MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

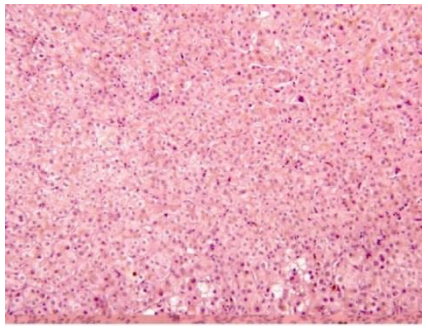
Asignatura: TUMORES HEPÁTICOS

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

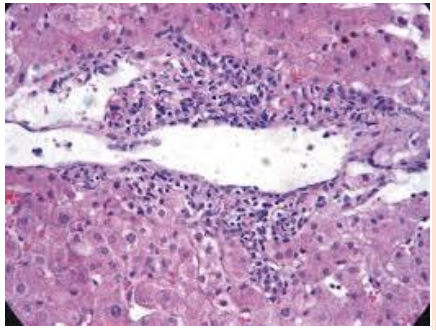
Ana María Matilla Peña

Hospital G.U. Gregorio Marañón. CIBERehd, Madrid

Carcinoma Hepatocelular: “Un tumor diferente”

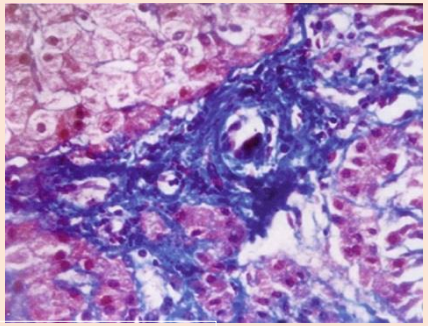


Hígado sano

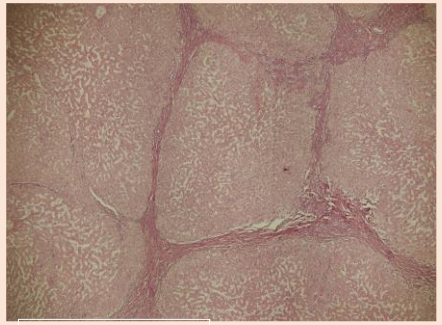


Cambios mínimos

Hepatitis crónica



Cirrosis incompleta

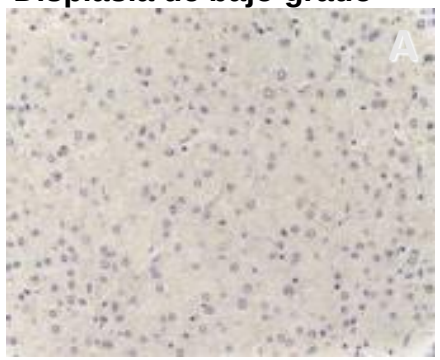


Cirrosis completa

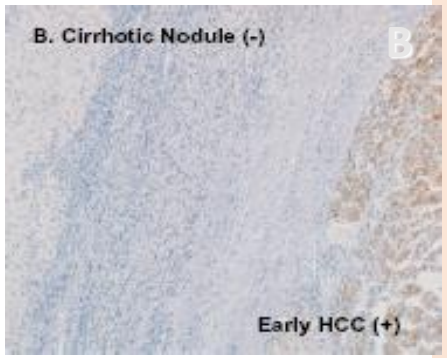
– **FIBROSIS** **+**

Etiología CHC: MAFLD | VHB | VHC y OH

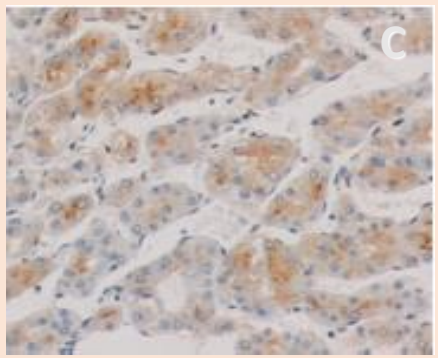
Displasia de bajo grado



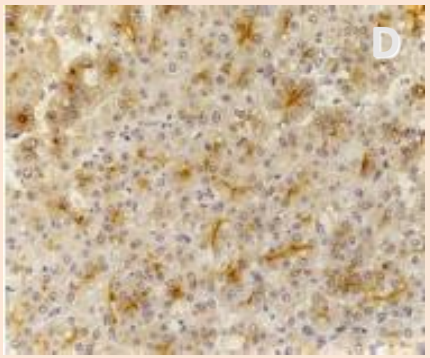
Nódulo cirrótico/ CHC



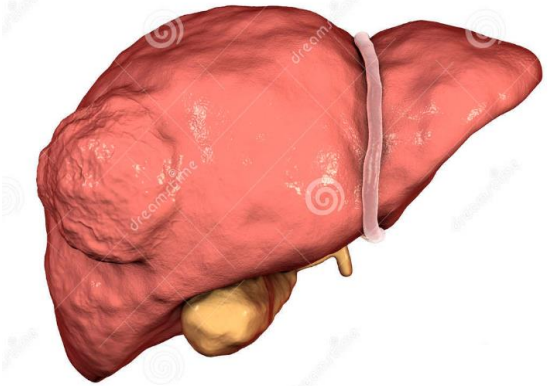
CHC Precoz



CHC avanzado



CIRROSIS



CÁNCER

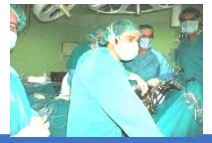
Cirrhosis and underlying liver function must be considered when making HCC treatment decisions

DESTRUCTIVE
to the tumor

CAREFULLY
with liver disease

HEPATOCELLULAR CARCINOMA

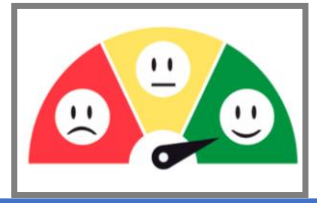
CIRRHOSIS



Limit surgical and interventional approaches to cancer treatment

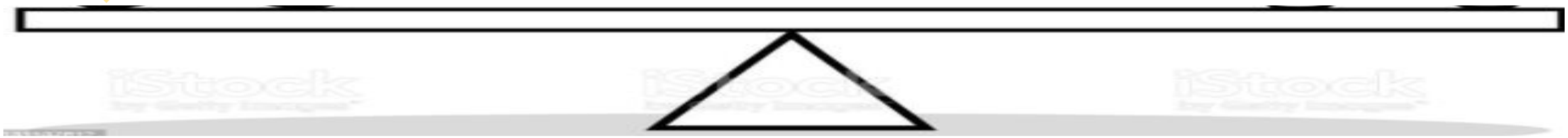
Render patients susceptible to hepatotoxicity

Influence the pharmacokinetics of anti-cancer drugs



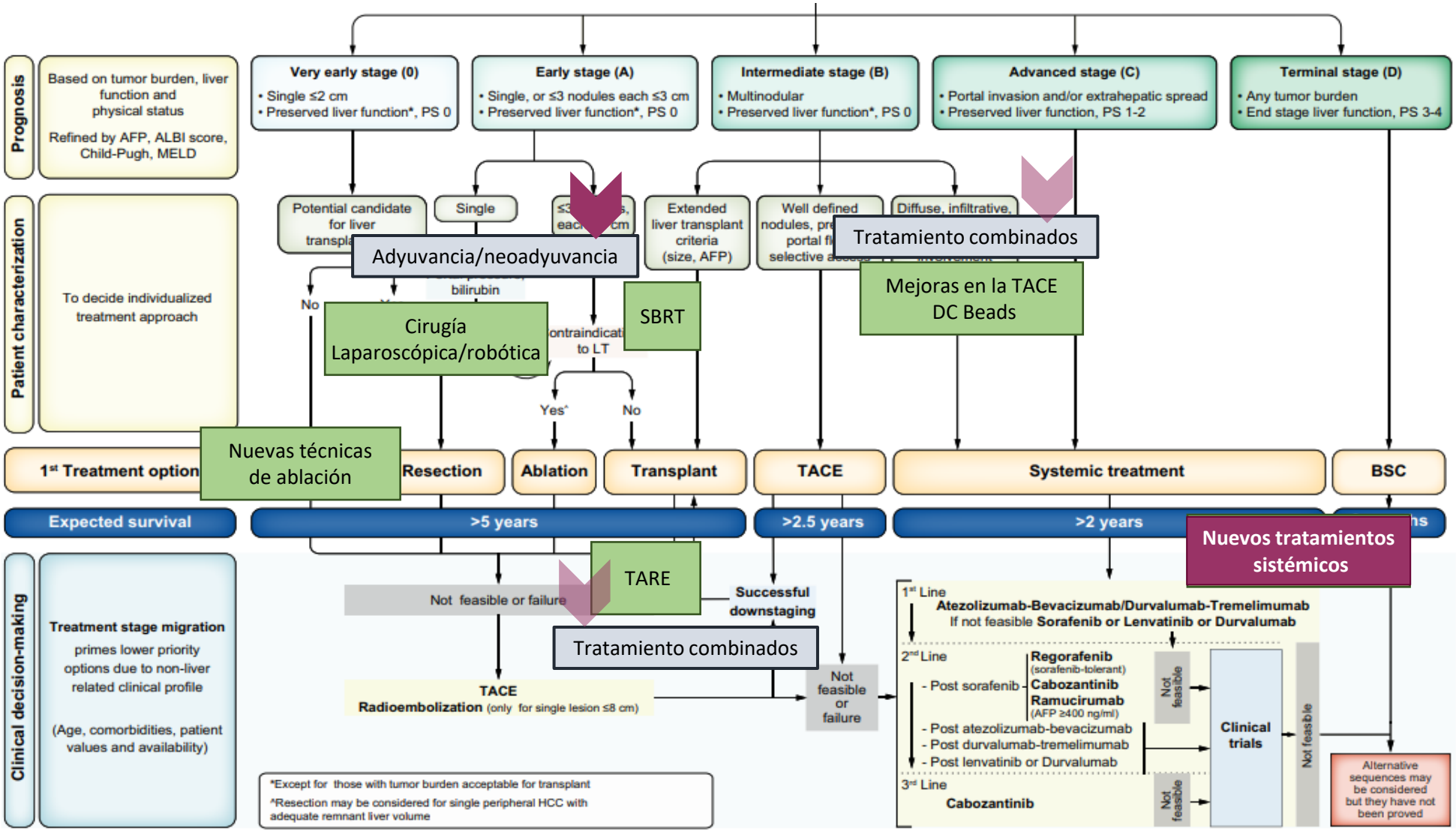
Impacts patient QoL

Conditions patient´s evolution



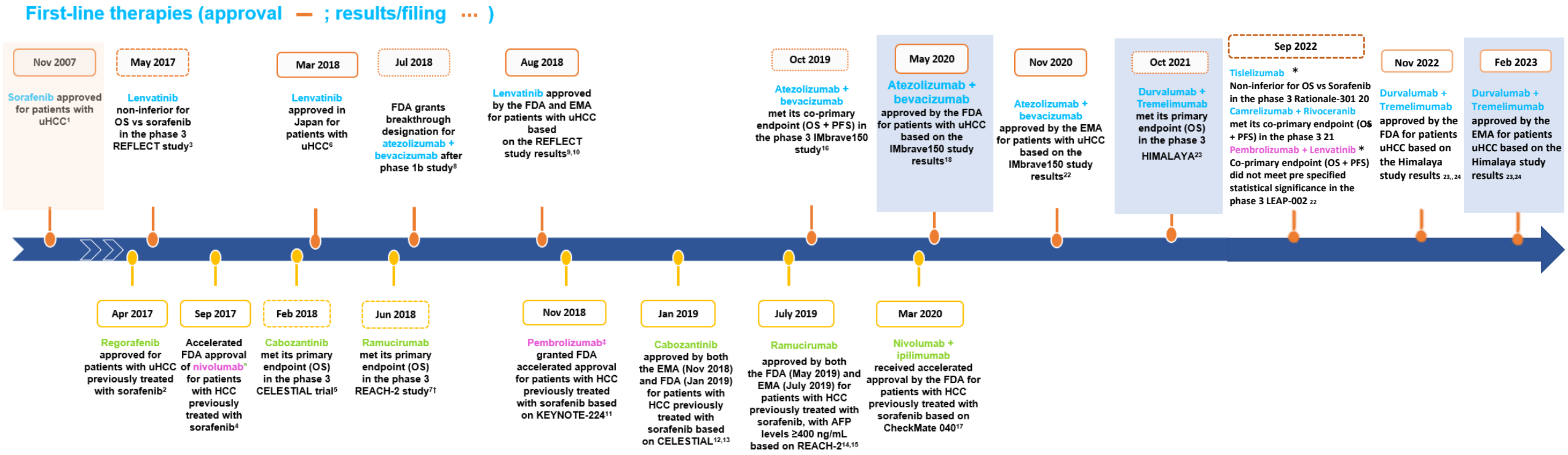
1. Pinter et al. ESMO Open 2016

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



Reig M, et al. J of Hepatol 2022; vol 76: 681–693.

