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PANMEP

PROGRAMA ANDALUZ DE FORMACIÓN EN MEDICINA
PERSONALIZADA Y DE PRECISIÓN

EXPERTO UNIVERSITARIO EN MEDICINA PERSONALIZADA Y DE PRECISIÓN

BIOLOGÍA Y PATOLOGÍA MOLECULAR EN CÁNCER (INMUNOONCOLOGÍA)

FORMACIÓN
IIVANTE
Fundación
Progreso y Salud

COLABORA

Johnson & Johnson

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i Universidad
Internacional
de Andalucía
A



Junta de Andalucía
Consejería de Salud y Consumo

Retos en la inmunoterapia del hepatocarcinoma

Inmunoterapia y hepatocarcinoma

María Reig

Head of Liver Oncology Unit - BCLC group

Consultat of Liver Unit

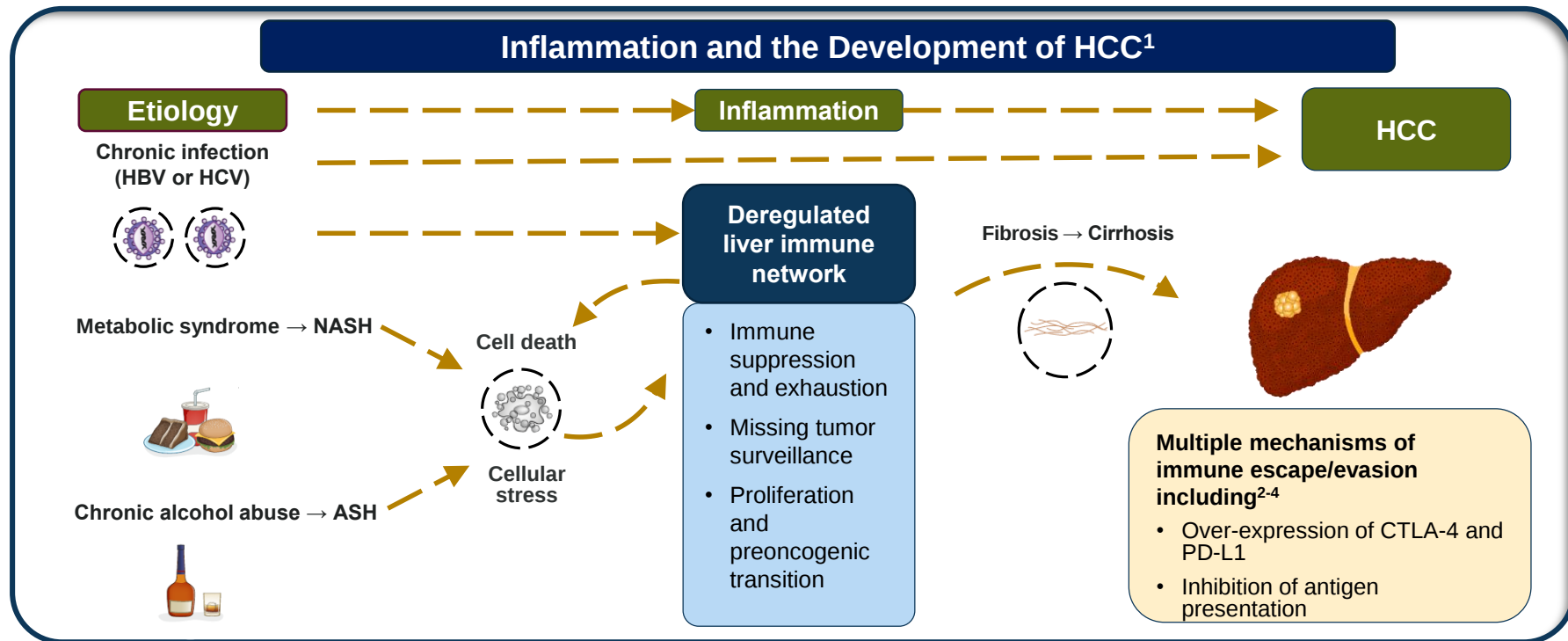
Hospital Clinic, IDIBAPs and CIBEREHD



I have an interest in relation to one or more organizations that could be perceived as a possible conflict of interest in the context of the subject of this presentation.

- **Employment:** Head of Liver Oncology Unit. Hospital Clinic Barcelona. Director of BCLC group at IDIBAPS/CIBEREHD.
- **Consultant or Advisory Role:** AstraZeneca, Bayer, BMS, Eli Lilly, Geneos, Ipsen, Merck, Roche, Universal DX, Engitix Therapeutics
- **Research Funding:** Yes (ISCIII, CIBER, AECC)
- **Speaking:** AstraZeneca, Bayer, BMS, Eli Lilly, Gilead, Roche, Guerbet, Biotoscana Farma S.A.
- **Travel support:** Astrazeneca, Roche, Bayer, BMS, Lilly, Ipsen
- **Principal or sub-Investigator of drug under development:** Abbvie, BMS, Adaptimmune, Nerviano, Bayer, Ipsen, Astrazeneca, Terumo, Incyte, Roche, Boston Scientific,
- **Grant Research Support (to the institution):** Bayer, Ipsen
- **Educational Support (to the institution):** Bayer, Astrazeneca, BMS, Eisai- Merck MSD, Roche, Ipsen, Lilly, Terumo, Next, Boston Scientific, Ciscar Medical, Eventy 03 LLC (Egypt)

