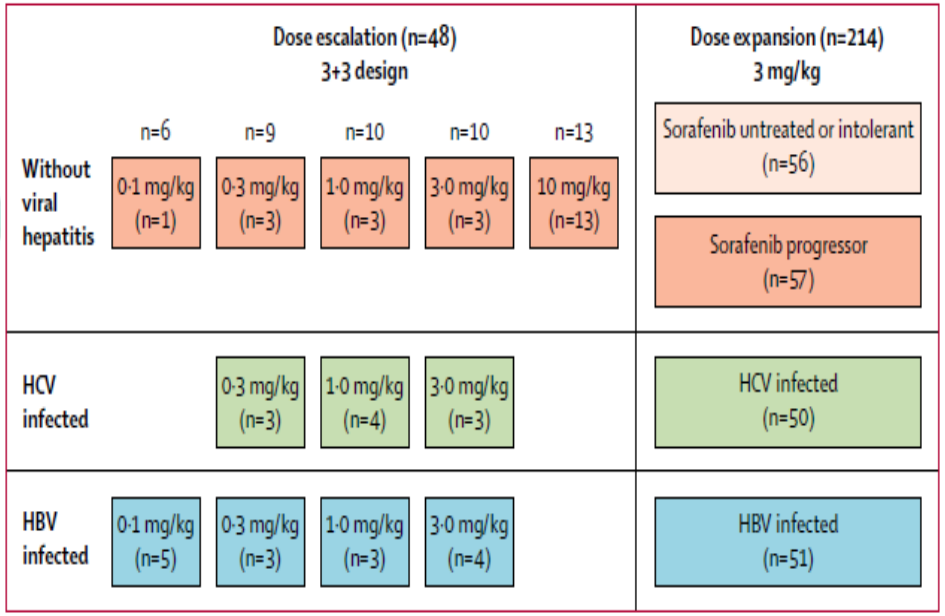
REACH-2 -G3/4 TOX: HTN(12%), LOW Na (5.6%)

Zhu et al @ESMO 2018

IMMUNOTHERAPY

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

*Anthony B El-Khoueiry, *Bruno Sangro, *Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero*



Dose escalation
ORR: 15%
DCR: 58%
mOS: 15 months
mDoR: 17 months

FDA

Dose expansion
ORR: 20%
DCR: 64%
mOS: NR (13.2 m in uninfected progr)
mDoR: 9.9 months

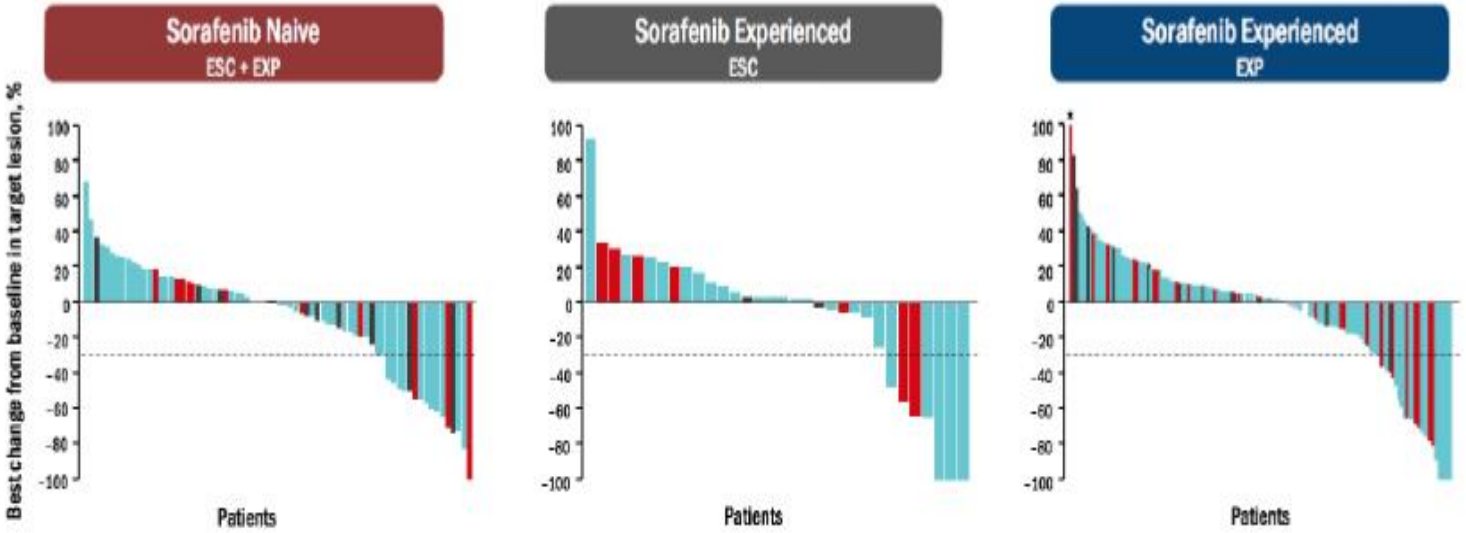
CP A or B7 (dose-escalation) and 6 or less (CP A) (dose-expansion), ECOG PS 0-1