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[17]; †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[18].

1 FT Sorafenib. 2 FT Regorafenib. 3 Kudo et al. Lancet. 2018. 4 El-Khoueiry et al. Lancet. 2017. 5 Abou-Alfa. N Engl J Med. 2018. 6 FT Lenvatinib 7 Zhu et al. Lancet Oncol. 2015. 8 Lee. Lancet Oncol. 2020.
9 FT Lenvatinib 10 Kudo. Eur J Cancer. 2022. 11 FT Cabozantinib 12 FT Ramucirumab 13 Finn. N Engl J Med. 2020. 14 FT Nivolumab. 15 FT Atezolizumab 16 FT Bevacizumab. 17 Yau Lancet Onclo 2022 18 Finn J Clin Oncol 2020 19 Abou-Alfa. N Engl J Med. 2022 20 Kudo Annals of Oncology 2022. 21 Qin Annals of Oncology 2022 22 Finn Annals of Oncology 2022 23 FT Durvalumab 24 FT Tremelimumab 25 Yau et al. JAMA Oncol 2020

*sin autorización EMA en CHC irresecable.

HCC May be a Candidate for Immuno-Stimulatory Therapies[1,2,3]

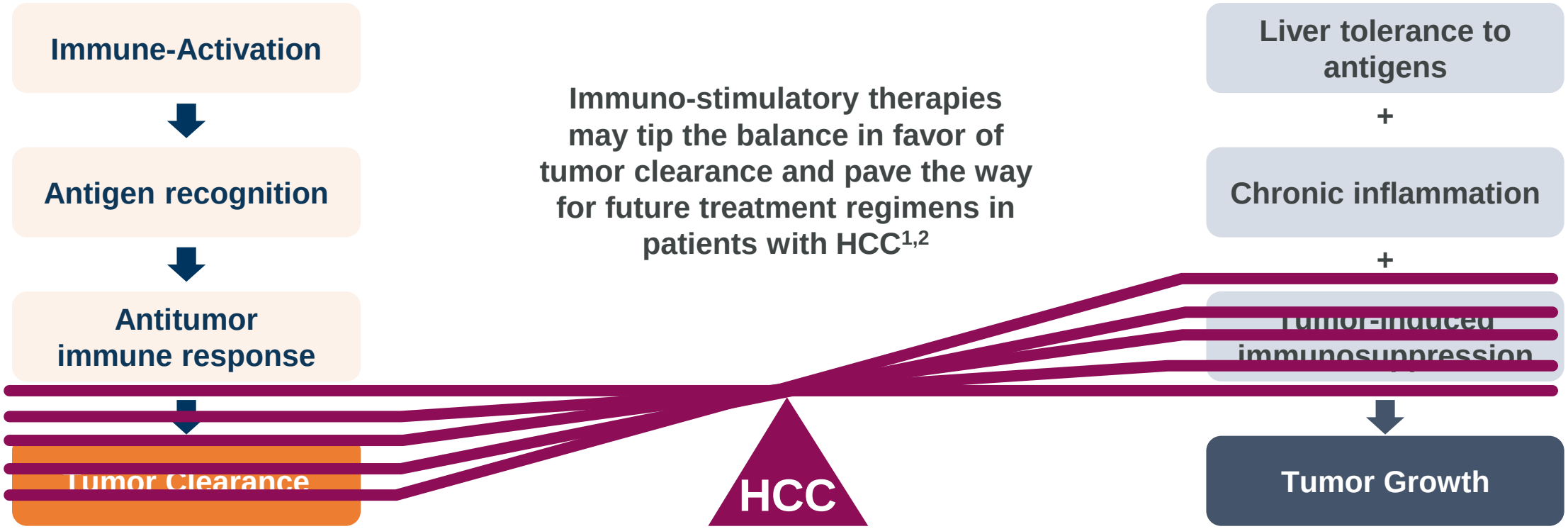


Figure adapted from Reference 3; Makarova-Rusher OV, et al, J Hepatol 2015;62:1420–1429 Copyright © 2018 Elsevier

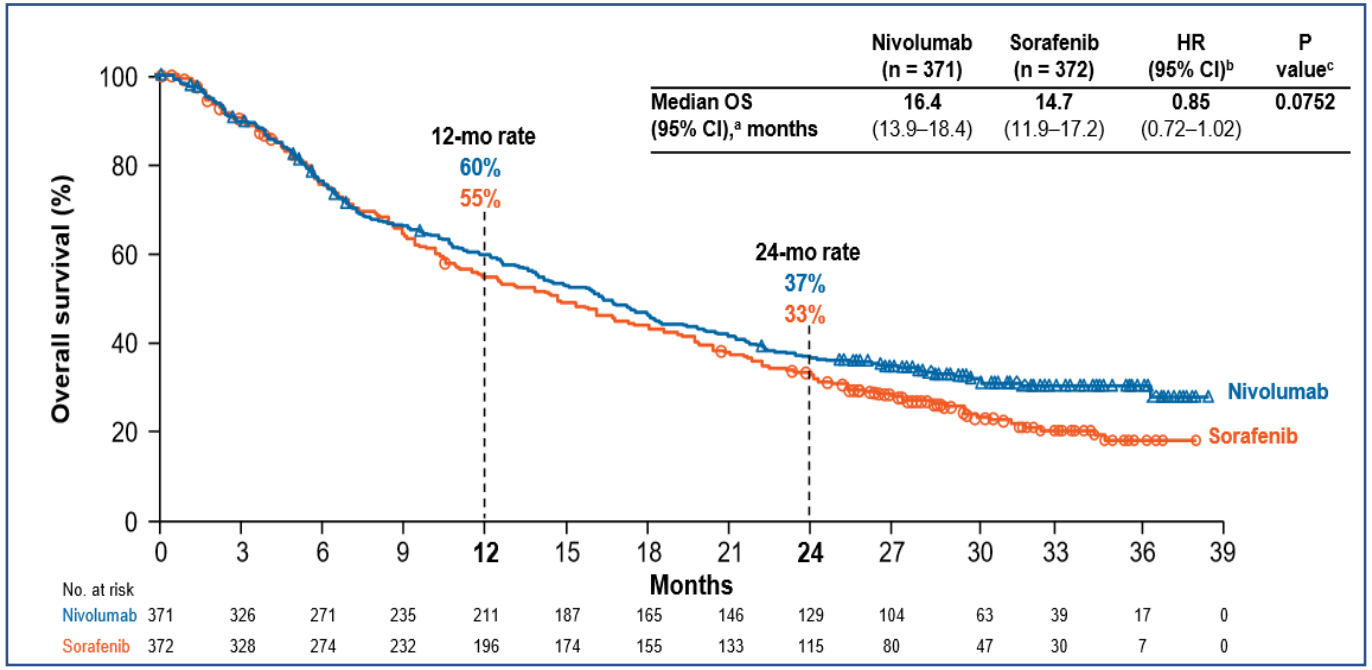
HCC = hepatocellular carcinoma.

1. Matsuzaki K, et al. *Hepatology*. 2007;46:48-57. 2. Zhang HH, et al. *J Viral Hepat*. 2010;17 (Suppl 1): 34-43. 3. Makarova-Rusher OV, et al. *J Hepatol.* 2015;62:1420–1429.

ES-18565 Abril 2022

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

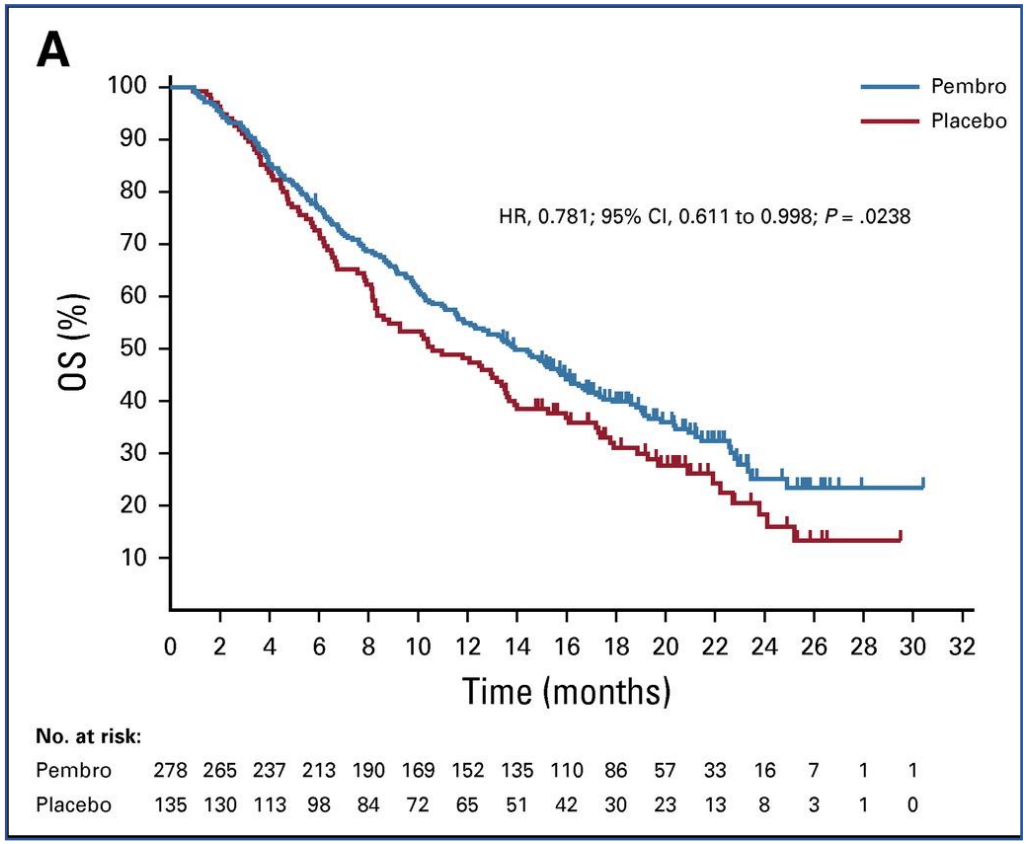
CheckMate 459 — 1 L



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.

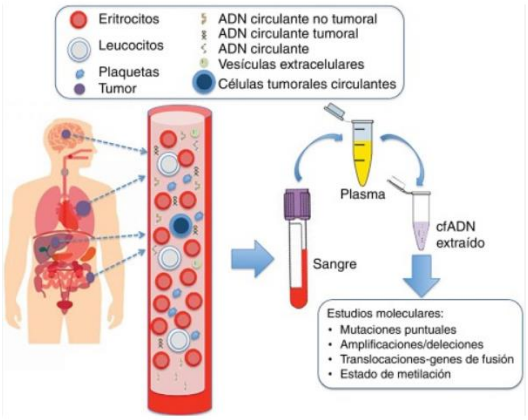
Two approaches could potentially address the lack of benefit with checkpoint inhibitors in HCC

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



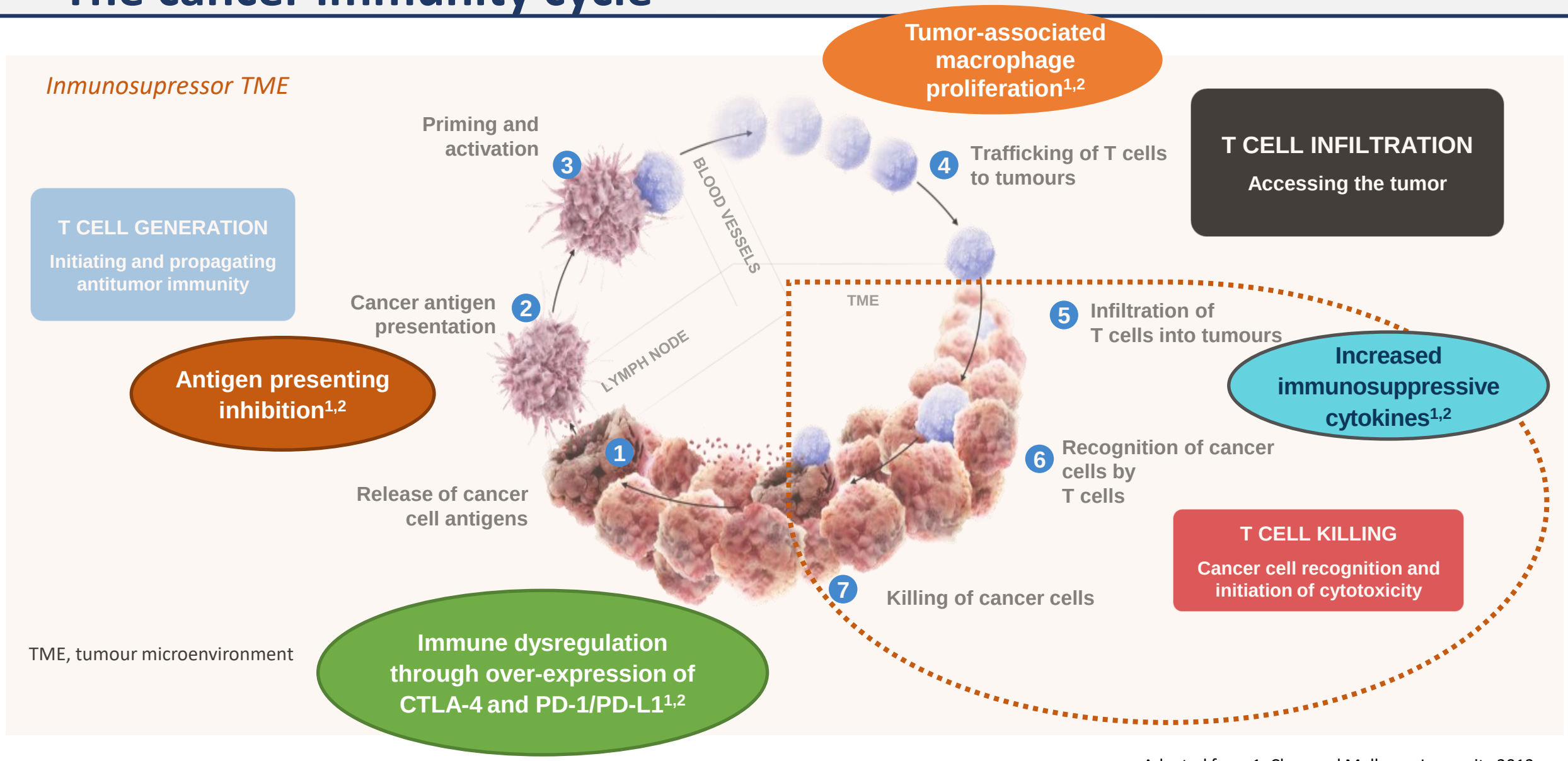
Combination treatment

Alter the tumour environment to promote tumour immune response with

- Check-point inhibitors
- Tiroxin kinasa inhibitors
- Angiogenesis inhibitors

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).
Kisiel JB, et al. Hepatology. 2019 March ; 69(3): 1180–1192. doi:10.1002/hep.30244.