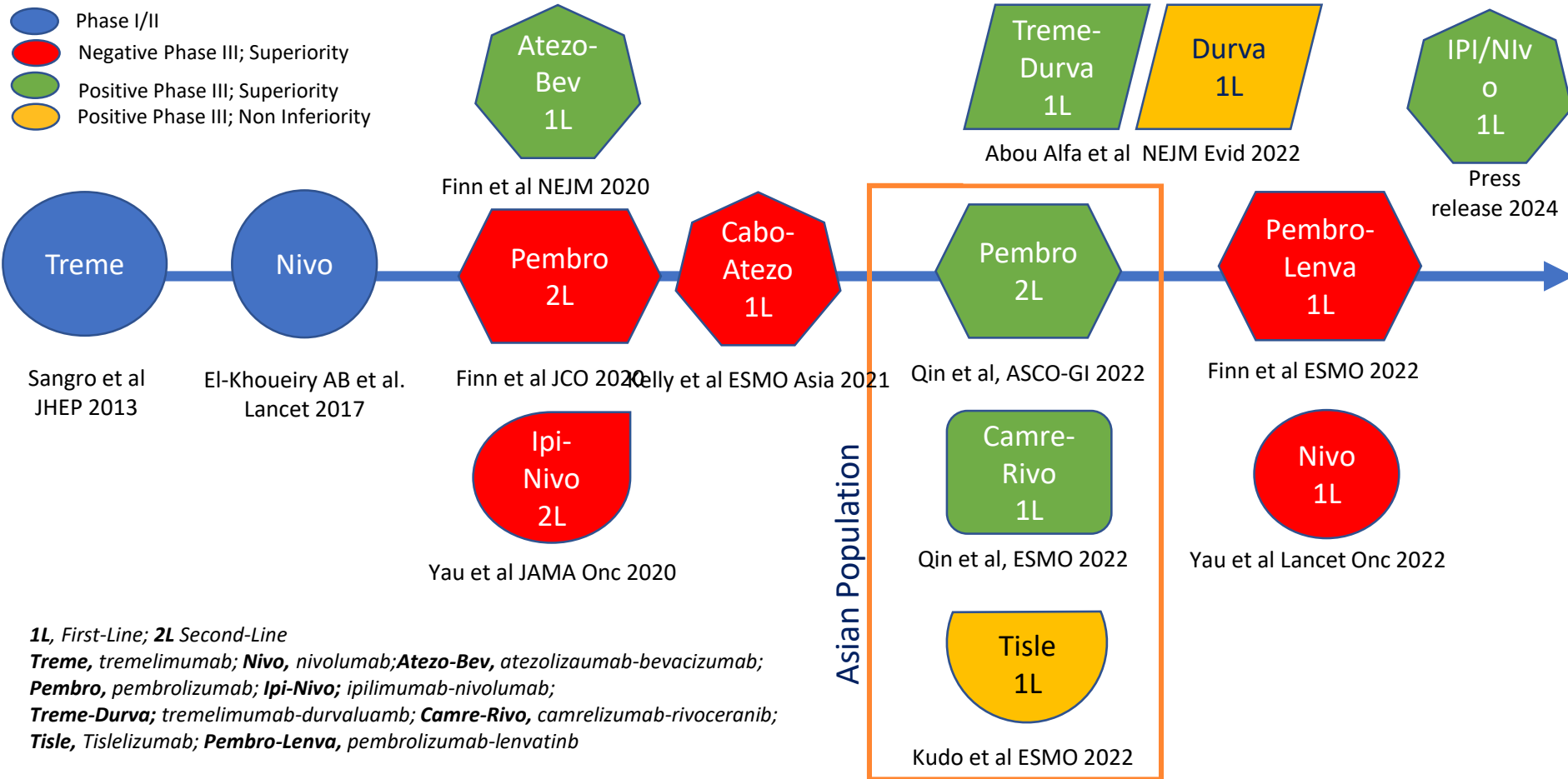
Inflammation and Immune Dysregulation Lead to HCC



ASH = alcoholic steatohepatitis; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NASH = nonalcoholic steatohepatitis; PD-L1 = programmed cell death ligand-1.

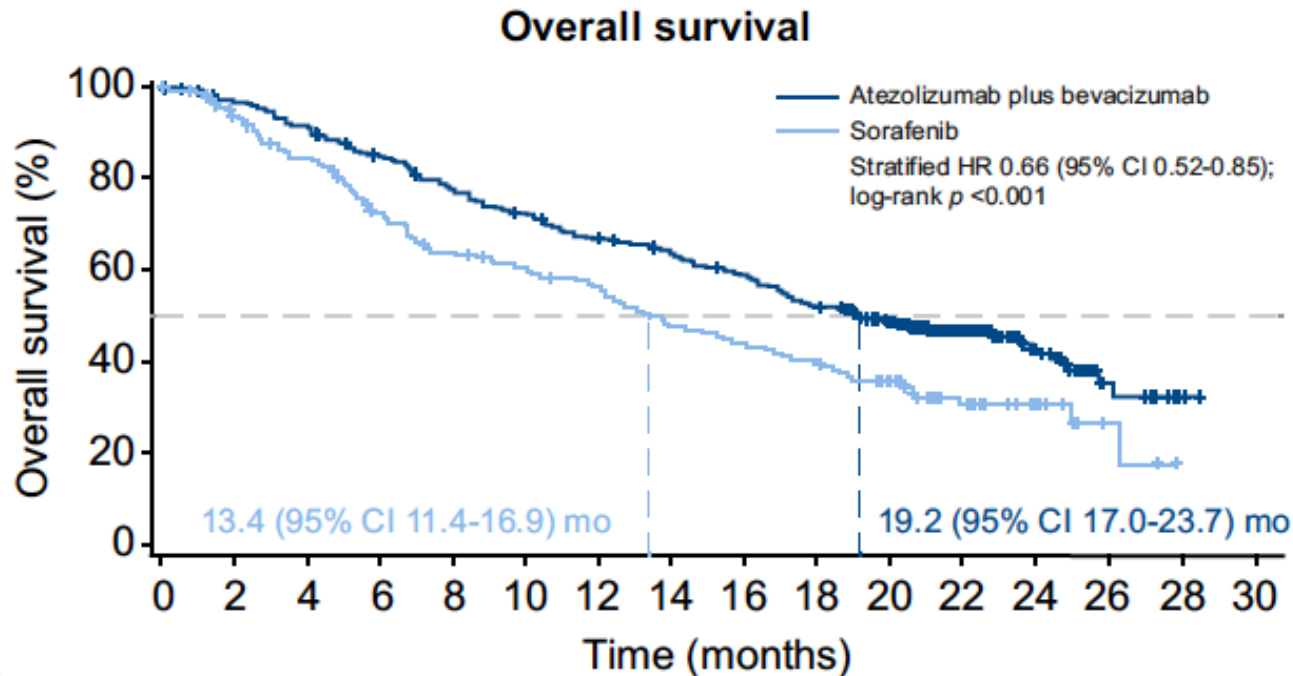
1. Ringelhan M, et al. *Nat Immunol*. 2018;19:222-232. 2. Longo V, et al. *Medicina*. 2019;55(10). 3. Matsuzaki K, et al. *Hepatology*. 2007;46(1):48-57.

