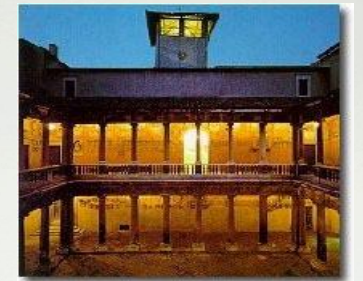




Up date on the systemic therapy of HCC F.Farinati - Padova

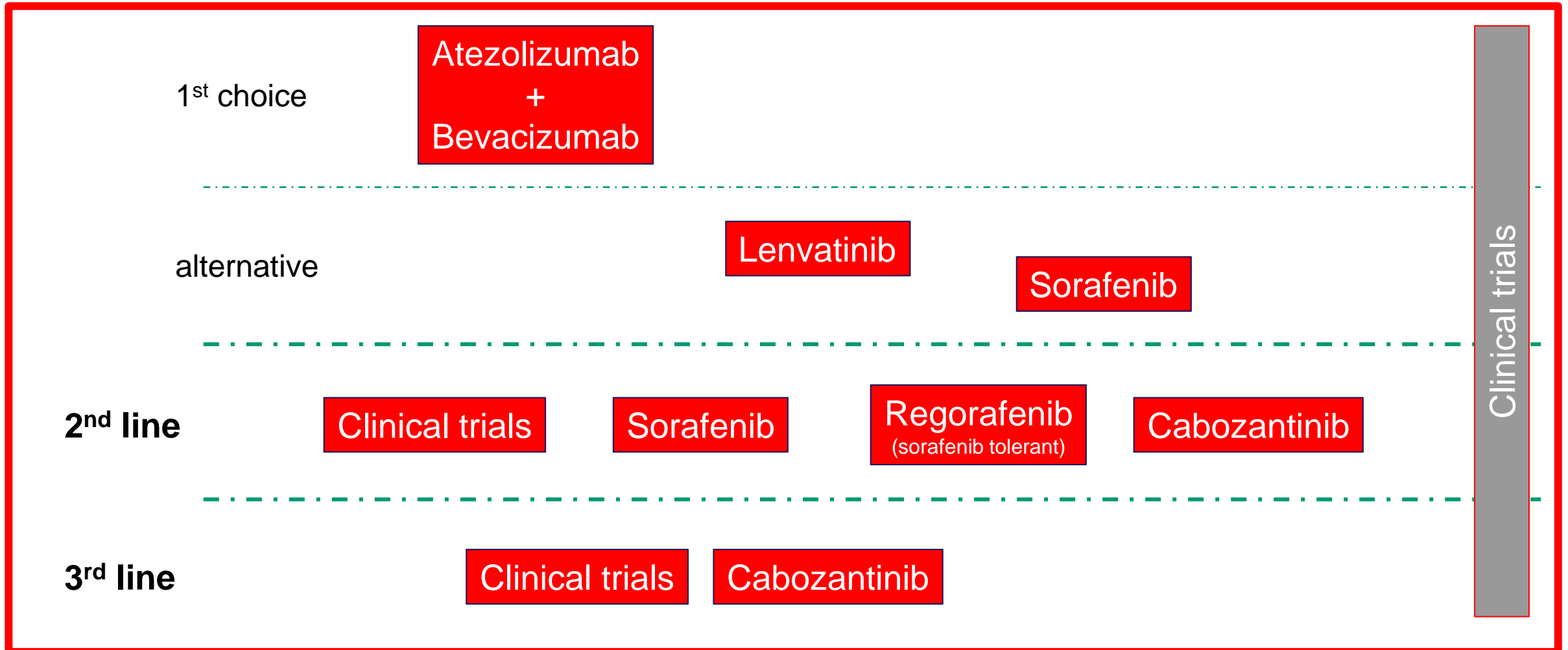
Meeting del 45° parallelo
IBD and liver hemisphere

No conflict of interest



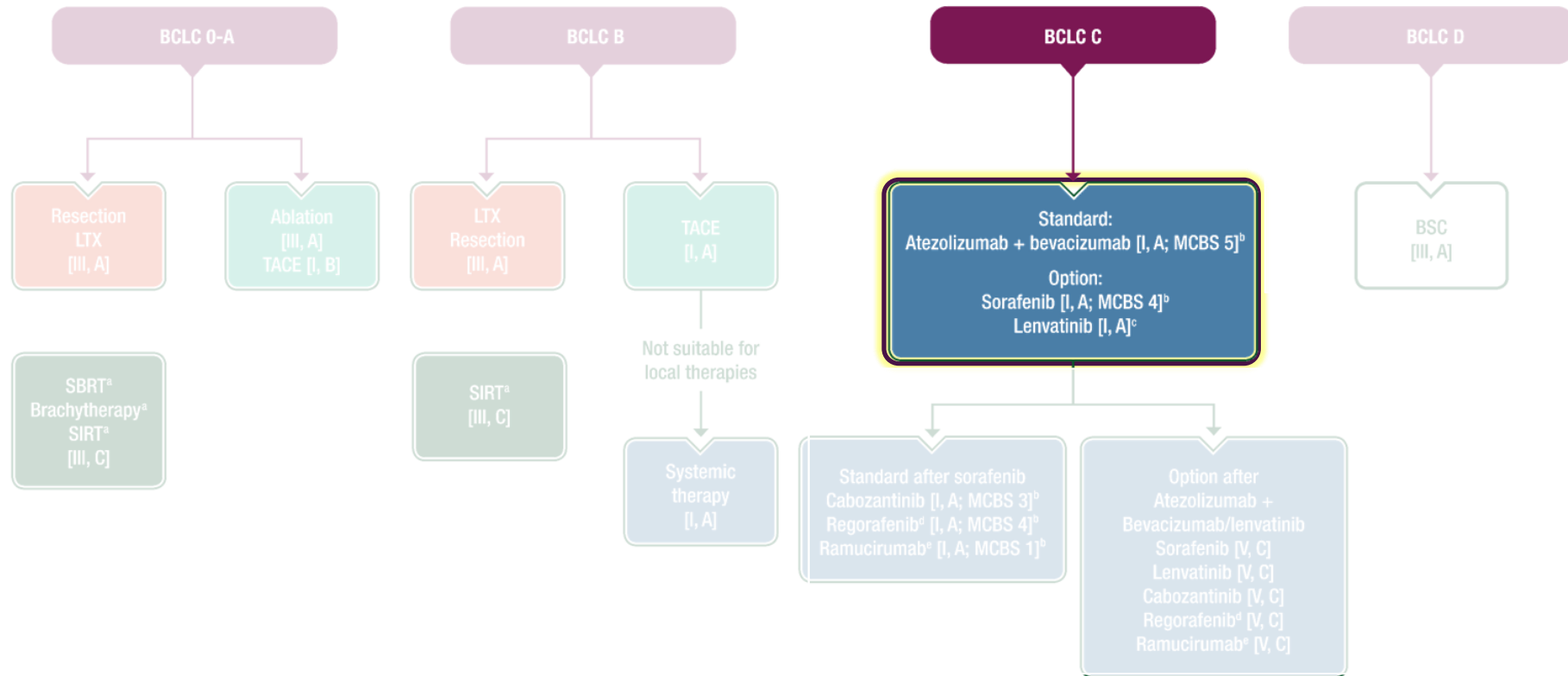
Systemic treatments for advanced HCC: Italy, TO DAY

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



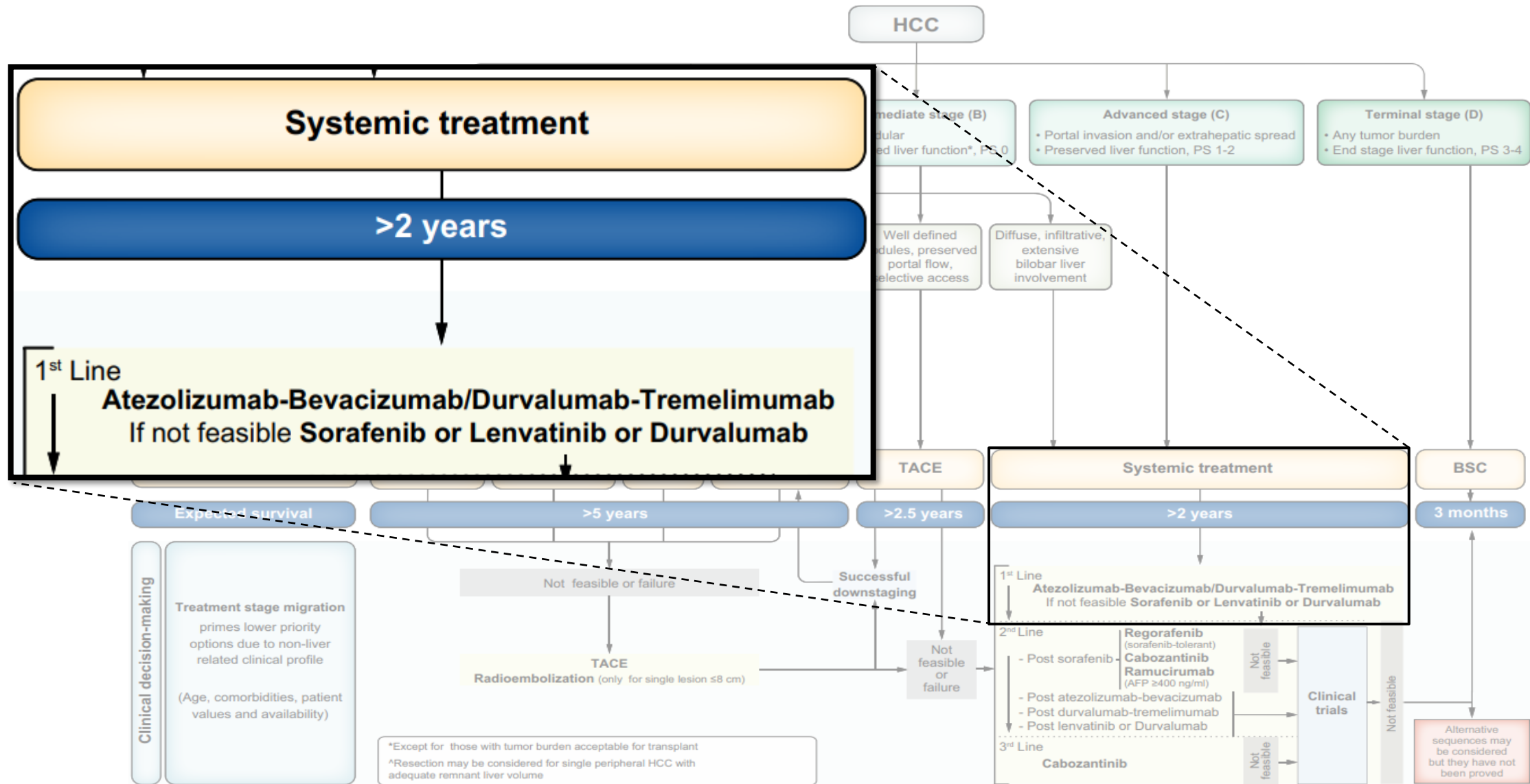
Current Recommendations: ESMO Guidelines