The cancer immunity cycle



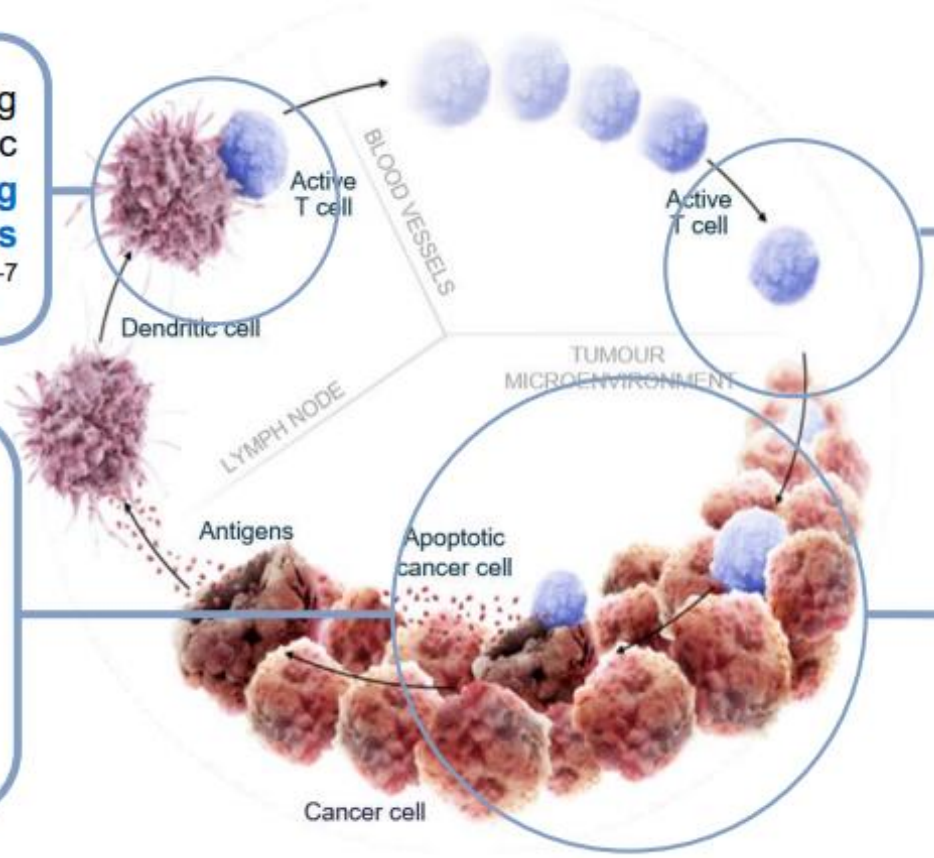
TME, tumour microenvironment

1. Sachdeva M, et al. *World J Hepatol.* 2015;7:2080–2090. 2. Harding JJ, et al. *Cancer.* 2016;122:367–377.

- 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.

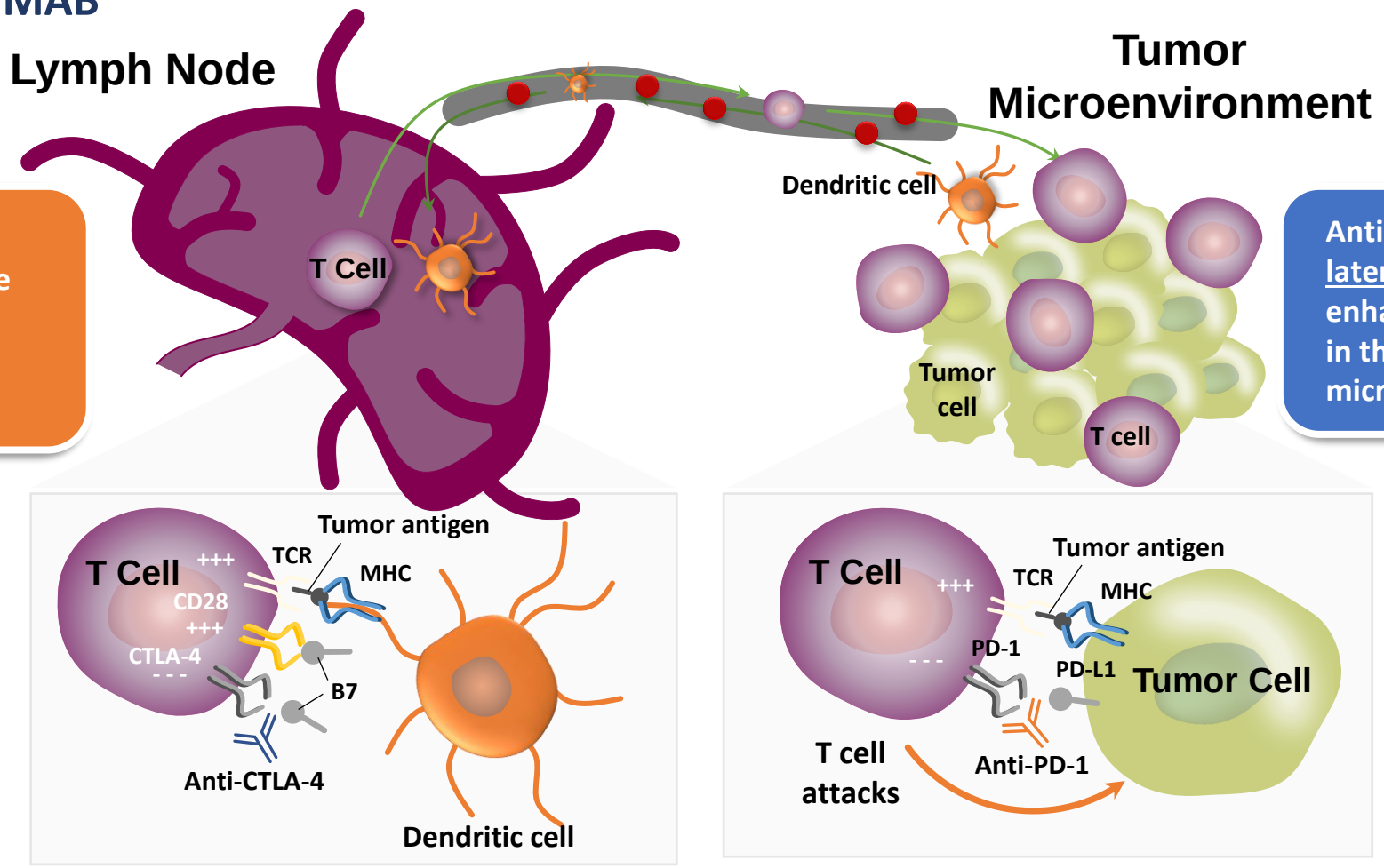
The Anti-CTLA-4 and PD-1/PD-L1 Pathways are Unique and Distinct[1]

TREMELIMUMAB

Anti–CTLA-4 therapy enhances T cell response <u>early</u> in an immune response, primarily in lymphoid tissue[2-5]

DURVALUMAB

Anti-PD-1/PD-L1 activity occurs <u>later</u> in immune response to enhance effector T cell function in the tumor microenvironment[2,6]



CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4; MHC = major histocompatibility complex; PD-1 = programmed cell death 1; PD-L1 = programmed death ligand-1; TCR = T cell receptor.

1. Carlino MS, et al. *Clin Cancer Res.* 2016;22(16):3992-3998. 2. Buchbinder EI, et al. *Am J Clin Oncol*. 2016;39:98–106. 3. Khan SK, et al. *Clin Immunol*. 2011;138:85–96. 4. Ménard C, et al. *Clin Cancer Res*. 2008;14:5242–9. 5. Stewart R, et al. *Cancer Immunol Res*. 2015;3:1052–62. 6. Barber DL, et al. *Nature*. 2006;439:682–7.

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Identify patients most likely to derive benefit

- Tumor-associated macrophages (TAMs)
- PD-L1,
- Tumorinfiltrating lymphocytes (TILs)
- Inmunoscore
- LAG3
- AFP kinetics might a potential surrogate biomarker

Combination treatment

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

- **ATEZO+BEVA**
- **DURVA+ TREME**
- Ipi+Nivo
- Atezo+Cabo
- Pembro+Lenva
- 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).
Zhu AX, et al. Abstract 0–18. Presented at: ILCA Annual Conference (Virtual) 11–13 September 2020

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

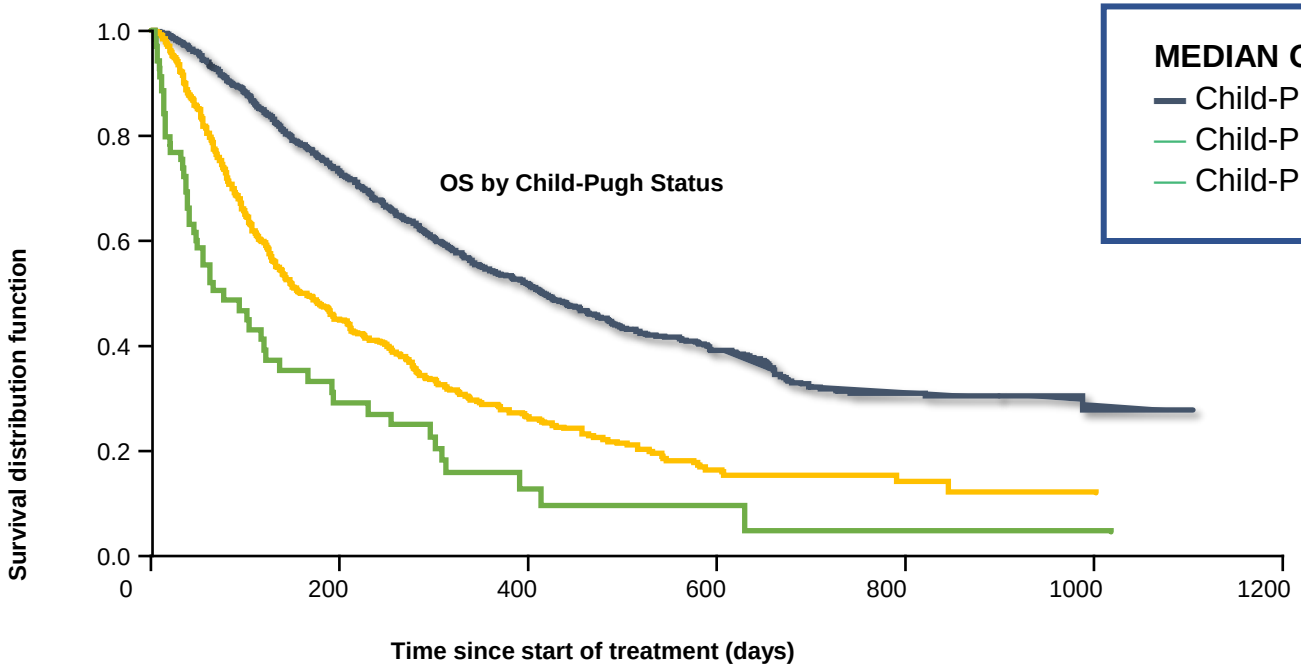
	SHARP[1]		Asia-Pacifico[2]		REFLECT[3]		IMbrave150[4]		Himalaya[5]		
	Sorafenib	Placebo	Sorafenib	Placebo	Lenvatinib	Sorafenib	Atezolizumab + bevacizumab	Sorafenib	Durva+ Treme	Durva	Sor
Criterios exclusión	NA		NA		**Invasión porta principal/Vía Biliar**		Enf autoinmune Coinfección VHB/VHC Infección 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)