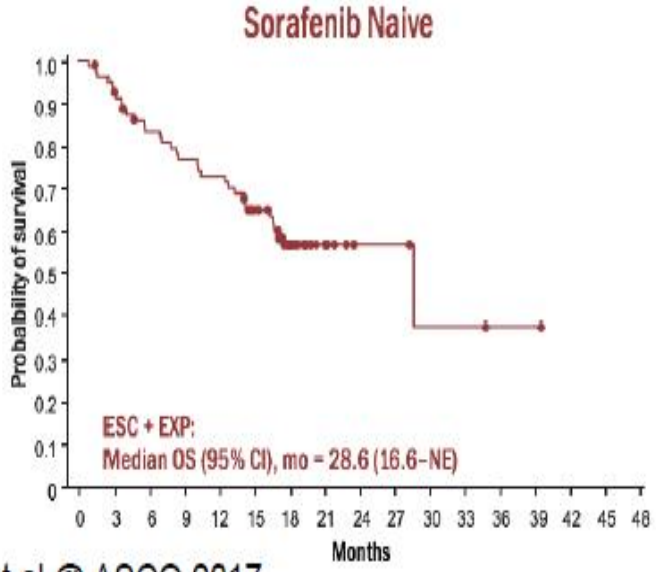
ORR by PDL-1: 26% (>1%)
vs 19% (<1% TC)

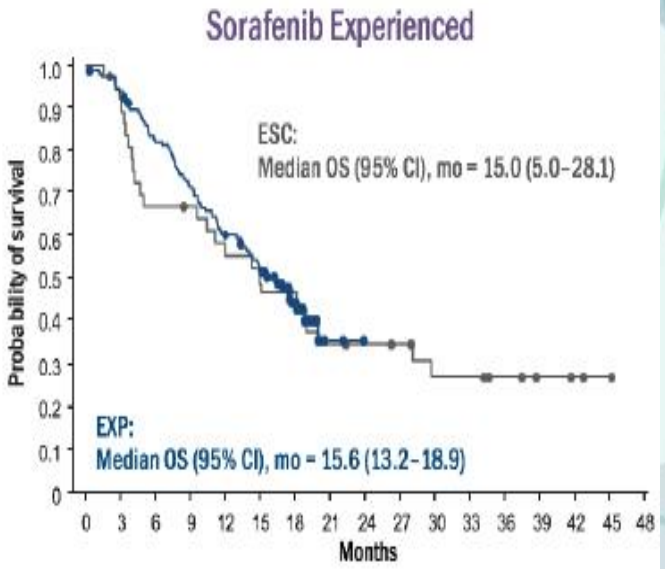
G3/4 tox: AST (4%), ALT (2%)/ most common (all grades): fatigue (23%), rash (15%), pruritus (21%)

Published Online
April 20, 2017

CHECKMATE-040: Nivolumab in 1st and 2nd line







MUNICH 2018 ESMO congress

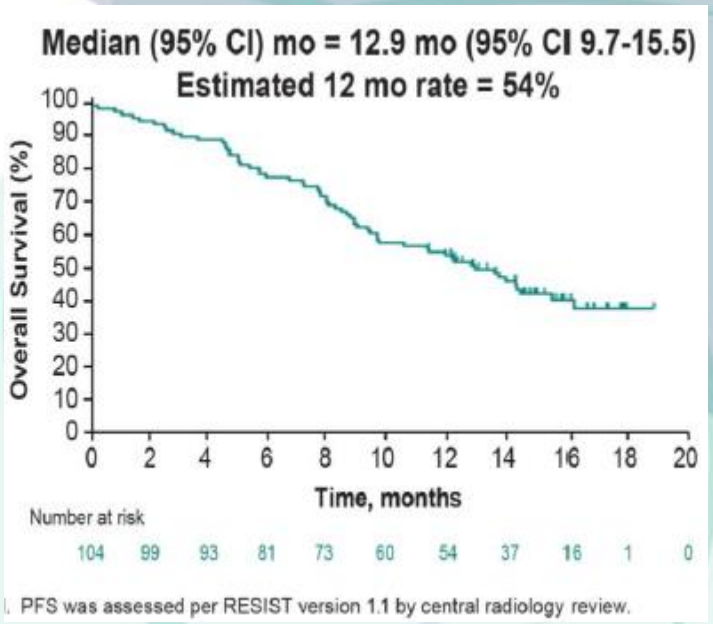
Crocenzi et al @ ASCO 2017

Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial

*Andrew X Zhu, Richard S Finn, Julien Edeline, Stephane Cattan, Sadahisa Ogasawara, Daniel Palmer, Chris Verslype, Vittorina Zagonel, Laetitia Fartoux, Arndt Vogel, Debashis Sarker, Gontran Verset, Stephen L Chan, Jennifer Knox, Bruno Daniele, Andrea L Webber, Scot W Ebbinghaus, Junshui Ma, Abby B Siegel, Ann-Lii Cheng, Masatoshi Kudo, for the KEYNOTE-224 investigators**