4. Zhang HH, et al. *J Viral Hepat*. 2010;17 Suppl 1:34-43. Diagram adapted from Ref 1.



Unprecedented survivals with ICI

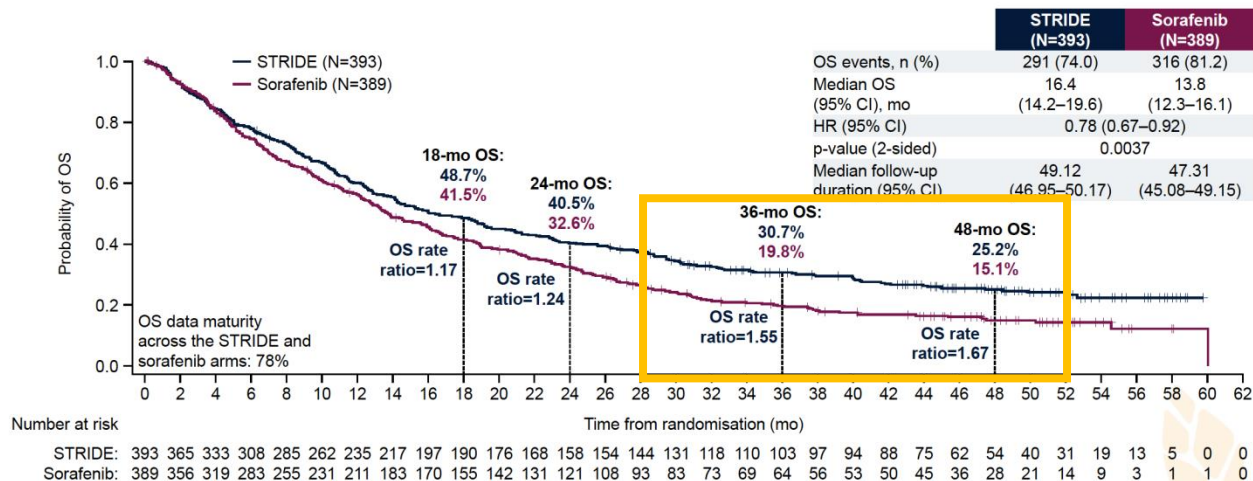
Atezolizumab + Bevacizumab



Tremelimumab + Durvalumab

Four-year updated overall survival for STRIDE versus sorafenib

STRIDE demonstrated an unprecedented one in four survival rate at 4 years



OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. 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; MVI, macrovascular invasion; OS, overall survival; PS, performance status.



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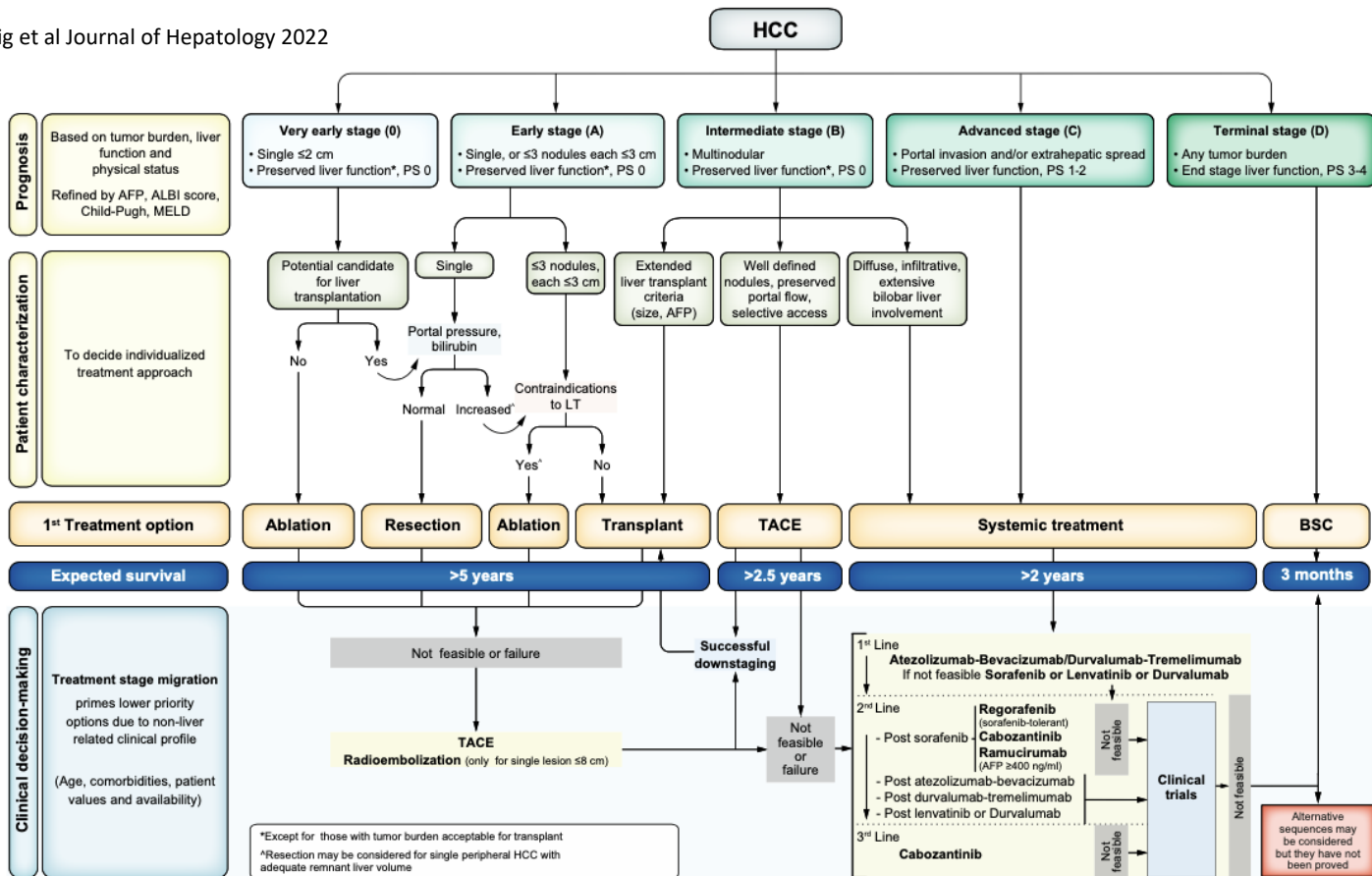
Bristol Myers Squibb Announces CheckMate -9DW Trial Evaluating Opdivo (nivolumab) Plus Yervoy (ipilimumab) Meets Primary Endpoint of Overall Survival for the First-Line Treatment of Advanced Hepatocellular Carcinoma

