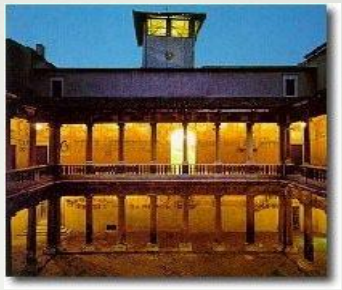
Up date on the systemic therapy of HCC

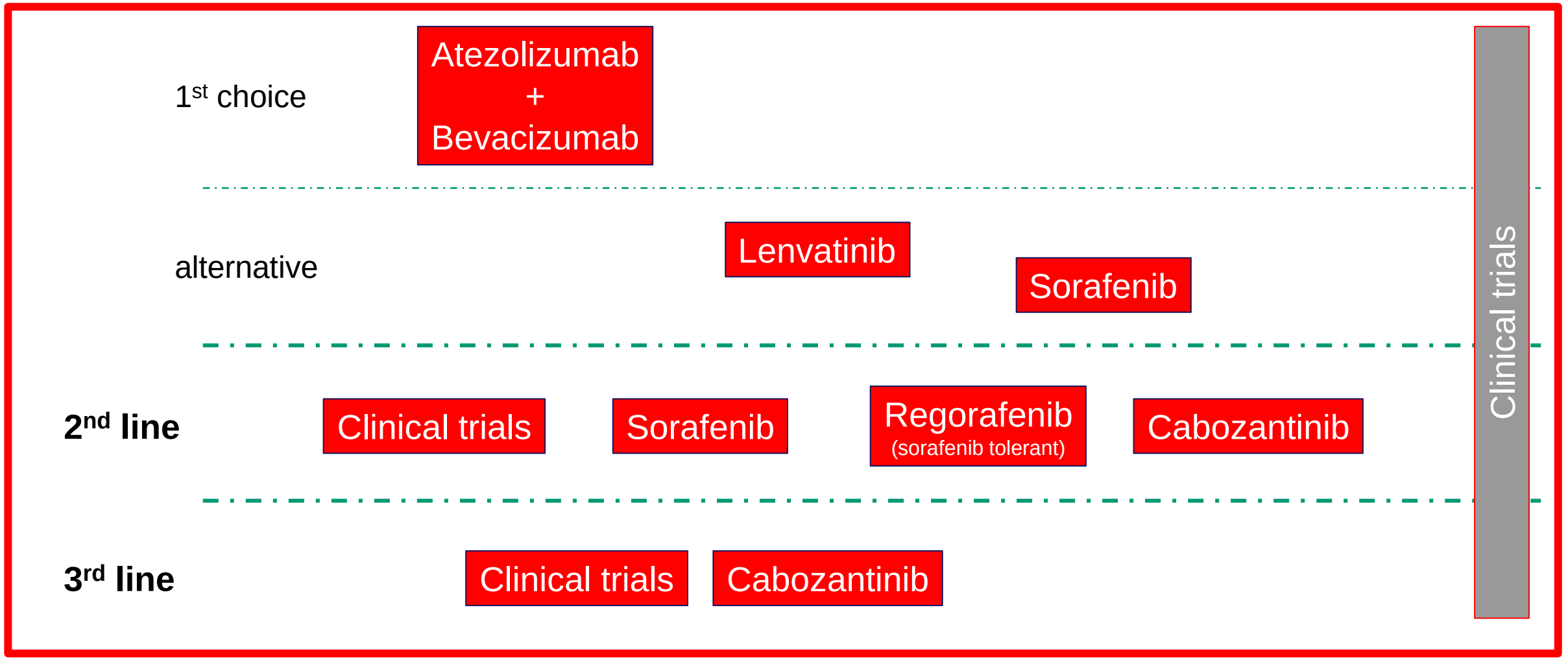
F.Farinati - Padova

No conflict of interest



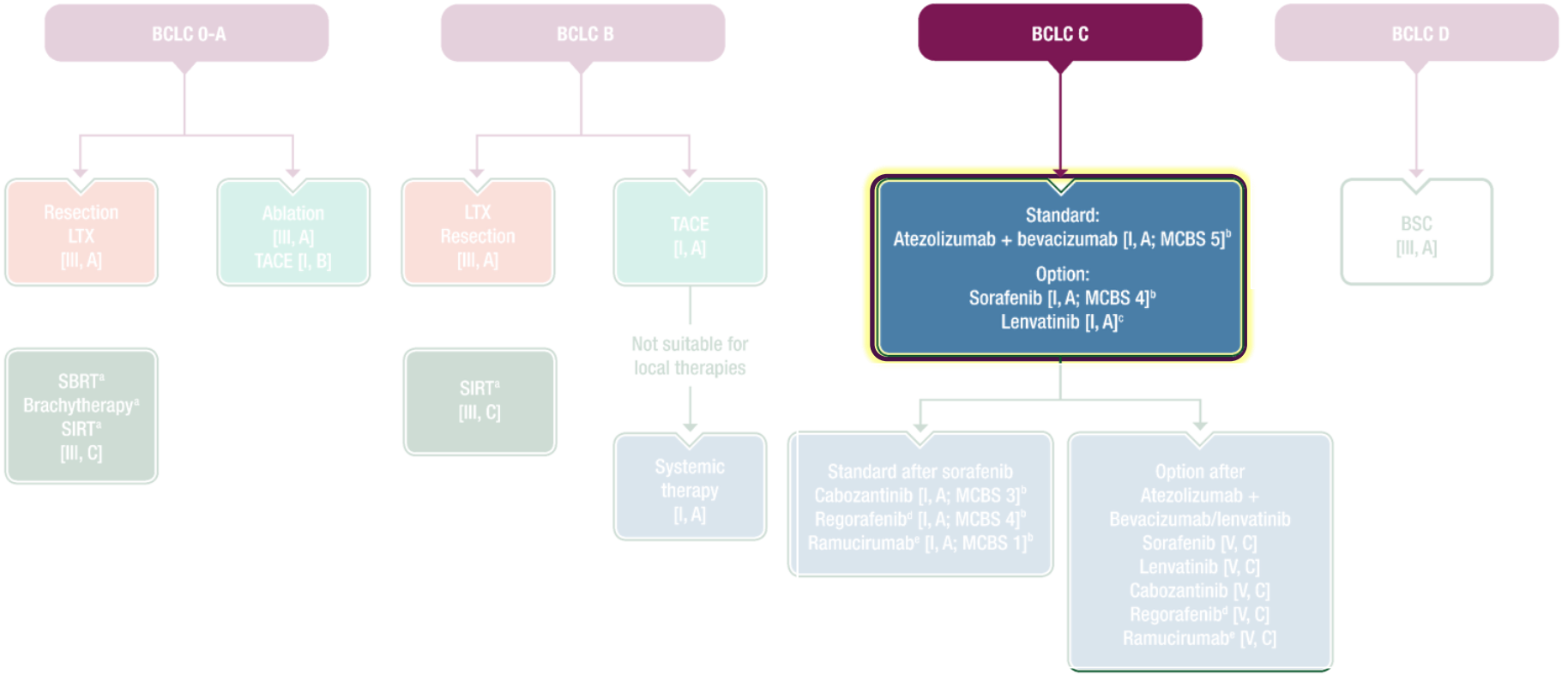
Systemic treatments for advanced HCC: Italy, TO DAY

Patient and drug selection [patient's willingness, CPT, ECOG-PS, staging, comorbidities (cardio-vascular risk, immunological-profile), bleeding risk (EGV, CT-scan, drugs)]



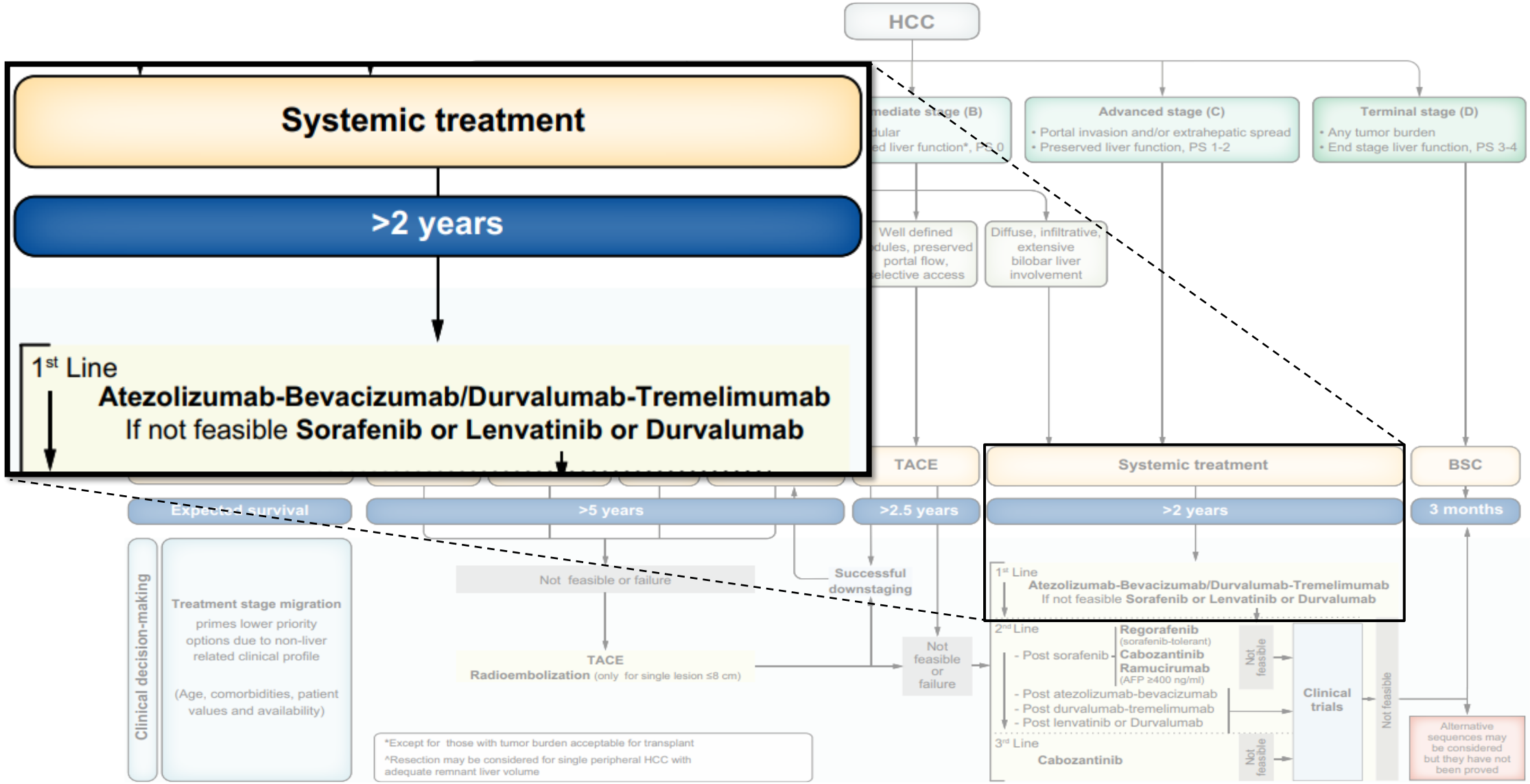
Current Recommendations: ESMO Guidelines

1) Atezo+Bev becomes the **standard first-line therapy whenever no contraindications preclude its use**
2) Sorafenib or lenvatinib are **alternative options for those patients not suitable for Atezo+Bev**



Galle PR, et al. J Hepatol. 2018;69(1):182-236. eUpdate available at: eUpdate: Hepatocellular Carcinoma Treatment Recommendations (esmo.org).