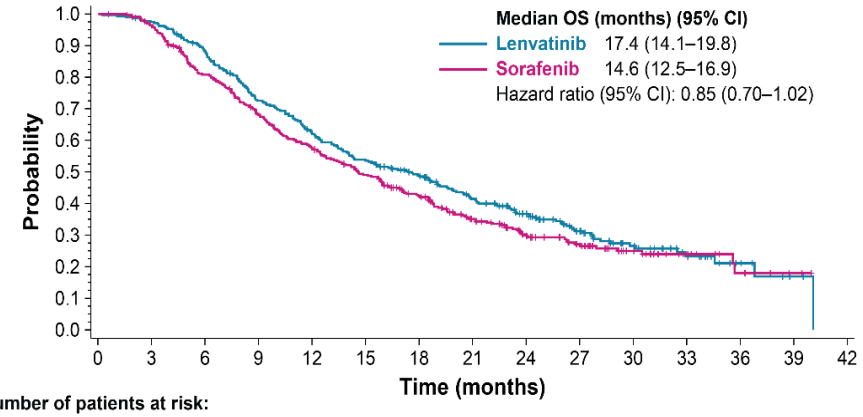
- Child-Pugh A: 13.6; 95% CI: (12.8-14.7)
- Child-Pugh B: 5.2; 95% CI: (4.6-6.3)
- Child-Pugh C: 2.6; 95% CI: (1.5-4.0)

- 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

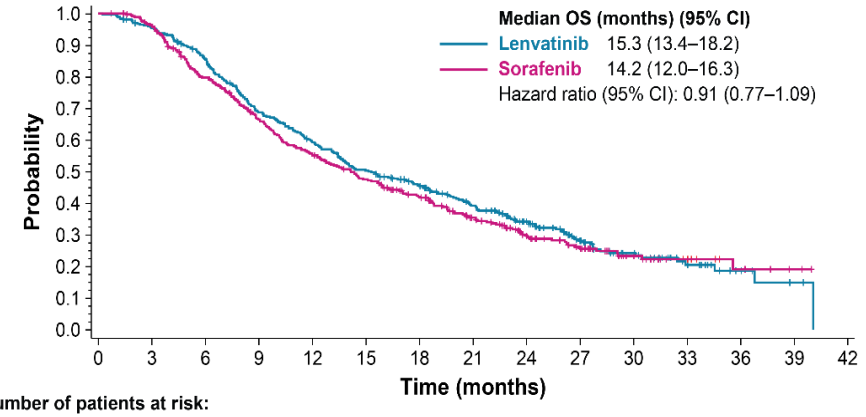
ALBI Grade 1



Number of patients at risk:

Lenvatinib	318	308	276	226	192	166	144	114	85	56	33	18	7	2	0
Sorafenib	340	324	267	223	187	159	128	94	67	46	26	13	6	2	0

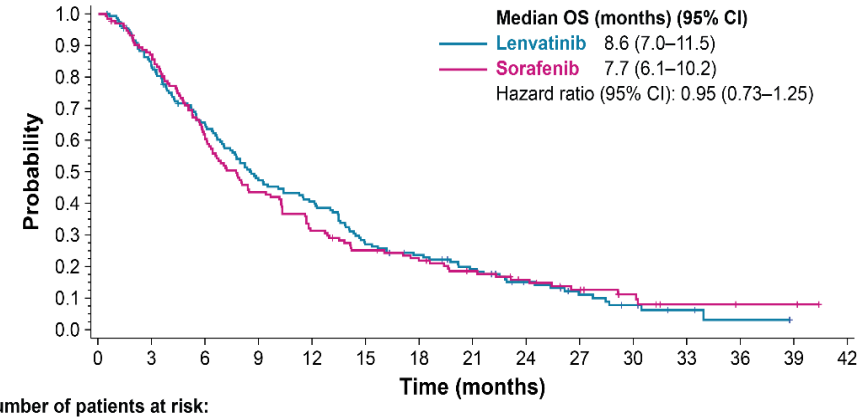
CPS-5



Number of patients at risk:

Lenvatinib	368	348	309	247	212	180	155	124	91	58	35	18	7	2	0
Sorafenib	357	340	277	229	190	162	134	100	70	46	24	12	6	2	0

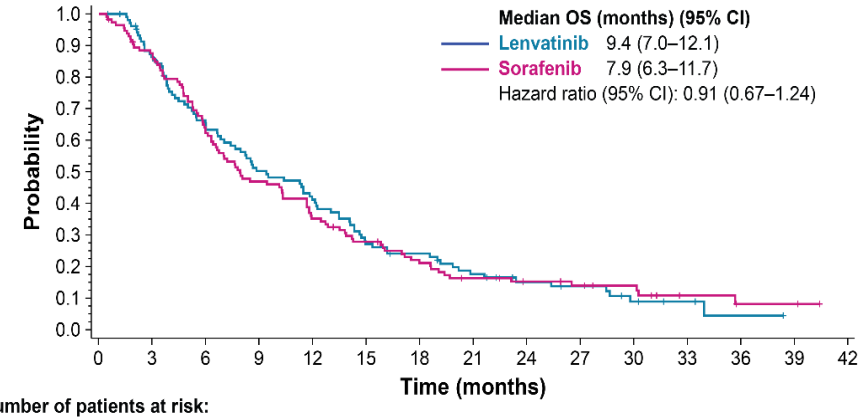
ALBI Grade 2



Number of patients at risk:

Lenvatinib	158	126	96	70	60	40	33	25	16	10	6	3	1	0	0
Sorafenib	134	114	79	57	41	32	27	21	16	11	7	3	2	2	0

CPS-6

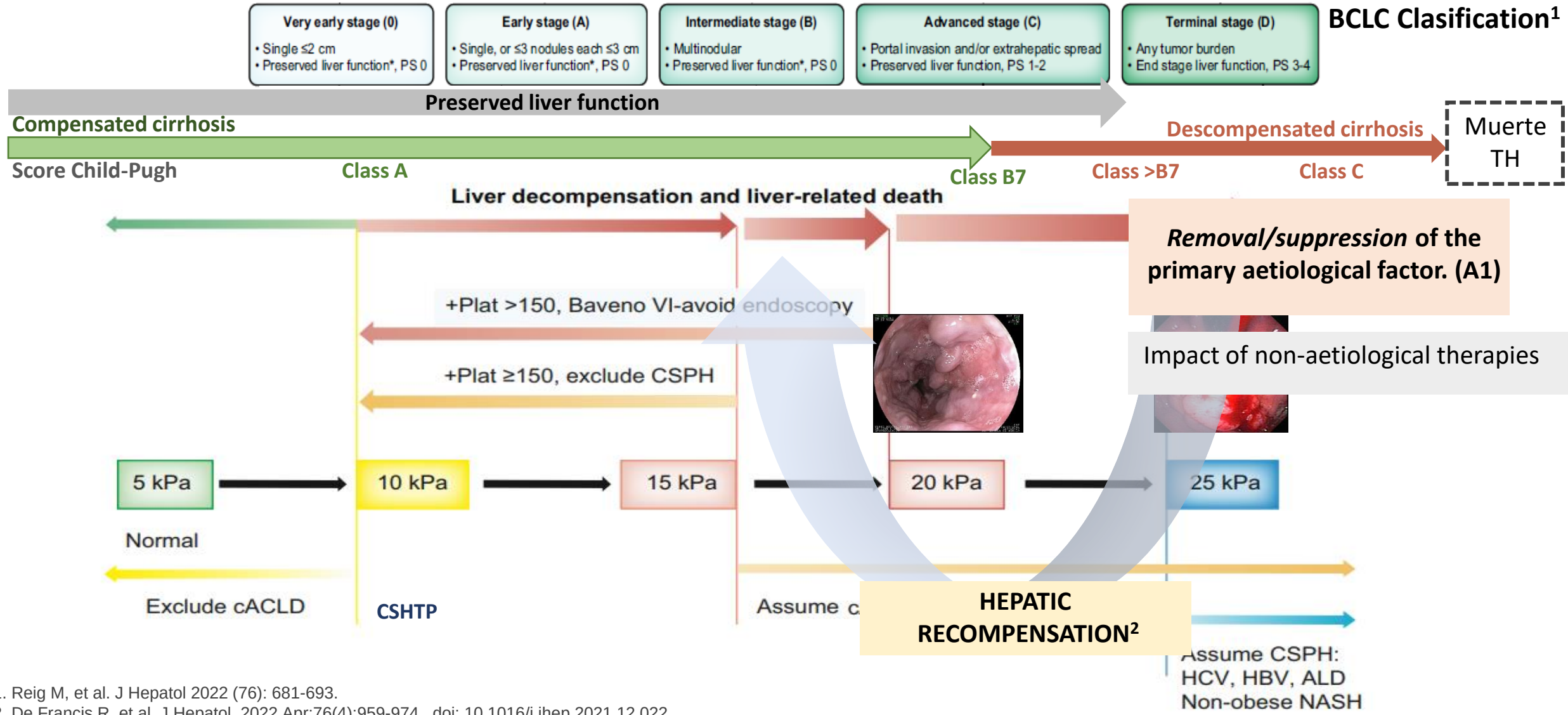


Number of patients at risk:

Lenvatinib	107	88	65	50	41	27	23	16	11	9	5	3	1	0	0
Sorafenib	114	97	69	52	39	30	22	16	13	11	9	4	2	2	0

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

The key role of liver function. "*Dynamic Concept*" of cirrhosis" and recompensation



1. Reig M, et al. J Hepatol 2022 (76): 681-693.
2. De Francis R, et al. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022.

*Sin indicación EMA en CHC irresecable.

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**						
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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.

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

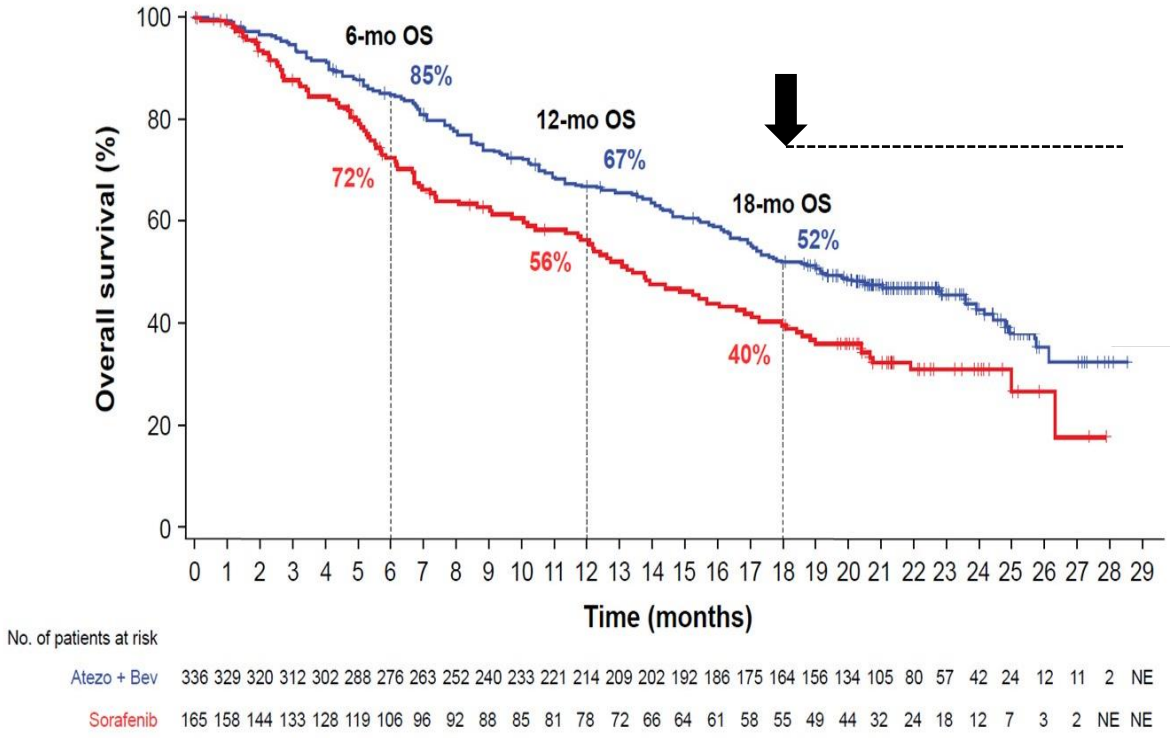
	IMbrave150 Update análisis[1]		HIMALAYA[2]		
	RECIST 1.1				
	Atezo + Bev (n = 326)	**Sorafenib** (n = 159)	**Treme 300+Durva** (n=393)	**Durva** (n = 389)	**Sorafenib** (n = 369)
Confirmed ORR (95% CI), %	**30**	**11**	**20.1**	**17.0**	**5.1**
CR, n (%)	25 (8)	1 (< 1)	12 (3,1)	6 (1.5)	0
PR, n (%)	72 (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.