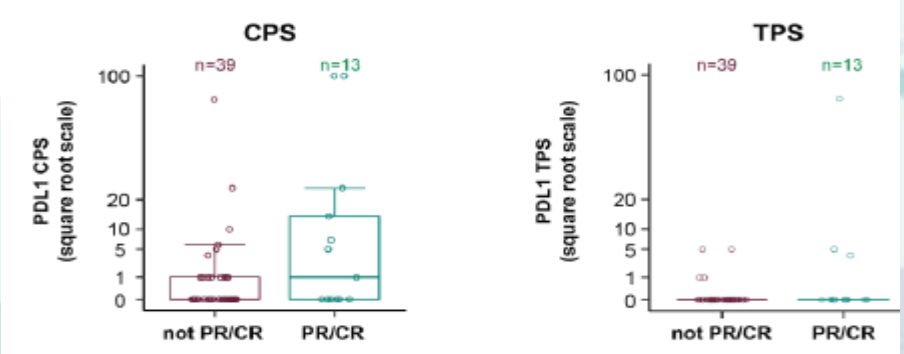
Eastern Cooperative Oncology Group performance status	
0	63 (61%)
1	41 (39%)
Child Pugh Class	
A	98 (94%)
B	6 (6%)
Barcelona Clinic Liver Cancer stage	
B	25 (24%)
C	79 (76%)
Reason for previous discontinuation of sorafenib	
Intolerance	21 (20%)
Progressive disease	83 (80%)
Extrahepatic disease	67 (64%)
Macrovascular invasion	18 (17%)

	All treated participants (n=104)
Objective response*	18 (17%; 11–26)
Best overall response†	
Complete response	1 (1%)
Partial response	17 (16%)
Stable disease	46 (44%)
Progressive disease	34 (33%)
Not assessable‡	6 (6%)
Disease control§	64 (62%; 52–71)
Median time to response, months (IQR)¶	2·1 (2·1–4·1)
Median duration of response, months (range) ¶‖	Not reached (3·1–14·6+**)
Duration of response ≥9 months¶‖	12 (77%)



‖ PFS was assessed per RESIST version 1.1 by central radiology review.

Tox G3/4: fatigue (4%), AST (7%), LOA (1%), ALT (4%) , adrenal (2%), T1DM (1%), rash (1%), hepatitis (3%)



FDA

Lancet Oncol 2018
Published Online
June 3, 2018

Safety and Clinical Activity of Atezolizumab + Bevacizumab in a Phase Ib Study in First-Line Hepatocellular Carcinoma

Abstract 340TiP
Poster 1263

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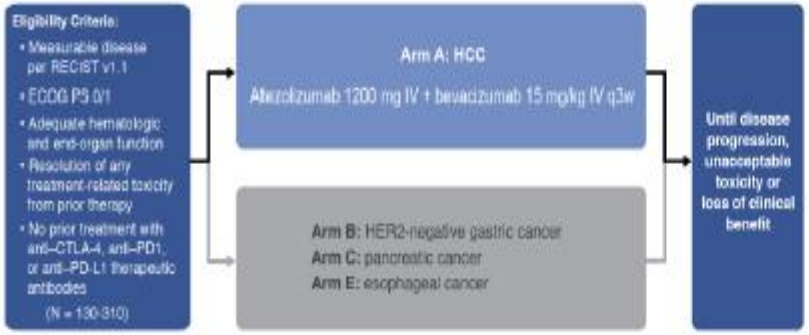
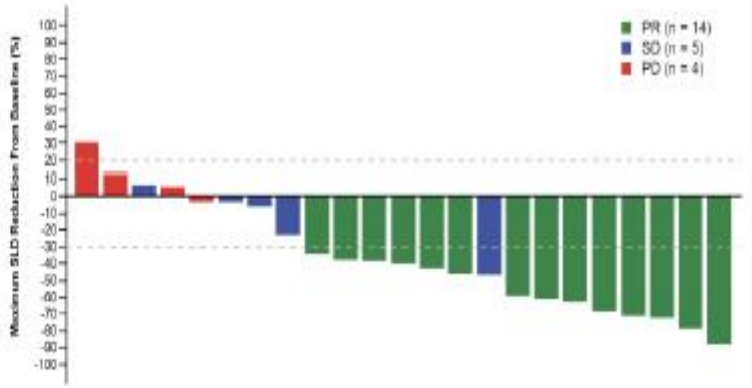
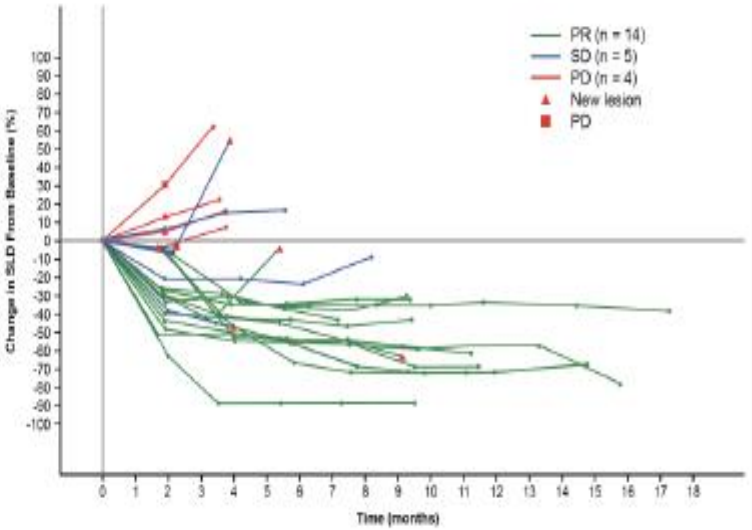