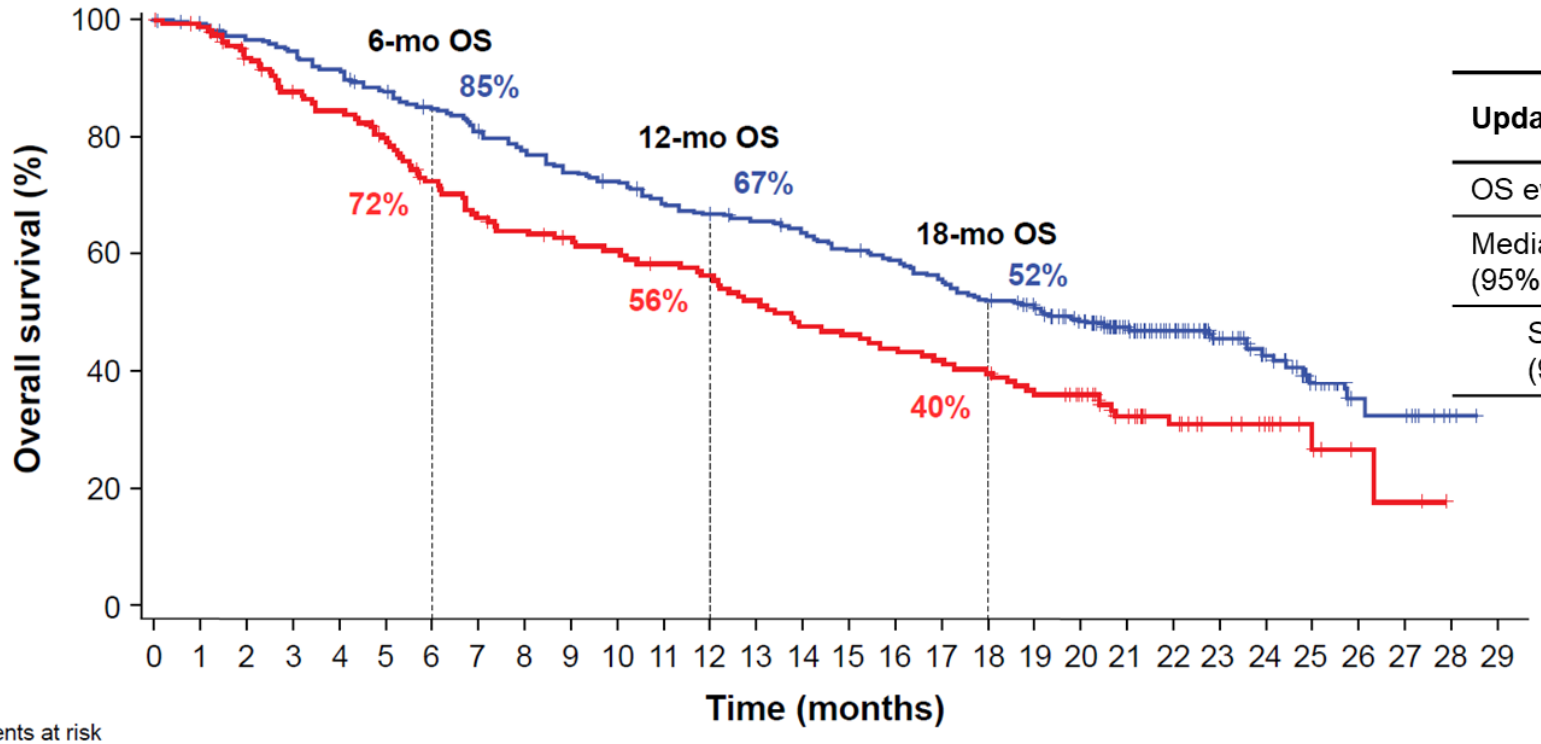
Systemic treatment in HCC : BCLC Guidelines



Reig M et al. Journal of Hepatology 2022 vol. 76 j 681–693.

IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib

Updated OS



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

No. of patients at risk

Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	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.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

ASCO GI 2021 Presented by RS Finn

Cheng et al. Journal of Hepatology 2022, 76,862-873


TIME
for
change

Systemic treatment for HCC: the HIMALAYA trial

Primary Endpoint – OS for STRIDE vs Sorafenib (superiority)

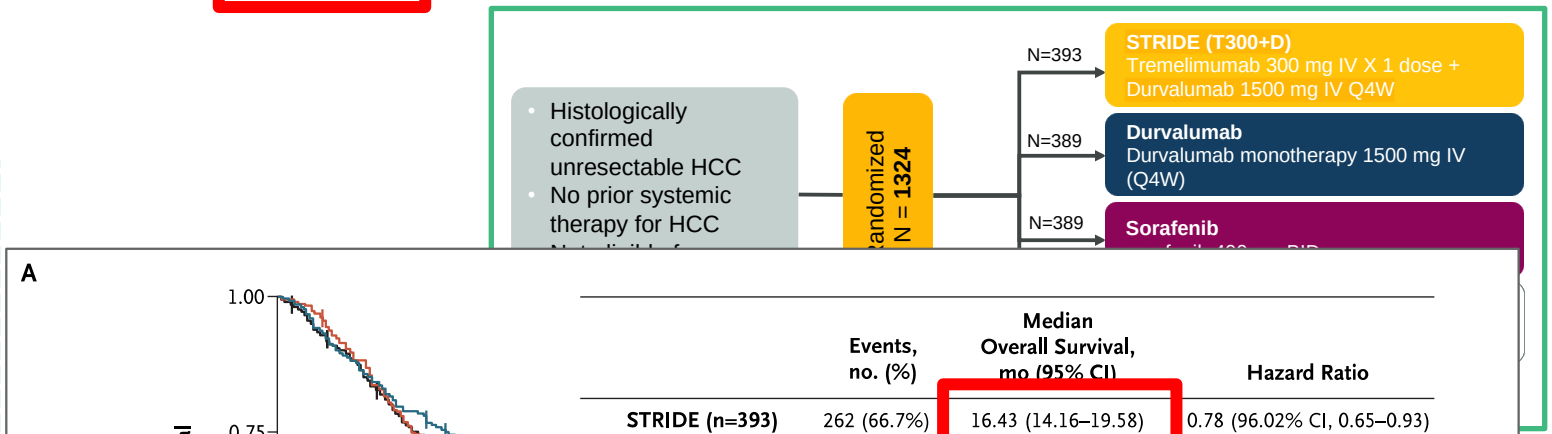
Atezolizumab + Bevacizumab

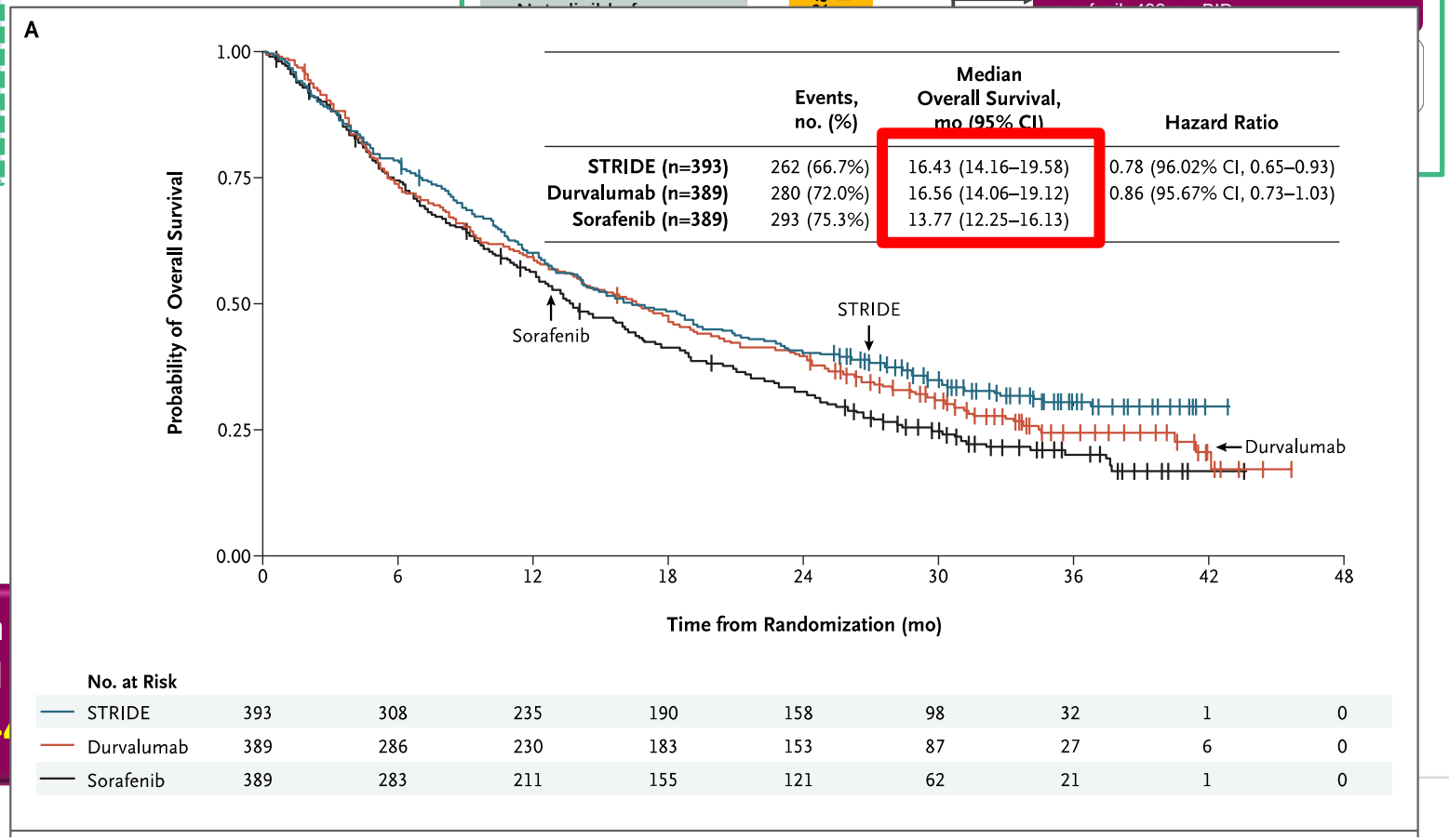
Durvalumab + Tremelimumab (STRIDE)

sorafenib superiority threshold

Durvalumab is an anti-**PD-L1** monoclonal antibody that primarily acts later in the immune response to enhance effector T cell function in the tumor