03/20/2024

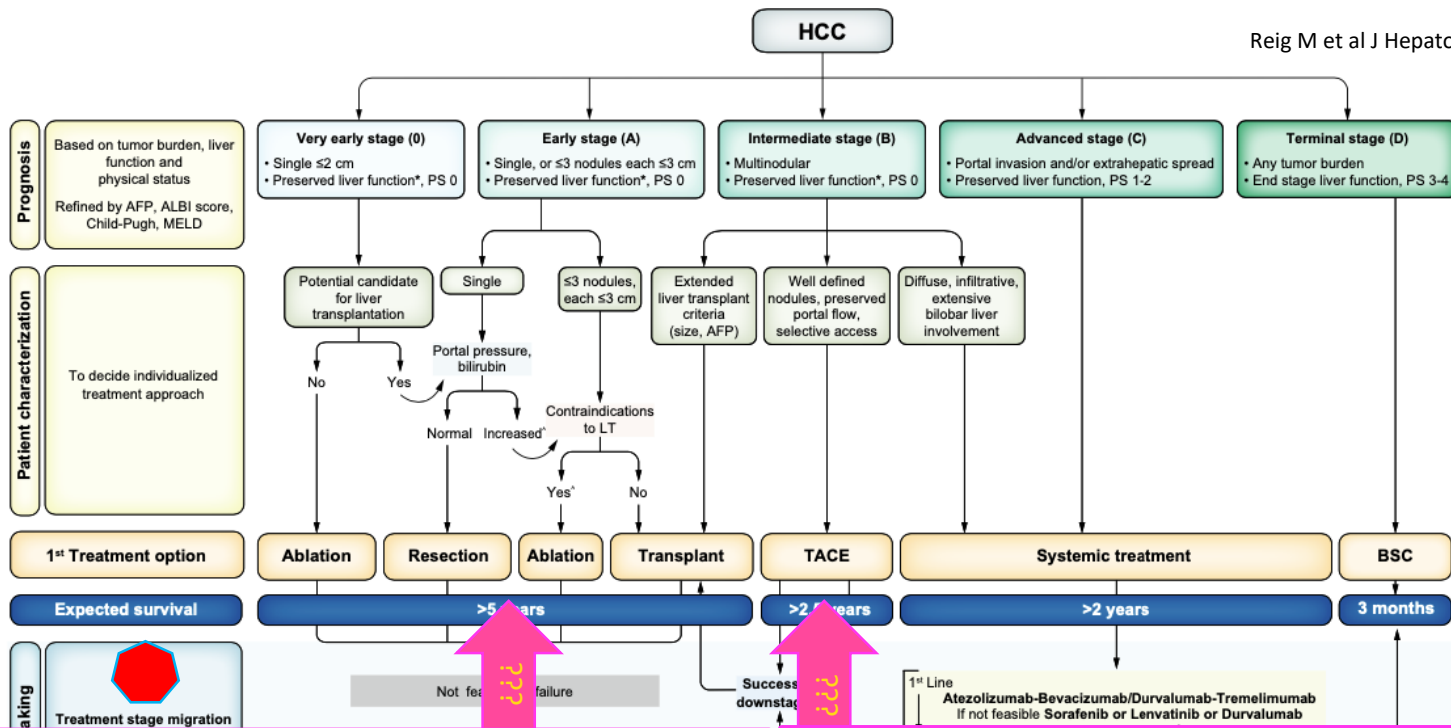
CATEGORY: [Corporate/Financial News](#)

Opdivo plus Yervoy demonstrates statistically significant and clinically meaningful improvement in overall survival compared to investigator's choice of sorafenib or lenvatinib