- 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



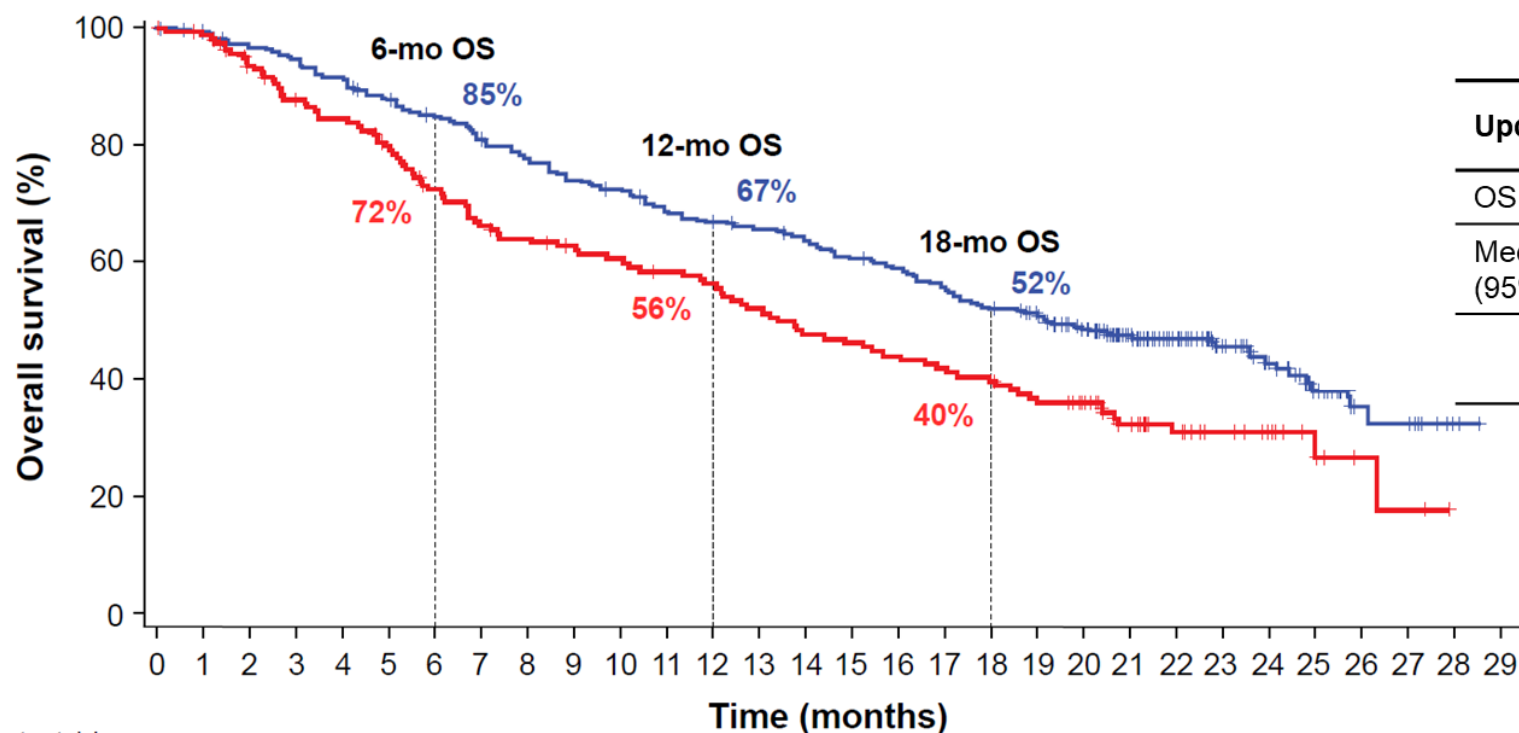


Systemic treatment in HCC : BCLC Guidelines



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) <i>P</i> = 0.0009 ^b	

No. of patients at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
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.

TIME

for
change

Systemic treatment for HCC: the HIMALAYA trial

Primary Endpoint – OS for **STRIDE** vs Sorafenib (superiority)

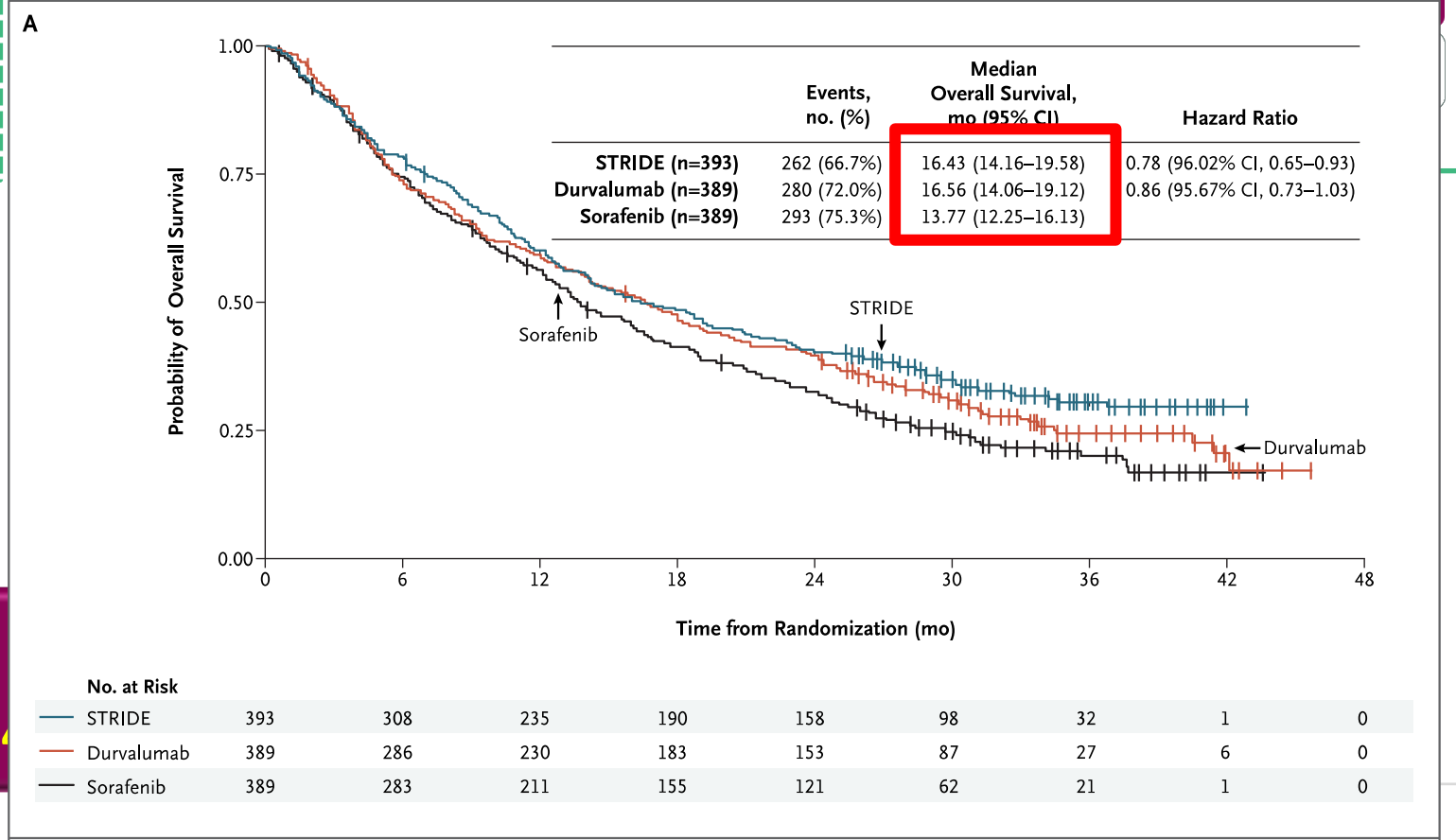
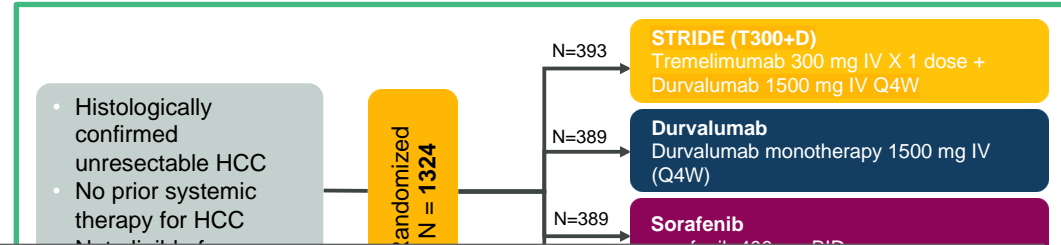
Atezolizumab
+
Bevacizumab