Beneficio en SG a largo plazo en el CHC de los tratamientos en 1ª L

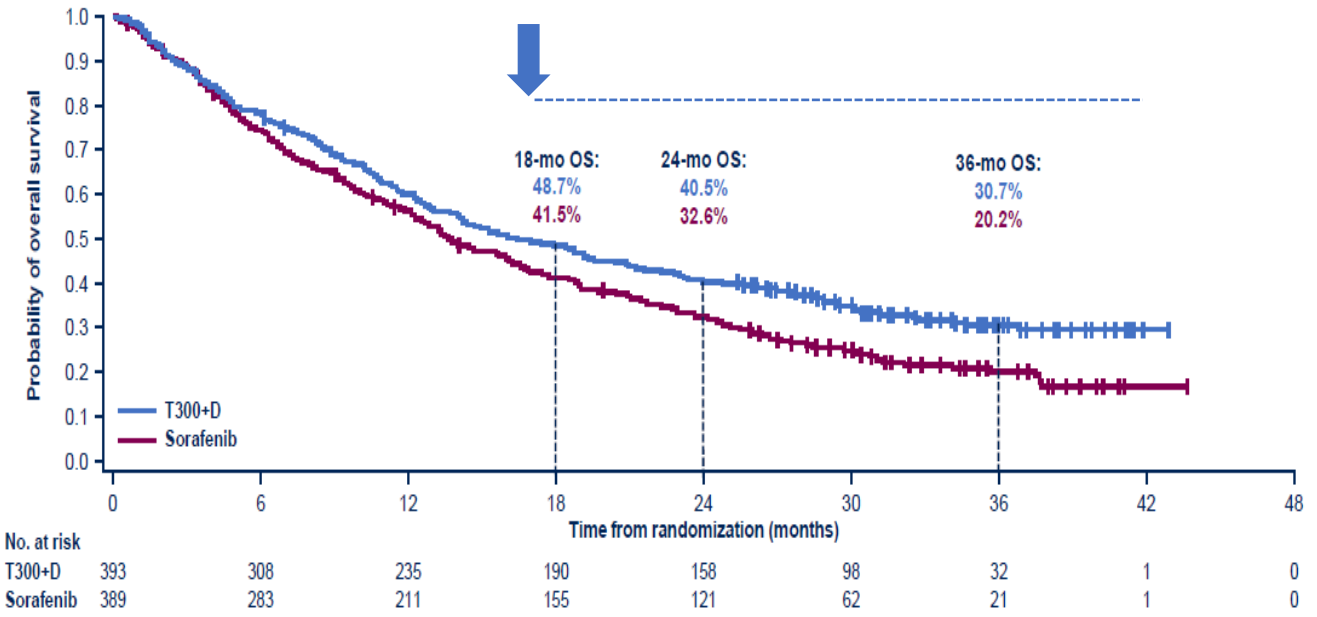
IMbrave150[1]

Clinical cutoff: August 31;2020; median follow-up 15.6 month



HYMALAYA[2]

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib



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

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

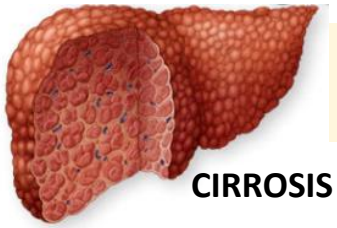
TRAE; treatment related adverse evento; b:Discontinuation of both drugs;; c: Discontinuation of Nivo due to IMAEs.

Modified from Sangro B, et al. Nat Rev Gastroenterol Hepatol. 2021 Aug;18(8):525-543

(1). Finn RS, et al. NEJM 2020;382:1894-905.
(2). Abou-Alfa GK, NEJM. Evid 2022;1:EVIDoa2100070.
(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), 47).

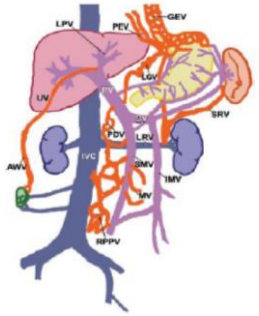
Sangrado por VE y tratamiento con antiangiogénicos

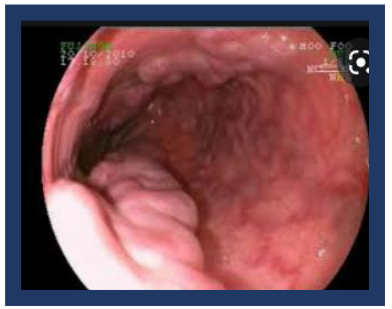
HTP en el paciente con cirrosis

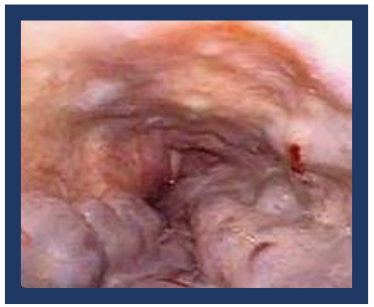


CIRROSIS

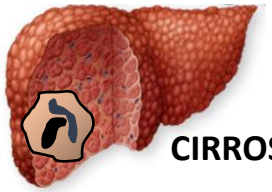
- Incidencia anual de desarrollar VE 5%[1]
- Riesgo anual de HDA por VE de 5-15%[2.]







HTP en el paciente con CHC avanzado



CIRROSIS

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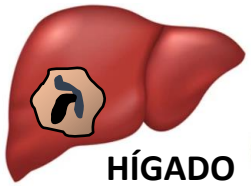
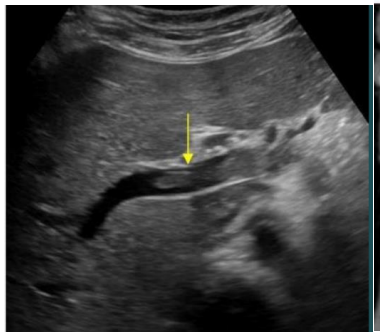
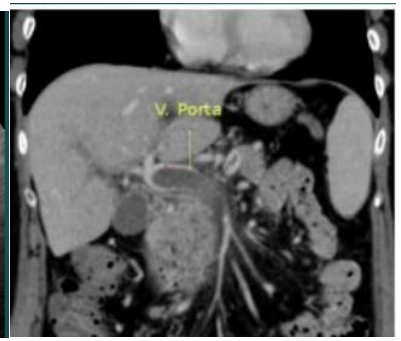


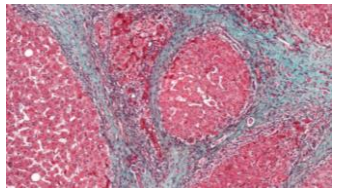
HÍGADO
SIN CIRROSIS





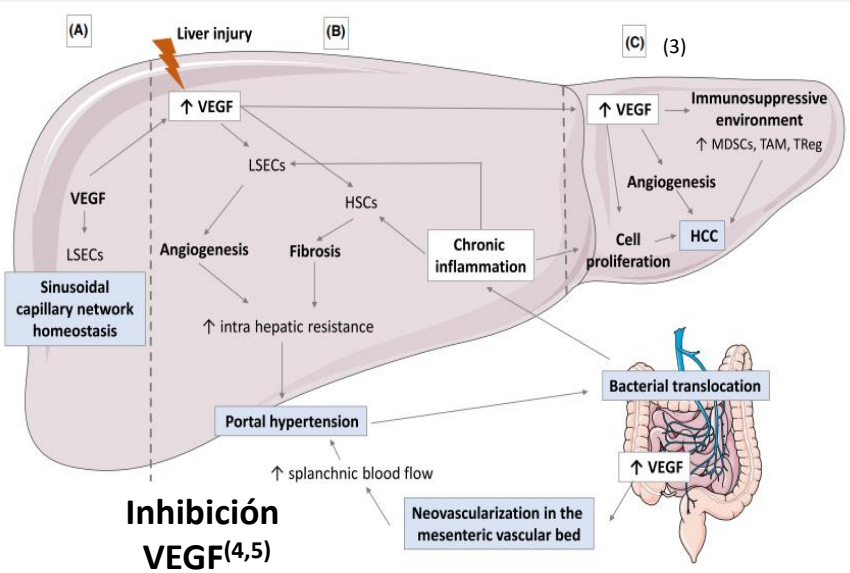
TROMBOSIS PORTAL MALIGNA

±



FIBROSIS/INFLAMACIÖN
POR EL TTO???

±



Inhibición
VEGF[(4,5)]

HTP ↑

↓ HTP

(1). Burroughs AK. J Hepatol 1993;17(Suppl 2):S10–13. (2). The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. N Engl J Med 1988;319:983–9 (3) Allaire M, et al. Liver Int. 2021 Aug;41(8):1734-1743. (4). Brusilovskaya, K., et al. Semin. Liver Dis. 39, 483–501 (2019. (5). Pinter M, et al. Aliment Pharmacol Ther 2012;35:83–91.

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

Phase II studies of bevacizumab monotherapy in HCC have shown a 10% rate of variceal bleeding[1]

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

Sangrado GI en el IMbrave150[3]: 7.5% A+B vs 5,7% Sor

	ATEZO+BEVA		SORAFENIB	
n (%)	**Todos G**	**G 3-4**	**Todos G**	**G 3-4**
Hemorragias	83 (25)	**21 (6.4)**	27(17,3)	**9(5.8)**
HDA por VE	**8 (2.4)**	6 (1.8)	**1 (0.6)**	1 (0.6)
Hemorragia GI	8 (2.4)	4 (1.2)	3 (1.9)	3 (1.9)
HDA	4 (1.2)	2 (0.6)	2 (1.3)	2 (1.3)

Safety by Risk Status in Patients

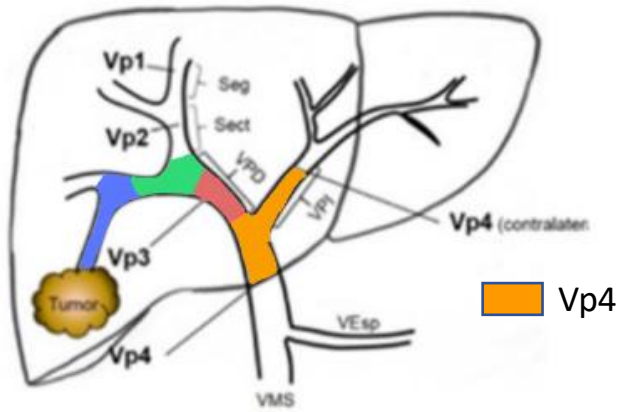
High-risk patients were defined as those who had **tumor invasion of the main trunk of the portal vein** and/or **the portal vein branch contralateral to the primarily involved lobe (Vp4)**, and/or **bile duct invasion** and/or **tumor occupancy of ≥50% of liver**

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.

[a] There were five Grade 5 upper gastrointestinal bleeding events among patients treated with atezo + bev, and all 5 patients had MVI (4 Vp4 and 1 Vp3).
[b] AE of gastrointestinal hemorrhage in patient from non–high-risk group was the only Grade 5 upper gastrointestinal bleeding event deemed related to treatment.



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. Fang P, et al. PLoS One 2012;7:e49717.
2. Finn et al. N Engl J Med 2020;382:1894-905.
3. Finn RS. IMbrave150 high-risk patients. AACR 2021 [abs #5080].

HIMALAYA: Treatment-related hepatic or hemorrhage SMQ events

Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

Event, n (%)	T300+D (n=388)		Durvalumab (n=388)		Sorafenib (n=374)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with hepatic SMQ TRAE	66 (17.0)	27 (7.0)	55 (14.2)	20 (5.2)	46 (12.3)	18 (4.8)
Patients with hemorrhage SMQ TRAE	7 (1.8)	2 (0.5)	3 (0.8)	0	18 (4.8)	6 (1.6)
Alanine aminotransferase increased	18 (4.6)	4 (1.0)	22 (5.7)			
Aspartate aminotransferase increased	22 (5.7)	9 (2.3)	25 (6.4)			
Blood bilirubin increased	6 (1.5)	1 (0.3)	6 (1.5)	0	10 (2.7)	2 (0.5)
Ascites	1 (0.3)	0				
Hepatic encephalopathy	0	0				
International normalized ratio increased	4 (1.0)	1 (0.3)				
Esophageal varices hemorrhage	0	0	0	0	0	0

SHARP[2]:
Severe bleeding: 9% Sor vs. 13% Placebo.
Variceal bleeding: 2% Sor vs. 4% Placebo.

IMbrave150[3]:
Sangrado GI en el IMbrave150[3]: 7% A+B vs 4.5% Sor.
Variceal bleeding 2,4% A+BE vs. 0.6 Sor.

Includes adverse events with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Treatment-related was as assessed by investigator.

SMQ, Standardized MedDRA Query; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TRAE, treatment-related adverse event.