Reig et al Journal of Hepatology 2022

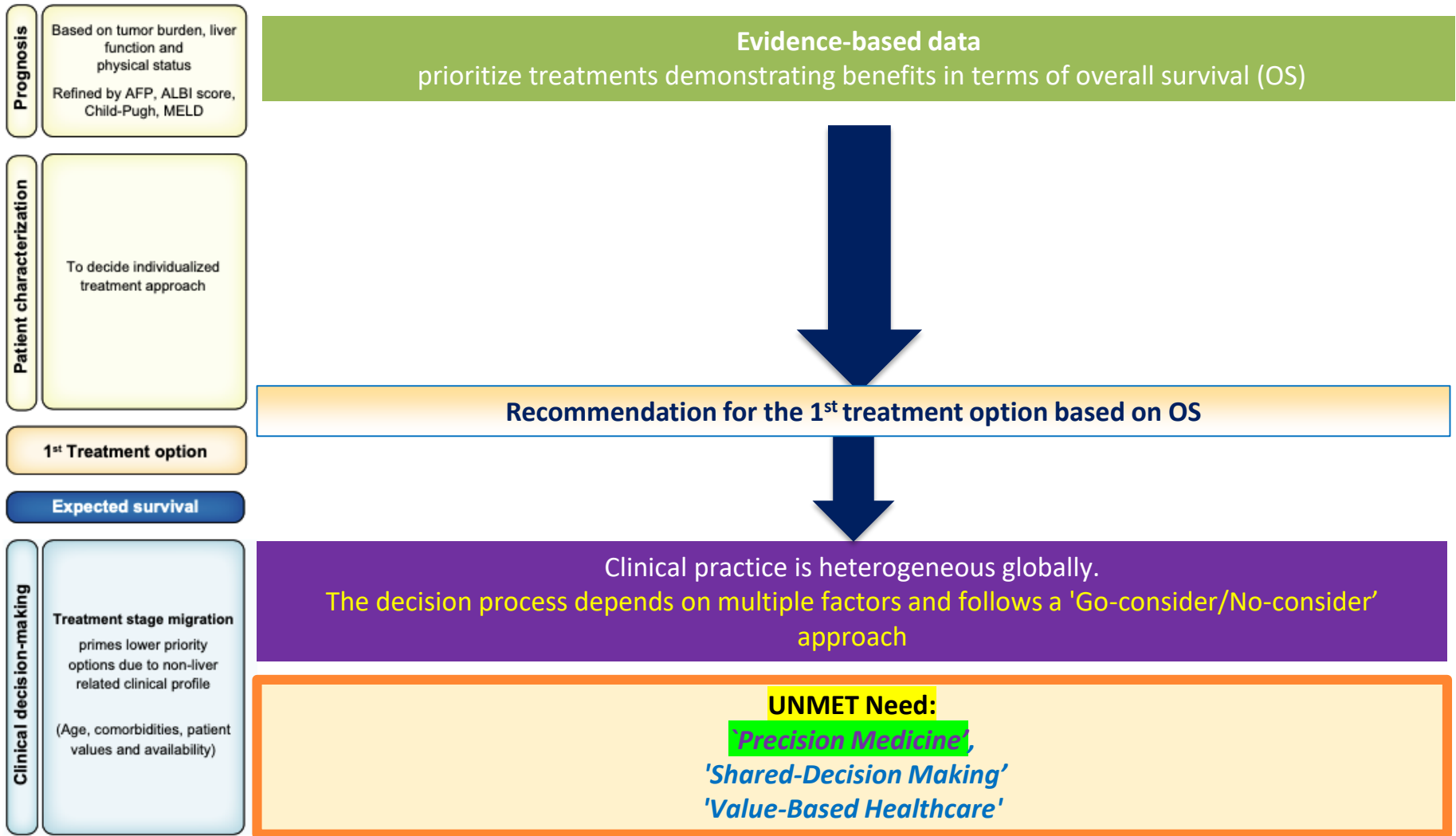


Reig M et al J Hepatol. 2022 Mar;76(3):681-693.

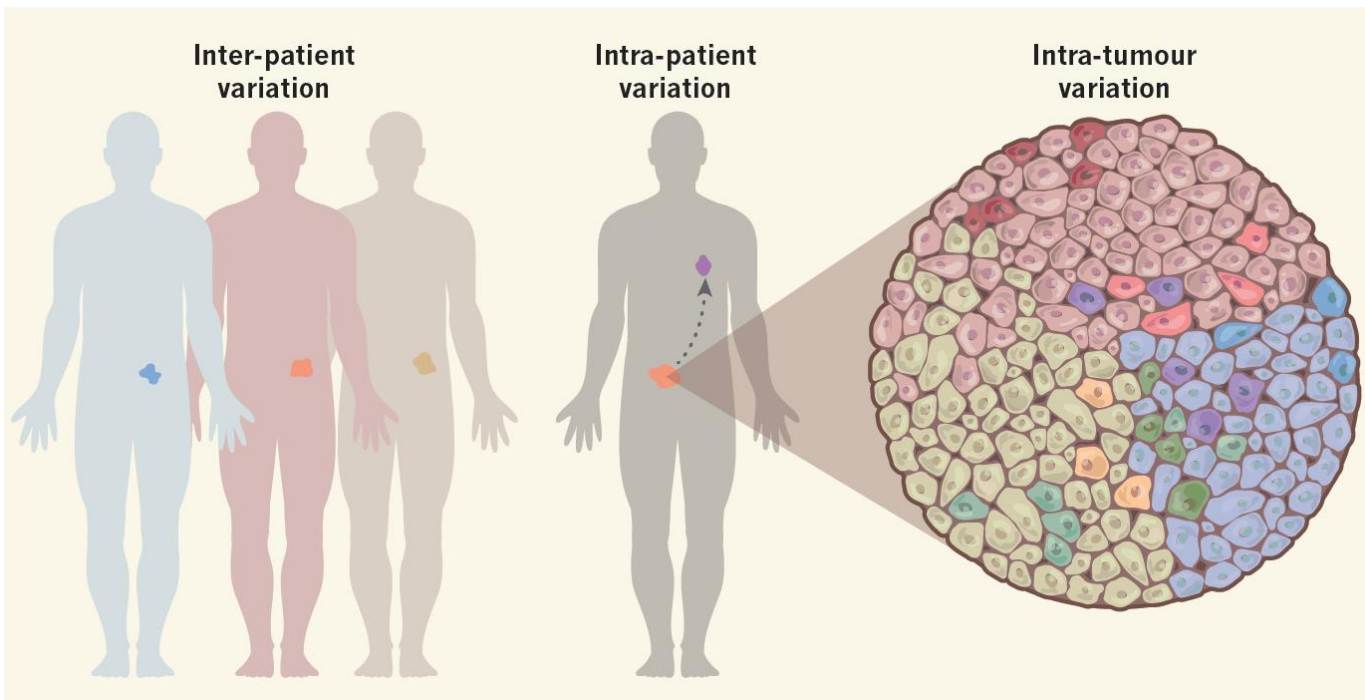


Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial

Imfinzi plus bevacizumab met primary endpoint for progression-free survival in liver cancer eligible for embolisation in EMERALD-1 Phase III trial

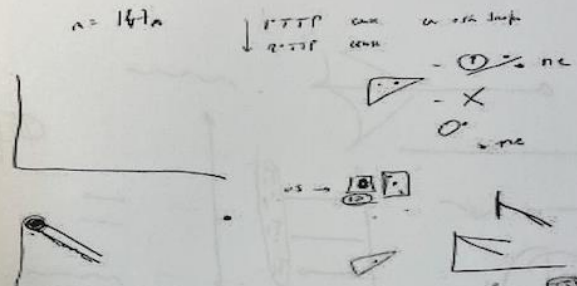


Molecular profile: One size does not fit all.



Hipótesis general del proyecto de tesis.

primer documento grafico de la hipótesis general.

