Teaching Cases from Investigators: The Application of Available Research to the Clinical Care of Patients with Hepatocellular Carcinoma

A CME Symposium Held in Conjunction with the 2025 ASCO® Gastrointestinal Cancers Symposium

Thursday, January 23, 2025

6:15 PM – 8:15 PM PT (9:15 PM – 11:15 PM ET)

Faculty

Anthony El-Khoueiry, MD

Richard S Finn, MD

Aiwu Ruth He, MD, PhD

Stacey Stein, MD

Moderator

Stephen “Fred” Divers, MD

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Faculty

Anthony El-Khoueiry, MD
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Associate Director for Clinical Research
Phase I Section Chief
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Moderator
Stephen "Fred" Divers, MD
Chief Medical Officer
American Oncology Network
Hot Springs, Arkansas

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Dr El-Khoueiry — Disclosures
Faculty

Advisory Committees and Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Eisai Inc, Elevar Therapeutics, Exelixis Inc, Genentech, a member of the Roche Group, Merck, Qurient, Terumo Medical Corporation
Contracted Research	Astex Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Auransa Inc, Fulgent

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Dr Finn — Disclosures
Faculty

Advisory Committees	CStone Pharmaceuticals, Zai Lab
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Eisai Inc, Genentech, a member of the Roche Group, Lilly, Novartis, Merck, Pfizer Inc, Zymeworks Inc
Contracted Research	Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Eisai Inc, Genentech, a member of the Roche Group, Merck, Pfizer Inc, Roche Laboratories Inc
Speakers Bureaus	Genentech, a member of the Roche Group

Dr He — Disclosures
Faculty

Advisory Committees	Bristol Myers Squibb
Consulting Agreements	Boston Scientific Corporation
Contracted Research	AstraZeneca Pharmaceuticals LP
Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Eisai Inc

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Dr Stein — Disclosures
Faculty

Advisory Committees	Cardinal Health, Exelixis Inc, Genentech, a member of the Roche Group, GSK, Merck, Regeneron Pharmaceuticals Inc
Data and Safety Monitoring Boards/Committees	Aethlon Medical Inc, Genentech, a member of the Roche Group, TransThera

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Dr Divers — Disclosures
Moderator

Advisory Committees	Daiichi Sankyo Inc
Community Oncology Panels	Caris Life Sciences, Johnson & Johnson Pharmaceuticals
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What Clinicians Want to Know: Biomarker Assessment and Related Treatment Decision-Making for Patients with Colorectal Cancer

A CME Symposium Held in Conjunction with the 2025 ASCO® Gastrointestinal Cancers Symposium

Friday, January 24, 2025

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Arvind Dasari, MD, MS

Van K Morris, MD

Jenny Seligmann, MBChB, PhD

Eric Van Cutsem, MD, PhD

Moderator

Christopher Lieu, MD

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Save The Date

Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, February 28 to March 2, 2025

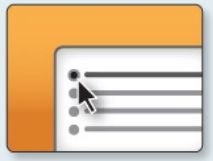
Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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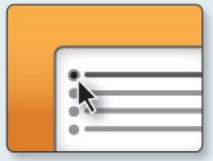
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Teaching Cases from Investigators: The Application of Available Research to the Clinical Care of Patients with Hepatocellular Carcinoma

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Moderator

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Consulting Faculty

Ghassan Abou-Alfa, MD, MBA
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San Francisco, California

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Agenda

Module 1: Adjuvant Systemic Therapy for Early-Stage Hepatocellular Carcinoma (HCC) — Dr El-Khoueiry

Module 2: Recent Developments in the Management of Intermediate-Stage HCC — Dr Finn

Module 3: Current First-Line Therapy for Advanced HCC — Dr He

Module 4: Promising Investigational Front-Line Strategies for Advanced HCC; Selection and Sequencing of Therapy for Relapsed/Refractory HCC — Dr Stein

Agenda

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USC Norris Comprehensive Cancer Center
Keck Medicine of USC

Adjuvant Systemic Therapy for Early-Stage Hepatocellular Carcinoma (HCC)

Anthony El-Khoueiry, MD
Associate Director for Clinical Research
Chief, Section of Developmental Therapeutics/Phase I program
Verna R. Richter Chair in Cancer Research
USC Norris Comprehensive Cancer Center

Surgical Resection for Hepatocellular Carcinoma

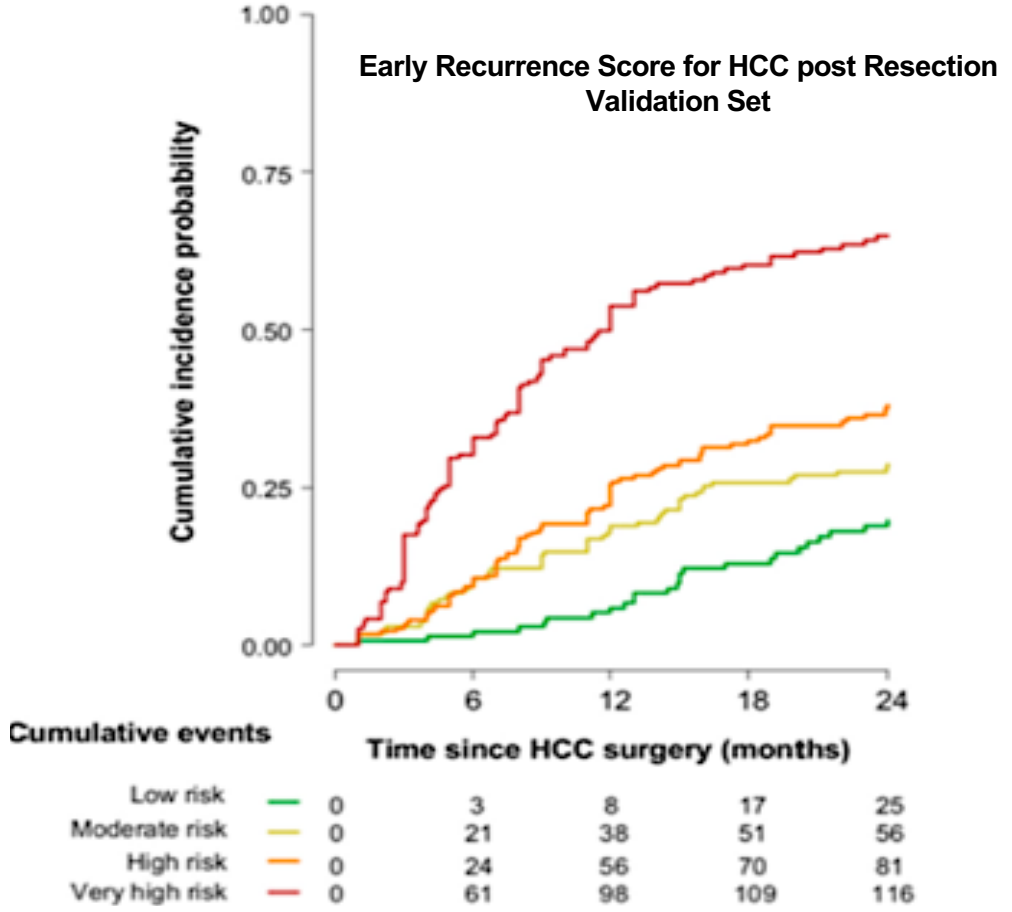
- Curative option for liver limited HCC (mostly BCLC 0/A)
  - Definition of resectability is highly variable
- High recurrence rates
  - as high as 70% at 5 years
  - majority of recurrences are intrahepatic (60-80%)
  - early recurrences (within 2 years): size greater than 5 cm, high histological grade, and presence of microvascular invasion
  - later recurrences (beyond 2 years): advanced cirrhosis, multinodularity, increasing age, male sex, increased AST levels
- 5-year overall survival rates: 45 to 75%

Tabrizian P et al, Ann Surg 2015
Chawla A, Ferrone C, Chin Clin Oncol 2018
Imamura H et al, J Hepatol 2003
Colecchia A et al, World J Gastroenterol 2014

Risk of recurrence

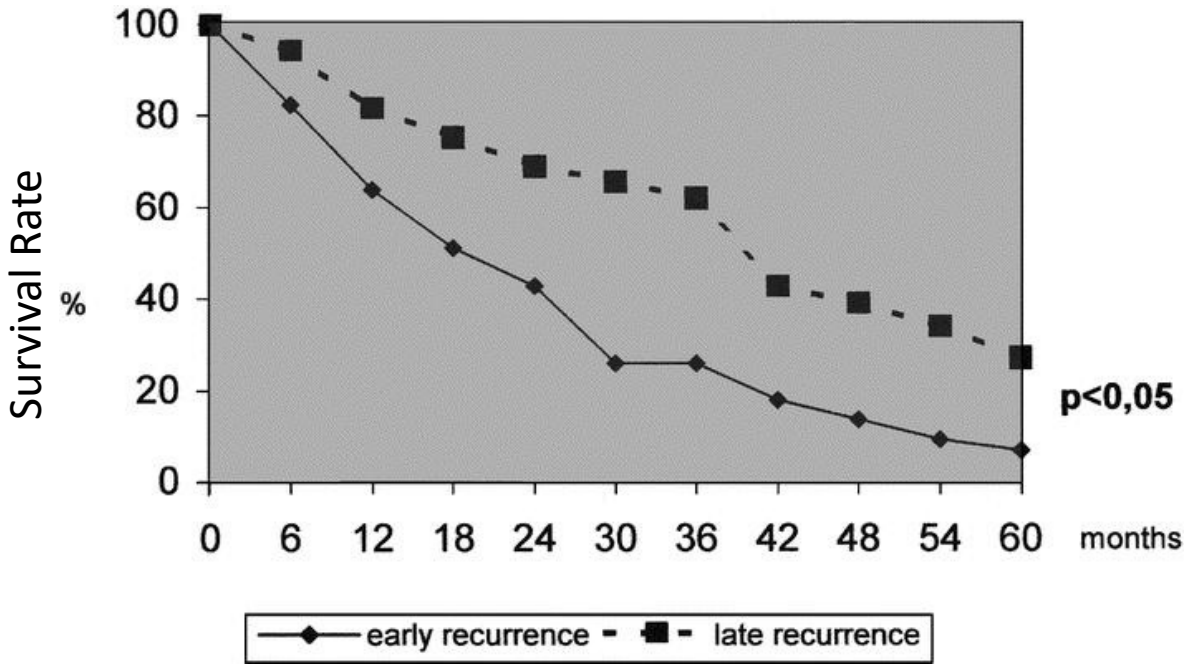
- Multiple prognostic/risk nomograms available

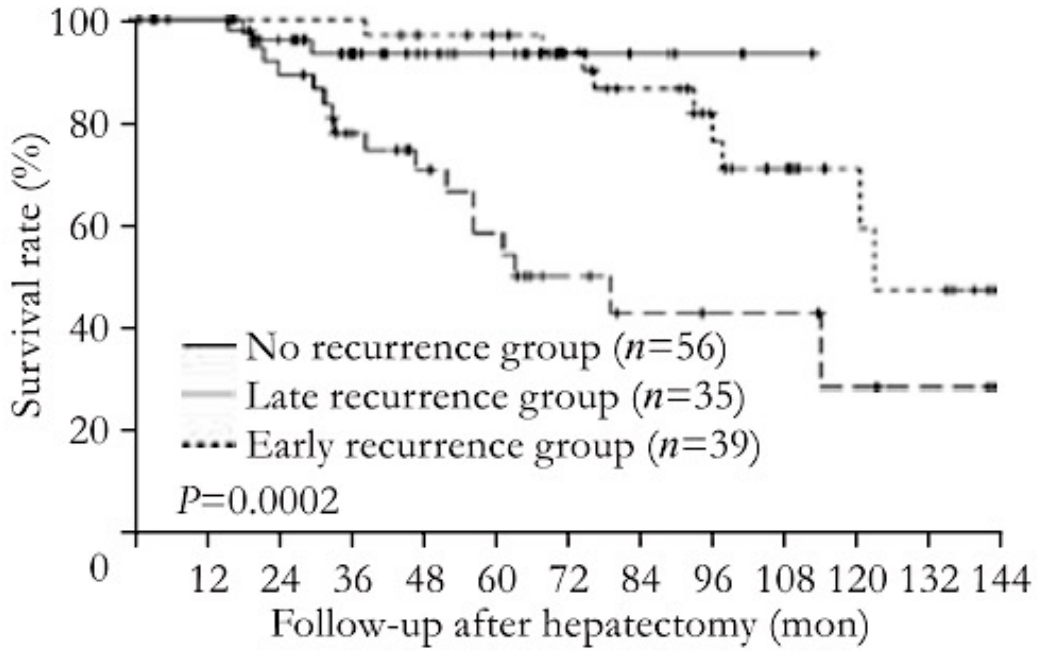
- Example: Early Recurrence Score (ERS)
  - N=2359 resected HCC patients, 2004-2017
  - 6 variables→11 points were associated with 2-year recurrence: AFP, size of largest tumor, multifocality, satellite nodules, vascular invasion, surgical margin positivity
    - AFP >100 ng/mL: 3 points (strongest predictor)



Costentin et al. Liver Int. 2023

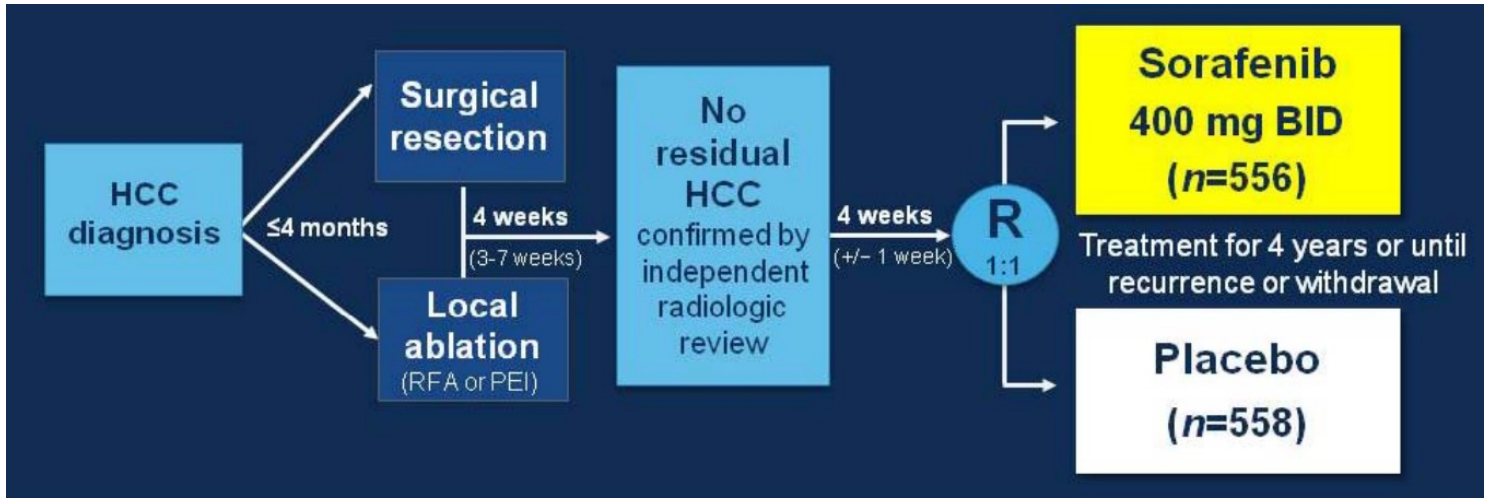
Early recurrence associated with worse outcomes





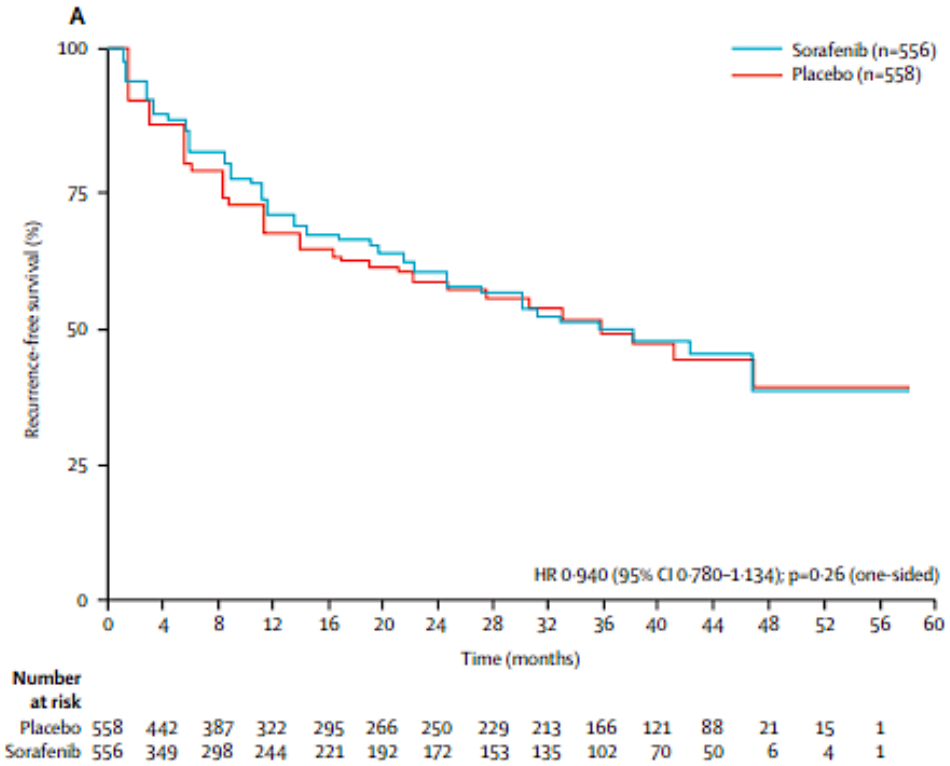
Portolani N et al, Ann Surg 2006
Kobayashi T et al, Hepatobiliary Pancreat Dis Int 2017

STORM trial: no benefit from adjuvant sorafenib



19% of patients had ablation

Risk of recurrence	Intermediate	High
Surgical resection[a]	All of the following: • Single tumor ≥2 cm • Well / moderately differentiated • Without microvascular invasion or satellite tumors	Single tumor any size and any of the following: • Microvascular invasion • Satellite tumors • Poorly differentiated *or* 2-3 tumors each ≤3 cm[a]
Ablation[b]	Single tumor 2-3 cm	Single tumor >3-5 cm *or* 2-3 tumors each ≤3 cm



Median RFS: 33.3 months

vs. 33.7 mos. (HR 0.94)

Bruix et al. Lancet Oncol. 2015

Leveraging anti cancer immunity in adjuvant setting: Cytokine induced killer cells

Randomized Phase III open-label trial

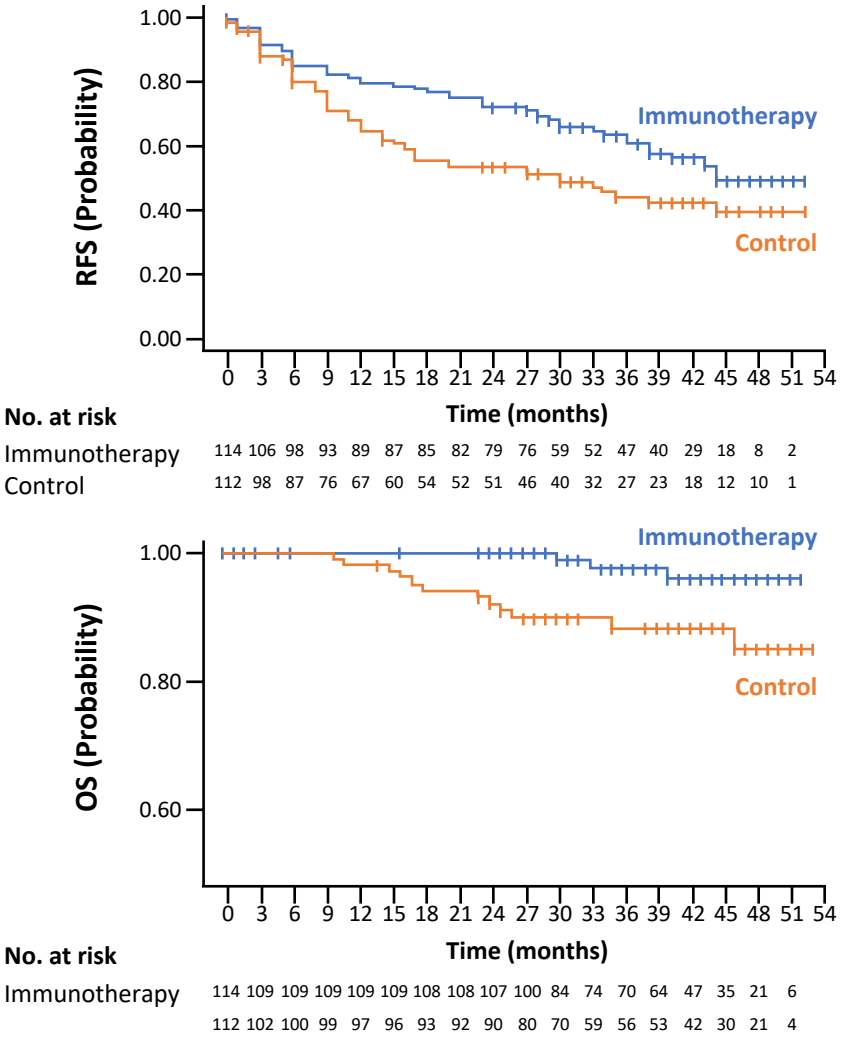
230 patients with HCC after resection, RFA, or ethanol injection

↓

Injection of activated cytokine-induced killer cells

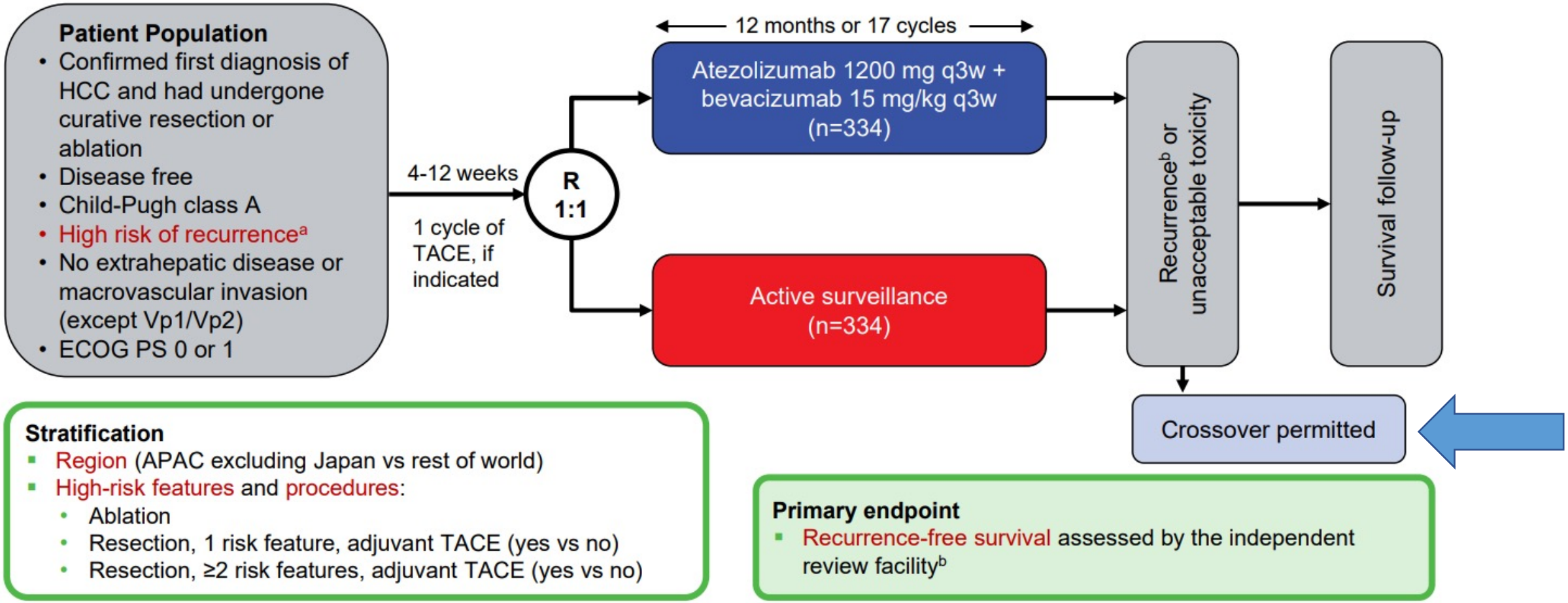
- **CD3+/CD56+ T cells**
- **CD3+/CD56– T cells**
- **CD3–/CD56+ natural killer cells**

- **Primary Endpoint: Recurrence-free survival**



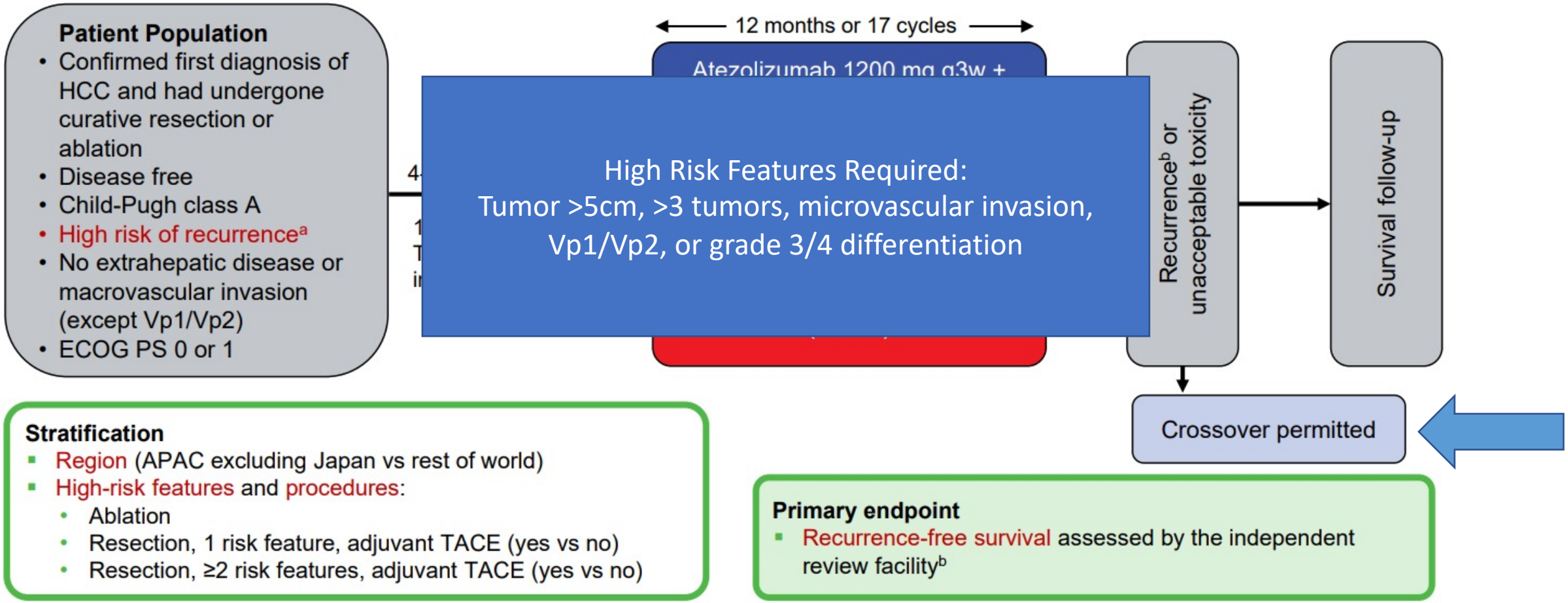
Lee JH et al. Gastroenterology. 2015

IMbrave050 Design



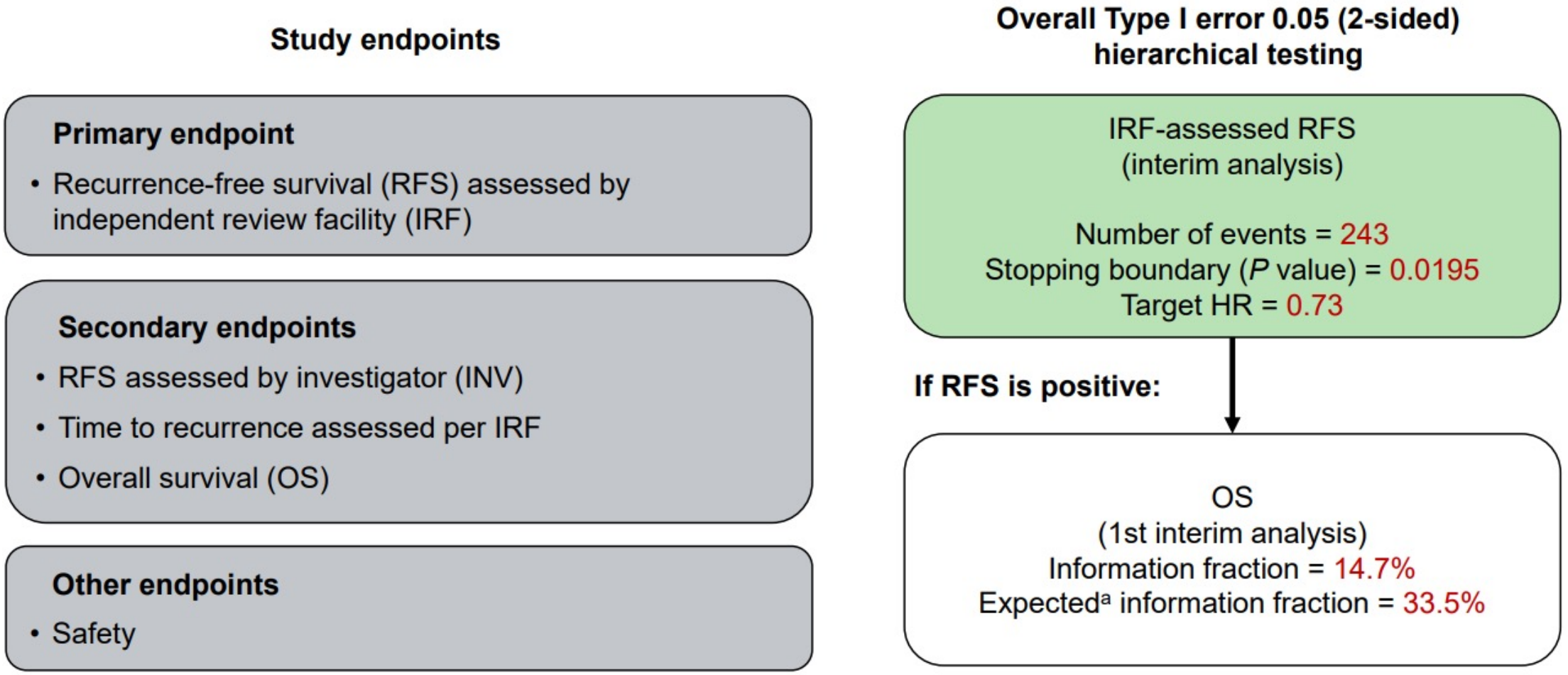
Chow et al. AACR 2023; Qin et al. Lancet. 2023;402:1835-47.

IMbrave050 Design



Chow et al. AACR 2023; Qin et al. Lancet. 2023;402:1835-47.

IMbrave050 statistics



Chow et al. AACR 2023; Qin et al. Lancet. 2023;402:1835-47.