BOR	INV-Assessed per RECIST v1.1 (n = 23)	IRF-Assessed per RECIST v1.1 (n = 23)
ORR, n (%)	**14 (61%)**	**15 (65%)**
CR	0	1 (4%)
PR	14 (61%)	14 (61%)
SD	5 (22%)	7 (30%)
PD	4 (17%)	1 (4%)
DCR, n (%)		
CR + PR + SD	**19 (83%)**	**22 (96%)**
CR + PR + SD ≥ 6 mo	**15 (65%)**	**16 (70%)**





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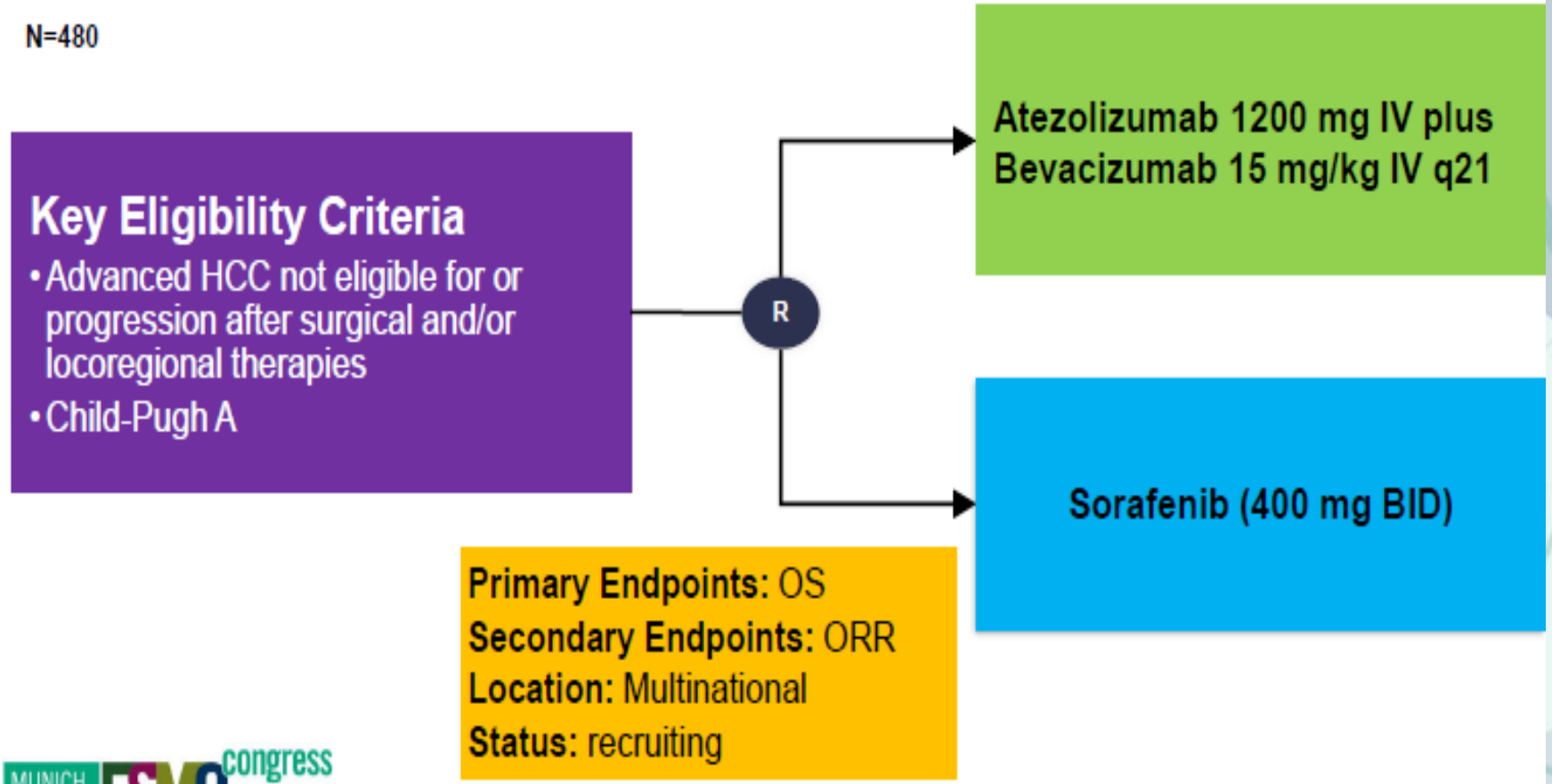
Stein et al. @ASCO 2018