- **Tremelimumab** is a human monoclonal **inhibitor of CTLA-**





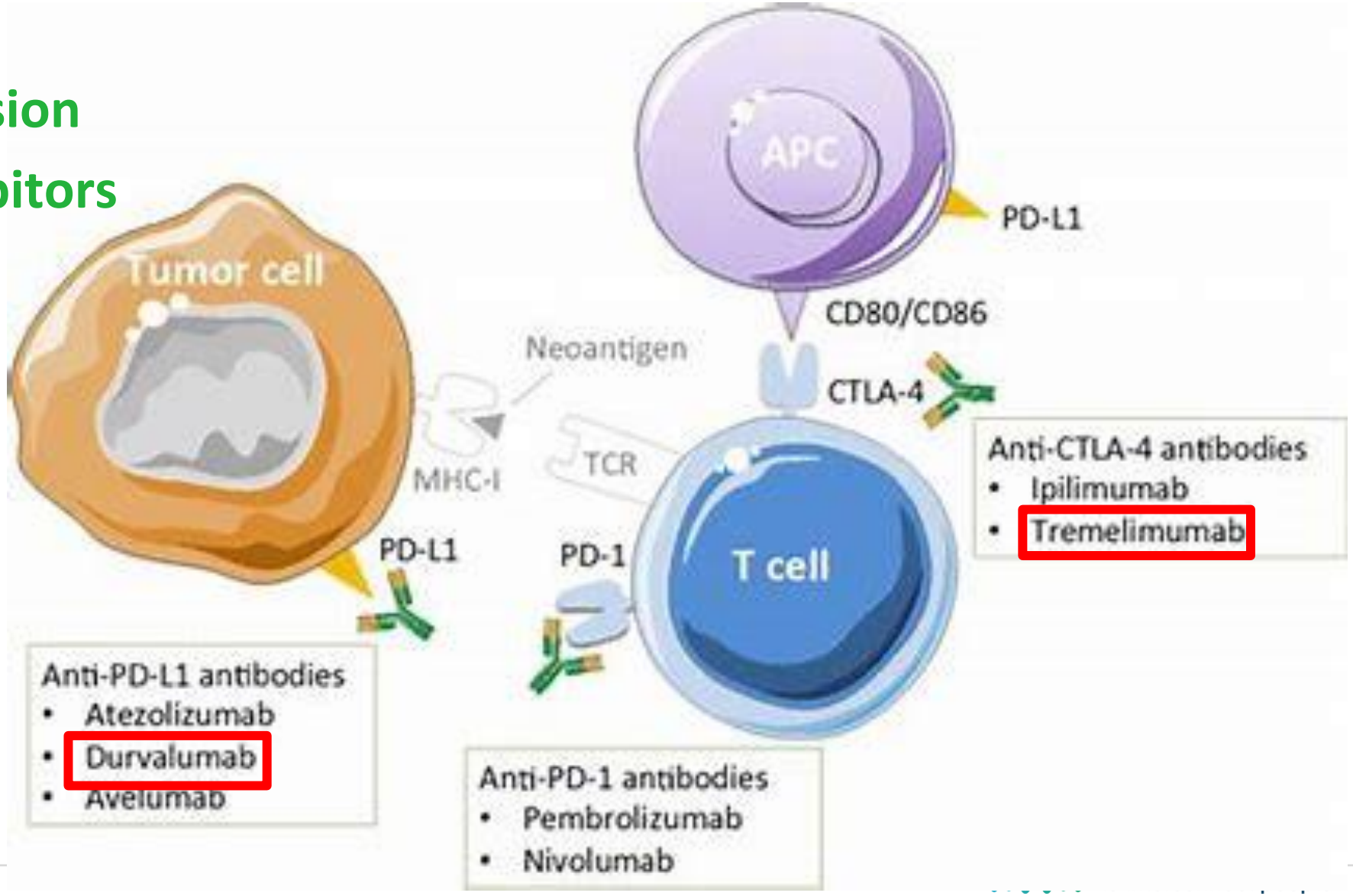
Abu-Alfa GK et al, N Eng J Med 2022

Tumor immunologic microenviroment

Reversing local

Immunosuppression

Check Point Inhibitors



Atezo/Beva vs Treme/Durva

Patients' choice

Eligibility
Anti-PD1/PDL1

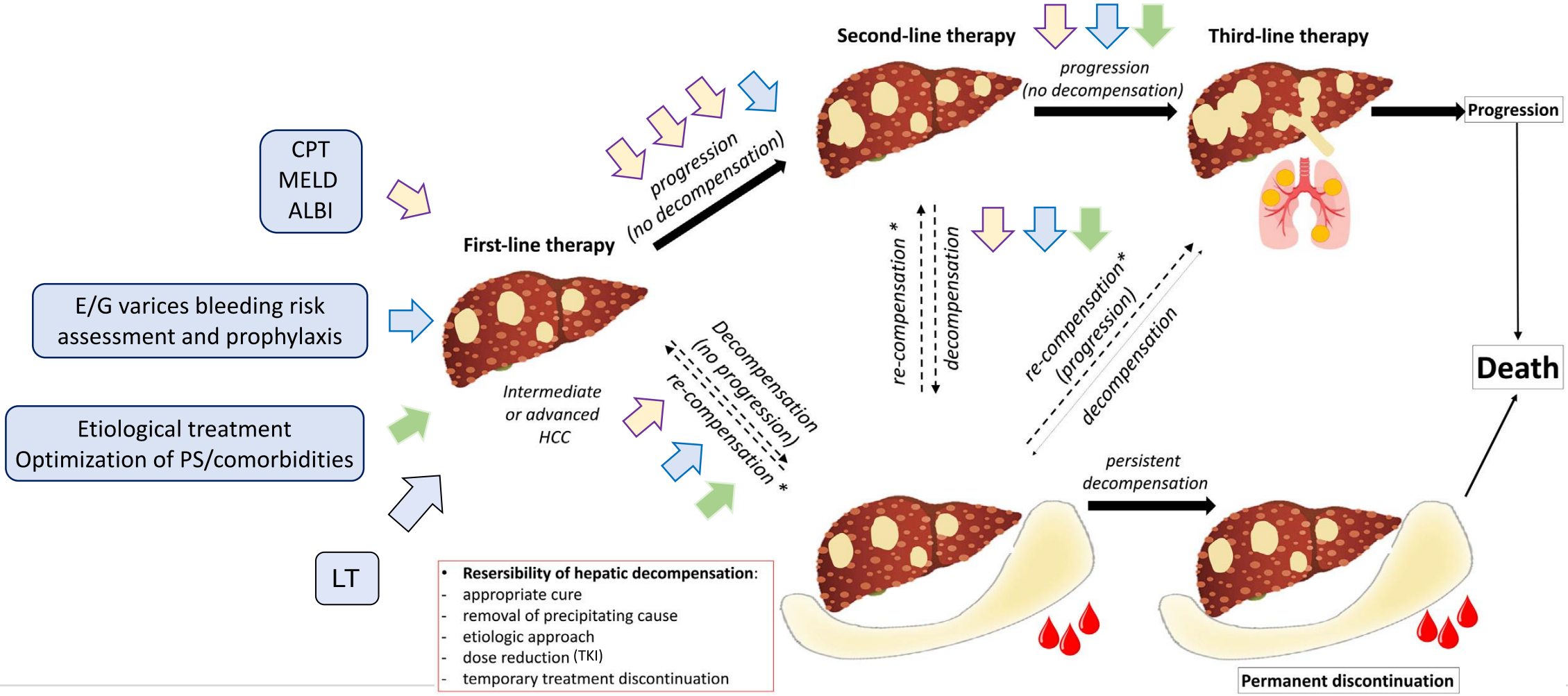
Costs

ology

BUILDING BRIDGES
to interconnect people

Patient's assessment

Patient and drug selection [patient's willingness, CPT, ECOG-PS, staging, comorbidities (cardio-vascular risk, immunological-profile), bleeding risk (EGV, CT-scan, drugs)]



Modified from Cabibbo G et al. Digestive and Liver Disease 2022

Potentially less suitable patients for an I/O + anti-angiogenic therapy regimen

PREVALENCE OF HISTORICAL MEDICAL CONDITIONS OR COMORBIDITIES WITH POTENTIAL ROLE IN CLINICAL DECISION MAKING RELATED TO SUITABILITY OF IMMUNO-ONCOLOGIC PLUS IV ANTI-ANGIOGENIC THERAPY IN NEWLY DIAGNOSED FIRST LINE UNRESECTABLE HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

Abstract Number: 511

Tammy Schuler Ph
1 Cardinal Health Spec

Table 4. Medical conditions and comorbidities at 1L initiation

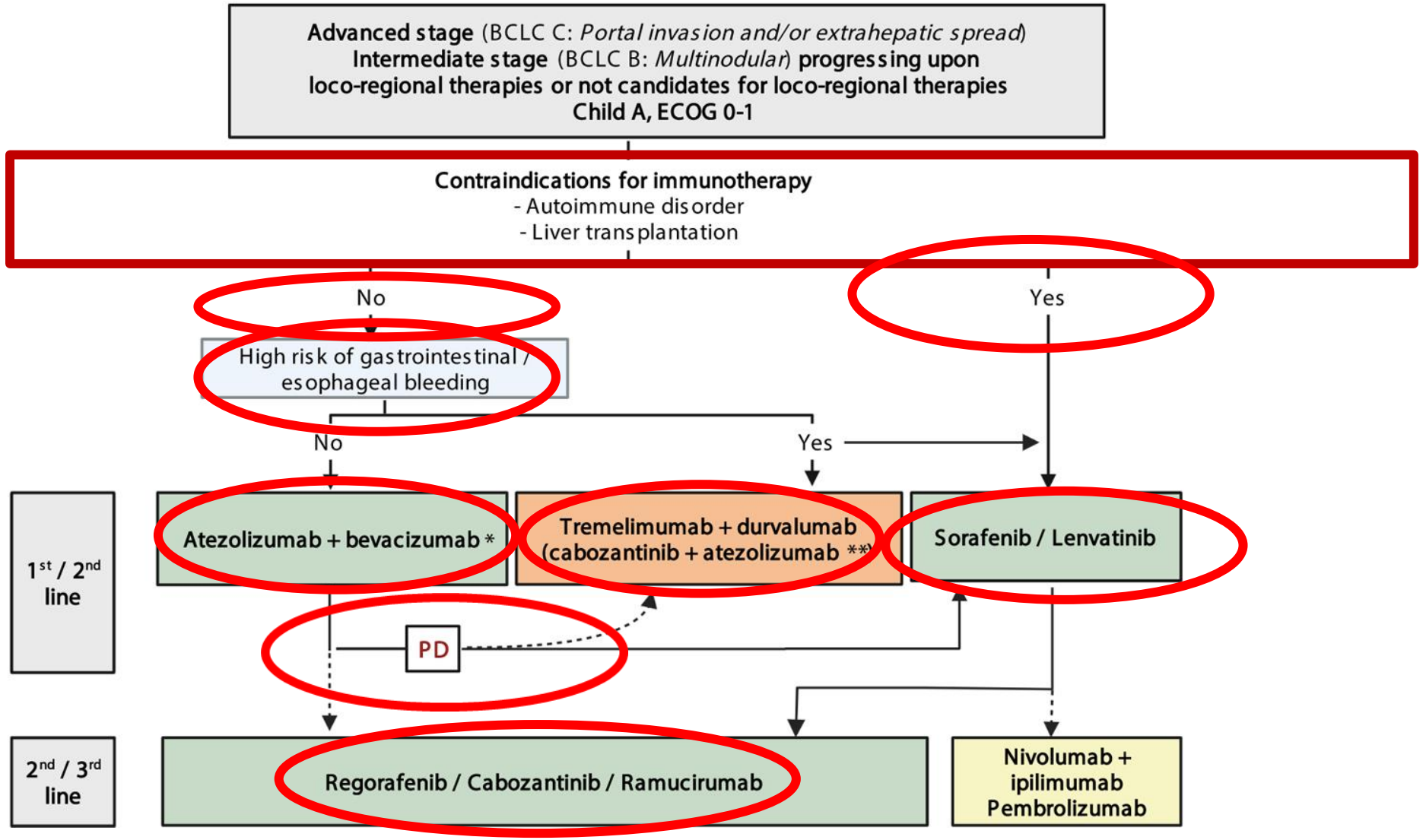
Upper/lower GI bleeding risk, n (%)	164 (37.9%)
Chronic kidney disease, n (%)	64 (14.8%)
Arterial/Venous thromboembolic event history, n (%)	50 (11.5%)
Autoimmune disorder history, n (%)	22 (5.1%)

1L, first-line, GI, gastrointestinal

Presented at the ASCO Gastrointestinal Cancers Symposium, January 19-21, 2023, San Francisco, CA

LT?

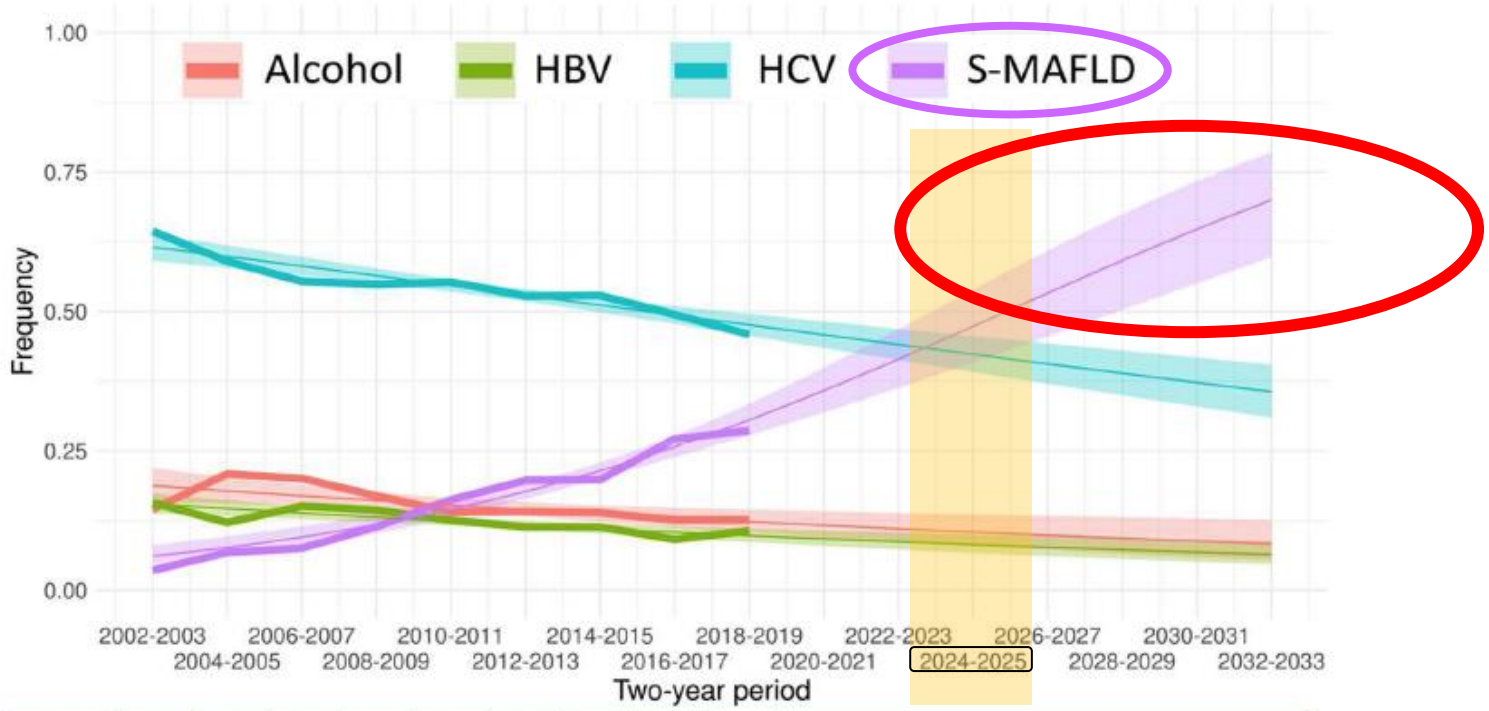
Some treatment algorithms are already published



Llovet JM, Pinyol R, Kelley RK, et al. Molecular pathogenesis and systemic therapies for hepatocellular carcinoma. Nat Cancer. 2022;3(4):386-401.