Baseline characteristics were balanced across treatment arms

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

Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Median age (range), years	60 (19-89)	59 (23-85)
Male sex, n (%)	277 (82.9)	278 (83.2)
Ethnicity, n (%)		
Asian	276 (82.6)	269 (80.5)
White	35 (10.5)	41 (12.3)
Other	23 (6.9)	24 (7.2)
Geographic region, n (%)		
Asia Pacific excluding Japan | rest of world	237 (71.0) | 97 (29.0)	238 (71.3) | 96 (28.7)
ECOG PS score, n (%)		
0 | 1	258 (77.2) | 76 (22.8)	269 (80.5) | 65 (19.5)
PD-L1 status, n (%)[a,b]		
≥1% | <1%	154 (54.0) | 131 (46.0)	140 (50.2) | 139 (49.8)
Etiology, n (%)		
Hepatitis B	209 (62.6)	207 (62.0)
Hepatitis C	34 (10.2)	38 (11.4)
Non viral | unknown	45 (13.5) | 46 (13.8)	38 (11.4) | 51 (15.3)
BCLC stage at diagnosis, n (%)		
0	2 (0.6)	3 (0.9)
A	287 (85.9)	277 (82.9)
B	25 (7.5)	32 (9.6)
C	20 (6.0)	22 (6.6)

Chow et al. AACR 2023; Qin et al. Lancet. 2023;402:1835-47.

Baseline characteristics—curative procedures

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

Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Resection, n (%)	293 (87.7)	292 (87.4)
Longest diameter of the largest tumor at diagnosis, median (range), cm[a]	5.3 (1.0-18.0)	5.9 (1.1-25.0)
Tumors, n (%)		
1	266 (90.8)	260 (89.0)
2	20 (6.8)	29 (9.9)
3	4 (1.4)	2 (0.7)
4+	3 (1.0)	1 (0.3)
Adjuvant TACE following resection, n (%)	32 (10.9)	34 (11.6)
Any tumors >5 cm, n (%)	152 (51.9)	175 (59.9)
Microvascular invasion present, n (%)	178 (60.8)	176 (60.3)
Minor macrovascular invasion (Vp1/Vp2) present, n (%)	22 (7.5)	17 (5.8)
Poor tumor differentiation (Grade 3 or 4), n (%)	124 (42.3)	121 (41.4)
Ablation, n (%)	41 (12.3)	42 (12.6)
Longest diameter of the largest tumor at diagnosis, median (range), cm	2.5 (1.2-4.6)	2.6 (1.5-4.6)
Tumors, n (%)		
1	29 (70.7)	31 (73.8)
2	11 (26.8)	8 (19.0)
3	1 (2.4)	3 (7.1)

Chow et al. AACR 2023; Qin et al. Lancet. 2023;402:1835-47.

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

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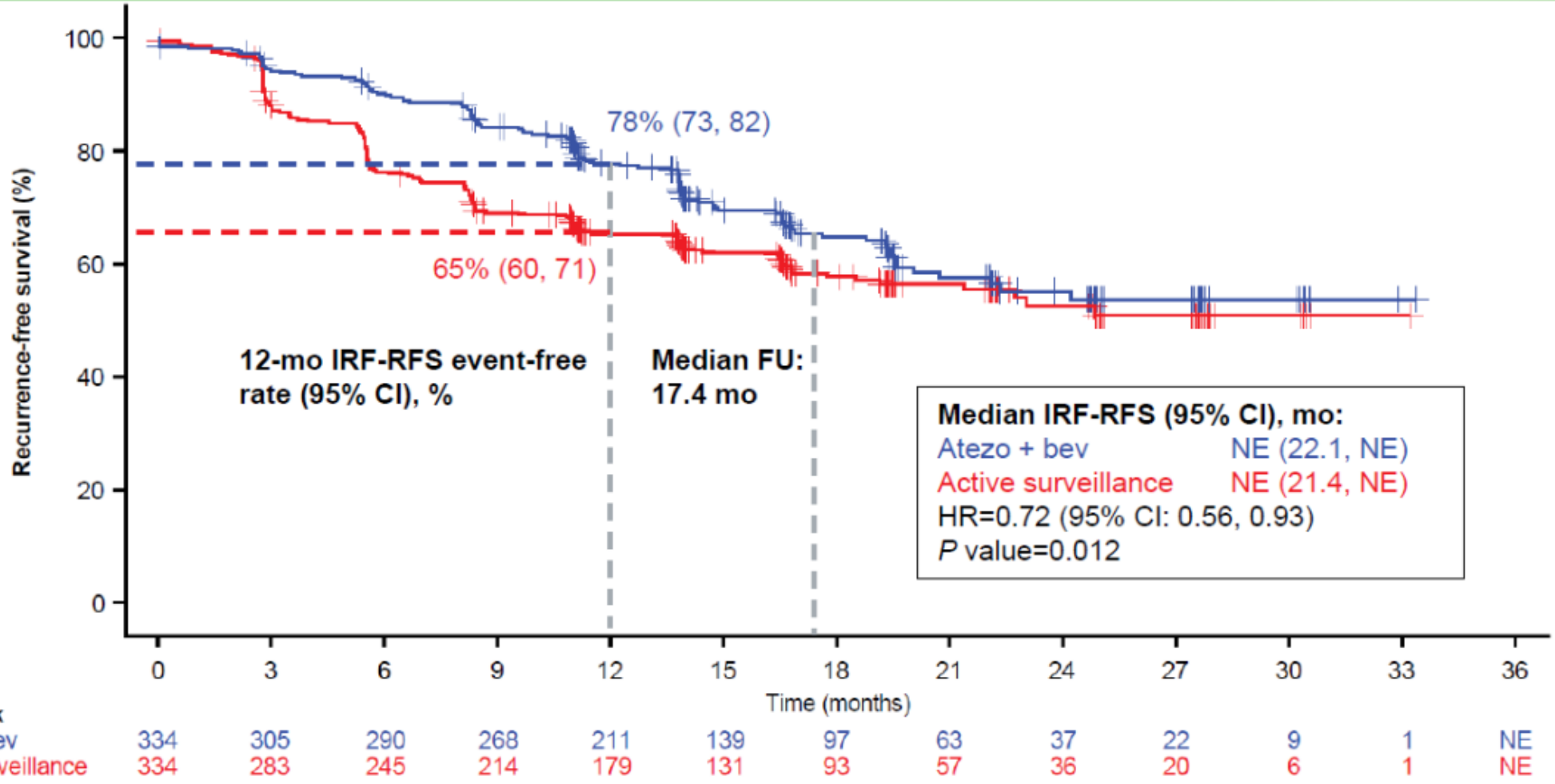
APRIL 14-19 • #AACR23



No. at risk													
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

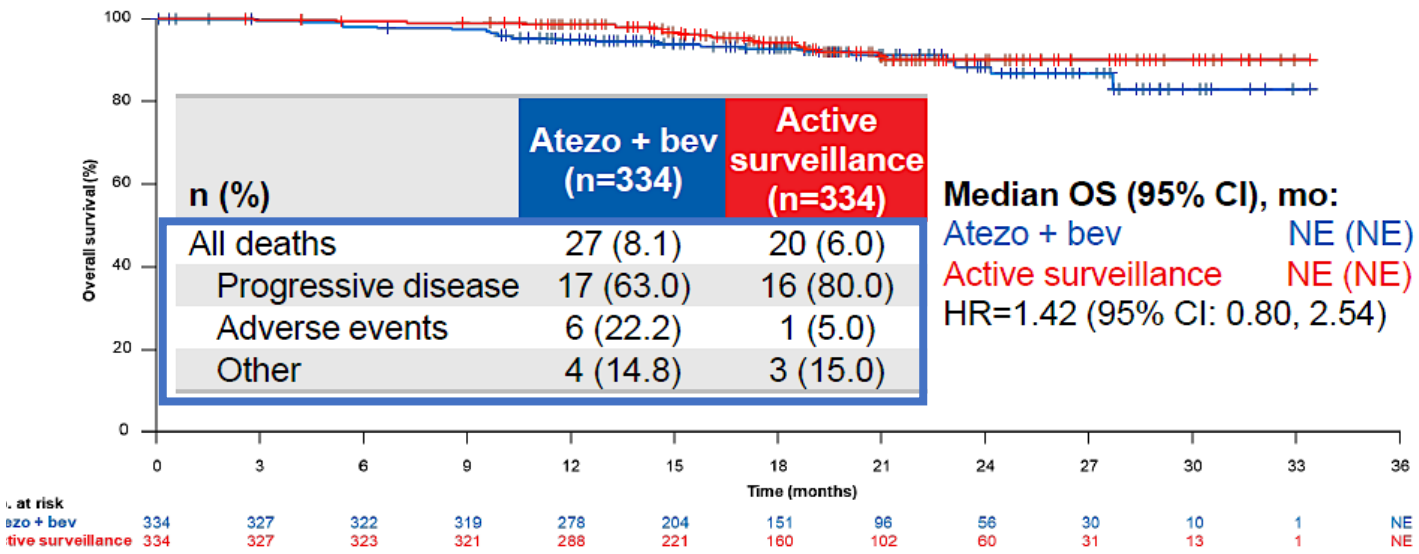
Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log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

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

Chow et al. AACR 2023; Qin et al. Lancet. 2023;402:1835-47.

Overall survival was highly immature

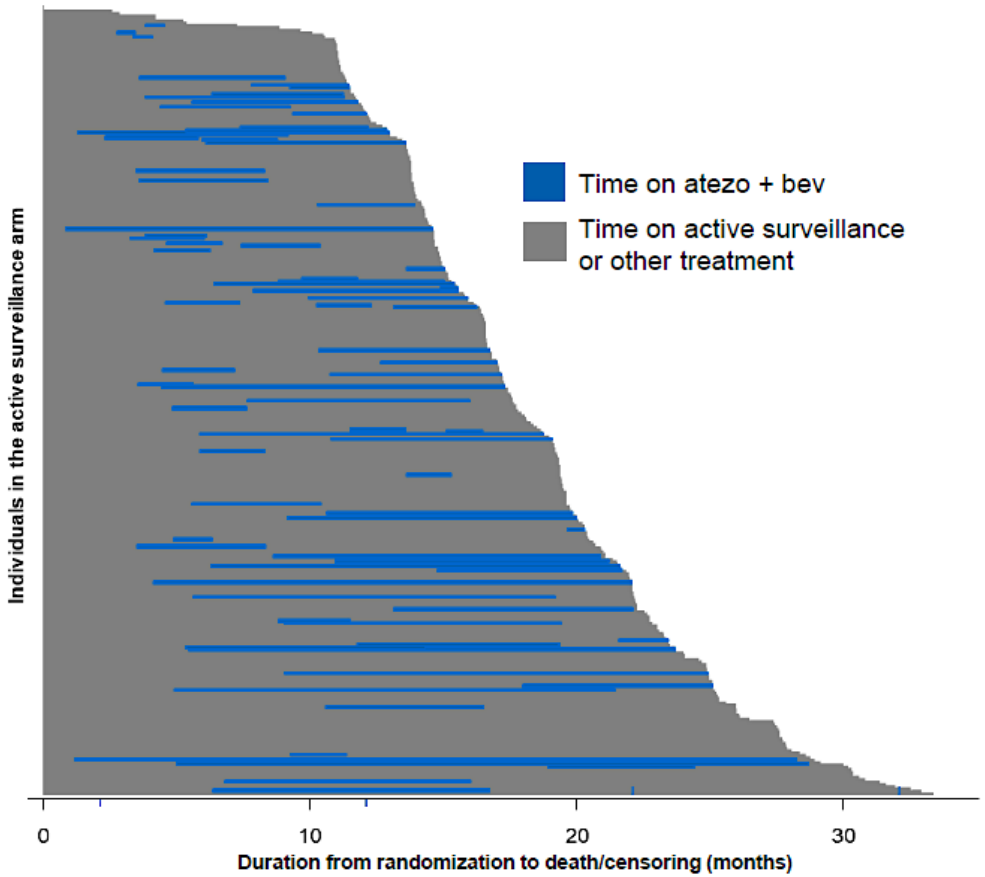
- **OS is highly immature, with a 7% event-patient ratio (n=47).** There were:
  - 7 more deaths in the atezo + bev arm (27 vs 20)
  - Similar number of deaths due to HCC recurrence
  - 3 COVID-19-related deaths within 1 year of randomization, all in the atezo + bev arm
- Patients in the active surveillance arm were allowed to cross over to receive atezo + bev either directly after IRF-confirmed recurrence or following a second resection or ablation



n (%)	Atezo + bev (n=334)	Active surveillance (n=334)
All deaths	27 (8.1)	20 (6.0)
Progressive disease	17 (63.0)	16 (80.0)
Adverse events	6 (22.2)	1 (5.0)
Other	4 (14.8)	3 (15.0)

Median OS (95% CI), mo:
Atezo + bev NE (NE)
Active surveillance NE (NE)
HR=1.42 (95% CI: 0.80, 2.54)

Of the 133 patients with an RFS event during active surveillance, **81 (61%) crossed over to atezo + bev**



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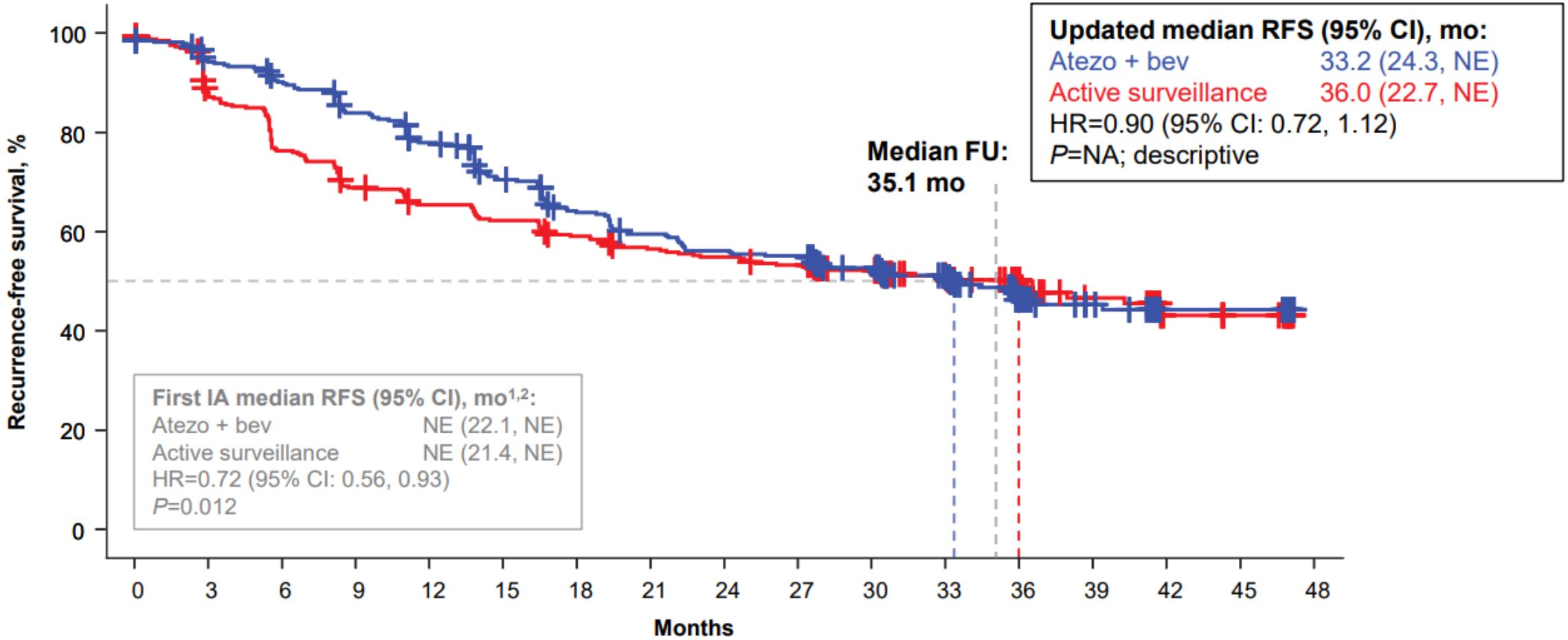
Chow et al IMbrave050
https://bit.ly/3ZPKzgM

Chow et al. AACR 2023; Qin et al. Lancet. 2023

Early RFS benefit was not maintained with longer follow-up



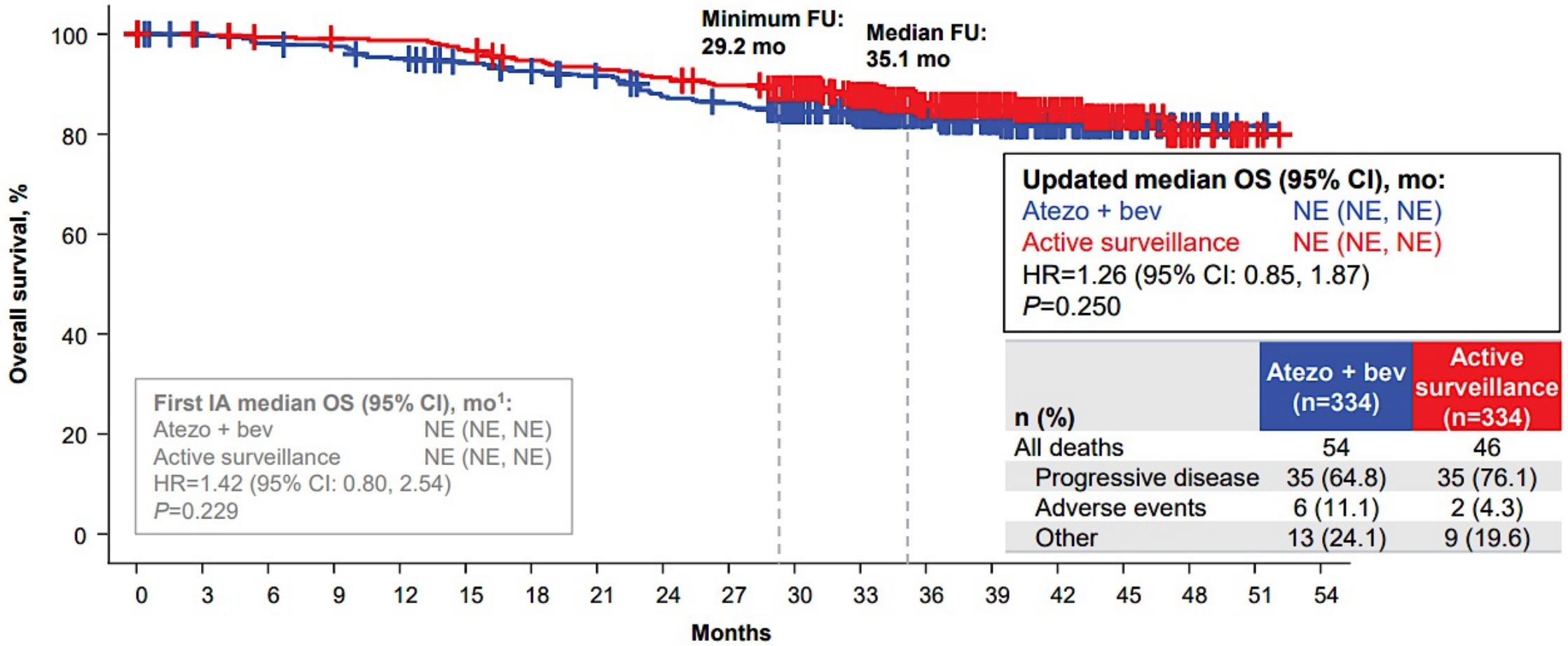
No. at risk

Atezo + bev	334	305	290	268	245	216	191	177	167	164	147	123	62	45	18	18	NE
Active surveillance	334	285	247	221	207	197	185	175	170	164	145	124	63	42	16	14	NE

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. At clinical cutoff, 162 of 334 patients (49%) in the atezo + bev arm and 164 of 334 (49%) in the active surveillance arm experienced disease recurrence or death. HRs are stratified. *P* values are log rank.
FU, follow-up; NA, not applicable; NE, not estimable. 1. Qin et al. Lancet 2023. 2. Chow et al. AACR 2023 [abstract CT003].

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

Updated OS remained immature but showed numerical improvement from the first IA



n (%)	Atezo + bev (n=334)	Active surveillance (n=334)
All deaths	54	46
Progressive disease	35 (64.8)	35 (76.1)
Adverse events	6 (11.1)	2 (4.3)
Other	13 (24.1)	9 (19.6)

No. at risk

Atezo + bev	334	327	322	319	310	301	294	286	271	266	243	206	142	101	60	34	16	3	NE
Active surveillance	334	327	323	321	320	314	304	299	293	286	266	226	157	108	71	38	15	3	NE

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. HRs are stratified. *P* values are log rank.

1. Qin et al. Lancet 2023.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

Recurrence patterns

First post-baseline unequivocal recurrence

	Atezo + bev (n=334)	Active surveillance (n=334)
Patients with recurrence, n	141	160
Location of recurrence, n (%)		
Intrahepatic only	103 (73.0)	109 (68.1)
Extrahepatic only	35 (24.8)	44 (27.5)
Both intra- and extrahepatic	3 (2.1)	7 (4.4)
Outside Milan criteria, n (%)		
Yes	51 (36.2)	67 (41.9)
No	89 (63.1)	89 (55.6)
NA[a]	1 (0.7)	4 (2.5)
Outside up-to-7 criteria, n (%)		
Yes	51 (36.2)	67 (41.9)
No	89 (63.1)	89 (55.6)
NA[a]	1 (0.7)	4 (2.5)

Patients with intrahepatic recurrence (regardless of extrahepatic recurrence)

	Atezo + bev (n=334)	Active surveillance (n=334)
Intrahepatic recurrence, n	106	116
Macrovascular invasion, n (%)		
Yes	14 (13.2)	15 (12.9)
No	92 (86.8)	100 (86.2)
Not evaluable	0	1 (0.9)
Tumour liver lobe invasion, n (%)		
Unilobar	99 (93.4)	110 (94.8)
Bilobar	7 (6.6)	6 (5.2)

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. [a] Patients were considered NA for Milan and up-to-7 criteria if they did not have extrahepatic spread or MVI and had ≥1 non-measurable lesion.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

Safety summary

	Atezo + bev (n=332)	Active surveillance (n=330)	IMbrave150[1,2] (n=329)
Treatment duration, median, mo	Atezo: 11.1 Bev: 11.0	NA	Atezo: 7.4 Bev: 6.9
Patients with ≥1 AE, n (%)	326 (98.2)	205 (62.1)	323 (98.2)
Treatment-related AE	293 (88.3)	NA	276 (83.9)
Grade 3/4 AE, n (%)	136 (41.0)	44 (13.3)	186 (56.5)
Treatment-related Grade 3/4 AE	116 (34.9)	NA	117 (35.6)
Serious AE, n (%)	80 (24.1)	34 (10.3)	125 (38.0)
Treatment-related serious AE	44 (13.3)	NA	56 (17.0)
Grade 5 AE, n (%)	6 (1.8)	1 (0.3)	15 (4.6)
Treatment-related Grade 5 AE	2 (0.6)[a]	NA	6 (1.8)
AE leading to dose interruption of any study treatment, n (%)	155 (46.7)	NA	163 (49.5)
AE leading to withdrawal from any study treatment, n (%)	63 (19.0)	NA	51 (15.5)

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. In safety-evaluable patients. AE, adverse event. NA, not available.
[a] Esophageal varices hemorrhage and ischemic stroke; 1 was related to atezo and bev and the other was related to bev only.
1. Finn et al. NEJM 2020. 2. Data on file.

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

Chow et al. AACR 2023; Qin et al. Lancet. 2023;402:1835-47.

Atezolizumab in combination with bevacizumab is NOT approved as adjuvant therapy in patients with hepatocellular carcinoma at high risk of recurrence after surgical resection or ablation and should not be used in this setting

August, 2024

Dear Healthcare Provider:

The purpose of this letter is to inform you of important new information that impacts the benefit-risk of off-label use of atezolizumab and bevacizumab in hepatocellular carcinoma (HCC) patients in the adjuvant setting, following curative resection or ablation.

Unfavorable benefit-risk for atezolizumab and bevacizumab as an adjuvant therapy for HCC patients

- The combination of atezolizumab and bevacizumab is not approved or marketed in the United States or any other country for the adjuvant treatment of HCC. Based on the positive recurrence-free survival (RFS) results at the first interim analysis of the IMbrave050 study and the high-unmet need in this setting, the NCCN Clinical Practice Guidelines in Oncology for Hepatocellular Carcinoma and the AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma currently recommend the use of atezolizumab plus bevacizumab in the adjuvant setting for patients at high risk of recurrence.
- Based on an updated analysis of IMbrave050, this Direct Healthcare Professional Communication (DHCP) is being sent to advise against the off-label use of atezolizumab in combination with bevacizumab for the adjuvant treatment of HCC.
- There is no impact on the approved indication of unresectable or metastatic HCC, where the combination of atezolizumab and bevacizumab remains a standard of care treatment option.

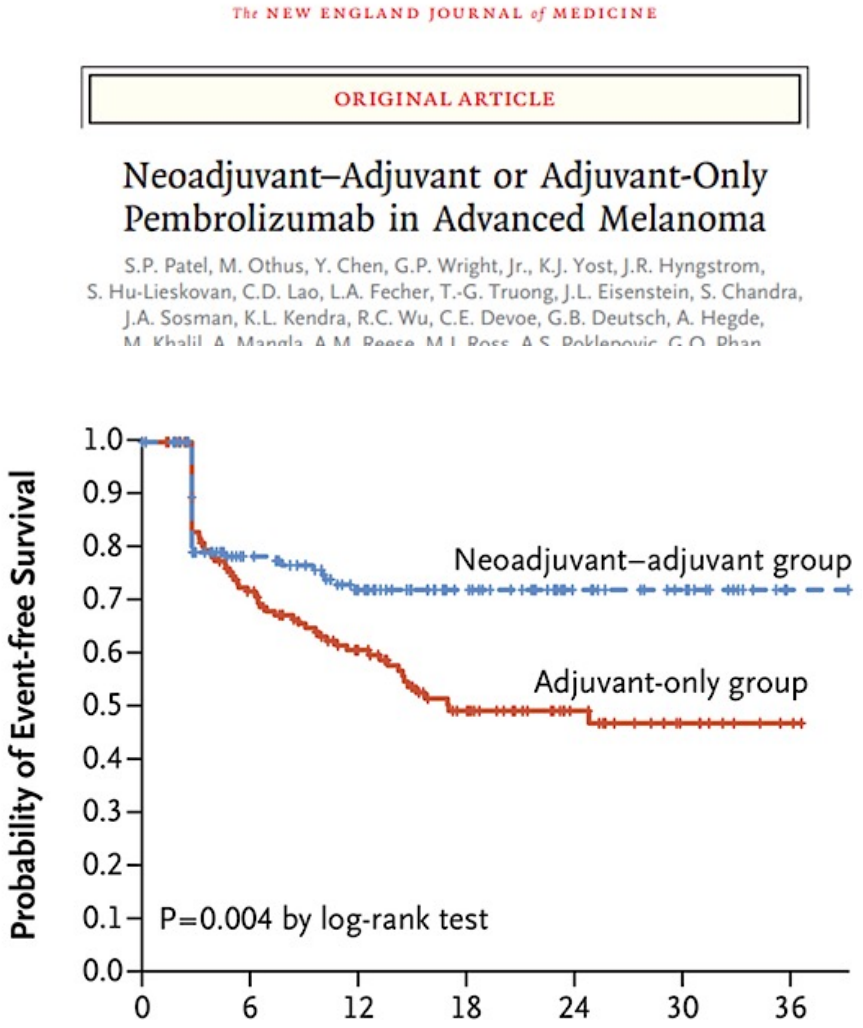
https://www.gene.com/download/pdf/Tecentriq_DHCP_Important_Drug_Warning_08-2024_Avastin.pdf

Other pending adjuvant trials

Agent	Study Design	Sample Size	NCT
Nivolumab (CheckMate 9DX)	RP3	545	NCT03383458
Pembrolizumab (KEYNOTE-937)	RP3	950	NCT03867084
Camrelizumab plus apatinib	RP3	687	NCT04639180
Durvalumab + bevacizumab (EMERALD-2)	RP3	908	NCT03847428
Durvalumab + tremelimumab	Phase 2	28	NCT05440864

Are we limited to adjuvant therapy? Emerging role of neoadjuvant approaches

- Potential advantages of neoadjuvant therapy:
  - Data suggest more intact anti-cancer immunity in early disease
  - Use tumor as a source of neoantigens
  - Ability to assess response and utility
  - Test biology
  - Critical resource for biomarker development
  - May enhance resectability



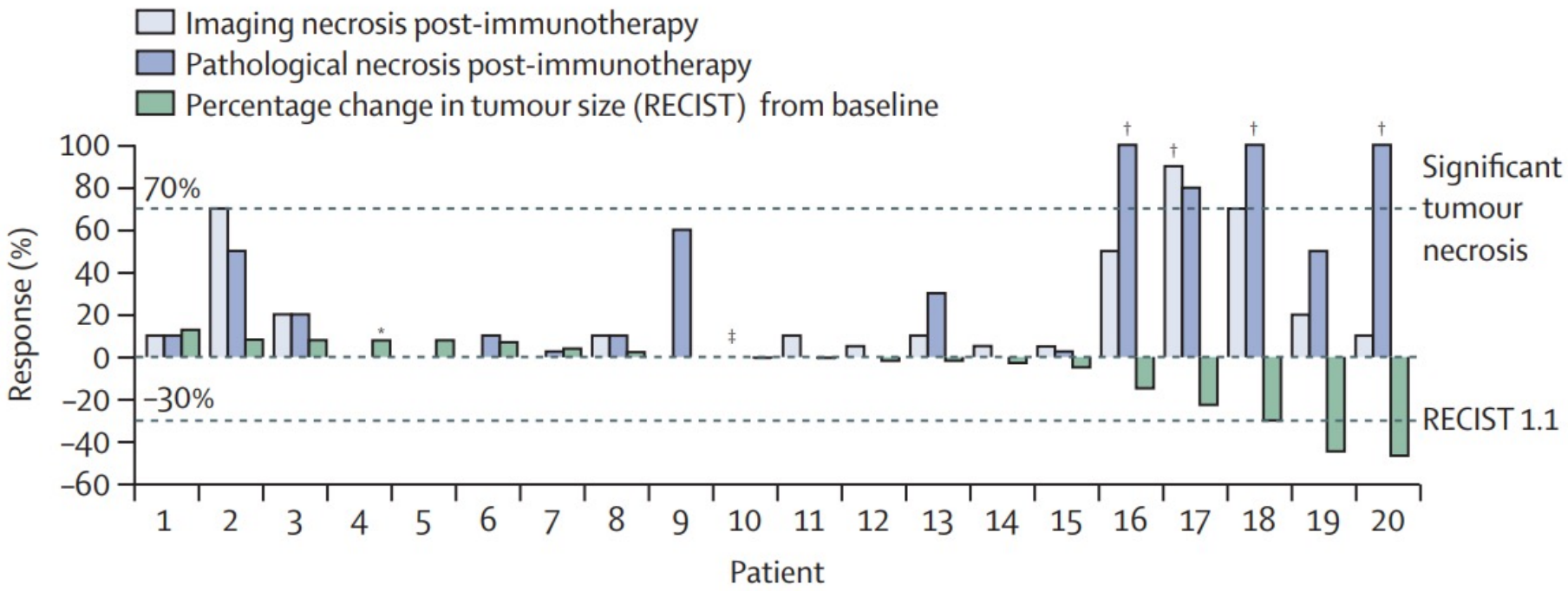
Liu J. Cancer Discov. 2016
Cascone T. Cancer Res. 2018.

