Panorama de la terapia sistémica en Carcinoma Hepatocelular

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Oncología Clínica
Centro Especialistas San Vicente Fundación – Clínica El Rosario
Diciembre de 2019

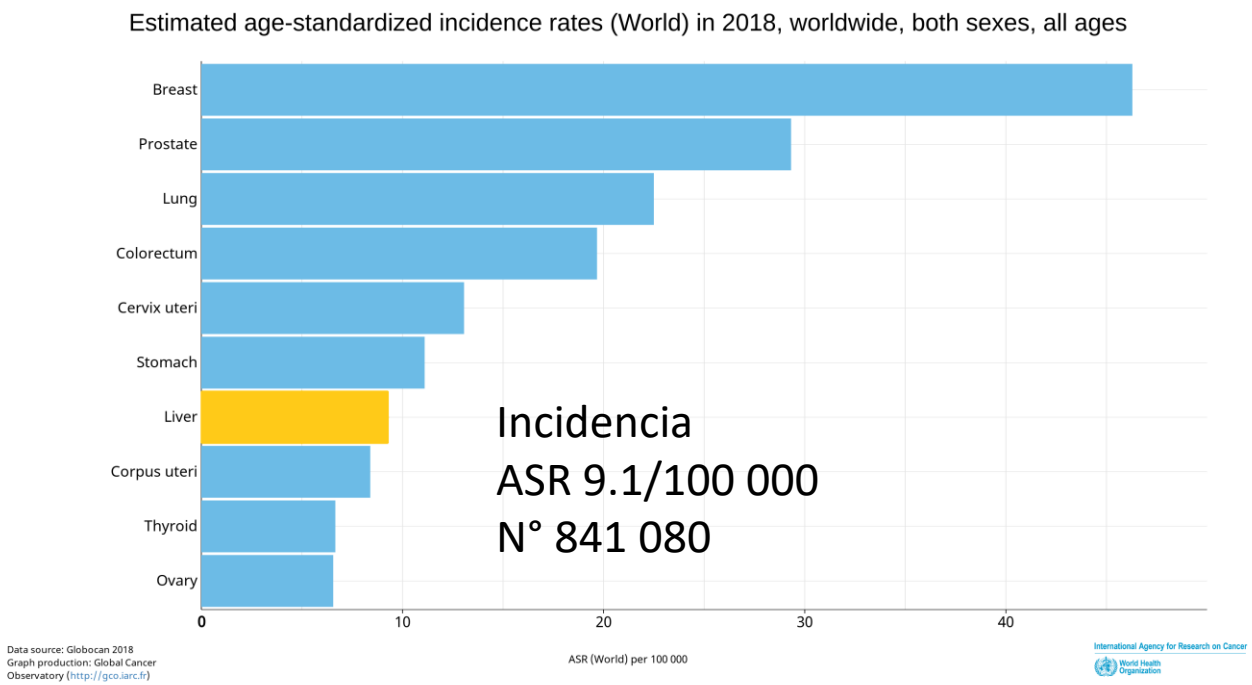
Conflictos de interés

- Esta charla es patrocinada por Bayer
- Colaborador en actividades académicas
  - Bristol-Mayers
  - Novartis
  - Astra Zeneca
  - MSD
  - Boehringer Ingelheim

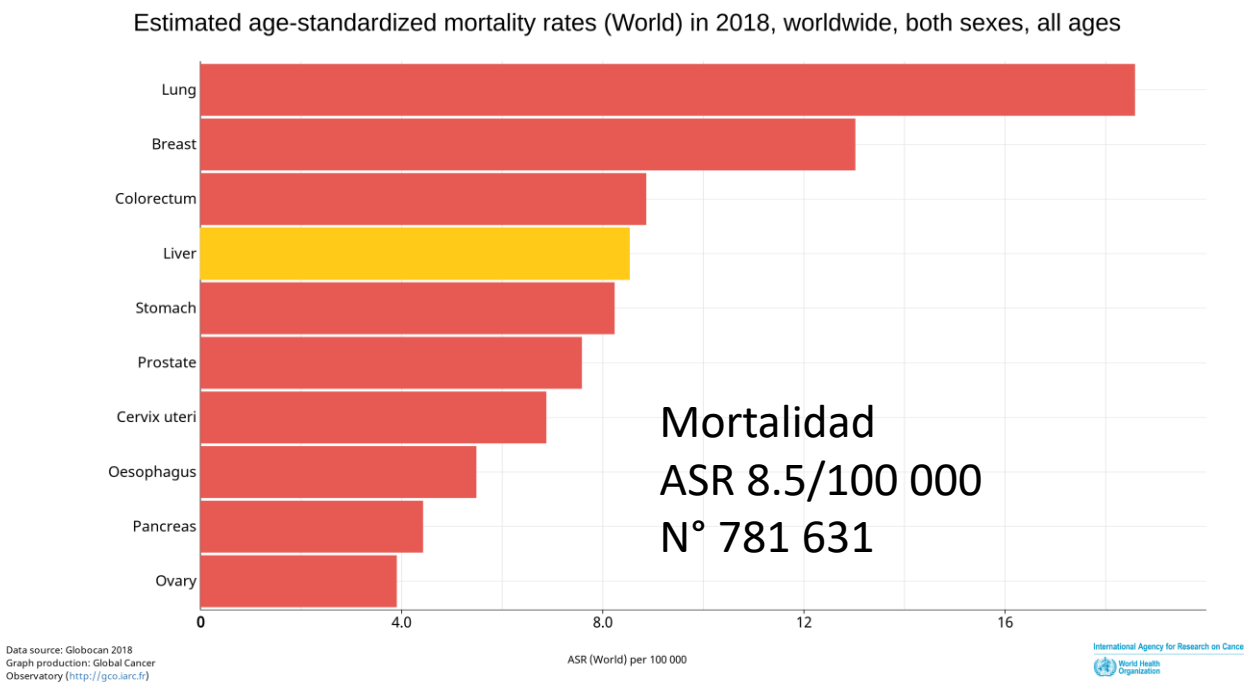
Agenda

- Datos puntuales en Epidemiología
  - Importancia
- Opciones de tratamiento en 1ª línea
  - Migración de la terapia
- Opciones de tratamiento en 2ª línea
  - Líneas posteriores
- Conclusiones