Evolving aetiology of HCC

(ITA.LI.CA database 2018)

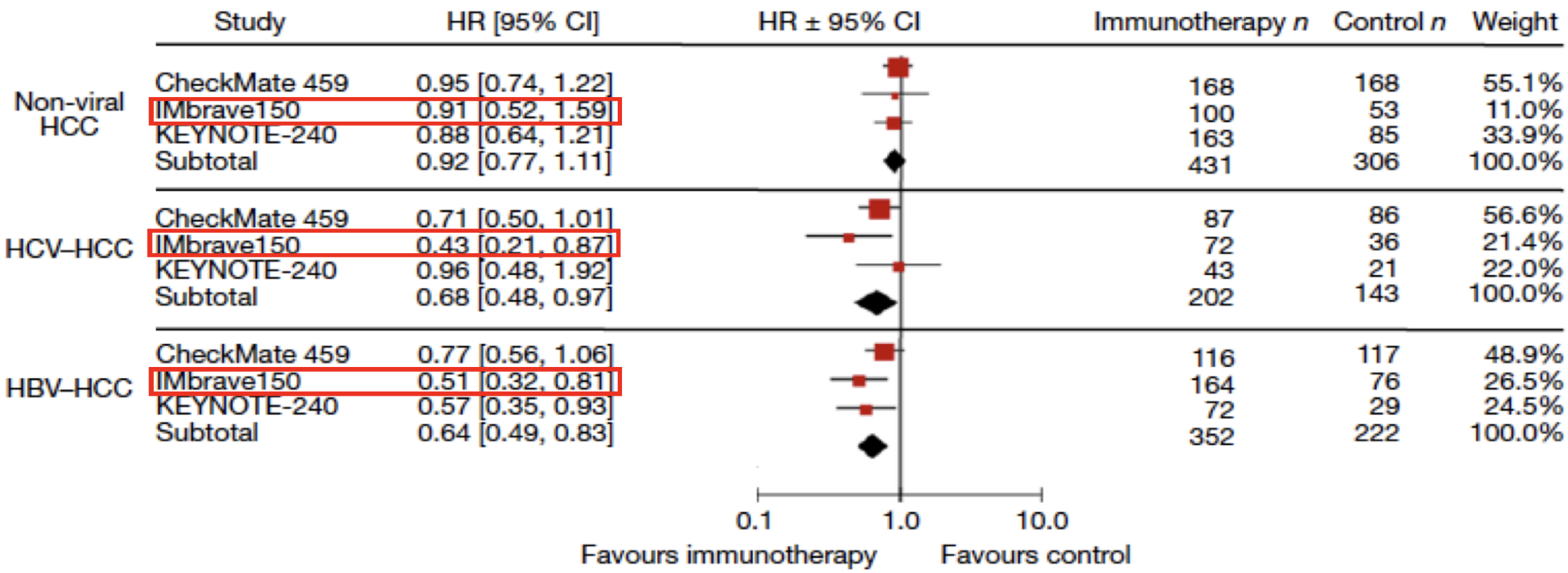


S-MAFLD	28	28	35	76	146	208	230	261	169	---
Alcohol	102	86	93	113	125	150	159	124	73	---
HBV	104	50	70	96	113	120	130	86	62	---
HCV	450	243	257	366	496	557	608	469	268	---

Vitale A et al., for ITA.LI.CA. Gut Gut. 2023; 72:141-152

HCC NASH etiology

Meta-analysis of Immuno Check Point Inhibitors Therapy of HCC
1,656 Patients in RCTs

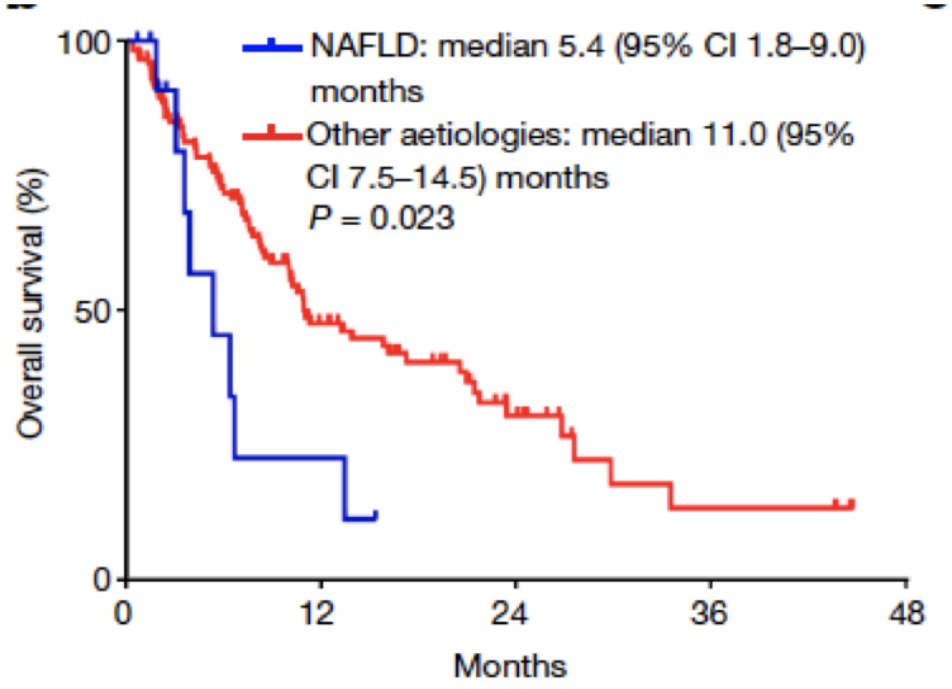


Pfister D et al Nature Research 2021

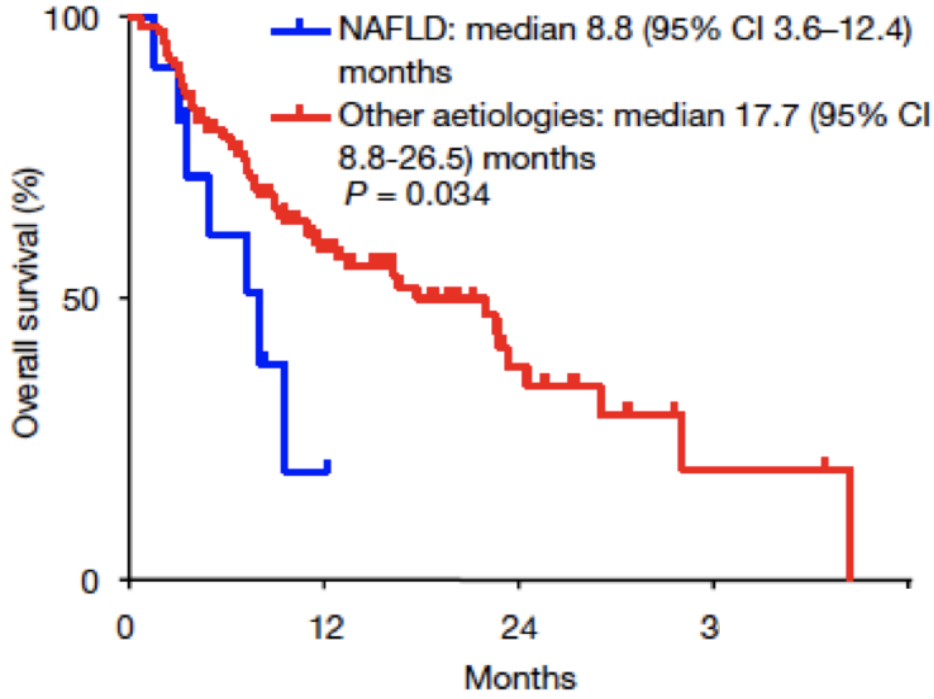
HCC NASH etiology

Real-life Treatment of HCC with PD(L)1-targeted Immunotherapy

N = 130 patients

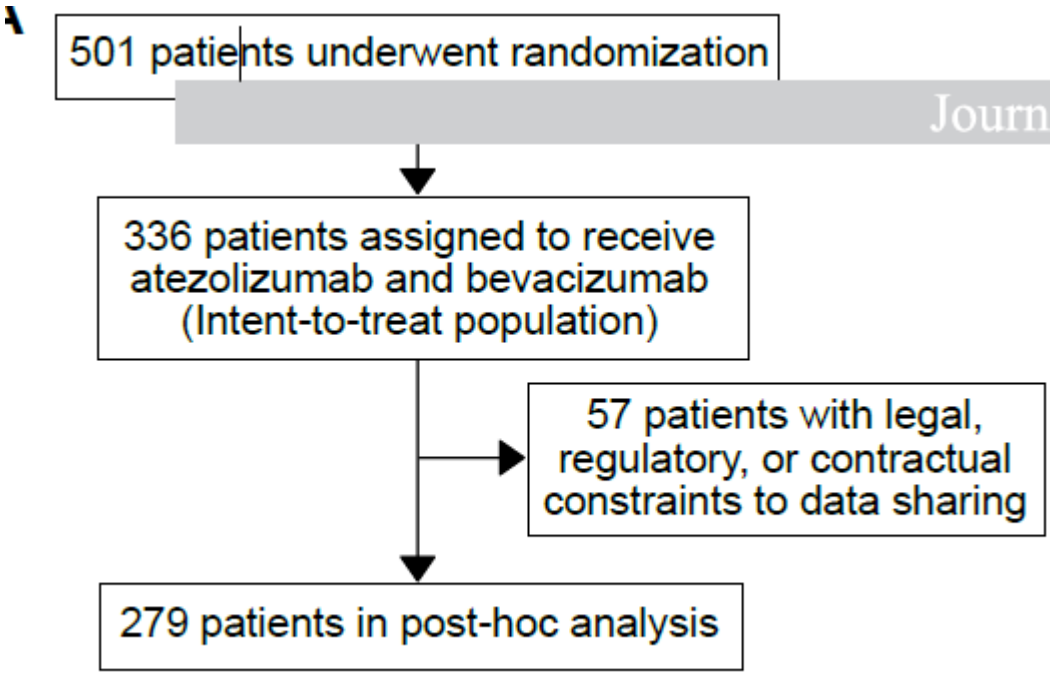


N = 118 patients



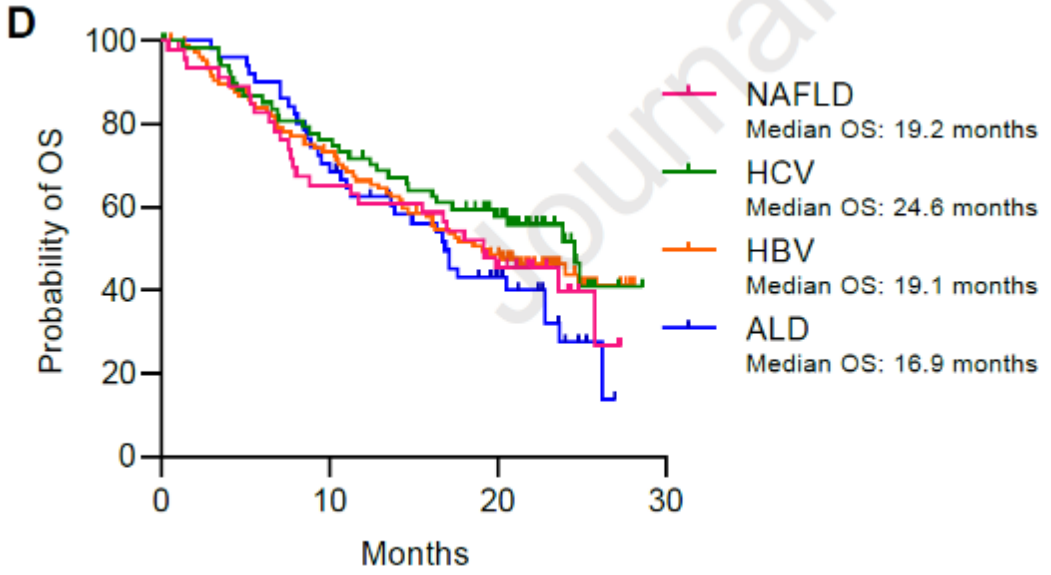
Pfister D et al Nature Research2021

Atezo-beva according to etiology



- NAFLD: 47 patients
- HCV: 70 patients
- HBV: 108 patients
- ALD: 51 patients
- Other/unknown causes: 3 patients

mOS



Not significant different across multiple comparisons

Log-rank test: multiple curves p=0.41

- NAFLD vs HCV HR=1.34, p=0.26
- NAFLD vs HBV HR=1.1, p=0.68
- NAFLD vs ALD HR=0.89, p=0.65

Espinoza M et ak. Gastroenterology. 2023;S0016-5085(23)00234-2.