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-4**

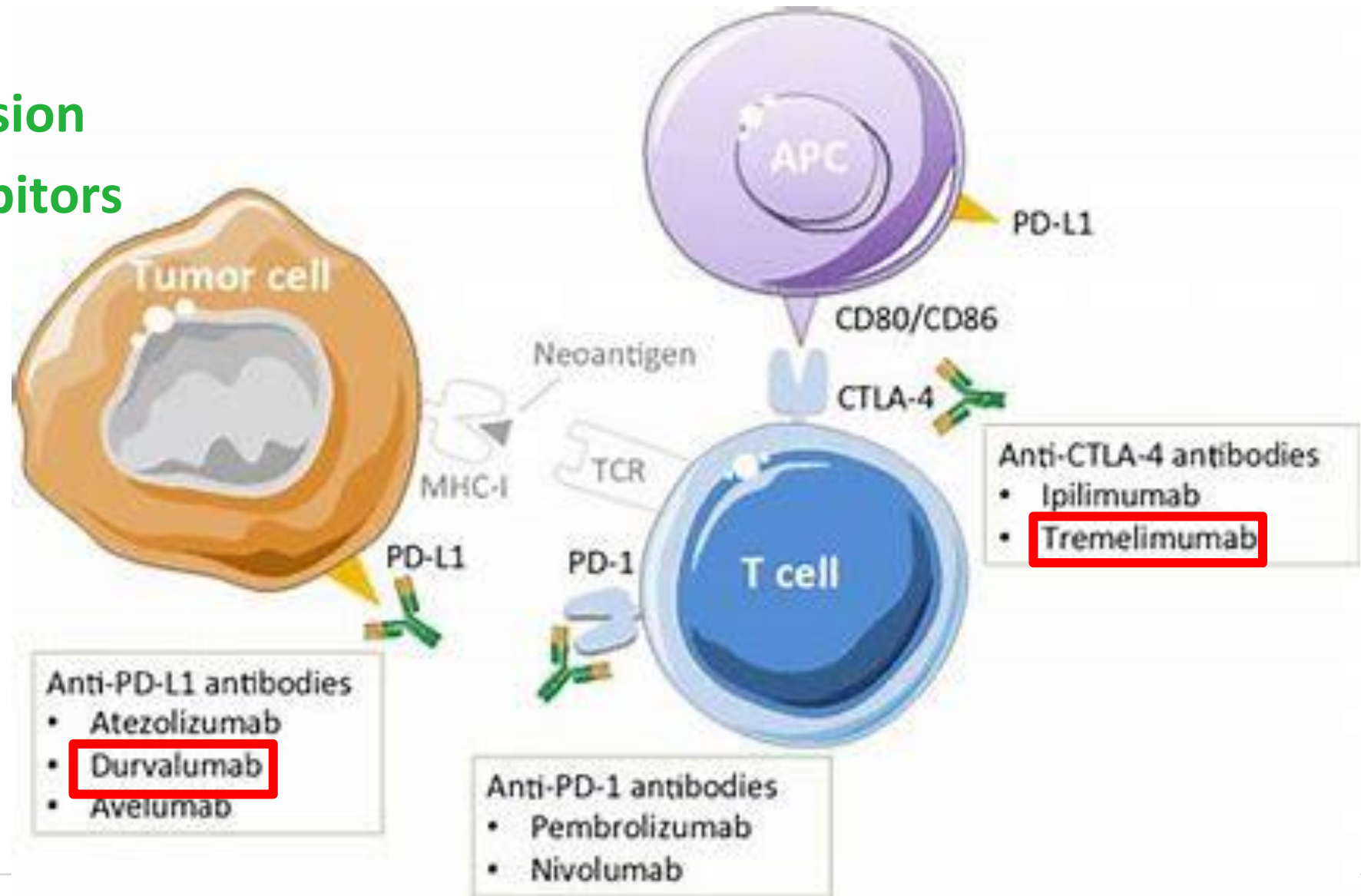


Tumor immunologic microenvironment

Reversing local

Immunosuppression

Check Point Inhibitors



Atezo/Beva vs Treme/Durva

Patients'
choice

Costs

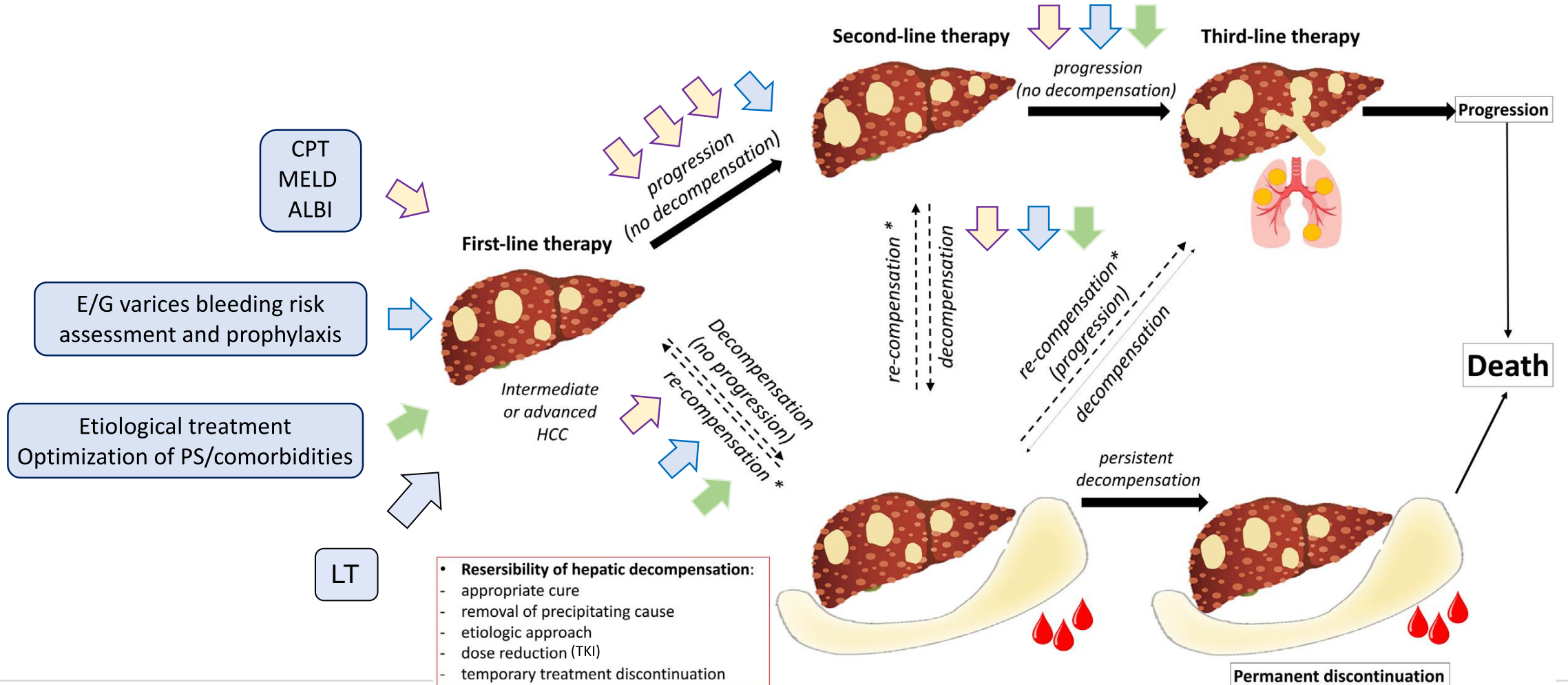


Eligibility
Anti-PD1/PDL1

ology

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)]





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 PhD
1 Cardinal Health Spec

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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

- The treatment landscape in been undergoing rapid chan
- In late May of 2020, the first uHCC was approved as first
- As with any new therapy, it listed in patient medical his choice of 1L therapy in uHCC

- The objective of this study reported as part of patient patients initiating 1L system 2020 and April 2022 in the U

- Inclusion criteria**
- Aged ≥ 18 years
 - Diagnosed with uHCC (i.e.,)
 - Initiated 1L systemic treatm
 - BCLC stage B or C

- Medical conditions and comorbidities:**
- Physician-reported dise
 - Chronic kidney disease
 - Autoimmune disorders
- Comorbidities:**
- Physician-reported arte

- Treating physicians from Cardinal Health Specialty Solutions a clinical proficiency oncology Provider Extended Network (OPEN) abstracted deidentified, patient-level data from electronic health records from March to May of 2022.
- The OPEN community comprises providers in oncology, hematology, and urology across the U.S. and providers practice predominantly in community practices (~75%).
- Patients were indexed to date of 1L systemic therapy initiation.
- Descriptive analyses characterized patient demographic and clinical characteristics, including medical conditions reported as part of patient medical history and/or comorbidities (based on the warnings and precautions section of the U.S. FDA labels,^{1,2} [Table 1]).
- Descriptive analysis also assessed risk of bleeding by physician-reported record of EGD.
- Less suitable to receive an I/O + IV anti-angiogenic therapy regimen was defined as the occurrence of ≥ 1 medical condition and/or comorbidity reported in the medical record.

1L=first-line, BCLC=Barcelona Cancer Liver Clinic, EGD=endoscopic gastroenteroscopy, FDA=Food and Drug Administration, GI=gastrointestinal, I/O=immuno-oncologic, uHCC=unresectable hepatocellular carcinoma, U.S.=United States

Baseline demographic characteristics (Table 2)

- Mean age was 64 years at uHCC diagnosis.
- The majority of patients were male (287 [66.3%]).
- More than half [244 [56.4%]] were Caucasian, 115 (26.6%) were African American, and 46 (10.6%) were Asian.

Baseline clinical characteristics (Table 3)

- Three-quarters of patients (333 [76.9%]) were BCLC C stage and 160 (37.0%) were Child-Pugh B class.
- One quarter [99 [22.9%]] of patients had non-alcoholic steatohepatitis (NASH), 176 (41.1%) had positive Hepatitis C etiology (among those tested), and 294 (67.9%) had liver cirrhosis.
- Three-quarters of patients (316 [73.0%]) had ECOG performance status of 0-1.

Hepatitis C test result history at uHCC diagnosis, n (%)^a

Positive 176 (41.1%)

Liver cirrhosis history at 1L initiation, n (%)

Positive 294 (67.9%)

ECOG performance status at 1L initiation, n (%)

0-1 316 (73.0%)

> 2 117 (27.0%)

Note: n=428/453 patients underwent testing for hepatitis C by the time of uHCC diagnosis. 1L, first-line; BCLC, Barcelona Clinic Liver Cancer stage; ECOG, Eastern Cooperative Oncology Group performance status; NASH, non-alcoholic steatohepatitis; uHCC, unresectable hepatocellular carcinoma

risk ratio for each patient.

REFERENCES

- Food and Drug Administration. <https://www.fda.gov/drugs/development-resources/2020/11/17/2020-11-17-atezolizumab-plus-bevacizumab-unresectable-hepatocellular-carcinoma>. Accessed November 17, 2022.
- Food and Drug Administration. Full prescribing information TECENTRIQ. https://www.accessdata.fda.gov/drugatc_docs/label/2020/761034s029106.pdf. Updated May, 2020. Accessed November 21, 2022.
- Food and Drug Administration. Full prescribing information AVASTIN. https://www.accessdata.fda.gov/drugatc_docs/label/2020/125085s321061.pdf. Updated May, 2020. Accessed November 21, 2022.

ion listed as medical history/comorbidity as less suitable to receive an I/O + IV anti-

kidney disease were reported among 37.9% and embolic events and autoimmune disorders were 15, respectively.

OD) had received EGD within the previous 3 months. bilities at 1L initiation

	164 (37.9%)
	64 (14.8%)
nt	50 (11.5%)
	22 (5.1%)

DISCUSSION

il-world data on the prevalence of nditions that could potentially make anti-angiogenic therapy regimen. patients in this study were found to have local history/comorbidity that could make I/O + IV anti-angiogenic therapy regimen. ce of medica o therapy sel

LT?

- The study was supported by Eisai, Inc.
- All authors contributed to and approved the presentation.

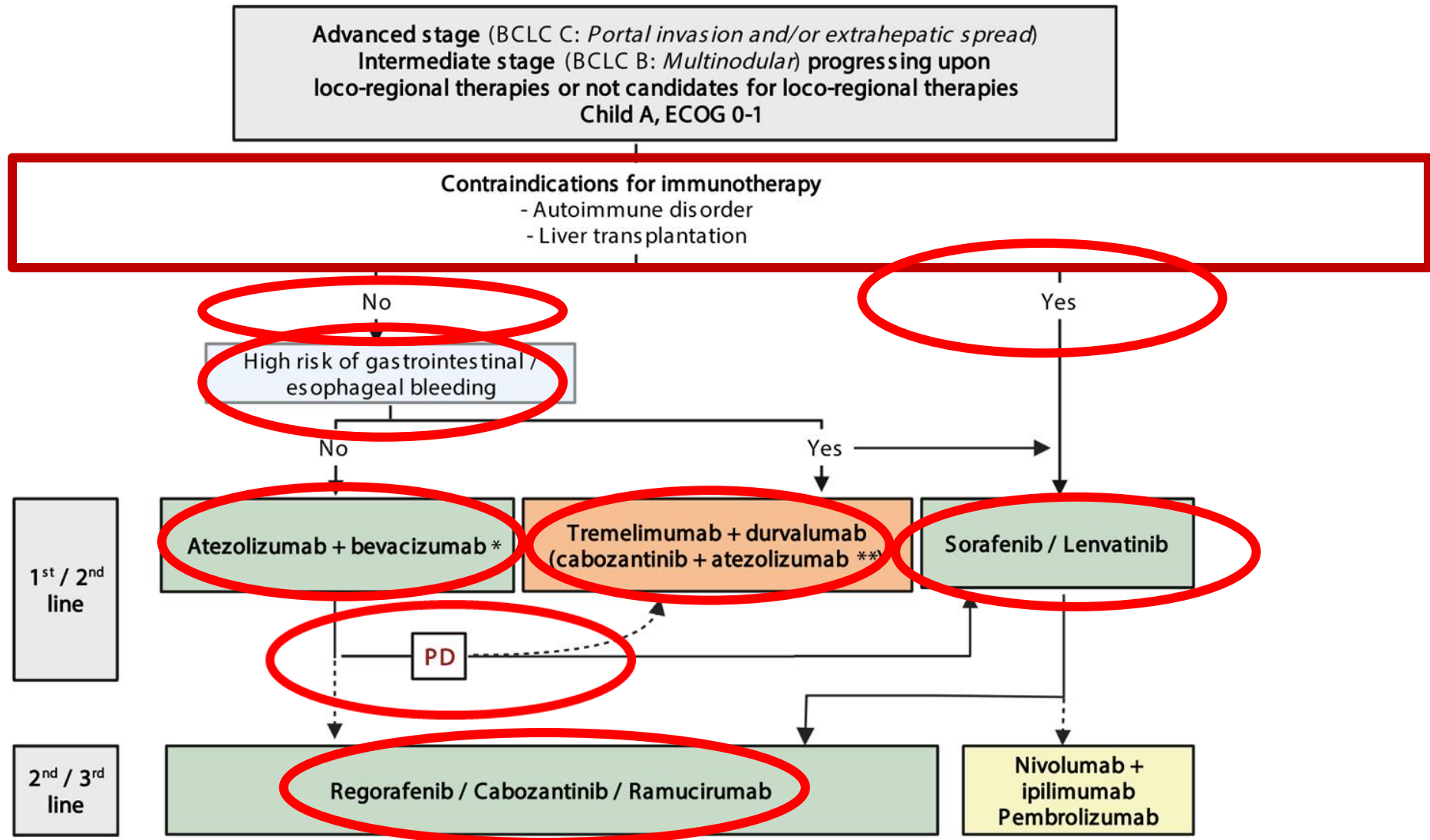
Presented at the ASCO Gastrointestinal Cancers Symposium, January 19-21, 2023, San Francisco, CA

Email: tammy.schuler@cardinalhealth.com

Tammy Schuler, Emily Bland, Bruce Feinberg. Current Employment: Cardinal Health. Leonardo Passos Chaves. Current Employment: Eisai Inc. Shital Kamble. Current employment: Merck & Co., Inc.