Epidemiología - Global



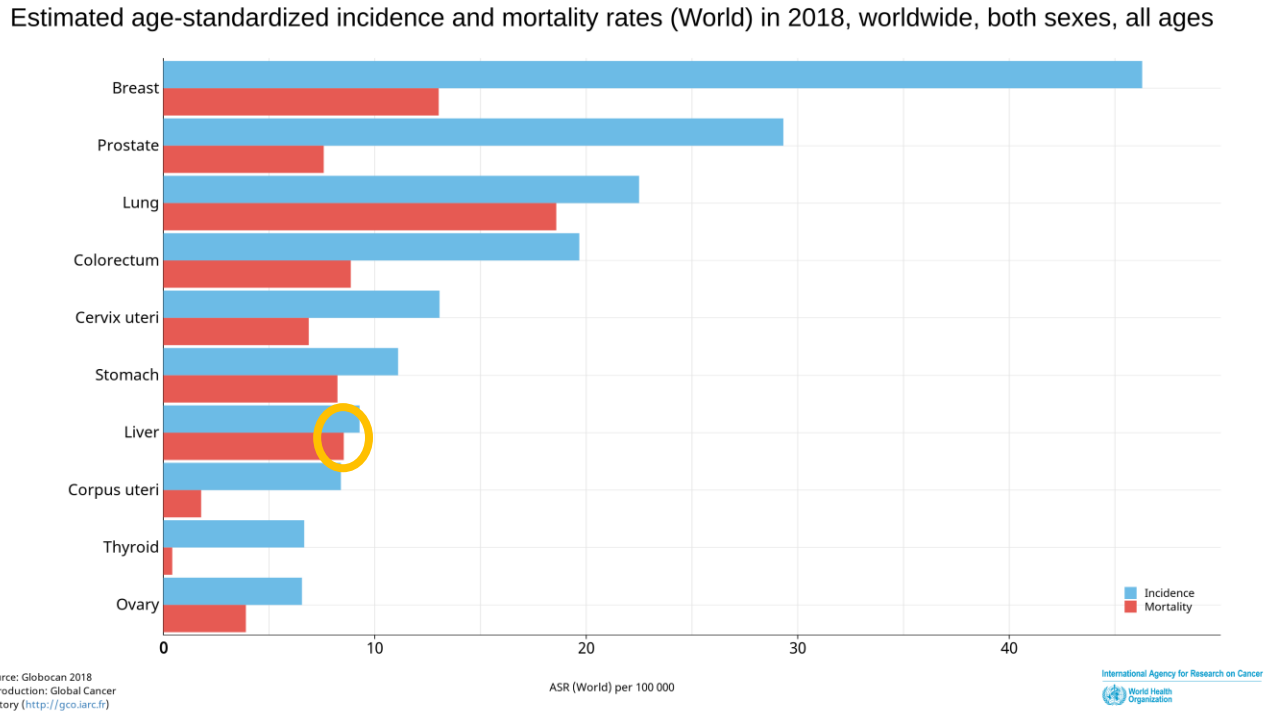
Incidencia
ASR 9.1/100 000
N° 841 080

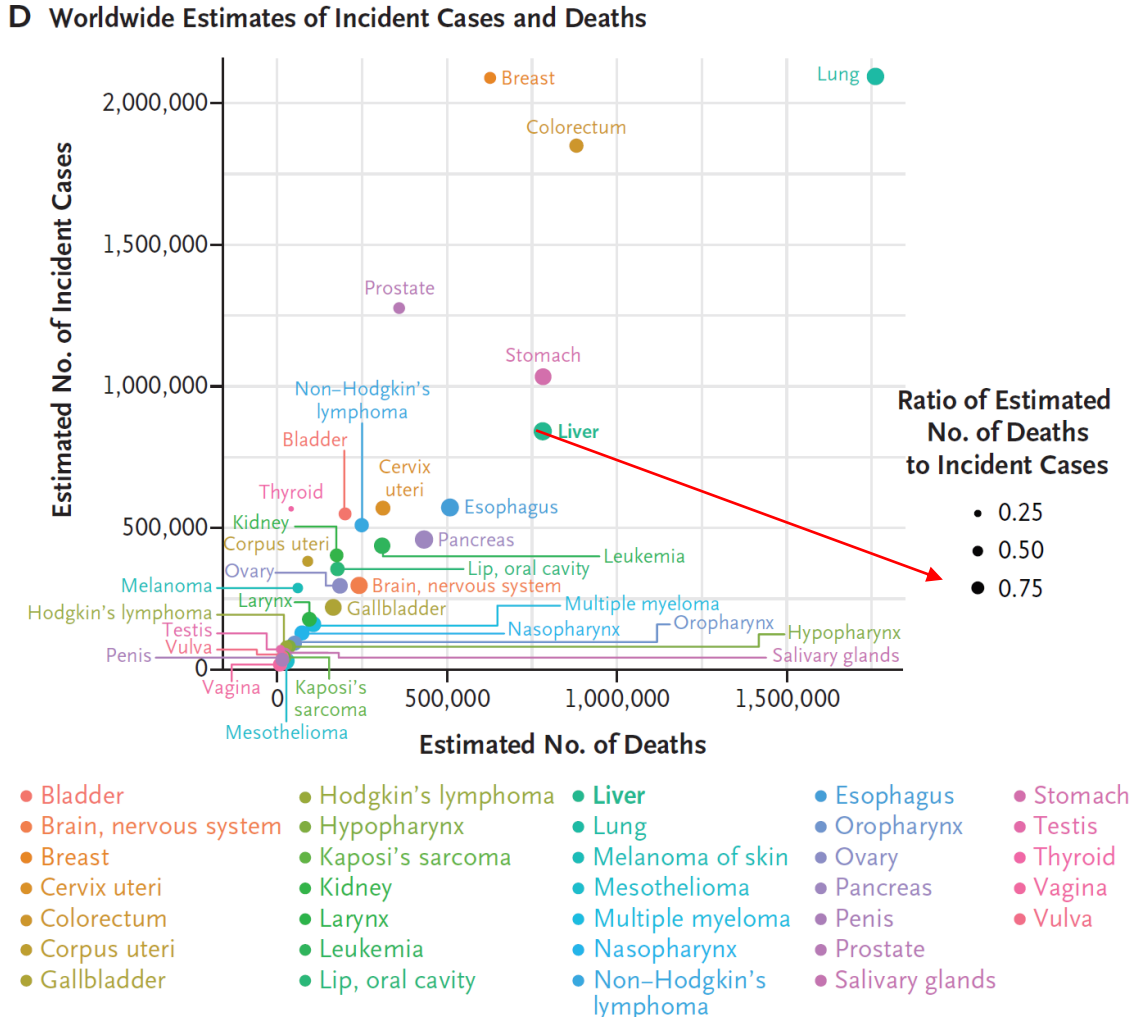


Mortalidad
ASR 8.5/100 000
N° 781 631

Globocan 2018

Epidemiología - Global

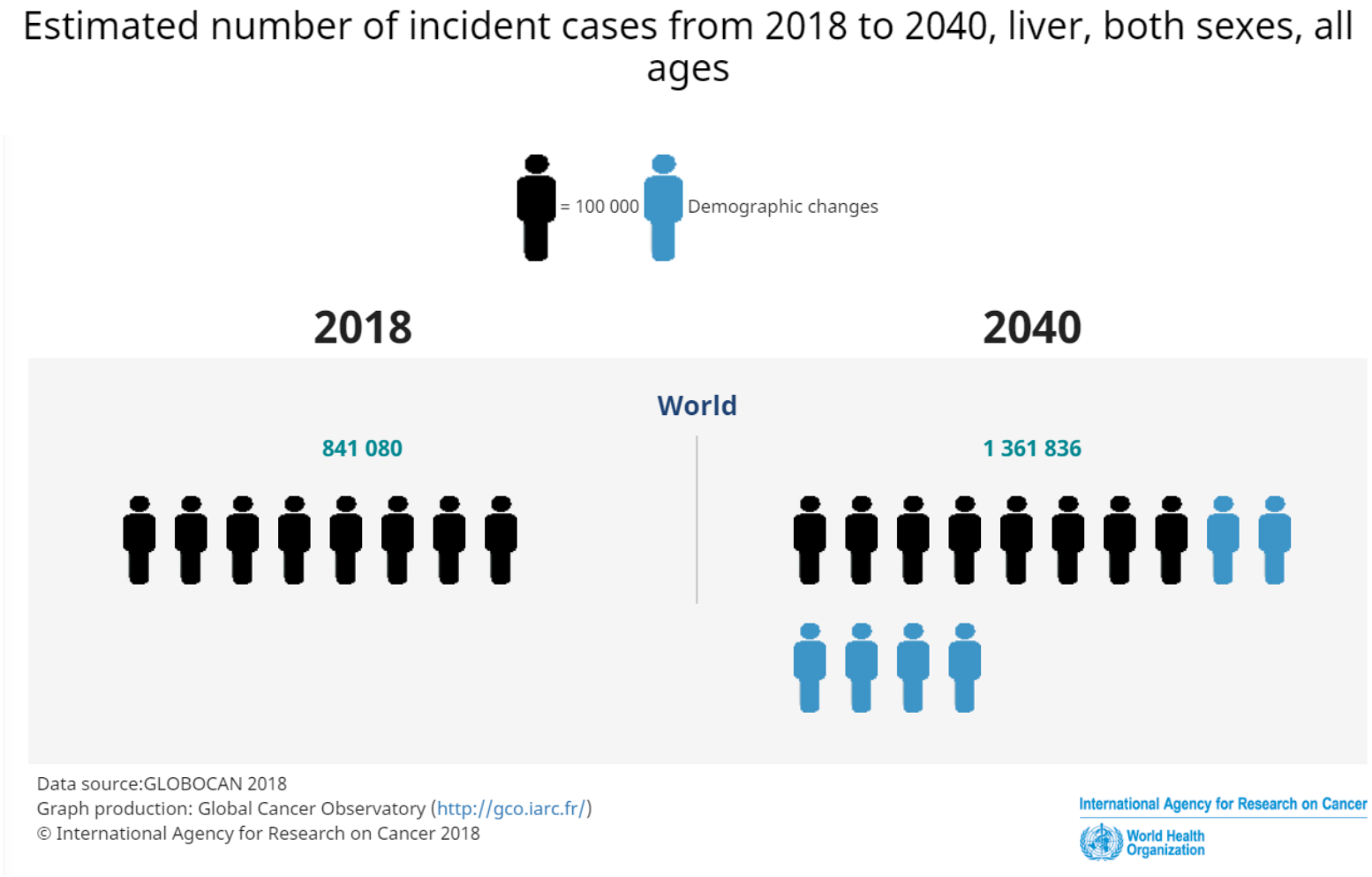




Globocan 2018

Villanueva A. N Eng J Med 2019

Epidemiología - Global



Globocan 2018

Epidemiología – Colombia

Índice de Letalidad:
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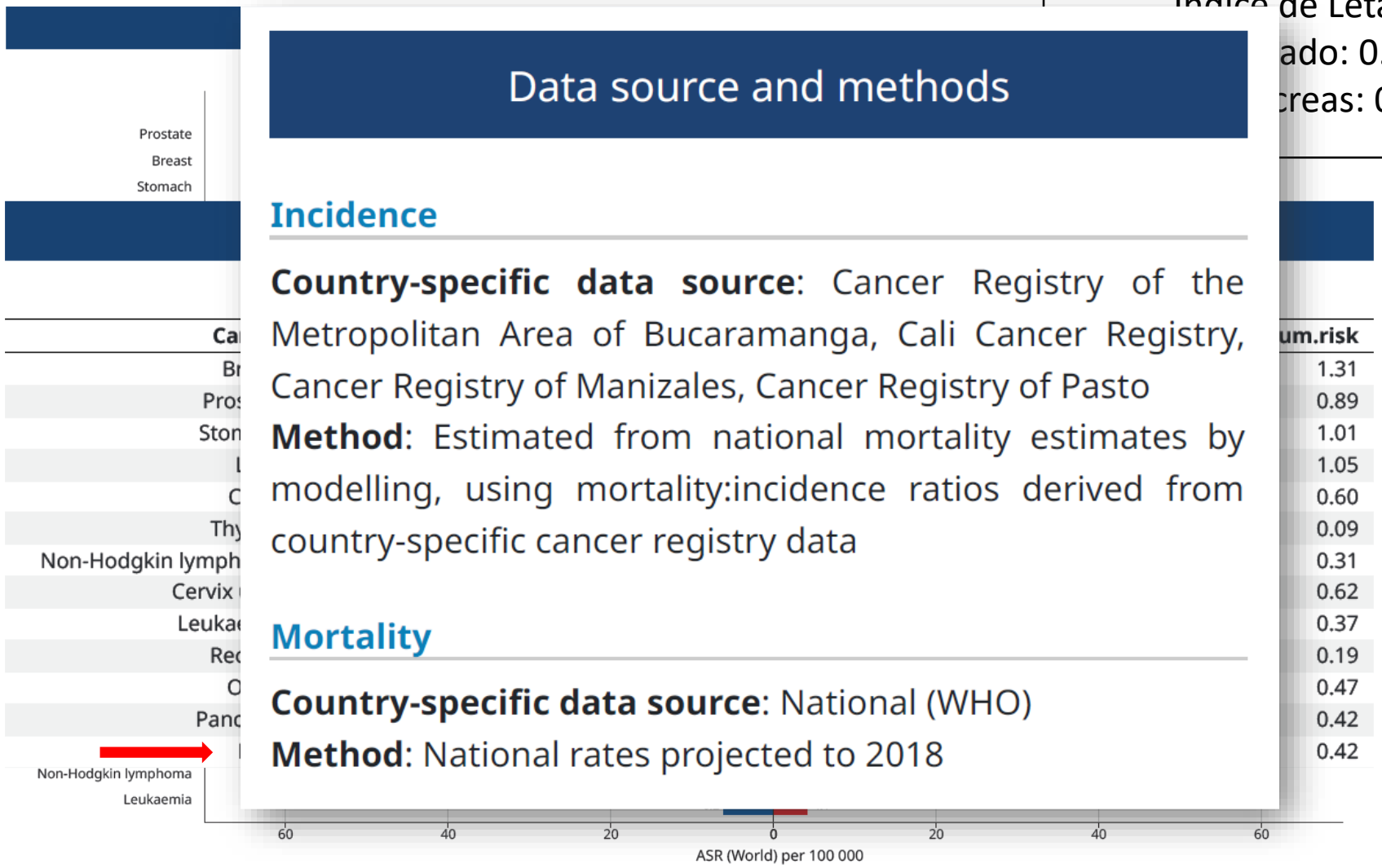
creas: 0.92



Data source and methods

Incidence