IMBRAVE150: Atezo und Beva

A Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma



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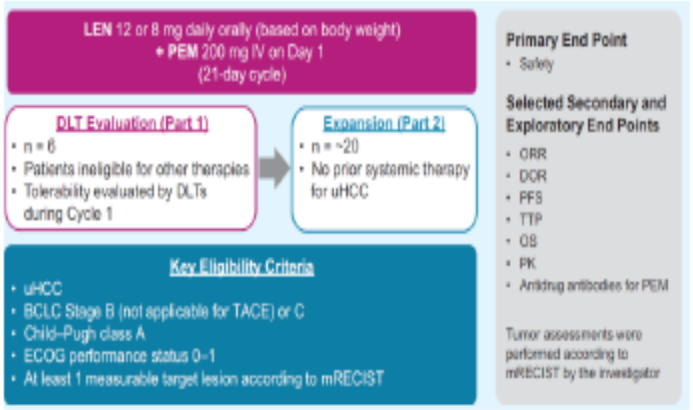
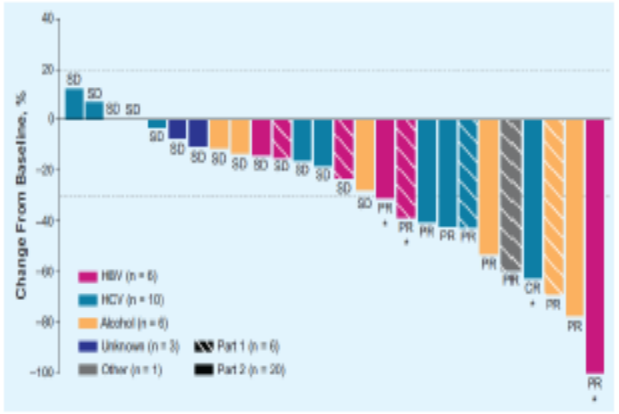
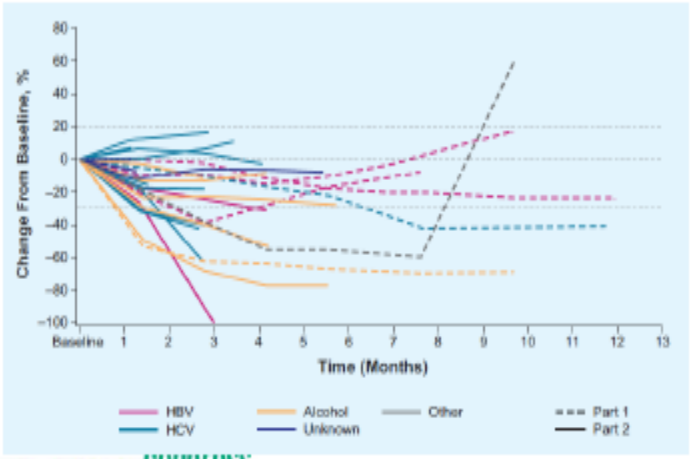
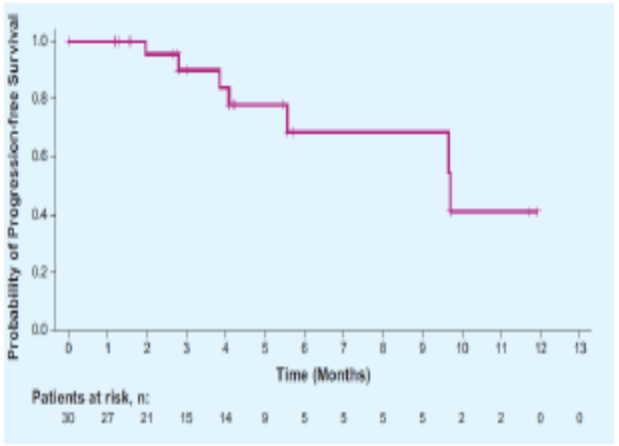
Clinicaltrials.gov. NCT03434379

A Phase 1b Trial of Lenvatinib (LEN) Plus Pembrolizumab in Patients With Unresectable HCC









