Lunch with the Investigators: Hepatobiliary Cancers

Friday, May 31, 2024

11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)

Faculty

Edward Kim, MD

Arndt Vogel, MD, PhD

Moderator

Robin K (Katie) Kelley, MD

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Faculty

Edward Kim, MD
Director, Interventional Oncology
Professor of Radiology and Surgery
Division of Interventional Radiology
Mount Sinai Health System
New York, New York

Moderator
Robin K (Katie) Kelley, MD
Professor of Clinical Medicine, Division of Hematology/Oncology
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco (UCSF)
San Francisco, California

Arndt Vogel, MD, PhD
Professor of Medicine, University of Toronto
Longo Family Chair in Liver Cancer Research
Division of Gastroenterology and Hepatology
Toronto General Hospital
Medical Oncology
Princess Margaret Cancer Centre
Toronto General Hospital Research Institute
Schwartz Reisman Liver Research Centre
Toronto, Ontario, Canada

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Dr Kim — Disclosures
Faculty

No relevant conflicts of interest to disclose.

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Prof Vogel — Disclosures
Faculty

Consultancy and Advisory; Speaker	Amgen Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Boehringer Mannheim, Bristol Myers Squibb, Eisai Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, MSD, Pierre Fabre, Roche Laboratories Inc, Servier Pharmaceuticals LLC, Taiho Oncology Inc

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Dr Kelley — Disclosures
Moderator

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Contracted Research (Payment to Institution for Trial Conduct)	Agios Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Compass Therapeutics, EMD Serono Inc, Exelixis Inc, Genentech, a member of the Roche Group, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Partner Therapeutics, QED Therapeutics, Servier Pharmaceuticals LLC, Surface Oncology, Taiho Oncology Inc, Tyra Biosciences
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Dr Love — Disclosures

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This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Incyte Corporation, Jazz Pharmaceuticals Inc, and Taiho Oncology Inc.

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Friday May 31	**Hepatobiliary Cancers** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Non-Small Cell Lung Cancer with an EGFR Mutation 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday June 1	**Antibody-Drug Conjugates in the Treatment of Lung Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 2	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 3	**Colorectal Cancer (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 4	**Bispecific Antibodies in the Management of Lymphoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

Hepatobiliary Cancers

Friday, May 31, 2024

11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)

Faculty

Robin K (Katie) Kelley, MD
Edward Kim, MD
Arndt Vogel, MD, PhD

Antibody-Drug Conjugates in Lung Cancer

Saturday, June 1, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rebecca S Heist, MD, MPH
Luis Paz-Ares, MD, PhD
Jacob Sands, MD

Non-Small Cell Lung Cancer with an EGFR Mutation

Friday, May 31, 2024

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Jonathan W Goldman, MD
Corey J Langer, MD
Joel W Neal, MD, PhD
Zofia Piotrowska, MD, MHS
Joshua K Sabari, MD
Helena Yu, MD

Prostate Cancer

Saturday, June 1, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Neeraj Agarwal, MD, FASCO
Emmanuel S Antonarakis, MD
Andrew J Armstrong, MD, ScM
Tanya B Dorff, MD
Matthew R Smith, MD, PhD

Exciting CME Events in Chicago You Do Not Want to Miss

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Multiple Myeloma

Sunday, June 2, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rafael Fonseca, MD
María-Victoria Mateos, MD, PhD
Elizabeth O'Donnell, MD

LIVE WEBCAST

Colorectal Cancer

Monday, June 3, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Scott Kopetz, MD, PhD
John Strickler, MD

Ovarian and Endometrial Cancer

Sunday, June 2, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Floor J Backes, MD
Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Angeles Alvarez Secord, MD, MHSc
Brian M Slomovitz, MD

Metastatic Breast Cancer

Monday, June 3, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Aditya Bardia, MD, MPH
Harold J Burstein, MD, PhD
Professor Giuseppe Curigliano, MD, PhD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

LIVE WEBCAST

Bispecific Antibodies in Lymphoma

Tuesday, June 4, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

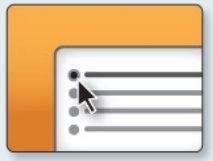
Faculty

Joshua Brody, MD
Ian W Flinn, MD, PhD
Tycel Phillips, 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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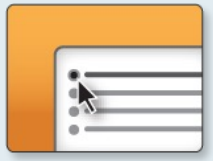
Clinicians Attending via Zoom