Country-specific data source: Cancer Registry of the Metropolitan Area of Bucaramanga, Cali Cancer Registry, Cancer Registry of Manizales, Cancer Registry of Pasto

Method: Estimated from national mortality estimates by modelling, using mortality:incidence ratios derived from country-specific cancer registry data

Mortality

Country-specific data source: National (WHO)

Method: National rates projected to 2018

Globocan 2018

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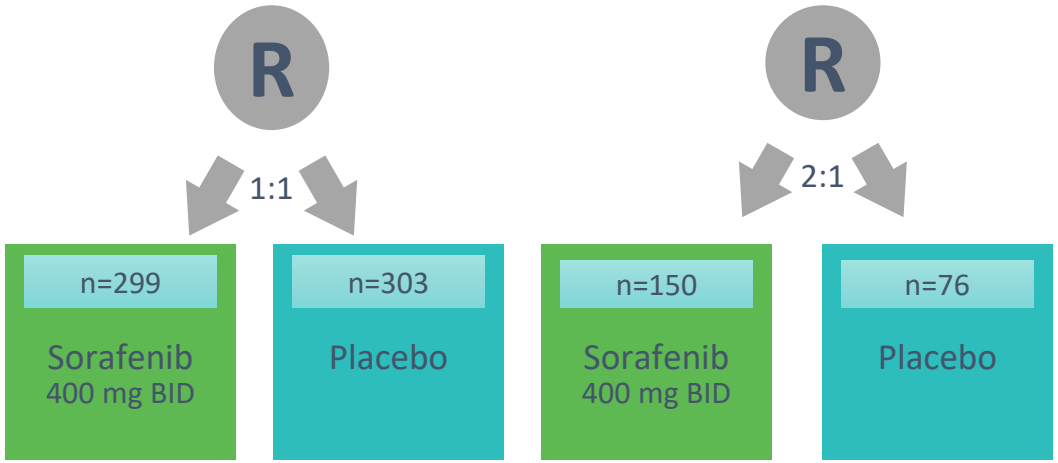
- Conclusiones

Sorafenib

SHARP/ Asia Pacific

Población: NO terapia sistémica previa, BCLC B-C Irresecable, ECOG 0-2, Child-Pugh: A