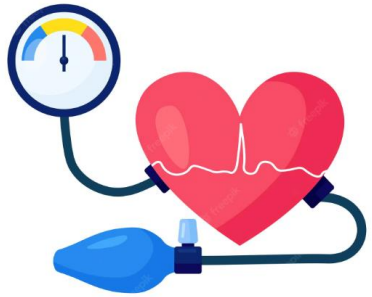
T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

How many patients had cirrhosis and cirrhosis with CSPH ?

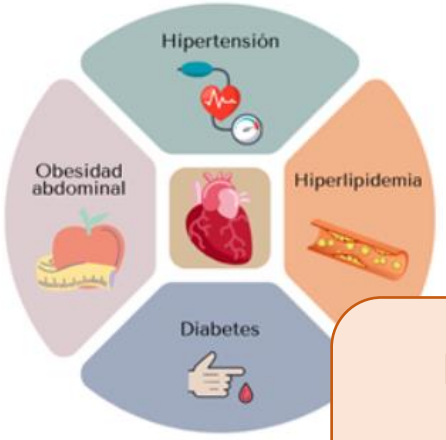
1. Abou-Alfa GK, et al. ASCO Gastrointestinal Cancer Symposium GI 22.

“RIESGO CARDIOVASCULAR” en los pacientes con CHC en España[1]

¡Alto riesgo cardiovascular!



Varón de 51-75 años
Raza blanca
OH/EHDG
HTA/Obeso/DL
Fumador



Variables cuantitativas/variables categóricas	Mediana/n	Rango/%
Edad en años (n = 666)	66,8	27,4-93,8
Edad en años categorizada (n = 666)		
< 50	52	7,8
51-65	272	40,8
66-75	181	27,2
> 75	161	24,2
Sexo (n = 684)		
Hombre/mujer, % varones	559/125	81,7
Raza: blanca/negra/asiática (n = 682)	667/7/8	97,8/1/1,2
Hígado sano/hepatitis crónica/cirrosis (n = 676)	27/61/588	4/9/87
Etiología: alcohol/VHC/alcohol + VHC/EHGNA/VHB/otros (n = 659)	233/196/97/39/25/69	35,4/29,7/14,7/5,9/3,8/10,5
Child-Pugh: A/B/C (n = 622)	391/182/49	62,9/29,3/7,1
MELD (n = 628)	9	6-42
Diabetes (n = 674)	247	37
HTA (n = 672)	301	44,8
Dislipidemia (n = 671)	85	12,7
IMC en kg/m² (n = 429)	27,6	15,14-46
IMC en kg/m² (n = 429)		

Evolución EHDG: 5.8% en 2014-15 vs 2% en 2008-09, p <0.001)[1,2].

Incremento de la diabetes (38.7% 2014-15 vs 29.7% 2008-9, p=0.002).

Incremento proporción de obesos (34.4% 2014-15 vs 15.1% 208-9, p<0.001).

1. Rodríguez de Lope C, et al. *Med Clin (Barc) 2017;* Jul 21;149(2):61-71.
2. Varela M, et al. Med Clin (Barc) 2010;134(13):569-576.

“Riesgo de toxicidad CV” asociado a los inhibidores VEGF

PACIENTE

VEGFi-related cardiovascular toxicities

	HTN	HF	↑QTc	VTE	ATE	MI
Monoclonal antibodies						
Aflibercept	◉				◉	●
Bevacizumab[a]	◉	◉		◉	◉	●
Ramucirumab[a]	◉				◉	●
VEGF TKI						
Axitinib	◉	◉		◉	◉	◉
Cabozantinib	◉	●	◉	◉	◉	●
Lenvatinib	◉	◉	◉		◉	◉
Pazopanib	◉	●	◉	◉	●	◉
Regorafenib	◉	●			●	●
Sorafenib	◉	◉	●			◉
Sunitinib	◉	●	●	◉		●
Vandetanib	◉	●	◉			●

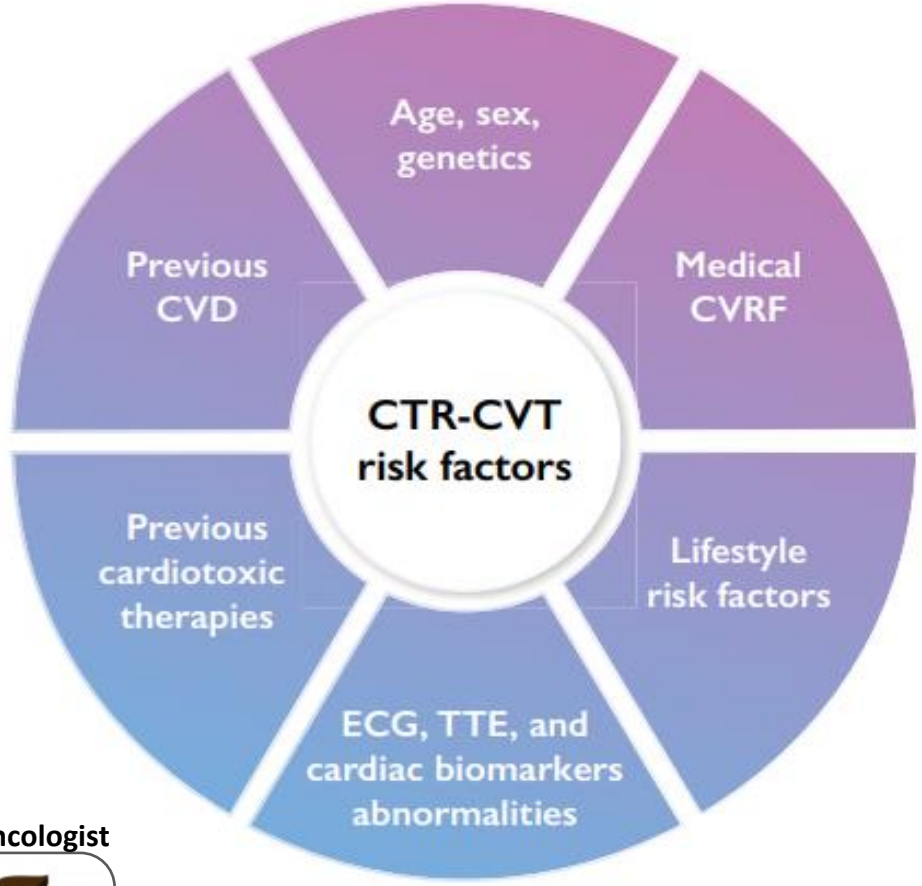
◉ Very common: ≥10% incidence
◉ Common: 1% to <10% incidence
◉ Uncommon: 0.1% to < 1% incidence
● Rare: <0.1% incidence

ESC

ATE, arterial thromboembolism; HF, heart failure; HTN, hypertension; MI, myocardial infarction; ↑QTc, corrected QT interval prolongation; VTE, venous thromboembolism. Adverse reactions reported in multiple clinical trials or during post-marketing use are listed by system organ class (in MedDRA) and frequency

Patients who experienced hypertension in pivotal trials:
- SOR 5%,
- LENVA 42%
- REGO 31%
- CABO 29%
- BEVA 31%

Baseline CV toxicity risk assessment



Cardio-oncologist

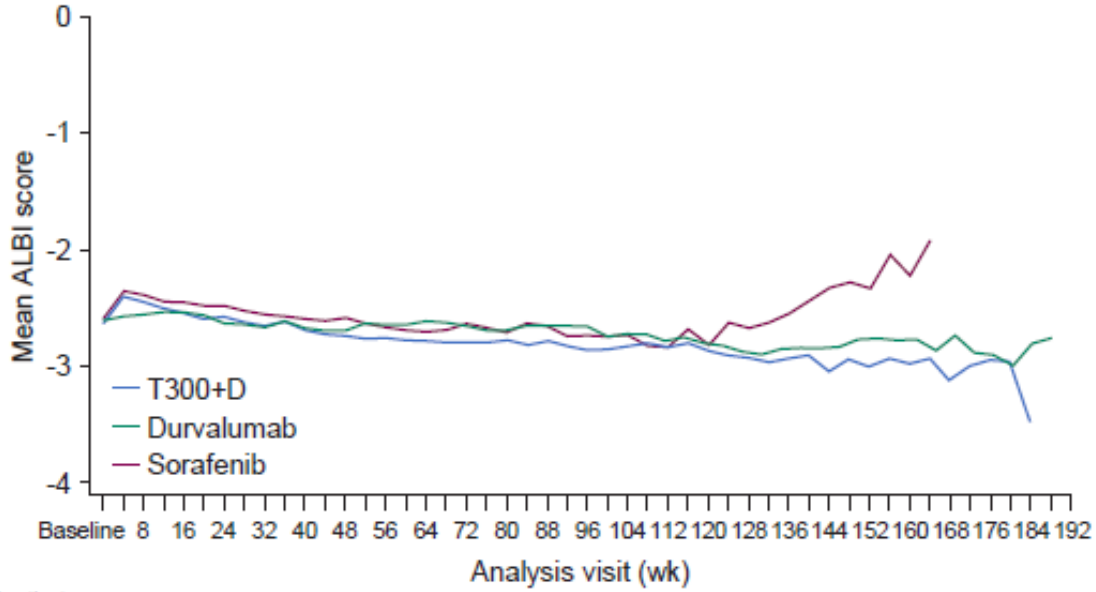
Clinical assessment
- Cancer treatment history
- CV history
- CVRF
- Physical examination
- Vital signs measurement[a]

Complementary tests
- BNP or NT-proBNP[b]
- cTn[b]
- ECG
- Fasting plasma glucose / HbA1c
- Kidney function / eGFR
- Lipid profile
- TTE[c]

Lyon Ar, et al. 2022 ESC Guidelines on cardio-oncology. European Heart Journal (2022) 43, 4229–4361

Liver function was stable over time in STRIDE and durvalumab groups

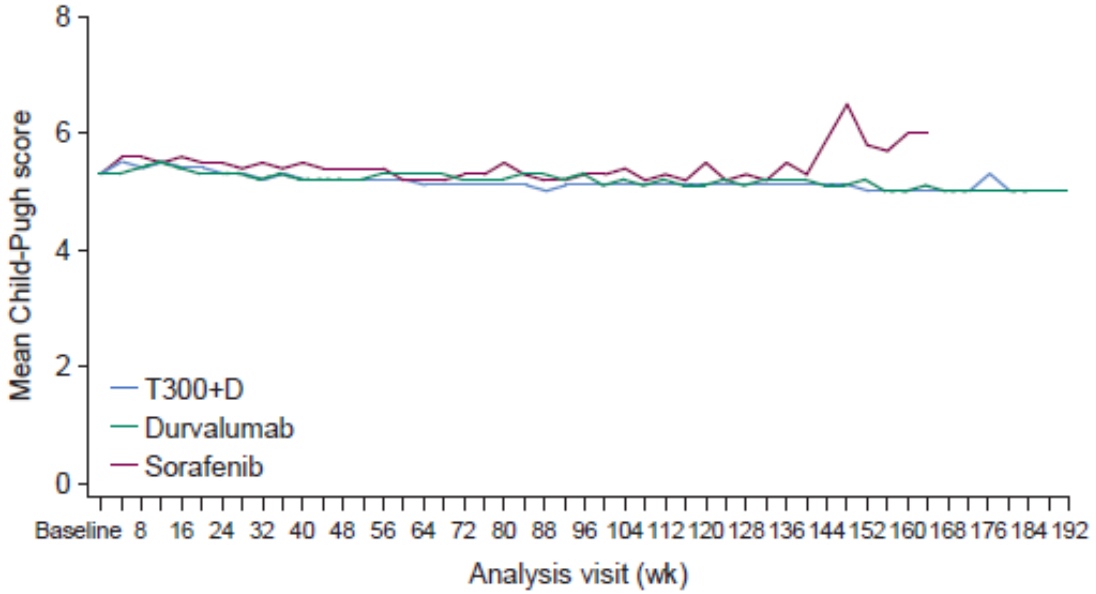
Mean ALBI score over time



Number of patients

	Baseline	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	160	168	176	184	192
T300+D	387	320	257	206	172	146	128	107	99	91	80	72	70	66	56	43	37	30	20	14	9	4	4	1	0
Durvalumab	388	331	261	189	154	125	109	98	88	78	67	60	55	50	45	38	33	23	17	12	10	6	4	2	1
Sorafenib	374	300	227	166	138	102	82	56	57	58	47	40	37	34	29	17	15	11	8	4	2	0	0	0	0

Mean Child-Pugh score over time



Number of patients

	Baseline	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	160	168	176	184	192
T300+D	387	285	240	189	163	137	119	106	97	89	76	66	69	61	55	41	36	30	18	14	9	4	4	1	0
Durvalumab	388	317	232	177	145	118	110	93	84	77	62	59	52	48	44	39	30	23	15	12	9	6	4	2	1
Sorafenib	374	289	218	156	130	99	77	56	52	50	45	37	37	34	26	18	15	10	7	4	2	0	0	0	0

Voguel A, et al. World Congress on Gastrointestinal Cancer. June 2022.

