MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

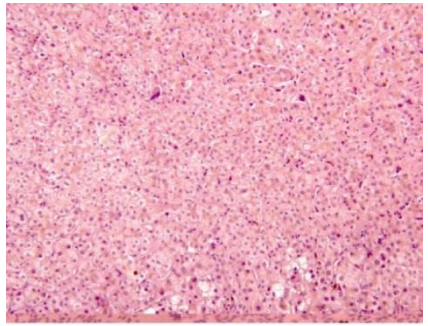
Asignatura: Hepatocarcinoma

"Tratamiento médico del CHC. Evolución de las alternativas de tratamiento y perspectivas de futuro".

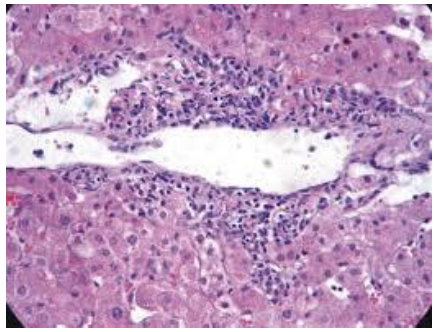
Ana María Matilla Peña

Hospital G.U. Gregorio Marañón. CIBERehd, Madrid

Carcinoma hepatocelular: Un tumor diferente

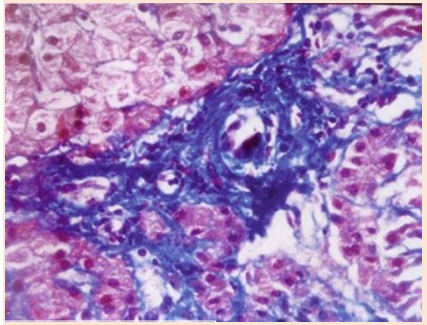


Hígado sano

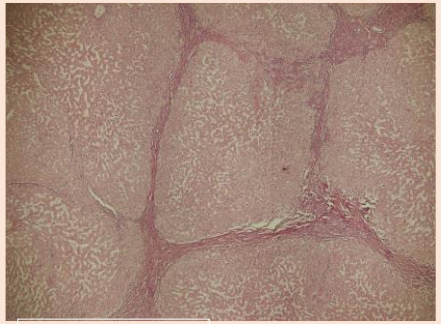


Cambios mínimos

Hepatitis crónica



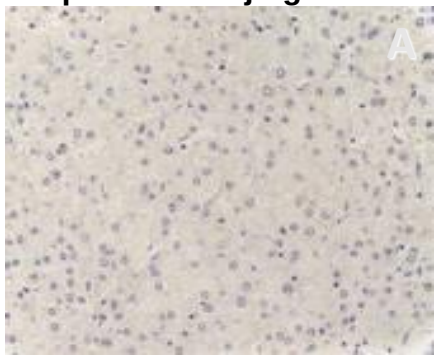
Cirrosis incompleta



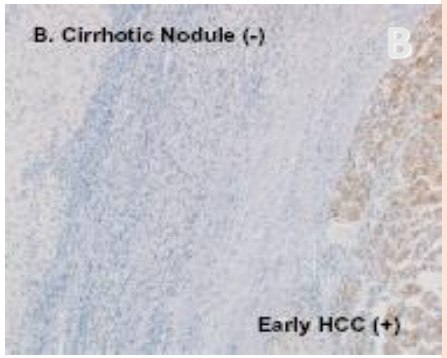
Cirrosis completa

1% FIBROSIS 3-7%

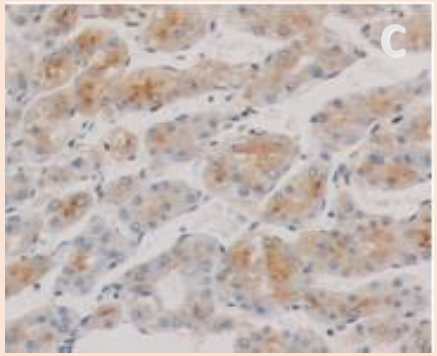
Displasia de bajo grado



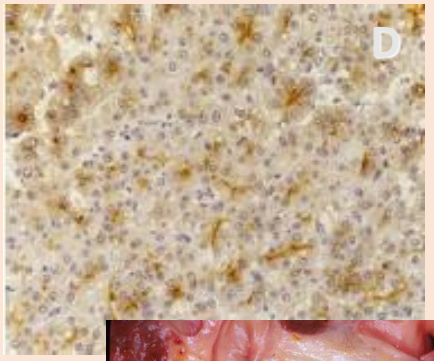
Nódulo cirrótico/ CHC

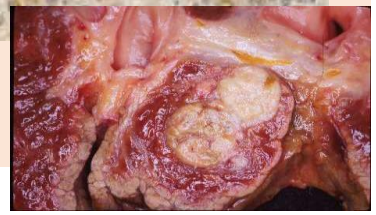


CHC Precoz

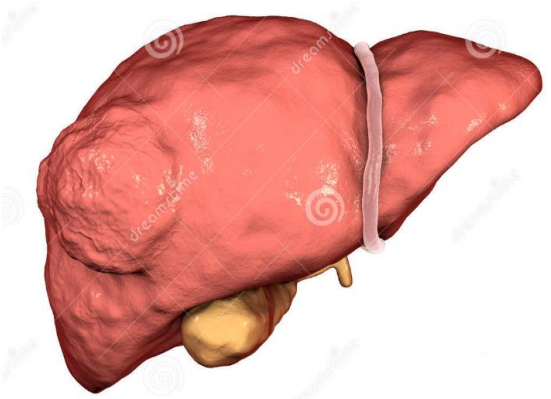


CHC avanzado





CIRROSIS



CÁNCER

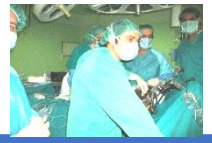
Cirrhosis and underlying liver function must be considered when making HCC treatment decisions

DESTRUCTIVE
to the tumor

CAREFULLY
with liver disease

HEPATOCELLULAR CARCINOMA

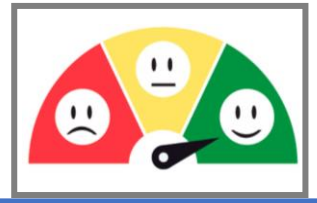
CIRRHOSIS



Limit surgical and interventional approaches to cancer treatment

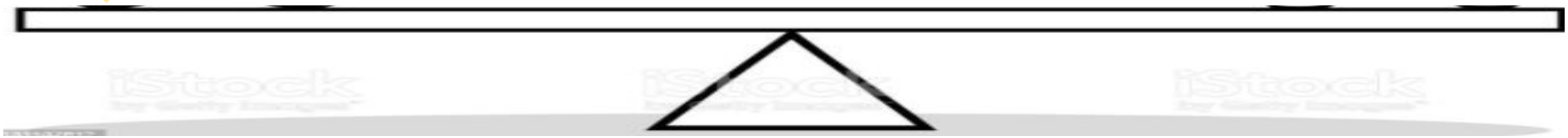
Render patients susceptible to hepatotoxicity

Influence the pharmacokinetics of anti-cancer drugs



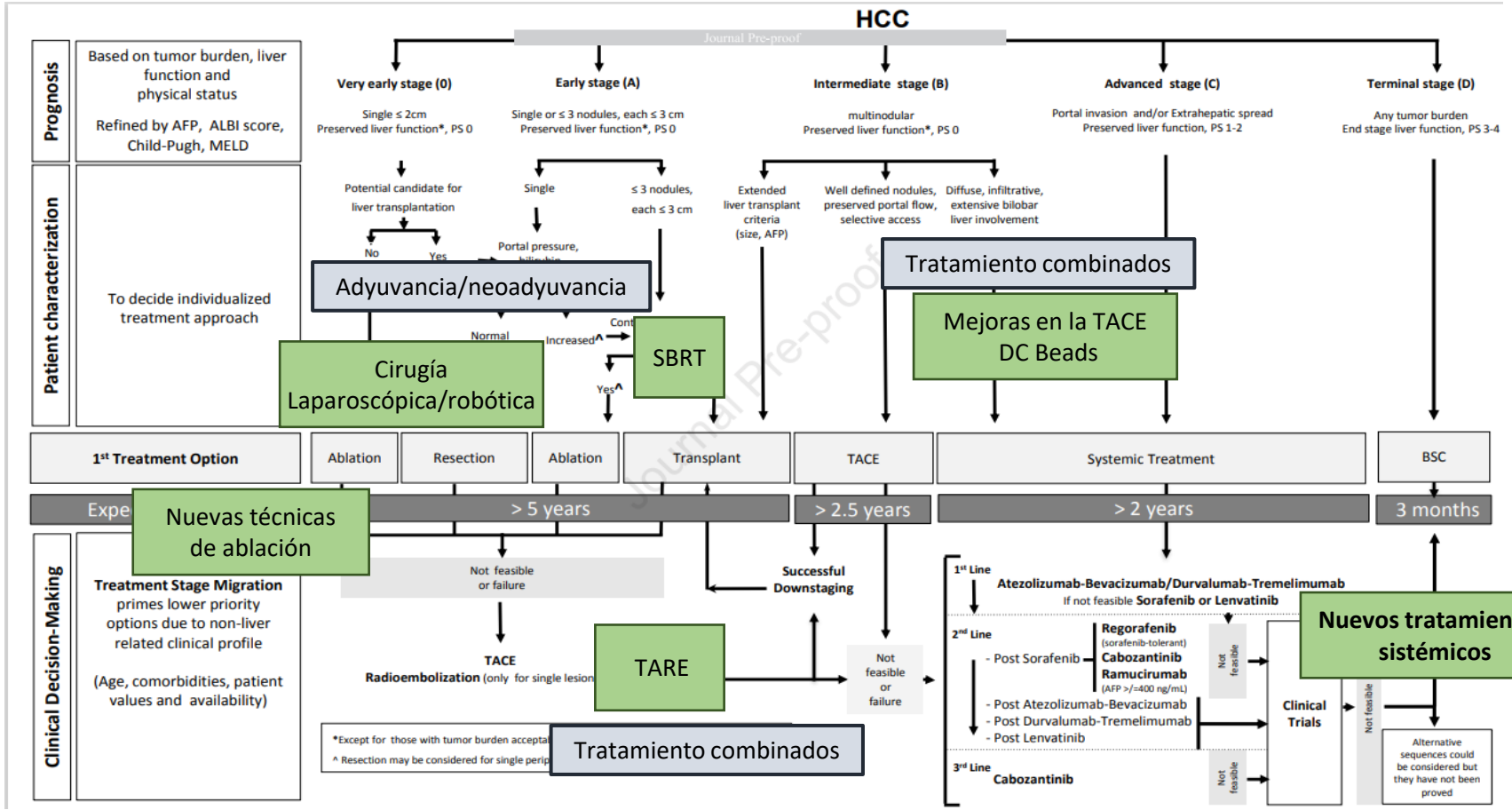
Impacts patient QoL

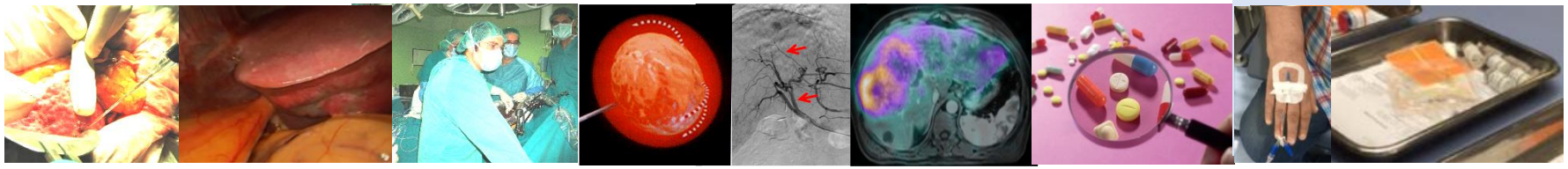
Conditions patient´s evolution



1. Pinter et al. ESMO Open 2016

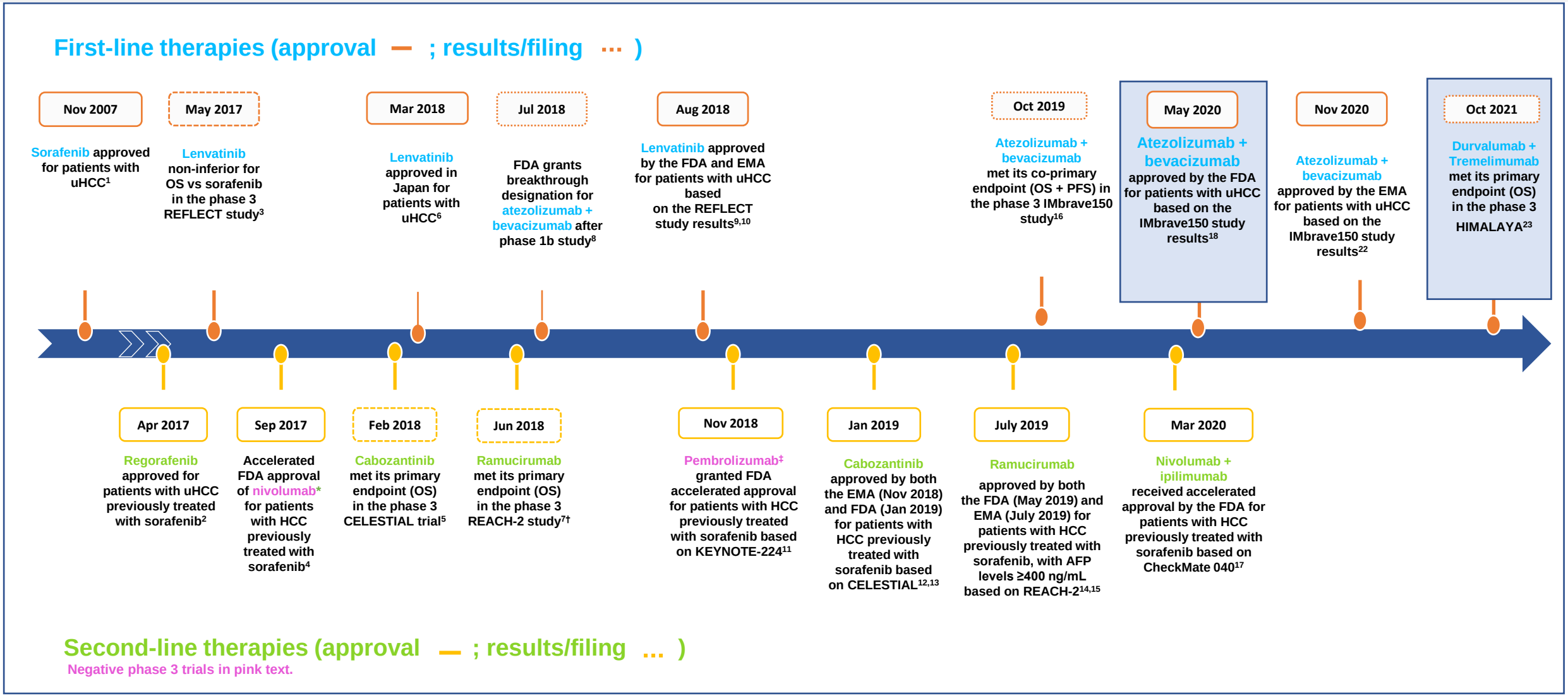
BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update.





Reig M, et al. J Hepatol 2021 Nov 18;S0168-8278(21)02223-6.