Neoadjuvant approaches in HCC

- Small studies, mostly single institution
- Regimens evaluated:
  - PD1 single agent
  - PD1/TKI
  - PD1/CTLA4
- Variability in endpoints, eligibility and treatment duration
- Emerging signal with 20 to 30% major and complete pathologic response

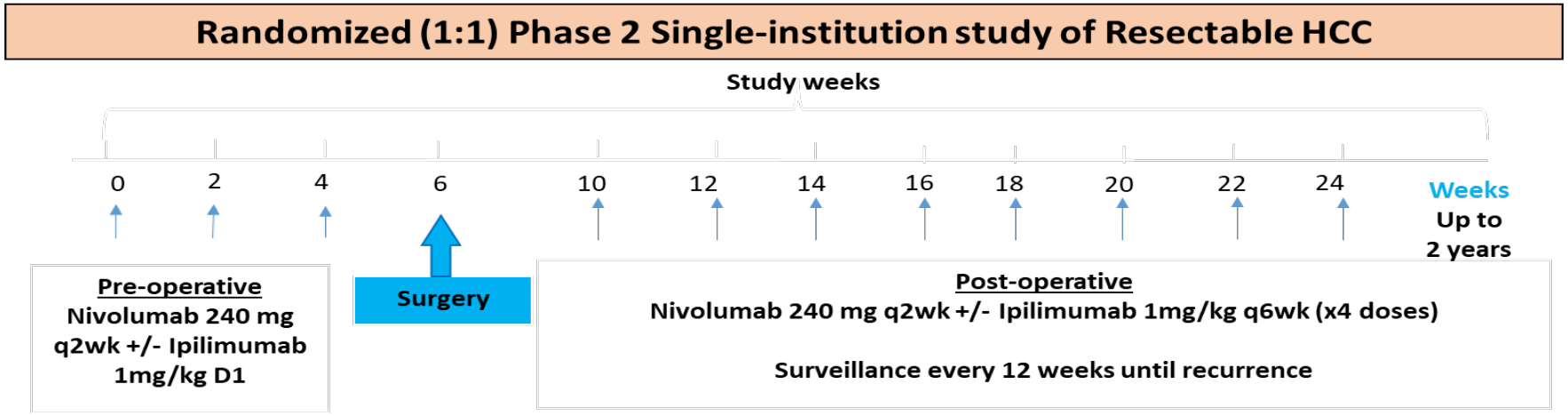
Neoadjuvant single agent PD-1 in resectable HCC

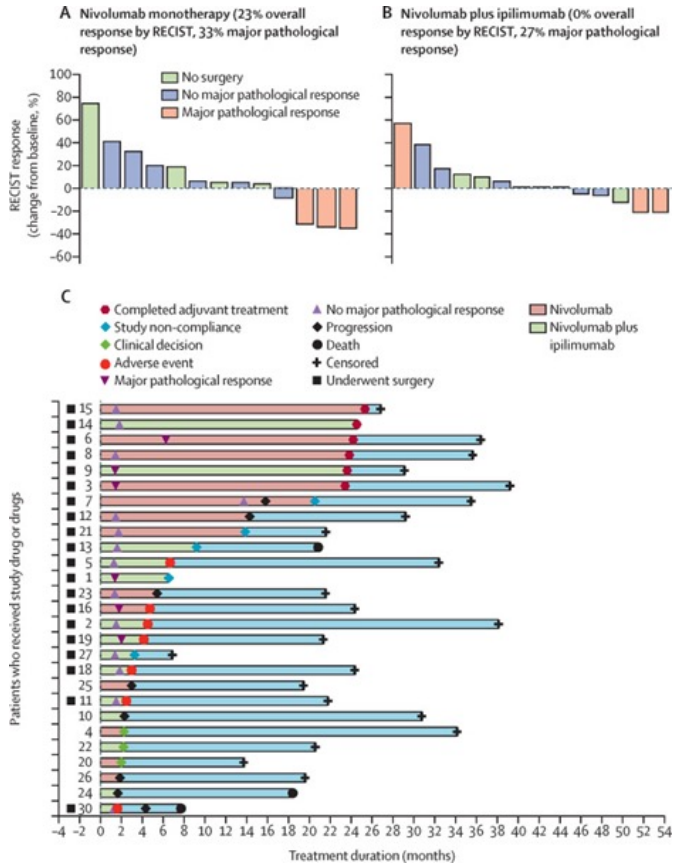
- Patients with resectable disease
- Single agent cemiplimab x 2 cycles
- 20/21 enrolled underwent surgery
- 4/20 with major pathologic response



Marron TU. Lancet Gastroenterol Hepatol. 2022; 7: 219–29

Neoadjuvant nivolumab or nivolumab/ipilimumab

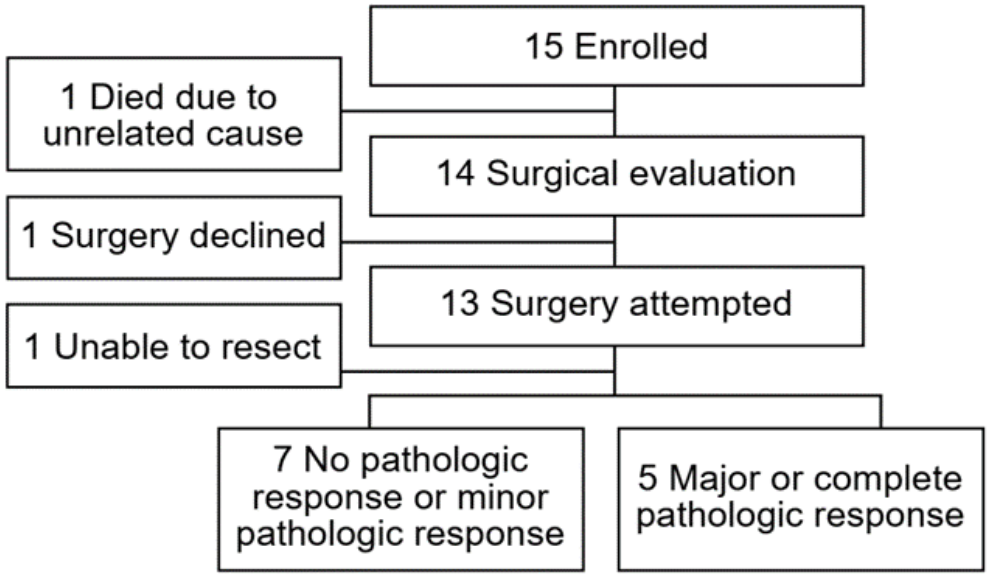


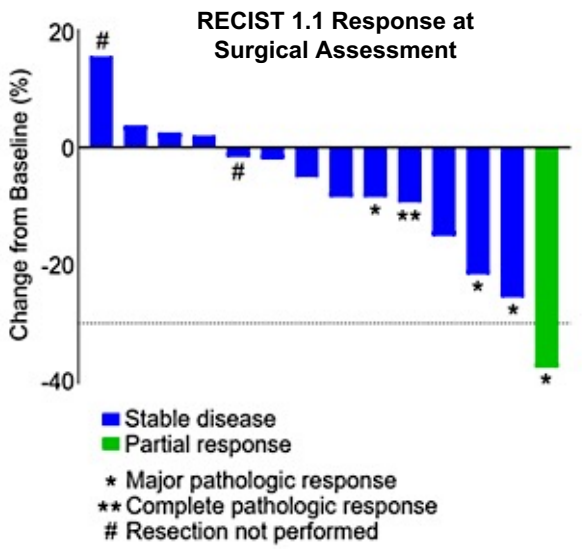


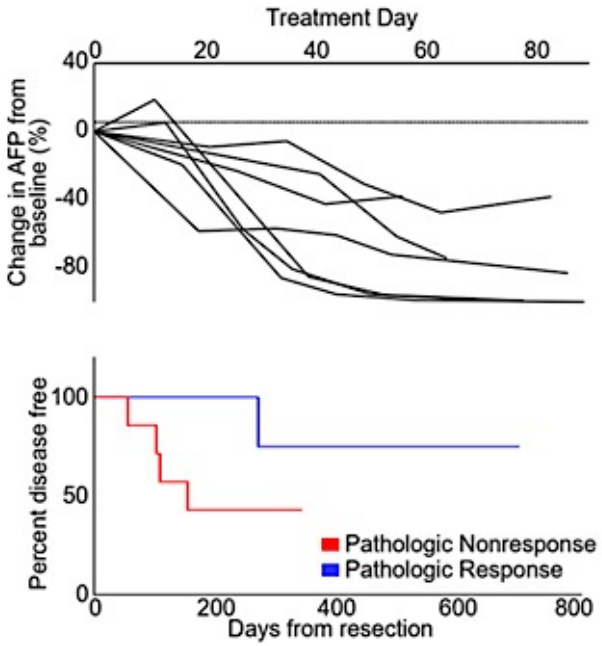
- Patients with resectable HCC
- No surgery cancelations due to toxicity
- 4 cancelations due to PD
- 20/27 treated underwent surgery
- 6/20 (30%) major pathologic response

Kaseb AO et al. Lancet Gastroenterol Hepatol. 2022.

Neoadjuvant nivolumab/cabozantinib in locally advanced/borderline resectable HCC







- 12 of 15 patients achieved successful margin-negative resections
- 5/15 patients achieved major or complete pathologic responses

Ho WJ et al. Nat Cancer. 2021

Summary and Conclusions

- Resection is an important curative modality for HCC
- Recurrence rates are high
- IMbrave050: adjuvant atezolizumab + bevacizumab
  - RFS benefit lost on longer follow-up
- Results pending from multiple other trials
- Neoadjuvant therapy appears feasible based on small studies
  - Promising signals with pathologic response
  - Optimal regimen not known
  - Variability in patient populations
  - Is pathologic response a good surrogate for RFS and OS?

Video Cases and Questions for the Faculty

RTP
RESEARCH
TO PRACTICE

IMbrave050: Adjuvant systemic treatment for high-risk resected HCC

Dr Katie Kelley

Dr Thomas Abrams

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

In what nonprotocol situations, if any, do you utilize adjuvant systemic treatment for patients with HCC?

What is the current and future role of bespoke cell-free DNA assays such as Signatera™ in making decisions about implementing or discontinuing adjuvant systemic treatment for HCC?

What are your thoughts about ongoing clinical trials investigating this treatment strategy?

Neoadjuvant systemic therapy for patients with borderline resectable HCC

Dr Thomas Abrams

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

In what situations, if any, do you utilize neoadjuvant systemic therapy for patients with borderline resectable HCC?

What has been your clinical experience with this treatment strategy?

What are your thoughts about ongoing clinical trials investigating this treatment strategy?

70-year-old man with locally advanced HCC and tumor thrombus extending into right atrium

Dr Ghassan Abou-Alfa

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RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How would you have managed this case initially and at the present time?

How do you generally manage HCC in patients with disease extension into the heart?

What has been your clinical experience with this approach?

Agenda

Module 1: Adjuvant Systemic Therapy for Early-Stage Hepatocellular Carcinoma (HCC) — Dr El-Khoueiry

Module 2: Recent Developments in the Management of Intermediate-Stage HCC — Dr Finn

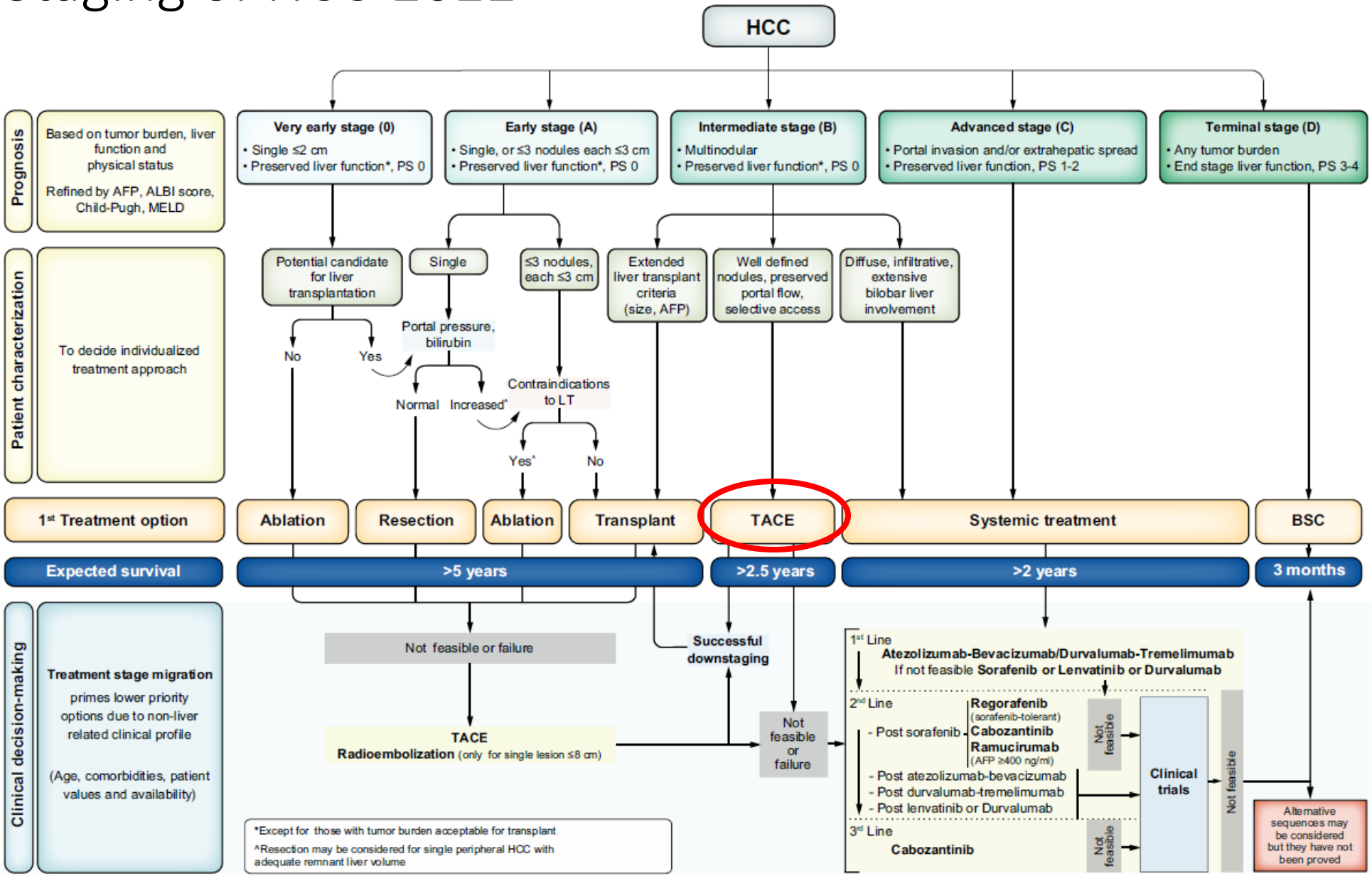
Module 3: Current First-Line Therapy for Advanced HCC — Dr He

Module 4: Promising Investigational Front-Line Strategies for Advanced HCC; Selection and Sequencing of Therapy for Relapsed/Refractory HCC — Dr Stein

Recent Developments in the Management of Intermediate-Stage HCC

Richard S. Finn, MD
Professor of Clinical Medicine
Division of Hematology/Oncology
Geffen School of Medicine at UCLA

BCLC Staging of HCC-2022



- Reig M et al J Hep 2022

Chemoembolization: Randomized Trials
(Nearly Identical Techniques)

Lo et al[1]: N = 80 with newly diagnosed unresectable HCC, 80% HBV positive, 7-cm tumors (60% multifocal)

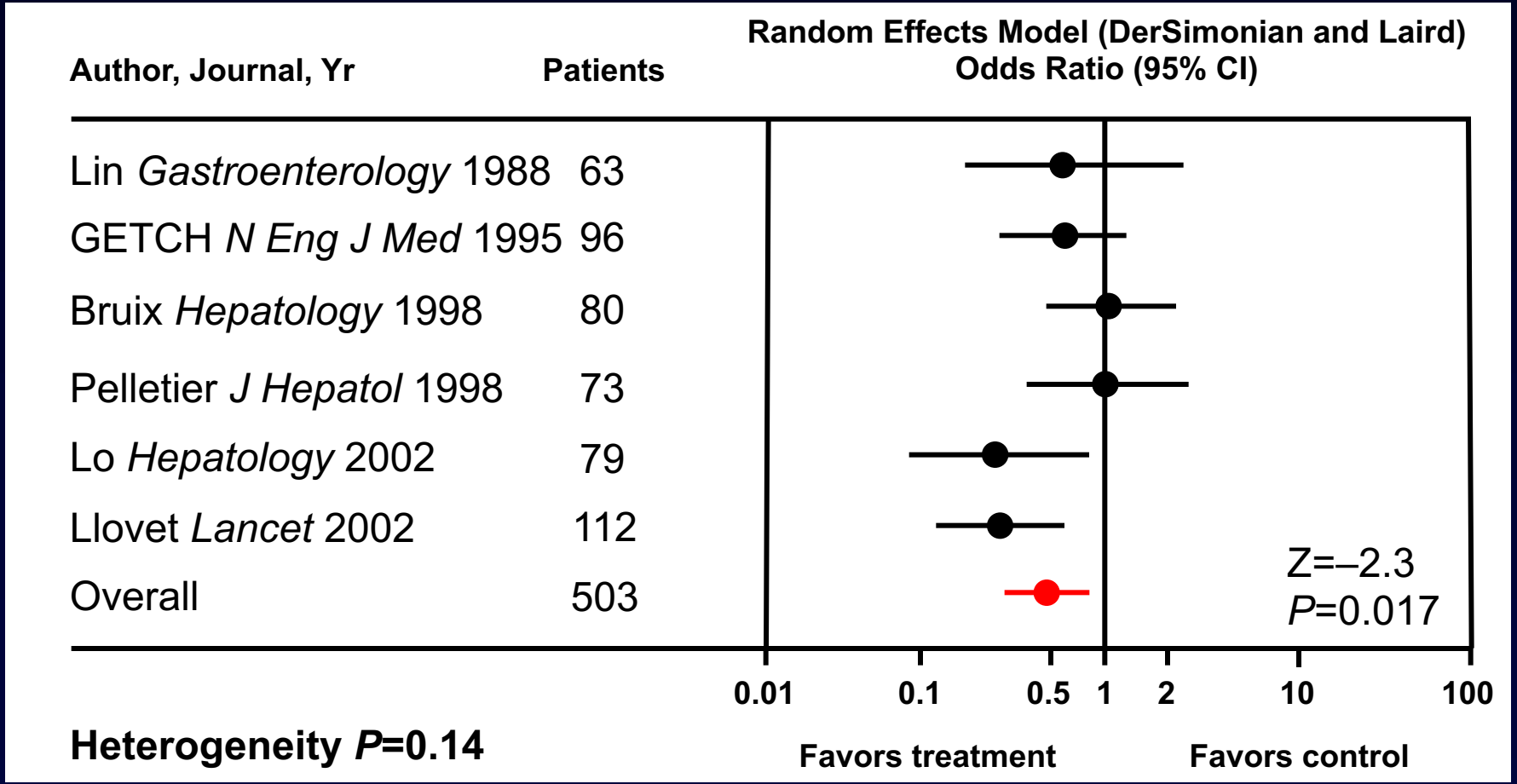
Technique	Survival, %		
	Year 1	Year 2	Year 3
TACE	57	31	26
Supportive care	32	11	3

Llovet et al[2]: N = 112 with unresectable HCC, 80% to 90% HCV positive, 5-cm tumors (~ 70% multifocal)

Technique	Survival, %	
	Year 1	Year 2
TACE	82	63
Supportive care	63	27

1. Lo CM et al. *Hepatology.* 2002;35:1164-1171. 2. Llovet JM et al. *Lancet.* 2002;359:1734-1739.

TAE/TACE vs Best Supportive Care/Suboptimal Therapy: Meta-analysis of RCTs (2-Yr Survival)

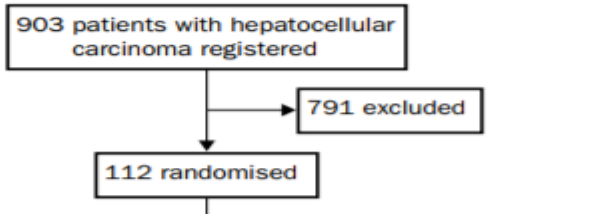


CI=confidence interval; TAE=transarterial embolization.

Llovet. *Hepatology.* 2003;37:429.

When having a closer look at the data, lesion sizes matter

Llovet, et al. Lancet 2002



	Embolisation (n=37)	Chemoembolisation (n=40)	Control (n=35)
Disease characteristics			
Diameter main nodule (mm)*	52 (46–60)	49 (40–58)	44 (39–49)
Bilobar disease	18 (49%)	19 (47%)	18 (51%)
Child-Pugh class A/B[16]	27/10	31/9	21/14
Okuda stage I/II[15]	24/13	27/13	22/13
BCLC stage B/C[2]	28/9	35/5	27/8
Performance status[14]			
0	28	35	27
1	7	4	4
2	2	1	4

Data are numbers of patients unless otherwise indicated. *Mean (95% CI). †Solitary tumours with or without satellites.

Table 1: **Baseline characteristics**

main lesion of ~5cm in diameter only

Lo, et al. Hepatology 2002

Table 4. Comparison of Survival Between the Chemoembolization and Control Groups Stratified by Baseline Prognostic Variables

	Chemoembolization	Control	*P*
Presenting symptom			
Asymptomatic	25.4 (17.5)	16.6 (2.5)	.039
Symptomatic	11.2 (2.6)	5.2 (1.4)	.019
Unilobar portal vein obstruction			
Negative	18.0 (3.5)	9.2 (5.6)	.008
Positive	5.1 (2.2)	2.6 (2.3)	NS (.406)
Tumor size (cm)			
≤5	29.8 (12.2)	11.5 (3.0)	.003
>5	11.2 (1.8)	5.3 (1.4)	NS (.115)
Okuda stage			
I	25.4 (9.1)	11.5 (5.8)	.016
II	9.2 (4.1)	5.2 (1.5)	.040

NOTE. Values are median survival times in months with standard errors in parentheses.

Shorter survival for tumor >5cm

Heterogeneity of Patients with Intermediate (BCLC B) Hepatocellular Carcinoma: Proposal for a Subclassification to Facilitate Treatment Decisions

Luigi Bolondi, MD[1] Andrew Burroughs, MBChBHons, FMedSci[2] Jean-François Dufour, MD[3]
Peter R. Galle, MD, PhD[4] Vincenzo Mazzaferro, MD[5] Fabio Piscaglia, MD, PhD[1]
Jean Luc Raoul, MD, PhD[6] Bruno Sangro, MD, PhD[7]

Up to Seven = largest tumor (cm) + number of tumors

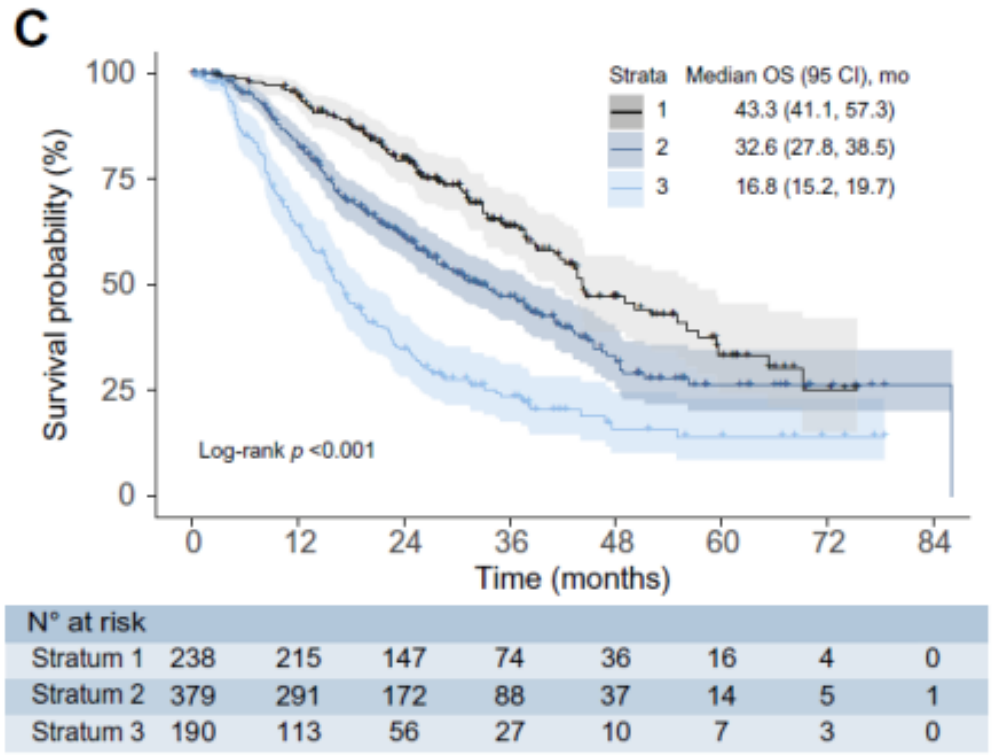
BCLC Sub-Stage	B1	B2	B3	B4
CPT score	5-6-7	5-6	7	8-9*
Beyond Milan and within Ut-7	IN	OUT	OUT	ANY
ECOG (Tumor Related) PS	0	0	0	0-1
PVT	NO	NO	NO	NO
1st option	**TACE**	TACE or TARE		**BSC**
Alternative	LT TACE + ablation	SOR	Research trials TACE SOR	LT**

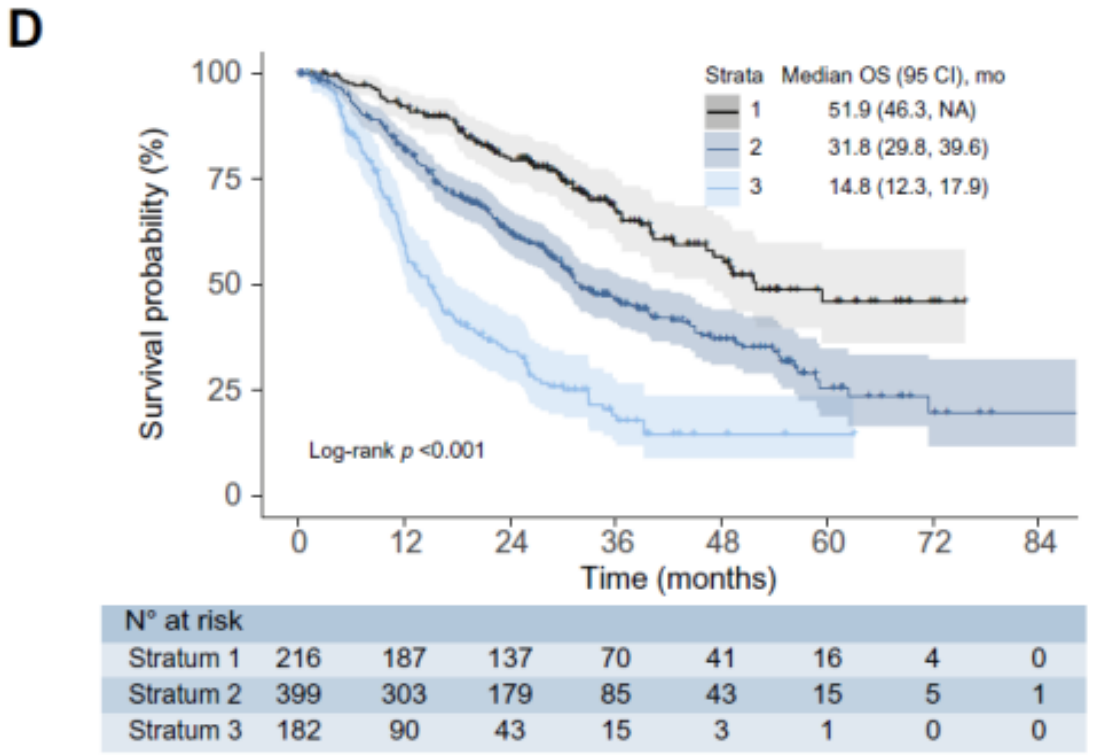
Three prognostic groups based on sum of tumor size and number:

Group 1 ≤ 6

Group 2 >6 but ≤ 12

Group 3 >12





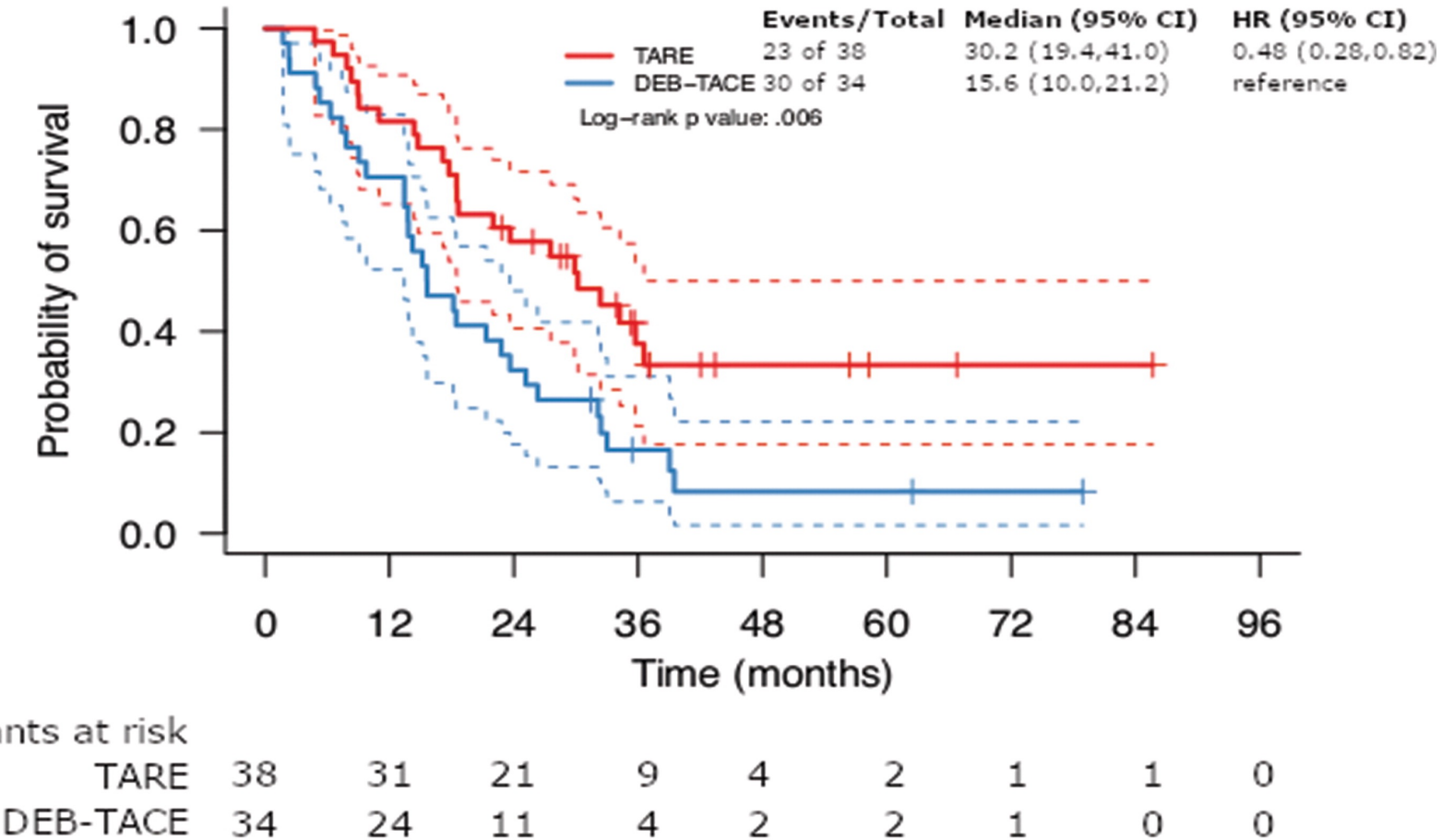
Wang J Hep 2019

Radiology

ORIGINAL RESEARCH • VASCULAR AND INTERVENTIONA

^{90}Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial

Elisabeth Dhondt, PhD, MD • Bieke Lambert, PhD, MD[1] • Laurens Hermie, MD • Lynn Huyck, PhD • Peter Vanlangenhove, PhD, MD • Anja Geerts, PhD, MD • Xavier Verhelst, PhD, MD • Maridi Aerts, MD[2] • Aude Vanlander, MD • Frederik Berrevoet, PhD, MD • Roberto Ivan Troisi, PhD, MD[3] • Hans Van Vlierberghe, PhD, MD • Luc Defreyne, PhD, MD

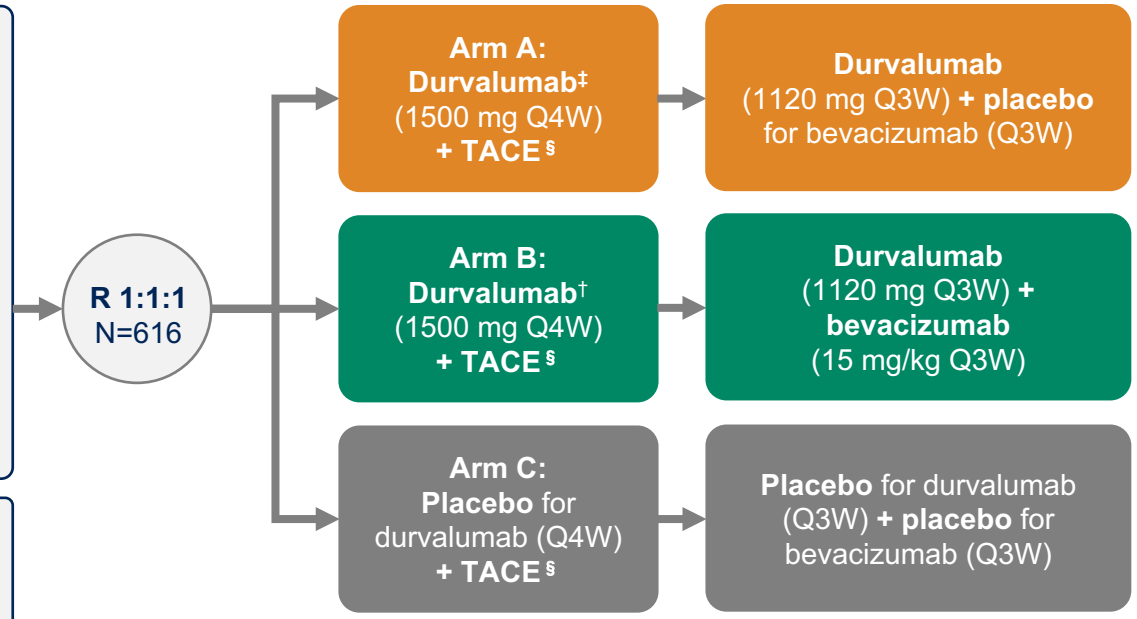


EMERALD-1 study design

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.