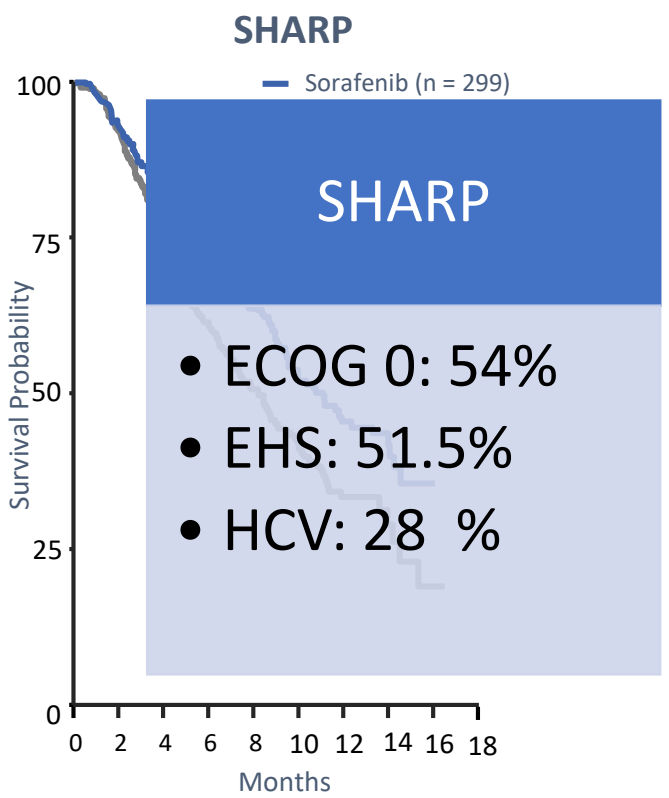
EP1: OS, TTSP

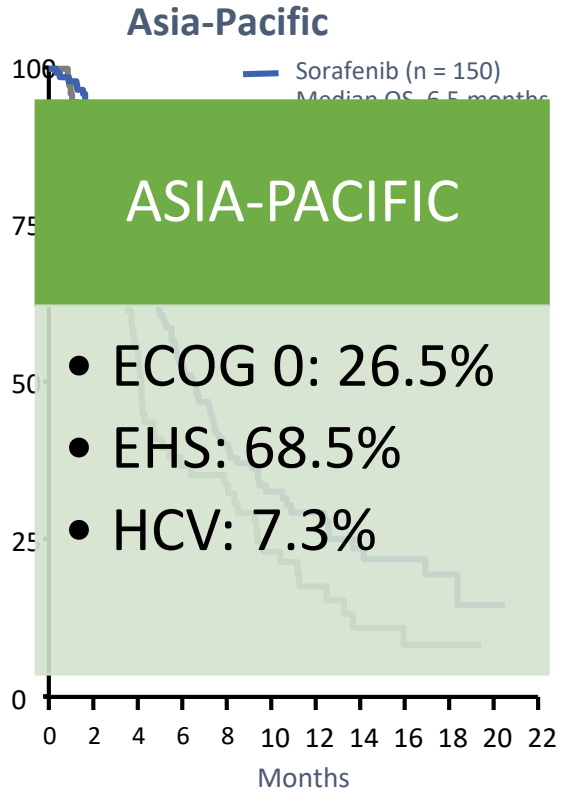
EP2: TTP, DCR, seguridad

Estratos: PS, región, MVI, EHS

EP: OS, TTSP, TTP, DCR, seguridad

Estratos: PS, región, MVI, EHS

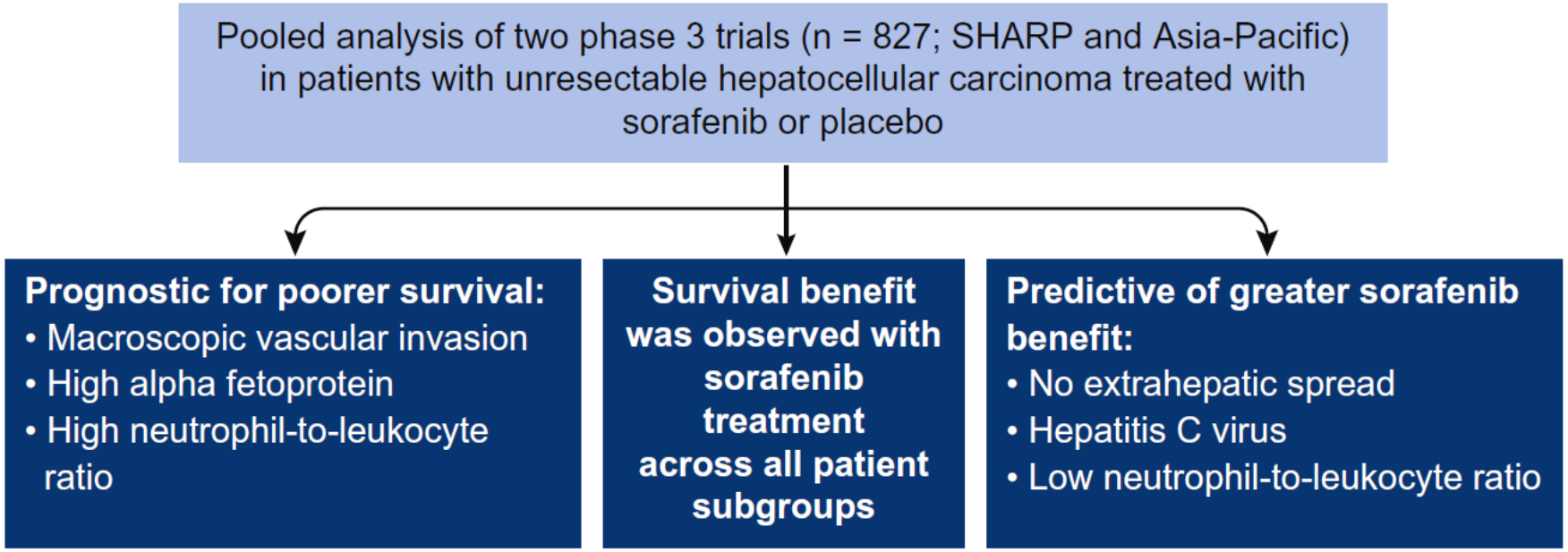




Llovet JM, et al. N Engl J Med. 2008
Cheng A-L, et al. Lancet Oncol. 2009

Sorafenib

Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies

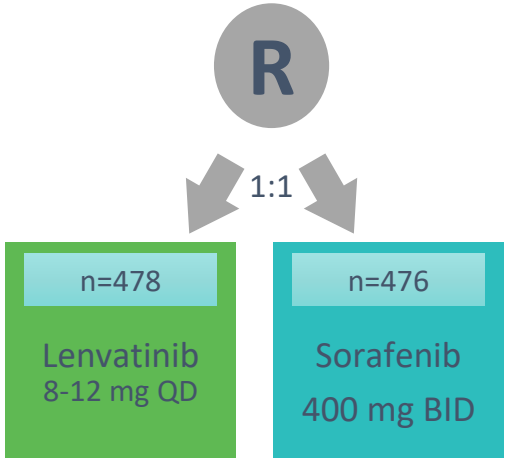


Bruix J, et al. J Hepatol 2017

Lenvatinib

REFLECT

Población: NO terapia sistémica previa, irresecable, ECOG 0-1, Child-Pugh A, BCLC B-C



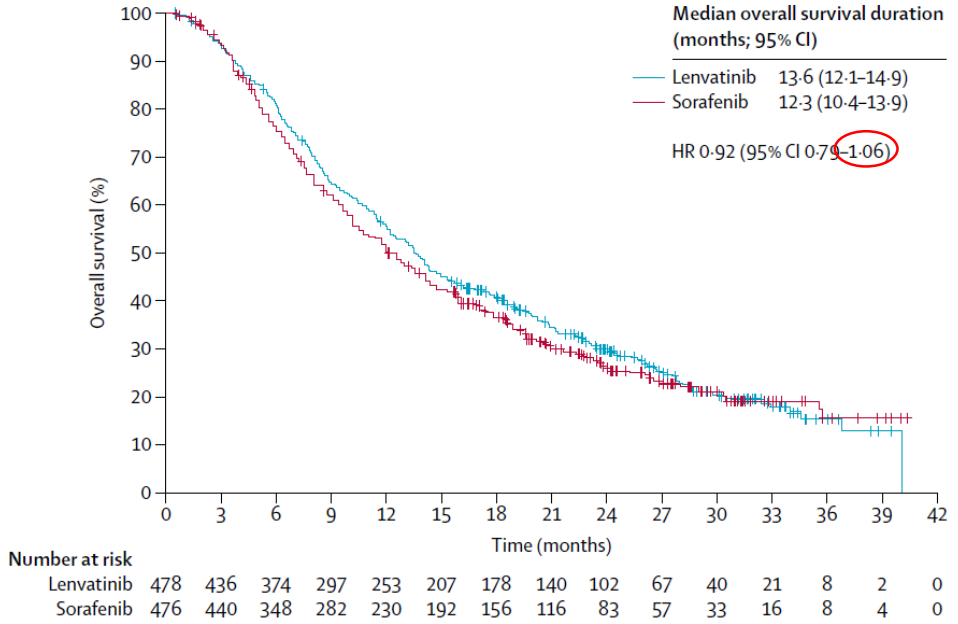
Exclusión:

- 50% ocupación hepatica
- Invasión de vía biliar
- Invasión porta (tronco)

EP1: OS – No inferioridad 1.08

EP2: PFS, TTP, ORR, QoL, Fcocinética

Estratos: PS, región, MVI, EHD, peso



Investigator review according to mRECIST			
Overall survival (months)	13·6 (12·1–14·9)	12·3 (10·4–13·9)	HR 0·92 (0·79–1·06)
Progression-free survival (months)	7·4 (6·9–8·8)	3·7 (3·6–4·6)	HR 0·66 (0·57–0·77)
Time to progression (months)	8·9 (7·4–9·2)	3·7 (3·6–5·4)	HR 0·63 (0·53–0·73)
Objective response (%, 95% CI)	115 (24·1%, 20·2–27·9)	44 (9·2%, 6·6–11·8)	OR 3·13 (2·15–4·56)

Kudo M, et al. The Lancet 2018

Estudios positivos1ª línea

SHARP

- Superic
- RCT fas
- EP1: OS
- Inclusió
- Exclusió biliar y portal.
- Otros:
  - DC

Efectos adversos Grado 3, n (%)	Lenvatinib (n=476)	Sorafenib (n=475)	SHARP (n=297)
Hipertensión	111 (23)	68 (14)	(2)
Eritrodisestesia palmo-plantar	14 (3)	54 (11)	(8)
Hipotiroidismo	78(16)	8 (2)	NR
Disfonía	1 (<1)	0	0
Diarrea	20 (4)	20 (4)	(8)
Pérdida de peso	36 (8)	14 (3)	(2)
Fatiga	18 (4)	17 (4)	(4)

Llovet JM, et al. N Engl J Med. 2008
Kudo M, et al. The Lancet 2018

Otros estudios en 1ª línea

DROGA-ESTUDIO	Población	Diseño/Intervención	Resultados
SUNITINIB (EGFR) Cheng A (Asia)	n=1074 BCLC B-C, ECOG 0-1	RCT Fase III. No inferioridad. **SUNITINIB** vs Sorafenib	IC 95% no alcanzo la meta de no inferioridad

Bristol-Myers Squibb Announces Results from CheckMate -459 Study Evaluating Opdivo (nivolumab) as a First-Line Treatment for Patients with Unresectable Hepatocellular Carcinoma

CATEGORY: R&D NEWS

MONDAY, JUNE 24, 2019 6:59 AM EDT

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced topline results from CheckMate -459, a randomized Phase 3 study evaluating *Opdivo* (nivolumab) versus sorafenib as a first-line treatment in patients with unresectable hepatocellular carcinoma (HCC). The trial did not achieve statistical significance for its primary endpoint of overall survival (OS) per the pre-specified analysis (HR=0.85 [95% CI: 0.72-1.02]; p=0.0752). No new safety signals were observed with *Opdivo*. The full study results will be presented at an upcoming medical meeting.