The HCC systemic treatment landscape has rapidly evolved since 2017



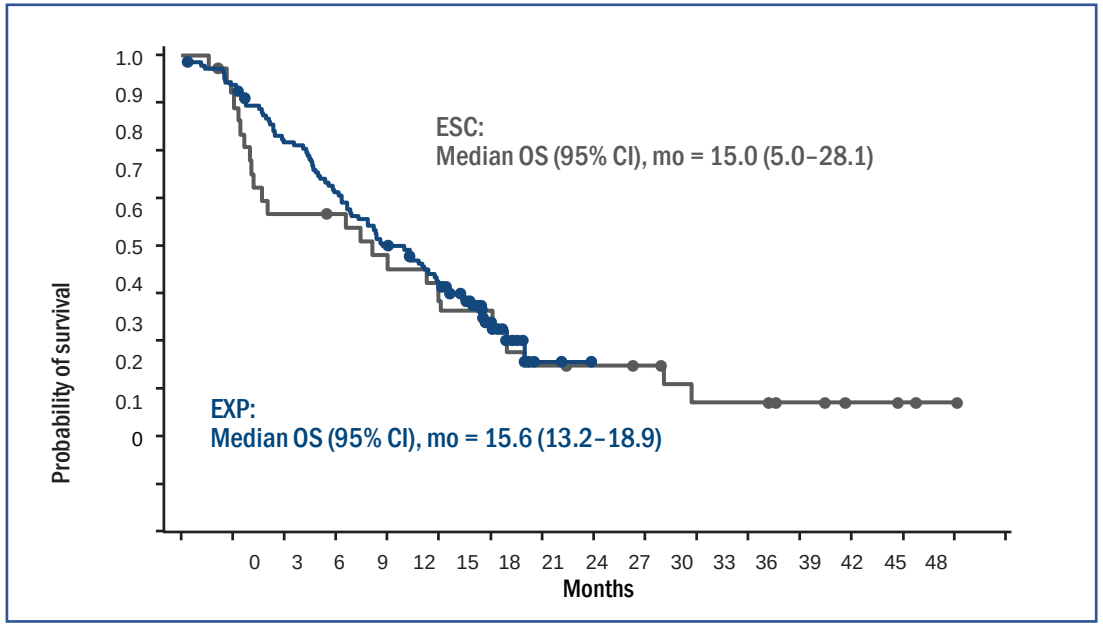
*CheckMate 459: Nivolumab did not achieve statistical significance for the primary endpoint of OS vs sorafenib[19]; †Patients with AFP ≥400 ng/mL; ‡Pembrolizumab failed to significantly improve OS and PFS (co-primary endpoints) vs placebo in the phase 3 KEYNOTE-240 trial[20,21].

References are listed in the notes section.

2ª L: Overall Survival With antiPD-1

CheckMate 040 F I/II — Nivolumab

Sorafenib Experienced



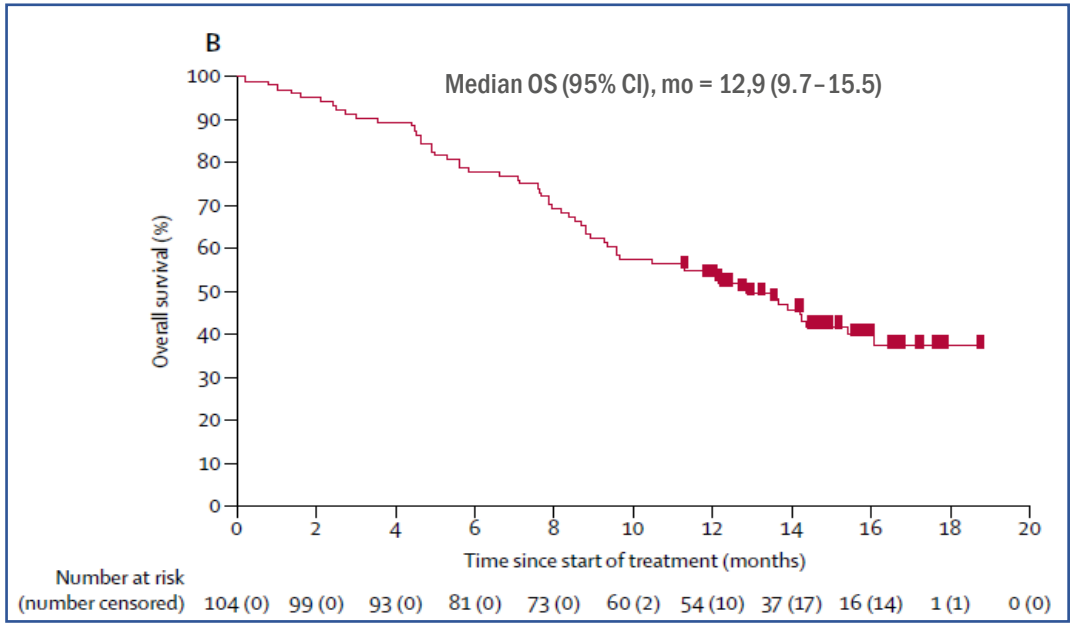
OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2–72.2)	60 (51.4–67.5)
18 months	46 (29.5–61.7)	44 (35.3–51.9)

The objective response rate was 20% (95% CI 15–26)

Crocenzi T, et al. Oral presentations. 4013. ASCO 2017.

KEYNOTE-224 F II — Pembrolizumab

Sorafenib Experienced



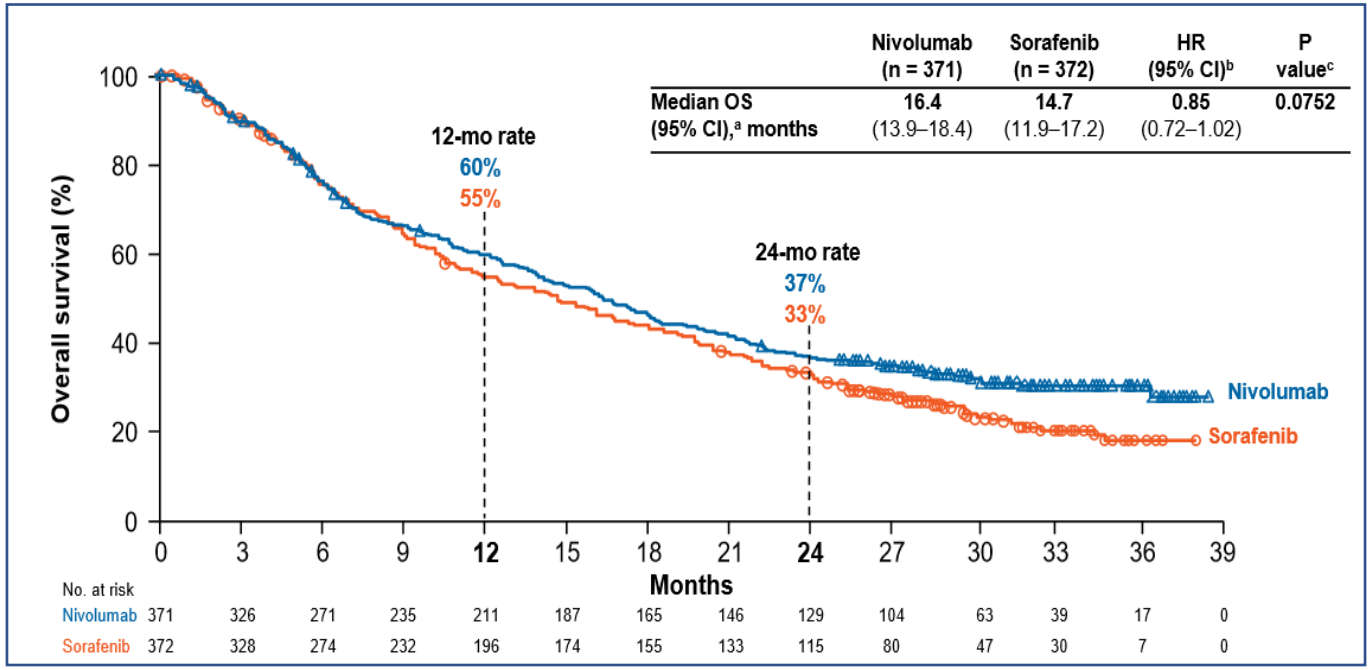
OS Rate (95% CI), %	
12 months	54 (44–63)

The objective response rate was 17% (95% CI 11–26)

Zhu AX, Lancet Oncol 2018;19(7):940-952.

Inmunoterapia en el CHC: ¿Fracasan los EC F III?

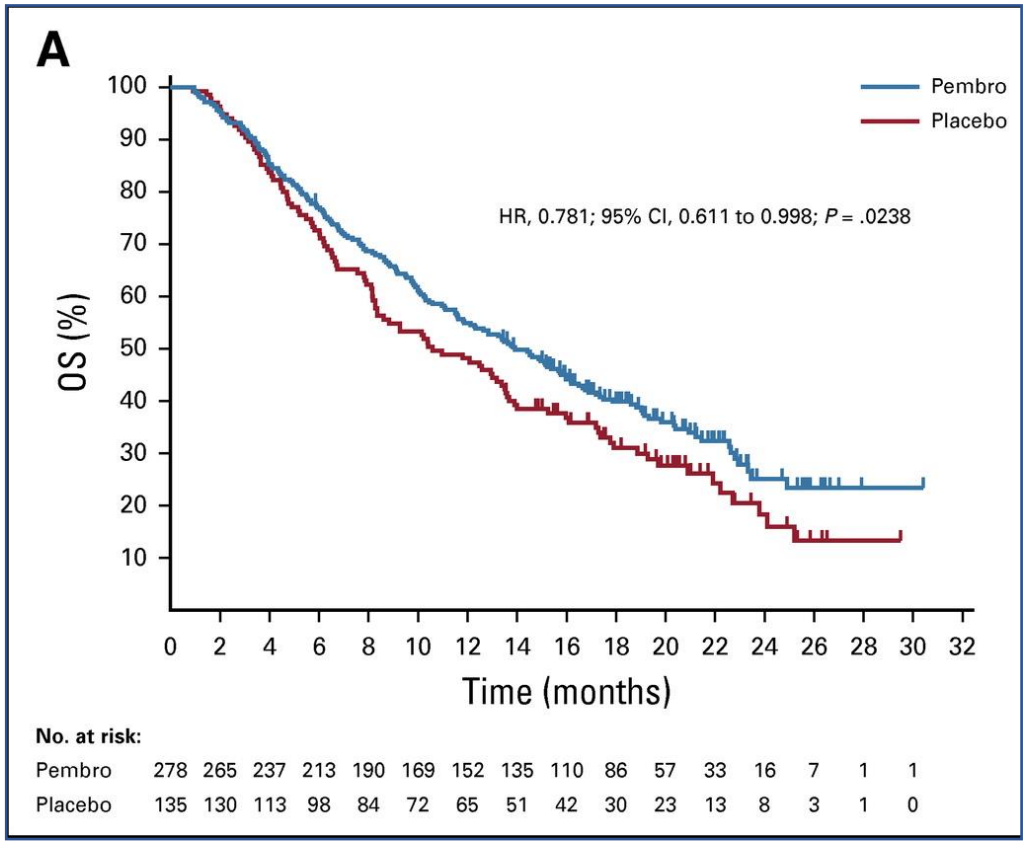
CheckMate 459 — 1 L



Duración de respuesta mayor (mediana 7.5 Nivo vs 5.7 meses Sor)..
Mejor perfil de seguridad (< TRAES ≥3 (22% vs 49%).
Menos eventos que obligaron a discontinuer el tratamiento.
Menor impacto en calidad de vida.
Incrementa la tasa de *"largos supervivientes"*.

Yau Thomas et al. ESMO Barcelona Sep 2019.
El-Khoueiry, A. B. et al. Lancet 389, 2492–2502 (2017).
Sangro, B. et al. [abstract LBA-3]. Ann. Oncol. 31 (Suppl. 3), S241–S242 (2020).

KEYNOTE-240 — 2 L



Finn RS, et al. J Clin Oncol. 2020 Jan 20;38(3):193-202.

Two approaches could potentially address the lack of benefit with checkpoint inhibitors in HCC

Opportunities to enhance outcomes with cancer immunotherapy in HCC

Better biomarkers

Identify patients most likely to derive benefit

- Tumor-associated macrophages (TAMs)
- PD-L1,
- Tumorinfiltrating lymphocytes (TILs)
- Inmunoscore
- LAG3

Combination treatment

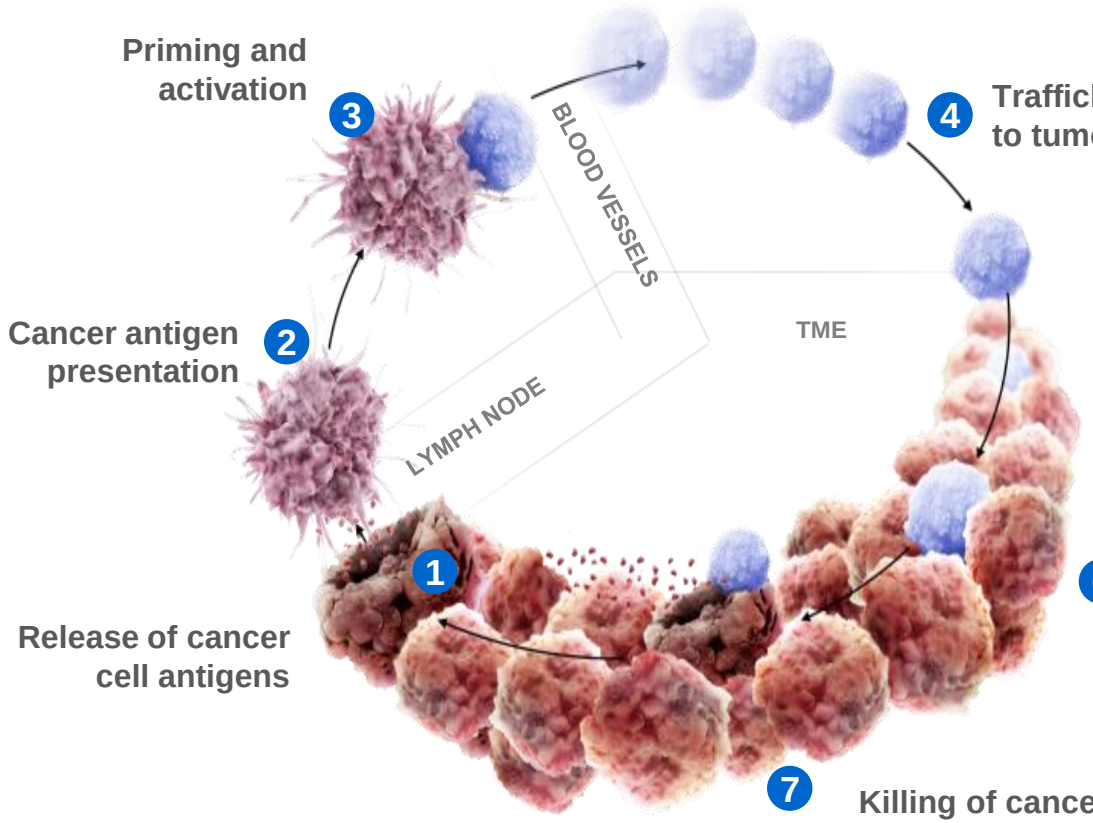
Alter the tumour environment to promote tumour immune response with cancer immunotherapy

Tang XQ. Cancer Lett. 2013;332(1):3–10. https://doi.org/10.1016/j.canlet.2013.01.024. 148.
Nishino M, et al. Nat Rev Clin Oncol. 2017;14(11):655–68. https://doi.org/10.1038/nrclinonc.2017.88. 149.
Yi M, Jiao D. Mol Cancer. 2018;17(1):129. https://doi. org/10.1186/s12943-018-0864-3.
Zhou, G. et al. Gastroenteroly 153, 1107–1119.e10 (2017).

