CURSO DE AVANCES EN GASTROENTEROLOGÍA
PERSPECTIVAS FUTURAS EN GASTROENTEROLOGÍA
17 - 19 Julio 2024 - Hotel InterContinental, Stgo.
SChGE

Hepatocarcinoma Avanzado

Terapia sistemica

“VISION DEL HEPATOLOGO”

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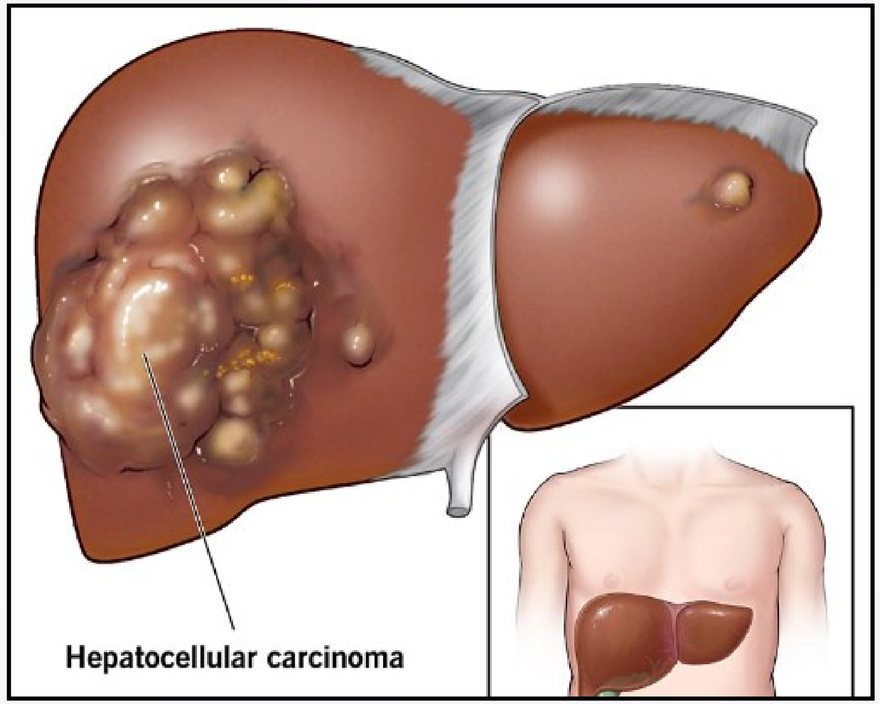
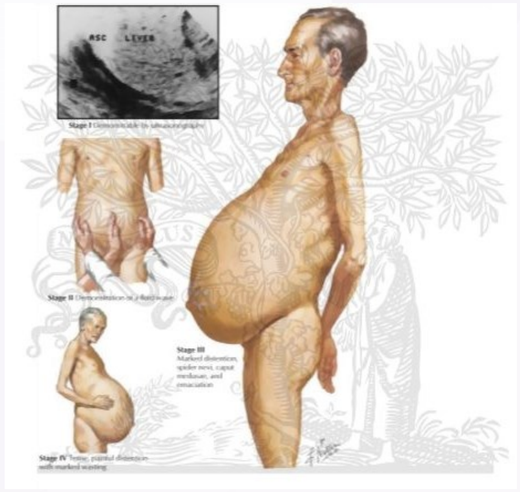
Hospital de Puerto Montt



Introducción

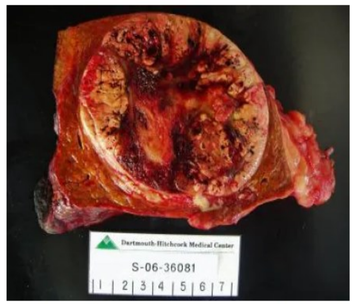


Enfermedad de órgano blanco

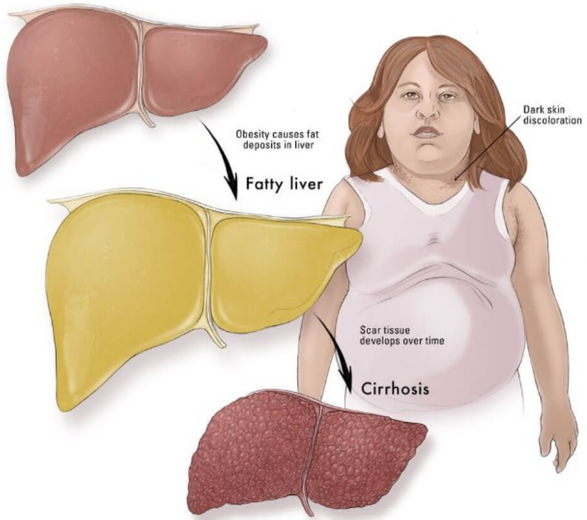
CIRROSIS-FIBROSIS

Enfermedad oncológica

Hepatocarcinoma



Large hepatocellular carcinoma. Image courtesy of Arief Suriawinata, MD, Department of Pathology, Dartmouth Medical School.