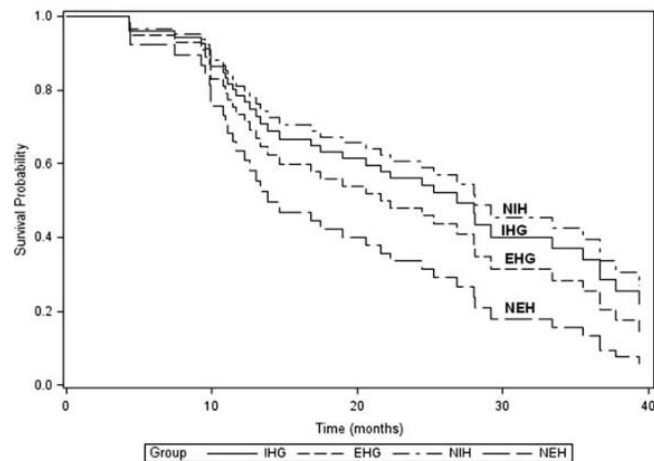


2008

HEPATOLOGY

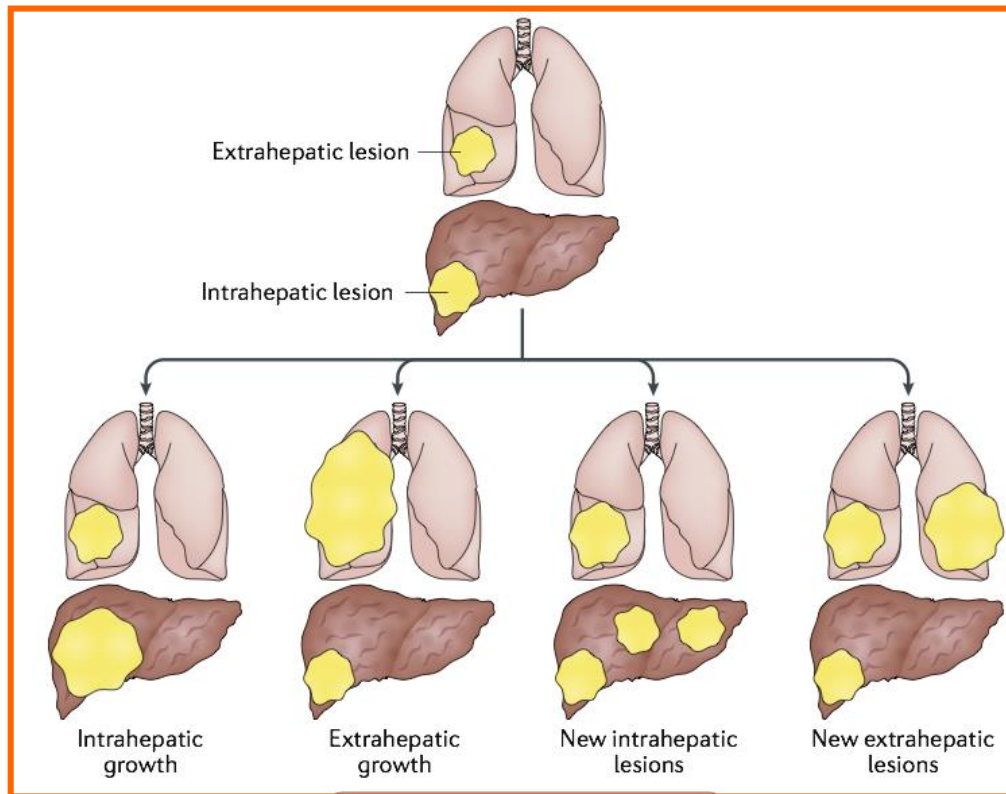
Postprogression Survival of Patients With Advanced Hepatocellular Carcinoma: Rationale for Second-Line Trial Design

Maria Reig,^{1,2} Jordi Rimola,^{2,3} Ferran Torres,⁴ Anna Darnell,³ Carlos Rodríguez-Lope,^{1,2} Alejandro Forner,^{1,2} Neus Llarch,^{1,2} José Ríos,⁴ Carmen Ayuso,^{2,3} and Jordi Bruix^{1,2}



What does 'pattern of progression' mean?

Pattern of progression



Impact of Pattern of progression on Post-Progression Survival

Sorafenib

Iavarone et al. Hepatology 2015; Ogasawara et al Invest New Drugs. 2016;