The cancer immunity cycle

T CELL GENERATION

Initiating and propagating antitumor immunity



T CELL INFILTRATION

Accessing the tumor

T CELL KILLING

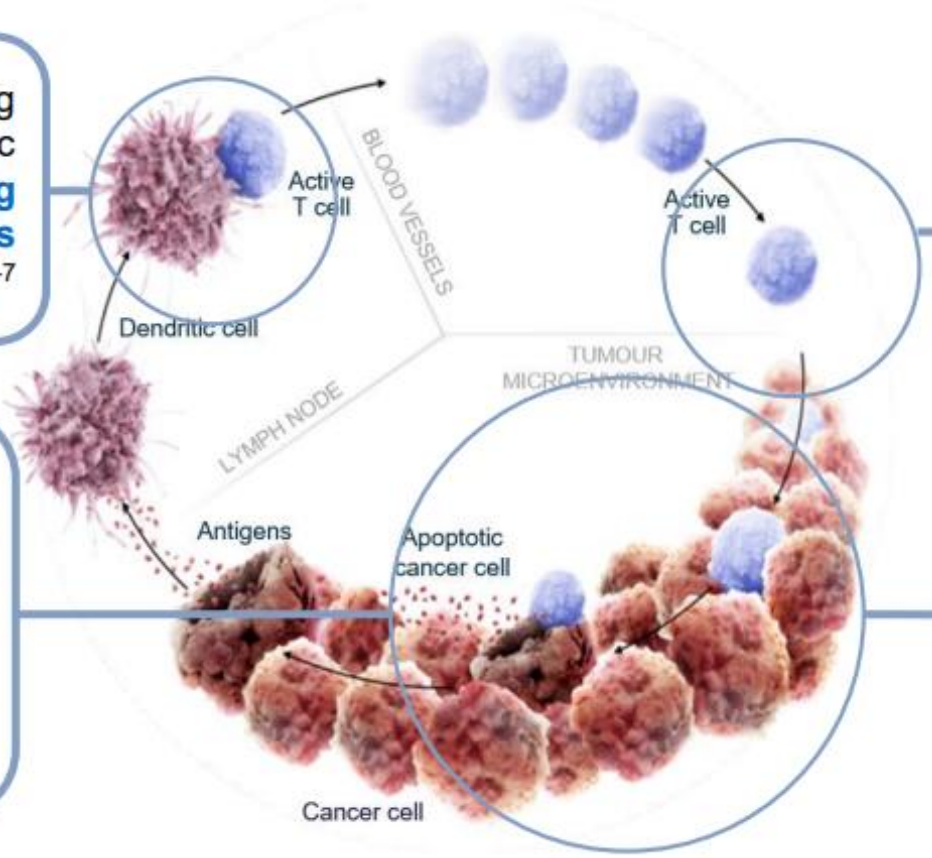
Cancer cell recognition and initiation of cytotoxicity

TME, tumour microenvironment

- Adapted from 1. Chen and Mellman. Immunity 2013

Synergies between Atezolizumab and Bevacizumab

Bevacizumab, by inhibiting VEGF-mediated suppression of dendritic cell maturation, enables **efficient priming and activation of T-cell responses** against tumour antigens (**Recognise**)[1–7]



Bevacizumab **normalises the tumour vasculature**, resulting in an increased infiltration of T cells into the tumour (**Recruit**)[1,7–13]

Atezolizumab's **ability to restore anti-cancer immunity, through T-cell mediated cancer cell killing**, is further enhanced through bevacizumab's VEGF-mediated immunomodulatory effects (**Restore**)[7,18–20]

Bevacizumab, by decreasing the activity of MDSCs and T_{reg} cells, enables **reprogramming of the tumour microenvironment** from immune suppressive to immune permissive (**Reprogramme**)[1,7,14–17]

Improve the *tumor microenvironment* and enhance the *antitumor immune response.*

1. Chen and Mellman. Immunity 2013. 2. Hegde et al. Semin Cancer Biol 2017. 3. Ferrara et al. Nat Rev Drug Discov 2004. 4. Gabrilovich et al. Nat Med 1996. 5. Gabrilovich et al. Blood 1998. 6. Oyama et al. J Immunol 1998. 7.Guermonprez et al. Annu Rev Immunol 2002. 8. Villadangos and Schnorrer. Nat Rev Immunol 2007. 9. Griffioen et al. Blood 1996. 10. Griffioen et al. Cancer Res 1996, 11. Goel et al. Physiol Rev 2011. 12. Motz et al. Nat Med 2014. 13. Hodi et al. Cancer Immunol Res 2014. 14. Wallin et al. Nat Commun 2016. 15. Gabrilovich and Nagaraj. Nat Rev Immunol 2009. 16. Huang et al. Cancer Res 2006. 17. Ko et al. Clin Cancer Res 2009. 18. Kusmartsev et al. J Immunol 2008.

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Combination treatment

Alter the tumour environment to promote tumour immune response with cancer immunotherapy

- Ipi+Nivo
- **Treme+Durva**
- Atezo+Cabo
- Pembro+Lenva
- **Atezo+Beva**
- Sintilimab+Beva

Tang XQ. Cancer Lett. 2013;332(1):3–10. https://doi.org/10.1016/j.canlet.2013.01.024. 148.
Nishino M, et al. Nat Rev Clin Oncol. 2017;14(11):655–68. https://doi.org/10.1038/nrclinonc.2017.88. 149.
Yi M, Jiao D. Mol Cancer. 2018;17(1):129. https://doi. org/10.1186/s12943-018-0864-3.
Zhou, G. et al. Gastroenteroly 153, 1107–1119.e10 (2017).

Fármacos con beneficio en SG en 1 L: Población de estudio

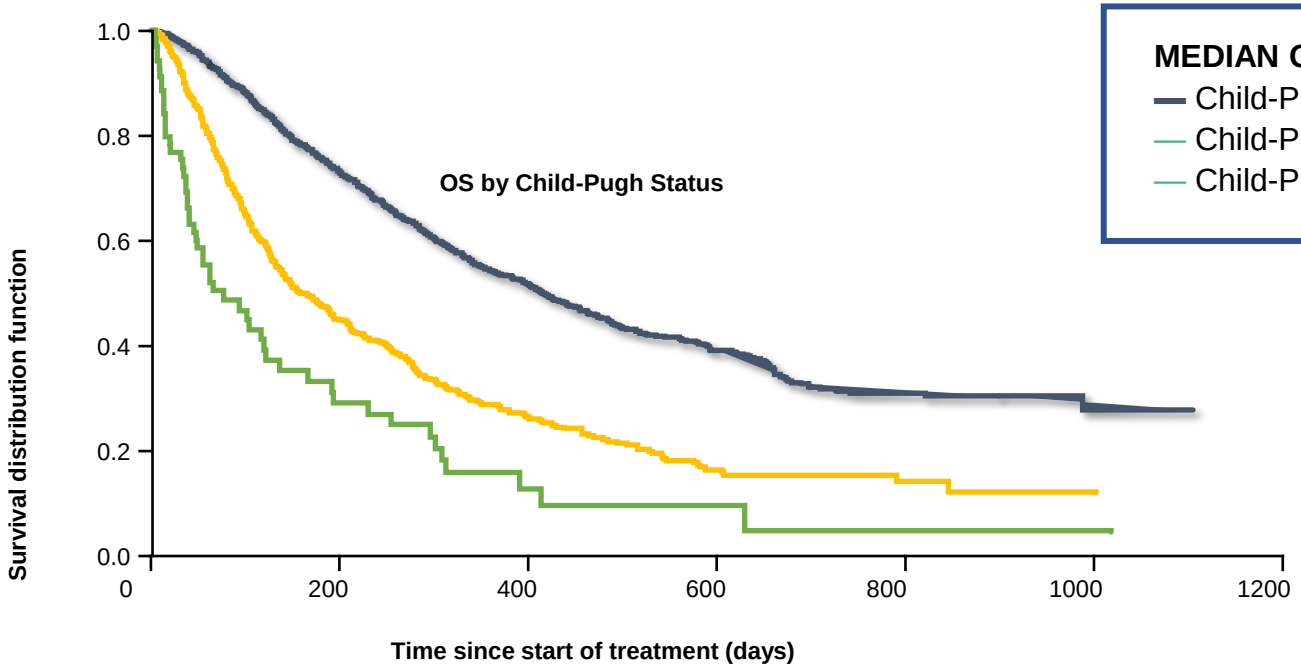
	SHARP[1]		Asia-Pacifico[2]		REFLECT[3]		IMbrave150[4]		Himalaya[5]		
	Sorafenib	Placebo	Sorafenib	Placebo	Lenvatinib	Sorafenib	Atezolizumab + bevacizumab	Sorafenib	Durva+ Treme	Durva	Sor
Criterios exclusión	NA		NA		**Invasión porta principal/Vía Biliar**		Enf autoinmune Coinfección VHB/VHC Infección VHB CV alta **VE o VG de riesgo**		Enf autoinmune Coinfección VHB/VHC Infección VHB CV alta **Invasión porta principal**		
diferente a estudio SHARP					**Infiltración de > 50% hígado**						
					> 2 medicamentos anti-HTA						
Características basales de la población incluida en el estudio											
Child-Pugh A (%)	95	98	97.3	97.4	99	99	99	100	99.7	99.7	99.2
PS 0 (%)	54	54	**25.3**	**27.6**	64	63	62	62	62.1	60.9	62.0
Invasión vascular(%)	36	41	36	34.2	**23**	**19**	38	43	**26.2**	**24.2**	**25.7**
Enf. extrahepática(%)	53	50	**68.3**	**68.4**	61	62	63	56	53.2	54.5	52.2
BCLC-C (%)	82	83	95.3	96.1	78	81	82	81	80.4	79.4	83
AFP≥400ng/mL *>200	NR		NR		46*	39*	38	37	*36.9*	*35.2*	*31.9*
Hepatitis B(%)	19	18	**70.7**	**77.6**	53	48	**49**	**46**	31	30.6	30.6
Hepatitis C(%)	29	27	**10.7**	**3.9**	19	26	21	22	28	27.5	26.7
Alcohol (%)	26	26	**NR**		8	4	NR		**NR**	**NR**	**NR**
NAFLD(%)	**NR**				**NR**						

1. *Llovet JM et al. N Engl J Med 2008;359:378–90.* ***2***. *Cheng A, et al. Lancet Oncol 2009;10:25–34. 3*. Kudo M et al. Lancet. 2018;pii:S0140-6736(18)30207–1. 4. Finn RS, et al. N Engl J Med 2020;382:1894-905. 5. Abou-Alfa GK, et al. ASCO GIS GI 22.

Modificado de Reig M, et al. Med Clin (Barc). 2021 Jan 15:S0025-7753(20)30769-7. doi: 10.1016/j.medcli.2020.09.022.

Real-life Evidence Shows Greater Survival Benefits with Sorafenib When Used in Patients with Better Liver Function

GIDEON: Non-interventional Study of 3,000 patients in 5 regions US, EU, Japan, Asia



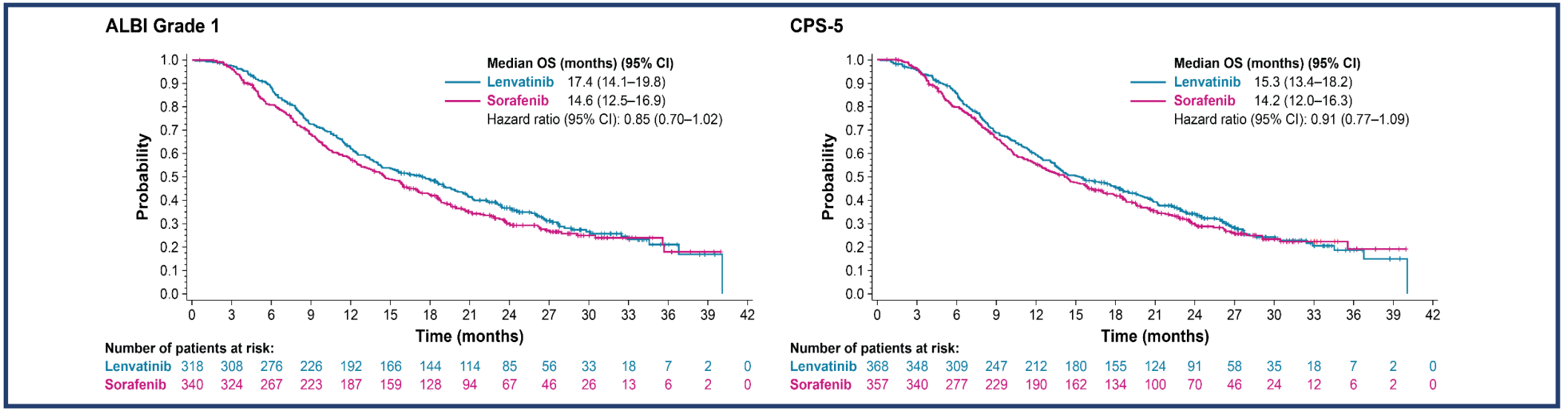
MEDIAN OS (months)

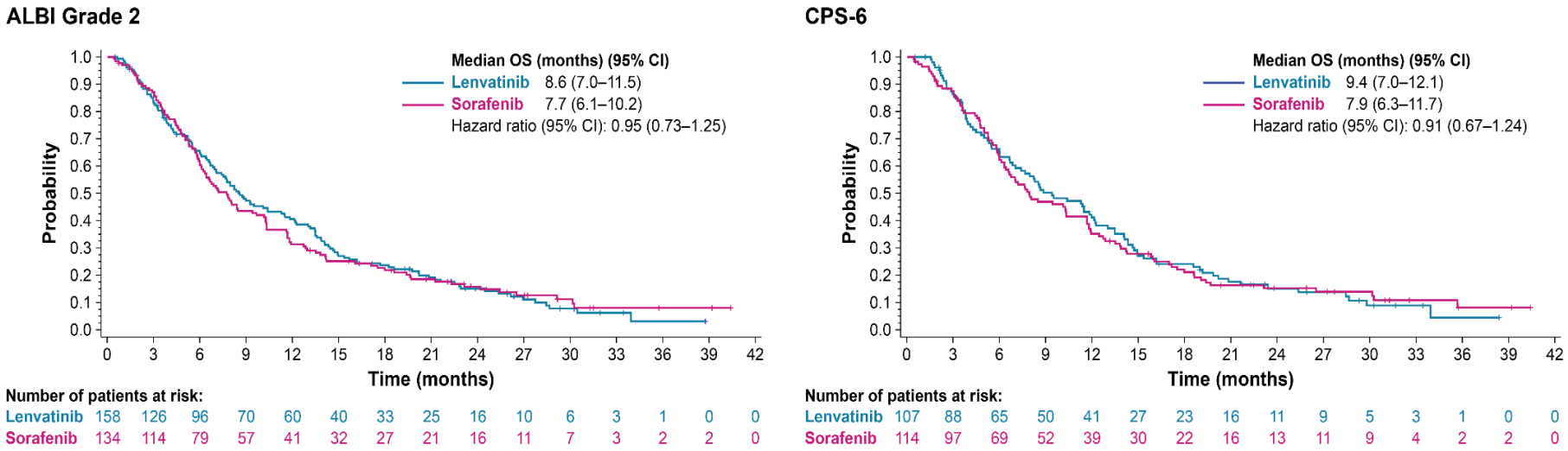
- Child-Pugh A: 13.6; 95% CI: (12.8-14.7)
- Child-Pugh B: 5.2; 95% CI: (4.6-6.3)
- Child-Pugh C: 2.6; 95% CI: (1.5-4.0)

- The intent-to-treat population was comprised of 3213 patients
- Median OS (months) was longer in Child-Pugh A patients than in Child-Pugh B and Child-Pugh C patients (13.6 vs 5.2 and 2.6, respectively)

Marrero J, et al. *J Clin Oncol*. 2013;31:Abstract 4126.

REFLECT trial: Baseline liver function impacts Efficacy





- Vogel A, et al. Presented at ASCO GI Symposium, San Francisco, USA. Jan 23-25, 2020. Abstract No. #524.

Fármacos con beneficio en SG en 1 L: Población de estudio

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Alcohol (%)	26	26	**NR**		8	4	NR		**NR**	**NR**	**NR**
NAFLD(%)	**NR**				**NR**						

1. *Llovet JM et al. N Engl J Med 2008;359:378–90.* ***2***. *Cheng A, et al. Lancet Oncol 2009;10:25–34. 3*. Kudo M et al. Lancet. 2018;pii:S0140-6736(18)30207–1. 4. Finn RS, et al. N Engl J Med 2020;382:1894-905. 5. Abou-Alfa GK, et al. ASCO GIS GI 22.

Modificado de Reig M, et al. Med Clin (Barc). 2021 Jan 15:S0025-7753(20)30769-7. doi: 10.1016/j.medcli.2020.09.022.

Fármacos con beneficio en SG en 1 L: Resultados

	SHARP[1]		Asia-Pacifico[2]		REFLECT[3]		IMbrave150[4]		HIMALAYA[5]		
	Sorafenib	Placebo	Sorafenib	Placebo	Lenvatinib	Sorafenib	Atezo + beva	Sorafenib	Durva+ Treme	Durva	Sor
Mediana de tiempo en tratamiento (meses)	5.3	4.3	NR		5.7	3.7	A 8.4; Bev 7	2.8	NR		
Discontinuación por EA-relacionados con el tratamiento (%)	11	5	19.5	13.3	9	7	7*	10*	13.4	7.8	16.8
Mediana de tiempo a progresión (RECIST 1.1)	5.5	2.8	2.8	1.4	7.4	3.7	NR		5.42	3.75	5.55
HR (95% CI)	0.58; 0.45 - 0.74; P<0.001		0.57;0.42–0.79; p=0·0005		0.61; 0·51–0·72;<0·0001		0.59; 0.47–0.76; p<0.001		NR		
Mediana de tiempo a progresión (mRECIST)	NA		NA		7.4	3.7	ND		ND		
HR (95% CI)					0.60; 0·51–0·71; p<0·0001						
Mediana supervivencia libre de progresión (RECIST 1.1)	NR		NR		7.3	3.6	6.9	4.3	3.78	3.65	4.07
HR (95% CI)					0.65; 0·56–0·77; p<0·0001		0.65 ; 95% IC 0.53-0.81; p < 0.001		0.90 (0.77-1.05)	1.02 (0.88-1.19	
Mediana supervivencia libre de progresión (mRECIST)	NA		NR		7.3	3.6	ND		ND		
HR (95% CI)					0.64; 0·55–0·75;p<0·0001						
Mediana de supervivencia global (meses)	10.7	7.9	6.5	4.2	13.6	12.3	19.2	13.4	16.4	16.6	13.8
HR (95% CI)	0.69; 0.55 - 0.87; p<0.001				HR 0.92, 0.79–1.06		0.66; 95% IC 0.52, 0.85;p= 0.001		0.78 (0.65-0.92)	0.86 (0.73–1.03)	

1. *Llovet JM et al. N Engl J Med 2008;359:378–90.* ***2***. *Cheng A, et al. Lancet Oncol 2009;10:25–34. 3*. Kudo M et al. Lancet. 2018;pii:S0140-6736(18)30207–1. 4. Finn RS, et al. N Engl J Med 2020;382:1894-905. 5. Abou-Alfa GK, et al. ASCO GIS GI 22.