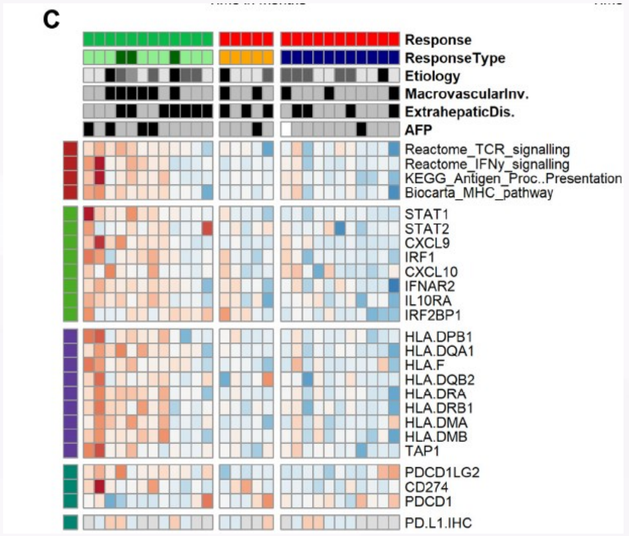
Hipertensión portal

Función de síntesis
CHILD-MELD
Historia de descompensaciones

AFP

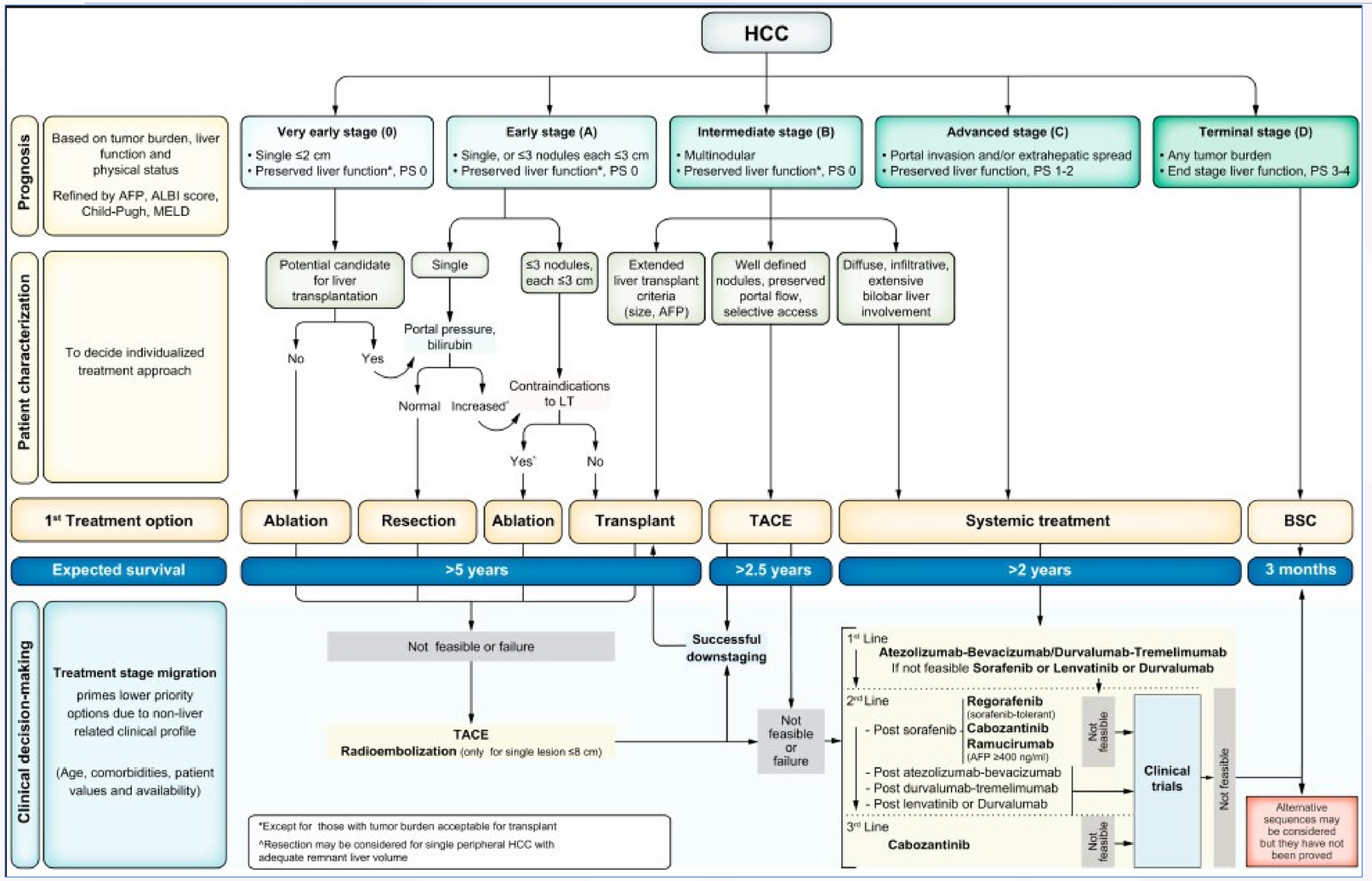
INVASIÓN VASCULAR
Invasión extrahepática