European Journal of Cancer
Available online 25 November 2022
In Press, Journal Pre-proof

Original Research

Atezolizumab plus bevacizumab versus Lenvatinib for unresectable hepatocellular carcinoma: a large real life worldwide population

Andrea Casadei-Gardini [a] [1] ✉, Margherita Rimini [b, 1], Toshifumi Tada [c], Goki Suda [d], Shigeo Shimose [e], Masatoshi Kudo [f], Jaekyung Cheon [g], Fabian Finkelmeier [h], Ho Yeong Lim [i], Lorenza Rimassa [j, k], José Presa [l], Gianluca Masi [m], Changhoon Yoo [n], Sara Lonardi [o], Francesco Tovoli [p], Takashi Kumada [q], Naoya Sakamoto [d], Hideki Iwamoto [e], Tomoko Aoki [f], Hong Jae Chon [g] ...Alessandro Cucchetti [aw]

Study Design

- HCC diagnosed histopathologically or clinically
- No prior systemic treatment
- Retrospectively collected between May 2015 and April 2022
- Western and Eastern populations from 42 centers in 5 countries (Italy, Germany, Portugal, Japan, and the Republic of Korea)

Atezo-bev
1200mg – 15mg/kg IV every 3 weeks
n=864

Lenvatinib
8mg/day if > 60kg
12mg/day if ≤ 60kg
n=1341

IPTW

Atezo-bev
1200mg – 15mg/kg IV every 3 weeks
n=864

Lenvatinib
8mg/day if > 60kg
12mg/day if ≤ 60kg
n=1343

- TTP
- OS
- Safety

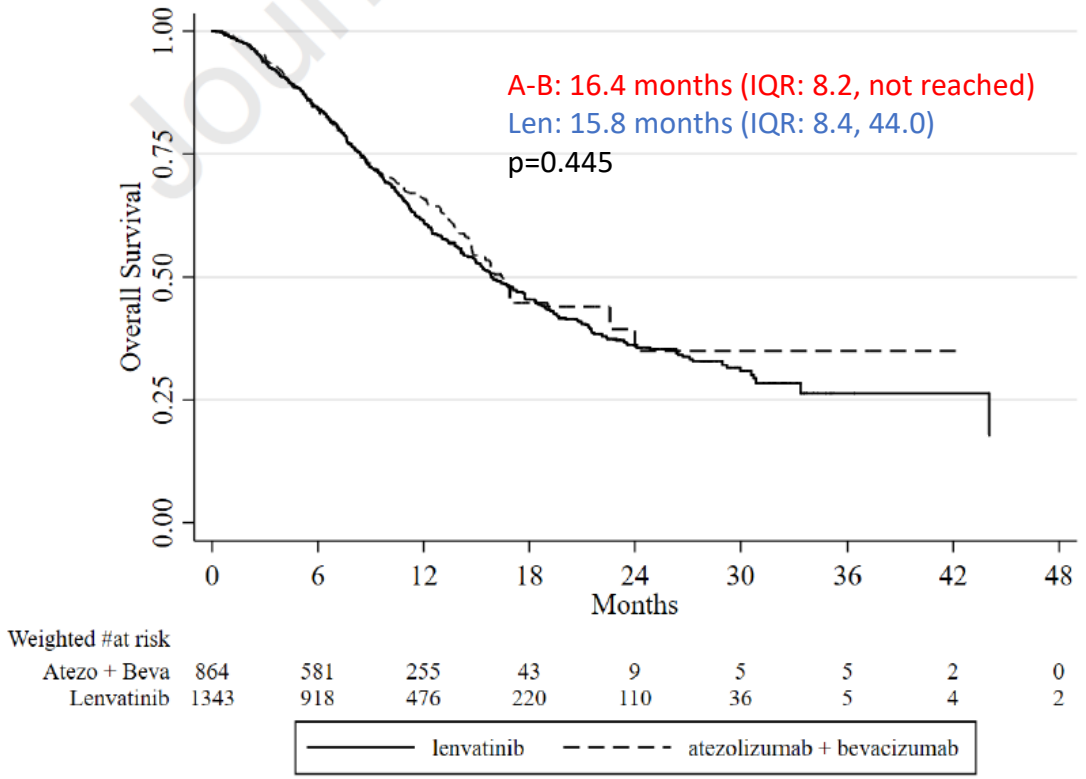
Follow-up
Atezo-bev: 11.1 months (6.8, 15.0)
Lenvatinib: 13.8 months (7.6, 22.9)

IPTW: Inverse Probability of Treatment Weights

Casadei-Gardini et al. European Journal of Cancer 180 (2023) 9e20

Overall Survival

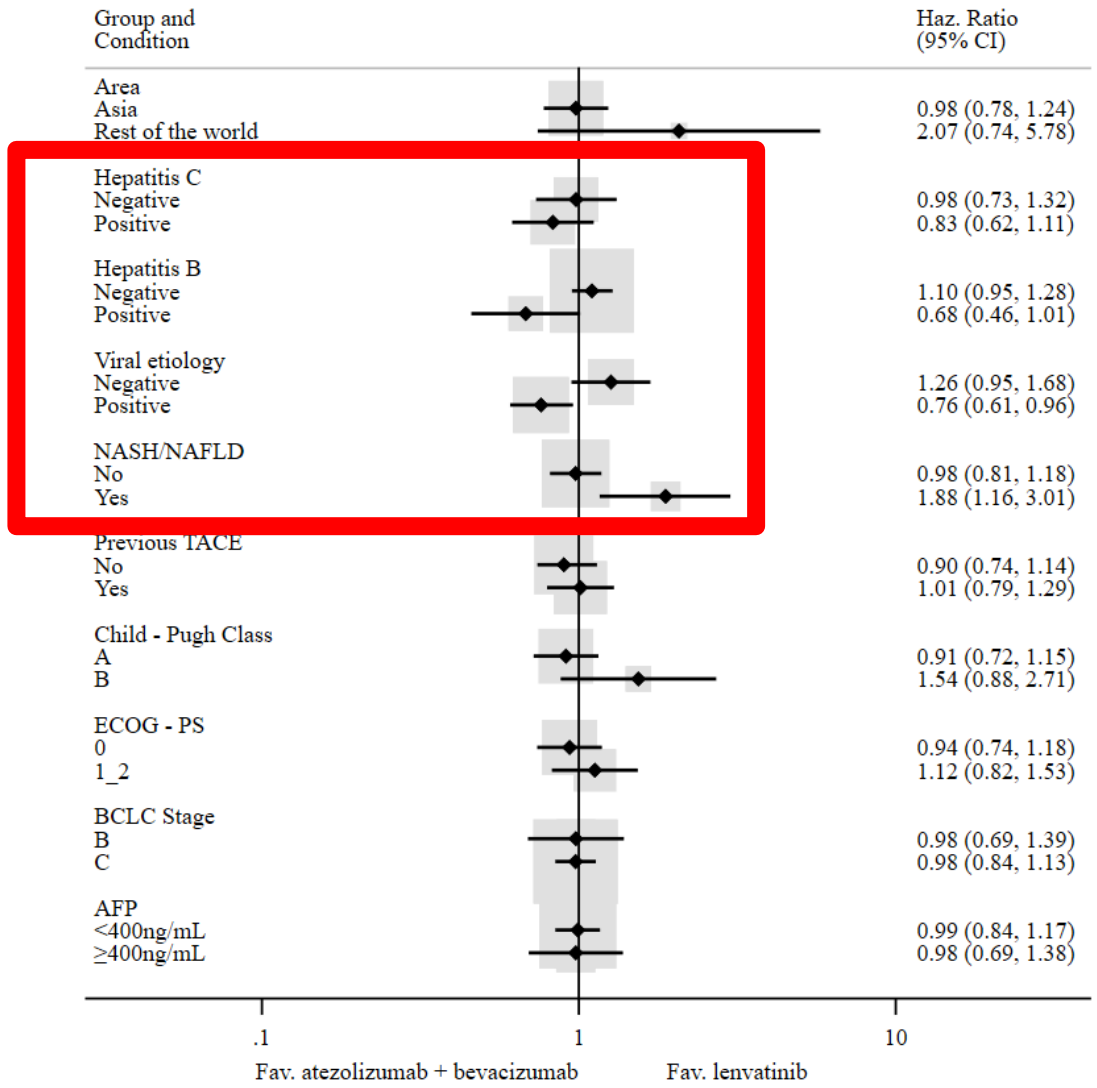
All etiologies



- After adjustment for centres' effect and 2L therapies received, no significant difference was observed, given a HR for atezo-bev of 0.97 (95%CI: 0.80, 1.17; p=0.739).

Casadei-Gardini et al. European Journal of Cancer 180 (2023) 9e20

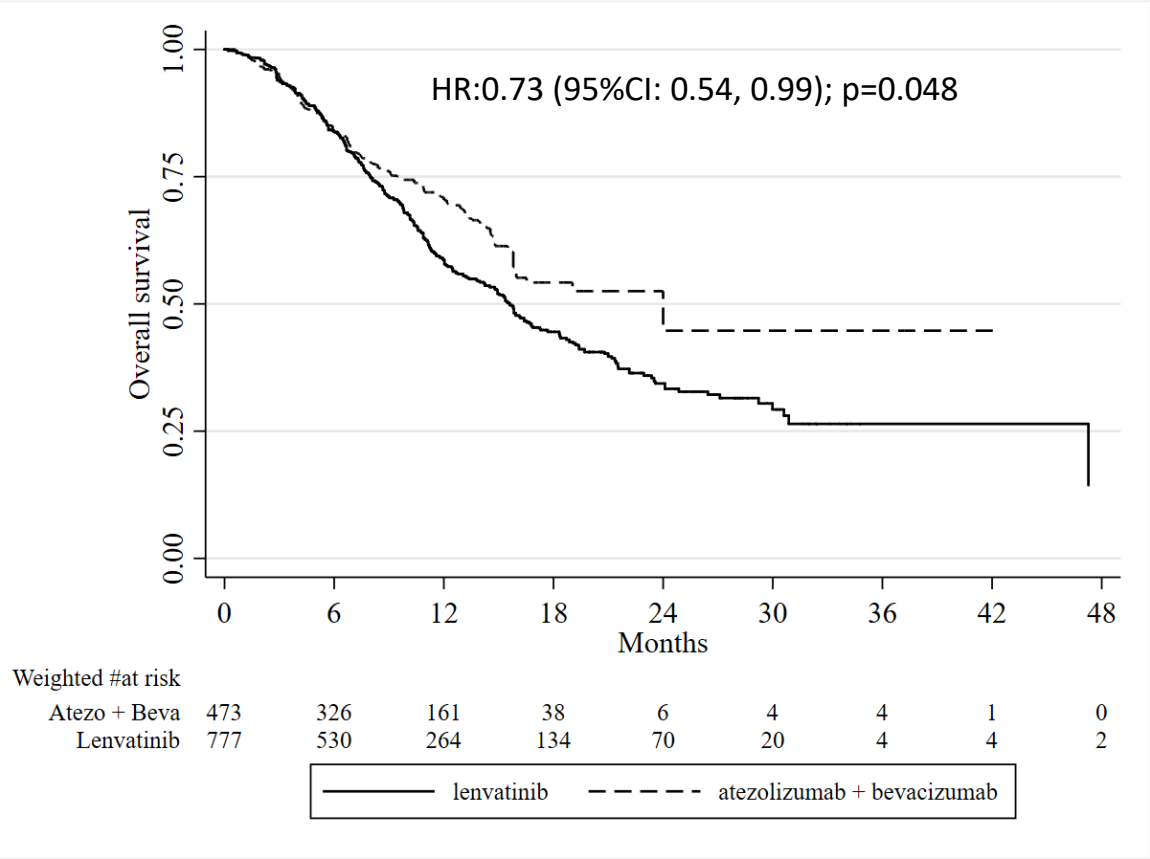
OS subgroup analysis



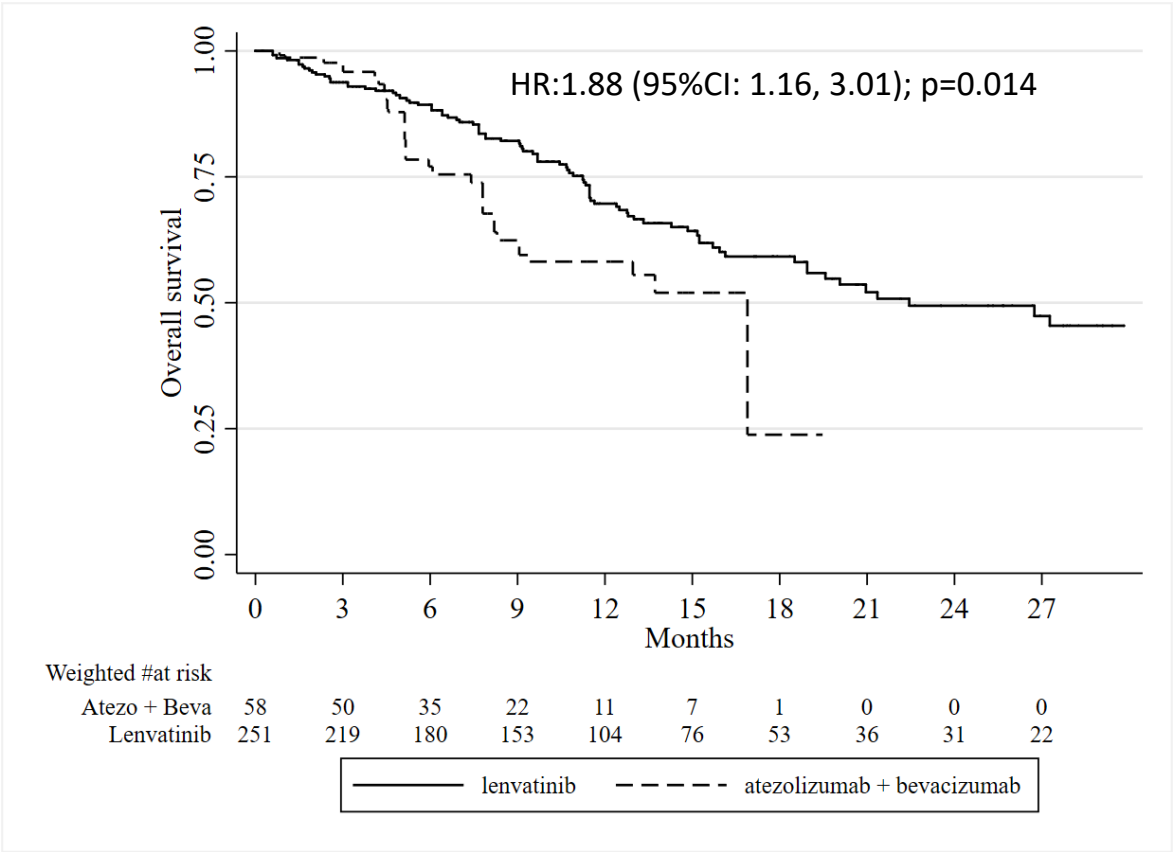
Casadei-Gardini et al. European Journal of Cancer 180 (2023) 9e20

Overall Survival by Etiology

Viral



NASH/NAFLD



Casadei-Gardini et al. European Journal of Cancer 180 (2023) 9e20

NAFLD/MAFLD/MASLD/SLD and CPI:   ?