Regorafenib

Bruix et al. Lancet. 2016

Tivantinib

Rimassa et al. Lancet Oncol. 2018

Ramucirumab

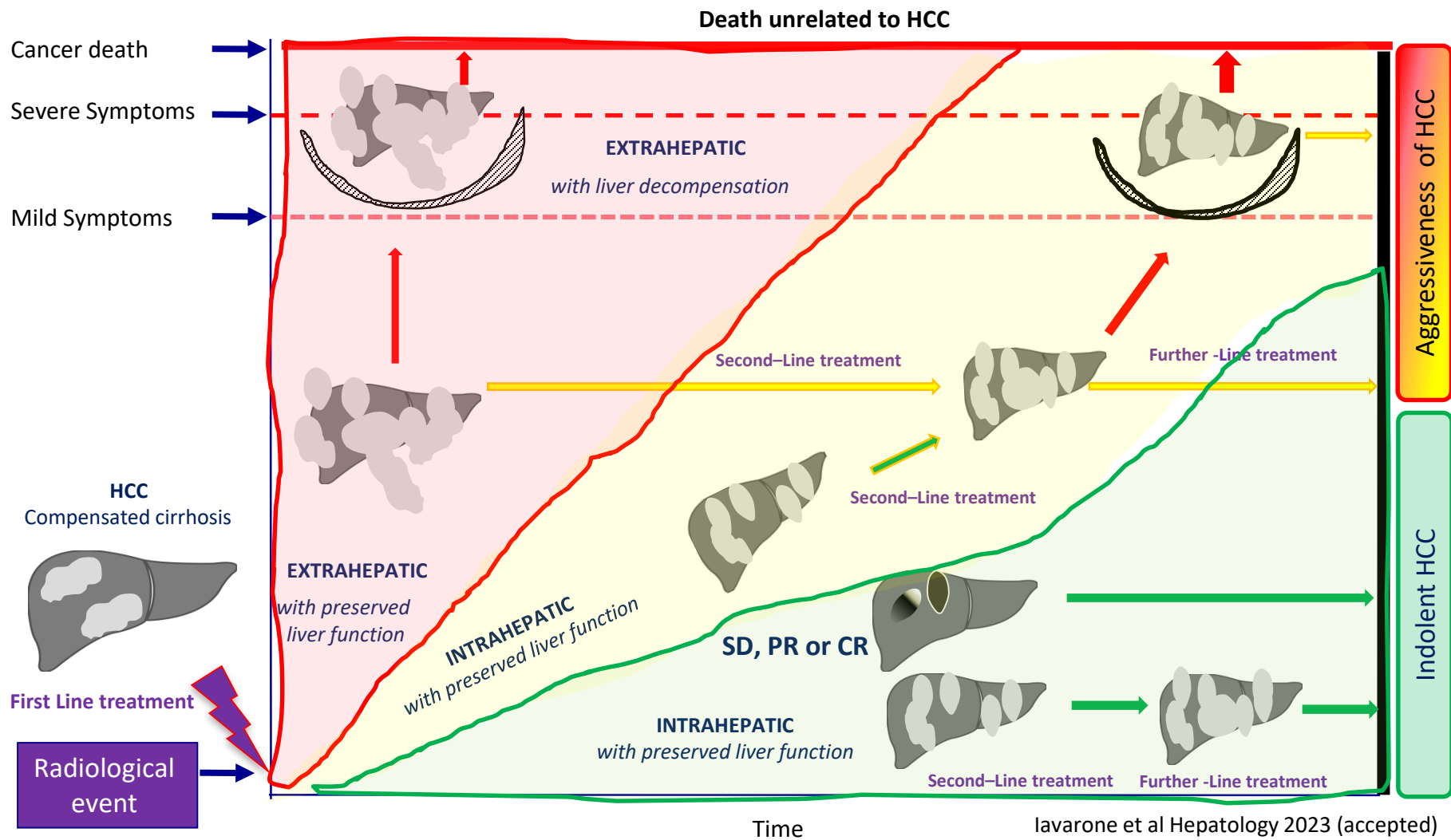
Reig et al Liver International 2021

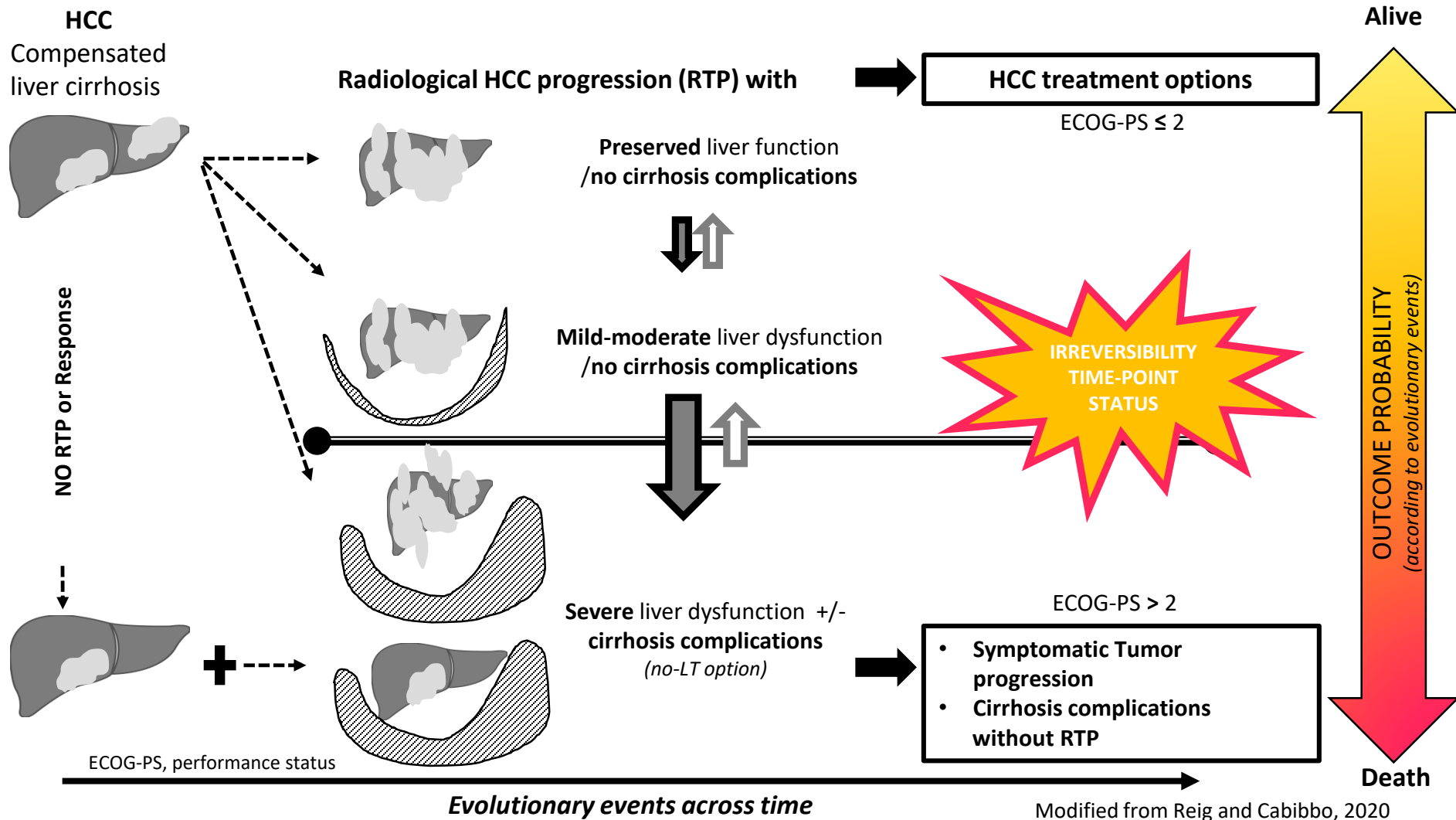
Radioembolization

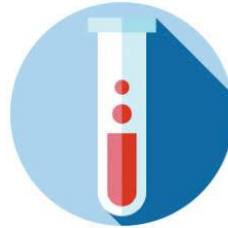
de la Torre-Aláez et al. Cardiovasc Intervent Radiol 2020

Atezolizumab-Bevacizumab

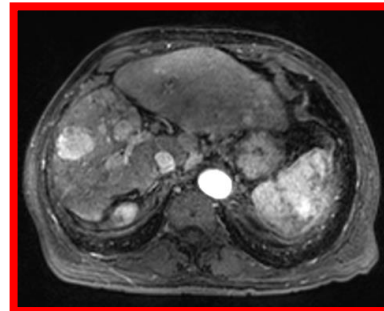
Talbot et al. Liver International 2022; Campani et al Hepatology 2023







AFP
Liver Function
Biochemical test



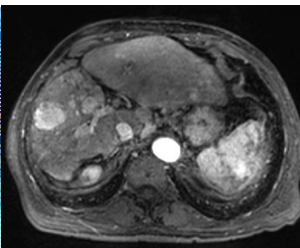
2024 - Tools to monitoring immunotherapy

Proposals and preliminary data



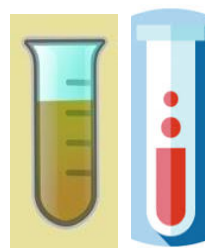
Radiomics

Ho et al Cancers 2023, 15, 1105



Liquid Biopsy

Winograd et al. Hepatol Commun. 2020.