Sangro et al Lancet 2025

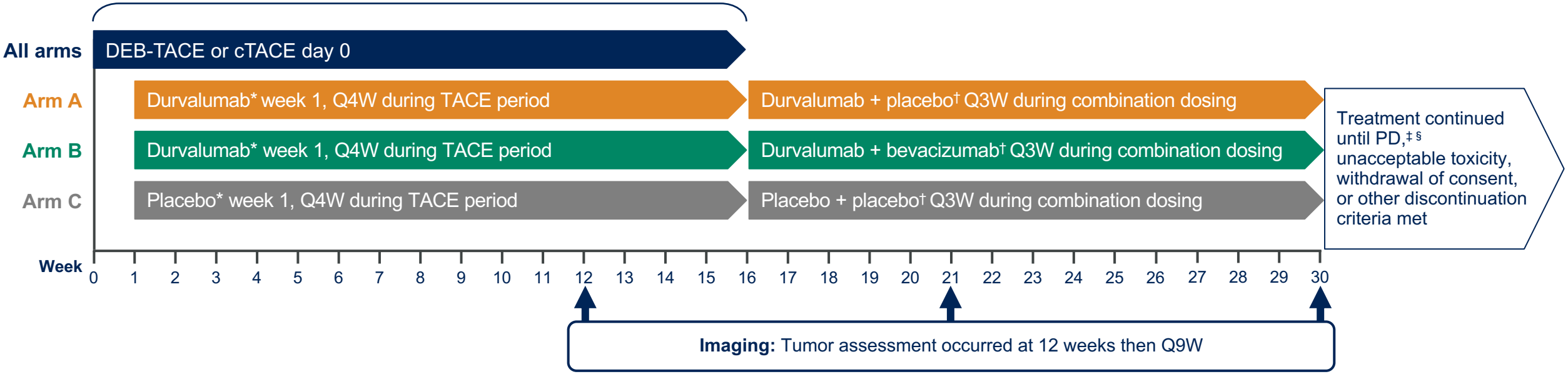
EMERALD-1 study schema

Number and timings of TACE at the investigator's discretion:

- 1–4 TACE procedures within 16 weeks

Combination therapy begins after the final TACE procedure

- Median (range) start of combination systemic therapy: 14 (2–113) weeks post first dose of TACE at Day 0



*Durvalumab / placebo started at least 7 days after TACE; doses moved to accommodate TACE if necessary. Durvalumab 1500 mg. Durvalumab / placebo Q4W until ≥14 days after last TACE. †Durvalumab 1120 mg. Bevacizumab 15 mg/kg. Durvalumab / bevacizumab / placebos Q3W. ‡Investigator-determined mRECIST-defined radiological disease progression. §Participants with mRECIST-defined progression may continue to receive study treatment, including additional TACE, at the discretion of the investigator and participant, and in consultation with the AstraZeneca study physician.
cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead-transarterial chemoembolization; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; TACE, transarterial chemoembolization; Q3W / Q4W / Q9W, every 3 / 4 / 9 weeks.

Sangro et al Lancet 2025

Baseline characteristics

Baseline characteristics were generally well balanced

		D + TACE (n=207)*	D+B + TACE (n=204)*	Placebos + TACE (n=205)*
Age (years)	Median	65.0	64.5	66.0
Sex, n (%)	Male	156 (75.4)	162 (79.4)	163 (79.5)
Geographical region, n (%)	Japan	15 (7.2)	15 (7.4)	15 (7.3)
	Asia (non-Japan)	108 (52.1)	107 (52.4)	107 (52.1)
	Others	84 (40.5)	82 (40.1)	83 (40.4)
TACE modality, n (%)	DEB-TACE	81 (39.1)	84 (41.2)	84 (41.0)
	cTACE	123 (59.4)	119 (58.3)	120 (58.5)
Etiology of liver disease, n (%)	HBV	70 (33.8)	75 (36.8)	74 (36.1)
	HCV	48 (23.2)	42 (20.6)	54 (26.3)
	Non-viral	88 (42.5)	86 (42.2)	76 (37.1)
BCLC stage, n (%)	A	59 (28.5)	51 (25.0)	49 (23.9)
	B	114 (55.1)	117 (57.4)	122 (59.5)
	C	33 (15.9)	35 (17.2)	31 (15.1)
Portal vein invasion, n (%)	No	194 (93.7)	188 (92.2)	192 (93.7)
	Yes	13 (6.3)	16 (7.8)	13 (6.3)
Screening ECOG PS, n (%)	0	173 (83.6)	167 (81.9)	175 (85.4)
	1	34 (16.4)	37 (18.1)	30 (14.6)
Baseline PD-L1†, n (%)	High (≥1%)	63 (30.4)	61 (29.9)	64 (31.2)
	Low (<1%)	97 (46.9)	93 (45.6)	88 (42.9)
	Unknown	47 (22.7)	50 (24.5)	53 (25.9)
Child-Pugh score, n (%)	A	201 (97.1)	200 (98.0)	201 (98.0)
	B	6 (2.9)	4 (2.0)	4 (2.0)
ALBI at baseline, n (%)	Grade 1	107 (51.7)	117 (57.4)	126 (61.5)
	Grade ≥2	100 (48.3)	87 (42.6)	79 (38.5)
Tumor burden at baseline, n (%)	Within up-to-7 criteria (≤7)	97 (46.9)	97 (47.5)	102 (49.8)
	Beyond up-to-7 criteria (>7)	110 (53.1)	106 (52.0)	103 (50.2)
HAP score, n (%)	A	63 (30.4)	66 (32.4)	64 (31.2)
	B	72 (34.8)	74 (36.3)	75 (36.6)
	C	52 (25.1)	41 (20.1)	48 (23.4)
	D	20 (9.7)	20 (9.8)	18 (8.8)
	Missing	0	3 (1.5)	0

*ITT: all randomized participants with treatment groups assigned in accordance with the randomization, regardless of the treatment actually received. †Baseline PD-L1 TAP expression.
ALBI, albumin-bilirubin; B, bevacizumab; BCLC, Barcelona Clinical Liver Cancer; cTACE, conventional transarterial chemoembolization; D, durvalumab; DEB-TACE, drug-eluting bead-transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; HAP, hepatoma arterial-embolization prognostic; HBV, hepatitis B virus; HCV, hepatitis C virus; ITT, intention-to-treat; PD-L1, programmed cell death ligand-1; PS, performance status; TACE, transarterial chemoembolization; TAP, tumor area positivity.

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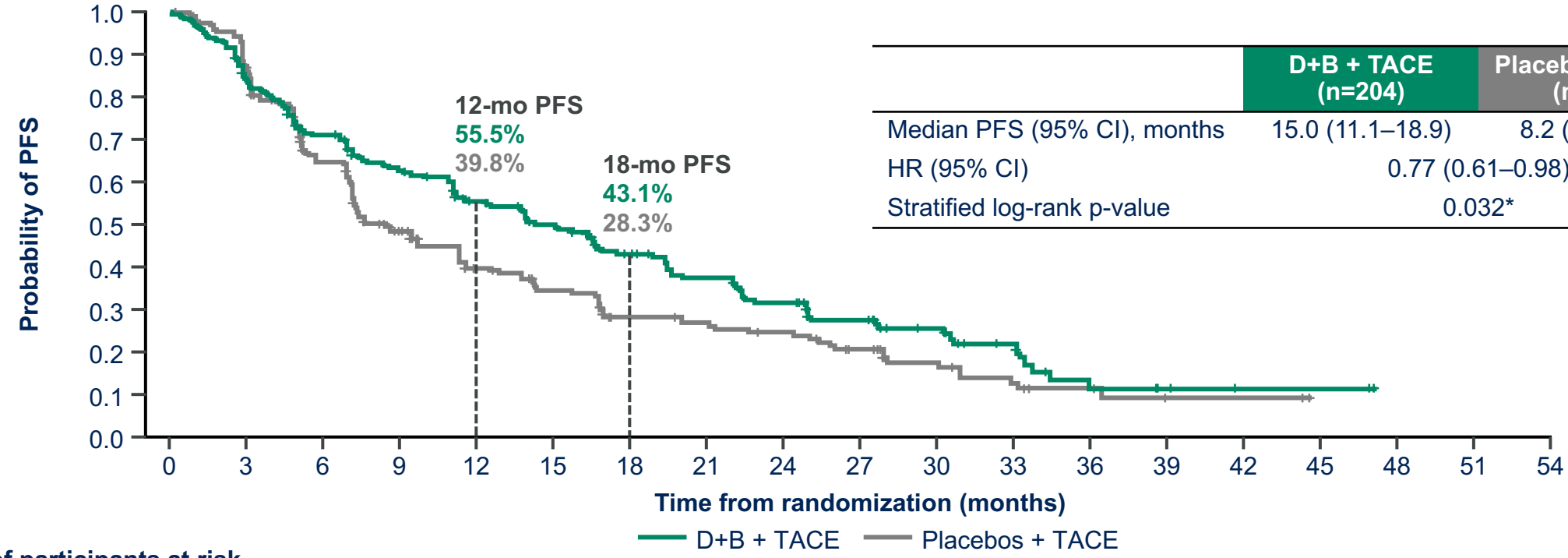
Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE

PFS with D+B + TACE versus placebos + TACE: primary endpoint



	D+B + TACE (n=204)	Placebos + TACE (n=205)
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*	

No. of participants 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

Median (range) duration of follow-up in censored participants, D+B + TACE 16.7 (0.03–47.1) months, Placebos + TACE 10.3 (0.03–44.3) months. Median (95% CI) duration of follow-up in all participants using the reverse Kaplan-Meier method, D+B + TACE 22.2 (16.7–27.3) months, Placebos + TACE 26.3 (16.7–30.4) months. PFS was assessed by BICR (RECIST v1.1)

*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, months, PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

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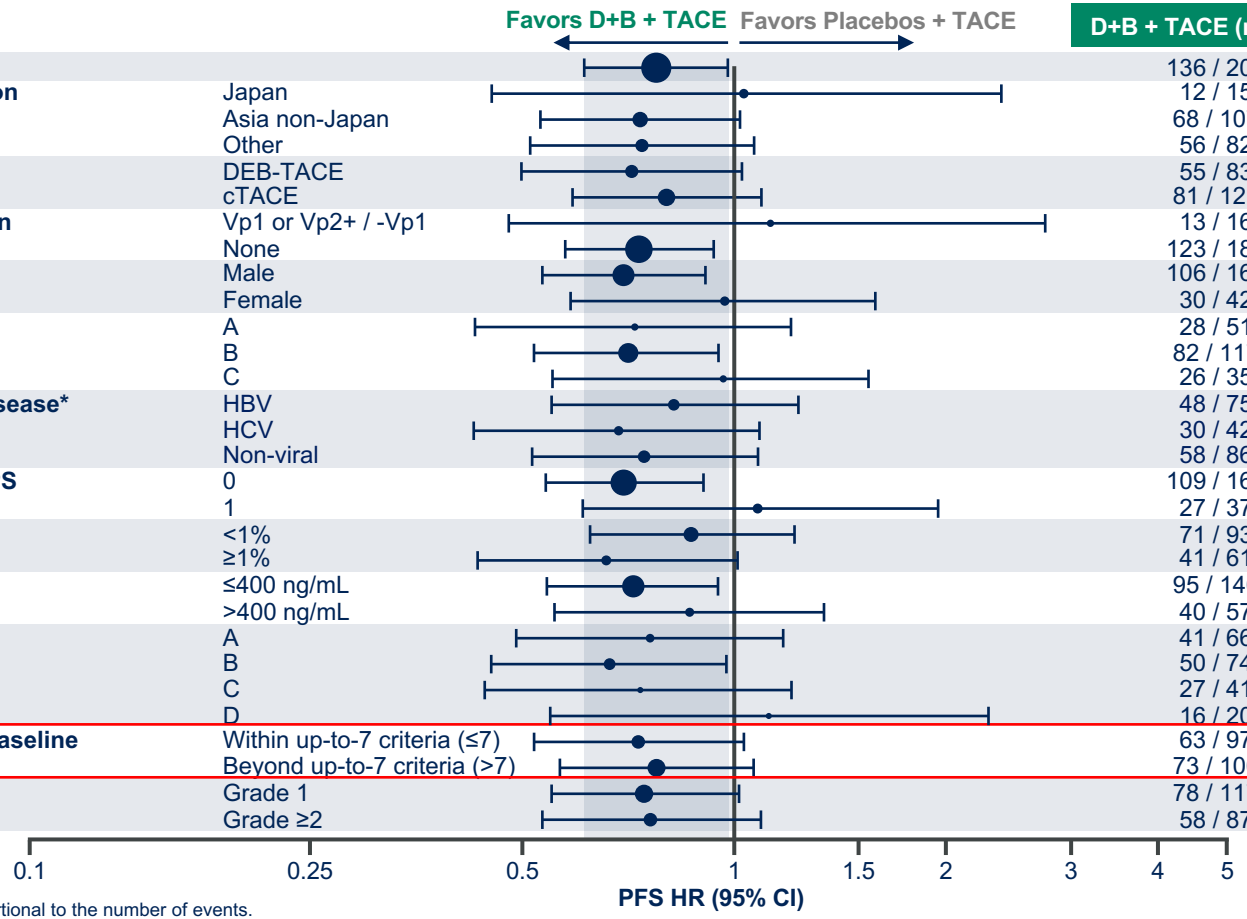
PFS with D+B + TACE versus placebos + TACE in key subgroups

PFS benefit with D+B + TACE was generally consistent across subgroups



		D+B + TACE (n=204), n / N (%)	Placebos + TACE (n=205), n / N (%)	HR (95% CI)
All participants:		136 / 204 (66.7%)	149 / 205 (72.7%)	0.77 (0.61–0.98)
Geographical region	Japan	12 / 15 (80.0%)	11 / 15 (73.3%)	1.03 (0.45–2.39)
	Asia non-Japan	68 / 107 (63.6%)	77 / 107 (72.0%)	0.74 (0.53–1.02)
	Other	56 / 82 (68.3%)	61 / 83 (73.5%)	0.74 (0.51–1.07)
TACE technique	DEB-TACE	55 / 83 (66.3%)	67 / 85 (78.8%)	0.71 (0.50–1.02)
	cTACE	81 / 121 (66.9%)	82 / 120 (68.3%)	0.80 (0.59–1.09)
Portal vein invasion	Vp1 or Vp2+ / -Vp1	13 / 16 (81.3%)	10 / 13 (76.9%)	1.12 (0.48–2.76)
	None	123 / 188 (65.4%)	139 / 192 (72.4%)	0.73 (0.57–0.93)
Sex	Male	106 / 162 (65.4%)	116 / 163 (71.2%)	0.70 (0.53–0.91)
	Female	30 / 42 (71.4%)	33 / 42 (78.6%)	0.96 (0.58–1.58)
BCLC stage	A	28 / 51 (54.9%)	31 / 49 (63.3%)	0.72 (0.43–1.21)
	B	82 / 117 (70.1%)	91 / 122 (74.6%)	0.71 (0.52–0.95)
	C	26 / 35 (74.3%)	25 / 31 (80.6%)	0.96 (0.55–1.68)
Etiology of liver disease*	HBV	48 / 75 (64.0%)	48 / 74 (64.9%)	0.82 (0.55–1.23)
	HCV	30 / 42 (71.4%)	44 / 54 (81.5%)	0.68 (0.43–1.09)
	Non-viral	58 / 86 (67.4%)	57 / 76 (75.0%)	0.74 (0.51–1.08)
Screening ECOG PS	0	109 / 167 (65.3%)	128 / 175 (73.1%)	0.70 (0.54–0.90)
	1	27 / 37 (73.0%)	21 / 30 (70.0%)	1.08 (0.61–1.94)
Baseline PD-L1†	<1%	71 / 93 (76.3%)	67 / 88 (76.1%)	0.87 (0.62–1.21)
	≥1%	41 / 61 (67.2%)	47 / 64 (73.4%)	0.66 (0.43–1.01)
AFP	≤400 ng/mL	95 / 146 (65.1%)	107 / 150 (71.3%)	0.72 (0.54–0.94)
	>400 ng/mL	40 / 57 (70.2%)	42 / 55 (76.4%)	0.86 (0.56–1.33)
HAP score	A	41 / 66 (62.1%)	41 / 64 (64.1%)	0.76 (0.49–1.17)
	B	50 / 74 (67.6%)	56 / 75 (74.7%)	0.66 (0.45–0.98)
	C	27 / 41 (65.9%)	37 / 48 (77.1%)	0.73 (0.44–1.21)
	D	16 / 20 (80.0%)	15 / 18 (83.3%)	1.12 (0.55–2.29)
Tumor burden at baseline	Within up-to-7 criteria (≤7)	63 / 97 (64.9%)	68 / 102 (66.7%)	0.73 (0.52–1.03)
	Beyond up-to-7 criteria (>7)	73 / 106 (68.9%)	81 / 103 (78.6%)	0.78 (0.56–1.07)
ALBI at baseline	Grade 1	78 / 117 (66.7%)	87 / 126 (69.0%)	0.74 (0.55–1.01)
	Grade ≥2	58 / 87 (66.7%)	62 / 79 (78.5%)	0.76 (0.53–1.09)

Size of circles are proportional to the number of events.
*One participant in each arm had both HBV and HCV. Neither of these participants experienced a PFS event. †Baseline PD-L1 TAP expression.
AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; B, bevacizumab; BCLC, Barcelona Clinical Liver Cancer; CI, confidence interval; cTACE, conventional transarterial chemoembolization; D, durvalumab; DEB-TACE, drug-eluting bead-transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; HAP, hepatoma arterial-embolization prognostic; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PS, performance status; TACE, transarterial chemoembolization; TAP, tumor area positivity.

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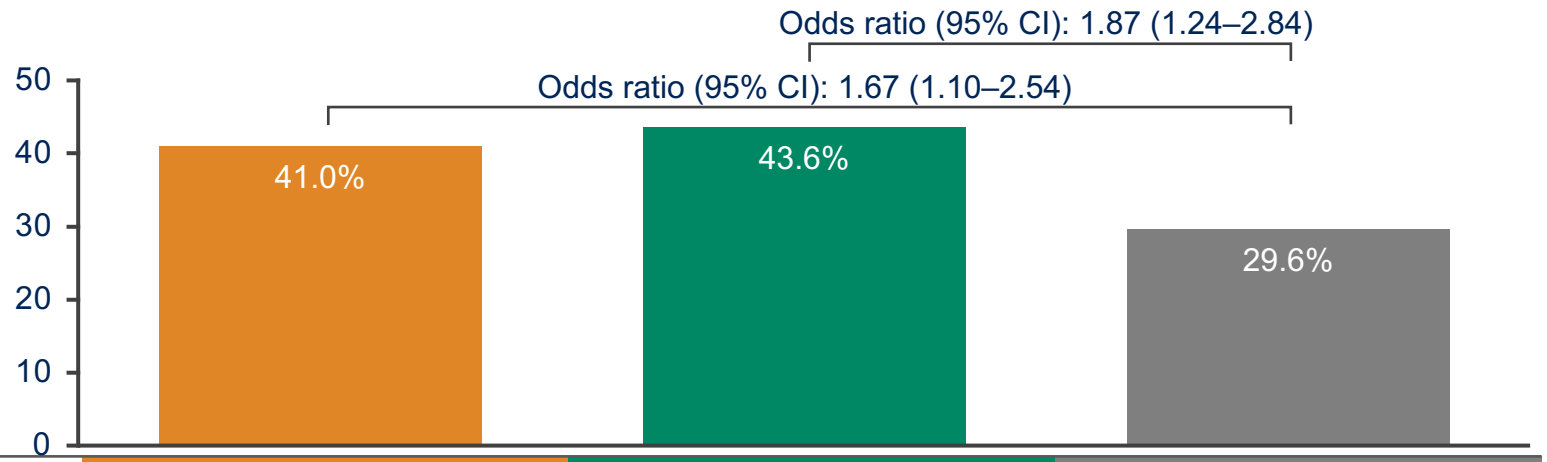
ORR using BICR per RECIST v1.1

ORR was improved with both D + TACE and D+B + TACE versus placebos + TACE



	D + TACE (n=207)	D+B + TACE (n=204)	Placebos + TACE (n=205)
Participants with measurable disease at baseline	205	202	203
Confirmed response,* n (%)	84 (41.0)	88 (43.6)	60 (29.6)
Complete response, n (%)	3 (1.5)	6 (3.0)	5 (2.5)
Partial response, n (%)	81 (39.5)	82 (40.6)	55 (27.1)
Stable disease ≥20 weeks, n (%)	42 (20.5)	45 (22.3)	63 (31.0)
Median duration of response, (LQ–UQ) months	14.0 (6.9–30.7)	22.1 (11.2–30.3)	16.4 (6.3–26.3)

*Responses included confirmed complete or partial response.
B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; LQ, lower quartile; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; UQ, upper quartile.

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AEs were consistent with the known safety profiles of durvalumab, bevacizumab, and TACE

Safety: summary

	D + TACE (n=232)*	D+B + TACE (n=154)*	Placebos + TACE (n=200)*
Any AE, n (%)	**215 (92.7)**	**151 (98.1)**	**186 (93.0)**
Possibly related to study treatment	117 (50.4)	124 (80.5)	90 (45.0)
Possibly provoked by TACE	101 (43.5)	78 (50.6)	95 (47.5)
SAEs (including AEs with outcome of death), n (%)	**84 (36.2)**	**74 (48.1)**	**62 (31.0)**
Possibly related to any treatment	13 (5.6)	30 (19.5)	10 (5.0)
Any AE of max CTCAE Grade 3 or 4, n (%)	**64 (27.6)**	**70 (45.5)**	**46 (23.0)**
Any AE possibly related to study treatment of max CTCAE Grade 3 or 4 , n (%)	**15 (6.5)**	**41 (26.6)**	**12 (6.0)**
Any AE possibly provoked by TACE of max CTCAE Grade 3 or 4, n (%)	**21 (9.1)**	**13 (8.4)**	**17 (8.5)**
Any AE with outcome of death, n (%)	**21 (9.1)**	**16 (10.4)**	**11 (5.5)**
Possibly related to study treatment	3 (1.3)	0	3 (1.5)
Possibly related to durvalumab / placebo	2 (0.9)	0	1 (0.5)
Possibly related to bevacizumab / placebo	1 (0.4)	0	2 (1.0)
AE leading to discontinuation, n (%)	**28 (12.1)**	**38 (24.7)**	**14 (7.0)**
Possibly related to study treatment	8 (3.4)	13 (8.4)	6 (3.0)
Possibly related to durvalumab / placebo	6 (2.6)	7 (4.5)	3 (1.5)
Possibly related to bevacizumab / placebo	3 (1.3)	9 (5.8)	4 (2.0)
Possibly provoked by TACE	2 (0.9)	0	2 (1)

*Safety analysis set: all randomized patients who received any amount of study treatment (i.e. durvalumab, bevacizumab, or placebo) regardless of arm randomized to.
AE, adverse event; B, bevacizumab; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab; NA, not applicable; SAE, serious adverse event; TACE, transarterial chemoembolization.

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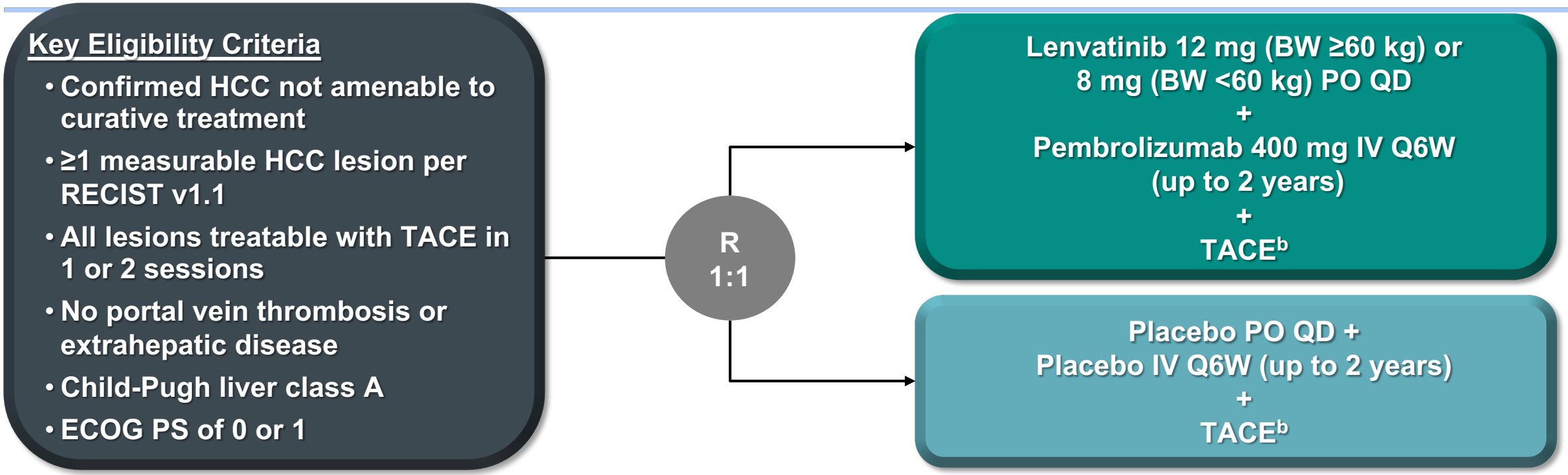
LEAP-012 Study Design (NCT04246177)



Stratification Factors

- Study site
- Alpha fetoprotein (≤400 ng/mL vs >400 ng/mL)
- ECOG PS (0 vs 1)
- ALBI grade (1 vs 2 or 3)
- Tumor burden score[1,a] (≤6 vs >6 but ≤12 vs >12)

End Points

- Primary: PFS[c] and OS
  - IA1 is the final analysis for PFS
  - Initial alpha of 0.025 (1-sided) allocated to PFS; passed to OS if PFS is statistically significant
- Secondary: ORR,[c,d] DOR,[c,d] DCR,[c,d] TTP,[c,d] PFS,[d] and safety

1. Wang Q et al. *J Hepatol.* 2019;70:893-903.

[a]Largest tumor in centimeters + number of tumors. [b]2-4 weeks after the start of systemic therapy with a maximum of 2 treatments per tumor (4 total) and no more than 1 treatment per month.
[c]Per RECIST v1.1 by BICR. [d]Per mRECIST by BICR.

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Baseline Characteristics

	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 243
Age, median (range), yrs	65.0 (31-87)	66.0 (21-85)
Age, ≥65 yrs	128 (54.0)	137 (56.4)
Sex, male	192 (81.0)	206 (84.8)
Geographic region, Asia (without Japan)	135 (57.0)	137 (56.4)
ECOG PS 0	216 (91.1)	213 (87.7)
HBV status – positive[a]	153 (64.6)	144 (59.3)
HCV status – positive[b]	42 (17.7)	39 (16.0)
Viral etiology[c]	179 (75.5)	167 (68.7)
Alcohol etiology	107 (45.1)	112 (46.1)
AFP ≤400 ng/mL	200 (84.4)	203 (83.5)

	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 243
Child-Pugh score A5	204 (86.1)	217 (89.3)
BCLC stage[d]		
A	80 (33.8)	68 (28.0)
B	135 (57.0)	146 (60.1)
C	21 (8.9)	29 (11.9)
ALBI grade 1[e]	171 (72.2)	174 (71.6)
Tumor burden score[1,f]		
≤6	112 (47.3)	116 (47.7)
>6 and ≤12	120 (50.6)	117 (48.1)
>12	5 (2.1)	10 (4.1)

1. Wang Q et al. *J Hepatol.* 2019;70:893-903. [a]Defined as a positive result for anti-HBc, HBsAg or HBV DNA; 2 patients had missing HBV status in each treatment group. [b]3 patients had missing HCV status in the lenvatinib + pembrolizumab +TACE group. [c]4 patients in the lenvatinib + pembrolizumab + TACE group and 1 patient in the dual placebo + TACE group had missing viral etiology. [d]1 patient had BCLC stage 0 in the lenvatinib + pembrolizumab + TACE group. [e]1 patient had missing ALBI grade in the lenvatinib + pembrolizumab + TACE group; no patients had an ALBI grade of 3. [f]Largest tumor in centimeters + number of tumors. Data are n (%) unless otherwise noted. Data cutoff date for IA1: January 30, 2024.