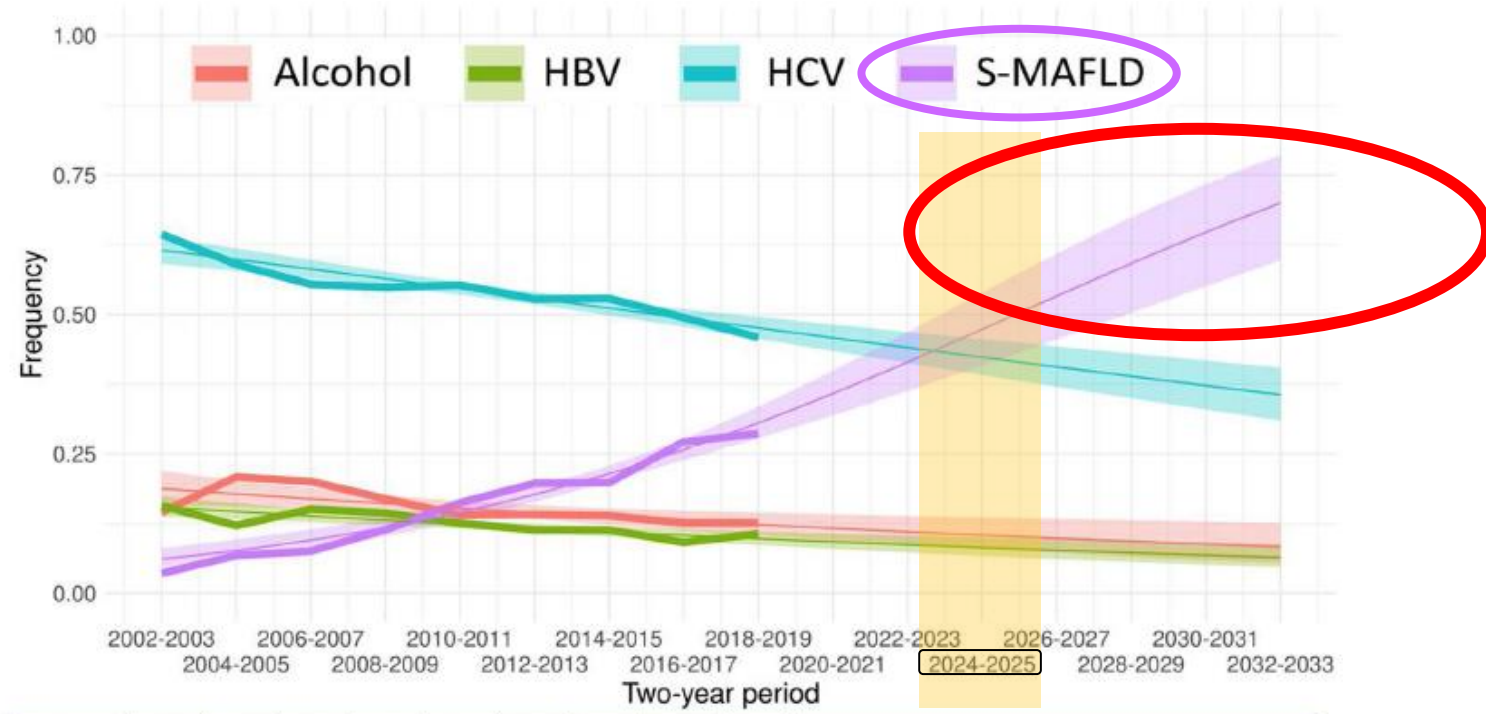


Some treatment algorithms are already published



Evolving aetiology of HCC

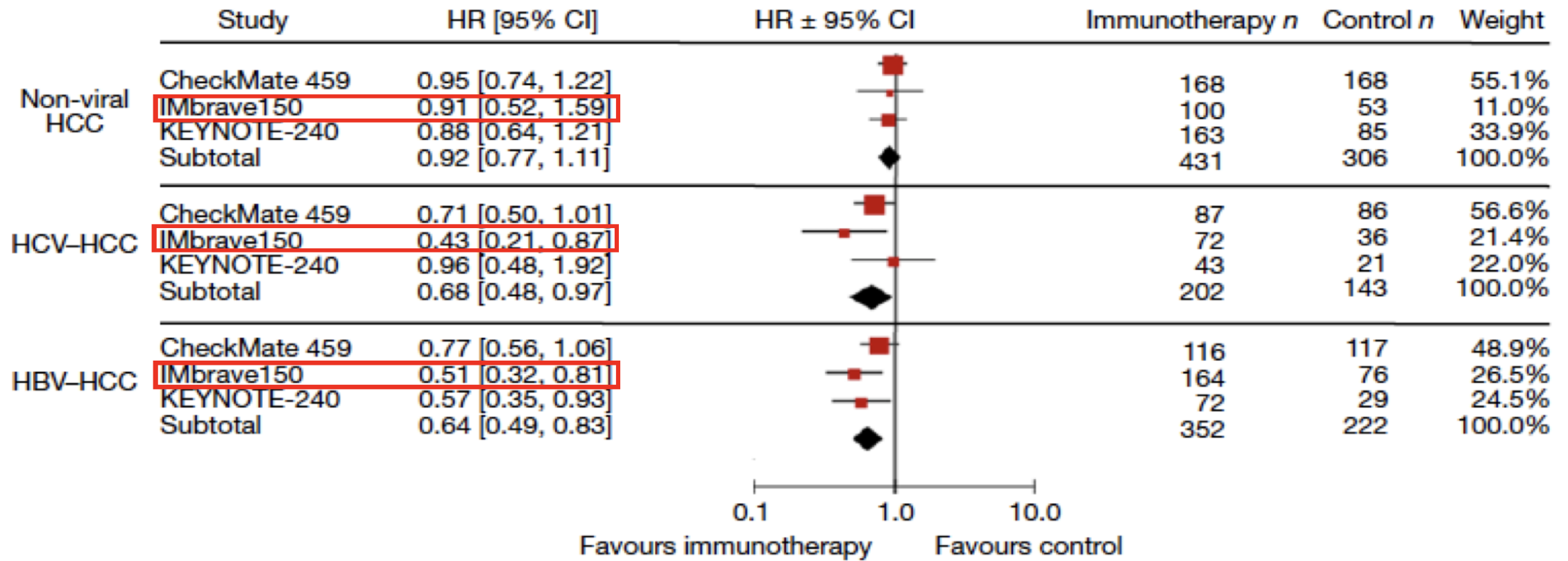
(ITA.LI.CA database 2018)



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	---

HCC NASH etiology

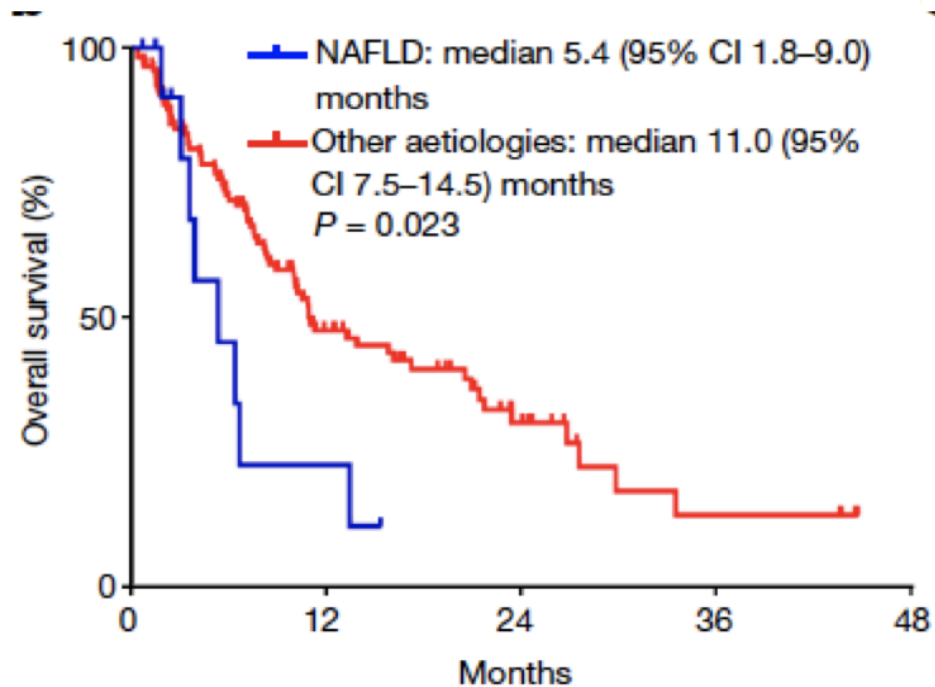
Meta-analysis of Immuno Check Point Inhibitors Therapy of HCC 1,656 Patients in RCTs



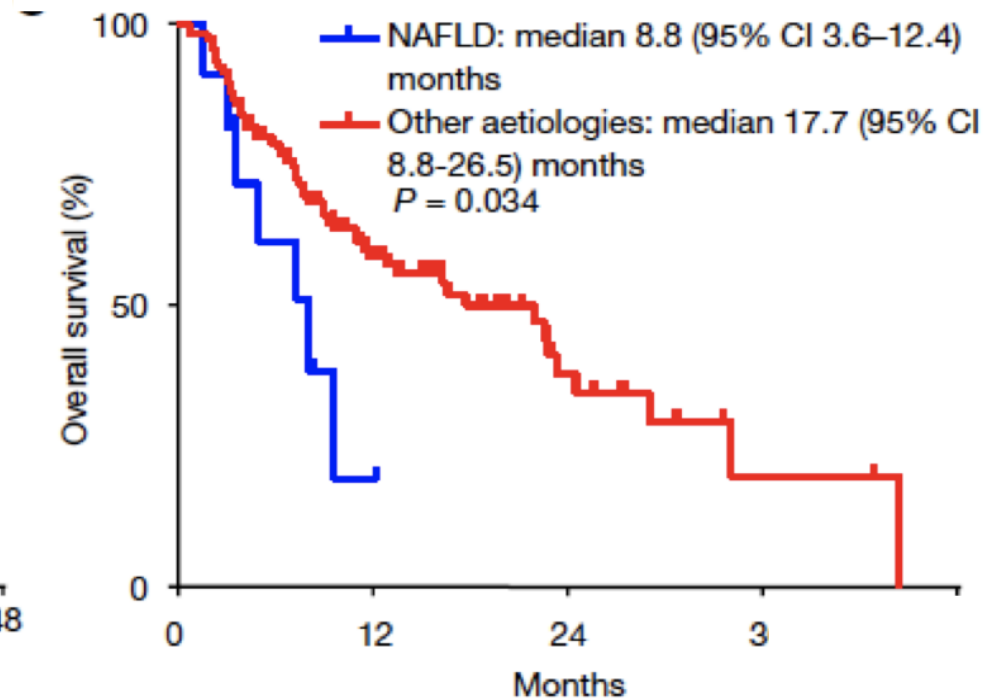
HCC NASH etiology

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

N = 130 patients

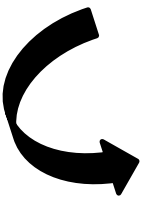
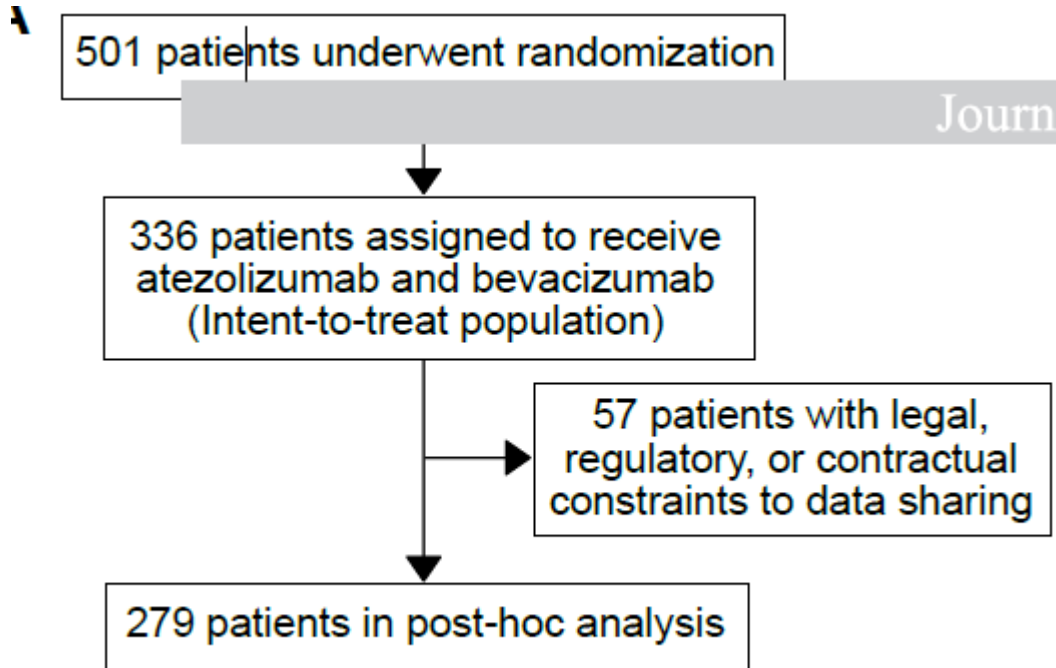