Do not forget Lenva!

New challenges

Liver Cancer

Editorial

Liver Cancer 2022;11:487–496
DOI: 10.1159/000527404

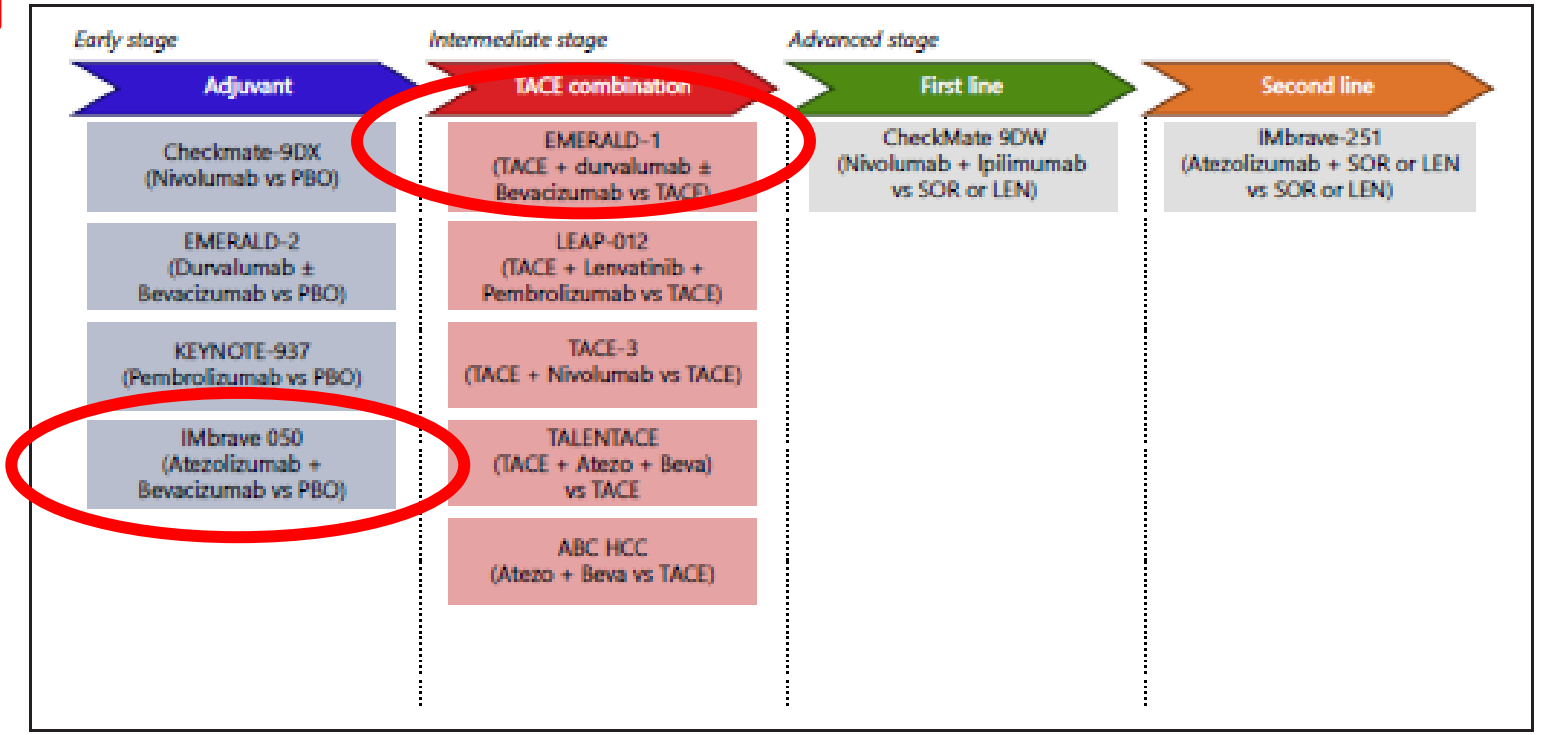
Received: September 5, 2022
Accepted: September 20, 2022
Published online: October 6, 2022

Implications of the TACTICS Trial: Establishing the New Concept of Combination/Sequential Systemic Therapy and Transarterial Chemoembolization to Achieve Synergistic Effects

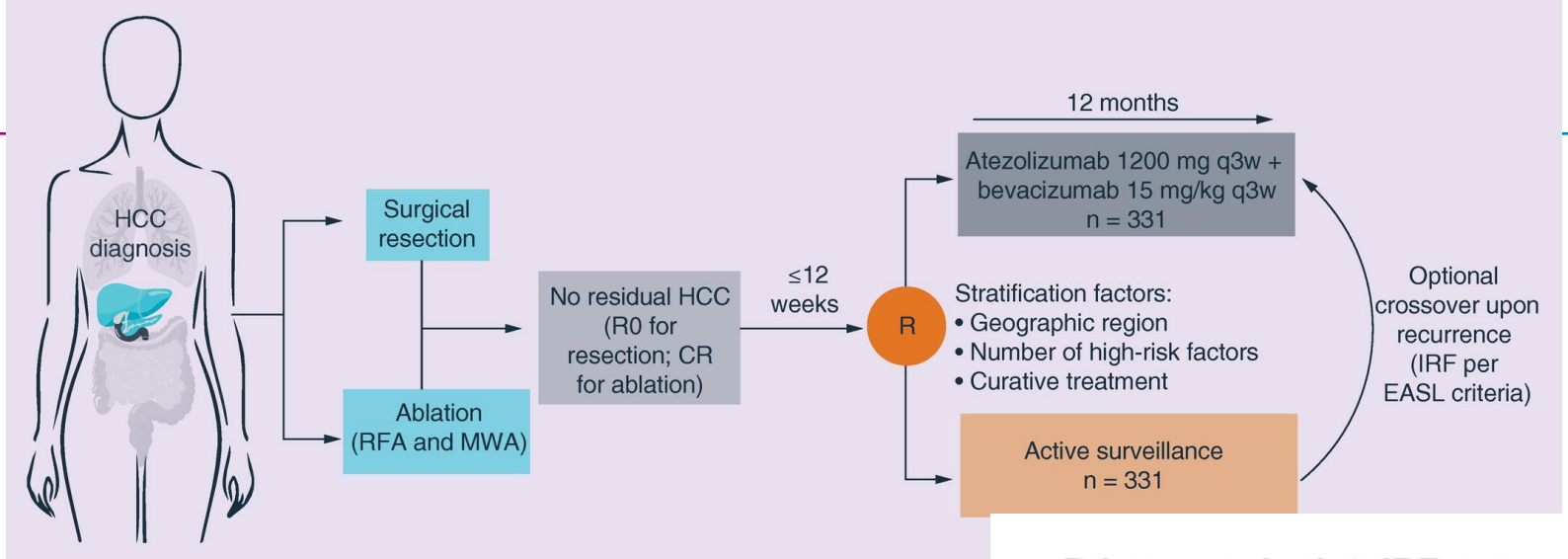
Masatoshi Kudo

Prof. M. Kudo

Editor *Liver Cancer*



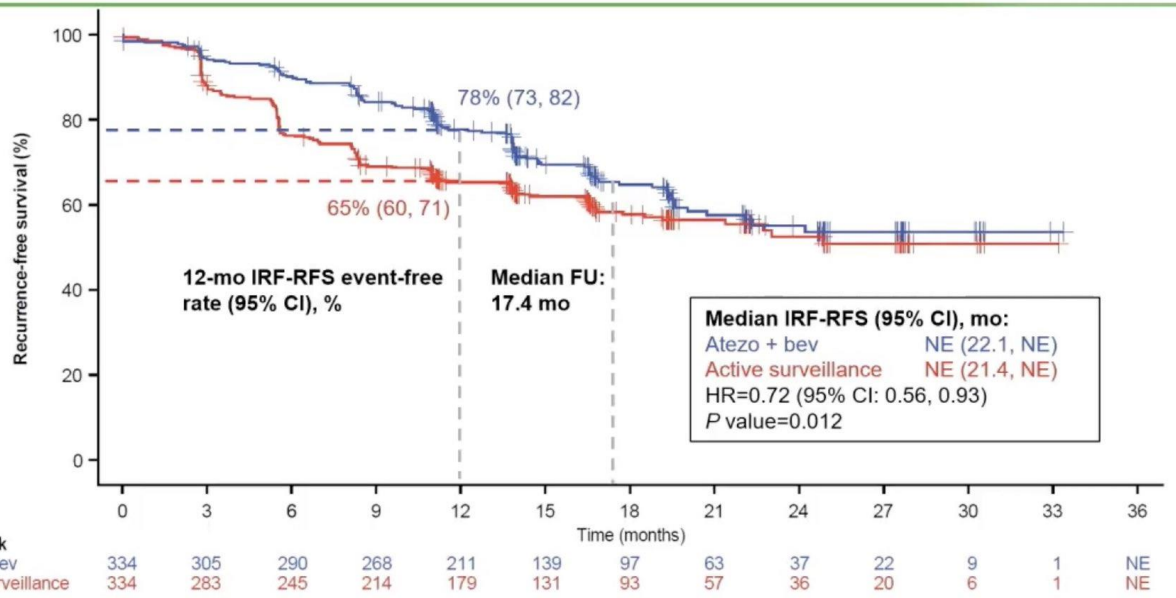
Adjuvant treatments



IMBRAVE 050

Primary endpoint: IRF-assessed RFS was significantly improved with atezo + bev vs active surveillance

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

Chow et al IMbrave050 https://bit.ly/3ZPKzgM 12

ASCO Gastrointestinal Cancers Symposium

EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization

Riccardo Lencioni*[1], Masatoshi Kudo[2], Joseph Erinjeri[3], Shukui Qin[4], Zhenggang Ren[5], Stephen L Chan[6], Yasuaki Arai[7], Jeong Heo[8], Anh Mai[9], Jose Escobar[10], Yamil Alonso Lopez Chuken[11], Jung-Hwan Yoon[12], Won Young Tak[13], Tanita Suttichaimongkol[14], Mohamed Bouattour[15], Shi-Ming Lin[16], Magdalena Żotkiewicz[17], Stephanie Udoye[18], Gordon J Cohen[18], **Bruno Sangro*[19]**

[1]Department of Diagnostic and Interventional Radiology, University of Pisa School of Medicine, Pisa, Italy; [2]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan; [3]Interventional Radiology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Cancer Center of Nanjing, Jinling Hospital, Nanjing, China; [5]Department of Hepatic Oncology, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China; [6]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Sir Yue-Kong Pao Center for Cancer, The Chinese University of Hong Kong, Hong Kong SAR, China; [7]Department of Diagnostic Radiology, National Cancer Center, Chuo-ku, Tokyo, Japan; [8]Department of Internal Medicine, College of Medicine, Pusan National University and Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea; [9]General Surgery Department, Nhan Dan Gia Dinh Hospital, Ho Chi Minh City, Vietnam; [10]Hospital San Lucas Cardiológica del Sureste, Chiapas, Mexico; [11]I Can Oncology Centre, New León, Mexico; [12]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [13]Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea; [14]Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [15]Medical Oncology, AP-HP Hôpital Beaujon, Paris, France; [16]Department of Internal Medicine, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan; [17]Oncology Biometrics, Late Oncology Statistics, AstraZeneca, Warsaw, Poland; [18]Global Medicines Development, AstraZeneca, Gaithersburg, MD, USA; [19]Liver Unit and HPB Oncology Area, Clínica Universidad de Navarra and CIBEREHD, Pamplona, Spain