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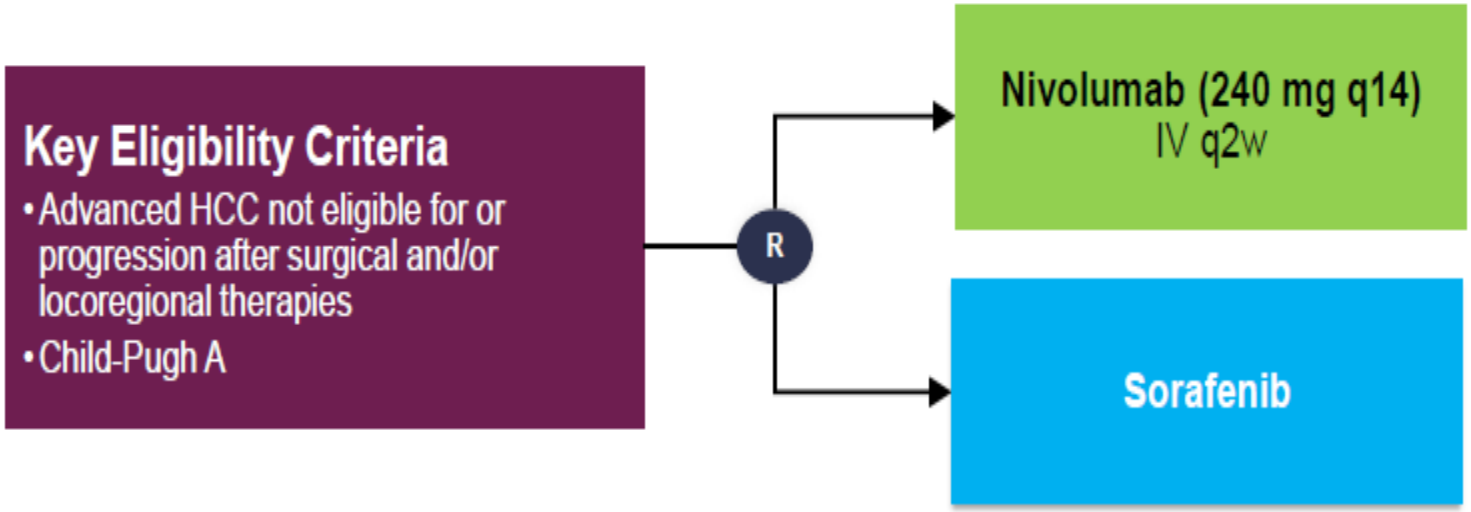
Ikeda et al. @ASCO 2018

CHECKMATE-459: Nivolumab

PHASE 3 TRIAL OF NIVOLUMAB VS SORAFENIB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED HCC

N=726



- **Start Date:** November 2015
- **Primary Endpoints:** OS
- **Secondary Endpoints: ORR***, PFS, biomarker analysis (including PD-L1)
- **Location:** Multinational
- **Status:** Ongoing, not recruiting

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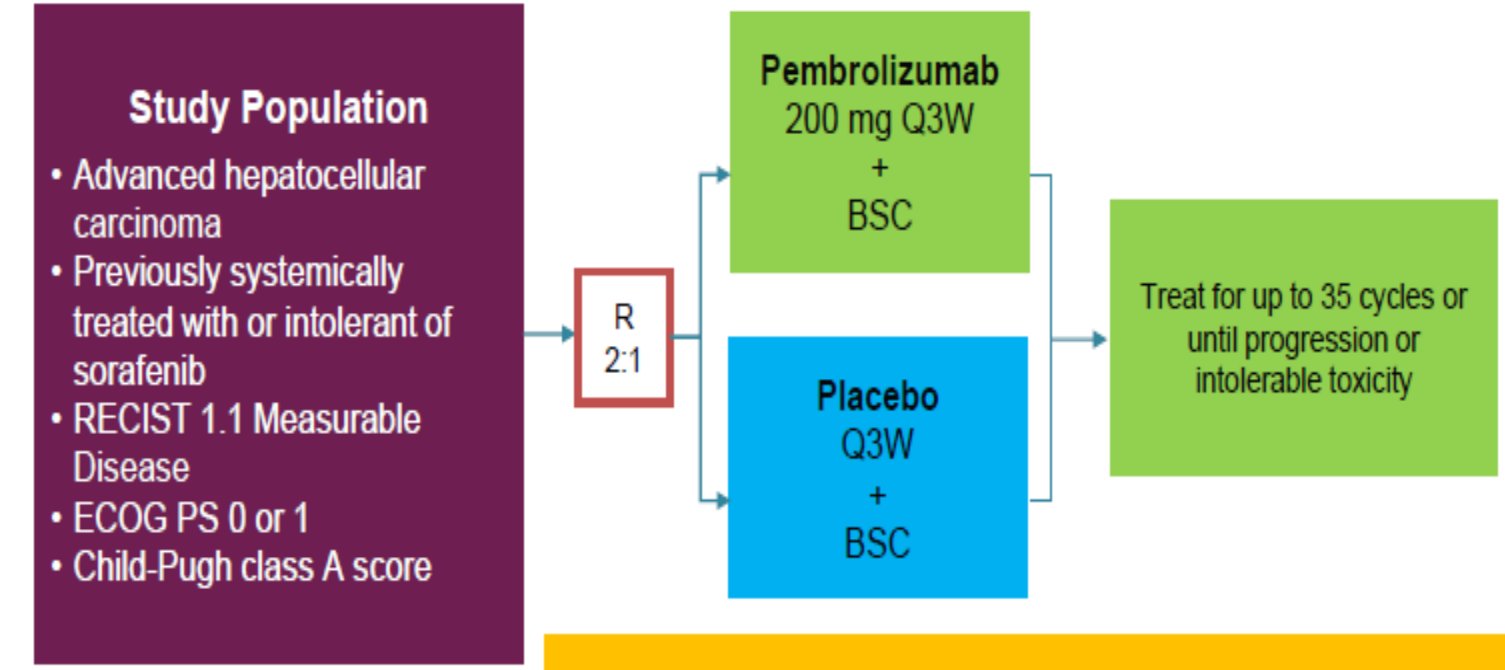
Clinicaltrials.gov. NCT02576509
Sangro B et al. @ASCO 2016