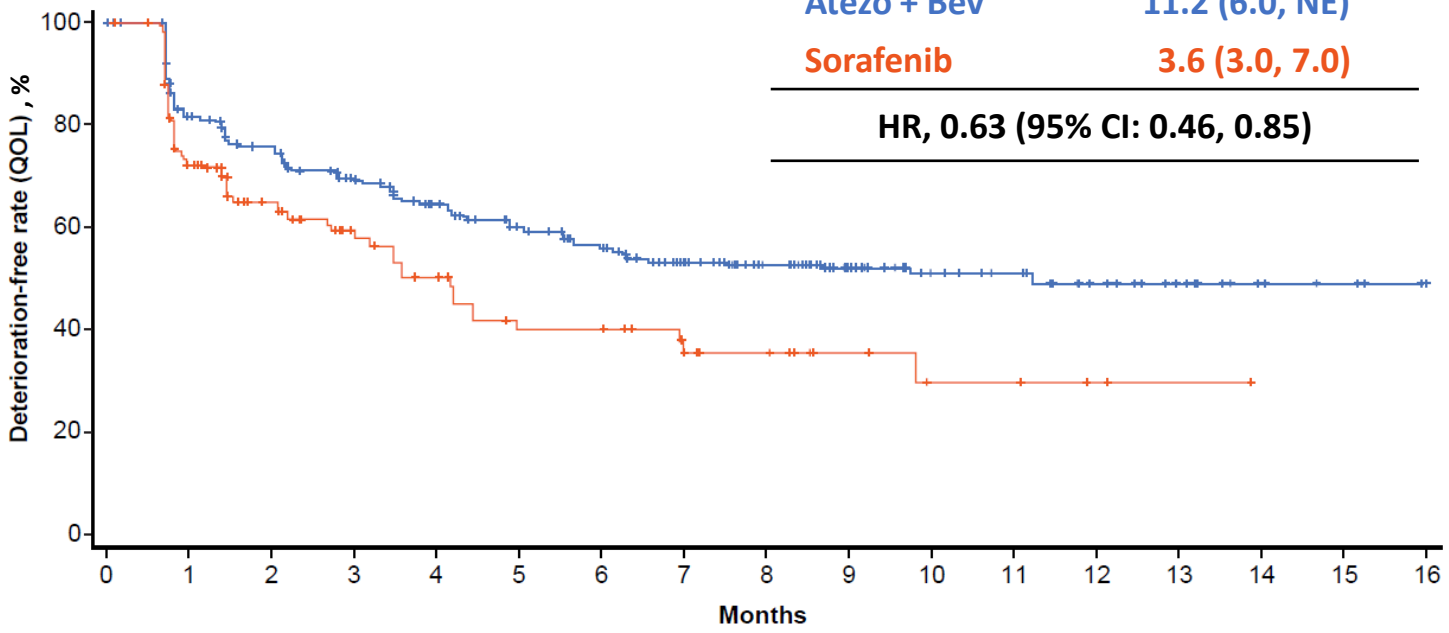
IMbrave150: Patient-reported outcomes[a]

La tasa de cuestionarios completos fue alta **(≥92%)** durante la mayor parte del periodo de tratamiento.

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

Atezo+Beva triplicó el tiempo hasta el deterioro en calidad de vida en comparación con sorafenib: 11.2 *vs* 3.6 meses[1,2,3]

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)	



No. at risk																	
Sorafenib	165	93	60	39	31	22	22	14	12	7	4	4	2	1	NE	NE	NE
Atezo + Bev	336	239	208	181	157	134	121	99	78	58	40	32	20	14	7	5	NE

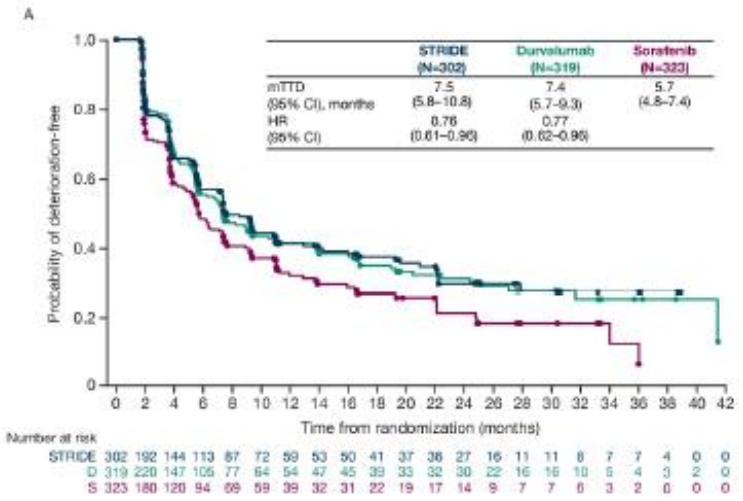
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire for Cancer; TTD, time to deterioration.
[a] Pre-specified secondary endpoint that was not formally tested; EORTC QLQ-C30 administered every 3 weeks on treatment and every 3 months after treatment discontinuation 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.

2.- ASCO GI 2020: PROs in IMbrave150 - presentado por Galle PR https://cutt.ly/pORXWrg **3.** - Galle, P. R. et al. Lancet Oncol. 22, 991–1001. https://doi.org/10.1016/S1470-2045(21)00151-0 (2021)

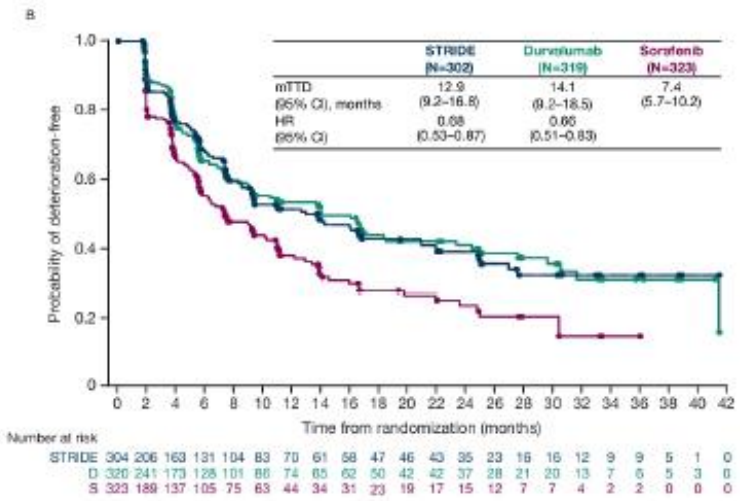
HIMALAYA: Patient-reported outcomes

Across traetment arms, compliance rates for PROs were >77% at baseline ans >72% overall.

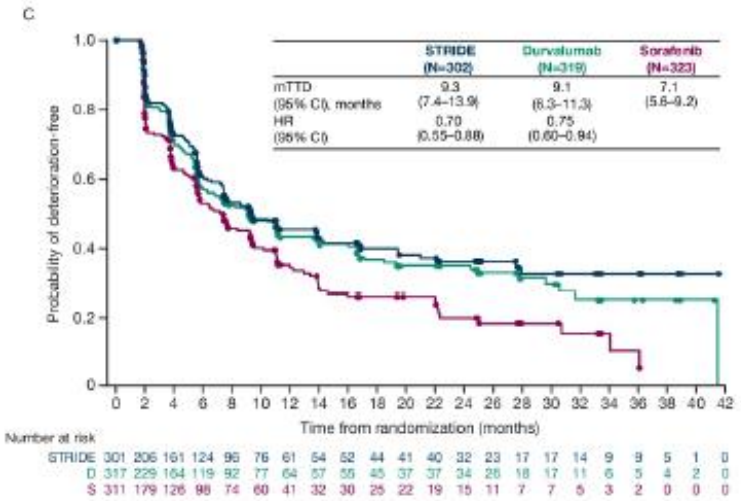
TTD in GHS/QoL



TTD in physical functioning



TTD in role functioning



HRs were calculated vs sorafenib

CI, confidence interval; GHS, Global Health Status; HR, hazard ratio; mTTD, median time to deterioration; QoL, quality of life; TTD, time to deterioration

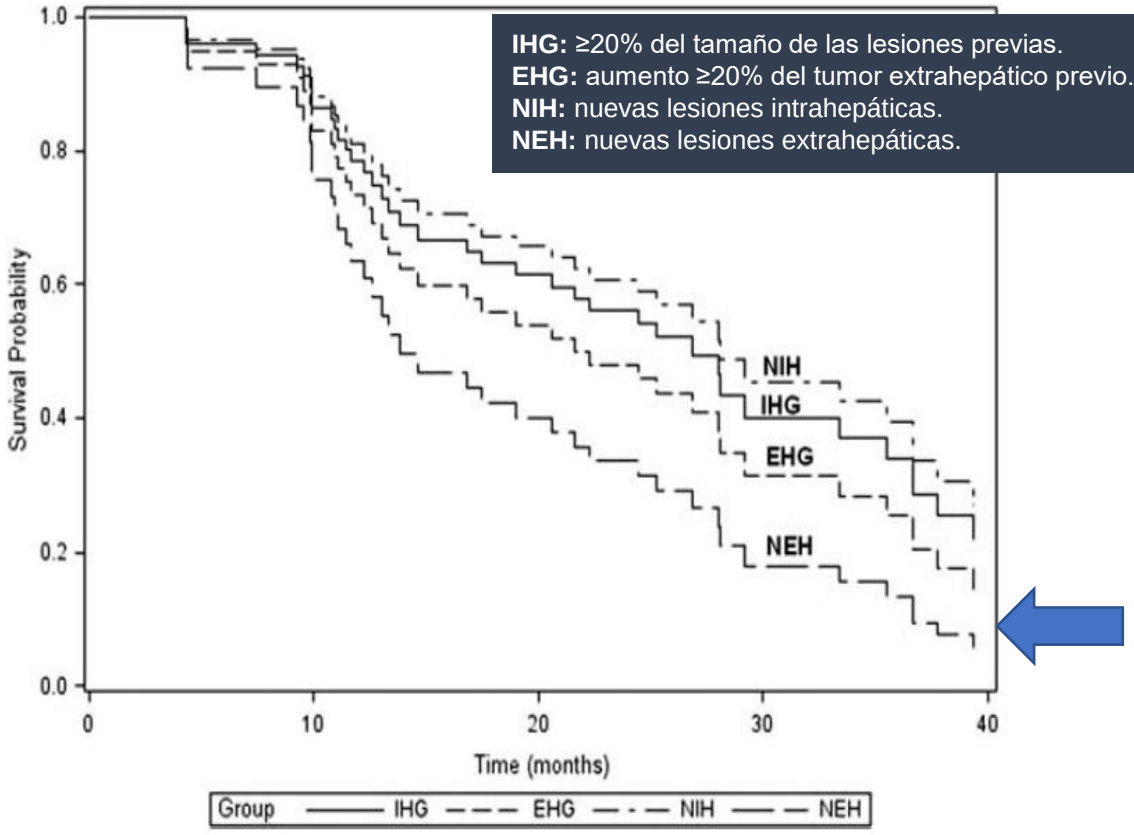
Time to deterioration (TTD) in PROs was defined as time from randomization to first clinically meaningful deterioration (worsening ⩾10 points) confirmed at a subsequent visit or death