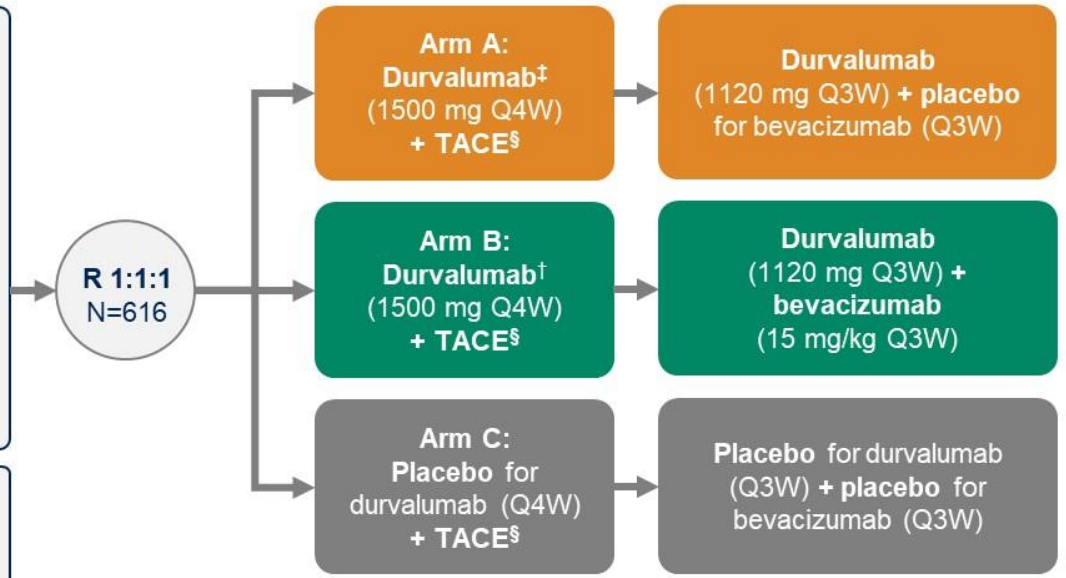
**Co-principal investigators*

EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)



Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

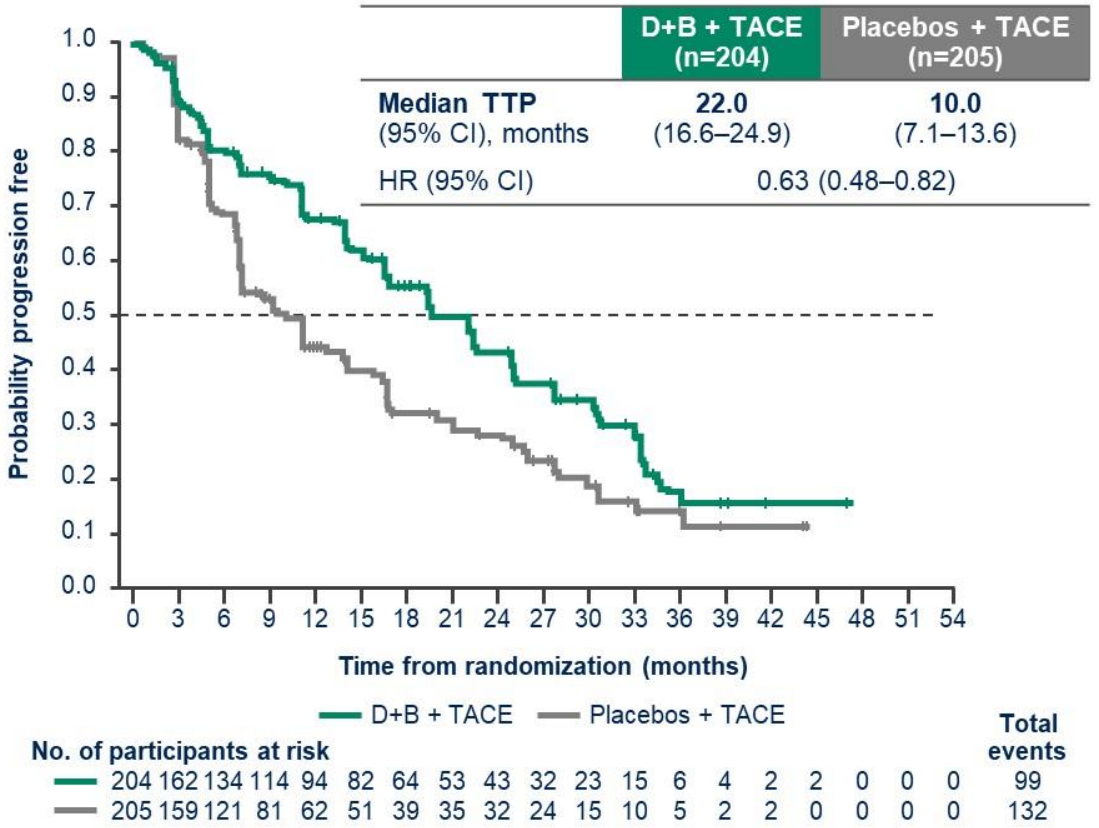
Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

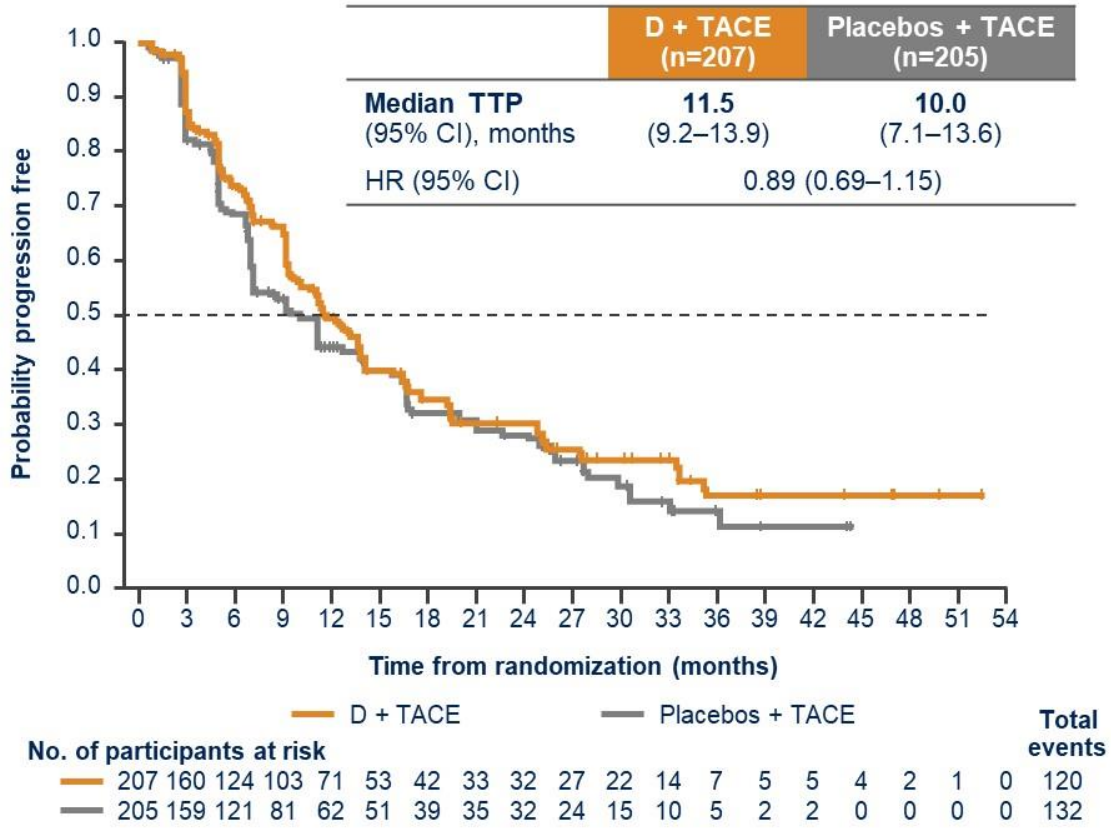
*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡Durvalumab / placebo started ≥7 days after TACE. §DEB-TACE or cTACE. Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure. ‖Only new lesions consistent with progression that were not eligible for TACE occurring prior to the first on study imaging at 12 weeks were considered progression events; standard mRECIST progression criteria were used after the 12-week imaging.

BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead-transarterial chemoembolization; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W / Q4W, every 3 / 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

TTP

Median TTP was improved by 12 months with D+B + TACE versus placebos + TACE



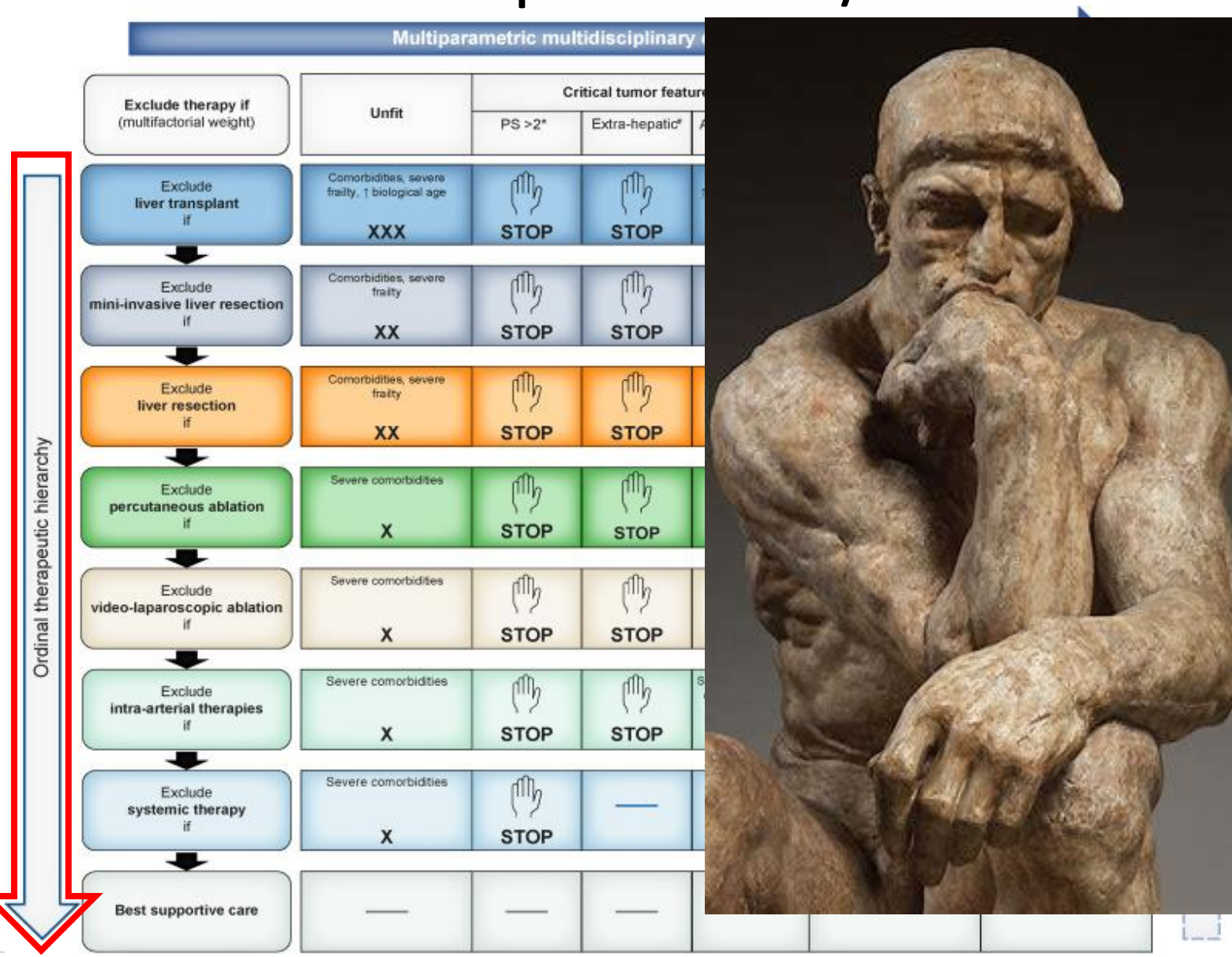


TTP was assessed by BICR (RECIST v1.1)
B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; mo, months; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TTP, time to progression.