KEYNOTE-240: Pembrolizumab in 2nd line

A Phase III Study of Pembrolizumab (MK-3475) vs. Best Supportive Care as Second-Line Therapy in Subjects With Previously Systemically Treated Advanced Hepatocellular Carcinoma (KEYNOTE-240)



- Response assessment: every 6 weeks
- Primary end point : PFS per RECIST 1.1, OS
- Secondary end points: ORR per RECIST 1.1, DOR, DCR, TTP, safety

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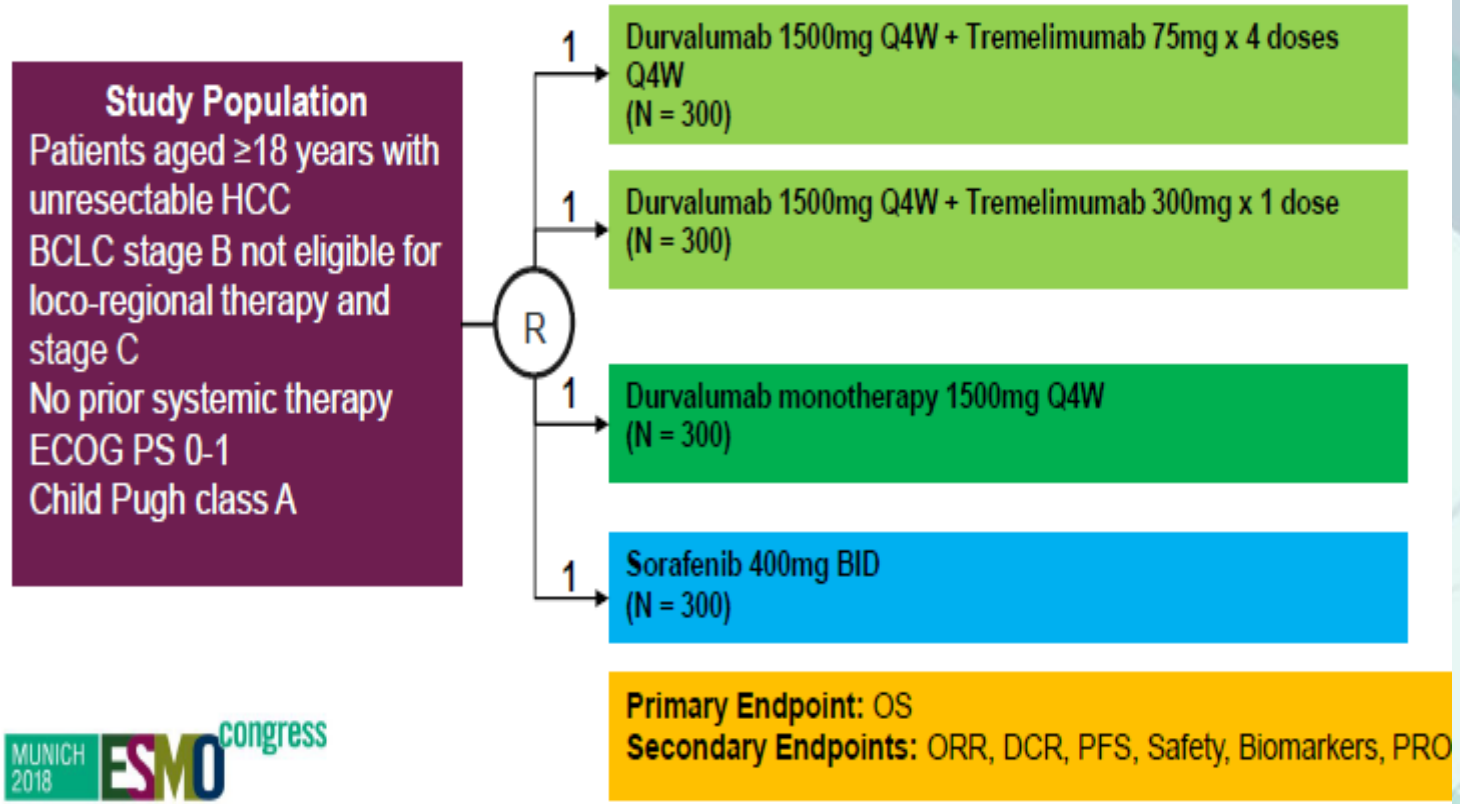
HIMALAYA: Study Design