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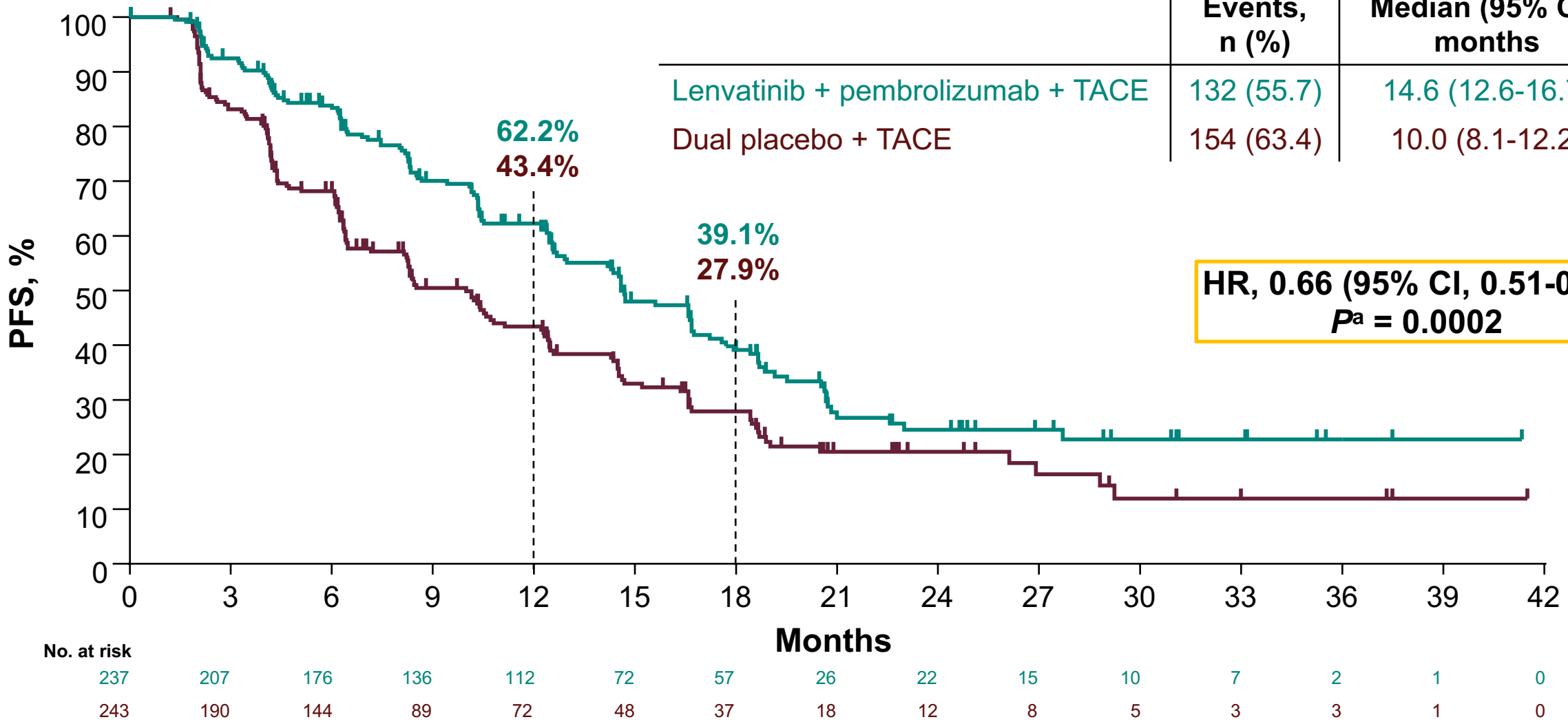
Progression-Free Survival per RECIST v1.1 by BICR

	Events, n (%)	Median (95% CI), months
Lenvatinib + pembrolizumab + TACE	132 (55.7)	14.6 (12.6-16.7)
Dual placebo + TACE	154 (63.4)	10.0 (8.1-12.2)



[a]One-sided *P* from re-randomization test; threshold *P* = 0.025. Data cutoff date for IA1: January 30, 2024.

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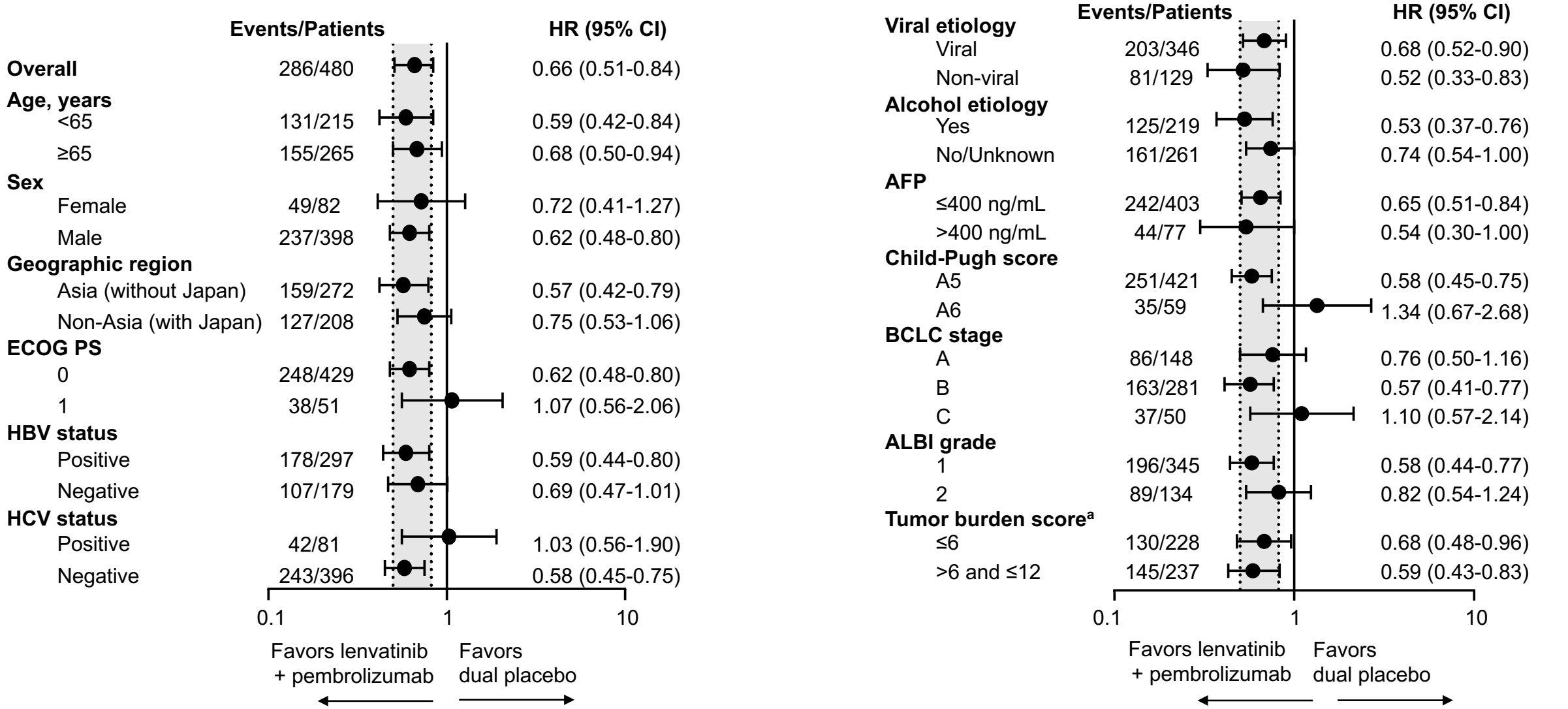
Progression-Free Survival per RECIST v1.1 by BICR in Prespecified Subgroups



[a]Largest tumor in centimeters + number of tumors. Data cutoff date for IA1: January 30, 2024.

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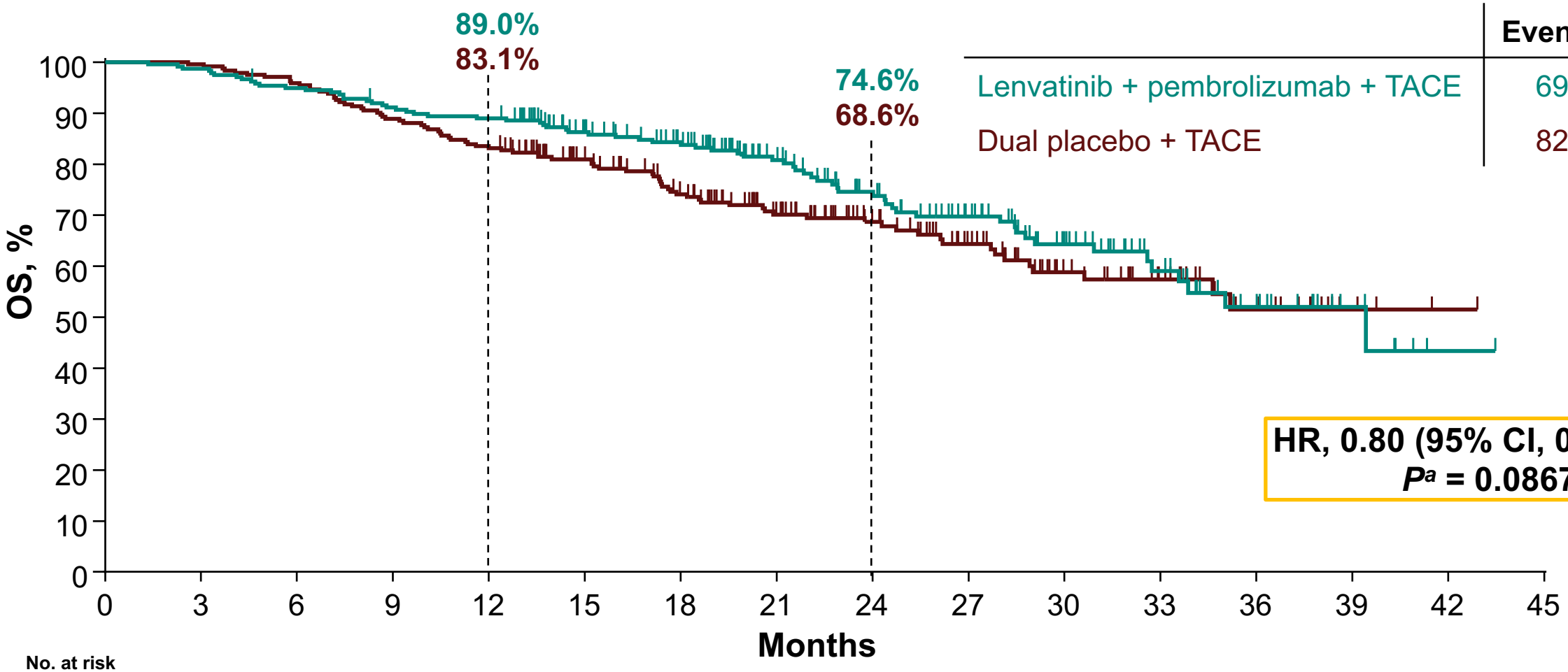
Overall Survival



	Events, n (%)
Lenvatinib + pembrolizumab + TACE	69 (29.1)
Dual placebo + TACE	82 (33.7)

HR, 0.80 (95% CI, 0.57-1.11)
***P*[a] = 0.0867**

No. at risk

237	234	224	214	209	180	161	124	95	74	49	31	17	7	1	0
243	242	233	216	202	173	145	112	86	65	42	27	15	4	1	0

[a]One-sided *P* from re-randomization test; threshold *P* = 0.0012. Data cutoff date for IA1: January 30, 2024.

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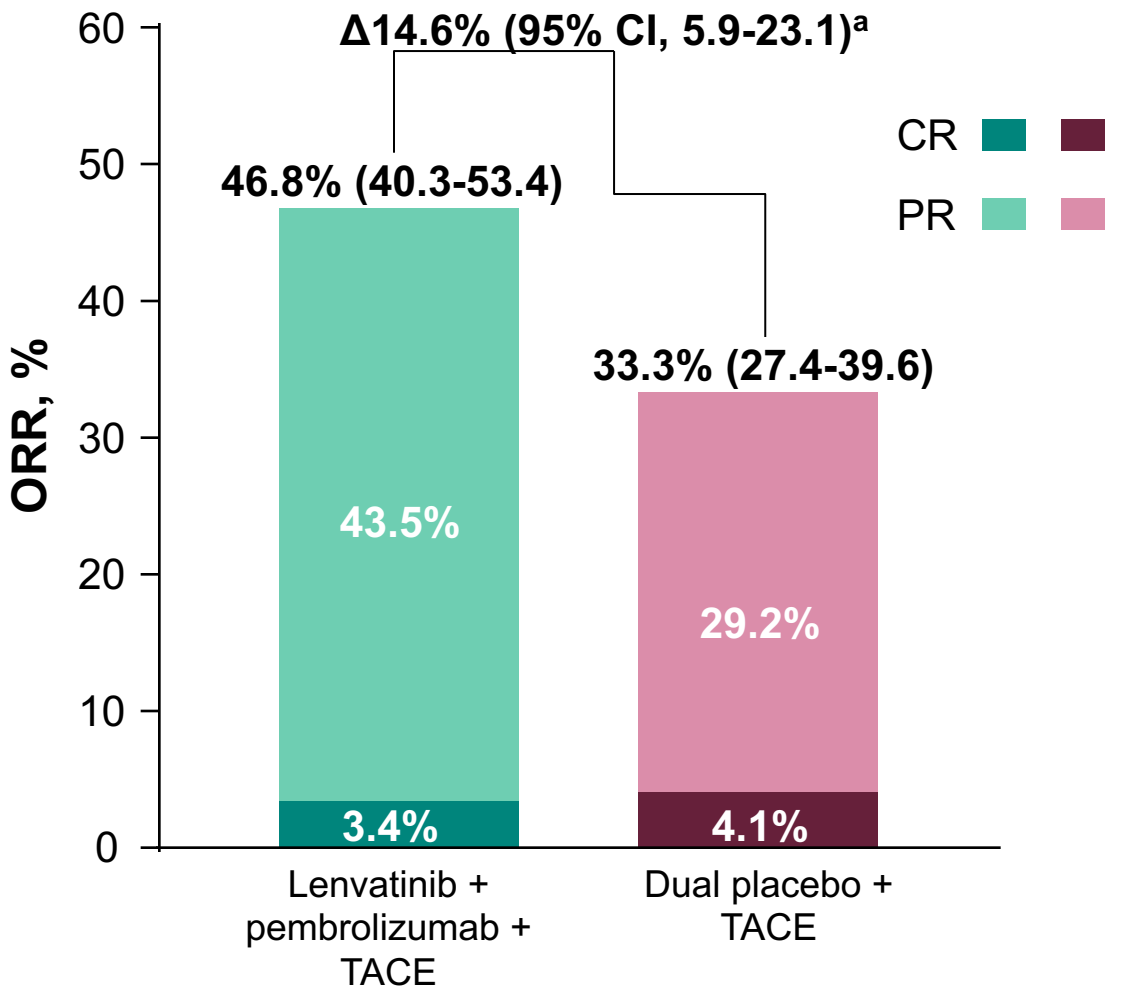
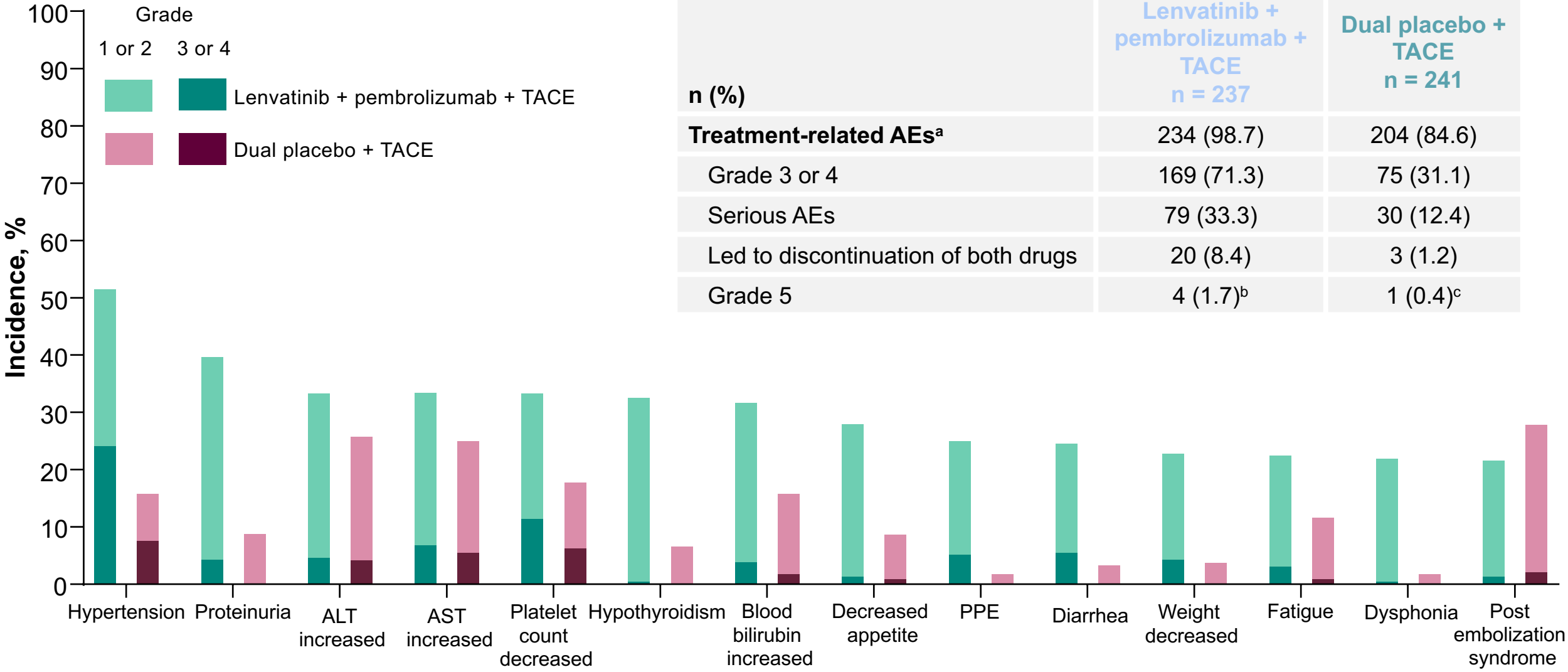
Objective Response Rate per RECIST v1.1 by BICR



	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 243
Best overall response, % (95% CI)[b,c]		
Complete response	3.4 (1.5-6.5)	4.1 (2.0-7.4)
Partial response	43.5 (37.1-50.0)	29.2 (23.6-35.4)
Stable disease	42.6 (36.2-49.2)	48.1 (41.7-54.6)
Progressive disease	6.8 (3.9-10.7)	14.8 (10.6-19.9)
Duration of response, median (range), months	12.6 (1.3+ to 39.1+)	10.7 (2.0+ to 39.5+)
Disease control rate	89.5 (84.8-93.1)	81.5 (76.0-86.2)

[a]Estimated from stratified analysis. [b]Patients with insufficient data for assessment of response: 2.1% in the lenvatinib + pembrolizumab + TACE group and 1.6% in the dual placebo + TACE group. [c]Patients without postbaseline assessments: 1.7% in the lenvatinib + pembrolizumab + TACE group and 2.1% in the dual placebo + TACE group. Data cutoff date for IA1: January 30, 2024.

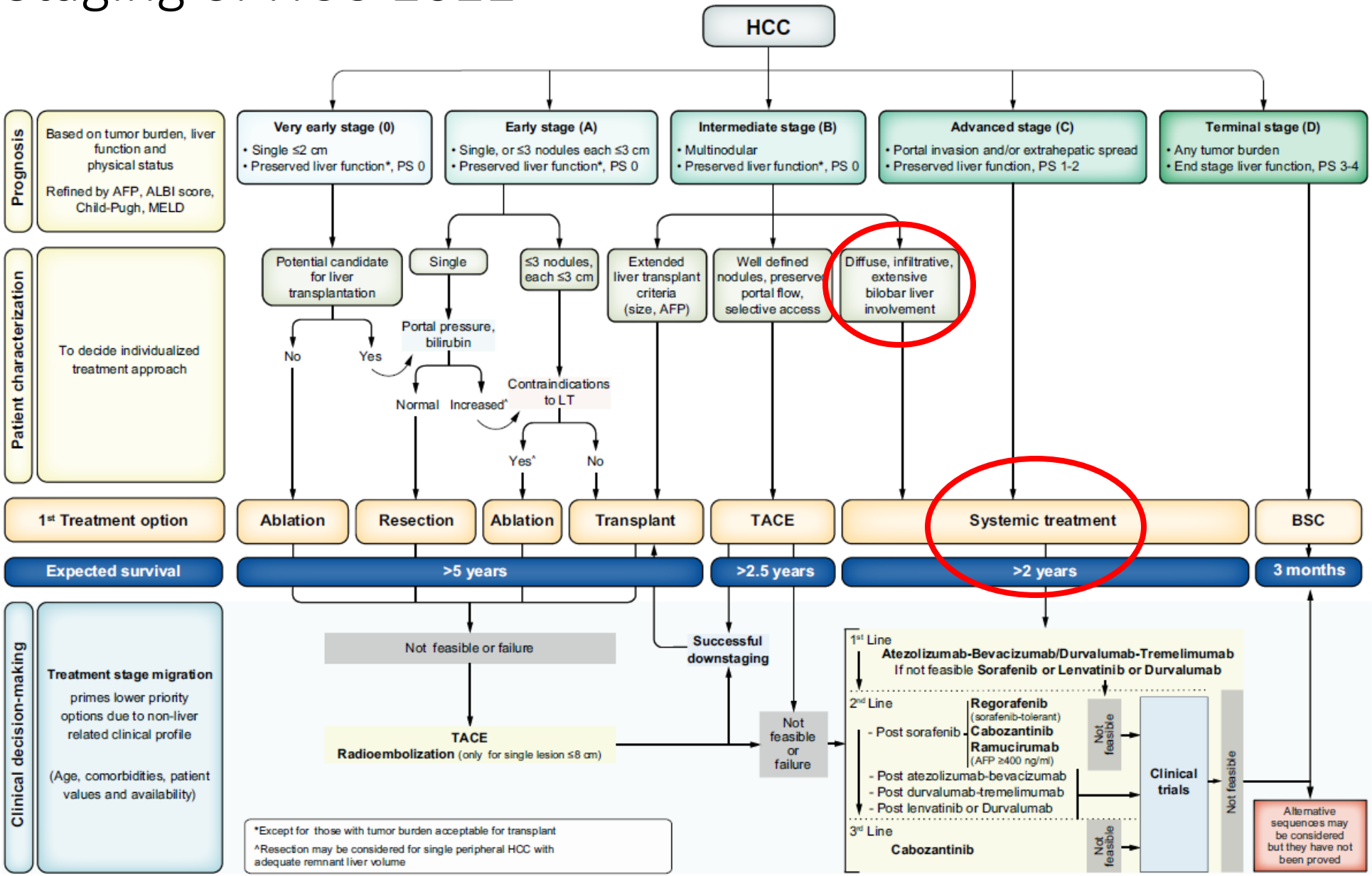
Most Common Treatment-Related Adverse Events[a] (≥25%)



n (%)	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 241
Treatment-related AEs[a]	234 (98.7)	204 (84.6)
Grade 3 or 4	169 (71.3)	75 (31.1)
Serious AEs	79 (33.3)	30 (12.4)
Led to discontinuation of both drugs	20 (8.4)	3 (1.2)
Grade 5	4 (1.7)[b]	1 (0.4)[c]

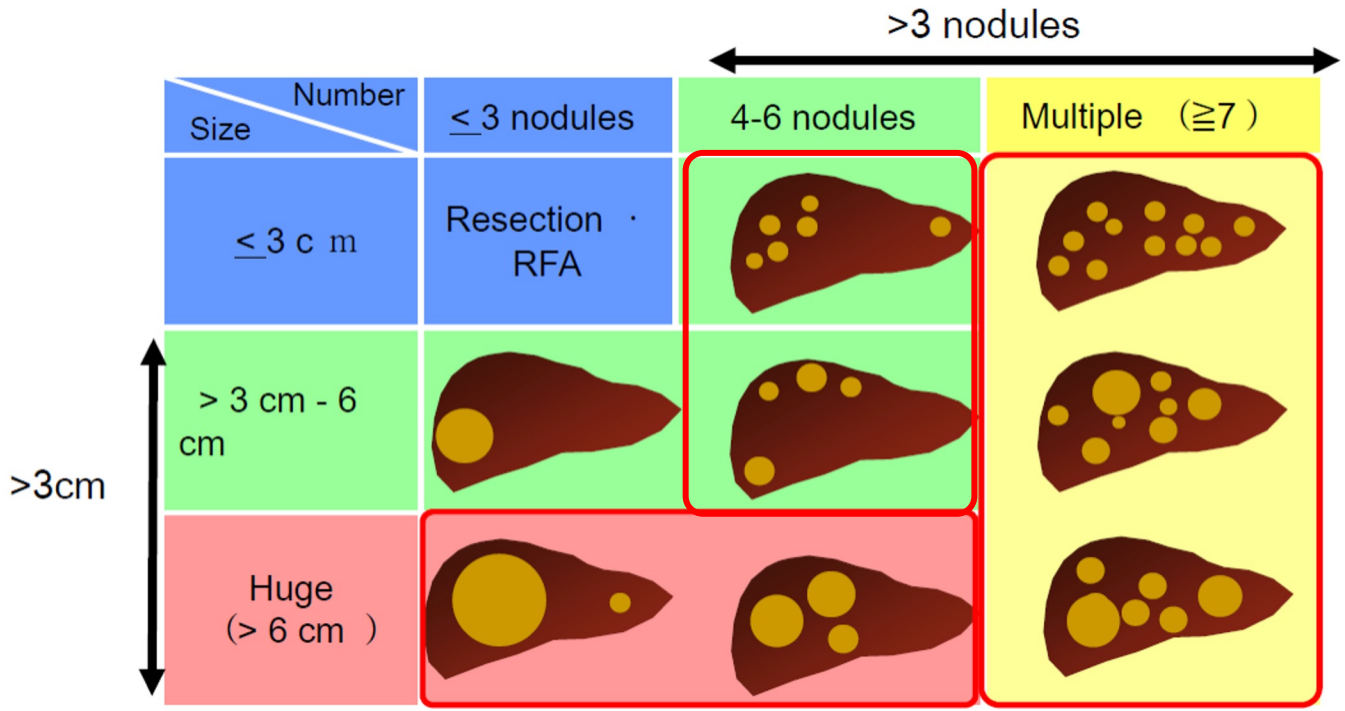
[a]Related to pembrolizumab, lenvatinib, and/or TACE. [b]1 patient each died from hepatic failure, gastrointestinal hemorrhage, myositis, and immune-mediated hepatitis. [c]1 patient died from brain stem hemorrhage.
Data cutoff date for IA1: January 30, 2024.

BCLC Staging of HCC-2022

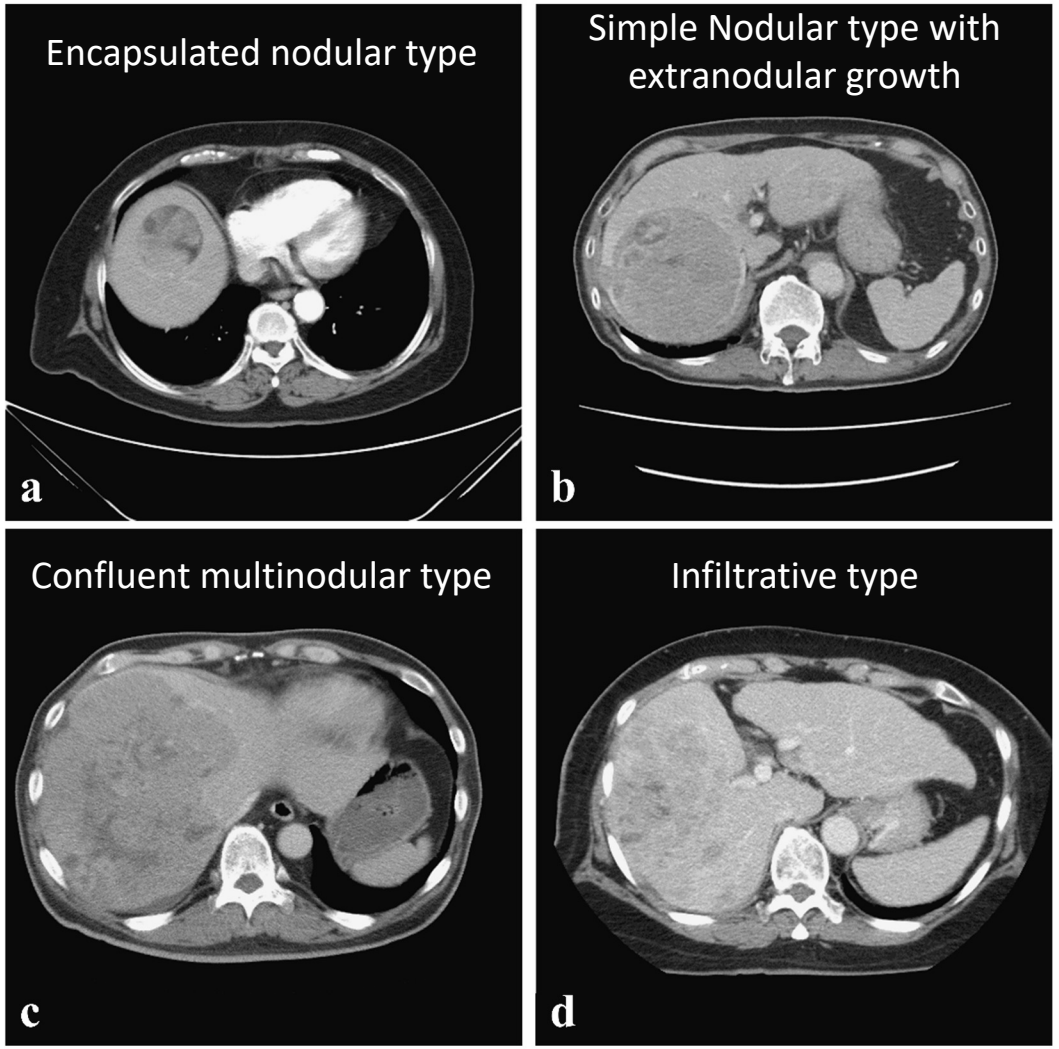


- Reig M et al J Hep 2022

TACE may not be equally effective for all BCLC B tumors



green — Good response to cTACE subgroup (within up-to-7 criteria)
pink — Poor response to cTACE subgroup (**beyond up-to-7** criteria)
yellow — Poor response to cTACE subgroup (**beyond up-to-7** criteria, Bilobar multifocal tumors)

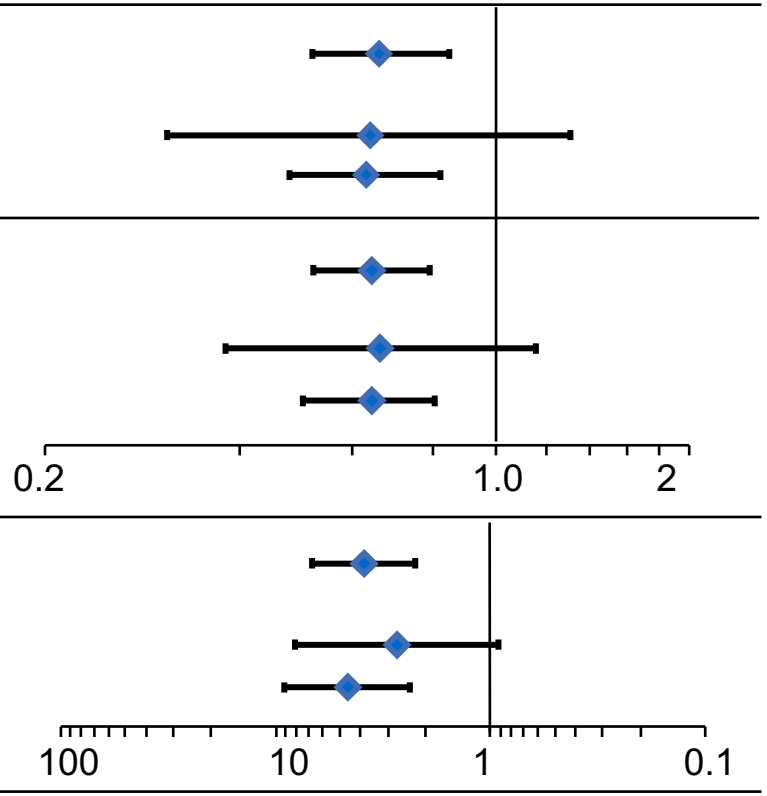


1. M Kudo, et al. Treatment of Intermediate-Stage HCC: APPLE Consensus Statement. Liver Cancer 2020;9:245–260. 2 Hung YW, et al. Liver Cancer 2023 DOI: 10.1159/000530950 Published online: May 15, 2023.