Número y tamaño de lesiones
Expresión genética del tumor



Chile ↑ DM ↑ MAFLD

Introducción

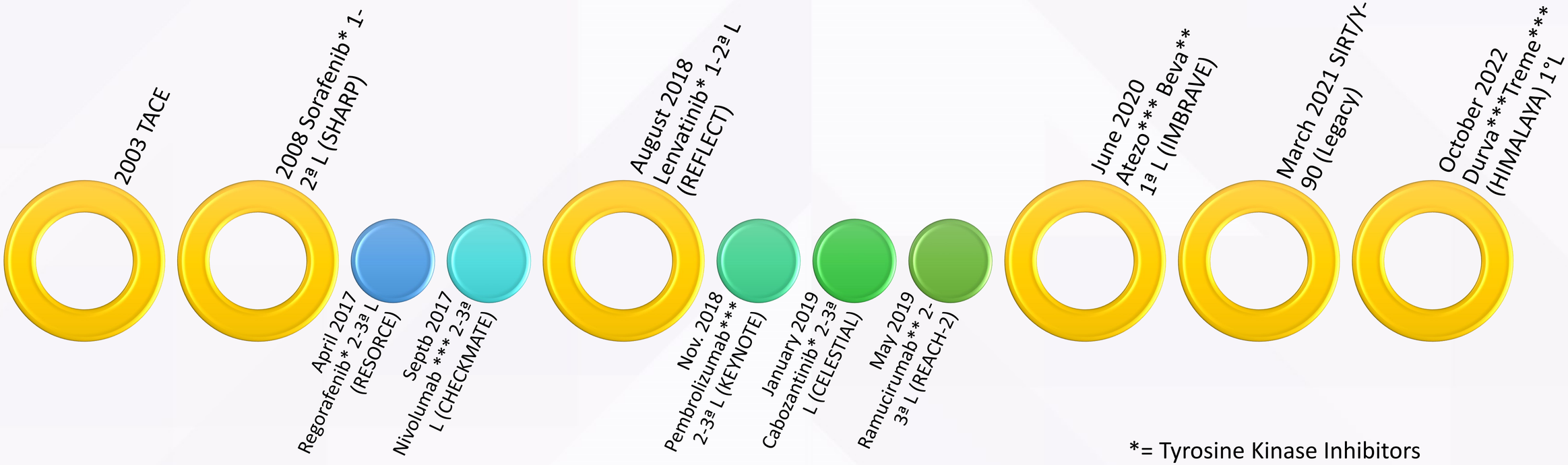


Concepto de tratamiento según etapas
TS previamente solo en enfermedad con invasión portal y/o extrahepática.

Cambio en el paradigma en la medida que se demuestra beneficio en pacientes con etapa intermedia , es decir enfermedad sólo confinada al hígado.

Reig et al. Journal of Hepatology.2022

Introducción



*= Tyrosine Kinase Inhibitors
**= Monoclonal Antibody
***=Immune Checkpoint Inhibitor

TS 2008

The phase III SHARP trial led to global approval of sorafenib for 1L treatment of unresectable HCC

- Confirmed HCC
- No previous systemic therapy
- Unresectable/ineligible for LRT
- Child-Pugh class A
- ECOG PS ≤2
- Total bilirubin ≤3mg/dL

(N=602)

R 1:1

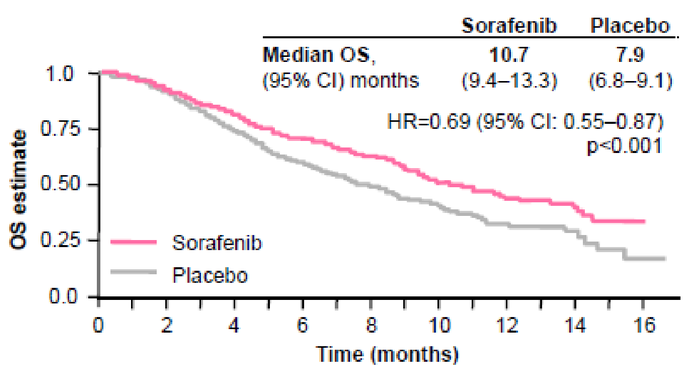
Sorafenib 400mg po bid (n=299)

Placebo (n=303)