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.
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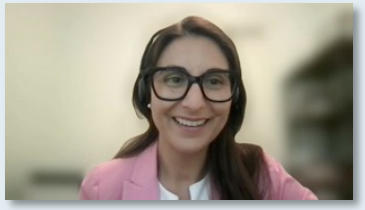
Consulting Oncologists

Neil Love, MD
Research To Practice
Miami, Florida



Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky

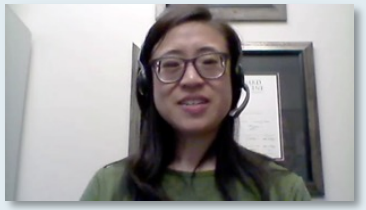
Spencer H Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

Gigi Chen, MD
John Muir Health
Pleasant Hill, California

Sunil Gandhi, MD
Florida Cancer Specialists
& Research Institute
Lecanto, Florida

Shaachi Gupta, MD, MPH
Florida Cancer Specialists
& Research Institute
Lake Worth, Florida



Kimberly Ku, MD
Bloomington, Illinois

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Estelamari Rodriguez, MD, MPH
Sylvester Comprehensive Cancer Center
Miami, Florida

Erik Rupard, MD
Intermountain Health
St George, Utah

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Agenda

Module 1: Recent Developments in the Management of Early- and Intermediate-Stage Hepatocellular Carcinoma (HCC) — Dr Kim

Module 2: First-Line Therapy for Advanced HCC and Biliary Tract Cancers (BTCs) — Prof Vogel

Module 3: Integration of Targeted Therapy into the Management of Advanced BTCs — Dr Kelley

Agenda

Module 1: Recent Developments in the Management of Early- and Intermediate-Stage Hepatocellular Carcinoma (HCC) — Dr Kim

Module 2: First-Line Therapy for Advanced HCC and Biliary Tract Cancers (BTCs) — Prof Vogel

Module 3: Integration of Targeted Therapy into the Management of Advanced BTCs — Dr Kelley

Consulting Faculty Comments

Selection of first-line treatment for HCC in patients with a solitary lung metastasis; determining candidacy for TACE treatment by interventional radiologists

Dr Gigi Chen
(Pleasant Hill, California)

Dr Erik Rupard
(St George, Utah)

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Consulting Faculty Comments

Dr Gigi Chen
(Pleasant Hill, California)

Case Presentation: 49-year-old woman with metastatic recurrence of HCC 2 years after resection of Stage IIIA disease

2022: MRI abdomen: 11.6cm solid mass arising from the anterior segment right lobe of liver, (segment 5), consistent with HCC. No other sites of disease

3/2024:

MRI abdomen: New 3.8x2.8cm lesion posterior right hepatic lobe highly suspicious for hepatoma. 5mm RLL pulmonary nodule, not present in previous CT chest

8mm RLL nodule, small bilateral lung nodules measuring up to 4mm

Resection of RLL lung nodule: path met HCC
Resection of liver recurrence: HCC

Currently recovering from surgery

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QUESTIONS FOR THE FACULTY

Are there any situations in which you would be tempted to employ atezolizumab/bevacizumab in the adjuvant setting outside of a trial today?

If so, which specific situations?

QUESTIONS FOR THE FACULTY

In patients with intermediate-stage HCC for whom you are not considering transplant, how do you determine whether locoregional liver-directed therapy or systemic therapy is more appropriate?

Is there a specific degree of intrahepatic tumor burden that you use as a cutoff when making this determination?

QUESTIONS FOR THE FACULTY

Are there any situations in which you would be tempted to employ TACE in combination with durvalumab/bevacizumab outside of a trial today?