N = 118 patients

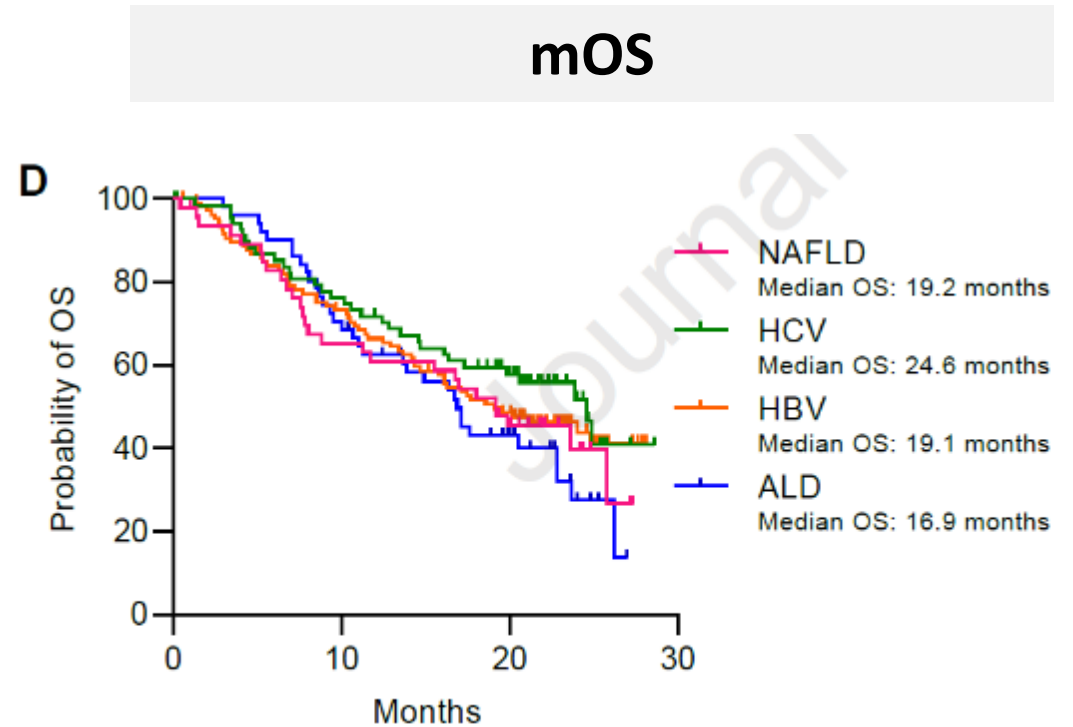




Atezo-beva according to etiology



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



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, $p=0.65$



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

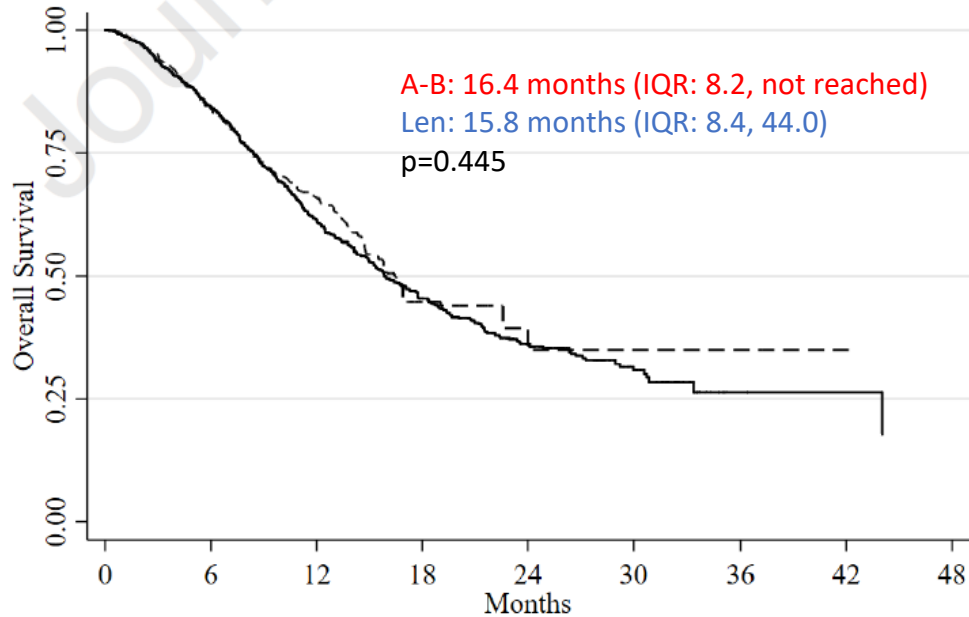
Atezo-bev: 11.1 months (6.8, 15.0)

Lenvatinib: 13.8 months (7.6, 22.9)

IPTW: Inverse Probability of Treatment Weights

Overall Survival

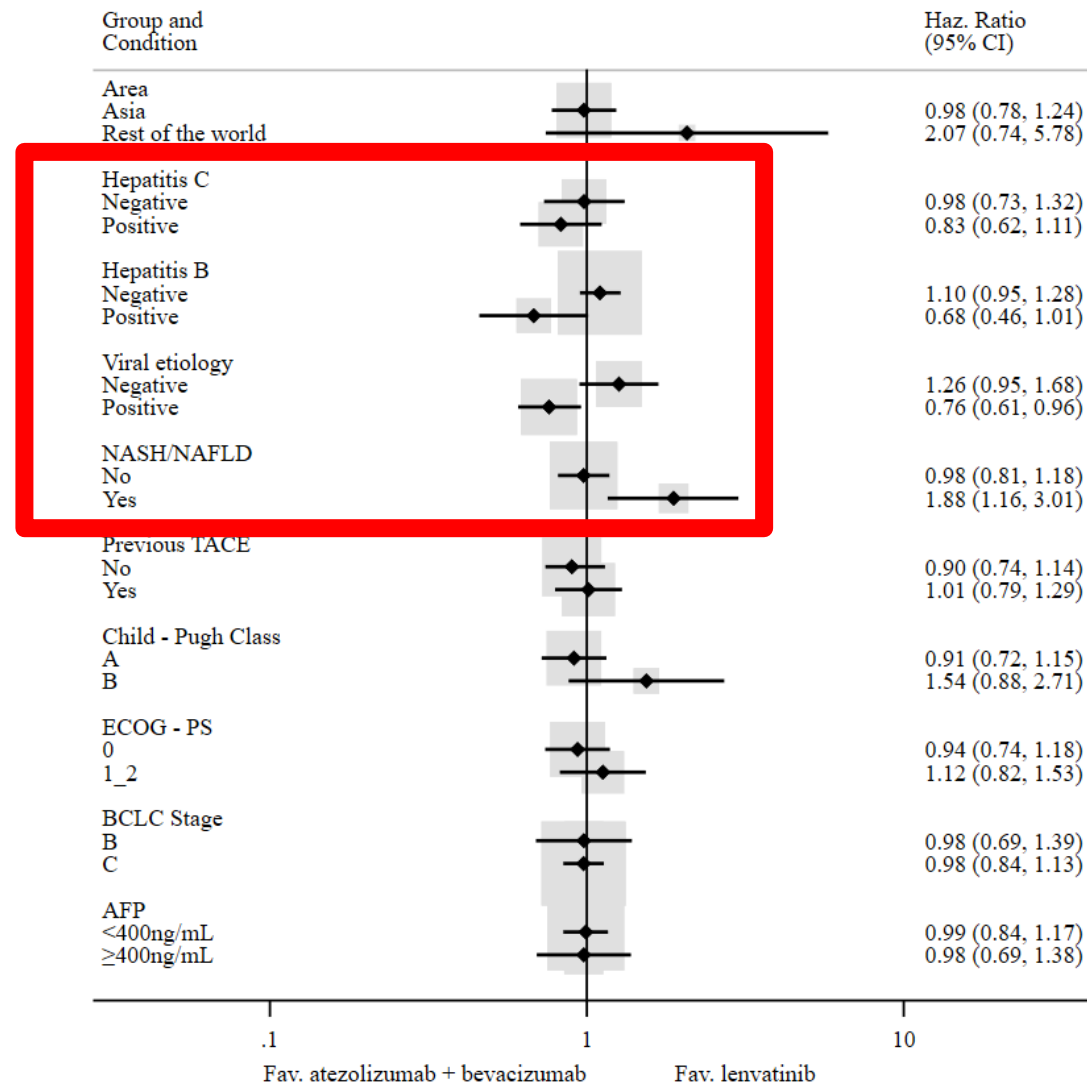
All etiologies



Weighted #at risk		0	6	12	18	24	30	36	42	48
Atezo + Beva	864	581	255	43	9	5	5	2	0	
Lenvatinib	1343	918	476	220	110	36	5	4	2	

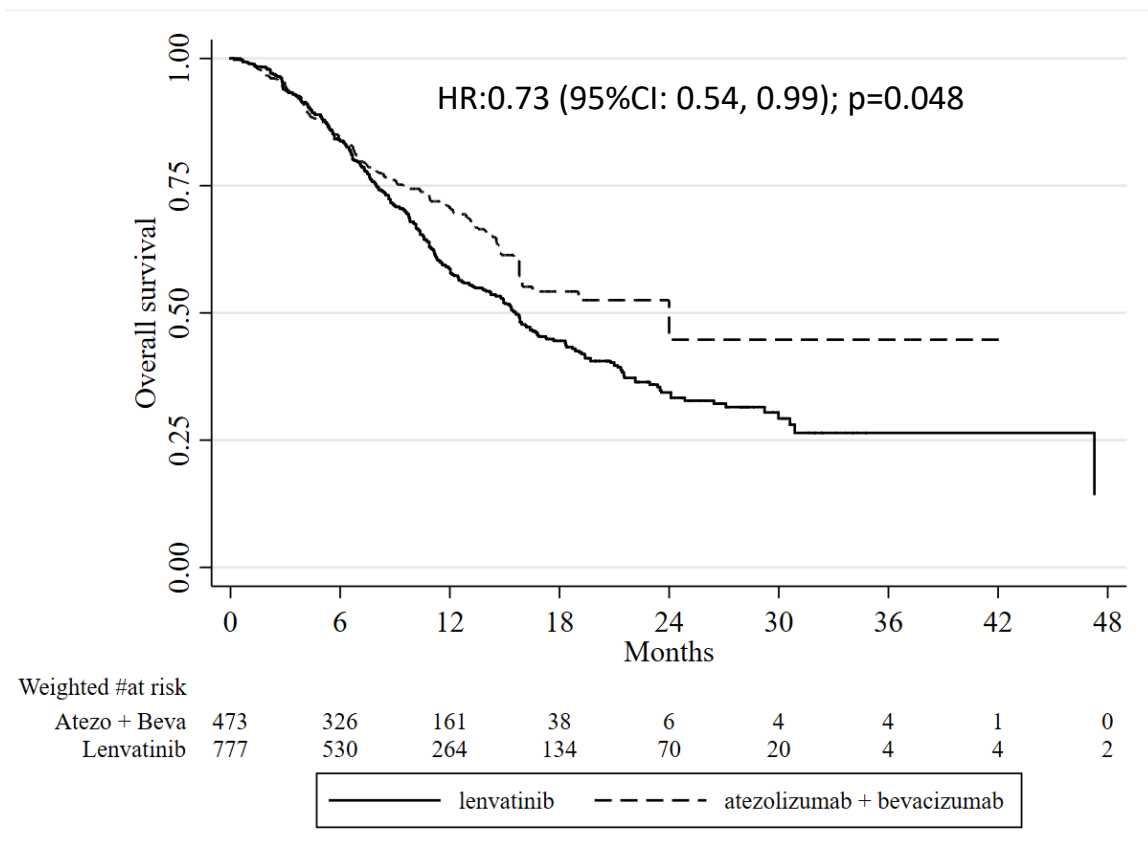
➤ After adjustment for centres' effect and 2L therapies received, no significant difference was observed, given a HR for atezo-bev of 0.97 (95%CI: 0.80, 1.17; p=0.739).