LENVATINIB (cMET, VEGF, FGF y PDGF) Ikeda M (Asia) J Gastroenterology 2017	n=46 BCLC B-C, Child Pugh A-B	No RCT Fase II **LENVATINIB**	Eficacia, Seguridad y Tolerancia adecuados Mejor TTP pero no OS

Agenda

- Datos puntuales en Epidemiología
  - Importancia
- Opciones de tratamiento en 1ª línea
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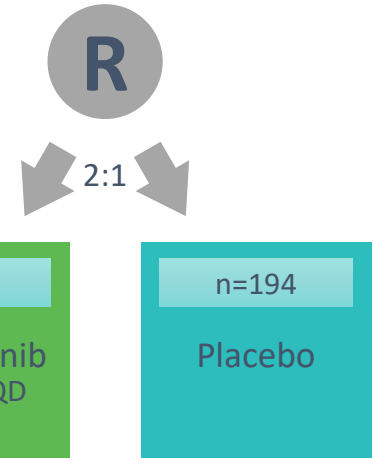
- Opciones de tratamiento en 2ª línea
  - Líneas posteriores
- Conclusiones

Regorafenib

RESORCE

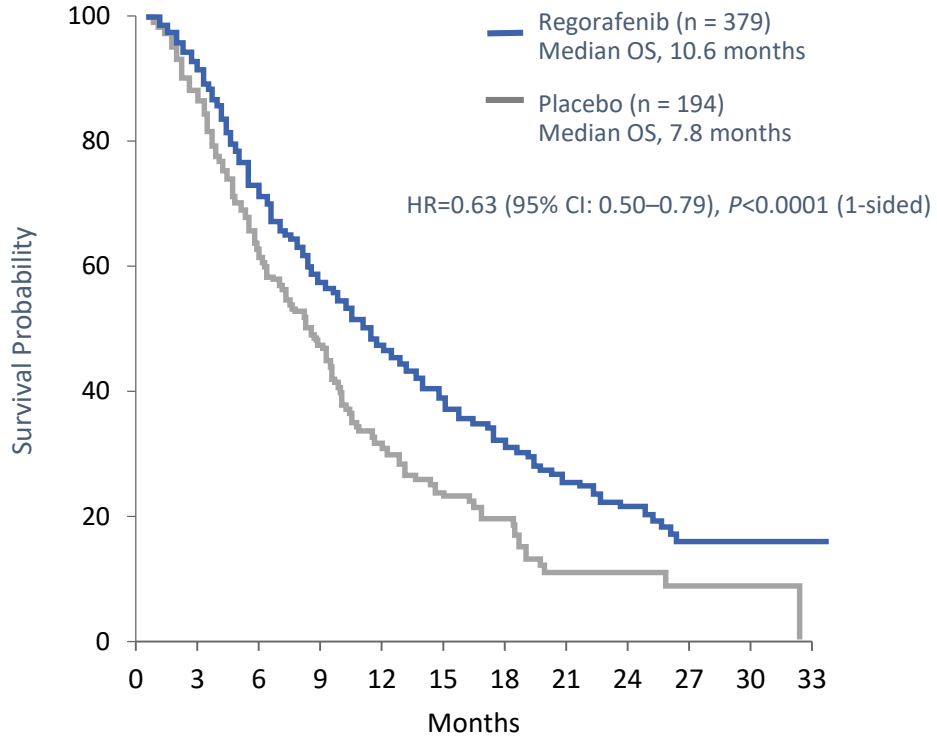
Población: progresión a sorafenib, ECOG 0-1, BCLC B-C, Child-Pugh A

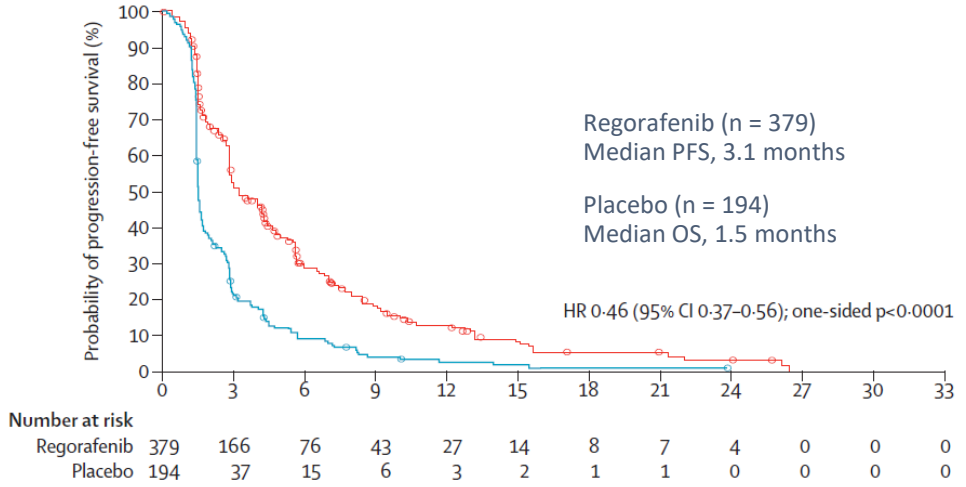


EP1: OS

EP2: TTP, PFS, DCR, seguridad

Estratos: región, MVI, EHS, AFP, ECOG



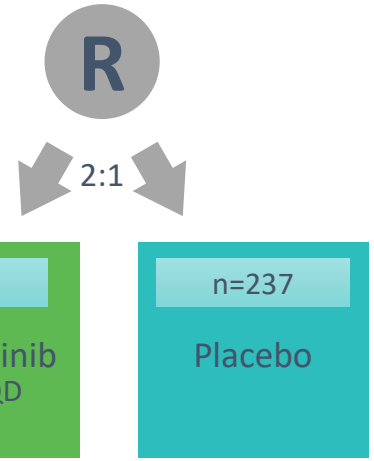


Bruix J, et al. Lancet 2017

Cabozantinib

CELESTIAL

Población: progresión a sorafenib y hasta 2 terapias, ECOG 0-1, BCLC B-C, Child-Pugh A

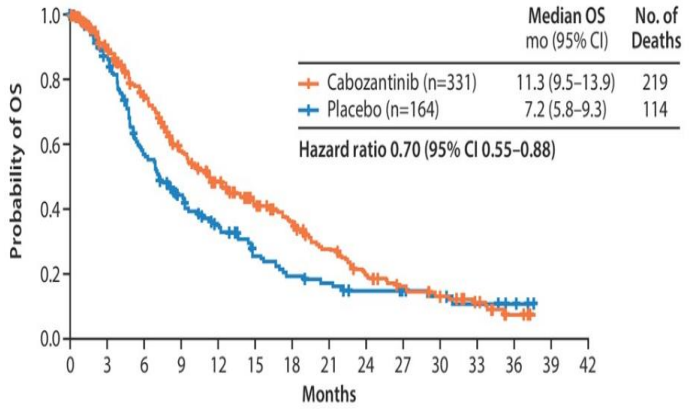


EP1: OS

EP2: PFS, ORR

Estratos: etiología, región, MVI, EHS

Number of prior systemic anticancer regimens for advanced HCC, n (%)		
0¶	3 (1)	0
1	335 (71)	174 (73)
2	130 (28)	62 (26)
≥3	2 (<1)	1 (<1)
Prior systemic anticancer therapy, n (%)		
Sorafenib	470 (100)	237 (100)
Regorafenib	6 (1)	2 (1)
Lenvatinib	0	1 (<1)
Tivantinib	1 (<1)	2 (1)
Ramucirumab	8 (2)	1 (<1)
Anti-PD-1/PD-L1	14 (3)	3 (1)
Cytotoxic chemotherapy	41 (9)	30 (13)
Doxorubicin	22 (5)	10(4)
Investigational agent	60 (13)	20 (8)