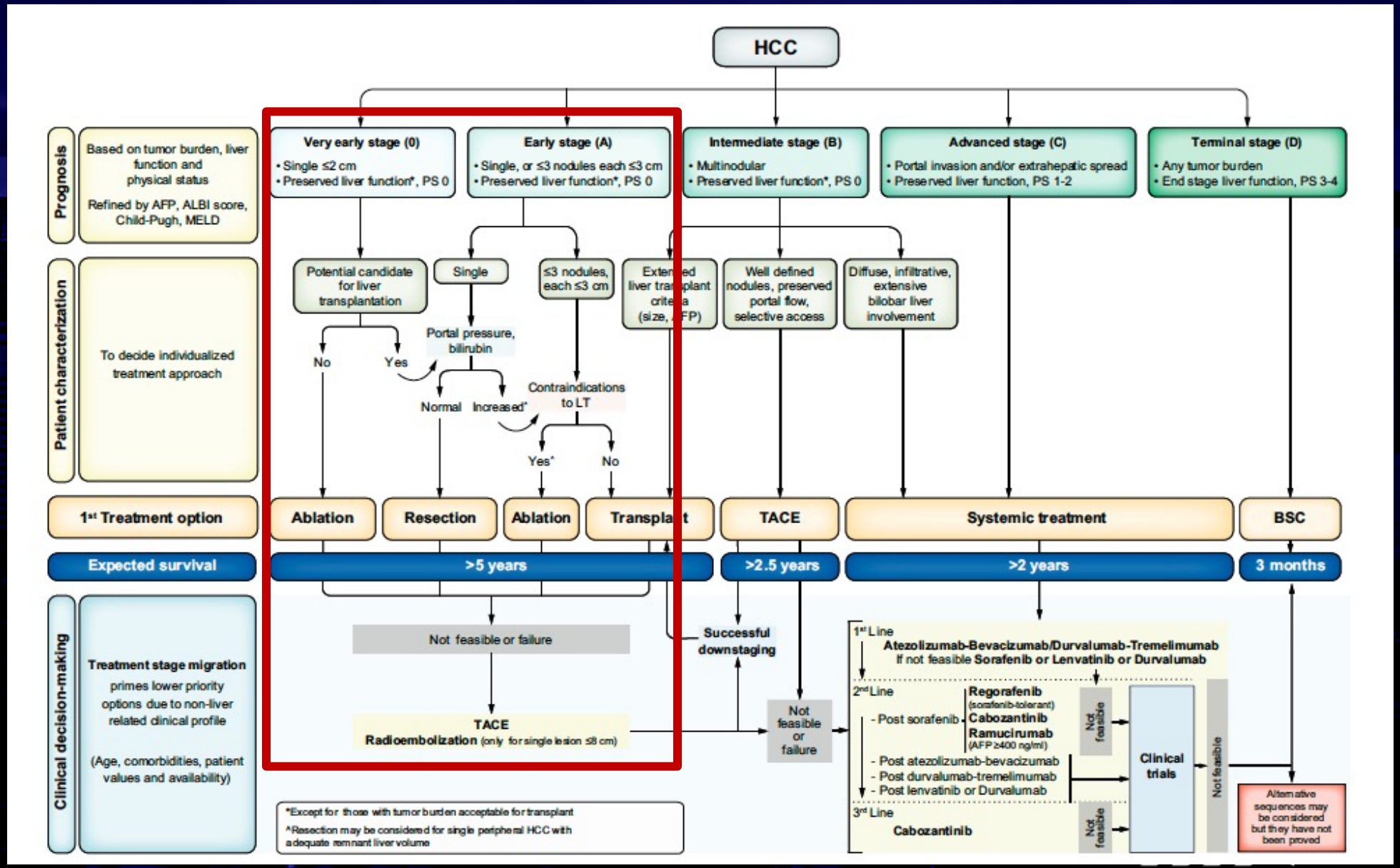
If so, which specific situations?

Recent Developments in the Management of Early- and Intermediate-Stage Hepatocellular Carcinoma

Edward Kim, MD FSIR
Professor of Radiology and Surgery
Director, Interventional Oncology
Mount Sinai Health System
New York, NY

Mount Sinai

BCLC staging and treatment strategy



Multidisciplinary HCC team

Oncology
- Systemic chemotherapy

Radiation oncology
- SBRT

Interventional Radiology
- TACE
- Y90
- ablation

Hepatology
- Transplant
- Management of underlying liver disease

Surgery
- Resection
- Transplant

1. Matsumoto MM et al. *Cardiovasc Intervent Radiol*. 2021;44:1070-1080.

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Curative-intent treatments

	Recurrence Rate	Overall Survival	Ideal Candidate	Exclusion	Key Issues
Ablation	73–80%	70%	- very small HCC ≤2cm in size - not a surgical candidate - location easily accessible via the percutaneous route	- adjacent to major blood vessels or bile ducts due to heat sink effect - typically, not used over 3 cm in size - dome lesions close to the diaphragm	if a patient is a transplant candidate with a very small HCC, observation until >2 cm may be recommended in order to obtain MELD exception points
Resection	70%	70–80%	- no cirrhosis or CP A cirrhosis without clinically significant portal hypertension - solitary mass - location will allow for an adequate liver remnant after resection	- clinically significant portal hypertension - multifocal/bilobar disease	if the size of the future liver remnant is a concern, preoperative portal vein embolization can be performed to induce hypertrophy of the future liver remnant
Transplant	10–15%	80%	- cirrhosis severity precludes resection - within the Milan criteria	not expected to survive a major surgery	- expanded criteria available if the patient is not within the Milan criteria, with regional variations - downstaging to Milan is possible with local regional therapies
Y90 Radiation Segmentectomy	ORR 88-100%	57-75%	Solitary lesions up to 8 cm • Best outcomes reported for lesions up to 3 cm	Elevated lung shunt	- Potential transplant within 30 days