Modificado de Reig M, et al. Med Clin (Barc). 2021 Jan 15:S0025-7753(20)30769-7. doi: 10.1016/j.medcli.2020.09.022.

Benefit in radiological response and duration of response

IMbrave150 *vs.* HIMALAYA

	IMbrave150 Update análisis[1]		HIMALAYA[2]		
	RECIST 1.1				
	Atezo + Bev (n = 326)	**Sorafenib** (n = 159)	**Treme 300+Durva** (n=393)	**Durva** (n = 389)	**Sorafenib** (n = 369)
Confirmed ORR (95% CI), %	**30**	**11**	**20.1**	**17.0**	**5.1**
CR, n (%)	25 (8)	1 (< 1)	12 (3,1)	6 (1.5)	0
PR, n (%)	72 (22)	17 (11)	67 (17,0)	60 (15.4)	20 (5.1)
SD, n (%)	144 (44)	69 (43)	157 (39,9)	147 (37.8)	216 (55.5)
DCR, n (%)	241 (74)	87 (55)	60.1	54.8	60.7
PD, n (%)	63 (19)	40 (25)	157 (39,9)	176 (45.2)	153 (39.3)
Median DOR (95% CI), months	18,1 (14,6 NE)	14.9 (4.9, 17.0)	22,34	16,82	18.43
Median TTR (95% CI), months	NR	NR	2.17 (1.84-3.98)	2.09 (1.87-3.98)	3.78 (1.89-8.44)
Ongoing response n (%) 15,6 months	54 (56)	5 (28)	NA	NA	NA
Remaining in response, % **6 months** **12 months**	NA	NA	82.3 65.8	81.8 57.8	78,9 63.2

(1). Finn RS, et al. N Engl J Med 2020;382:1894-905
(2). Abou-Alfa GK, et al. ASCO GIS GI 22.

Safety and tolerability of combined treatments

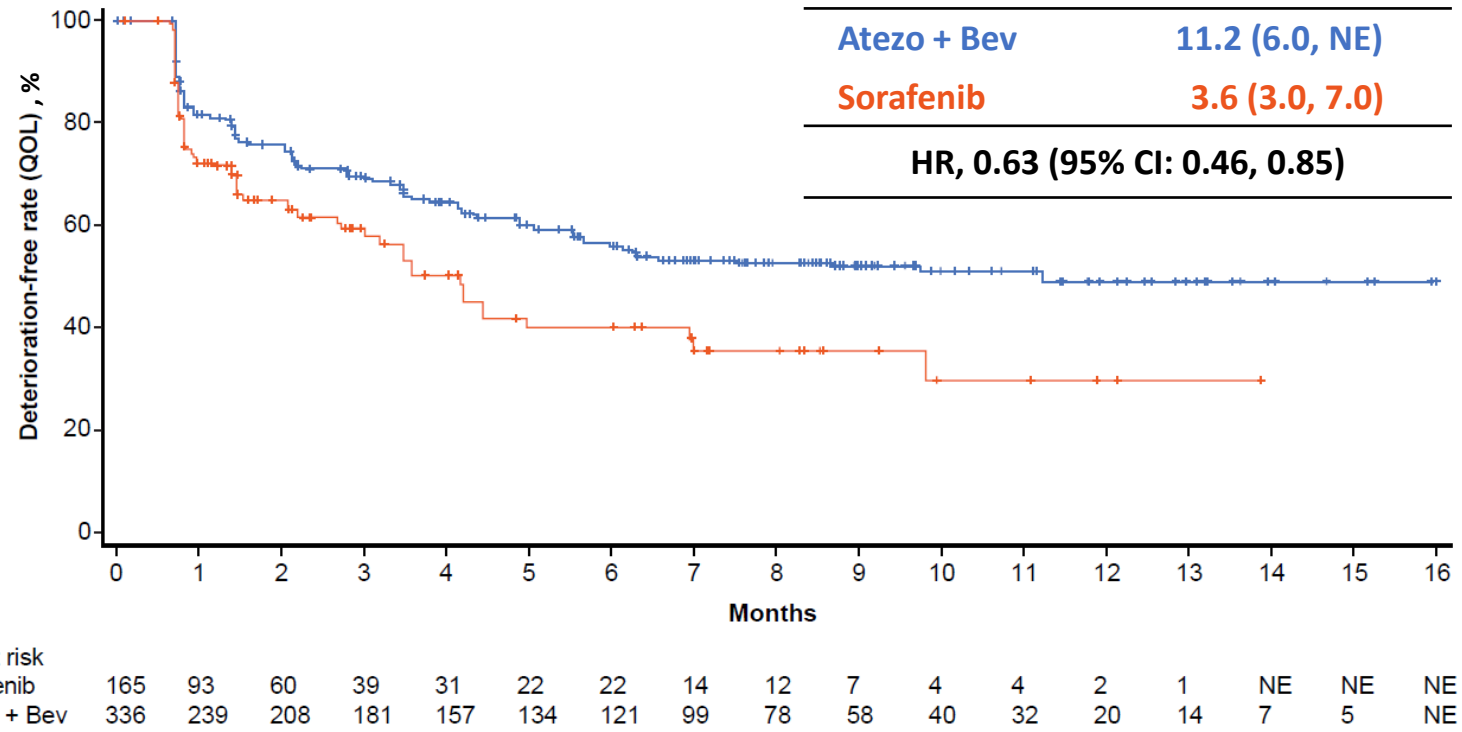
PD1/PDL1 agent (dose)	TRAE (%)				AST (%)	
	Total	Grade ≥3	Leading to discontinuation	Serious	Any grade	Grade≥3
Atezolizumab (1,200mg every 3 weeks) **Bevacizumab** (15mg/kg every 3 weeks)[1]	84	38	15 (7c)	17	19,5	7
Durvalumab (1,500mg every 4 weeks) **Tremelimumab** (300mg single dose on day 1)[2]	75,8	25,8	8.2	17.5	5.7	2.3
Pembrolizumab (200mg every 3 weeks) **Lenvatinib** (8 or 12mg per day)[3]	94	80	10	59	31	18
Nivolumab (240mg every 2 weeks) **Cabozantinib** (40mg per day)[4]	89	47	NR (6c)	NR	14	8
Nivolumab (240mg every 2 weeks) **Ipilimumab** (1mg/kg every 6 weeks plus **Cabozantinib** (40mg per day)[4]	94	71	15.5 (7b)	NA	29	23

(1). Finn RS, et al. N Engl J Med 2020;382:1894-905
(2). Abou-Alfa GK, et al. ASCO GIS GI 22.
(3). Zhu, A. X. et al. [abstract]. J. Clin. Oncol. 38 (Suppl. 15), 4519 (2020)
(4). . Yau, T. et al. [abstract]. J. Clin. Oncol. 38 (Suppl. 4), 478 (2020)

IMbrave150: Patient-reported outcomes[a]

- Atezolizumab + bevacizumab delayed the time to deterioration of patient-reported quality of life compared with sorafenib

Quality of life Median TTD (95% CI), mo[b]	
Atezo + Bev	11.2 (6.0, NE)
Sorafenib	3.6 (3.0, 7.0)
HR, 0.63 (95% CI: 0.46, 0.85)	



EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire for Cancer; TTD, time to deterioration.

[a] Pre-specified secondary endpoint that was not formally tested; EORTC QLQ-C30 administered every 3 weeks on treatment and every 3 months after treatment discontinuation or progression. [b] Time to deterioration defined as first decrease from baseline of ≥ 10 points[1] in the patient-reported health-related global health status/quality of life (GHS/QoL) scale of the EORTC QLQ-C30 maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.

1. Osoba D, et al. *J Clin Oncol.* 1998.

Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Risk of GI bleeding Bevacizumab in advanced HCC

F. 2 CT: Bevacizumab monotherapy

US study: adverse events[1]

Adverse event, n (%)	All grades	Grade 3 or 4
Proteinuria	19 (41)	2 (4)
Hypertension	15 (33)	7 (15)
Fatigue	15 (33)	0
Haemorrhage	12 (26)	5 (11)*
Increased bilirubin	12 (26)	5 (11)
Increased AST	10 (22)	1 (2)
Increased ALT	9 (20)	1 (2)
Rash	6 (13)	0
Thrombocytopenia	6 (13)	0
Ascites	5 (11)	2 (4)
Anorexia	5 (11)	1 (2)
Increased ALP	5 (11)	1 (2)
Epistaxis	5 (11)	0
Nausea	5 (11)	0
Vomiting	5 (11)	0
Arterial thrombosis	2 (4)	2 (4)
Venous thrombosis	1 (2)	1 (2)

*Gastroesophageal varices rupture, n=3; gastric ulcer, n=1; no Grade 4 haemorrhage
‡Primary liver tumour bleeding with haemoperitoneum
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase

France study: adverse events[2]

Adverse event, n (%)	All grades	Grade 3 or 4
Asthenia	38 (88)	5 (12)
ALT/AST elevation	34 (79)	3 (7)
Epistaxis	17 (40)	0
Arterial hypertension	11 (26)	0
Proteinuria	5 (12)	1 (2)
Thrombocytopenia	5 (12)	1 (2)
GI haemorrhage*	4 (9)*	2 (5)
Tumour haemorrhage‡	1 (2)	1 (2)
Pulmonary embolism	1 (2)	1 (2)
Transient cerebral ischaemia	1 (2)	1 (2)

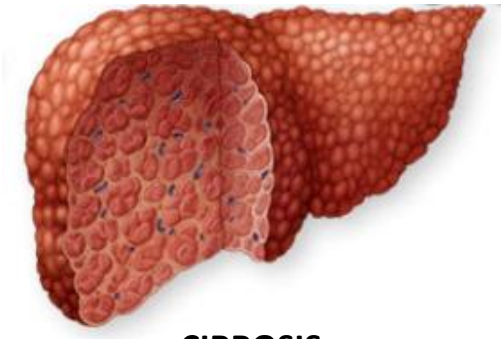
*** GI bleeding: gastroesophageal varices rupture n=3 cases and gastric ulcer n=1.**

SHARP[3]: 9-13% severe bleeding.
Variceal bleeding 2 Sor vs. 4% Placebo

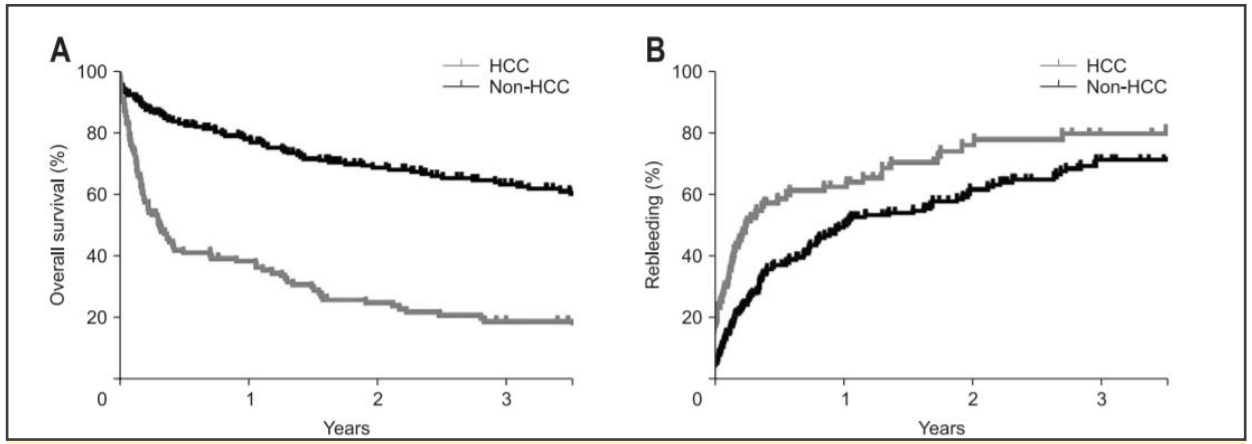
1. Siegel AB, et al. J Clin Oncol 2008;26:2992-2998.
2. Boige V, et al. The Oncologist 2012;17:1063–1072.
3. Llovet JM et al. N Engl J Med 2008;359:378–90.

¿Existe más riesgo de sangrado por VE durante el tratamiento con Atezo+Beva?

HTP en el paciente con cirrosis



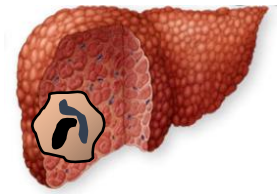
CIRROSIS



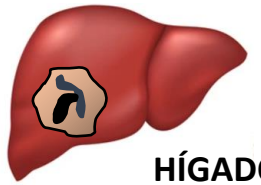
(1) Patients with and without HCC, patients with HCC had higher rates of 5-day treatment failure, 6-week mortality, and cirrhosis-related complications of acute variceal bleeding.[1]

HTP en el paciente con CHC avanzado

¿Responden igual a los tratamientos establecidos?

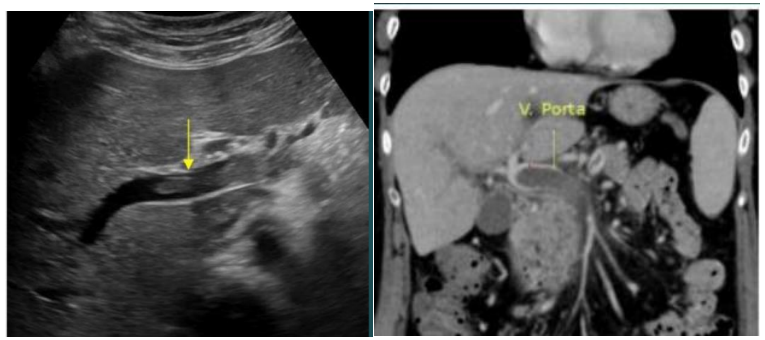


CIRROSIS



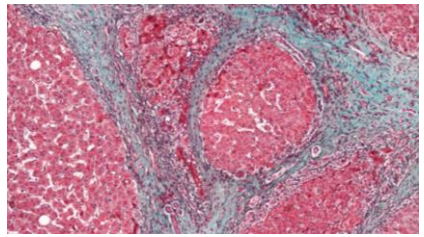
HÍGADO SIN CIRROSIS

±



TROMBOSIS PORTAL MALIGNA

±



FIBROSIS POR EL TTO???

± **Inhibición VEGF[(2)]**

(1). Lee YR, et al. Gut Liver 2020 Jul 15;14(4):500-508.

(2). Brusilovskaya, K., et al. Semin. Liver Dis. 39, 483–501 (2019

Risk of GI bleeding with Atezo+Bevacizumab in advanced HCC. Imbrave150

¿Mayor riesgo de sangrado por VEG con Atezo+Beva F.3[1]?