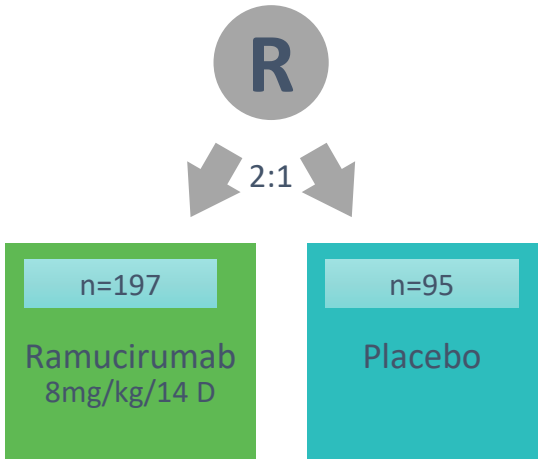


Abou-Alfa G. K, et al. N Eng J Med 2018

Ramucirumab

REACH-2

Población: progresión a sorafenib, AFP ≥400ng/mL, ECOG 0-1, BCLC B-C, Child-Pugh A



EP1: OS

EP2: PFS, ORR, TTSP (ECOG), seguridad

Estratos: región, MVI, ECOG

Efficacy	Ramucirumab (n=197)	Placebo (n=95)	HR (95% CI)
Median OS, months	8.5	7.3	0.710 (0.531–0.949) P=0.0199
Survival rate, %			
12 months	37	30	P=0.2930
18 months	25	11	P=0.0187
Median PFS, months	2.8	1.6	0.452 (0.339–0.603) P<0.0001
ORR, %	4.6	1.1	P=0.1697
DCR, %	59.9	38.9	P=0.0006

Zhu AX, et al. Lancet Oncol 2019

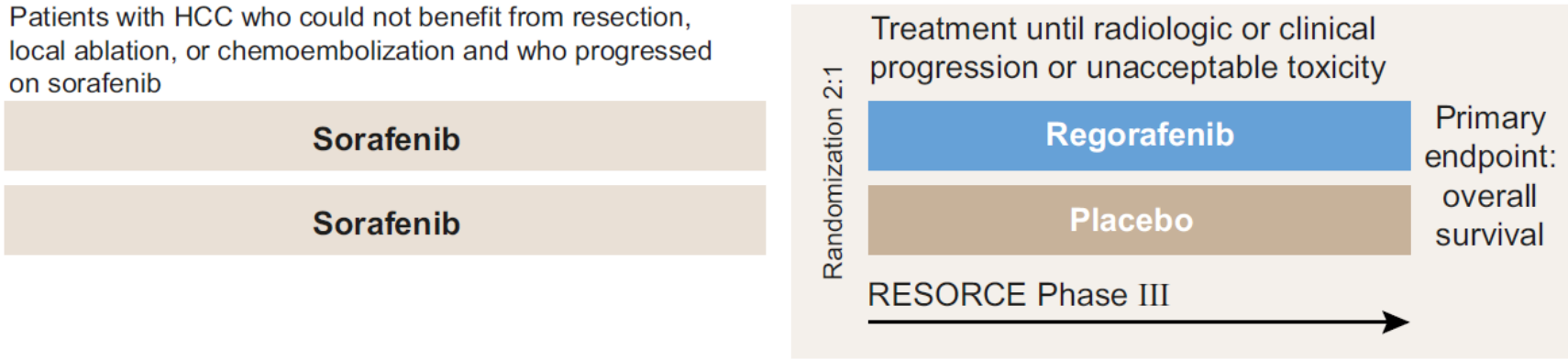
Estudios positivos en 2ª línea

ESTUDIO	RESORCE	CELESTIAL	REACH-2
Diseño	RCT, fase III, doble ciego	RCT, fase III, doble ciego	RCT, fase III, doble ciego
Población	Índice	Hasta 2 terapias	AFP>400
EP1	HR 0.63	HR 0.76	HR 0.71
mOS	10.6 meses	10.2 meses	8.5 meses
Otros EP	AFP <400 HR 0.43 AFP ≥400 HR 0.53 Secuencia sora-rego*	Solo sorafenib mOS 11.3m, HR 0.70	PFS mPFS 2.8 vs.1.6m, HR 0.45

Bruix J, et al. Lancet 2017
Abou-Alfa G. K, et al. N Eng J Med 2018
Zhu AX, et al. Lancet Oncol 2019

Secuencia sora- rego*

Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial



- Median survival from start of sorafenib: 26.0 months (sorafenib–regorafenib) *vs* 19.2 months (sorafenib–placebo)
- Estimated survival rates from start of sorafenib (sorafenib–regorafenib *vs* sorafenib–placebo): 31% *vs* 20% at 3 years; 16% *vs* 3% at 5 years
- Time to progression on regorafenib by quartile of time to progression on sorafenib showed benefit for regorafenib across all quartiles; hazard ratios ranged from 0.26 to 0.66
- Rates of adverse events on regorafenib by last sorafenib dose (800 mg/day *vs* <800 mg/day) were generally similar

Finn RS, et al. J Hepatol 2018

Otros estudios en 2ª línea

Second line						
Regorafenib*	Bruix et al (2016)[76]	Regorafenib (n=379) *vs* placebo (n=194)	3·9 *vs* 1·5	<0·0001	10·6 *vs* 7·8	<0·0001
Brivanib	Llovet et al (2013)[136]	Brivanib (n=263) *vs* placebo (n=132)	4·2 *vs* 2·7	0·001	9·4 *vs* 8·2	NS
Everolimus	Zhu et al (2014)[137]	Everolimus (n=362) *vs* placebo (n=184)	2·9 *vs* 2·6	NS	7·6 *vs* 7·3	NS
Ramucirumab	Zhu et al (2015)[138]	Ramucirumab (n=283) *vs* placebo (n=282)	3·5 *vs* 2·6	<0·0001	9·2 *vs* 7·6	NS
Tivantinib	Rimassa et al (2017)[139]	Tivantinib (n=226) *vs* placebo (n=114)	NA	NA	8·4 *vs* 9·1	0·81

NS=non-significant. NA=not available. *Agents with survival benefit. †Open-label trial. ‡Non-inferiority design.

Table 2: **Targeted therapies evaluated in phase 3 trials in hepatocellular carcinoma**

Forner A, et al. Lancet 2018

Pembrolizumab

Results of KEYNOTE-240: Phase 3 Study of Pembrolizumab vs Best Supportive Care for Second-Line Therapy in Advanced Hepatocellular Carcinoma

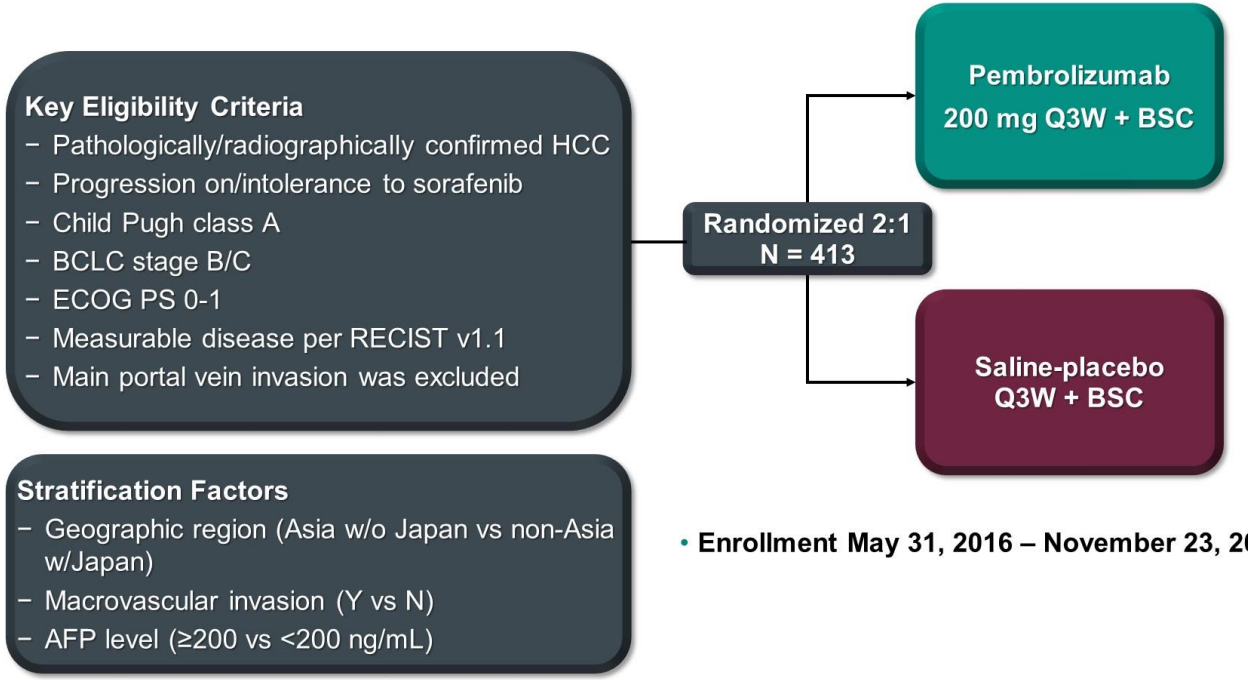
Richard S. Finn,[1] Baek-Yeol Ryoo,[2] Philippe Merle,[3] Masatoshi Kudo,[4] Mohamed Bouattour,[5] Ho-Yeong Lim,[6] Valeriy Breder,[7] Julien Edeline,[8] Yee Chao,[9] Sadahisa Ogasawara,[10] Thomas Yau,[11] Marcelo Garrido,[12] Stephen L. Chan,[13] Jennifer Knox,[14] Bruno Daniele,[15] Scot W. Ebbinghaus,[16] Erluo Chen,[16] Abby B. Siegel,[16] Andrew X. Zhu,[17] Ann-Lii Cheng,[18] for the KEYNOTE-240 Investigators