OS subgroup analysis

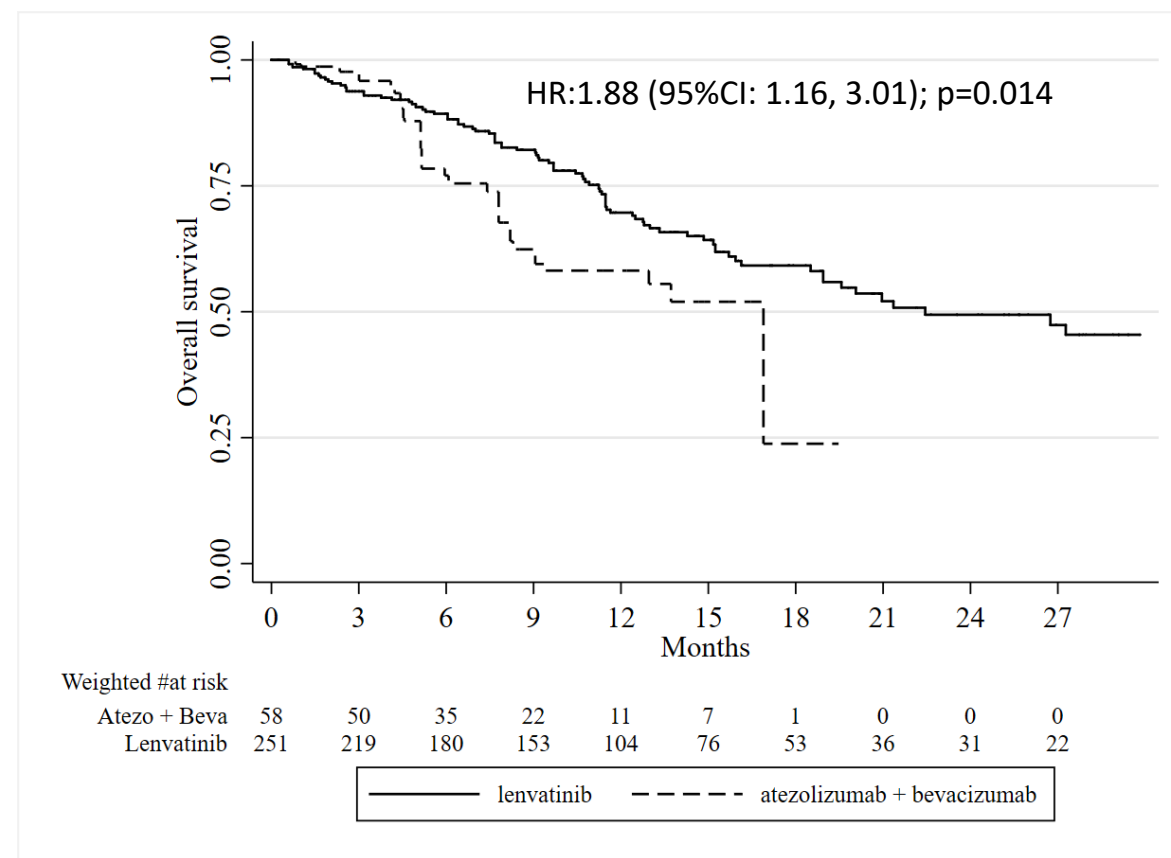


Overall Survival by Etiology

Viral



NASH/NAFLD



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

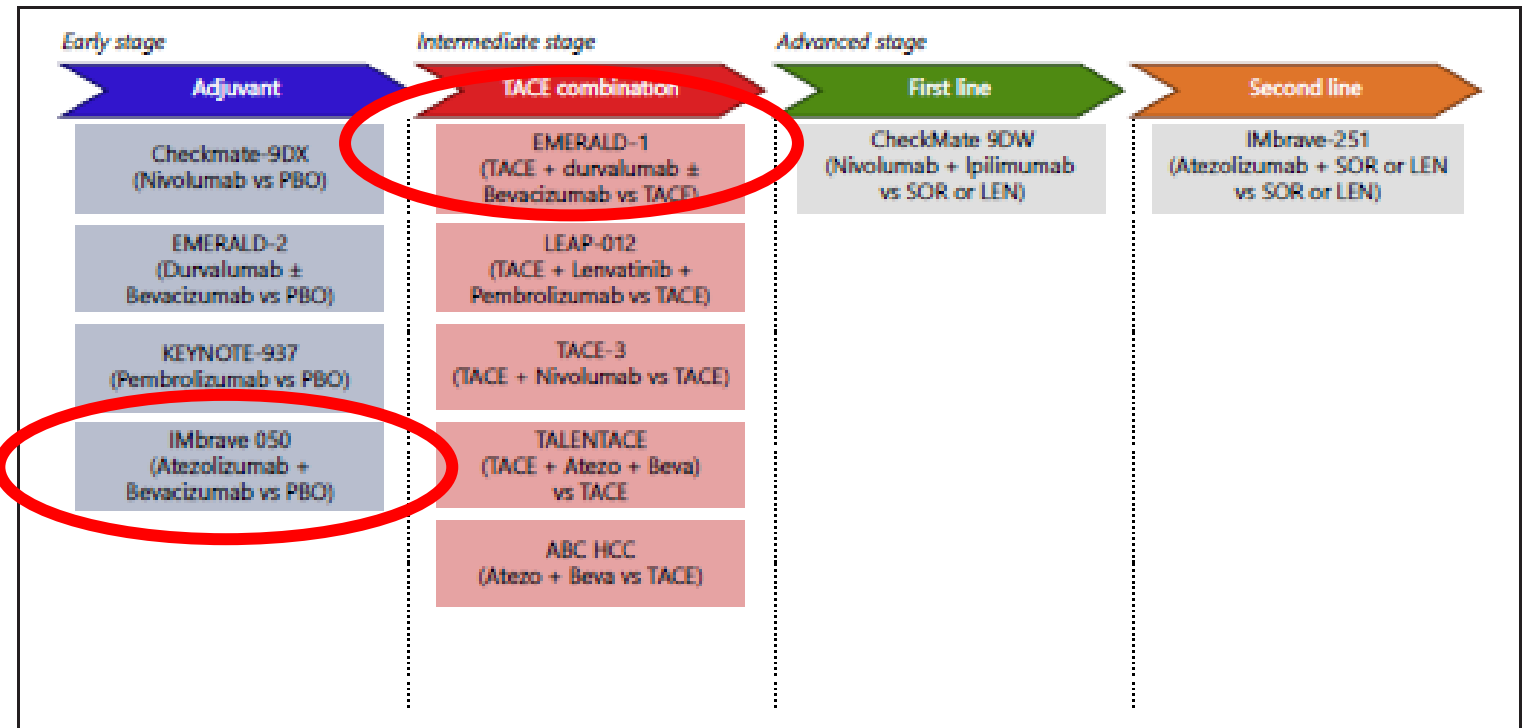
Implications of the TACTICS Trial: Establishing the New Concept of **Combination/Sequential Systemic Therapy** and Transarterial Chemoembolization to Achieve Synergistic Effects

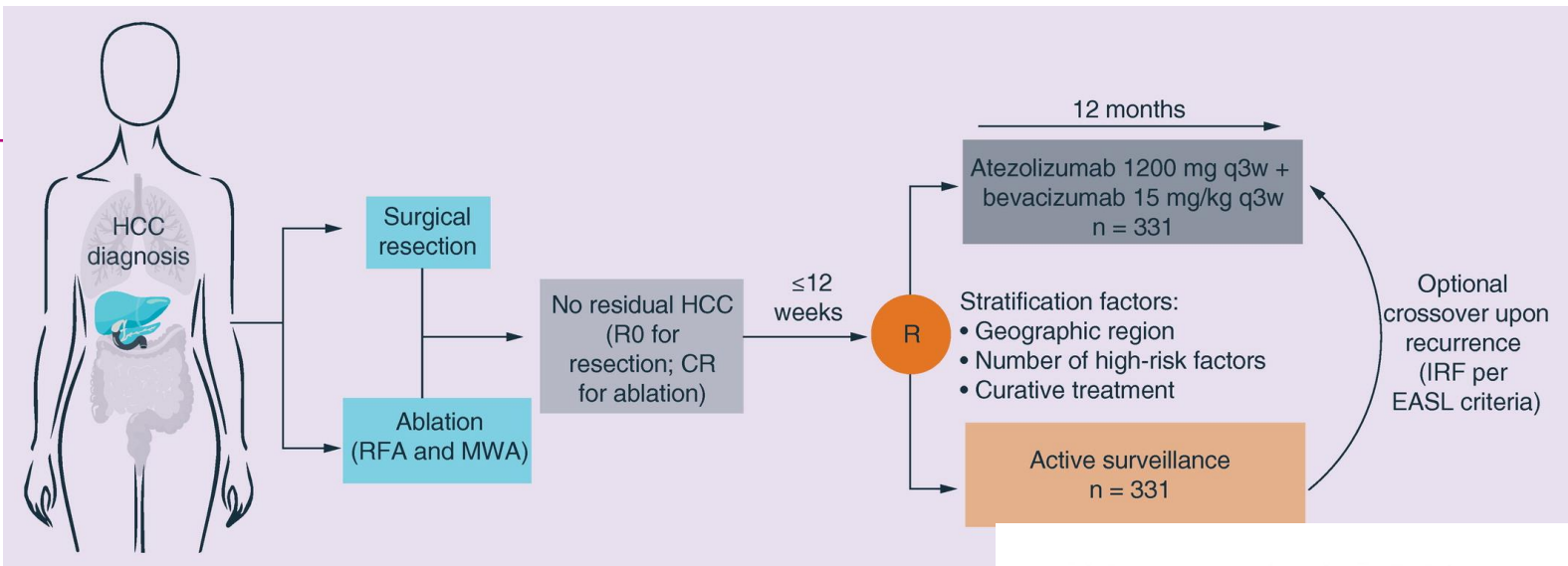
Masatoshi Kudo



Prof. M. Kudo

Editor Liver Cancer



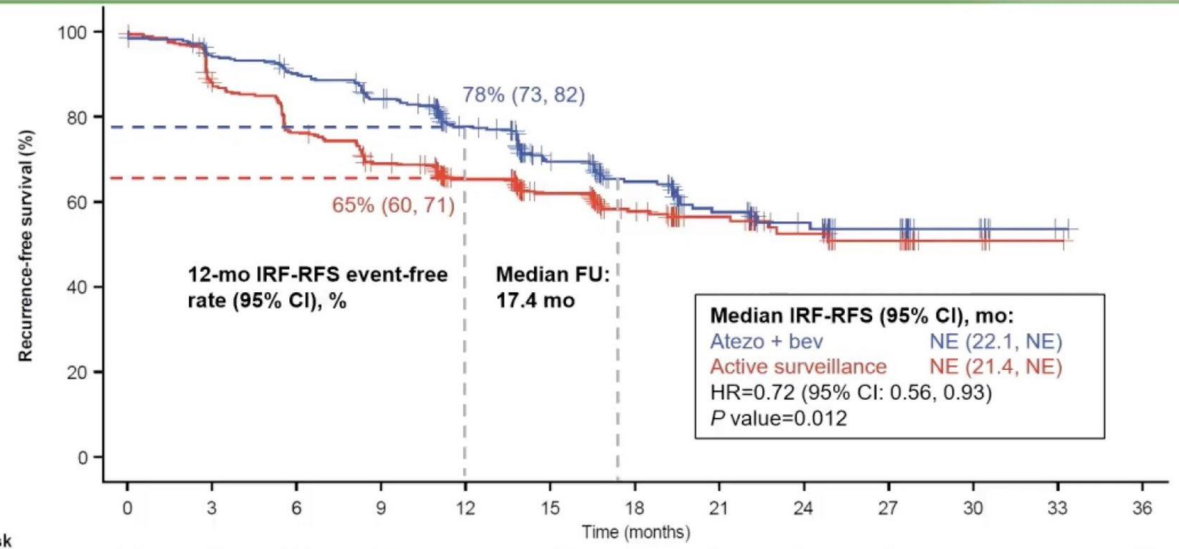


Adjuvant treatments

IMBRAVE 050

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

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



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Atezo + bev	334	305	290	268	211	139	97	63	37	22	9	1	NE
Active surveillance	334	283	245	214	179	131	93	57	36	20	6	1	NE