Microbiome

Zeng et al. J Immunother Cancer. 2019



Deep Learning Approaches

Zeng et al. J Hepatol . 2022 Jul;77(1):116-127.

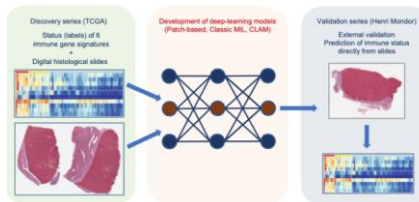


Antidrug Antibodies Against

Kim et al. JAMA Oncol . 2022 Dec 1;8(12):1825-1829.

Molecular analyses

Havel et al. Nat Rev Cancer. 2019 Zhu et al. Nat Med . 2022 Aug;28(8):1599-1611.



- Tumour antigens and mutation burden
- Neoantigen-based prediction
- Mutation signatures and microsatellite instability.
- The immune microenvironment

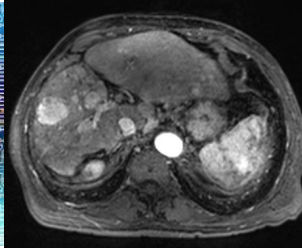
The new paradigm of knowledge

What is the winning paradigm?

Knowledge

Promotion

Financing



Diversification

Collective Intelligence

MINISTERIO -CIBER



MINISTERIO
DE CIENCIA
E INNOVACIÓN



Financiado por
la Unión Europea
NextGenerationEU



Subdirección General de Evaluación
y Fomento de la Investigación



2022

CONVOCATORIA PROYECTOS DE INVESTIGACIÓN DE MEDICINA PERSONALIZADA. GRUPO COORDINADOR. MEMORIA DE SOLICITUD

Expediente N°:
PMP22/00054

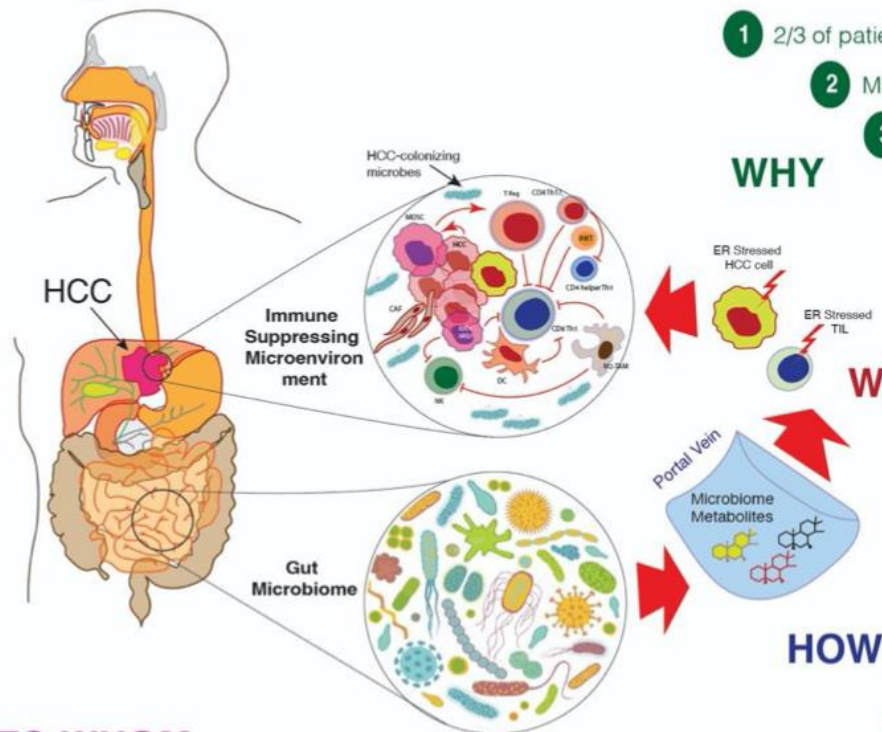
TÍTULO: Exploring the Feasibility of predictive and pharmacodynamics biomarkers of immunotherapy in solid tumors (Immune4ALL)

INVESTIGADOR PRINCIPAL: Enrique de Álava Casado

Modalidad: Multicéntrico con un centro solicitante

RETO

Rational to modulate the Microbiome-induced Endoplasmic Reticulum stress as tool to avoid the immune evasion in HCC



1

2/3 of patients with HCC do not respond to Immunotherapy (IT)

2

Microbiome modification has been reported to modify IT sensitivity

3

OUR preliminary data points to the enrichment of microbes HCC

4

Microbiome-derived metabolites are Endoplasmic Reticulum stressors

5

OUR preliminary data points to ER-stress response as an important cancer pathway related to immune surveillance

WHY

WHO

1

Multidisciplinary effort from 5 groups

2

260 HCC patients from 7 tertiary hospitals from 5 distant regions in Spain

3

Enhanced synergies between physicians, nurses, biologists, engineers, statisticians and the AECC

1

Identify the intratumoral bacteria involved in the response of HCC patients to immunotherapy

2

Generate a new panel of signatures to predict response/resistance to immunotherapy

3

Provide new mechanistic targets related to metabolite-derived ER Stress

4

Developing tools to predict HCC outcome

5

Establish the conditions for culturing and expanding IT-responders specific microbes

6

Integrating clinical and molecular data through an innovative informatic platform

HOW

TO WHOM

1

This project will make something new to improve the life of patients with HCC

2

This project will connect experts in different disciplines (Academia, Non-profit and industry)

3

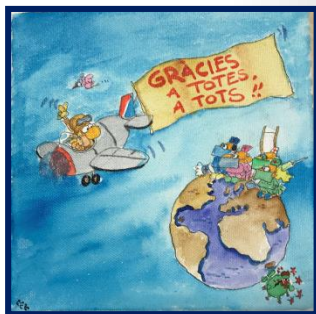
Promote direct interactions between patients with HCC, generating a science-driven patient network

FIGURE 3. Rational, Team, Objectives and expected broad outcomes of RETO coordinated project

Multidisciplinary organization



BCLC group 2024



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Gracias por su atención

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