Sangrado GI en el IMbrave150[3]: 7% A+B vs 4.5% Sor

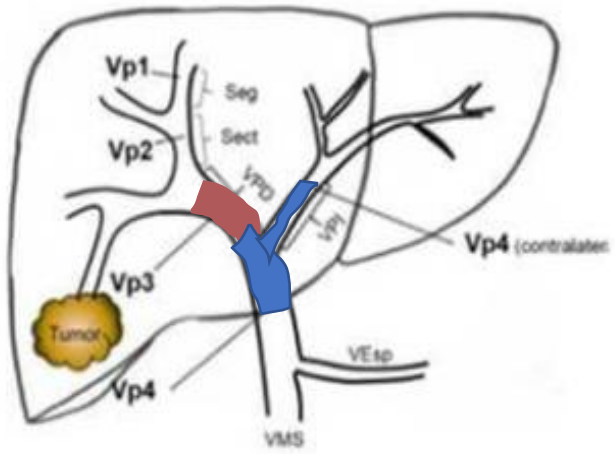
Safety by Risk Status in Patients

High-risk patients were defined as those who had **tumor invasion of the main trunk of the portal vein** and/or **the portal vein branch contralateral to the primarily involved lobe (Vp4)**, and/or **bile duct invasion** and/or **tumor occupancy of ≥50% of liver**

Grade 3/4 and Grade 5 AEs

	Safety population (n=485)			
	Non–high risk		High risk	
	Atezo + Bev (n=269)	Sorafenib (n=121)	Atezo + Bev (n=60)	Sorafenib (n=35)
Grade 3/4 AEs occurring in ≥5% of non–high-risk or high-risk patients, n (%)				
Hypertension	49 (18)	18 (15)	7 (12)	1 (3)
Aspartate aminotransferase increased	21 (8)	4 (3)	5 (8)	5 (14)
Blood bilirubin increased	9 (3)	3 (2)	4 (7)	7 (20)
Abdominal pain	1 (<1)	2 (2)	3 (5)	2 (6)
Esophageal varices hemorrhage	1 (<1)	1 (1)	5 (8)	0
Blood alkaline phosphatase increased	0	1 (<1)	5 (8)	0
Grade 5 AEs occurring in ≥2 patients in any group, n (%)				
Pneumonia	2 (1)	1 (1)	0	0
Hepatic cirrhosis	1 (<1)	2 (2)	0	0
Gastrointestinal hemorrhage	1 (<1)[a,b]	0	2 (3)[a]	0
Death, not otherwise specified	1 (<1)	0	0	2 (6)
Esophageal varices hemorrhage	0	0	2 (3)[a]	0

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.



There were five Grade 5 upper GI bleeding events among patients treated with A+B, and all 5 patients had MVI (4 Vp4 and 1 Vp3).

1. Finn et al. N Engl J Med 2020;382:1894-905.
2. Finn RS. IMbrave150 high-risk patients. AACR 2021 [abs #5080].

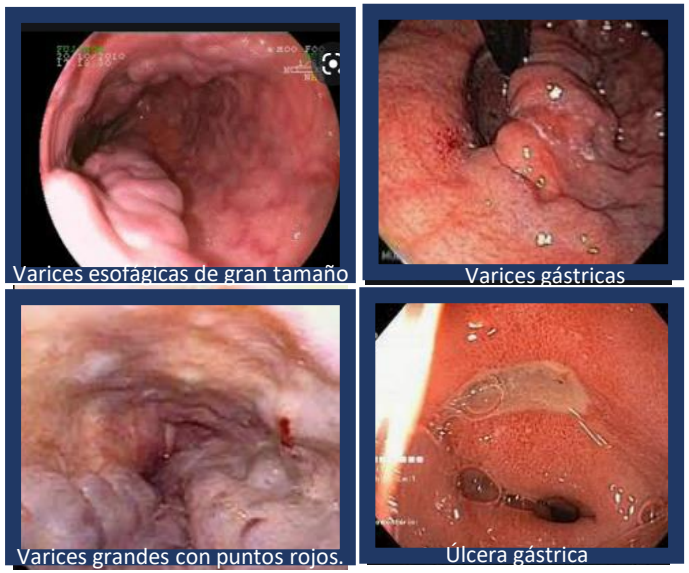
Riesgo de sangrado y tratamiento con antiangiogénicos

¿Cómo hacer el screening de VE?[1]
- Realizar GC basalmente.
- Repetir anualmente a juicio del clínico??

¿Riesgo de sangrado?[2,3]
- Presencia VE, tamaño, localización.
- Presencia de puntos rojos.
- Valoración patología péptica.

¿Cómo hacer la PROFILAXIS PRIMARIA?

¿MÁS AGRESIVA?



Propranolol, Nadolol, Carvedilol[4]
LEB[4]
BBNCS+LEB

Demorar inicio hasta reducir a G. I de VE con LEB?

Monitorización HD de respuesta al BBNCS?
(descenso GPVH ≥10% de se valor basal o < 12mmHG)

¿Rápido desarrollo de VE en paciente con invasión portal?[5]

1. Hsu C, et al. Ther Adv Med Oncol 2021; Jul 29;13:17588359211031141.
2. Angeli P, et al. J Hepatol 2018; 69: 406–460.
3. Sarin SK, et al. Hepatol Int 2008; 2: 429–439.
4. Mauro E, et al. Liver Int 2020; 40(Suppl. 1): 122–127.
5. Campion B, et a. Clinics and Research in Hepatol and Gastroenterol (2021), doi: https://doi.org/10.1016/j.clinre.2021.101785

Fármacos con beneficio en SG en 2 L: Población de estudio

	RESORCE[1]		CELESTIAL[2]		REACH-2[3]	
	Regorafenib	Placebo	**Cabozantinib**	Placebo	**Ramucirumab**	Placebo
Candidatos	Tolerantes a sorafenib		Segunda o Tercera línea		AFP ≥400 mg/dl	
Descripción de evolución durante el tratamiento con Sorafenib antes de entrar al Ensayo Clínico						
Mediana de tiempo en sorafenib (meses)	7.8	7.8	5.3	4.8	4.1	4.1
Mediana de tiempo entre última dosis sorafenib e inicio del ensayo clínico	0.9	0.9	1.4	1.2	1.2	1.1
Motivo por el cual se suspendió sorafenib						
Progresión radiológica	100		NR		84	80
Intolerancia a sorafenib*	NA				16	20
Características basales y evolución durante el tratamiento recibido durante el Ensayo Clínico						
Child-Pugh A (%)	98	97	98	99	62	57
PS 0 (%)	65	67	52	55	57	58
Invasión vascular(%)	29	28	27	34	36	35
Metástasis(%)	70	76	79	77	72	74
BCLC-C (%)	86	89	91	90	83	89
Hepatitis B(%)	38	38	38	38	36	38
Hepatitis C(%)	21	21	24	23	24	29
Alcohol (%)	24	28	24	16	24	22
NAFLD(%)	7	7	9	10	10	4

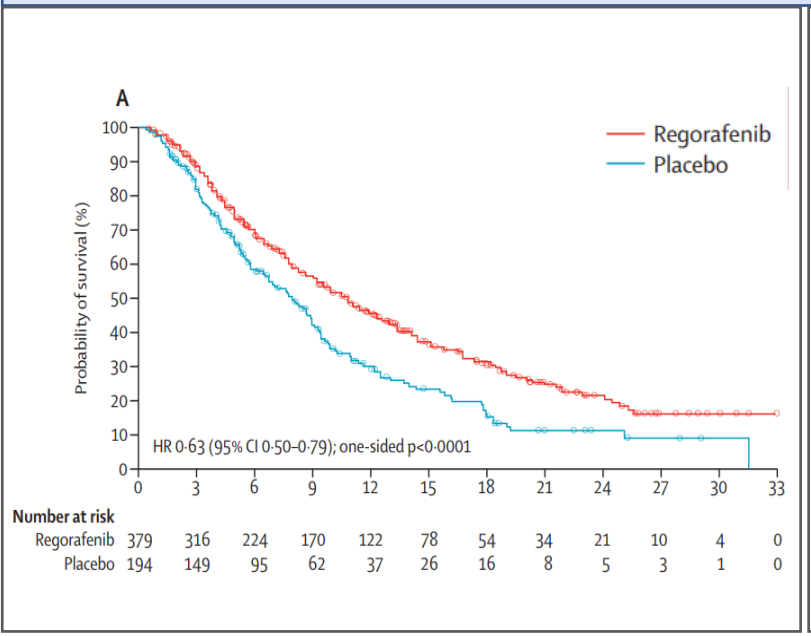
NA, no aplicable; NR, no reportado HTA, hipertensión arterial; PS, performance status; BCLC, Barcelona Clínic Liver Cancer; NAFLD, enfermedad hepática por hígado graso; RECIST, Response Evaluation *Criteria* in Solid Tumors; mRECIST, Response Evaluation *Criteria* in Solid Tumors modificado.

1. Bruix J, et al. *Lancet.* 2017;389:56–66. 2. Abou-Alfa GK, et al. N Engl J Med 2018 Jul 5;379(1):54-63. 3. Kudo M, et al. Liver Int. 2020 Apr 12. doi: 10.1111/liv.14462.

Extracted from Reig M, et al. Med Clin (Barc). 2021 Jan 16:S0025-7753(20)30769-7

Fármacos con beneficio en Supervivencia en 2 L: Resultados

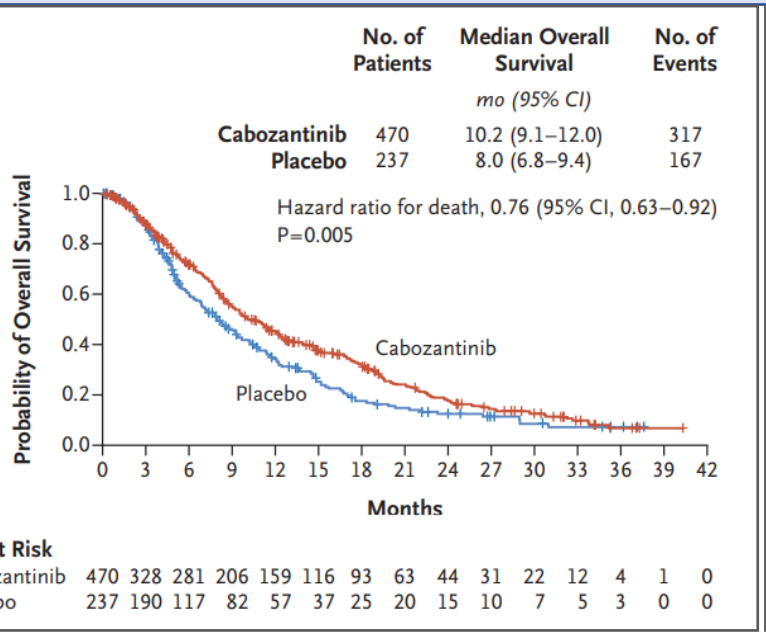
RESORCE[1]



10.6 meses | **7.8 meses**

HR 0.63(0.50–0.79);p<0·0001

CELESTIAL[2]

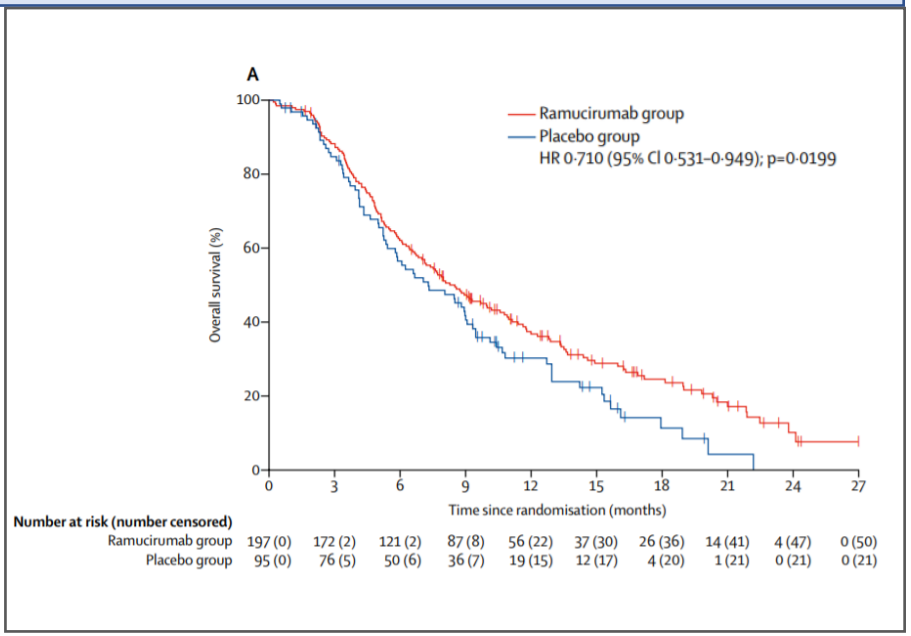


10.2 meses | **8 meses**

HR 0.76 (95% CI, 0.63 - 0.92); p= 0.005

OS between cabozantinib and regorafenib
(respectively 11.4 months vs 10.6 months, p=0.3474)[4]

REACH-2[3]



8.5 meses | **7.3 meses**

HR 0.710 [95% CI 0.531–0.949]; p=0.0199

1. Bruix J, et al. *Lancet.* 2017;389:56–66.
2. Abou-Alfa GK, et al. N Engl J Med 2018 Jul 5;379(1):54-63.
3. Zhu AX, et al. *Lancet Oncol* 2019;20:282–296.
4. Kelley RK, et al. P021, ILCA; 2019.

Fármacos con beneficio en Supervivencia en 2 L: Resultados

	RESORCE[1]		CELESTIAL[2]		REACH-2[3]	
	Regorafenib	Placebo	**Cabozantinib**	Placebo	**Ramucirumab**	Placebo
Mediana de tratamiento (meses)	3.6	1.9	3.8	2	3	2
Discontinuación por EA-relacionados al tratamiento (%)	10	4	16	3	11	3
Mediana de tiempo a progresión (RECIST)	3.9	1.5	NR		3	1.6
HR (95% CI)	0.41, 95% CI 0.34–0.51; p<0·0001				0.427 [95% CI 0.313–0.582]; p<0.0001	
Mediana de tiempo a progresión (mRECIST)	3.2	1.5			NR	
HR (95% CI)	0.44 (95% CI 0.36–0.55); p<0·0001					
Mediana supervivencia libre de progresión (RECIST)	3.4	1.5	5.2	1.9	2.8	1.6
HR (95% CI)	0.43, 95% CI 0.35–0.52; p<0·0001		0.44 (95% CI, 0.36 - 0.52; p<0.001		0.452 [95% CI 0.339–0.603]; p<0·0001	
Mediana supervivencia libre de progresión (mRECIST)	3.1	1.5	NR		NR	
HR (95% CI)	0.46 (95% CI 0.37–0.56); p<0·0001					
Median Supervivencia global (meses)	10.6	7.8	10.2	8	8.5	7.3
HR (95% CI)	0.63(0.50–0.79); p<0·0001		0.76 (95% CI, 0.63 - 0.92); p= 0.005		0.710 [95% CI 0.531–0.949]; p=0.0199	

NA, no aplicable; NR, no reportado HTA, hipertensión arterial; PS, performance status; BCLC, Barcelona Clínic Liver Cancer; NAFLD, enfermedad hepática por hígado graso; RECIST, Response Evaluation *Criteria* in Solid Tumors; mRECIST, Response Evaluation *Criteria* in Solid Tumors modificado.

1. Bruix J, et al. *Lancet.* 2017;389:56–66. 2. Abou-Alfa GK, et al. N Engl J Med 2018 Jul 5;379(1):54-63. 3. Kudo M, et al. Liver Int. 2020 Apr 12. doi: 10.1111/liv.14462.

Extracted from Reig M, et al. Med Clin (Barc). 2021 Jan 16:S0025-7753(20)30769-7

Pivotal clinical trials for agents approved for second-line treatment of patients with advanced HCC: safety, tolerability and HRQoL data

	REGORAFENIB[1]	CABOZANTINIB[2]	RAMUCIRUMAB[3]
Study	**RESORCE**	**CELESTIAL**	**REACH-2**
Patient (N)	573	707	292
Safety and tolerability			
Patients with ≥1 AEs, %	100 vs 93	99 vs 92	97.0 vs 86.3
Patients with ≥1 SAEs, %	44 vs 47	68 vs 36	58.9 vs 44.2
Patients who discontinued for treatment-related AEs, %	10 vs 4	16 vs 3	10.7 vs 3.2
Any AE-related dose modification, %	68 vs 31	62 vs 13	34.5 vs 13.7
HRQoL	No clinically meaningful difference	**Clinically and statistically significant benefit in means QALYs** and significantly more time without disease symptoms and toxicity	No difference in median time to deterioration in FHSI-8 total score and ECOG PS

1. Bruix J, et al. Lancet. 2017;389:56–66. 2. Abou-Alfa G.K. et al. NEJM 2018; 54-63. 10. 3. Zhu AX, et al. Lancet Oncol 2019; 20: 282–96.