IMbrave150 BCLC-B uHCC subgroup analysis:

Efficacy outcomes

		n	Atezo+Bev (month)	Sorafenib (month)	HR	95% CI
OS	All	501	19.2	13.4	0.66	(0.52–0.85)
	BCLC-B	**76**	**25.8**	**18.1**	**0.64**	**(0.31–1.31)**
	BCLC-C	411	17.5	11.8	0.63	(0.48–0.82)
PFS	All	501	6.9	4.3	0.64	(0.52–0.79)
	BCLC-B	**76**	**12.6**	**8.6**	**0.66**	**(0.38–1.15)**
	BCLC-C	411	6.5	4.2	0.64	(0.50–0.80)
			Atezo+Bev	Sorafenib	Odds	95%CI
ORR RECIST v1.1	All	485	30%	11%	3.32	(1.92–5.72)
	BCLC-B	**72**	**44%**	**25%**	**2.33**	**(0.79–6.91)**
	BCLC-C	400	27%	9%	3.95	(2.02–7.75)



BCLC-B ORR Pattern

Kudo et al Liver Cancer 2022.

Select ongoing trials investigating immunotherapy + TACE

Trial	Phase	Intervention	Primary endpoint(s)	Estimated completion
TALENTACE (NCT047126430)	Phase III	TACE + atezolizumab + bevacizumab vs TACE	TACE PFS, OS	2/2029
REPLACE (NCT04777851)	Phase III	Regorafenib + nivolumab vs TACE	PFS	4/2027
TACE-3 (NCT04268888)	Phase II/III	TACE + nivolumab vs TACE	TTTP, OS	6/2026

TTTP = time to TACE progression

www.clinicaltrials.gov. Accessed January 2025.

Conclusions:

- Local-regional approaches have been the standard of care for BCLC B/ Intermediate HCC
  - Globally TACE, increasingly Y-90 in the US
- LRT is not curative in this setting and patients will progress
  - Now with more active systemic regimens, medical rx may be more appropriate than LRT for some patients
- Now 2 randomized studies show an improvement in PFS with combination approaches vs LRT alone
  - EMERALD-1, durvalumab/ bevacizumab
  - LEAP-012, lenvatinib/ pembrolizumab
- Mature OS data for these studies is awaited

Video Cases and Questions for the Faculty

RTP
RESEARCH
TO PRACTICE

EMERALD-1 and LEAP-012 trials of TACE with immunotherapy

Dr Thomas Abrams

Dr Katie Kelley

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Have you utilized TACE combined with systemic treatment?

What has been your experience with this approach?

What are your thoughts about combining systemic treatment with yttrium-90?

Do you believe the available outcomes from the EMERALD-1 and LEAP-012 trials justify the use of these approaches today?

Systemic treatment for patients with Child-Pugh B cirrhosis and HCC

Dr Katie Kelley

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What is your usual approach to systemic therapy for patients with poor hepatic function?

What are the key variables you consider?

What has been your clinical experience with this scenario?

Use of immunotherapy for patients with autoimmune disorders: Man in his early 30s with active colitis and metastatic HCC receives first-line lenvatinib

Dr Thomas Abrams

Dr Ghassan Abou-Alfa

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you approach systemic therapy for patients with prior or current autoimmune disease?

What about patients with prior renal transplants? Prior liver transplants?

Agenda

Module 1: Adjuvant Systemic Therapy for Early-Stage Hepatocellular Carcinoma (HCC) — Dr El-Khoueiry

Module 2: Recent Developments in the Management of Intermediate-Stage HCC — Dr Finn

Module 3: Current First-Line Therapy for Advanced HCC — Dr He

Module 4: Promising Investigational Front-Line Strategies for Advanced HCC; Selection and Sequencing of Therapy for Relapsed/Refractory HCC — Dr Stein

GEORGETOWN UNIVERSITY
Lombardi Comprehensive Cancer Center

RUESCH CENTER FOR THE CURE OF GI CANCERS

Current First-Line Therapy for Advanced HCC

Aiwu Ruth He, MD, PhD

Scientific Lead of Hepatobiliary Cancer

Lombardi Comprehensive Cancer Center

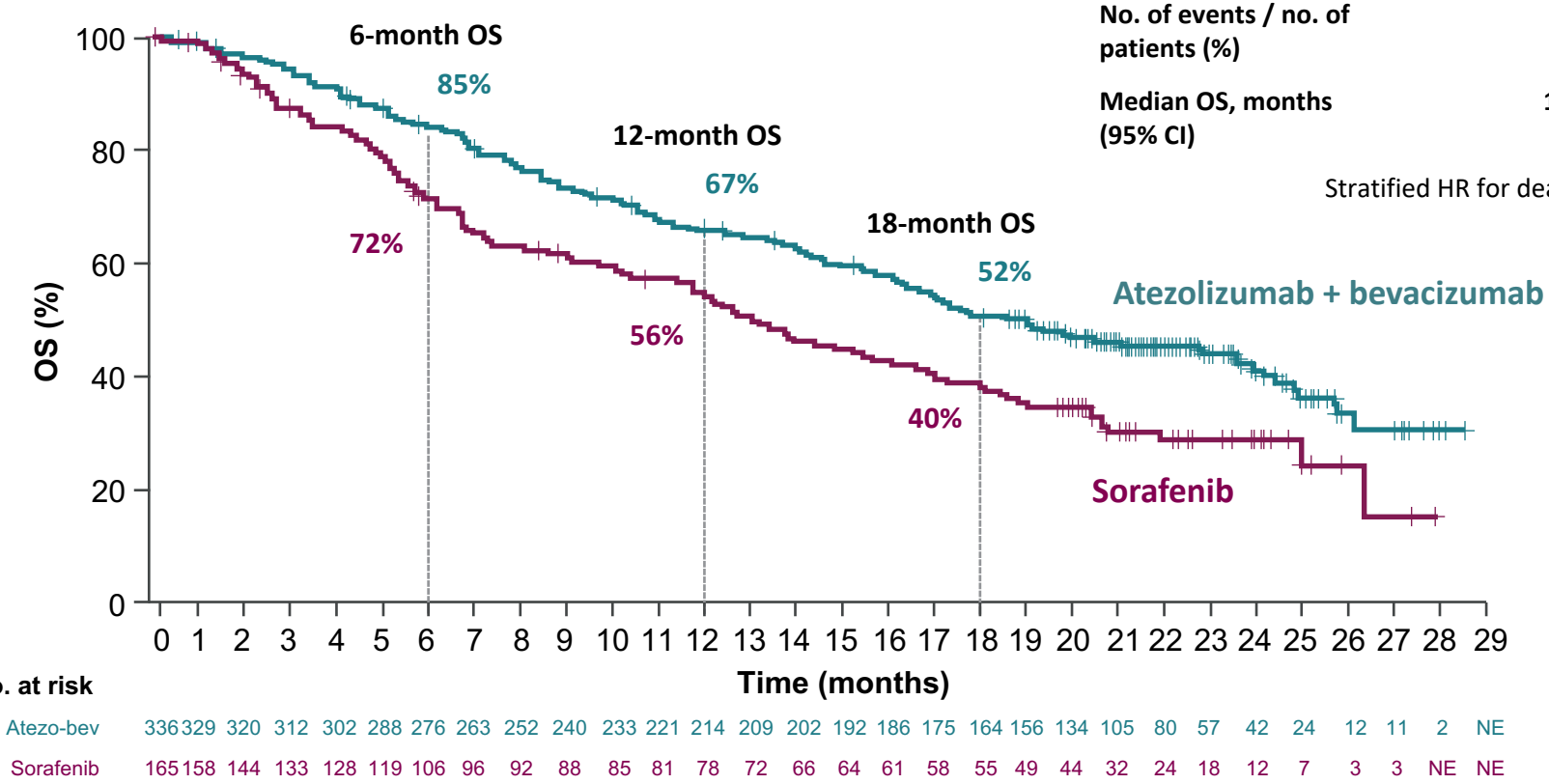
Georgetown University

Washington DC

Table of Contents:

- Long-term findings from the Phase III IMbrave150 study comparing first-line atezolizumab/bevacizumab to sorafenib for advanced unresectable HCC

IMBrave150: Atezolizumab/Bevacizumab had a median OS of 19 months



	Atezolizumab + bevacizumab (n=336)	Sorafenib (n=165)
No. of events / no. of patients (%)	180 / 336 (54)	100 / 165 (61)
Median OS, months (95% CI)	**19.2** (17.0–23.7)	**13.4** (11.4–16.9)

Stratified HR for death, **0.66**; 95% CI, 0.52–0.85; p=0.0009

Median follow-up: 15.6 months

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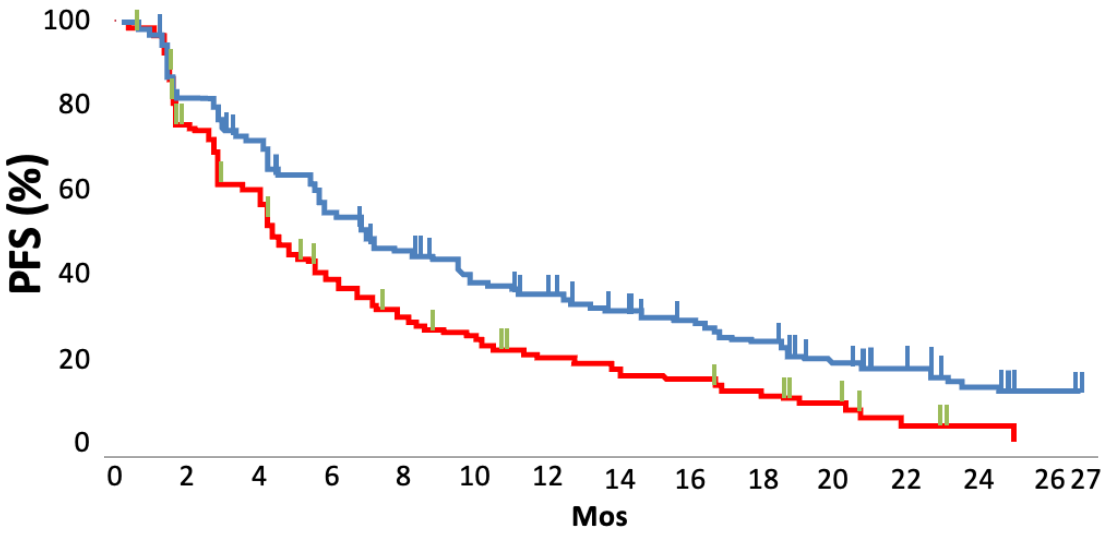
Atezolizumab/Bevacizumab had improved PFS and ORR

	Atezolizumab + bevacizumab (n=336)	Sorafenib (n=165)
Median PFS, mos	6.9	4.3
Stratified HR (95% CI)	0.65 (0.53-0.81)	



	Atezolizumab + Bevacizumab	Sorafenib
Objective response Complete Partial	25 (8%) 72 (22%)	1 (<1%) 17 (11%)
Stable disease	144 (44%)	69 (43%)
Disease control rate	241 (74%)	87 (55%)
Duration of response	18.1 (14.6 – NE)	14.9 (4.9 – 17.0)

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Atezolizumab/bevacizumab was well tolerated in IMBrave150

	Atezolizumab + bevacizumab (n=329)*	Sorafenib (n=156)*
Median treatment duration, months (range)	Atezolizumab=8.4 (3.5–18.3) Bevacizumab=7.0 (3.4–15.9)	2.8 (1.4–6.9)
Event, n (%)		
Any grade AE	322 (98)	154 (99)
Any TRAE	284 (86)	148 (95)
Any grade 3/4 AE†	207 (63)	89 (57)
Grade 3/4 TRAE†	143 (44)	72 (46)
Any serious AE	160 (49)	51 (33)
Serious TRAE	**76 (23)**	**25 (16)**
Any Grade 5 AE	23 (7)	9 (6)
Grade 5 TRAE	6 (2)	1 (<1)
AE leading to withdrawal from any component	**72 (22)**	**18 (12)**
AE leading to withdrawal from both components	34 (10)	0
AE leading to dose interruption of any study treatment	195 (59)	68 (44)
AE leading to dose modification of sorafenib‡	0	58 (37)

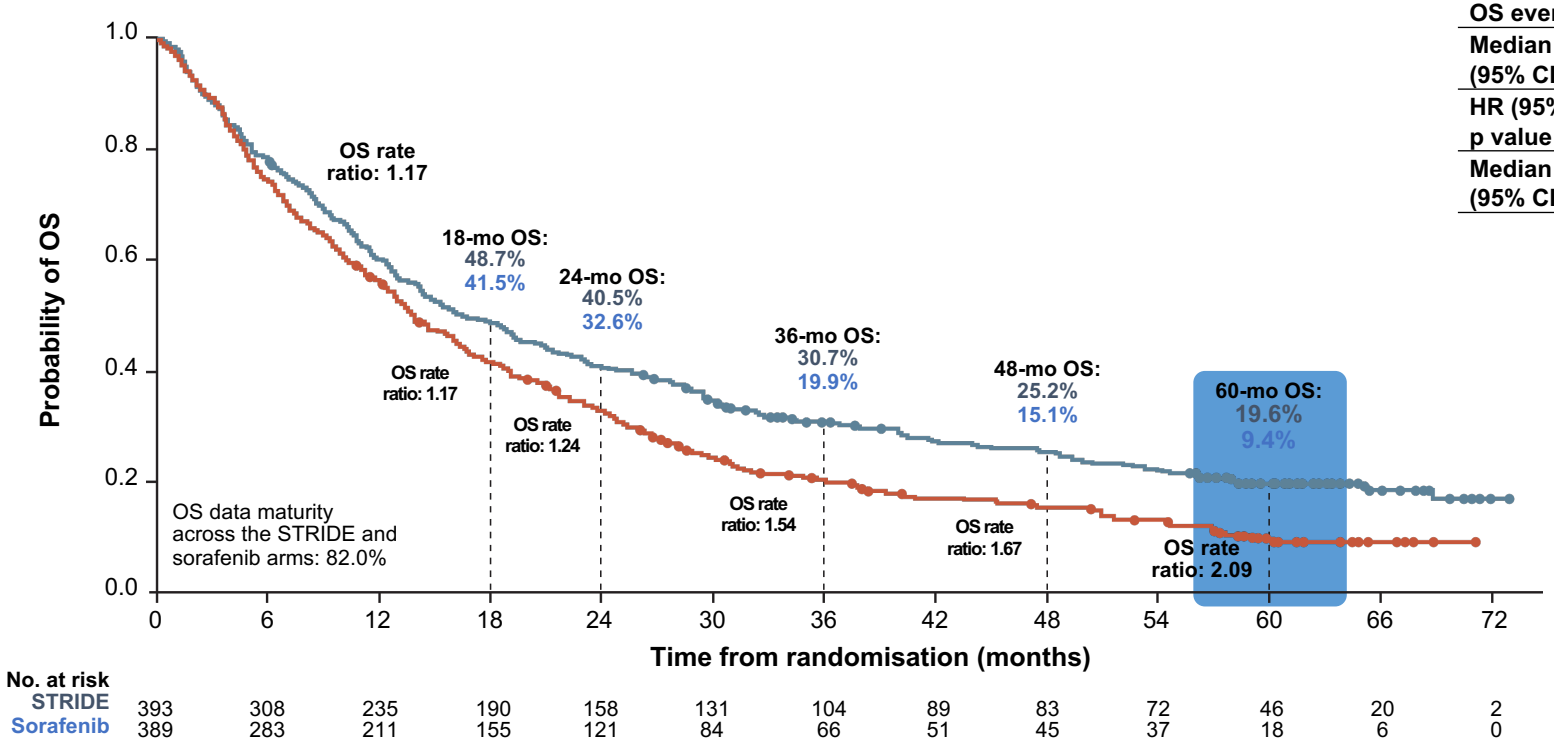
Journal of Hepatology 2022 vol. 76 j 862–873

- Published efficacy and safety findings, including 5-year OS results, from the Phase III HIMALAYA trial evaluating the combination of durvalumab/tremelimumab in patients with previously untreated advanced HCC

durvalumab + tremelimumab (HIMALAYA)

RESULTS: STRIDE Demonstrated a sustained OS benefit at 5 years

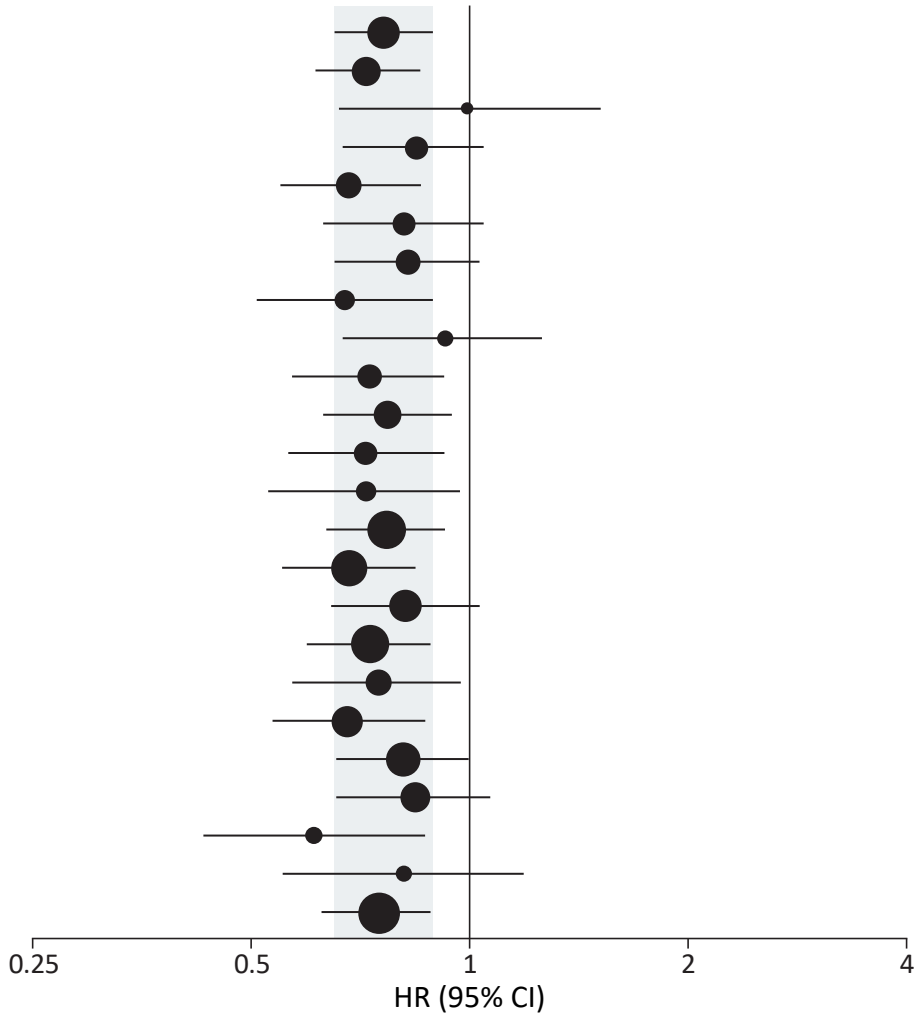
	STRIDE (n=393)	Sorafenib (n=389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS (95% CI), mo	16.43 (14.16-19.58(	13.77 (12.25-16.13)
HR (95% CI)	0.76 (0.65-0.89)	
p value (2-sided)	0.0008	
Median follow-up duration (95% CI), mo	62.49 (59.47-64.79)	59.86 (58.32-61.54)



STRIDE:	393	365	333	308	285	262	235	217	197	190	176	168	158	154	144	131	118	110	103	97	94	88	75	62	54	40	31	19	13	5	0	0
Sorafenib:	389	356	319	283	255	231	211	183	170	155	142	131	121	108	93	83	73	69	64	56	53	50	45	36	28	21	14	9	3	1	1	0

Rimassa L, et al. Presented at: ESMO Congress 2024; 13–17 September 2024; Barcelona, Spain. Mini oral 947MO.

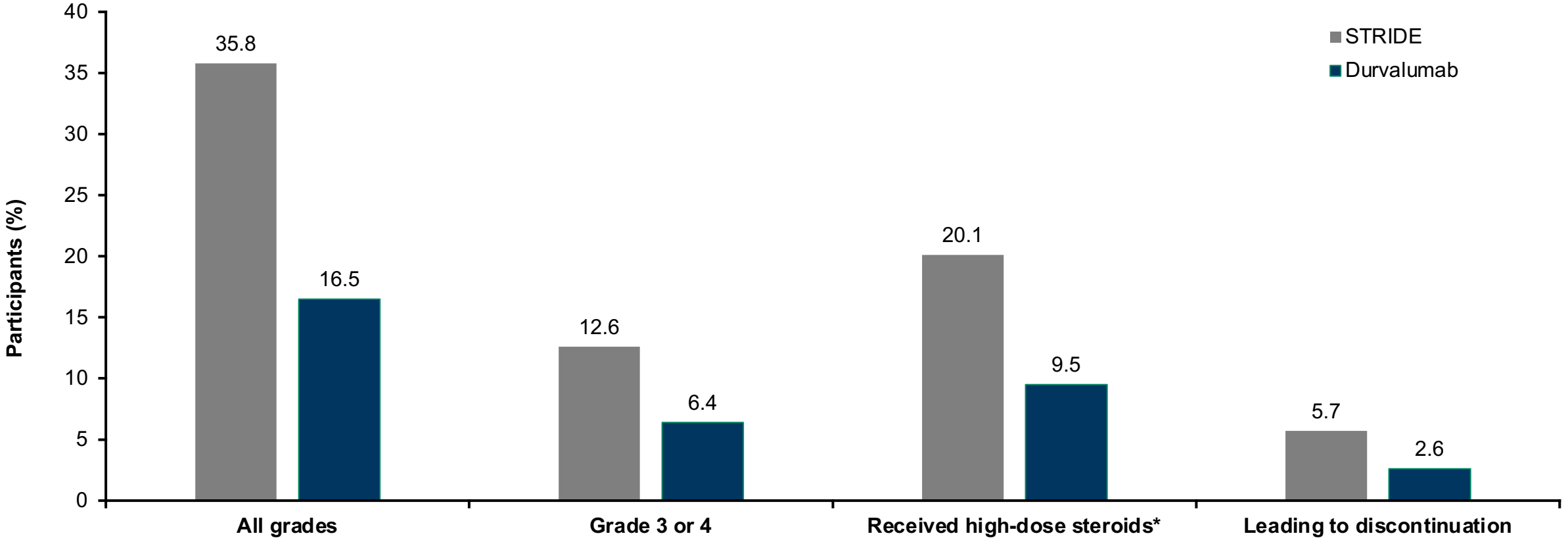
HIMALAYA 5-year exploratory analysis:* OS for STRIDE versus sorafenib by subgroup



	STRIDE	Sorafenib
All subjects	309 / 393 (78.6%)	332 / 389 (85.3%)
Sex: Male	257 / 327 (78.6%)	292 / 337 (86.6%)
Sex: Female	52 / 66 (78.8%)	40 / 52 (76.9%)
Age at randomisation: <65 years	158 / 195 (81.0%)	163 / 195 (83.6%)
Age at randomisation: ≥65 years	151 / 198 (76.3%)	169 / 194 (87.1%)
PD-L1 expression: Positive	116 / 148 (78.4%)	126 / 148 (85.1%)
PD-L1 expression: Negative	153 / 189 (81.0%)	156 / 181 (86.2%)
Aetiology of liver disease: HBV	101 / 122 (82.8%)	107 / 119 (89.9%)
Aetiology of liver disease: HCV	80 / 110 (72.7%)	78 / 104 (75.0%)
Aetiology of liver disease: others	128 / 161 (79.5%)	147 / 166 (88.6%)
ECOG PS at baseline: 0	182 / 244 (74.6%)	199 / 241 (82.6%)
ECOG PS at baseline: 1	126 / 148 (85.1%)	132 / 147 (89.8%)
MVI: yes	83 / 103 (80.6%)	90 / 100 (90.0%)
MVI: no	226 / 290 (77.9%)	242 / 289 (83.7%)
EHS: yes	168 / 209 (80.4%)	175 / 203 (86.2%)
EHS: no	139 / 182 (76.4%)	157 / 185 (84.9%)
MVI: yes and / or EHS: yes	212 / 263 (80.6%)	216 / 251 (86.1%)
MVI: no and EHS: no	95 / 128 (74.2%)	116 / 137 (84.7%)
Region: Asia (except Japan)	125 / 156 (80.1%)	141 / 156 (90.4%)
Region: Rest of World (includes Japan)	184 / 237 (77.6%)	191 / 233 (82.0%)
AFP at baseline: <400 ng / ml	130 / 167 (77.8%)	147 / 182 (80.8%)
AFP at baseline: ≥400 ng / ml	76 / 98 (77.6%)	63 / 71 (88.7%)
BCLC score: B	57 / 77 (74.0%)	54 / 66 (81.8%)
BCLC score: C	252 / 316 (79.7%)	278 / 323 (86.1%)

Rimassa L, et al. Presented at: ESMO Congress; 13–17 September 2024; Barcelona, Spain. Mini oral 947MO.

Side effects of the treatments



Adapted from Abou-Alfa GK*, et al. NEJM Evid.* 2022

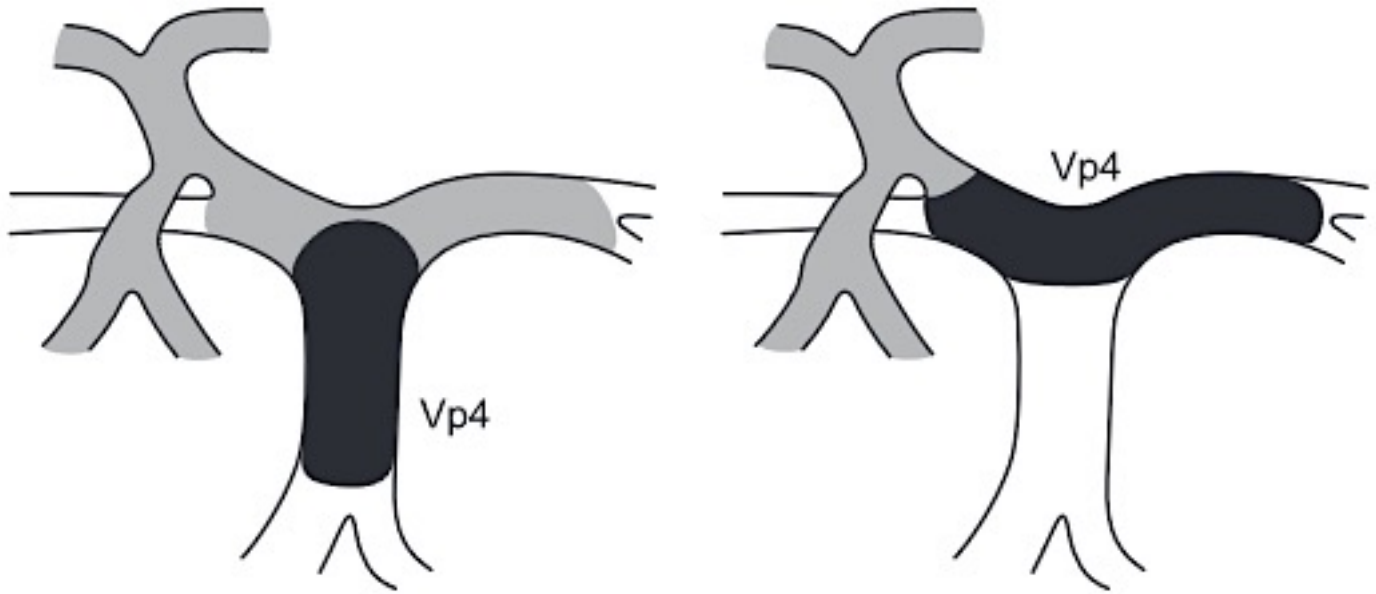
MAKE THE SELECTION!

Bevacizumab + Atezolizumab

Tremelimumab + Durvalumab

- Effect of comorbidity profile, hepatic reserve and other factors on the selection between up-front atezolizumab/bevacizumab and durvalumab/tremelimumab for advanced HCC

HCC patients with Vp4 cancer involvement.