Crossover not permitted

Primary endpoint: OS, TTSP

Secondary endpoints: TTP (per IRR), DCR (per RECIST), safety



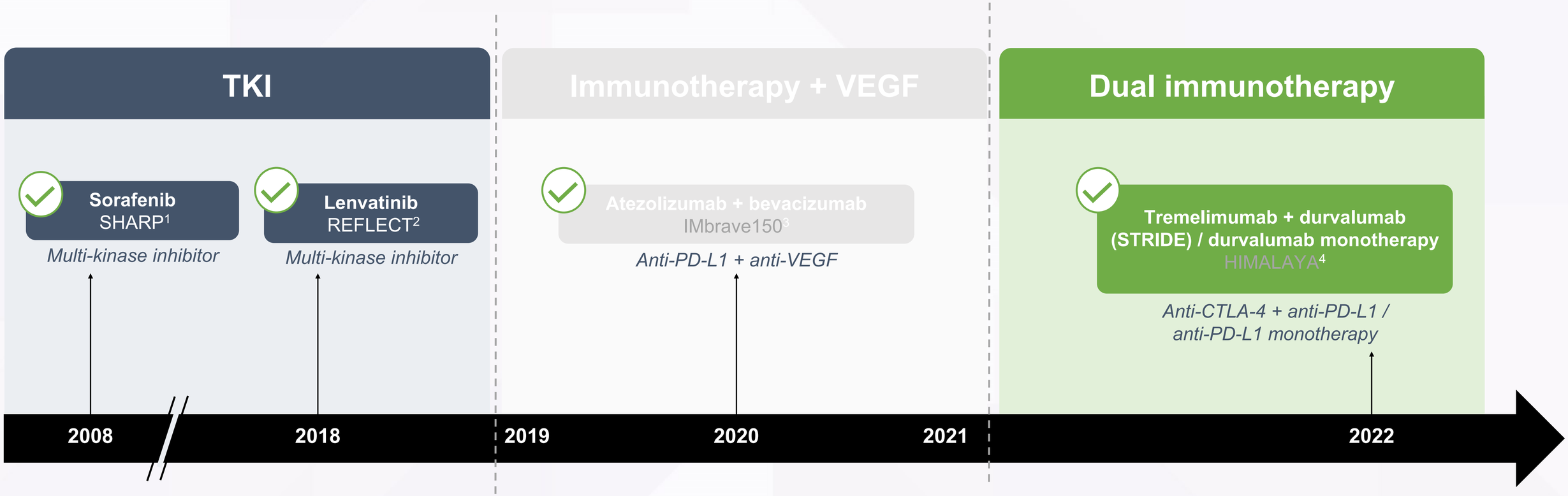
1L sorafenib treatment improved OS by ~3 months vs placebo in patients with unresectable HCC

Select efficacy parameters	Sorafenib (n=299)	Placebo (n=303)	HR (95% CI) p value
Median TTSP (95% CI), months	4.1 (3.5–4.8)	4.9 (4.2–6.3)	1.08 (0.88–1.31) p=0.77
DCR, %	43	32	– p=0.002
Median TTRP (95% CI), months	5.5 (4.1–6.9)	2.8 (2.7–3.9)	0.58 (0.45–0.74) p<0.001

bid, twice daily; CI, confidence interval; DCR, disease control rate; HR, hazard ratio; IRR, independent radiologic review; LRT, locoregional therapy po, orally; TTP, time to progression; TTRP, time to radiologic progression; TTSP, time to symptomatic progression

Llovet et al. N Engl J Med 2008

Evolución de las terapias de primera línea en HCC irresecable/metastásica



El panorama del tratamiento evoluciona continuamente para mejorar los resultados en pacientes con HCC irresecable, y se han observado avances recientes con combinaciones de inmunoterapia.

1. Llovet JM, et al. *N Engl J Med* 2008;359:378–390. 2. Kudo M, et al. *Lancet* 2018;391:1163–1173. 3. Finn RS, et al. *N Engl J Med* 2020;382:1894–1905. 4. Abou-Alfa GK, et al. *NEJM Evid* 2022;1:EVIDoa2100070.

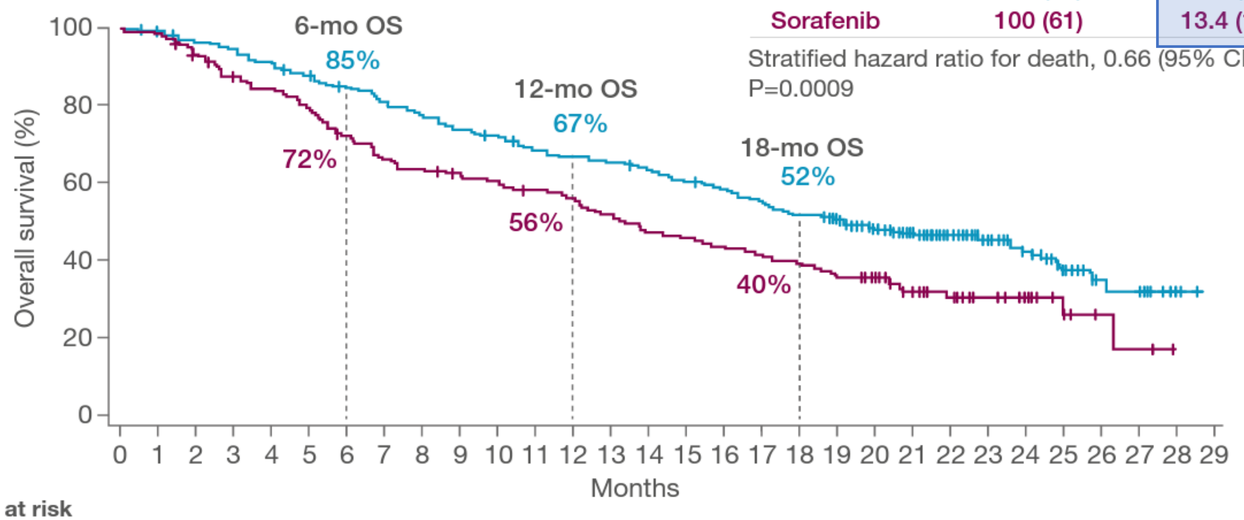
TS 2020

IMbrave150: Atezolizumab + bevacizumab

Overall survival

	No. of events/ no. of patients (%)	Median overall survival (95% CI)
Atezo + Bev	180 (54)	19.2 (17.0–23.7)
Sorafenib	100 (61)	13.4 (11.4–16.9)