Extrated from Rimassa L, et al. Liver Int. 2020 Aug;40(8):1800-1811. doi: 10.1111/liv.14533. Epub 2020 Jun 10.

Aspectos diferenciadores de los fármacos con beneficio en 2L

REGORAFENIB

- Beneficio en todos los subgrupos.
  (*Bruix J, et al. Lancet. 2017;389:56–66)*
- Beneficio independiente del patrón de progresión.
  (Bruix J, et al. . J Clin Oncol. 2017;35:229.)
- Beneficio independiente de la última dosis de SOR.
  (Finn RS, et al. J Hepatol. 2018;69:353–358.)
- Secuencia SOR-Rego 26 meses de mediana de SG.
  Mayor beneficio clínico en pacientes que tienen mayor TTP con el SOR.
  (Finn RS, et al. J Hepatol. 2018;69:353–358.)
- Beneficio en pacientes con AFP elevada. Respuesta de AFP se asocia a mayor SG
  (Bruix J, et al. Ann Oncol. 2019;30(Suppl 5):v291.)
- Desarrollo de toxicidad cutánea

CABOZANTINIB

- Beneficio en todos los subgrupos.
  (*Abou-Alfa G.K. et al. NEJM 2018; 54-63. 10)*
- Beneficio en 2L tras SOR.
  (SG 11.3 meses cabo vs. 7,2 meses placebo; HR 0.70, 95% CI 0.55-0.88.).
- Mejora la SG independientemente de la duración del tto con SOR en 1L
  (Kelley RK, et al. J Clin Oncol. 2018;36 (15_suppl): 4088. doi:10.1200/JCO.2018.36.15_suppl.4088*).*
- Beneficio en pacientes con AFP elevada.
  (Kelley RK, et al. . J Clin Oncol. 2019;37(4 Suppl):423.)
- EAs ≥ 3 HTA o toxicidad cutánea de cualquier grado se asocia a mayor SG y PFS.
  (Abou-Alfa GK, et al. J Clin Oncol. 2019;37(15 Suppl): 4088.)
- Mayor tasa de discontinuación por EAs relacionados con el tto (16%).

RAMUCIRUMAB

- Beneficio en todos los subgrupos.
  (*Zhu AX, et al.* Lancet Oncol 2019; 20: 282–96. *)*
- Aumenta la SG en todos los patrones de progresión (REACH y REACH-2).
  (Reig M, et al. Liver Int. 2021 Mar;41(3):598-607.)
- La evolución de la AFP se asocia a SG y TTP.
  (Finn RS, et al. J Clin Oncol. 2019;37(4 Suppl):326.)
  (Zhu AX, et al. Br J Cancer. 2021 Feb 3. doi: 10.1038/ s41416-021-01260-w.)
- No hay diferencias significativas en el impacto en QoL:
  -Mediana de tiempo de deterioro del score FHSI-8.
  - Mediana de tiempo de deterioro del ECOG-PS.
  (*Zhu AX, et al.* Lancet Oncol 2019; 20: 282–96. *)*

Regorafenib, Cabozantinib y Ramucirumab han sido aprobados por la FDA y EMA y ninguno está financiado en España

Efficacy of Nivolumab + Ipilimumab in Patients With HCC previously Treated With Sorafenib

The CheckMate 040 Randomized Clinical Trial

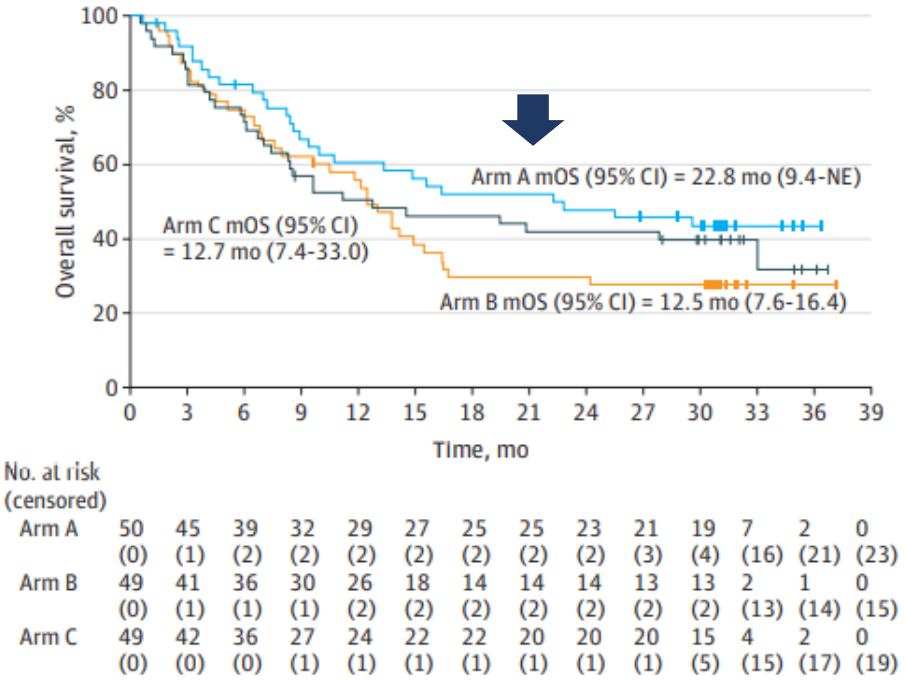
Arm A: NIVO1 + IPI3 Q3W × 4 → Nivolumab 240 mg IV Q2W flat dose

Arm B: NIVO3 + IPI1 Q3W × 4 → Nivolumab 240 mg IV Q2W flat dose

Arm C: NIVO3 Q2W + IPI1 Q6W

Characteristic	No. (%) Arm A[a] (n = 50)	Arm B[b] (n = 49)	Arm C[c] (n = 49)
Response by investigator assessment using RECIST v1.1			
Objective response rate, No. (%) [95% CI]	16 (32) [20 to 47]	13 (27) [15 to 41]	14 (29) [17 to 43]
Duration of response, median (range), mo	NE (8.3 to 33.7+)	15.2 (4.2 to 29.9+)	21.7 (2.8 to 32.7+)
Response by BICR using RECIST v1.1			
Objective response rate, No. (%) [95% CI][d]	16 (32) [20 to 47]	15 (31) [18 to 45]	15 (31) [18 to 45]
Best overall response			
Complete response	4 (8)	3 (6)	0
Partial response	12 (24)	12 (24)	15 (31)
Stable disease[e]	9 (18)	5 (10)	9 (18)
Progressive disease	20 (40)	24 (49)	21 (43)
Unable to determine[f]	3 (6)	4 (8)	4 (8)
Disease control rate[g]	27 (54)	21 (43)	24 (49)
Duration of response, median (range), mo[h]	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)
Duration of response of ≥24 mo[h]	5 (31)	4 (27)	5 (33)
Time to response, median (IQR), mo[h]	2.0 (1.3 to 2.7)	2.6 (1.3 to 4.0)	2.7 (1.3 to 2.8)
Response by BICR using mRECIST			
Objective response rate, No. (%) [95% CI][d]	17 (34) [21 to 49]	16 (33) [20 to 48]	15 (31) [18 to 45]

Kaplan-Meier Analysis of Median Overall Survival

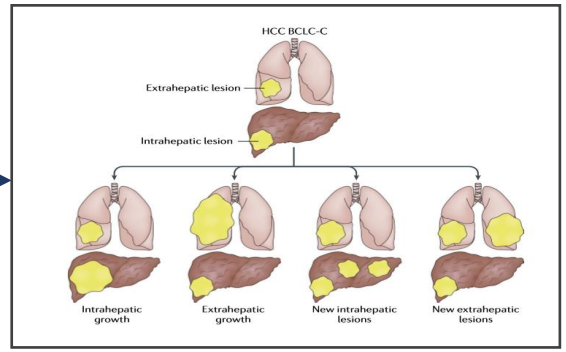


Yau T, et al. JAMA Oncol 2020. doi:10.1001/jamaoncol.2020.4564

Fármacos con beneficio en SG en 1 L: Siguientes líneas de tratamiento

	SHARP[1]		Asia-Pacifico[2]		REFLECT[3]		IMbrave150[4]		Himalaya[5]		
	Sorafenib	Placebo	Sorafenib	Placebo	Lenvatinib	Sorafenib	Atezo + beva	Sorafenib	Durva+ Treme	Durva	Sor
≥ 1L Tto sistémico n (%)	NR		NR		122 (26)	130 (27)	**120 (36)**	**86 (52)**	**160 (40.7)**	**168 (43.2)**	**175 (45)**
2L					NR		102 (30)	81 (49)	NR		
3L							33 (10)	39 (24)			

Potenciales escenarios durante el tto de 1L

- **Intolerancia** → ✓ → *Efectos adversos Grade III-IV*
- **Progresión radiológica** → ? → 

- **Progresión sintomática** → X → *ECOG ≥ 2*, *Descompensación hepática*
- **Muerte** → X

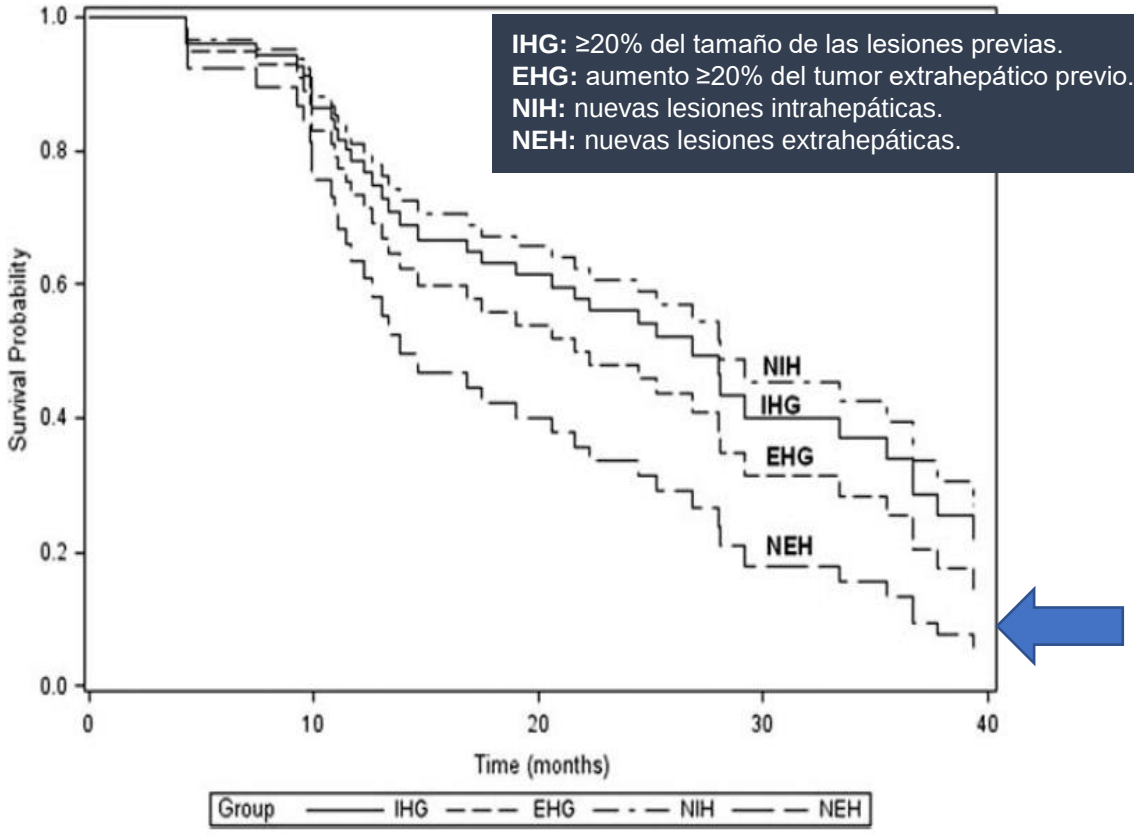
1. Llovet JM et al. N Engl J Med 2008;359:378–90. ***2****. Cheng A, et al. Lancet Oncol 2009;10:25–34. 3.* Kudo M et al. Lancet. 2018;pii:S0140-6736(18)30207–1. 4. Finn RS, et al. N Engl J Med 2020;382:1894-905. 5. Abou-Alfa GK, et al. ASCO GIS GI 22.

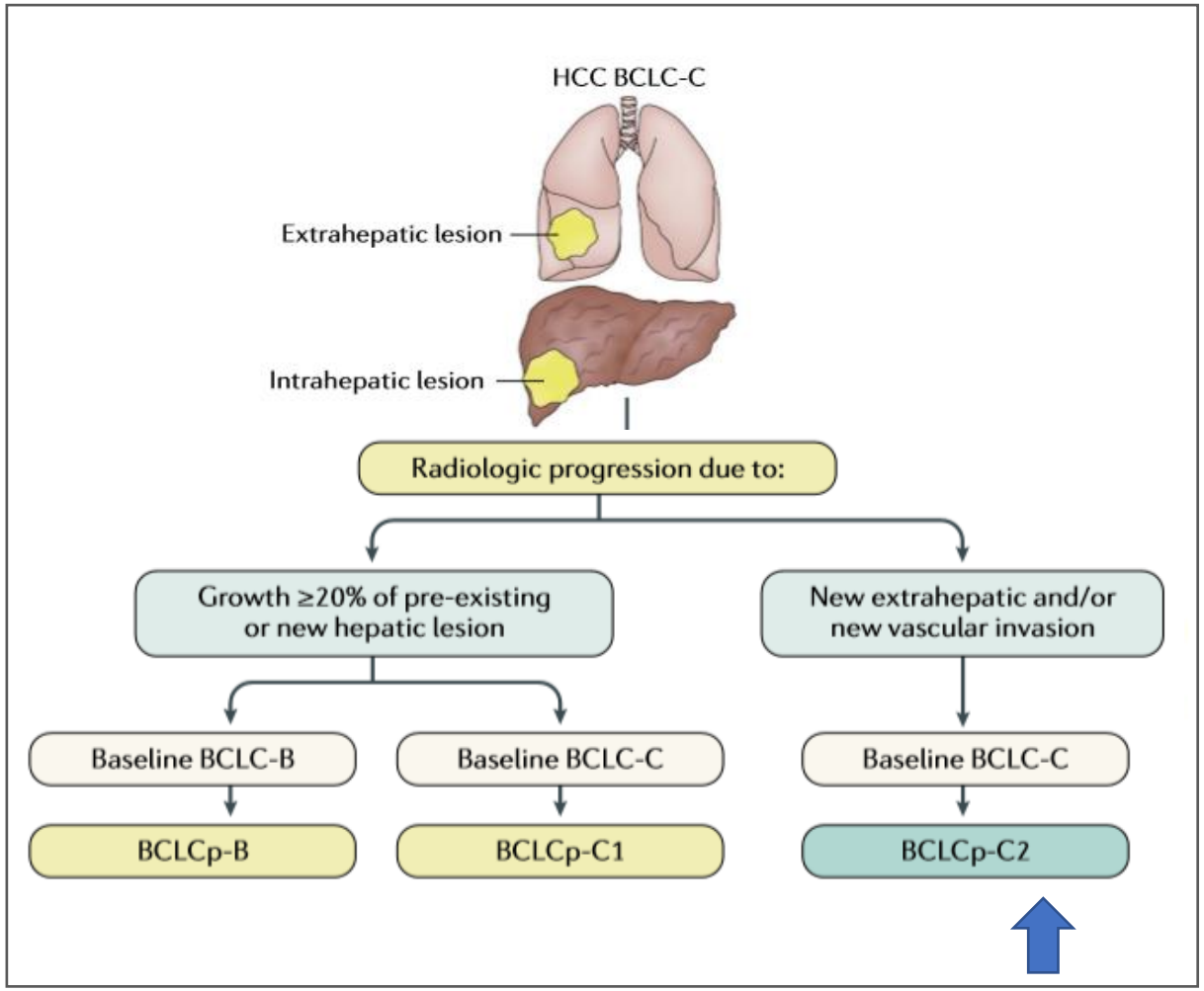
Modificated from Piñero F, et al. World J Gastroenterol 2020 April 28; 26(16): 1888-1900

Prognostic value of progression patterns

Post-progression survival to SOR[1]

IHG: ≥20% del tamaño de las lesiones previas.
EHG: aumento ≥20% del tumor extrahepático previo.
NIH: nuevas lesiones intrahepáticas.
NEH: nuevas lesiones extrahepáticas.