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



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

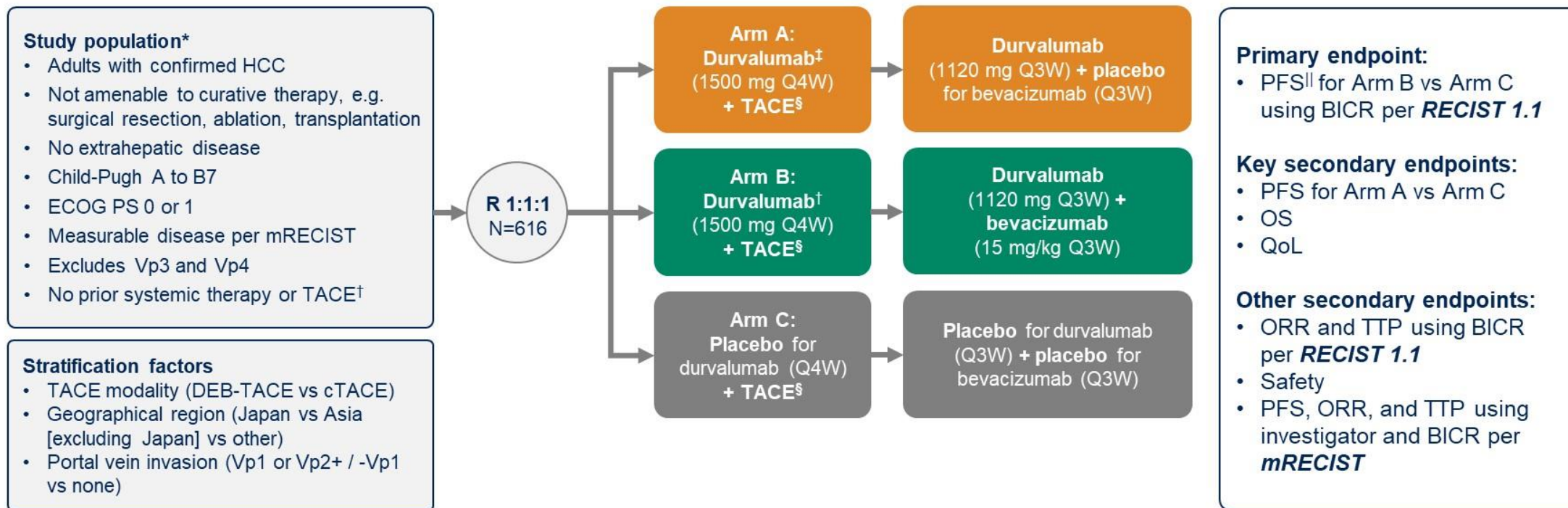
Riccardo Lencioni*¹, Masatoshi Kudo², Joseph Erinjeri³, Shukui Qin⁴, Zhenggang Ren⁵, Stephen L Chan⁶, Yasuaki Arai⁷, Jeong Heo⁸, Anh Mai⁹, Jose Escobar¹⁰, Yamil Alonso Lopez Chuken¹¹, Jung-Hwan Yoon¹², Won Young Tak¹³, Tanita Suttichaimongkol¹⁴, Mohamed Bouattour¹⁵, Shi-Ming Lin¹⁶, Magdalena Żotkiewicz¹⁷, Stephanie Udoye¹⁸, Gordon J Cohen¹⁸, **Bruno Sangro***¹⁹

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

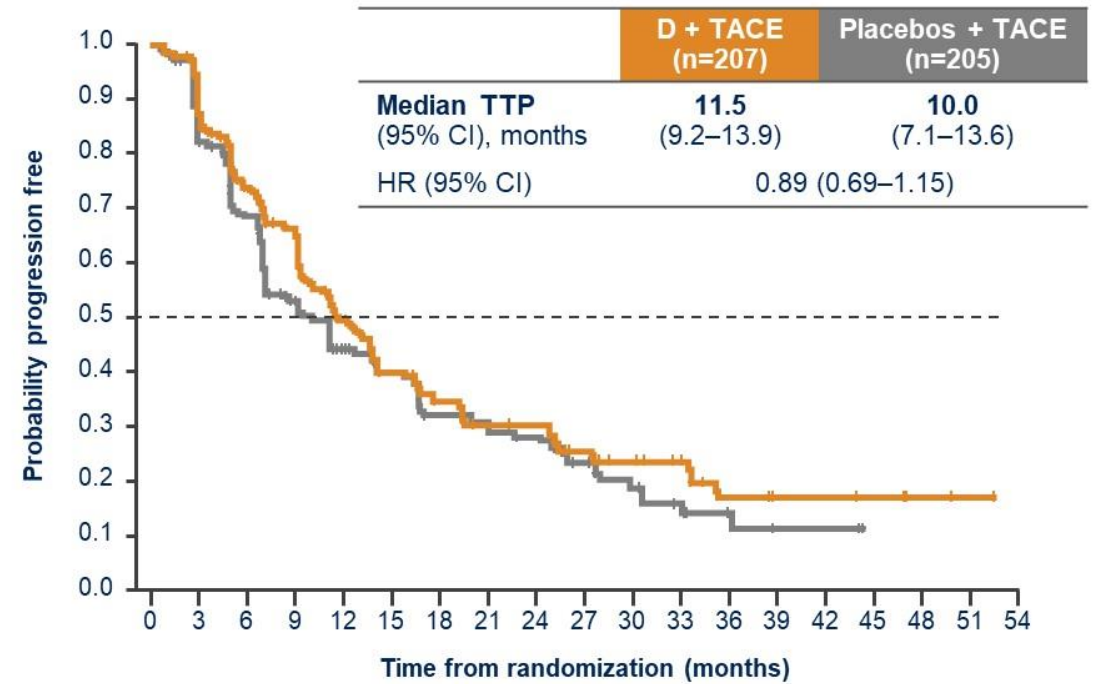
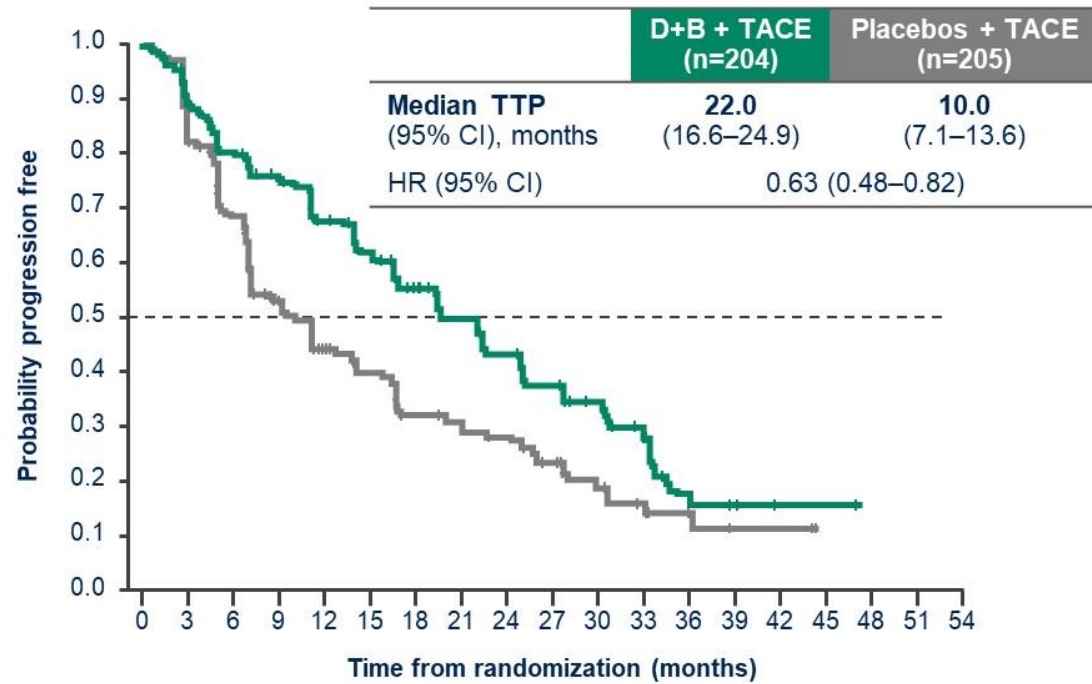


*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡Durvalumab / placebo started ≥7 days 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



No. of participants at risk	D+B + TACE															Placebos + TACE															Total events					
	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	205	159	121	81	62	51	39	35	32	24	15		10	5	2	2	0
	99															132																				

No. of participants at risk	D + TACE															Placebos + TACE															Total events					
	207	160	124	103	71	53	42	33	32	27	22	14	7	5	5	4	2	1	0	205	159	121	81	62	51	39	35	32	24	15		10	5	2	2	0
	120															132																				

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

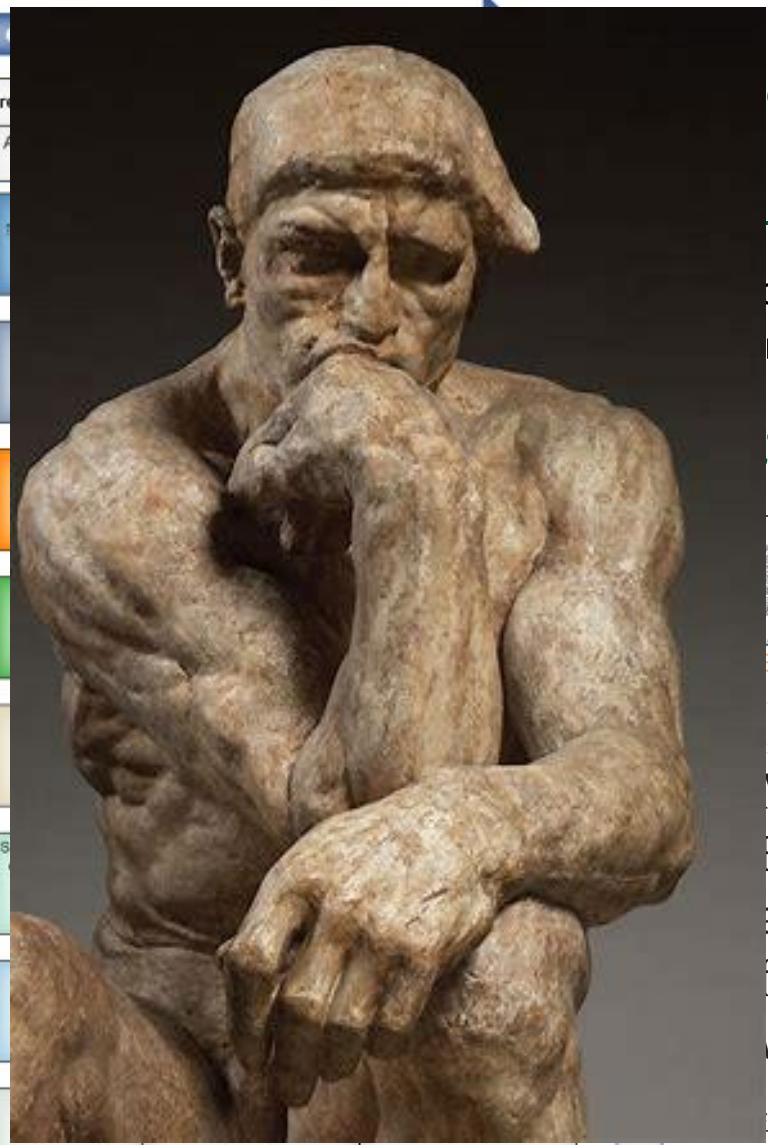
Aim: patient survival/cure

CONVERSION!

et Oncol 2023; 24: e312-22

Policy Review

Ordinal therapeutic hierarchy



Exclude therapy if (multifactorial weight)	Unfit	Critical tumor features	
		PS >2*	Extra-hepatic*
Exclude liver transplant if	Comorbidities, severe frailty, 1 biological age XXX	STOP	STOP
Exclude mini-invasive liver resection if	Comorbidities, severe frailty XX	STOP	STOP
Exclude liver resection if	Comorbidities, severe frailty XX	STOP	STOP
Exclude percutaneous ablation if	Severe comorbidities X	STOP	STOP
Exclude video-laparoscopic ablation if	Severe comorbidities X	STOP	STOP
Exclude intra-arterial therapies if	Severe comorbidities X	STOP	STOP
Exclude systemic therapy if	Severe comorbidities X	STOP	—
Best supportive care	—	—	—

Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept

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

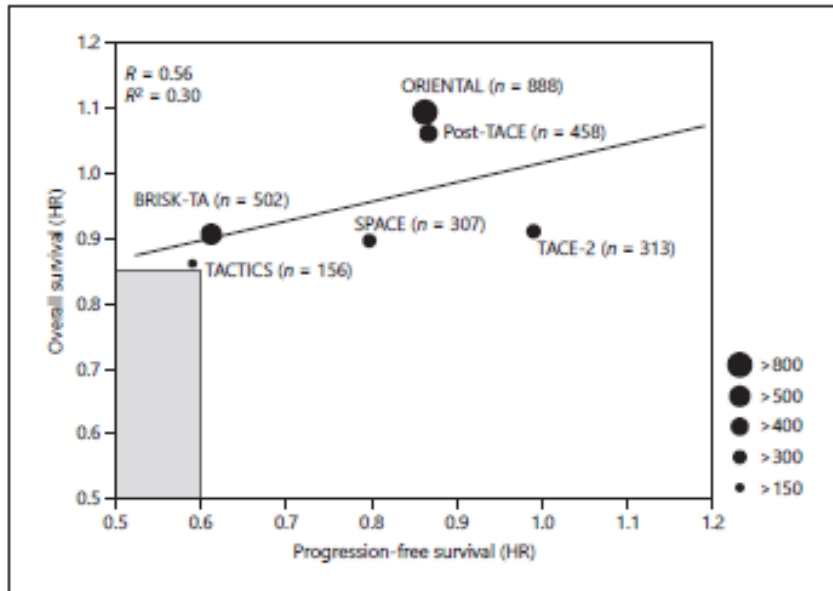
Journal of Hepatology
Available online 22 January 2024
In Press, Journal Pre-proof [What's this?](#)

Expert 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.