Stratified hazard ratio for death, 0.66 (95% CI, 0.52–0.85)
P=0.0009



No. at risk

Atezo + Bev	336	329	320	312	302	228	276	263	252	240	233	221	214	206	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

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

Finn NEJM 2020

TS 2022

Himalaya: Durvalumab + tremelimumab

Inclusion criteria:

- Patients aged ≥18 years with unresectable HCC
- BCLC stage B* or C
- No prior systemic therapy for HCC
- Child-Pugh Class A
- ECOG PS 0–1

Randomisation 1:1:1:1

Stratified by:

- *MVI (yes vs. no)*
- *Aetiology of liver disease (HBV vs. HCV vs. other)*
- *ECOG PS (0 vs.1)*

Arm A:
Durvalumab 1500 mg IV Q4W
(n=389)

Arm B:[†]
Durvalumab 1500 mg IV Q4W +
tremelimumab 75 mg x 4 doses Q4W
(n=153)

Arm C: STRIDE
Durvalumab 1500 mg IV Q4W +
tremelimumab 300 mg single dose
(n=393)

Arm D:
Sorafenib 400 mg BID
(n=389)

Objective radiological disease progression

Primary endpoint

- OS (Arm C vs. Arm D)[‡]

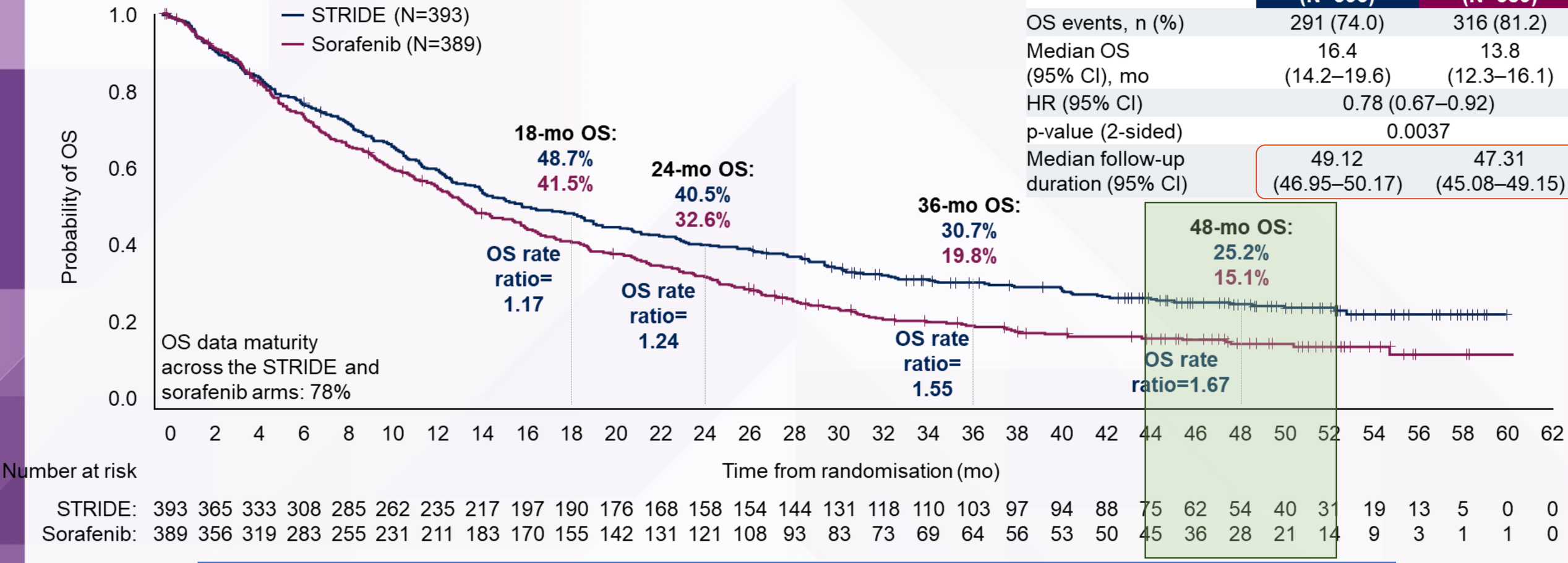
Secondary endpoints

- OS (Arm A vs. Arm D) [‡, §]
- ORR
- DCR
- DCR-16w/-24w
- DoR
- PFS
- TTP
- OS18/24
- HRQoL
- PK/PD
- ADAs
- Safety/tolerability