[1]University of California, Los Angeles, Los Angeles, CA, USA; [2]Asan Medical Center University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Lyon North Hospital, Hepatology Unit, Lyon, France; [4]Kindai University Faculty of Medicine, Osaka, Japan; [5]Beaujon University Hospital, APHP, Clichy, France; [6]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [7]NN Blokhin National Medical Research Center of Oncology *of MoH*, Moscow, Russian Federation; [8]Centre Eugène Marquis, Rennes, France; [9]Taipei Veterans General Hospital, Taipai, Taiwan; [10]Chiba University Graduate School of Medicine, Chiba, Japan; [11]The University at Hong Kong, Hong Kong, China; [12]Pontificia Universidad Catolica de Chile, Santiago, Chile; [13]State Key Laboratory of Translation Oncology, Sir YK Pao Centre for Cancer, The Chinese University of Hong Kong, Shatin, Hong Kong, China; [14]Princess Margaret Cancer Centre and University of Toronto, Toronto, Canada; [15]Ospedale del Mare, Napoli, Italy; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [18]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan

Presented By Richard Finn at 2019 ASCO Annual Meeting

Pembrolizumab

KEYNOTE-240 Study Design



- **Enrollment May 31, 2016 – November 23, 2017**

Study Endpoints

- **Primary**
  - OS
  - PFS (RECIST v1.1, central review)
- **Secondary**
  - ORR, DOR, DCR and TTP (all RECIST v1.1, central review)
  - Safety and tolerability
- **Response was assessed Q6W**

Presented By Richard Finn at 2019 ASCO Annual Meeting

Pembrolizumab

Baseline Demographics

Characteristic n (%)	Pembrolizumab (N=278)	Placebo (N=135)
Age, yr median (range)	67 (18-91)	65 (23-89)
Male Sex	226 (81.3)	112 (83)
Region of enrollment		
Asia (excluding Japan)	67 (24.1)	31 (23.0)
EU	96 (34.5)	43 (31.9)
Japan	40 (14.4)	19 (14.1)
US	21 (7.6)	16 (11.9)
Others[a]	54 (19.4)	26 (19.3)

[a]Includes Argentina, Australia, Canada, Chile, Colombia, Israel, Mexico, Norway, Russian Federation, and Turkey.
Data cut-off: Jan 2, 2019.

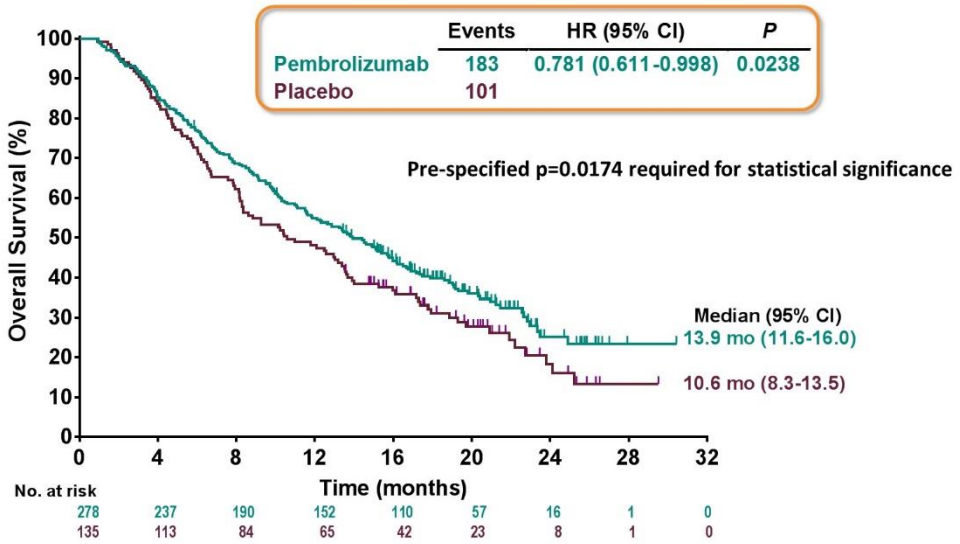
Baseline Characteristics

Characteristic n (%)	Pembrolizumab (N=278)	Placebo (N=135)
ECOG PS 1	116 (41.7)	64 (47.4)
Child Pugh Score		
A	277 (99.6)	133 (98.5)
B	1 (0.4)	2 (1.5)
Overall BCLC stage		
B	56 (20.1)	29 (21.5)
C	222 (79.9)	106 (78.5)
HBV-positive[a]	72 (25.9)	29 (21.5)
HCV-positive[a]	43 (15.5)	21 (15.6)
Discontinuation of prior sorafenib		
Intolerance	36 (12.9)	18 (13.3)
PD	242 (87.1)	117 (86.7)
Extrahepatic disease	195 (70.1)	93 (68.9)
Macrovascular invasion	36 (12.9)	16 (11.9)
Baseline AFP ≥200 ng/mL	129 (46.4)	58 (43.0)

[a]163 (58.6%) and 85 (63.0%) uninfected patients in pembrolizumab and placebo groups respectively.
Data cut-off: Jan 2, 2019.

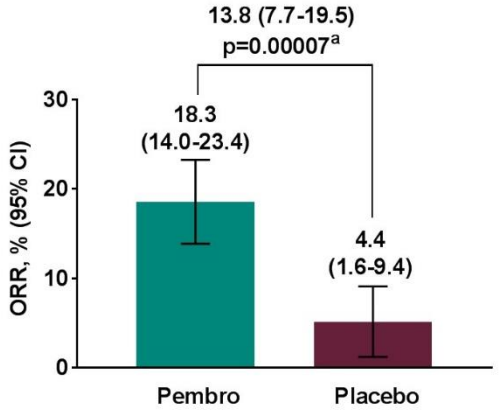
Pembrolizumab

Overall Survival



Data Cutoff: Jan 2, 2019.

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



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)

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)

[a]Nominal one-sided P-value based on the Miettinen and Nurminen method stratified by randomization factors. [b]From product-limit (Kaplan-Meier) method for censored data. [c]"+" indicates no PD by the time of last disease assessment. Data cutoff: Jan 2, 2019.