A phase 3, randomised, open-label, multi-center study of durvalumab and tremelimumab as first-line treatment in patients with unresectable HCC



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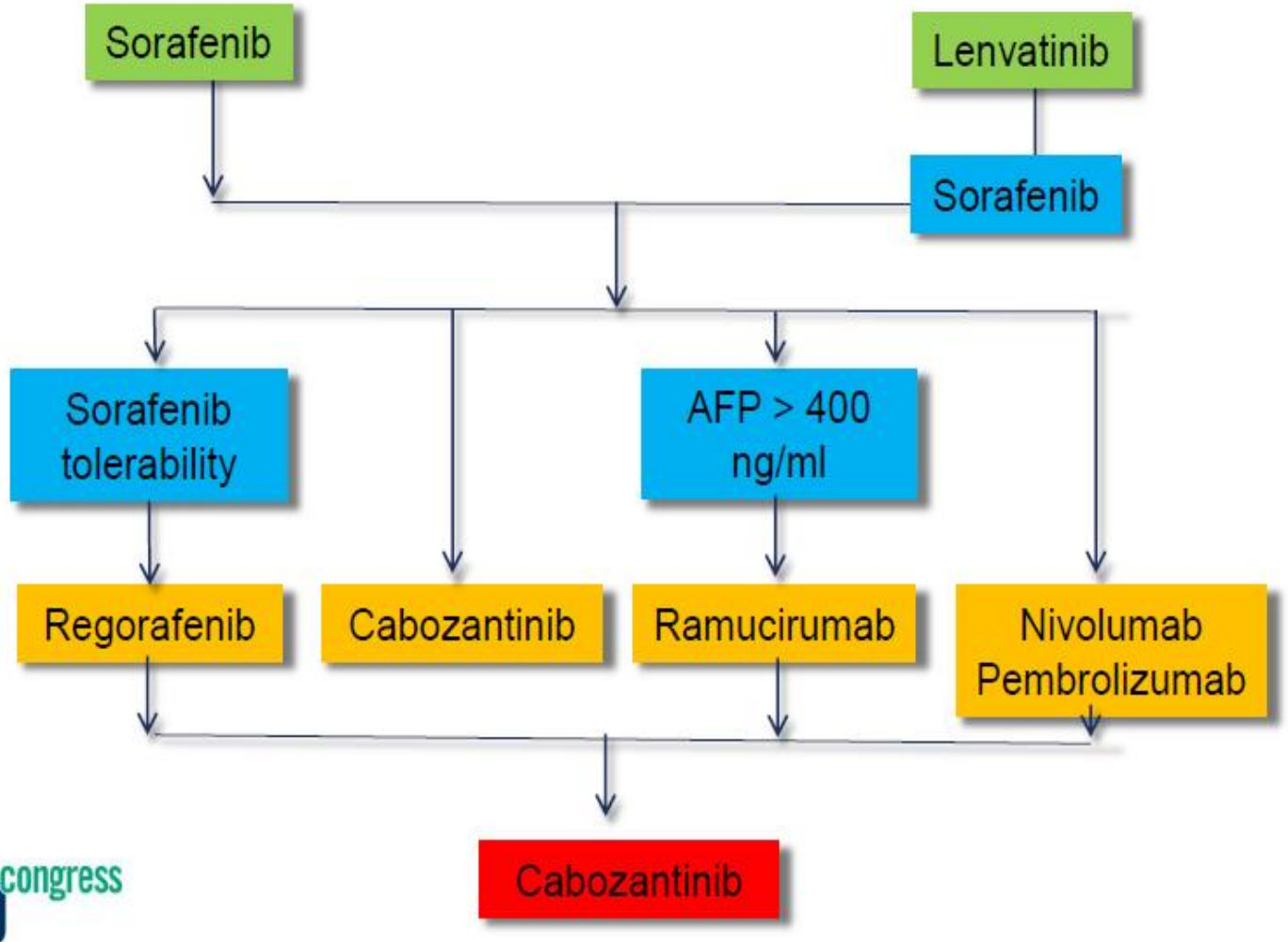
Systemic treatment of HCC 2018/ 2019



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Vogel, ESMO 2018


Thank
you!!