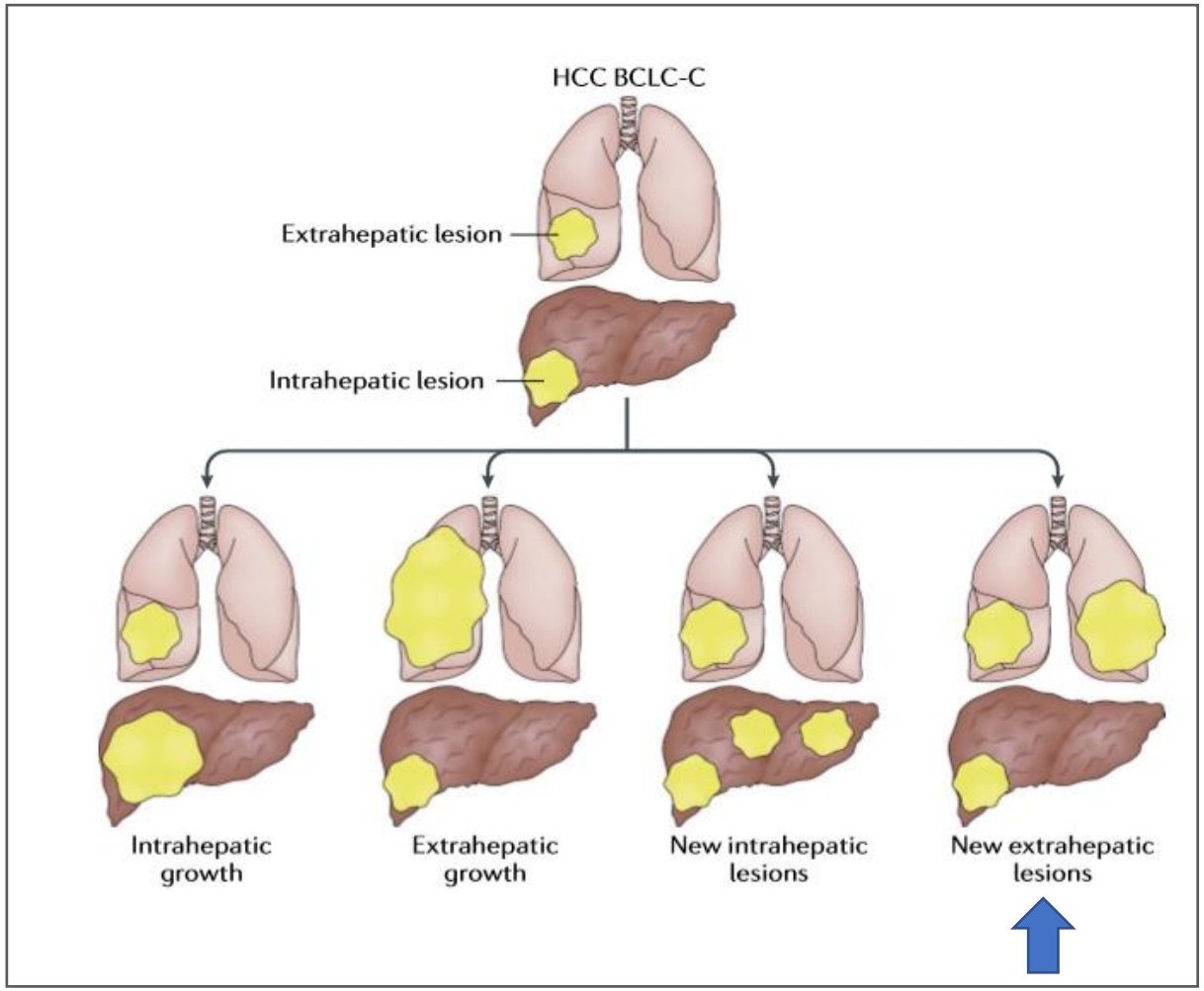
Sangro B, et al. Poster presented at 2022 ASCO Annual Meeting. Chicago. Illinois, USA. June 3-7, 2022.

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.

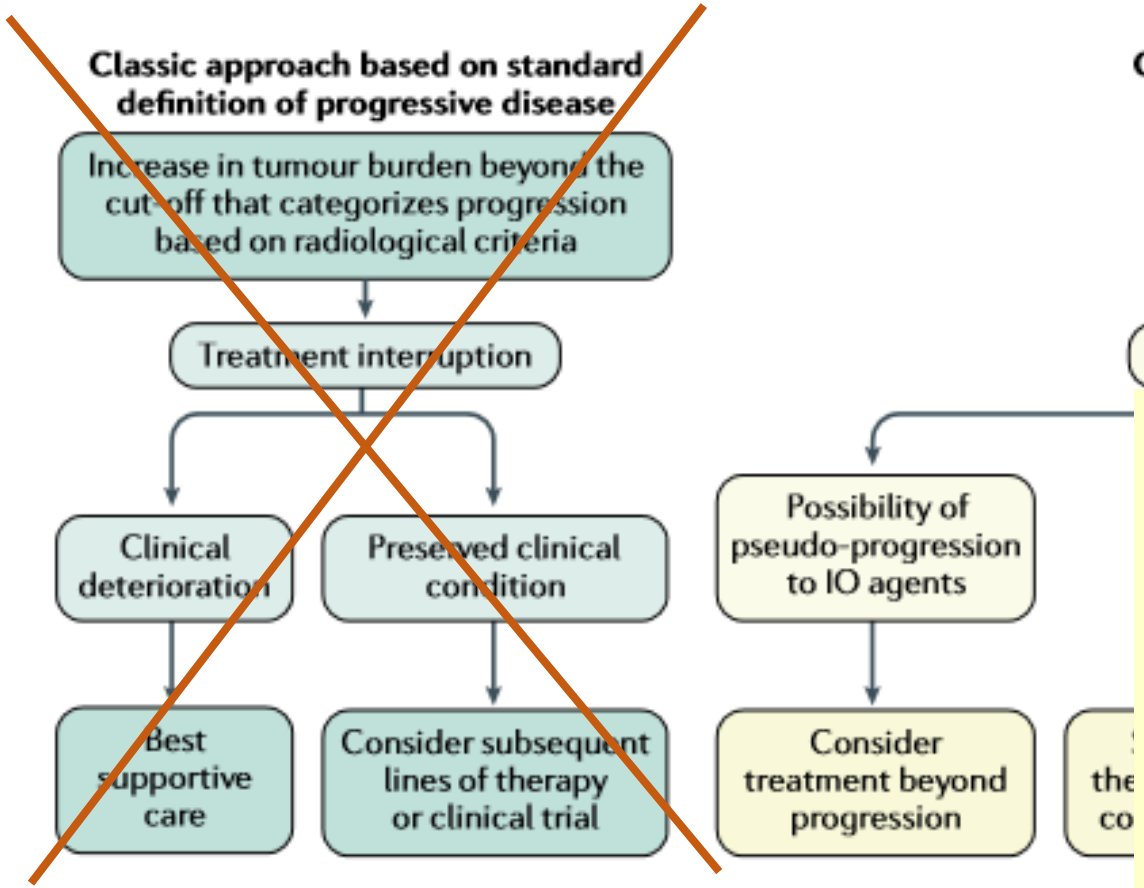


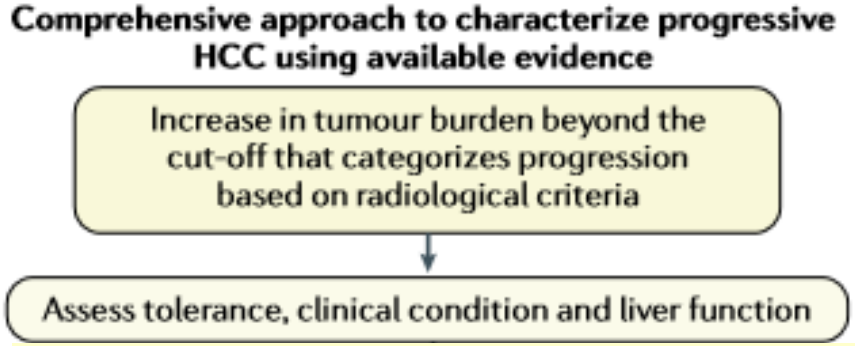


1. Reig M, et al. Hepatol 2013. Dic;58(6):2023-31.

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

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



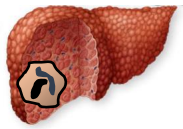


- ✓ ¿Cómo está tolerando el tratamiento?
- ✓ ¿Como ha sido la respuesta radiológica hasta ahora?
- ✓ ¿Como es la progresión: cuantía, patrón de progresión?
- ✓ ¿Cómo esta de función hepática?
- ✓ ¿Qué alternativas tengo para ofrecerle al paciente?

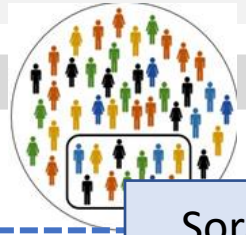
Bruix J, et al. Nat Rev Gastroenterol Hepatol. 2019 Oct;16(10):617-630

Secuencia de tratamiento en el CHC

Fx hepática preservada; ECOG 0-1



1L



2L

3L

Progresión a 1L con SOR

- Sorafenib → Hasta progresión desfavorable/sintomática.
- Regorafenib → Buen tolerante a SOR.
- Cabozantinib → Intolerante/progresión a SOR 2 o 3L
- Ramucirumab → Intolerante/progresión a SOR con AFP≥400 mg/dL
- **Nivo/Pembro Nivo+Ipi** → Contraindicación IMK/antiangiogénicos

Progresión a 1L con LENVA

Tto de 2L SOR....REGO, Cabo o Ramu, Nivo/Pembro??

Progresión a 1L con Atezo+Beva
Progresión a 1L con Durva+Treme

Tto de 2L SOR....REGO, Cabo o Ramu, ICPI??

Progresión tras IT o Combos en BCLC A o B

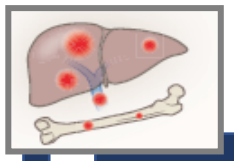
.....????

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 decidir la secuencia de tratamiento sistémico en cada paciente?

Evidencia EC

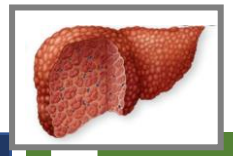
EXPERIENCIA en "vida real"



TUMOR

Intermedio/avanzado
Invasión portal

Infiltración biliar
Infiltración hepática >50%



CIRROSIS

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

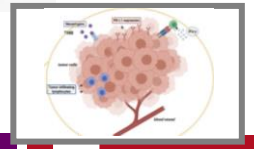
PACIENTE

Edad
Comorbilidad Cardiovascular
Comorbilidad renal.
Comorbilidad autoinmune.

Poblaciones especiales: HIV+

Seguridad QoL

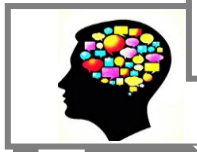
Perfil de seguridad
Experiencia del paciente
Impacto en QoL
Impacto en situación funcional
Síntomas relacionados



BIOMARCADORES

AFP≥ 400µg/mL/RAMUCIRUMAB

EVOLUCIÓN PREVIA



PREFE

Situación socio
Lugar residenci
Posología
Vía de adminis
Necesidad de v
Deseo de parti
Posible adhere

ENTORNO SANITARIO

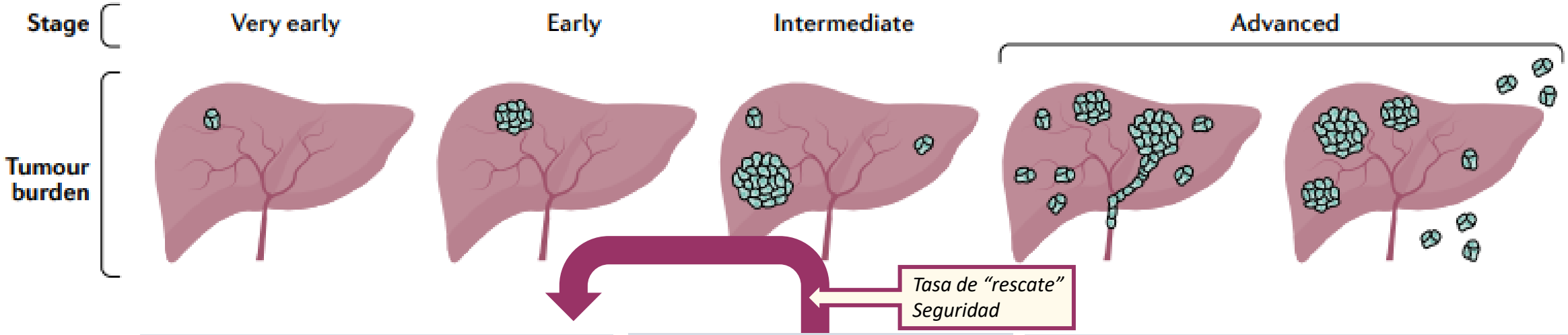
Acceso a los tratamientos
Protocolos de uso de fármacos
Disponibilidad/ocupación de H de Día
Investigación clínica

Oncoliver

En esta presentación se refleja opinión personal.

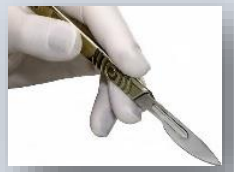
.....con una valoración integral e individualizada en cada caso.

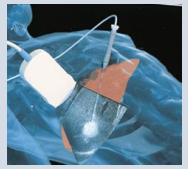
Desarrollo del tratamiento sistémico en el CHC en 2023



Pacientes de "alto riesgo" → Resección quirúrgica
Ablación local (RF, MW)

ADYUVANCIA

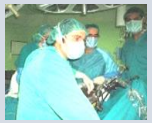




SLP

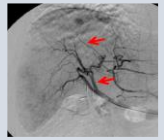
NEOADYUVANCIA

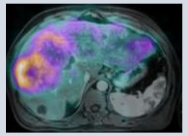
"Downstaging" y rescate con RQ o TH



ADYUVANCIA

Tto combinados: TACE/TARE/SBRT





SLP

NUEVOS TRATAMIENTOS COMBINADOS

Terapias diana/Inmunoterapia/ambos en 1 y 2ª L
Combinación con: SBRT vs TARE vs TACE
Nuevas "secuencias" de tratamiento
Biomarcadores: Selección de pacientes

SG

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

Hospital General Universitario Gregorio Marañón

SaludMadrid

CHGM
Grupo multidisciplinar

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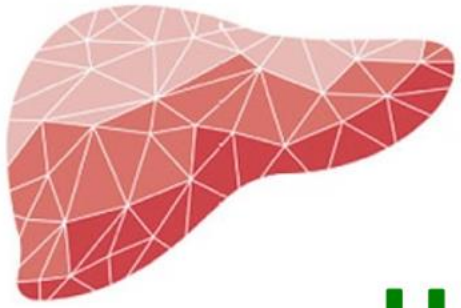
MÁSTER EN HEPATOLOGÍA



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