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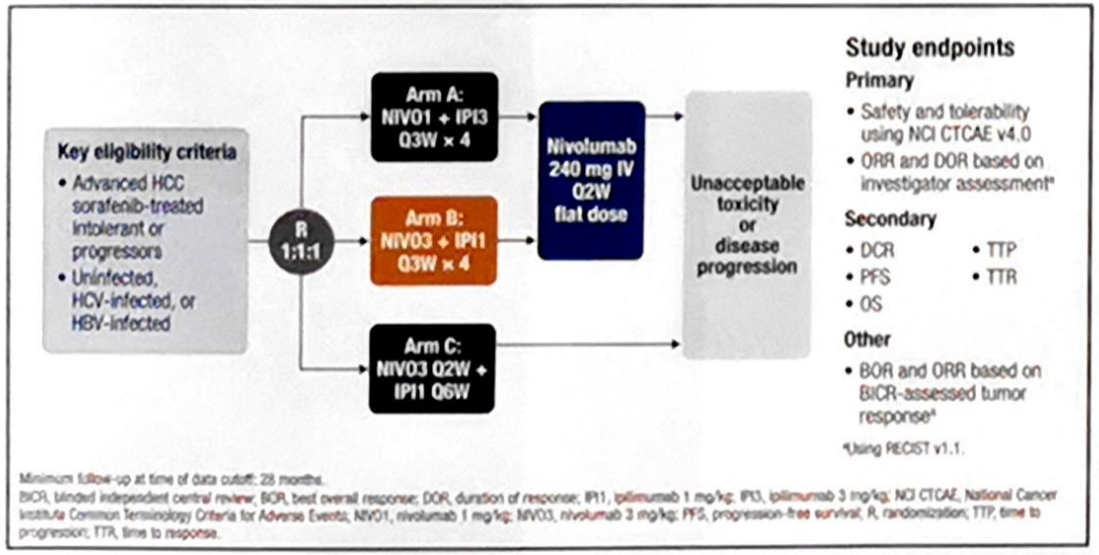
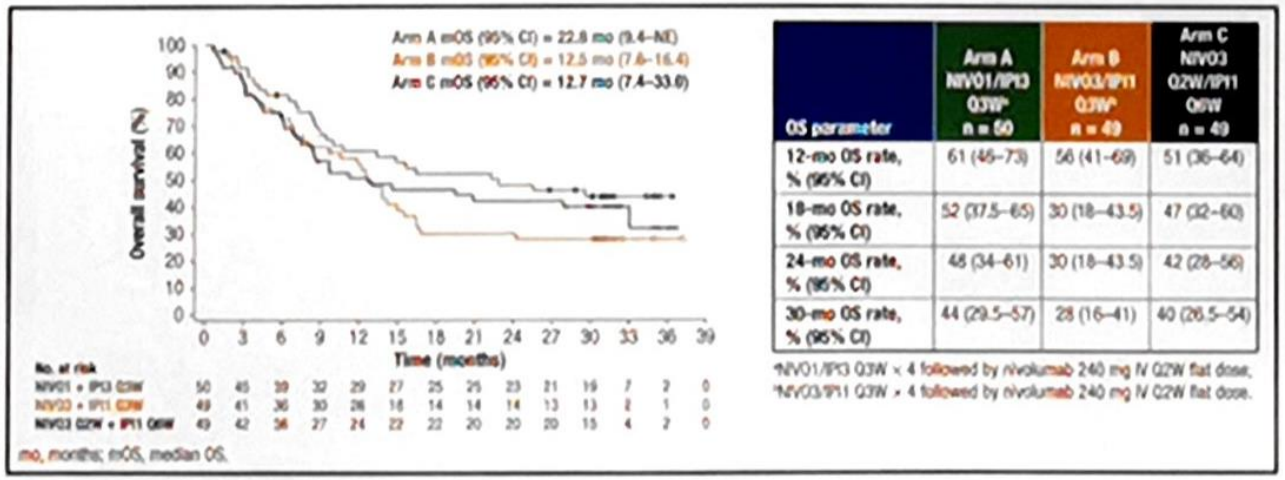
Nivolumab

Figure 1. CheckMate 040 nivolumab plus ipilimumab combination cohort study design



Minimum follow-up at time of data cutoff: 28 months.
BICR, blinded independent central review; BOR, best overall response; DOR, duration of response; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PFS, progression-free survival; R, randomization; TTP, time to progression; TTR, time to response.

Figure 3. Overall survival



mo, months; mOS, median OS.

OS parameter	Arm A NIVO1/IPI3 Q3W¶ n = 50	Arm B NIVO3/IPI1 Q3W¶ n = 49	Arm C NIVO3 Q2W/IPI1 Q6W n = 49
12-mo OS rate, % (95% CI)	61 (46–73)	56 (41–69)	51 (36–64)
18-mo OS rate, % (95% CI)	52 (37.5–65)	30 (18–43.5)	47 (32–60)
24-mo OS rate, % (95% CI)	48 (34–61)	30 (18–43.5)	42 (28–56)
30-mo OS rate, % (95% CI)	44 (29.5–57)	28 (16–41)	40 (26.5–54)

¶NIVO1/IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; ¶NIVO3/IPI1 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose.

Kudo M, et al. Presentado como Poster ASCO 2019

Agenda

- Datos puntuales en Epidemiología
  - Importancia
- Opciones de tratamiento en 1ª línea
  - Migración de la terapia
- Opciones de tratamiento en 2ª línea
  - Líneas posteriores
- Conclusiones

Opciones de tratamiento sistémico en uHCC: 2019

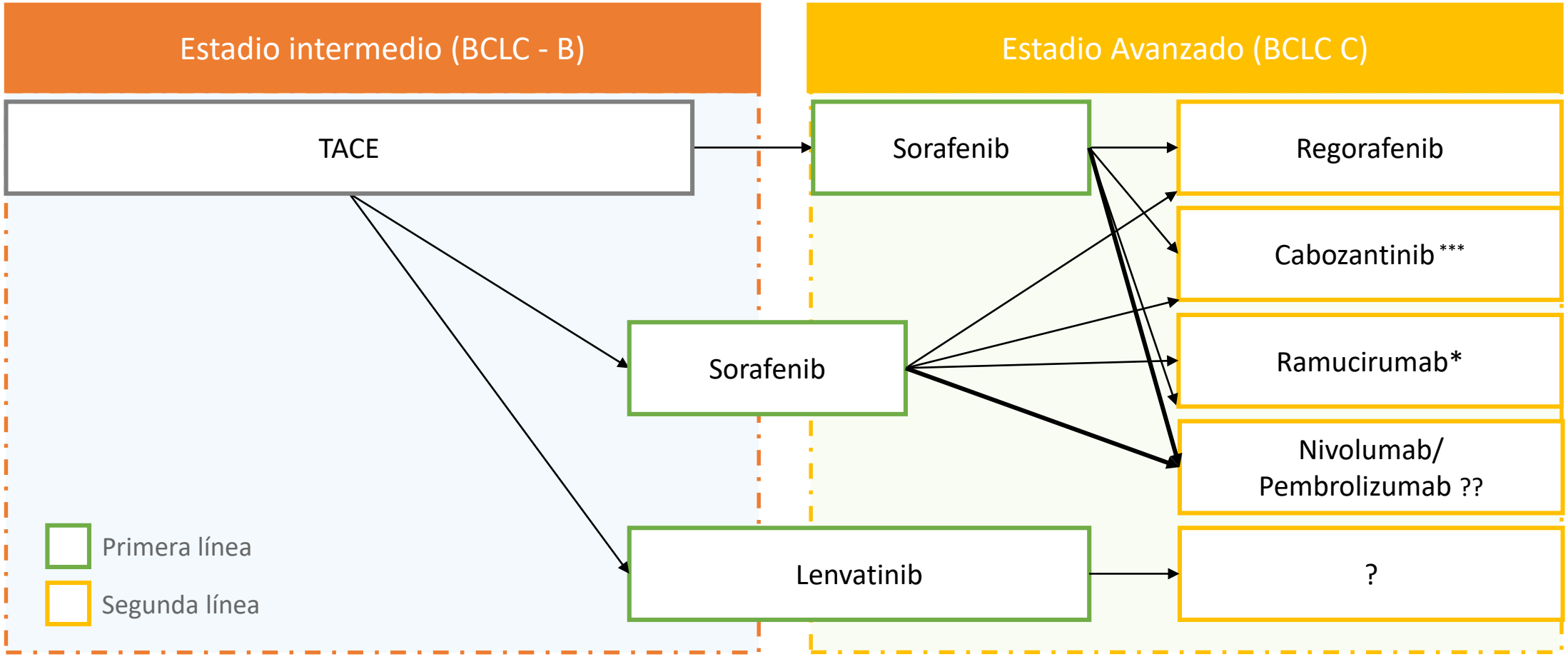


Figure adapted from latest EASL guidelines.[1]

Conclusiones

- Enfermedad heterogénea
- Alta mortalidad
- Opciones de tratamiento emergentes
  - Selección del paciente
  - Inmunoterapia ?

Atezolizumab in Combination with Bevacizumab Provides Superior Outcome Compared with Sorafenib in Unresectable HCC

IMbrave150 results may be practice changing in the first-line setting for unresectable hepatocelluar carcinoma

The study primary endpoints were met

With median follow-up of 8.6 months, median OS with the atezolizumab combination was not estimable (NE) compared to 13.2 months (95% confidence interval [CI], 10.4, NE) with sorafenib (hazard ratio [HR] 0.58; 95% CI, 0.42-0.79;p = 0.0006). Median PFS with the combination was 6.8 months (95% CI, 5.7-8.3) versus 4.5 (95% CI, 4.0-5.6) with sorafenib (HR 0.59 (95% CI, 0.47-0.76; p < 0.0001).

The response was doubled with atezolizumab plus bevacizumab over sorafenib

The ORR with the respective treatments was 27% versus 12% (p < 0.0001) per IRF RECIST v1.1. According to IRF HCC mRECIST criteria, the response was nearly 3-fold higher with atezolizumab plus bevacizumab compared to sorafenib; the ORR was 33% versus 13% (p < 0.0001), respectively.

According to the investigators, the results were generally consistent across the clinical subgroups evaluated. They also reported that atezolizumab/bevacizumab delayed deterioration of quality of life compared to sorafenib.

Gracias por su atención