1. Reig M, et al. Hepatol 2013. Dic;58(6):2023-31.

2. Bruix J, et al. Nat Rev Gastroenterol Hepatol. 2019 Oct;16(10):617-630

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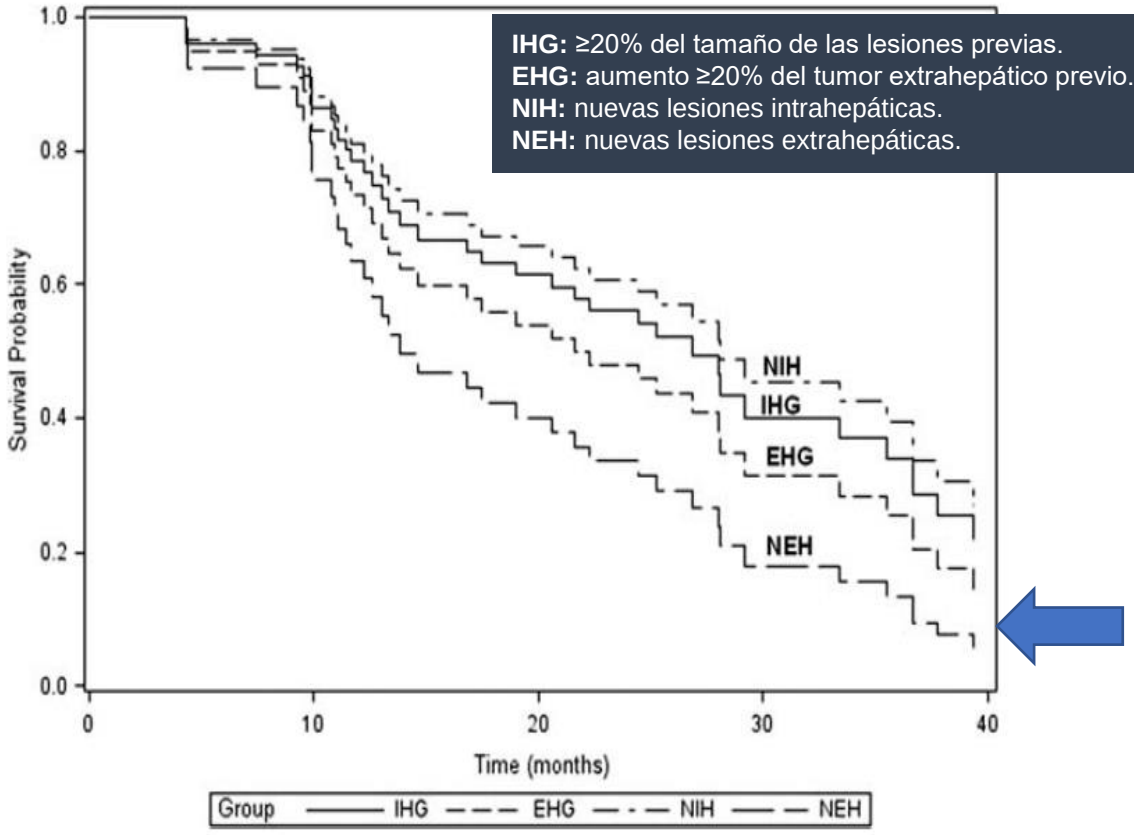

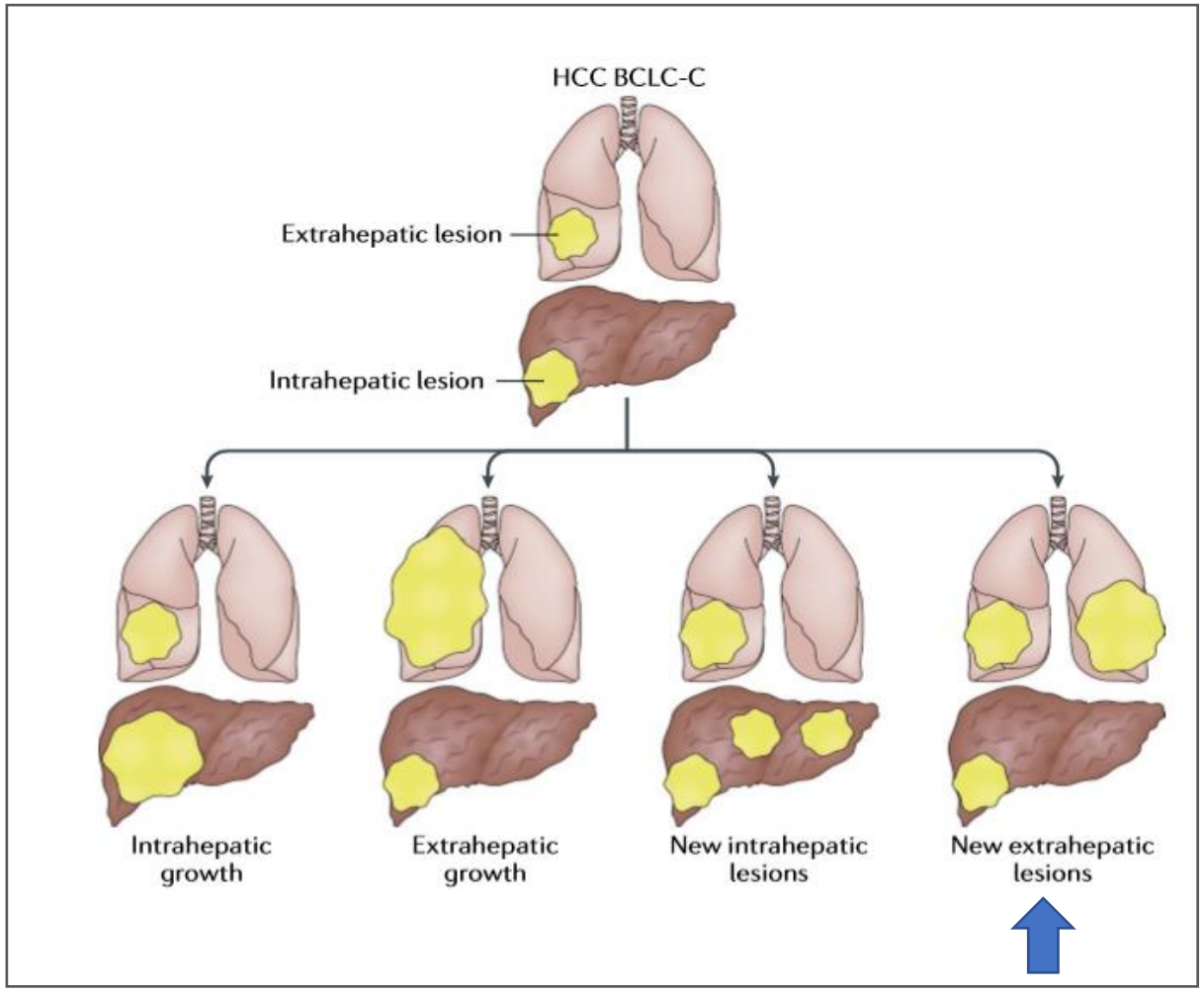

1. Reig M, et al. Hepatol 2013. Dic;58(6):2023-31.

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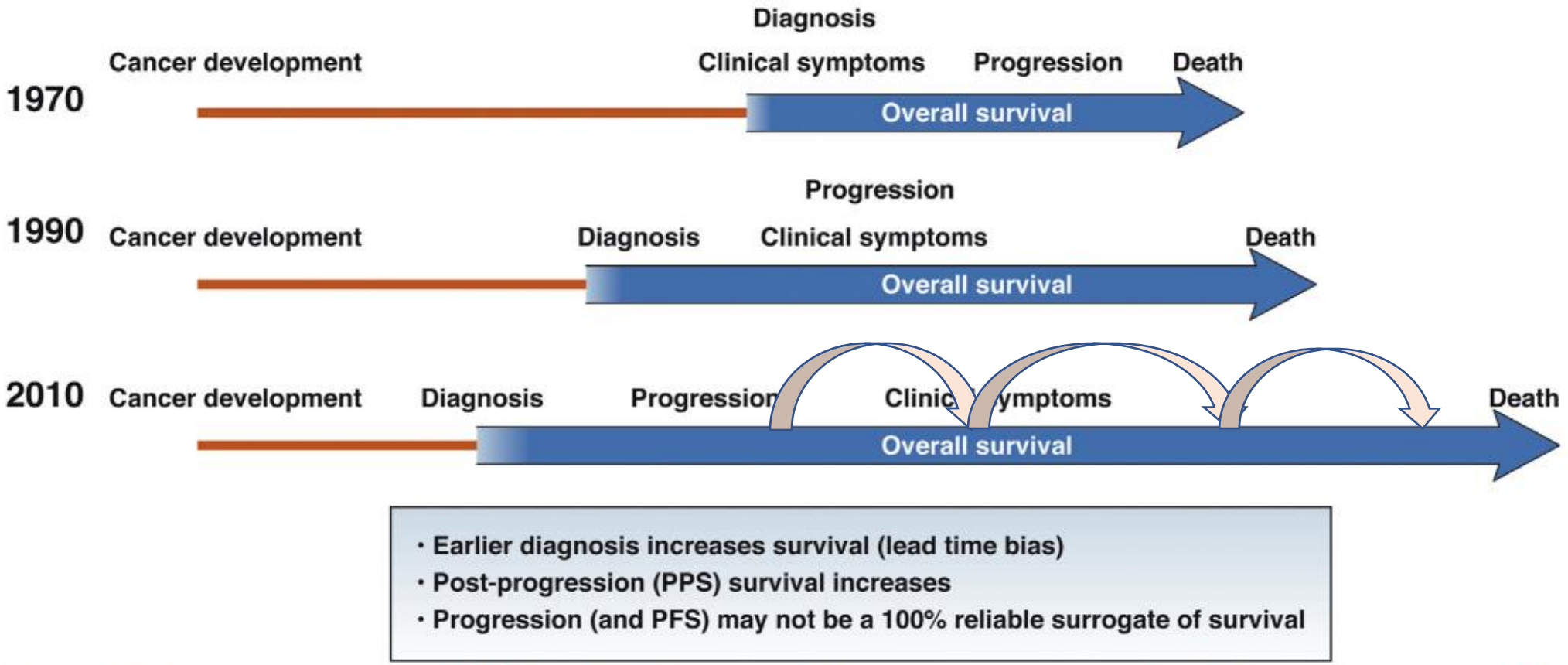
OBJETIVO terapéutico en el CHC avanzado: Supervivencia



La supervivencia de los pacientes con CHC avanzado puede mejorar optimizando el beneficio de los diferentes escalones terapéuticos en la secuencia de tto

Bruix J, et al. Gastroenterology 2016;150:835-853.

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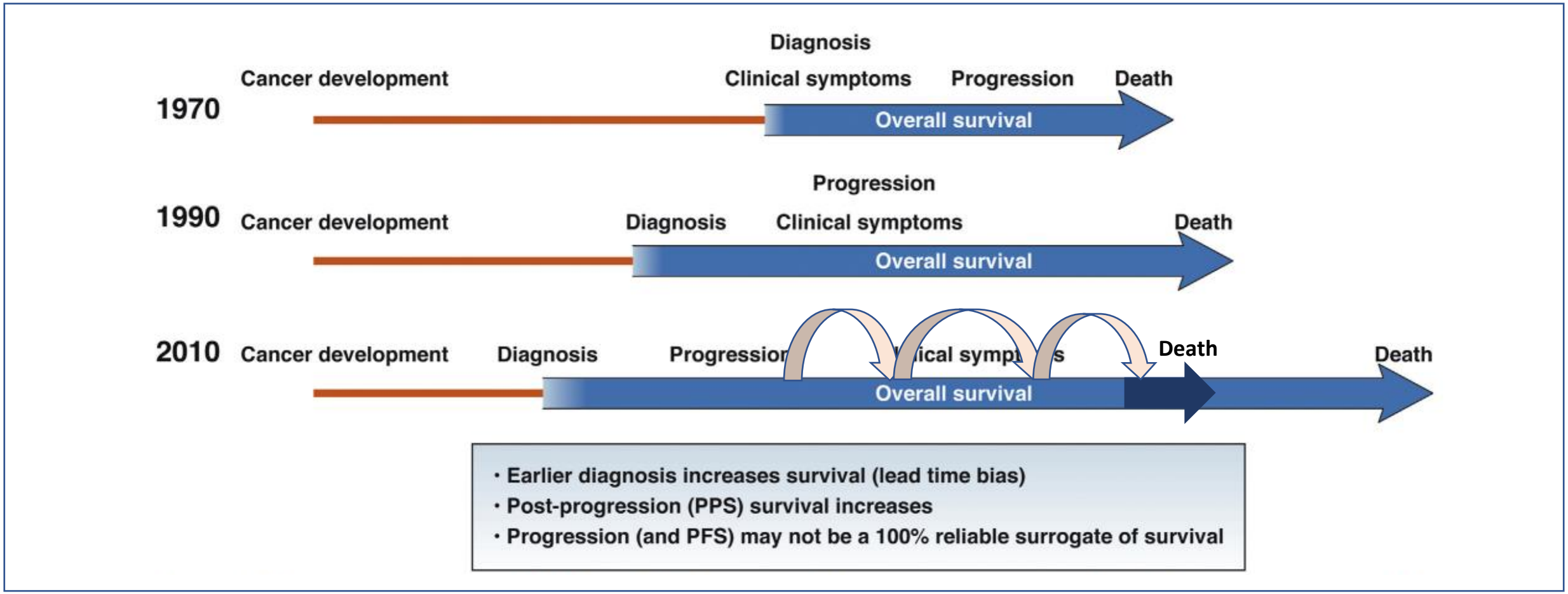

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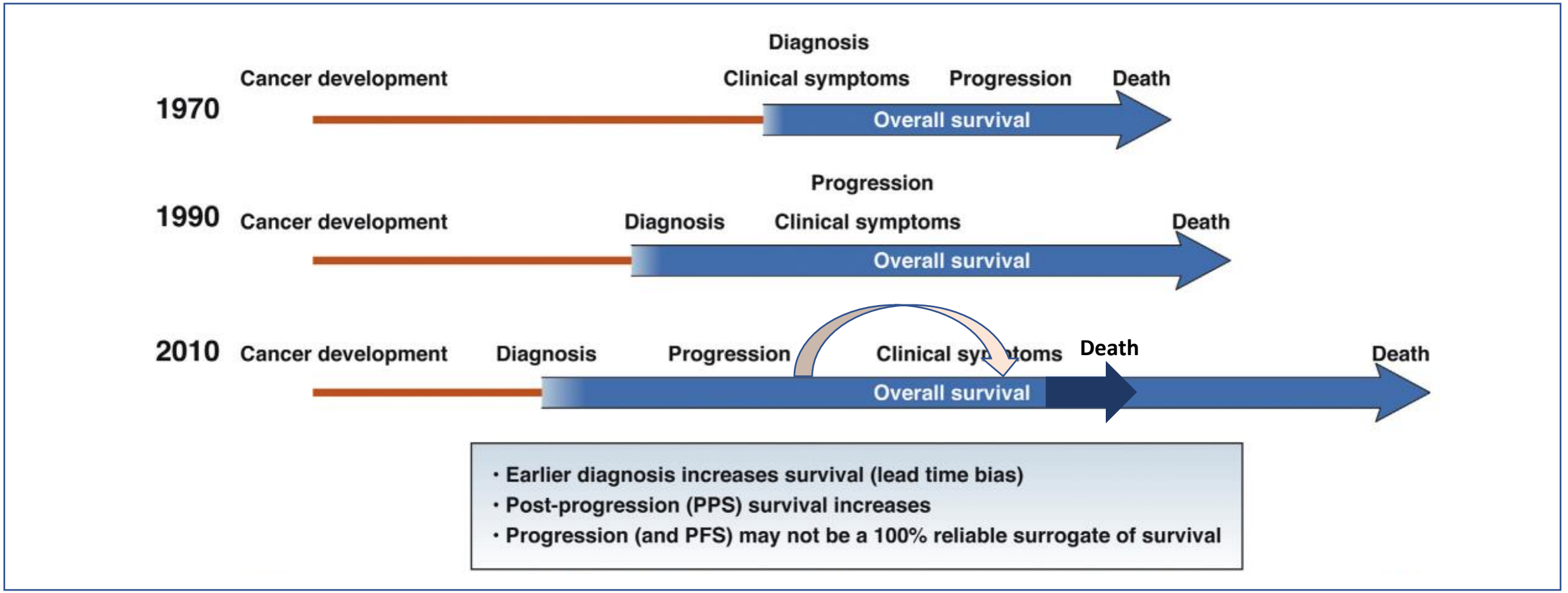