IMbrave150: exploratory subgroup analysis in patients with uHCC and Vp4 treated with atezo-bev versus sorafenib

Summary of efficacy in patients with Vp4 at baseline and the rest of the ITT population without Vp4 at baseline

	Patients with Vp4 (n=73)		Rest of ITT population (n=428)	
	Atezo-bev (n=48)	Sorafenib (n=25)	Atezo-bev (n=288)	Sorafenib (n=140)
Median (95% CI) OS, months	7.6 (6.0–13.9)	5.5 (3.4–6.7)	21.1 (18.0–24.6)	15.4 (12.6–18.6)
HR (95% CI)	**0.62 (0.34–1.11)**		**0.67 (0.51–0.88)**	
Median (95% CI) PFS per IRF RECIST 1.1, months	5.4 (3.6–6.9)	2.8 (1.5–5.3)	7.1 (6.1–9.6)	4.7 (4.2–6.1)
HR (95% CI)	**0.62 (0.35–1.09)**		**0.64 (0.51–0.81)**	

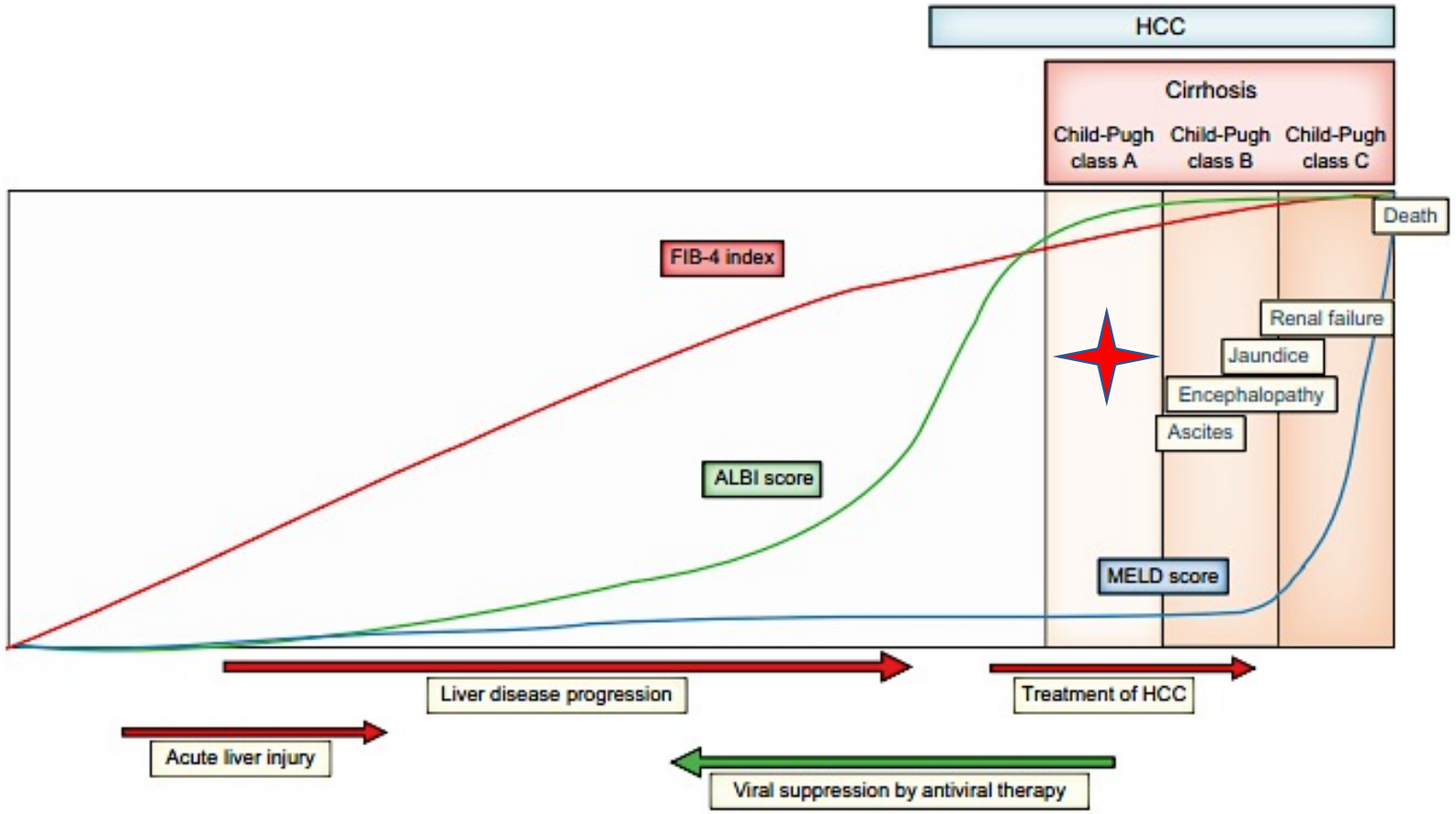
Summary of safety data in patients with Vp4 at baseline and the rest of the ITT population without Vp4 at baseline

	Patients with Vp4 (n=67)		Rest of ITT population (n=418)	
	Atezo-bev (n=44)	Sorafenib (n=23)	Atezo-bev (n=285)	Sorafenib (n=133)
AE related to any study treatment, n (%)	37 (84)	22 (96)	247 (87)	126 (95)
Related Gr 3/4 | 5 AE, n (%)	18 (41) | 1 (2)	11 (48) | 0	125 (44) | 5 (2)	61 (46) | 1 (1)
AE leading to withdrawal from any treatment, n (%)	11 (25)	2 (9)	61 (21)	16 (12)
AE leading to dose modification/interruption of any treatment, n (%)	26 (59)	17 (74)	169 (59)	80 (60)
Any-grade variceal bleeding, n (%)*	6 (14)	0	7 (2)	2 (2)

Breder VV, et al. *J Clin Oncol* 2021;39(15_suppl):4073–4073.
Fin, et al., Liver Cancer 2024;13:655–668 DOI: 10.1159/000539897

In patient with Child Pugh A class, the liver function is reflected by ALBI Score grade

$$\text{ALBI score} = (\log_{10}\text{bilirubin [µmol/L]} \times 0.66) + (\text{albumin [g/L]} \times -0.0852)$$



2 Minute Medicine®	Child-Pugh Score		2minutemedicine.com
Factor	**1 point**	**2 points**	**3 points**
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	**Class B**	**Class C**
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

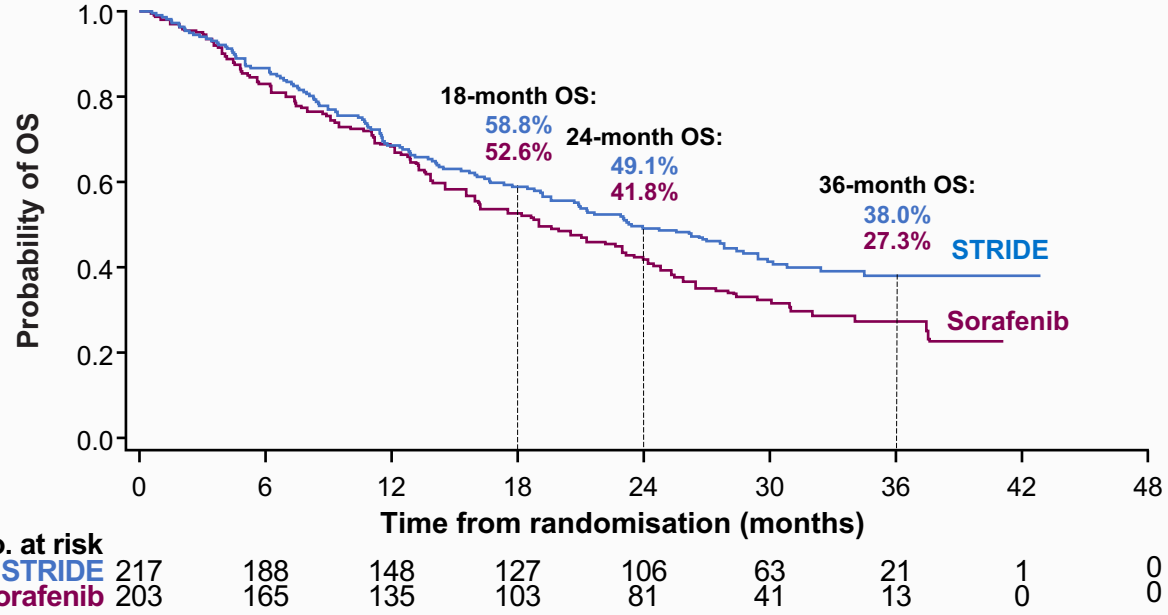
Table I. Child-Pugh score.

Toyoda et al, JHEP Reports Volume 4, Issue 10, October 2022, 100557 https://doi.org/10.1016/j.jhepr.2022.100557

HIMALAYA exploratory analysis: OS for STRIDE versus sorafenib by ALBI grade

OS by ALBI Grade 1 for STRIDE versus sorafenib (exploratory analysis; not tested for statistical significance)

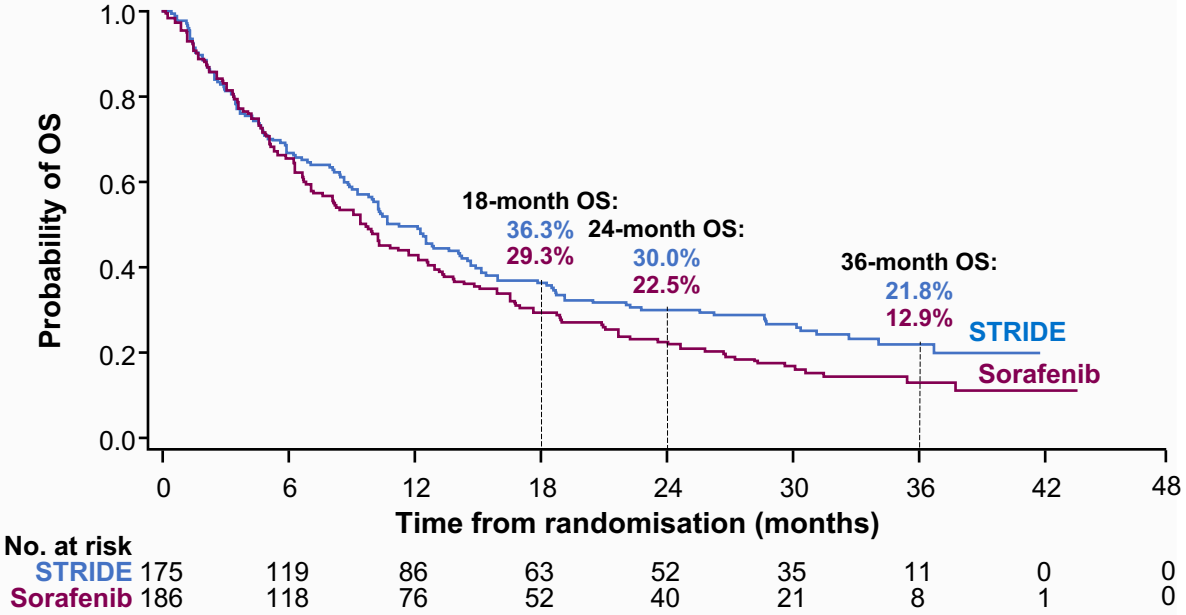
	STRIDE (n=217)	Sorafenib (n=203)
Median OS (95% CI), months	23.43 (19.19–28.75)	19.02 (15.67–23.16)
OS HR (95% CI)*	0.79 (0.62–1.01)	



No. at risk									
STRIDE	217	188	148	127	106	63	21	1	0
Sorafenib	203	165	135	103	81	41	13	0	0

OS by ALBI Grade 2 / 3 for STRIDE versus sorafenib (exploratory analysis; not tested for statistical significance)

	STRIDE (n=175)	Sorafenib (n=186)
Median OS (95% CI), months	11.30 (9.33–14.19)	9.72 (7.23–11.76)
OS HR (95% CI)*	0.83 (0.65–1.05)	



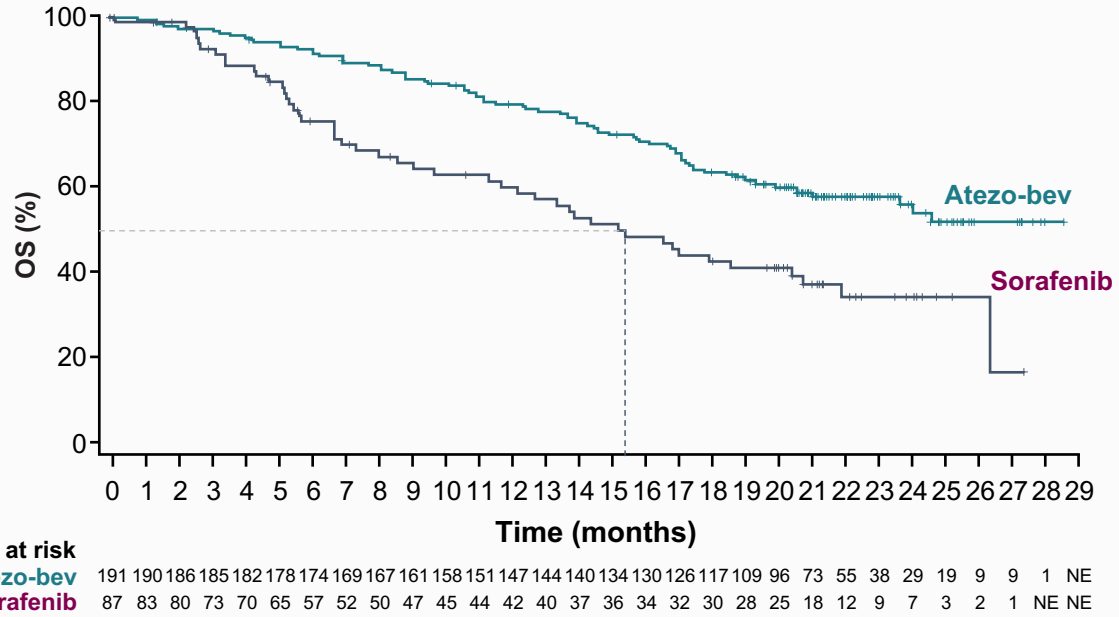
No. at risk									
STRIDE	175	119	86	63	52	35	11	0	0
Sorafenib	186	118	76	52	40	21	8	1	0

Vogel A, et al. Presented at: SIO Annual Scientific Meeting; 19–23 January 2023; Washington, DC, USA. Poster 1413.

IMbrave150 post hoc exploratory analysis: OS for atezo-bev versus sorafenib by ALBI Grade*

OS by ALBI Grade 1 in the atezo-bev and sorafenib arms

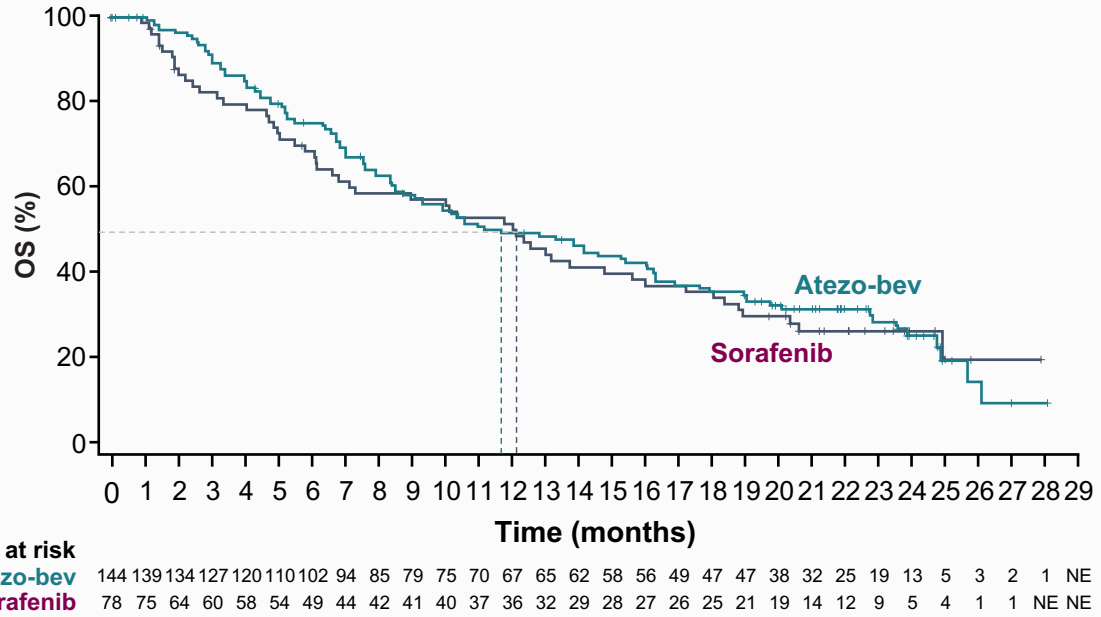
	Atezo-bev (n=191)	Sorafenib (n=87)
Patients with events, n (%)	79 (41)	47 (54)
Median (95% CI) OS, months	NE (23.7–NE)	15.4 (11.7–20.8)
HR (95% CI)	**0.50 (0.35–0.72)**	



No. at risk																													
Atezo-bev	191	190	186	185	182	178	174	169	167	161	158	151	147	144	140	134	130	126	117	109	96	73	55	38	29	19	9	9	1	NE
Sorafenib	87	83	80	73	70	65	57	52	50	47	45	44	42	40	37	36	34	32	30	28	25	18	12	9	7	3	2	1	NE	NE

OS by ALBI Grade 2 in the atezo-bev and sorafenib arms

	Atezo-bev (n=144)	Sorafenib (n=78)
Patients with events, n (%)	100 (69)	53 (68)
Median (95% CI) OS, months	11.7 (9.1–16.1)	12.2 (7.2–16.1)
HR (95% CI)	**0.92 (0.66–1.29)**	



No. at risk																													
Atezo-bev	144	139	134	127	120	110	102	94	85	79	75	70	67	65	62	58	56	49	47	47	38	32	25	19	13	5	3	2	1	NE
Sorafenib	78	75	64	60	58	54	49	44	42	41	40	37	36	32	29	28	27	26	25	21	19	14	12	9	5	4	1	1	NE	NE

Kudo M, et al. *Liver Cancer* 2023;12:479–493.

MAKE THE SELECTION!

Bevacizumab + Atezolizumab

Tremelimumab + Durvalumab

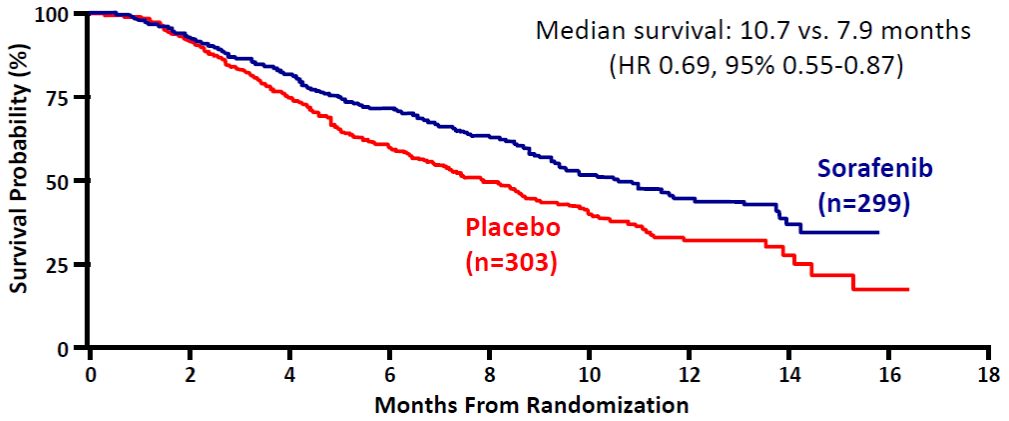
1. Bleeding Risk: Recent variceal bleeding, large varices, VP4 invasion, other bleeding risk?
2. ALBI Grade 2

- Indications for TKI monotherapy as first-line treatment for unresectable HCC; selection of appropriate patients for treatment with sorafenib or lenvatinib

Approval of TKIs as 1st line therapy in HCC

Sorafenib improves survival for advanced HCC

Sorafenib
Approved in 2007

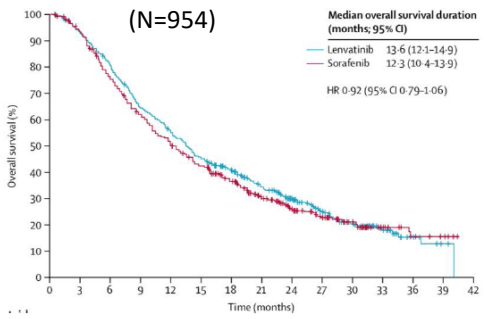


Llovet et al *NEJM* 2008

Medium overall survival
10.7m Sorafenib
vs. 7.9 m placebo

Lenvatinib is non-inferior to sorafenib in OS but provides better response rates

Lenvatinib
Approved in 2018



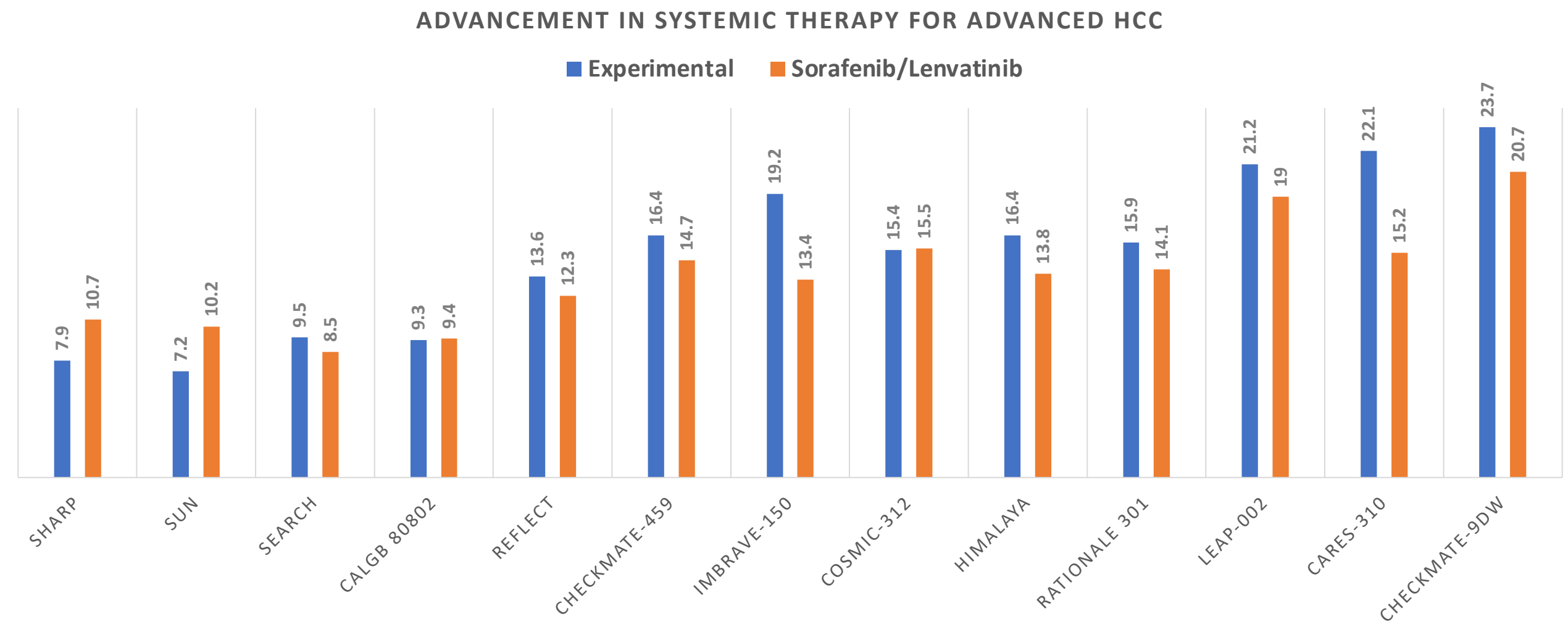
Response rates (mRECIST)

	Lenvatinib	Sorafenib
Response rate	41%	12%
Complete	2%	1%
Partial	38%	12%
Stable disease	33%	46%
Progressive disease	17%	32%
TTP (month)	7.4	3.7
	HR 0.60 (0.51 – 0.71)	

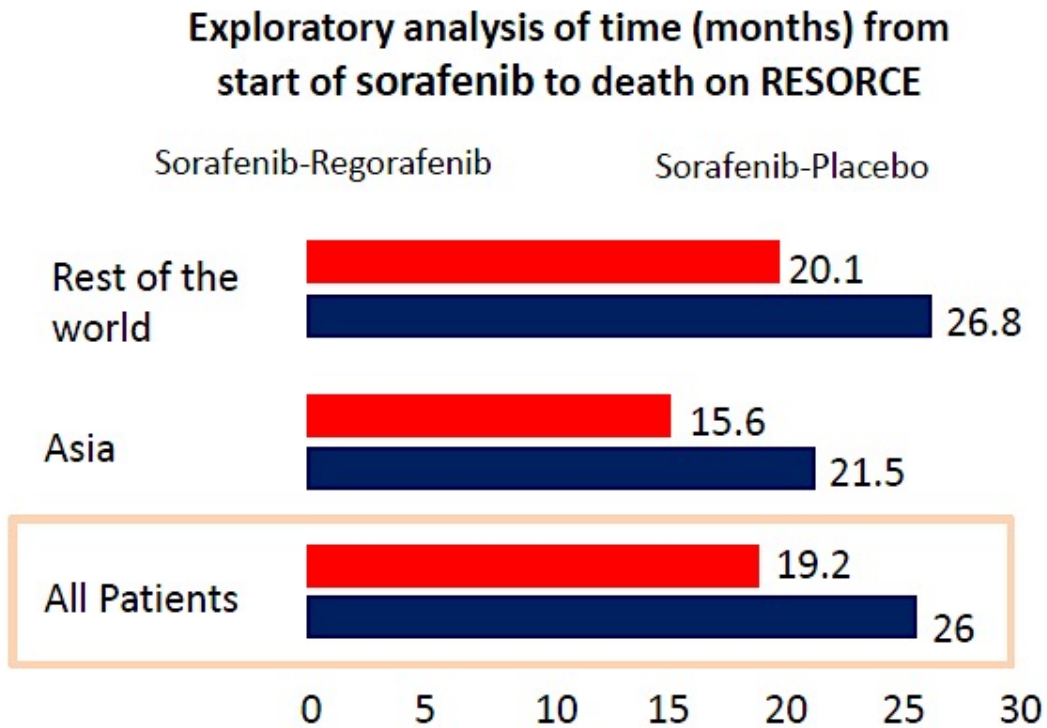
Kudo et al *Lancet* 2018

Medium overall survival
13.6 m Lenvatinib
12.3 m Sorafenib

Response rate:
mRECIST
41% Lenvatinib
12% Sorafenib


ADVANCEMENT IN SYSTEMIC THERAPY FOR ADVANCED HCC
Experimental
Sorafenib/Lenvatinib
7.9
10.7
7.2
10.2
9.5
8.5
9.3
9.4
13.6
12.3
16.4
14.7
19.2
13.4
15.4
15.5
16.4
13.8
15.9
14.1
21.2
19
22.1
15.2
23.7
20.7
SHARP
SUN
SEARCH
CALGB 80802
REFLECT
CHECKMATE-459
IMBRAVE-150
COSMIC-312
HIMALAYA
RATIONALE 301
LEAP-002
CARES-310
CHECKMATE-9DW

Sequential therapy can provide prolonged survival



Survival	Sorafenib-regorafenib (n-379)	Sorafenib-placebo (n=194)
6 months	97%	97%
12 months	82%	76%
24 months	53%	42%
36 months	31%	20%
48 months	19%	12%
60 months	16%	3%
72 months	10%	3%

Finn et al *J Hepatology* 2018

Medium overall survival: > 26 months in patients with advanced HCC with Sequential TKI

MAKE THE SELECTION!

Immunotherapy

TKIs (Lenvatinib/Sorafenib)

1. Contraindication to receive Immunotherapy:
   Autoimmune diseases; history of transplant
2. Prefer oral therapy
3. Biomarker is needed

Video Cases and Questions for the Faculty

RTP
RESEARCH
TO PRACTICE

Selection of first-line treatment regimen for advanced HCC

Dr Thomas Abrams

Dr Katie Kelley

Dr Ghassan Abou-Alfa

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you select first-line systemic treatment for HCC?

What are the key variables you consider when deciding between atezolizumab/bevacizumab and durvalumab/tremelimumab?

What are some of the ongoing clinical trials investigating first-line treatment for advanced HCC that you're most excited about?

Role of single-agent immunotherapy for the treatment of advanced HCC

Dr Katie Kelley

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

In what situations, if any, do you utilize a single-agent anti-PD-1/PD-L1 antibody? Do you prefer any one agent over the others?

What has been your experience with this treatment approach?

Management of HCC in patients with discordant tumor markers or mixed tumor histology

Dr Thomas Abrams

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

In what situations, if any, do you utilize systemic treatment for a patient with HCC without a tissue biopsy?

How do you approach patients with mixed tumor histology (HCC and cholangiocarcinoma)?

What has been your clinical experience in this situation?

Agenda

Module 1: Adjuvant Systemic Therapy for Early-Stage Hepatocellular Carcinoma (HCC) — Dr El-Khoueiry

Module 2: Recent Developments in the Management of Intermediate-Stage HCC — Dr Finn

Module 3: Current First-Line Therapy for Advanced HCC — Dr He

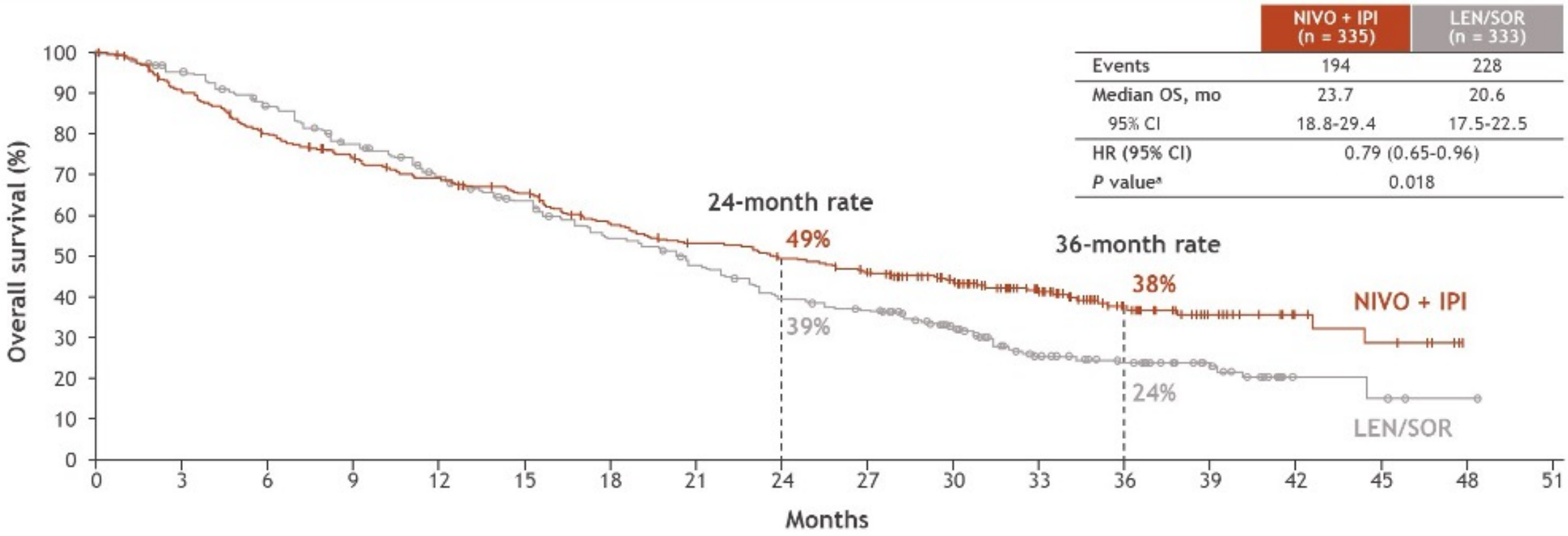
Module 4: Promising Investigational Front-Line Strategies for Advanced HCC; Selection and Sequencing of Therapy for Relapsed/Refractory HCC — Dr Stein

Promising Investigational Front-Line Strategies for Advanced HCC

Selection and Sequencing of Therapy for Relapsed/Refractory HCC

Stacey M Stein MD
Associate Professor of Medicine, Rutgers, CINJ

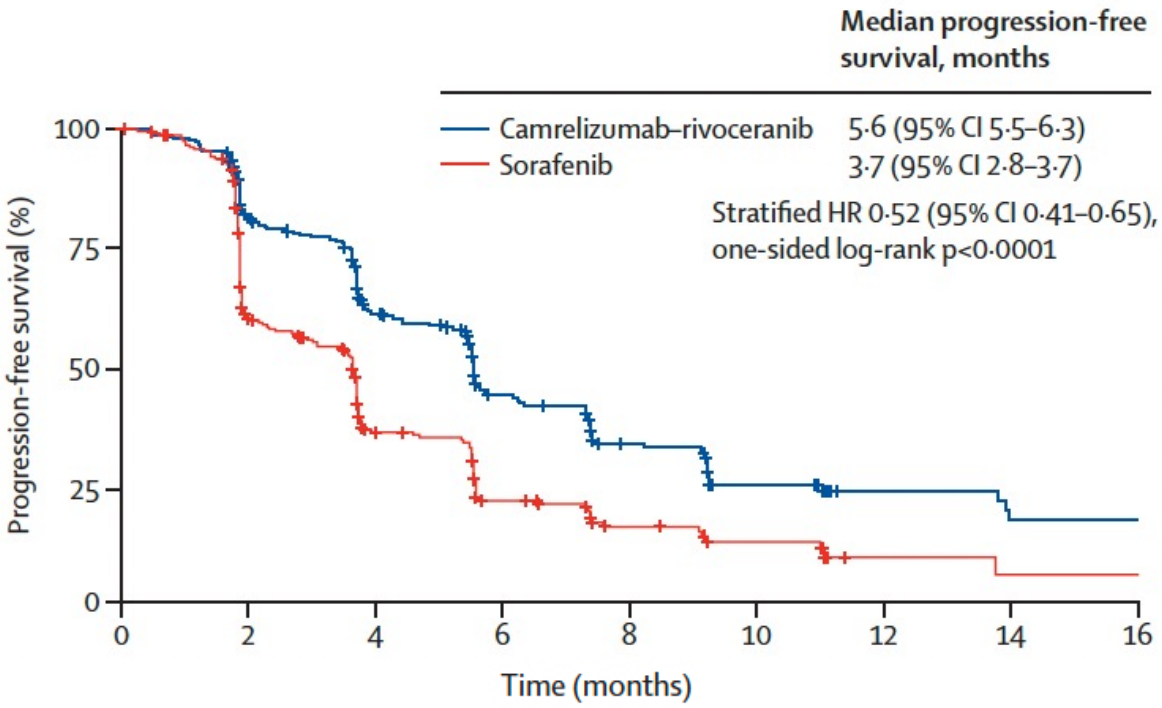
First Results from CheckMate 9DW: Nivolumab + Ipilimumab versus Lenvatinib or Sorafenib as First-Line Treatment for Unresectable HCC

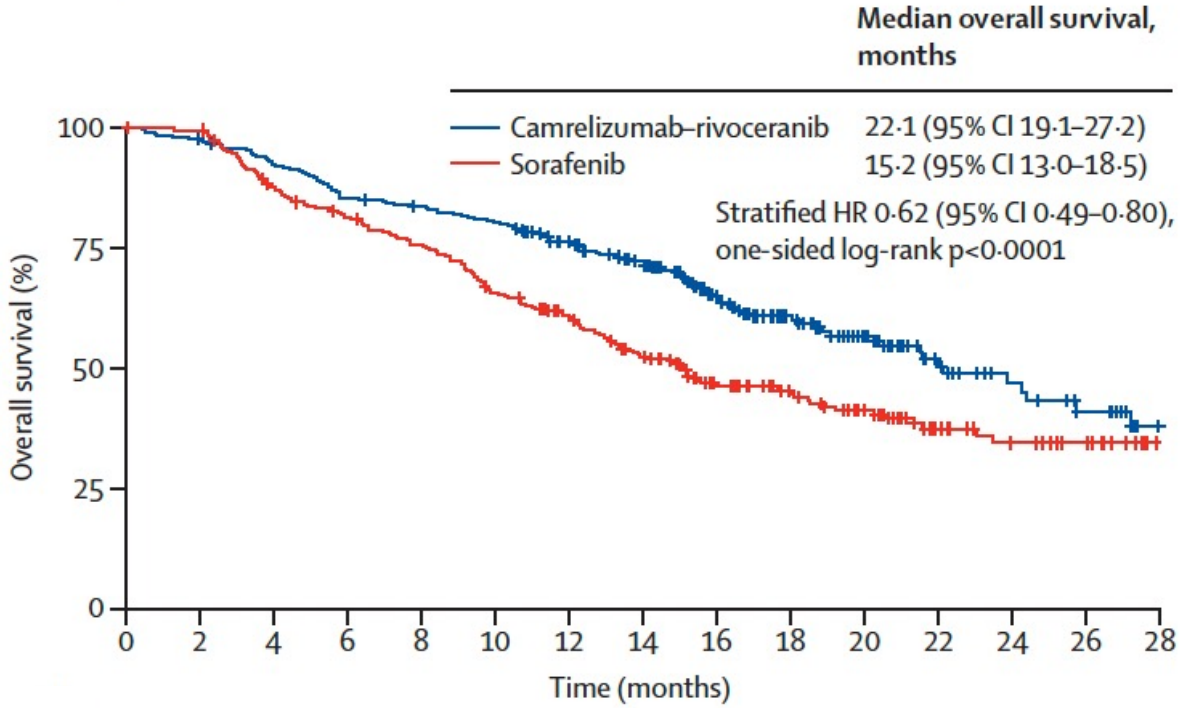


	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	194	228
Median OS, mo	23.7	20.6
95% CI	18.8-29.4	17.5-22.5
HR (95% CI)	0.79 (0.65-0.96)	
P value[a]	0.018	

Galle PR et al. ASCO 2024;Abstract LBA4008.