Multiparametric ORDINAL therapeutic hierarchy

Aim: patient survival/cure

CONVERSION!



et Oncol 2023; 24: e312–22

Policy Review

onalised management of patients with hepatocellular noma: a multiparametric therapeutic hierarchy concept

Vitale, Giuseppe Cabibbo, Massimo Iavarone, Luca Viganò, David J Pinato, Francesca Romana Ponziani, Quirino Lai, adei-Gardini, Ciro Celsa, Giovanni Galati, Martina Gambato, Laura Crocetti, Matteo Renzulli, Edoardo G Giannini, Fabio Farinati, isani, Umberto Cillo, on behalf of the HCC Special Interest Group of the Italian Association for the Study of the Liver*

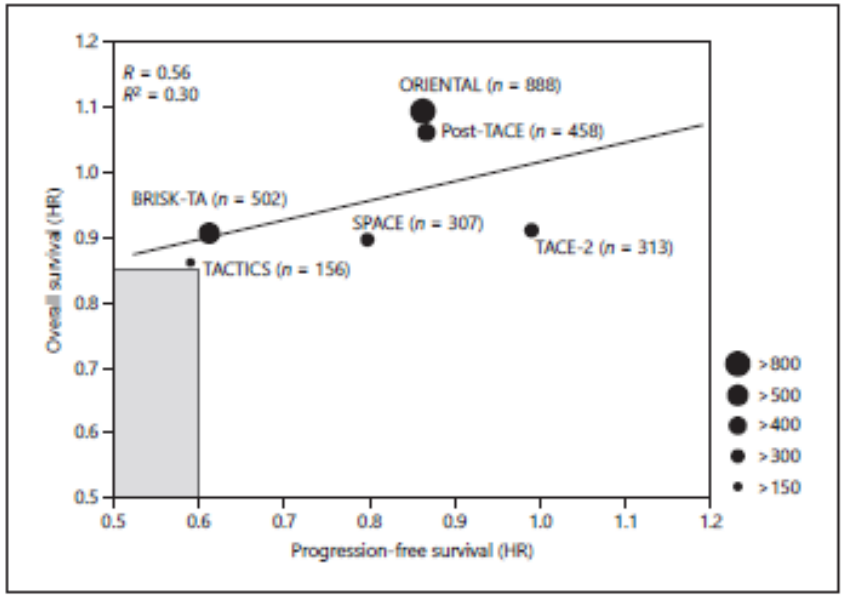
Journal of Hepatology
Available online 22 January 2024
In Press, Journal Pre-proof What's this?

xpert Opinion

Merits and boundaries of the Barcelona Clinic Liver Cancer Staging and Treatment Algorithm: learning from the past to improve the future with a novel proposal.

ranco Trevisani [1 2 a], Alessandro Vitale [3 a], Masatoshi Kudo [4], Laura Kulik [5], Joon-Won Park [6], David J. Pinato [7 8], Umberto Cillo [3]

CAVEATS…



Endpoints:
OS vs PFS vs ORR vs DCR vs QOL

Lack of direct comparisons between drugs with the only exception of sorafenib

Sequences/combined treatments TKI/Immunoth./Antiangiogenetic Adjuvant and neo-adjuvant sett.

BUILDING BRIDGES
to interconnect people

HCC management ….2000 -> 2010

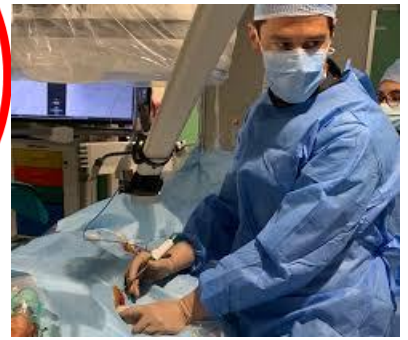
Epatologo

Gastro,
Med Int

Chirurgo

Oncologo

Radiologo



HCC management ….2020 -> 2024

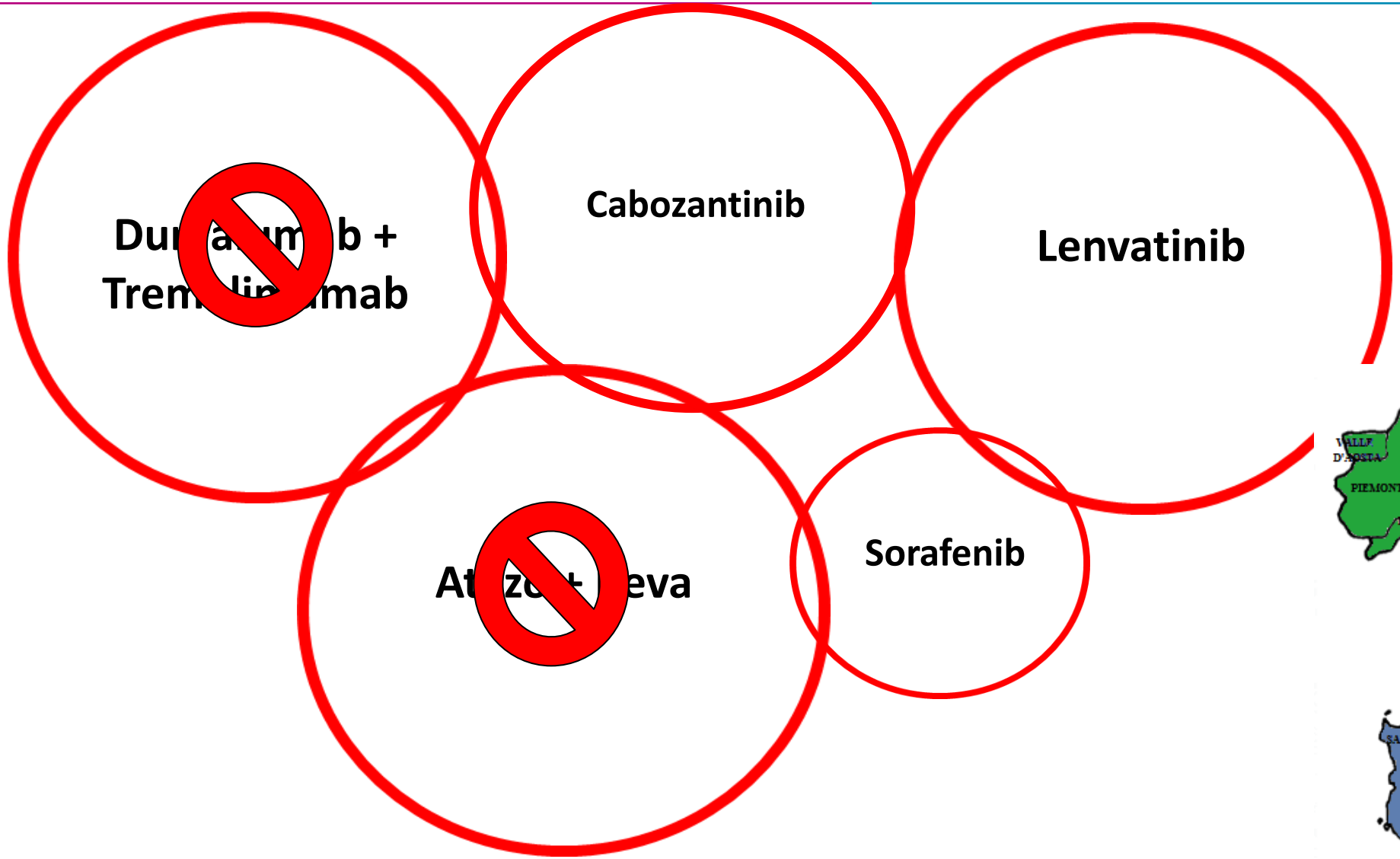
Epatologo (Gastro, Med Int)

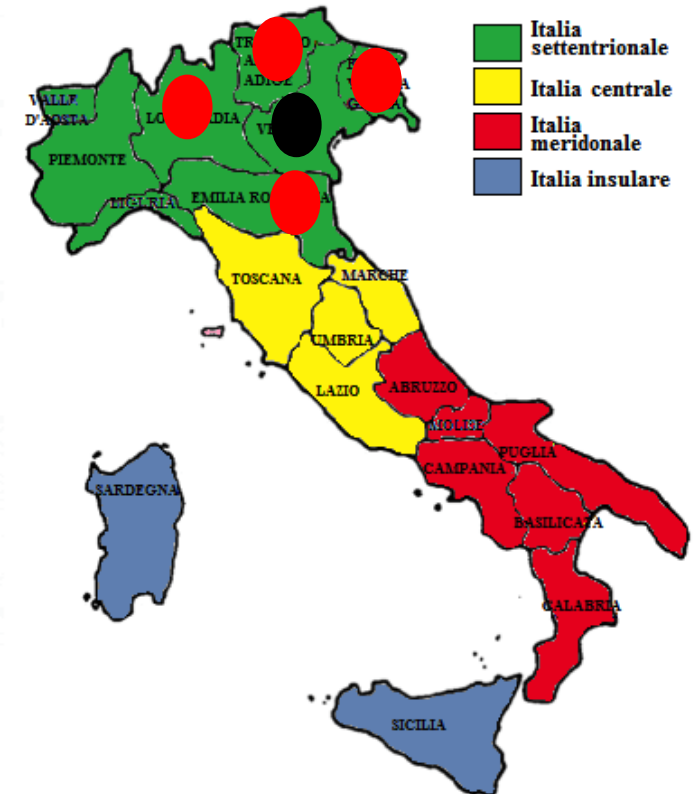
Chirurgo

Oncologo

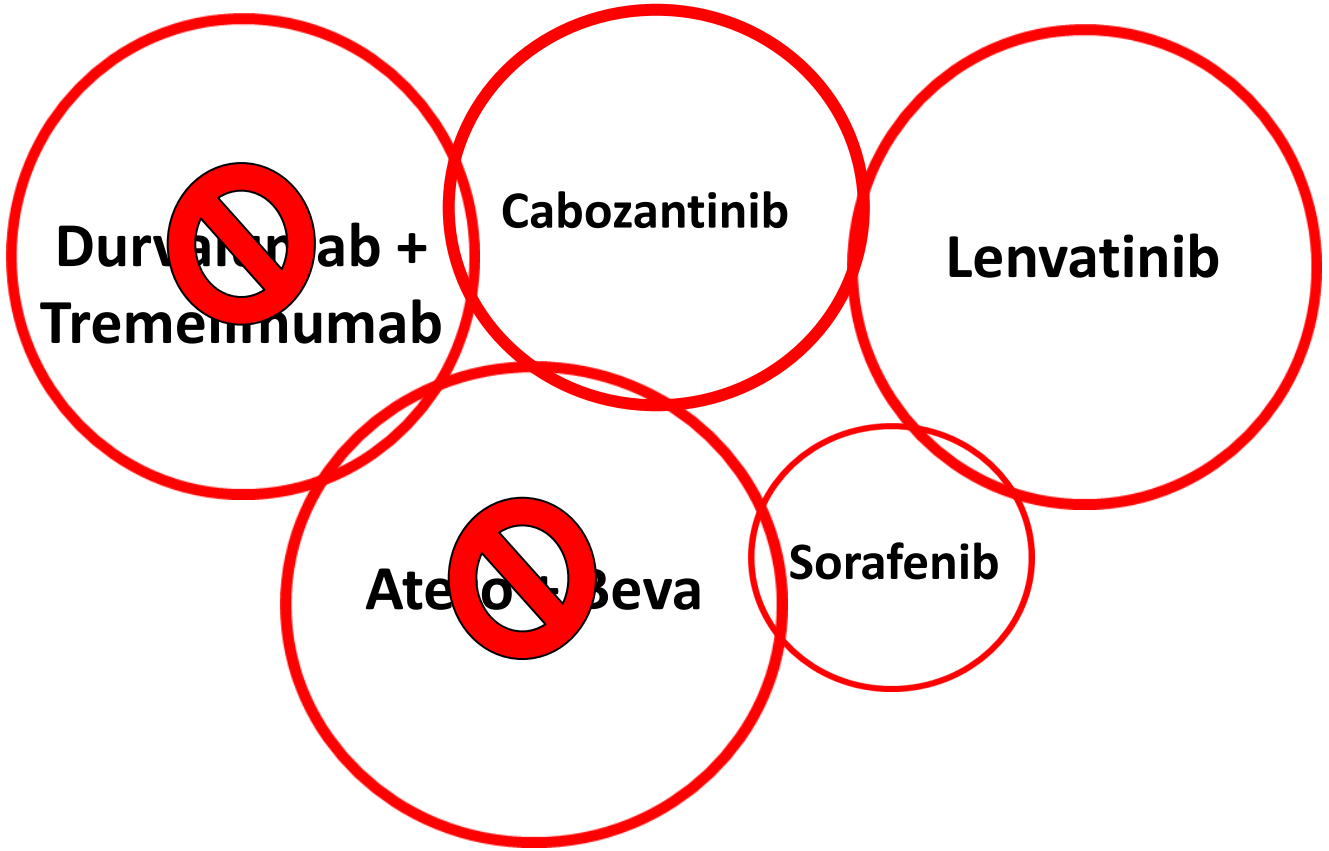
Radiologo

HCC management …. 2024





HCC management …. 2024



E allora?

Ambulatorio Multidisciplinare


Sebbene suo marito andasse spesso in viaggio per affari, ella odiava star sola.
"Ho risolto il nostro problema," disse egli. "Ti ho comprato un San Bernardo. Si chiama Estrema Riluttanza."
"Adesso, quando vado via, sai che ti lascio con Estrema Riluttanza!"
Ella lo col
mestolo.
Grazie!