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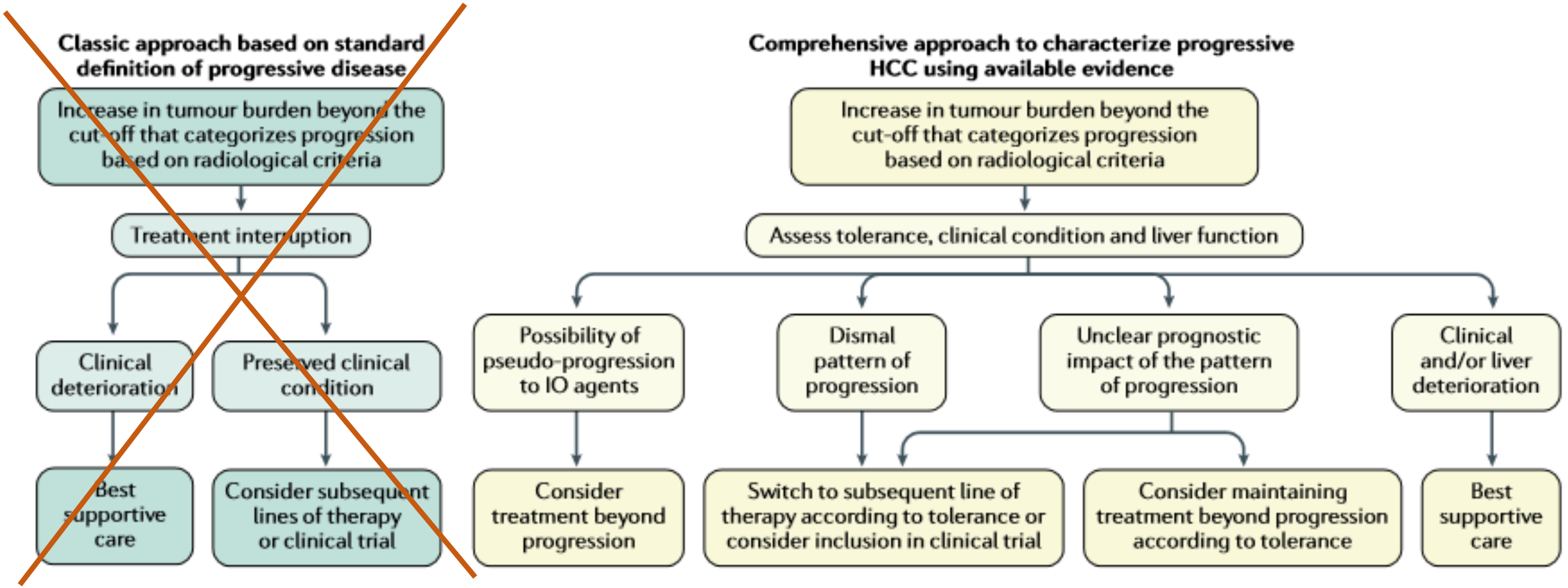
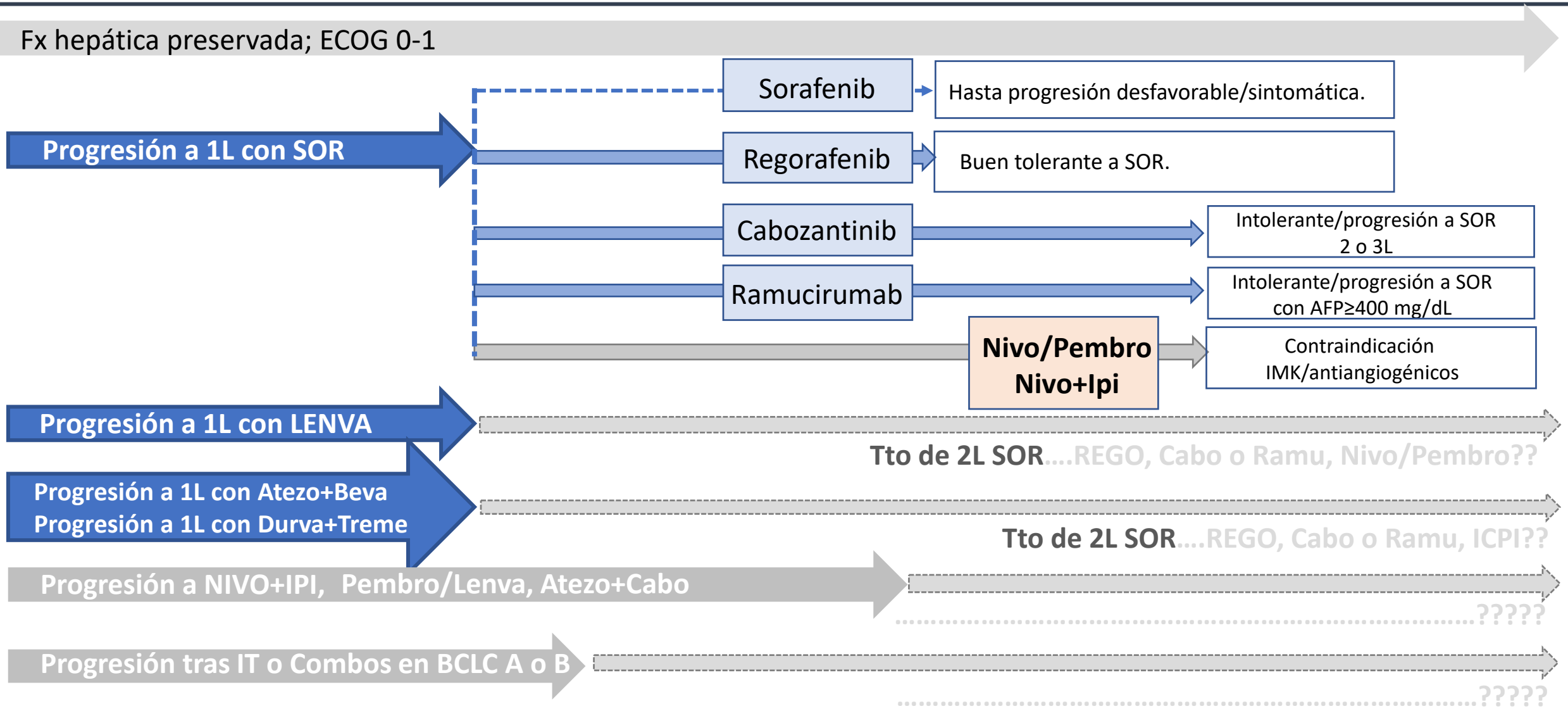
Clinical decision- making upon detection of progression at imaging according to common criteria such as RECIST 1.1



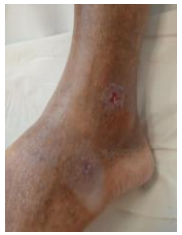
Bruix J, et al. Nat Rev Gastroenterol Hepatol. 2019 Oct;16(10):617-630

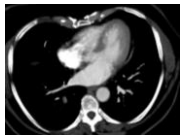
Tratamiento secuencial en el CHC: 2L



La secuencia de tto establecida para un paciente, momento del cambio y la elección del tto, va a tener impacto en el beneficio en términos de SG

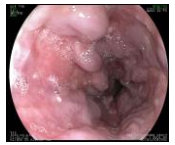
¿Cómo “elegir” la posible secuencia de tratamiento?





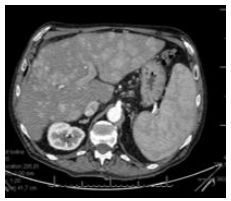
EAs más frecuentes
Seguimiento estrecho posible

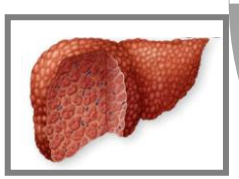
Edad
Comorbilidad
Situación socio-familiar
Posible adherencia

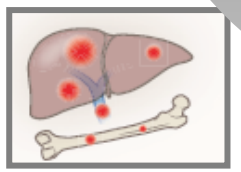


Reserva hepática funcional
Child-Pugh
Score Albi
Etiología
Presencia/tamaño de VE

Invasión portal
Infiltración biliar
Infiltración hepática >50%







EXPERIENCIA en vida real

NIVELES **AFP**

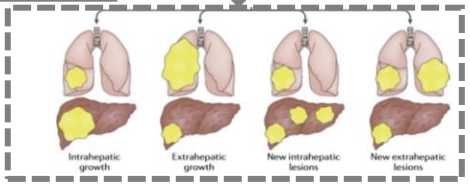
\+

Posología
Vía de administración
Necesidad de visitas
Deseo de participar en EC

Tolerancia al tto de 1L
Respuesta al tto 1L
EAs
Patrón de progresión y cuantía?

\+

EC
“Nivolumab”



En “vida real”…..

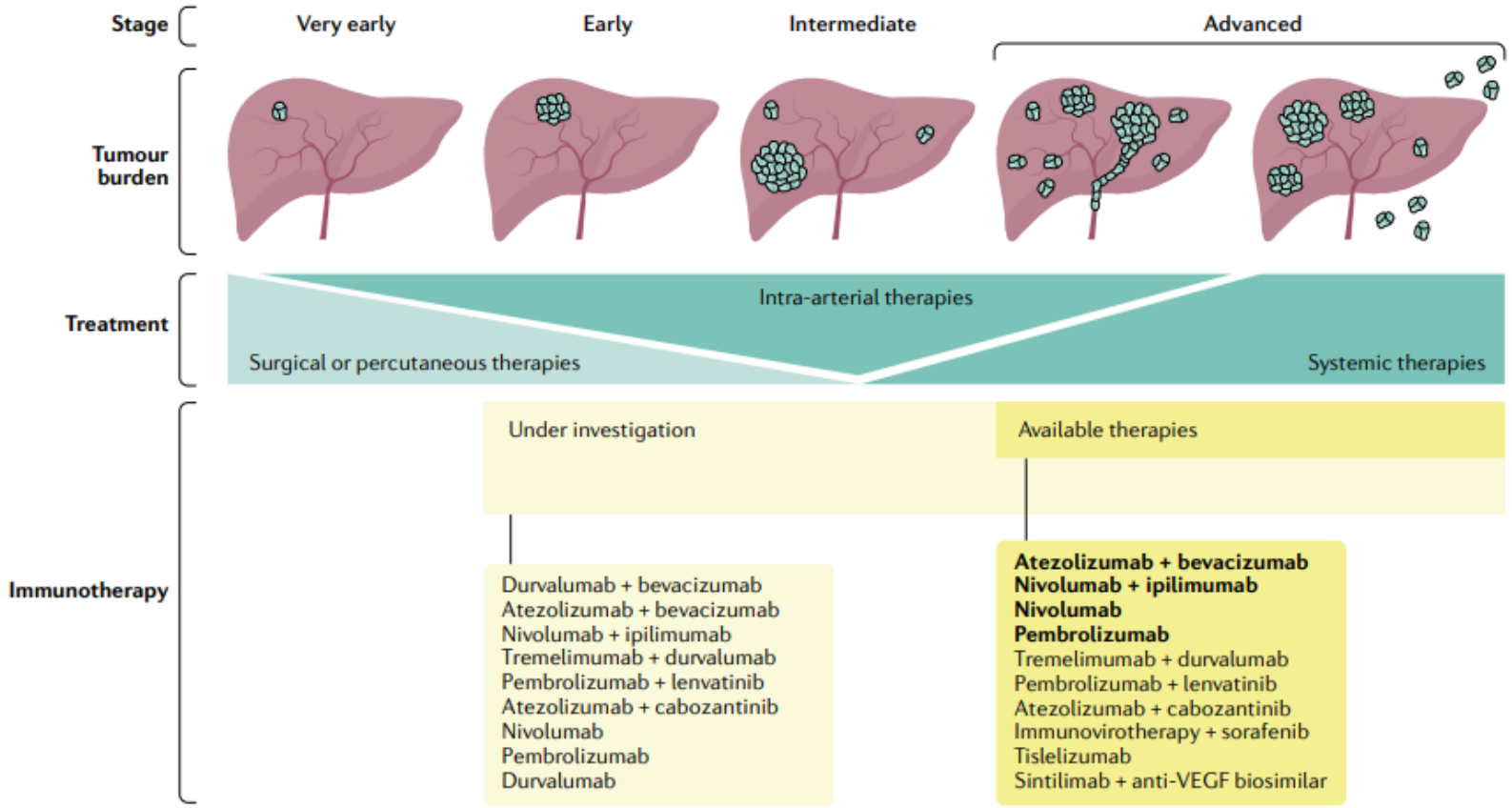
1ª
- **Atezo+Beva**
- Durva+Treme

2ª
- **Sorafenib**
- **Lenvatinib**

La combinación Durva-Treme NO tiene aprobación EMA

En esta presentación se refleja opinión personal.

Systemic treatment of HCC in 2022



Trial (NCT number)	Population under study	Therapies under comparison	Primary end points	Sample size (n)
KEYNOTE-937 (NCT03867084)	Patients with complete radiological response after resection or ablation	Pembrolizumab versus placebo	RFS and OS	950
CHECKMATE-9DX (NCT03383458)	Patients at high risk of recurrence after resection or ablation	Nivolumab versus placebo	RFS	530
EMERALD-2 (NCT03847428)	Patients at high risk of recurrence after resection or ablation	Durvalumab plus bevacizumab versus durvalumab plus placebo versus placebo plus placebo	RFS for placebo versus combination	888
IMBRAVE-050 (NCT04102098)	Patients at high risk of recurrence after resection or ablation	Atezolizumab plus bevacizumab versus active surveillance	RFS	662
Trial (NCT number)	**Population under study**	**Therapies under comparison**	**Primary end points**	**Sample size (n)**
EMERALD-1 (NCT03778957)	Candidates for first TACE	TACE plus durvalumab plus bevacizumab versus TACE plus durvalumab plus placebo versus TACE plus placebo plus placebo	PFS for placebo versus combination	710
CHECKMATE-74W (NCT04340193)	Candidates for first TACE	TACE plus nivolumab plus ipilimumab versus TACE plus nivolumab plus placebo versus TACE plus placebo plus placebo	TTTP and OS	765
LEAP-012 (NCT04246177)	Candidates for first TACE	TACE plus pembrolizumab plus lenvatinib versus TACE plus placebo plus placebo	PFS and OS	950
TACE-3 (NCT04268888)	Candidates for first TACE	DEB TACE plus nivolumab versus DEB TACE	OS (TTTP for the phase II portion)	522

030099564	**Locally advanced**	**Nivo+TARE**	**RRO**	**40**
03099564	Locally advanced	Pembro+TARE	PFS	30
04124991	Locally advanced	Durva+TARE	TTP	24
04605731	BCLC B stage	Durva+Treme +TARE	Safety RRO	32
03380130	Candidates to locoregional therapies	Nivo+TARE	Safety	41

Sangro B, et al. Nature Reviews | Gastroenterology & Hepatology 2021.
Clinical Trilals. gov

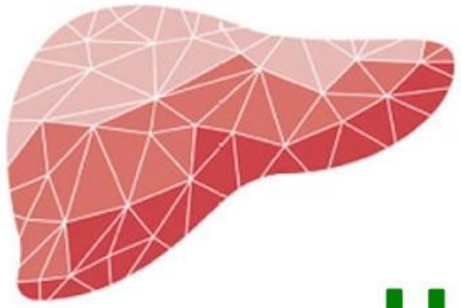
“Take-Home” Messages

- La cirrosis hepática no solo es el principal factor de riesgo para el desarrollo de CHC sino que condiciona el pronóstico y las posibilidades terapéuticas.
- Las combinaciones de A+B o D+T son actualmente el estándar de tratamiento, quedando el sorafenib y el lenvatinib para aquellos pacientes con contraindicación para la IT o para la 2L.
- La combinación de A+B tiene un buen perfil de seguridad salvo por el potencial riesgo de complicación hemorrágica en paciente con VE de riesgo o sin adecuada profilaxis primaria.
- La elección del tratamiento sistémico en 1/2 L debe considerar no solo la función hepática, estado general y carga tumoral de los pacientes, sino las comorbilidades.
- La consideración de una opción de tratamiento frente a otra debería estar basada en los CI/CE de los EC.
- La decisión de cambiar de tratamiento no debe basarse sólo en el comportamiento radiológico del tumor.
- Se recomienda contemplar el perfil de EAs e impacto de cada tratamiento según el patrón de progresión en la elección de los tratamientos de 2/3L.

MUCHAS GRACIAS

estudiosamatilla@gmail.com

MÁSTER EN HEPATOLOGÍA



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