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Weight of each variable as a relative contraindication in the multifactorial assessment:
 — Irrelevant **X** Low **XX** Intermediate **XXX** Relevant Contraindication

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./Antiangiogenic
Adjuvant and neo-adjuvant sett.**

HCC management ...2000 -> 2010



Epatologo

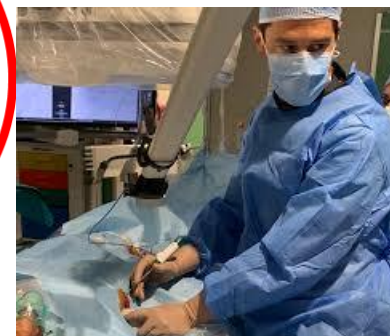
**Gastro,
Med Int**

Chirurgo



Radiologo

Oncologo



HCC management ...2020 -> 2024



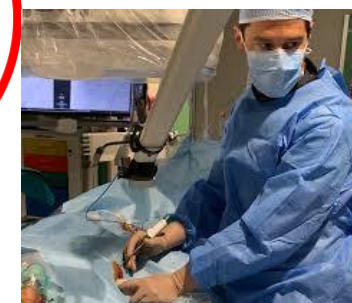
**Epatologo
(Gastro,
Med Int)**

Chirurgo

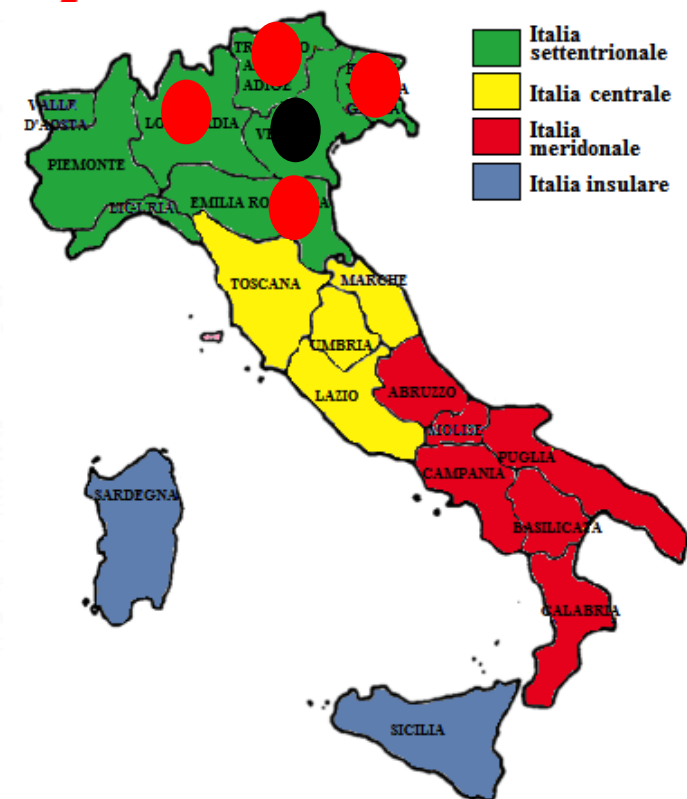
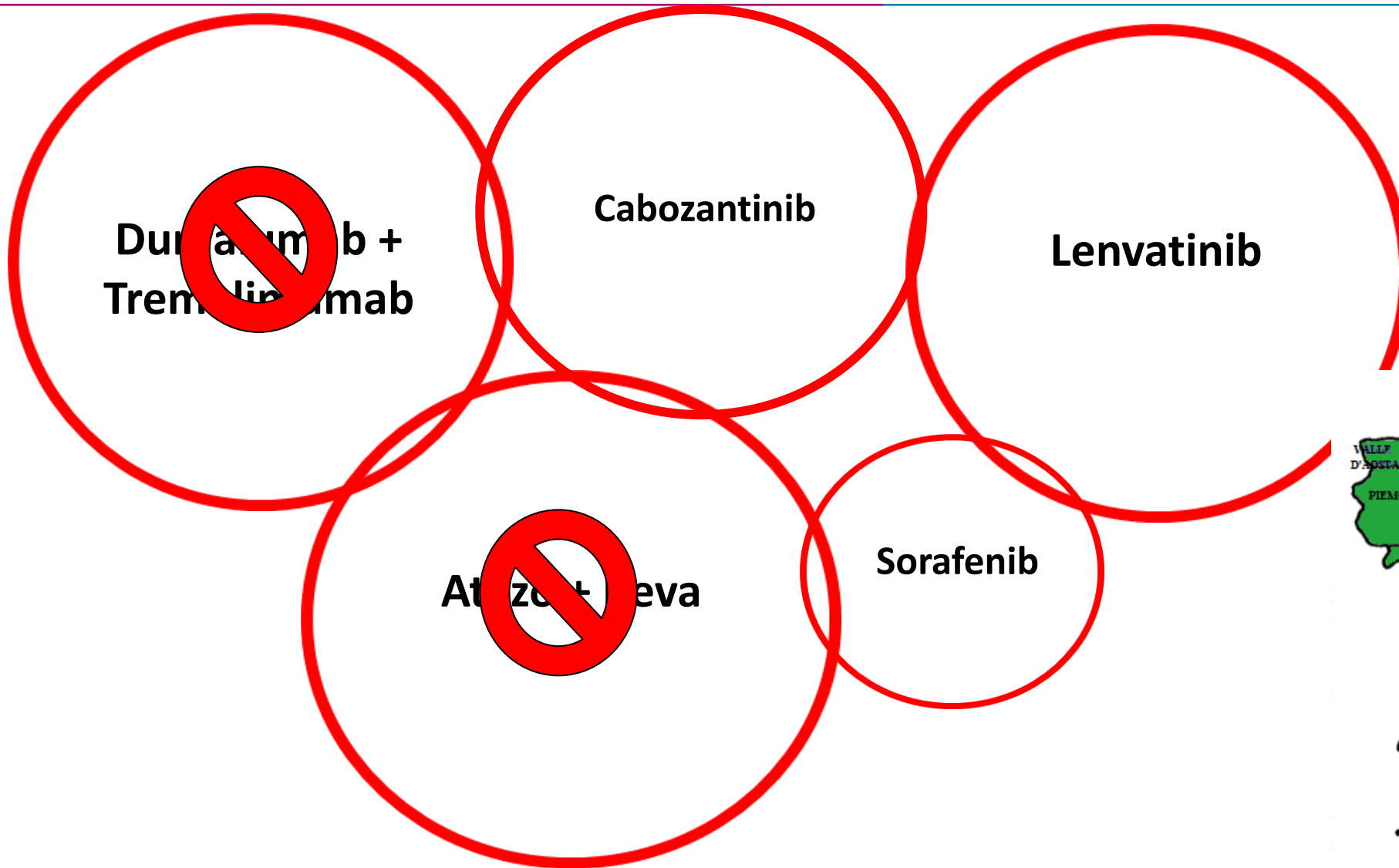


Oncologo

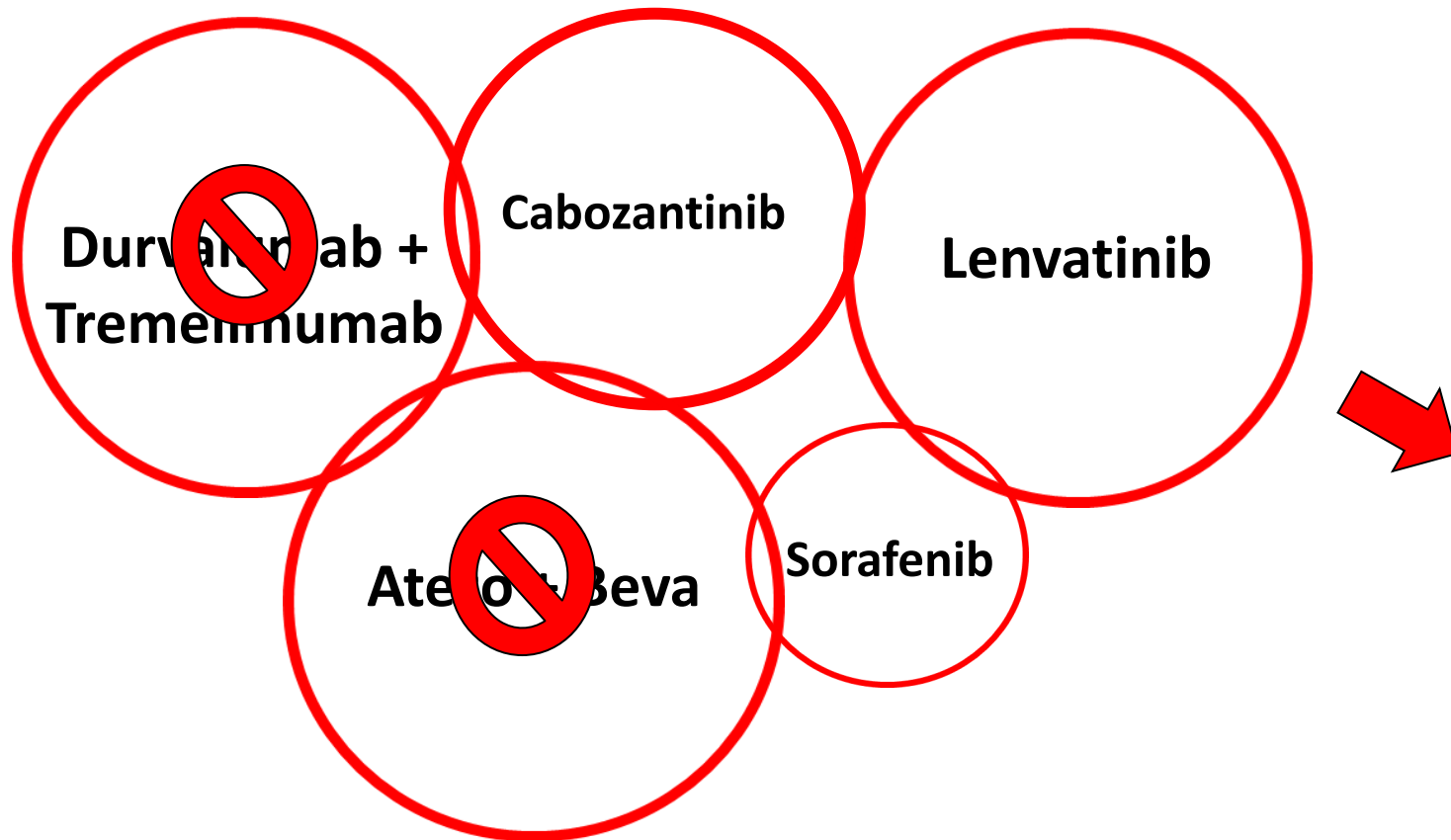
Radiologo



HCC management ... 2024



HCC management ... 2024





E allora?

Ambulatorio Multidisciplinare

«Epatologo»

«Oncologo»

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!