Study NCT03298451. Available at ClinicalTrials.gov; 2. AstraZeneca. Protocol D419CC00002 Amendment 6. 20 August 2019; 3. Abou-Alfa GK, et al. Presented at ASCO GI 2022. San Francisco; CA. Abstract #379

STRIDE vs sorafenib

	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), mo	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (95% CI)	0.78 (0.67–0.92)	
p-value (2-sided)	0.0037	
Median follow-up duration (95% CI)	49.12 (46.95–50.17)	47.31 (45.08–49.15)



Después de 4 años, uno de cada cuatro pacientes tratados con el regimen STRIDE sigue con vida

Los pacientes tratados con el regimen STRIDE tienen 22% menor probabilidad de morir por HCC a los 4 años de tto

OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG performance status, and macrovascular invasion. The 36-mo OS rate had a nominal 2-sided p-value of 0.0006. Updated analysis data cut-off: 23 January 2023.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, month; OS, overall survival.

HEPATOLOGY

CLINICAL OBSERVATIONS IN HEPATOLOGY | HEPATOLOGY, VOL. 72, NO. 4, 2020

Immunotherapy as a Downstaging Therapy for Liver Transplantation

Birgit Schwacha-Eipper,[1,2] Iulia Minciuna,[1] Vanessa Banz,[2] and Jean François Dufour[1,2]

Locoregional therapies are downstaging methods for patients with hepatocellular carcinoma (HCC) outside Milan criteria. Sorafenib was the first systemic therapy tested in a neoadjuvant setting of liver transplantation (LT) but showed unsatisfactory results due to a minimal response rate.[(1)] Recently, immune checkpoint inhibitors have been shown to control HCC in a significant fraction of patients and to even induce complete response.[(2,3)]

Case Presentation

A 62-year-old male patient with compensated alcohol-associated liver cirrhosis was referred for a liver lesion detected at abdominal ultrasound. Magnetic resonance imaging (MRI) revealed a 64-mm Liver Imaging Reporting and Data System (LI-RADS) 5 liver lesion in segment VI. Atypical laparoscopic resection was performed in March 2015, and histology showed a poorly differentiated HCC pT3NxV0L1R0.

At the 2-month follow-up, MRI revealed multiple LI-RADS 3 lesions in segments IV, V/VIII, and V ranging from 5 to 18 mm and one 25-mm LI-RADS 4 HCC lesion in segment IV. The tumor board recommended systemic therapy with sorafenib, which the patient took for 14 months, until radiological follow-up documented tumor progression.

The patient was enrolled in the REACH-II randomized double-blind trial, on the placebo arm, from which he was withdrawn after 2 months of treatment due to further tumor progression. Regorafenib was then initiated, but the treatment was stopped after 11 weeks due to severe dermatological adverse events. In June 2017, immunotherapy with nivolumab was initiated. Imaging reports before nivolumab initiation showed one 25-mm LI-RADS 4 liver lesion in segment 4 and three LI-RADS 3 lesions of <2 cm in segment IV, VI/VII, and VIII (Fig. 1).

In March 2018, abdominal computed tomography (CT) showed that under nivolumab there was a complete response of the segment VIII liver lesion, the other three lesions being stationary in size. Percutaneous CT-guided microwave ablation was performed for the lesion in segment VI/VII.

After tumor board discussion, the patient was inactively listed for orthotopic LT. Meanwhile, nivolumab therapy was continued for a total of 34 cycles. Due to potential nivolumab-induced liver rejection, nivolumab treatment was discontinued for 6 weeks before activating the patient on the waiting list. Since stopping nivolumab until LT, the alpha-fetoprotein level was stationary (1.5-2 kU/L).

In January 2019, the patient underwent LT without perioperative complications. Histology revealed an unifocal, poorly differentiated, 42-mm HCC in segment IVb/V, T2V0L0R0. One year later, the patient is doing well, without evidence of tumor recurrence or graft rejection.

Abbreviations: HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; LT, liver transplantation; MRI, magnetic resonance imaging.

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View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.31234

Potential conflict of interest: Advisory committees: Abbvie, Bayer, Bristol-Myers Squibb, Falk, Genfit, Genkyotex, Gilead Sciences, HepaRegenix, Intercept, Lilly, Merck, Novartis. Speaking and teaching: Bayer, Bristol-Myers Squibb, Intercept, Genfit, Gilead Sciences, Novartis, Roche.

The ImmunoXXL Study (ImmunoXXL)

ClinicalTrials.gov Identifier: NCT05879328

Recruitment Status : Recruiting
First Posted : May 30, 2023
Last Update Posted : May 30, 2023

See **Contacts and Locations**

View this study on the modernized ClinicalTrials.gov

Sponsor:
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Information provided by (Responsible Party):
Vincenzo Mazzaferro, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Study Description

Go to

Brief Summary:

This study is aimed at confirming data of efficacy and safety of liver transplantation (LT) in patients with hepatocellular carcinoma (HCC) beyond current transplant criteria who demonstrate a sustained partial or complete radiological response to the atezolizumab and bevacizumab combination treatment, prescribed after completion of loco-regional therapies or as a first line systemic treatment.