CARES-310: Camrelizumab + Rivoceranib versus Sorafenib as First-Line Therapy for Unresectable HCC





Qin S et al. *Lancet* 2023 Sep 30;402(10408):1133-46.

CARES-310: Select Adverse Events

	Camrelizumab–rivoceranib (n=272)				Sorafenib (n=269)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-related adverse event	45 (17%)	193 (71%)	26 (10%)	1 (<1%)	128 (48%)	128 (48%)	12 (4%)	1 (<1%)
Hypertension	87 (32%)	100 (37%)	2 (1%)	0	76 (28%)	40 (15%)	0	0
Aspartate aminotransferase increased	102 (38%)	42 (15%)	3 (1%)	0	85 (32%)	14 (5%)	0	0
Proteinuria	118 (43%)	16 (6%)	0	0	67 (25%)	5 (2%)	0	0
Alanine aminotransferase increased	92 (34%)	34 (13%)	1 (<1%)	0	72 (27%)	8 (3%)	0	0
Platelet count decreased	94 (35%)	28 (10%)	4 (1%)	0	85 (32%)	4 (1%)	0	0
Blood bilirubin increased	92 (34%)	24 (9%)	0	0	71 (26%)	4 (1%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	69 (25%)	33 (12%)	0	0	122 (45%)	41 (15%)	0	0
Diarrhoea	77 (28%)	6 (2%)	0	0	91 (34%)	14 (5%)	0	0
Reactive cutaneous capillary endothelial proliferation	72 (26%)	7 (3%)	0	0	0	0	0	0
Neutrophil count decreased	57 (21%)	14 (5%)	2 (1%)	0	24 (9%)	1 (<1%)	2 (1%)	0
White blood cell count decreased	66 (24%)	7 (3%)	0	0	35 (13%)	3 (1%)	0	0
Gamma-glutamyltransferase increased	39 (14%)	25 (9%)	2 (1%)	0	29 (11%)	15 (6%)	5 (2%)	0
Hypothyroidism	58 (21%)	0	0	0	16 (6%)	0	0	0
Fatigue	46 (17%)	7 (3%)	0	0	20 (7%)	1 (<1%)	0	0

Qin S et al. *Lancet* 2023 Sep 30;402(10408):1133-46.

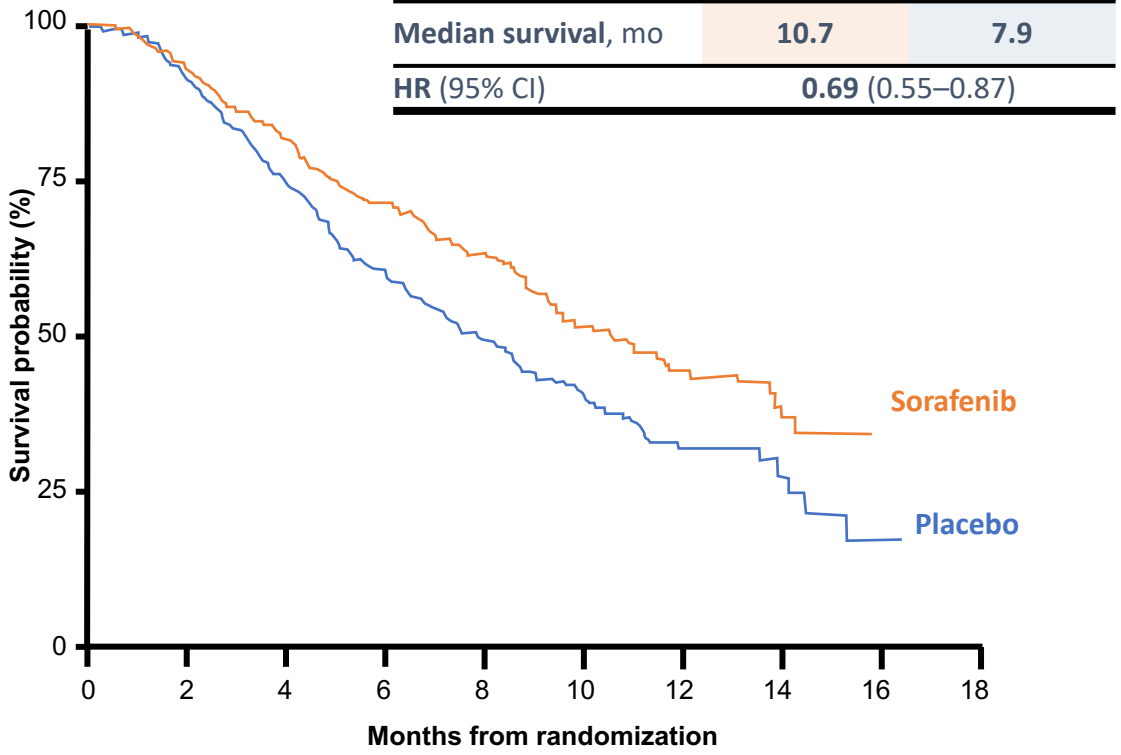
Role of TKIs in relapsed disease – second line therapy options

Although sorafenib and Lenvatinib were first line studies, now we often move sequentially

Survival Analysis With Sorafenib and Lenvatinib for Advanced Stage HCC

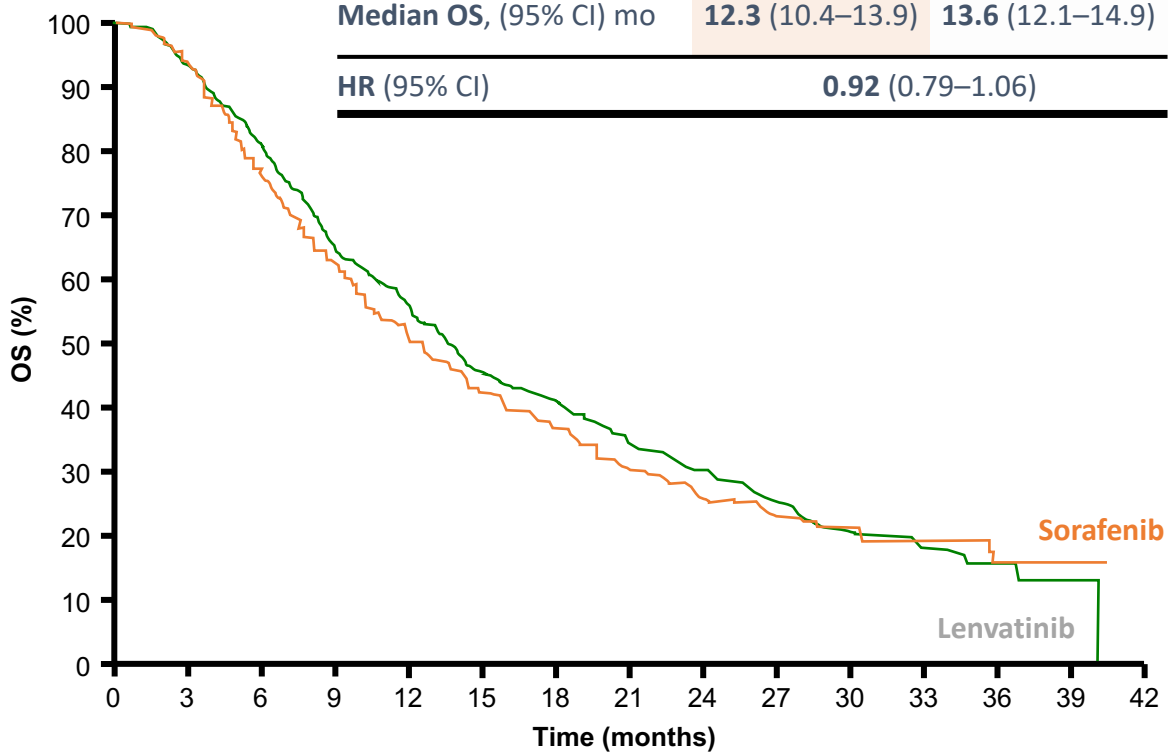
Kaplan-Meier Analysis of Overall Survival With Sorafenib vs Placbo[1]

	Sorafenib (n = 299)	Placebo (n = 303)
Median survival, mo	**10.7**	**7.9**
HR (95% CI)	**0.69** (0.55–0.87)	



Kaplan-Meier Estimate of Overall Survival With Sorafenib vs Levatinib[2]

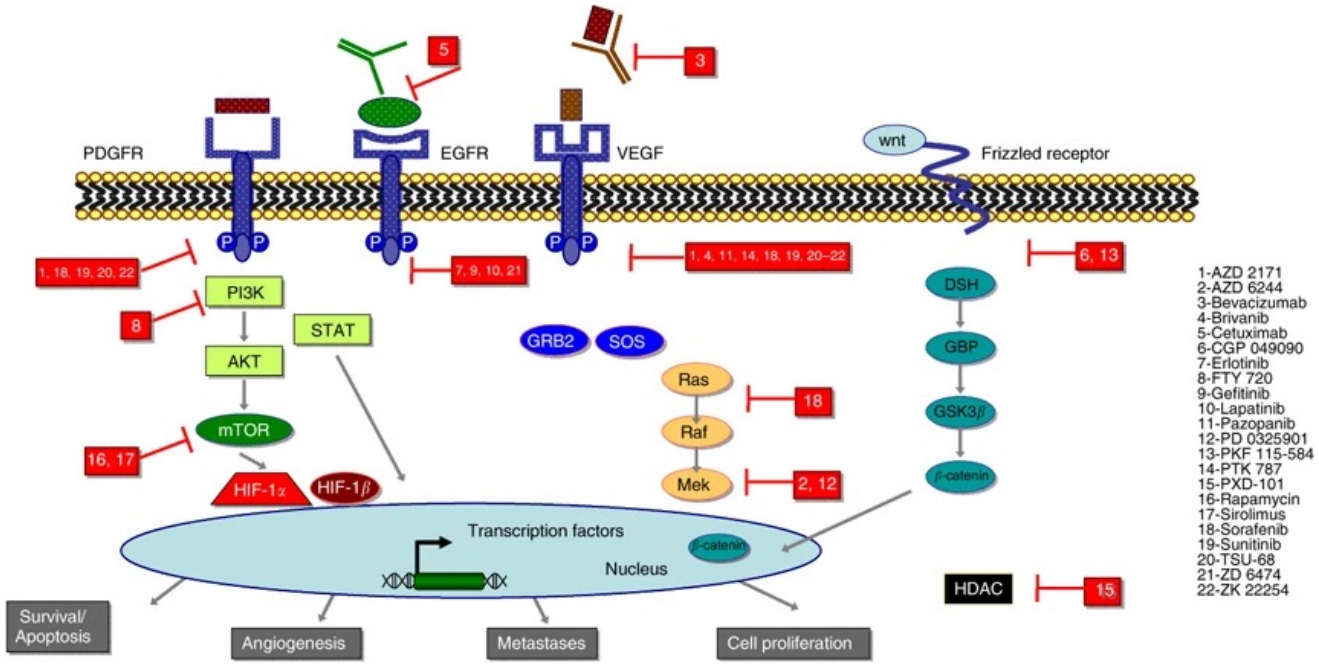
	Sorafenib	Lenvatinib
Median OS, (95% CI) mo	**12.3** (10.4–13.9)	**13.6** (12.1–14.9)
HR (95% CI)	**0.92** (0.79–1.06)	



Sorafenib and lenvatinib are tyrosine kinase inhibitors that improve survival for advanced stage HCC

1. Llovet, et al. *N Engl J Med*. 2008;359(4):378-390. 2. Kudo, et al. *Lancet*. 2018;391(10126):1163-1173.

Tyrosine Kinase Inhibition Pathways



Greten et al, BJC 2008

Drug	Targets
Sorafenib	VEGF, PDGFR, B/C-RAF
Lenvatinib	VEGF, PDGFR, RET, KIT, FGFR
Regorafenib	VEGF, PDGFR, RET, KIT, FGFR, TIE2 B/C-RAF
Cabozantinib	VEGF, RET, KIT, TIE2, C-MET, AXL

Llovet JM, et al. *N Engl J Med*. 2008;359(4):378-390.
Cheng AL, et al. *Lancet Oncol*. 2009;10(1):25-34.
Kudo M, et al. *Lancet*. 2018; pii:S0140-6736(18)30207-1.
Bruix J, et al. *Lancet*. 2017;389(10064):56-66.
Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63.

Multiple VEGF-Targeted Therapies Have Activity After Sorafenib: Phase III Data

RESORCE	CELESTIAL	REACH-2
Regorafenib vs placebo	Cabozantinib vs placebo (N = 707)	Ramucirumab vs placebo
Multitargeted TKI	Multitargeted TKI	Anti-VEGFR2 Ab
2L, sorafenib-tolerating patients only (N = 573)	2L or 3L (N = 707)	2L, AFP ≥400 ng/mL (N = 292)
Median OS: 10.6 vs 7.8 mo	Median OS: 10.2 vs 8.0 mo	Median OS: 8.5 vs 7.3 mo
HR: 0.63 (*P* < .0001)	HR: 0.76 (*P* = .005)	HR: 0.71 (P = .0199)

Bruix. Lancet. 2017;389:56. Abou-Alfa. NEJM. 2018;379:54. Zhu. Lancet Oncol. 2019;20:282.

TKIs Comparison of Adverse Events

All have common grade 2 Adverse events: Fatigue, weight loss, nausea, diarrhea, Hand-foot syndrome, Hypertension

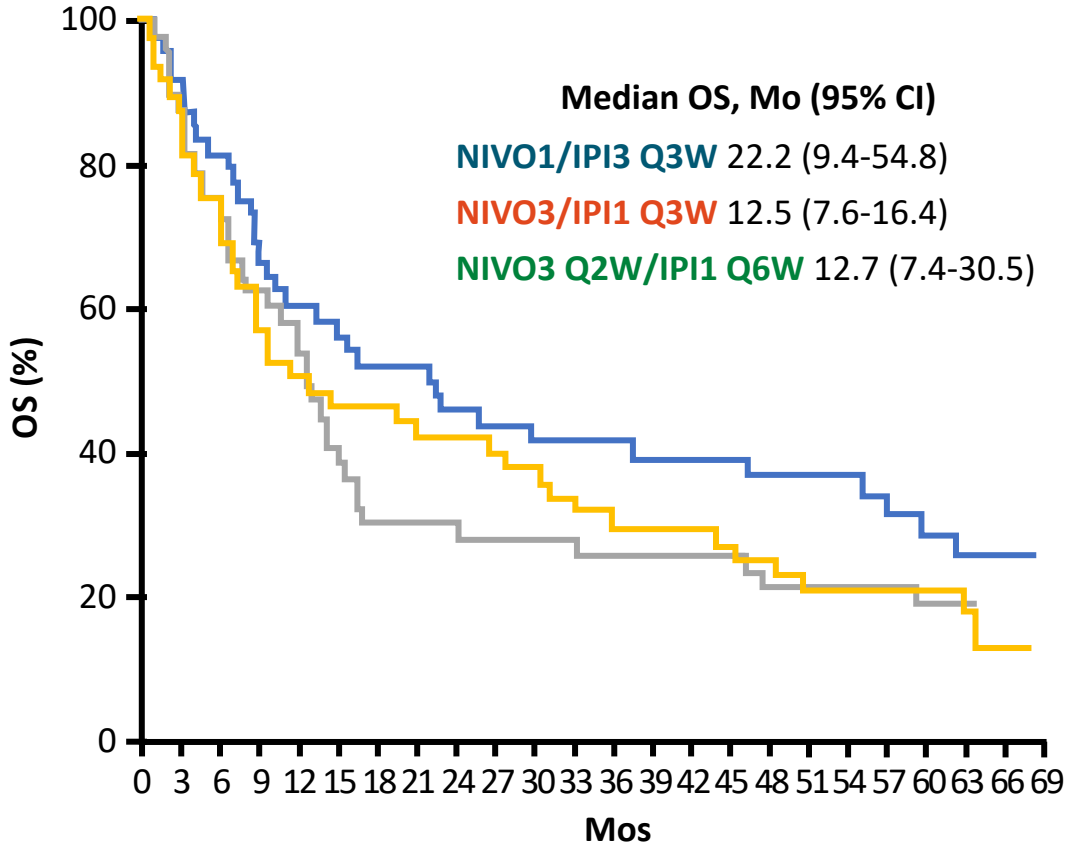
Drug	Additional Toxicity
Sorafenib	Alopecia, Rash, Voice changes
Lenvatinib	Alopecia, Abdominal pain, Rash Proteinuria, Voice changes, Hypothyroidism
Regorafenib	Fever, Oral mucositis, Vomiting, Hoarseness, Thrombocytopenia, Hypophosphatemia
Cabozantinib	Asthenia, Mucositis, Dysphonia, Dysgeusia, Thrombocytopenia

Llovet JM, et al. *N Engl J Med*. 2008;359(4):378-390.
Cheng AL, et al. *Lancet Oncol*. 2009;10(1):25-34.
Kudo M, et al. *Lancet*. 2018; pii:S0140-6736(18)30207-1.
Bruix J, et al. *Lancet*. 2017;389(10064):56-66.
Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63.

CheckMate 040: Nivolumab + Ipilimumab for Advanced HCC

- Open-label phase I/II trial of 3 different dosing schemes of nivolumab + ipilimumab for patients with advanced HCC and *prior sorafenib treatment*; Child-Pugh score A5-A6; ECOG PS 0/1

Outcome	NIVO1/IPI3 Q3W (n = 50)	NIVO3/IPI1 Q3W (n = 49)	NIVO3 Q2W/ IPI1 Q6W (n = 49)
ORR, % (95% CI)	32 (20-47)	31 (18-45)	31 (18-45)
▪ CR, %	8	6	2
DCR, %	54	43	49
Median TTR, mo	2.0	2.6	2.7
Median DoR, mo	17.5	22.2	16.6



- Combination FDA approved for patients who have been previously treated with sorafenib

Yau. JAMA Oncol. 2020;6:e204564. Melero. WCGI 2022. Abstr SO-12.

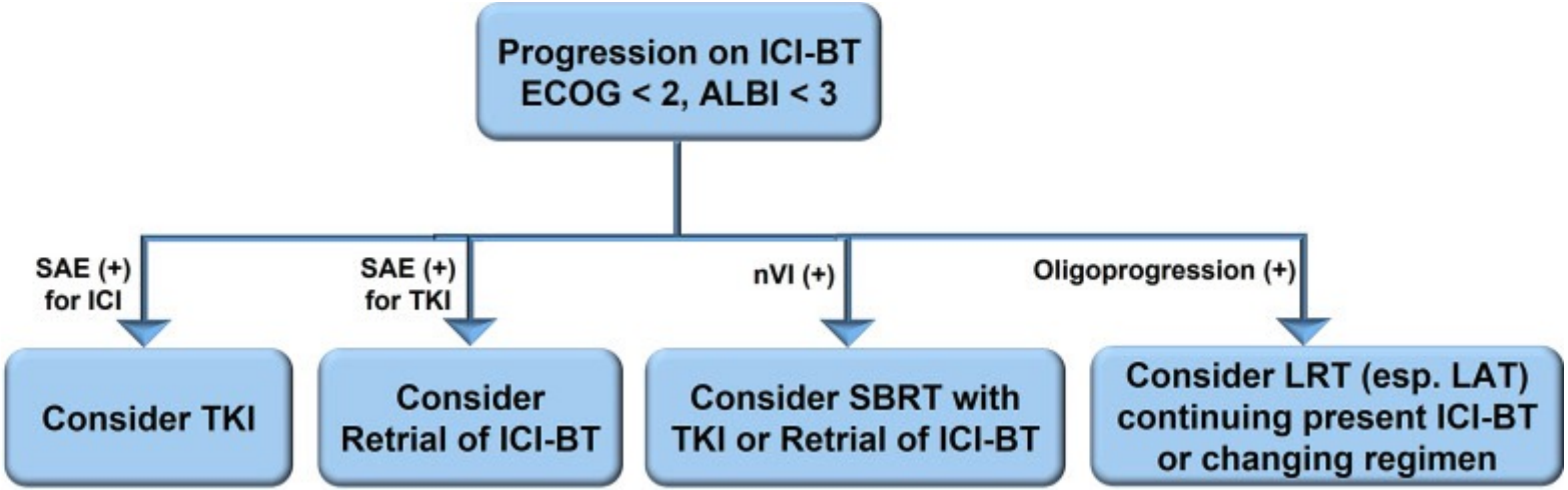
CheckMate 040: Safety

TRAE in >10%, n (%)	NIVO1/IPI3 Q3W (n = 49)		NIVO3/IPI1 Q3W (n = 49)		NIVO3 Q2W/IPI1 Q6W (n = 48)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TRAE	46 (94)	26 (53)	35 (71)	14 (29)	38 (79)	15 (31)
▪ Pruritis	22 (45)	2 (4)	16 (33)	0	14 (29)	0
▪ Rash	14 (29)	2 (4)	11 (22)	2 (4)	8 (17)	0
▪ Diarrhea	12 (24)	2 (4)	6 (12)	1 (2)	8 (17)	1 (2)
▪ AST increase	10 (20)	8 (16)	10 (20)	4 (8)	6 (13)	2 (4)
▪ Lipase increase	7 (14)	6 (12)	6 (12)	3 (6)	8 (17)	4 (8)
▪ Fatigue	9 (18)	1 (2)	6 (12)	0	5 (10)	0
▪ ALT increase	8 (16)	4 (8)	7 (14)	3 (6)	4 (8)	0
▪ Hypothyroidism	10 (20)	0	4 (8)	0	4 (8)	0
▪ Rash (maculopapular)	7 (14)	2 (4)	4 (8)	0	3 (6)	0
▪ Decreased appetite	6 (12)	0	4 (8)	0	3 (6)	0
▪ Malaise	6 (12)	1 (2)	3 (6)	0	3 (6)	0
▪ Adrenal insufficiency	7 (14)	1 (2)	3 (6)	0	2 (4)	0

- CheckMate 9DW: ongoing phase III trial of first-line nivolumab + ipilimumab vs sorafenib or lenvatinib for advanced HCC (NCT04039607)

Yau. JAMA Oncol. 2020;6:e204564. Melero. WCGI 2022. Abstr SO-12.

- Second Line Therapy after IO in HCC – Real World Data of TKI, Rechallenge, vs Local Therapy



Hwang et al, Liver Cancer 2023

Real World Data of Second Line Tx

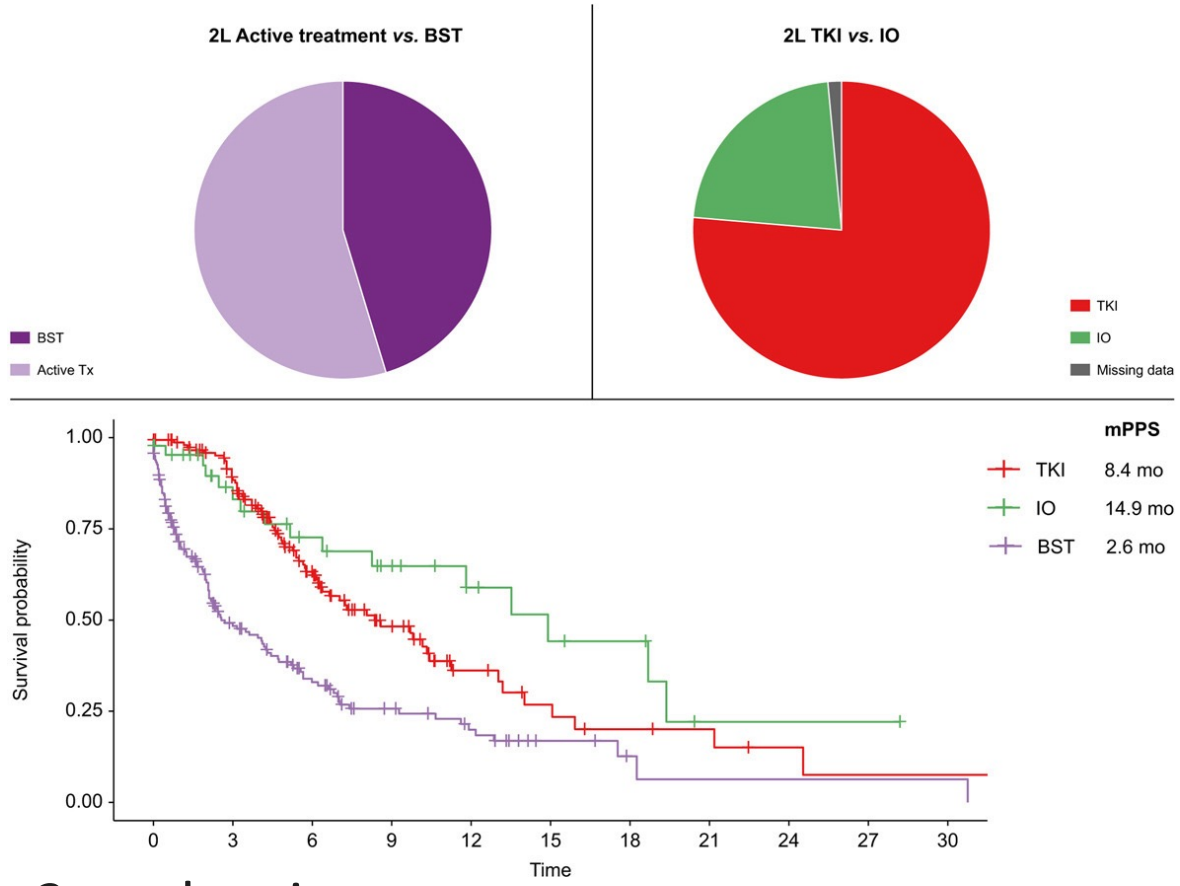
406 pts POD on A/B

45.3% (n = 184) BSC

54.7% (n = 222) received tx

155 pts received TKIs

45 pts received IO



mPPS of all pts = 6.0 months (95% CI 5.2-7.2)

Better PPS assoc with absence of PVTT, ECOG < 2, and active tx

mPPS active tx *vs.* BST (9.7 *vs.* 2.6 months; HR 0.41, p <0.001).

Pts receiving TKIs mPPS vs IO (8.4 *vs.* 14.9 months; HR 1.37, p = 0.256)

Wu et al, JHEP reports 2025

PPS = post-progression survival (defined as time from first radiographic progression on atezo/bev [A/B] to death)

IMbrave 251- Continue IO in 2nd line?

- Atezolizumab with Len or Sorafenib vs Len or Sorafenib alone after Atezo and Bev
- Primary outcome: OS
- Secondary Outcomes: PFS, ORR, TTP, DOR Time to confirmed deterioration, % of pts with AE

Video Cases and Questions for the Faculty

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Choice of tyrosine kinase inhibitor as second-line systemic treatment of HCC; prevention, monitoring and mitigation of lenvatinib-associated side effects

Dr Katie Kelley

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What are your thoughts about ipilimumab/nivolumab (CheckMate 9DW) as well as the combination of rivoceranib/camrelizumab?

What factors do you consider when selecting therapy for patients with disease progression on first-line IO-based regimens? Do you prefer one tyrosine kinase inhibitor versus the others in this situation?

How do you prevent, monitor and mitigate lenvatinib- and cabozantinib-associated toxicity? How problematic do you find the toxicities associated with these agents?

73-year-old man with metastatic HCC that rapidly progressed on atezolizumab/bevacizumab

Dr Ghassan Abou-Alfa

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QUESTIONS FOR THE FACULTY

In what situations, if any, do you rechallenge with an IO-based approach for patients with disease progression on atezolizumab/bevacizumab or single-agent anti-PD-1/PD-L1 therapy?

What have you observed clinically when using this strategy?

Supportive care measures to manage ascites in patients with HCC

Dr Thomas Abrams

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QUESTIONS FOR THE FACULTY

What is your clinical experience with cirrhosis-associated ascites?

What about other cirrhosis-related complications?

How helpful are hepatologists in this setting?

What Clinicians Want to Know: Biomarker Assessment and Related Treatment Decision-Making for Patients with Colorectal Cancer

A CME Symposium Held in Conjunction with the 2025 ASCO® Gastrointestinal Cancers Symposium

Friday, January 24, 2025

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Arvind Dasari, MD, MS

Van K Morris, MD

Jenny Seligmann, MBChB, PhD

Eric Van Cutsem, MD, PhD

Moderator

Christopher Lieu, MD

RTP RESEARCH TO PRACTICE

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Online/Zoom attendees: The CME credit link is posted in the chat room.

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