The aim of the study is to demonstrate that liver transplantation, after effective HCC downstaging with atezolizumab and bevacizumab combination, may confer a survival benefit over atezolizumab and bevacizumab maintained treatment alone and that this strategy (tested in a consecutive non-randomized cohort) is not undermined by added risks.

TS 2024: TS (IO) + TACE

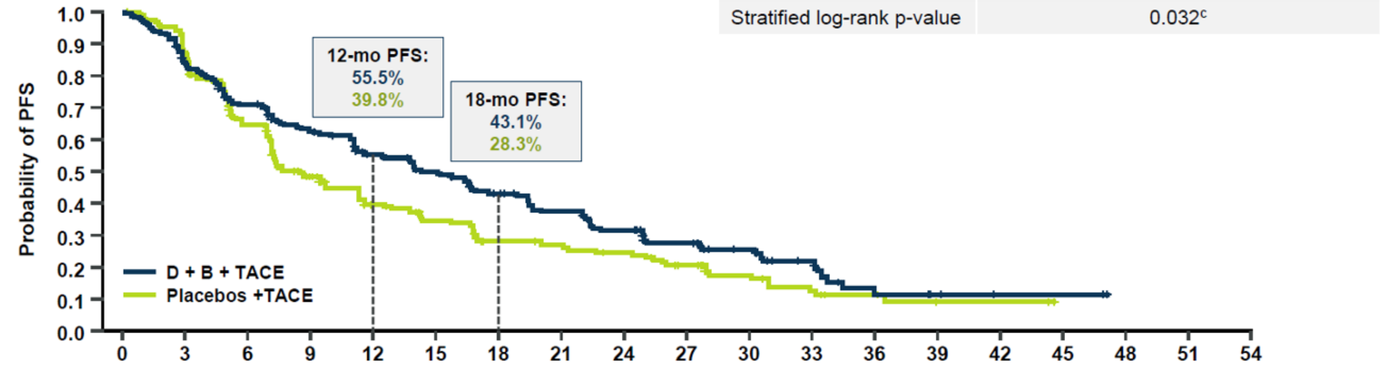
EMERALD 1-ASCO 2024

- En pacientes HCC etapa intermedia (susceptibles de tto con TACE). Agregar la combinación de durvalumab y bevacizumab dio mejor SLP.

PFS was assessed by BICR per RECIST v1.1

Primary endpoint was met: Median PFS improved by 6.8 months with durvalumab + bevacizumab + TACE vs. placebos + TACE

	D + B + TACE (n=204)[a]	Placebos + TACE (n=205)[b]
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032[c]	



Number at risk																				Total events
D + B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

[a]Median (range) duration of follow-up in censored patients was 16.7 (0.03–47.1) months and median (95% CI) duration of follow-up in all patients using the reverse Kaplan-Meier method was 22.2 (16.7–27.3) months; [b]Median (range) duration of follow-up in censored patients was 10.3 (0.03–44.3) months and median (95% CI) duration of follow-up in all patients using the reverse Kaplan-Meier method was 26.3 (16.7–30.4) months; [c]The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

B = bevacizumab; BICR = blinded independent central review; CI = confidence interval; D = durvalumab; HR = hazard ratio; mo = month; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1;

Visión 2024

- En el manejo de HCC avanzado-intermedio* → secuencia-combinación óptima de TLR – TS
- Variedad de estudios; TARE-TS (TKI), IO –TARE, SBRTO-TKI, IO –TACE
- Relevancia del Comites Multidiciplinarios para tomar decisiones

SIR Foundation

SPECIAL COMMUNICATION

Combination and Optimal Sequencing of Systemic and Locoregional Therapies in Hepatocellular Carcinoma: Proceedings from the Society of Interventional Radiology Foundation Research Consensus Panel

Lindsay M. Thornton, MD, Nadine Abi-Jaoudeh, MD, Howard J. Lim, MD, PhD, Katerina Malagari, MD, PhD, Benjamin Oren Spieler, MD, Masatoshi Kudo, MD, PhD, Richard S. Finn, MD, Riccardo Lencioni, MD, Sarah B. White, MD, MS, Nima Kokabi, MD, D. Rohan Jeyarajah, MD, Prosanto Chaudhury, MSc, MD, and David Liu, MD

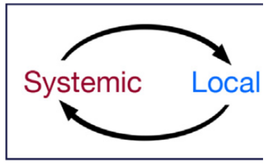


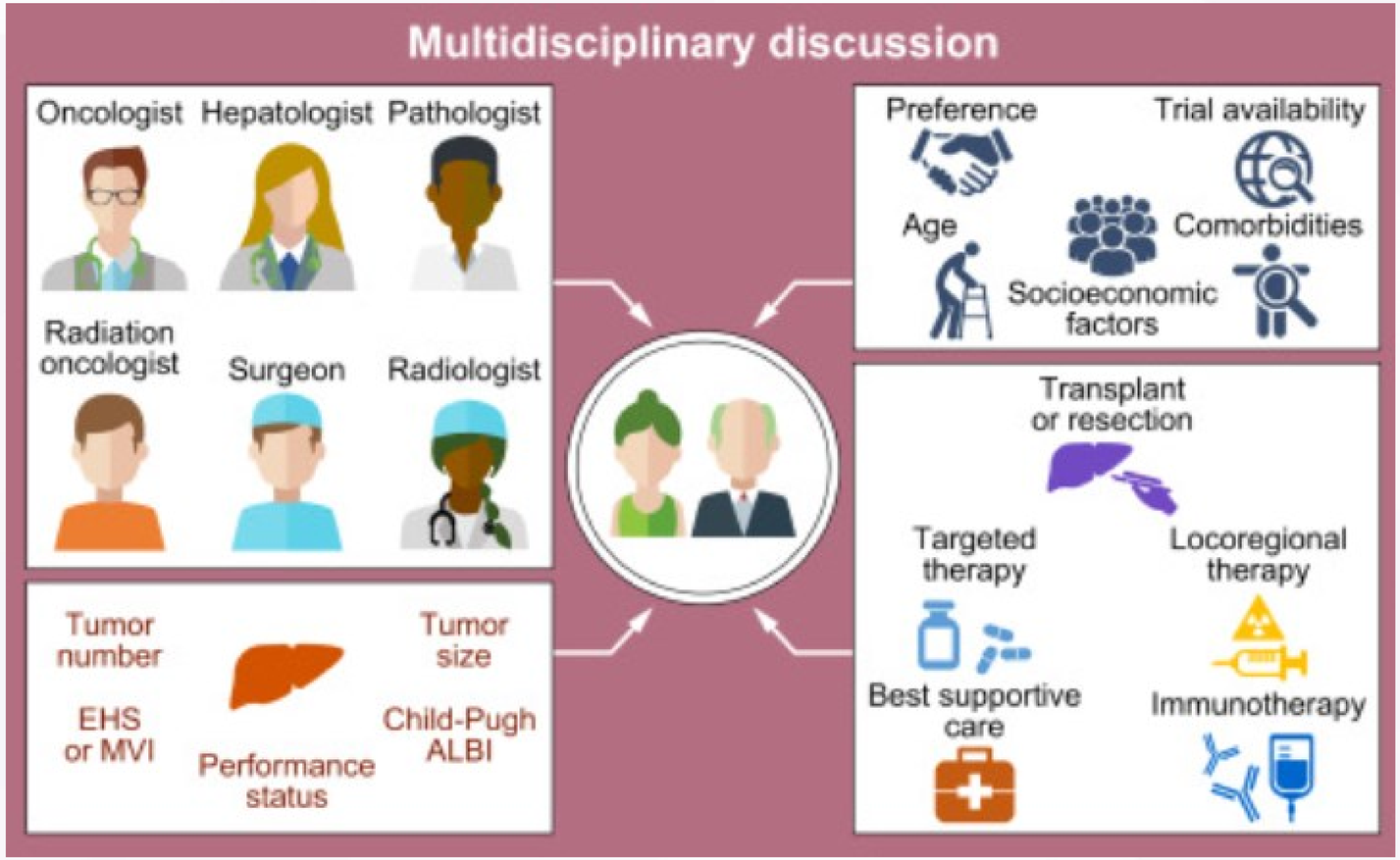
Table 2. All Voted on Research Topics

Rank	Research Priority
1	TARE + TKI/IO in <VP3 PVTT in patients with CPA
2	Induction with systemic agents prior to locoregional therapy
3	Tumor morphologic feature studied as a predictor of progression-free survival
4	Prospective registry of curative intent therapies
5	Locoregional therapy in patients with borderline hepatic function
6	TARE as an adjunctive therapy in those eligible for surgical management
7	Locoregional therapy plus antiangiogenic agent (ie, bevacizumab) safety registry

CPA = child pugh A; IO = immuno-oncology; PVTT = portal vein tumor thrombus; TARE = transarterial radioembolization.

J Vasc Interv Radiol 2024; 35:818–824

Importancia del MDT



- Considerar factores locales
- Criterios de trasplante en pacientes con hcc
- Expertise equipo quirúrgico
- Acceso a terapias locoregionales
- Acceso a terapias sistémicas

Arndt Vogel, Anna Saborowski. Journal of Hepatology 2021

TS – acceso- situación en Chile

Sorafenib por comité DAC

2021 ISP atezolizumab bevacizumab, sin mecanismo de financiamiento específico

2024.. ISP durvalumab tremelilumab, sin mecanismo de financiamiento específico

Conclusiones

- Avance importante en TS para HCC avanzado en últimos años
- La llegada de la inmunoterapia sin duda abre una nueva etapa
- MDT tiene como rol buscar la mejor alternativa de terapia para cada paciente, optimizando el acceso a TLR y TS
- BCLC es una base sólida, pero cada paciente tiene un camino individual
- En el futuro → mayor uso de TS en pacientes en etapas más tempranas y en combinación con TRL