Kinsey, E.; Lee, H.M. Management of Hepatocellular Carcinoma in 2024: The Multidisciplinary Paradigm in an Evolving Treatment Landscape. *Cancers.* **2024**,*16*,666.

Liver-directed therapies

	Advantages	Disadvantages
Ablation	- curative - well tolerated	- limited to small lesions, ideal for <3 cm - must be mindful of location (avoid dome lesions, adjacent to major vessels or bile ducts)
TARE-Y90	- can be used in the presence of portal vein thrombosis - outpatient procedure performed in two sessions (one mapping session and one treatment session) - well tolerated - Cost effective with a single treatment vs multiple TACE	- must pass the mapping procedure requirements (to avoid hepatopulmonary shunting or reflux)
TACE	- recommended as first-line liver-directed therapy in the treatment algorithm for BCLC stage B patients	- Usually requires multiple interventions - overnight stay in the hospital may be required to monitor for post-procedure pain and complications - cannot be used in patients with portal vein thrombosis

Kinsey, E.; Lee, H.M. Management of Hepatocellular Carcinoma in 2024: The Multidisciplinary Paradigm in an Evolving Treatment Landscape. *Cancers.* **2024**,*16*,666.

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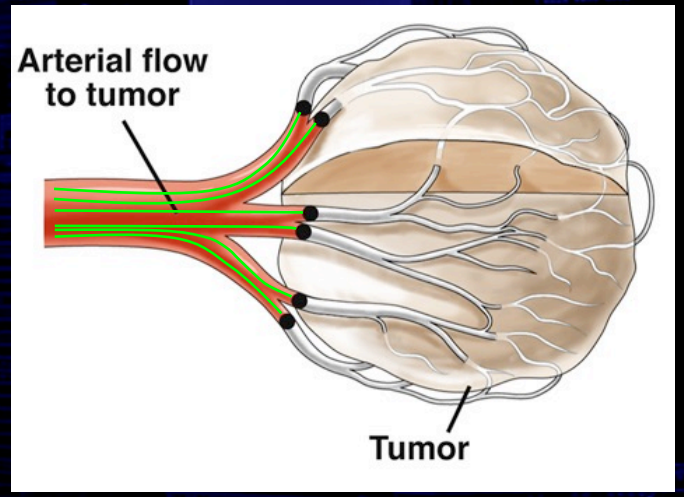
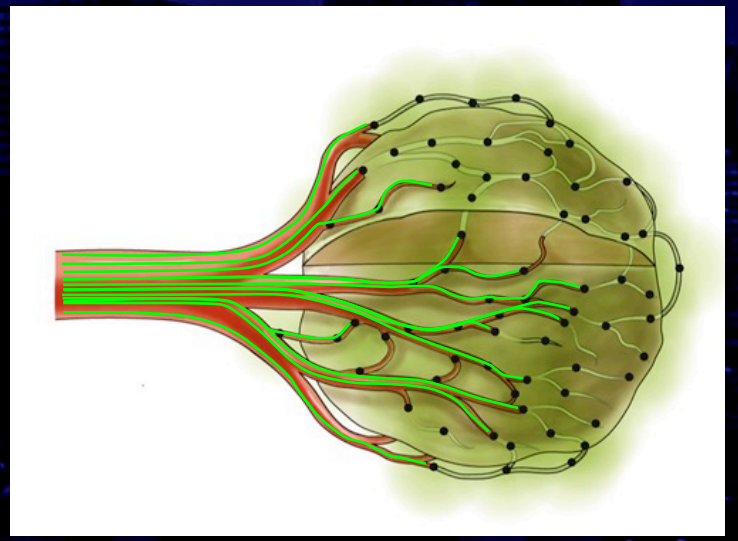
Transarterial Therapies

ARTERIAL EMBOLIZATION



Disruption of tumor blood supply resulting in tumor ischemia/hypoxia

RADIOEMBOLIZATION



Delivery of β–emitting microspheres that provide local, high dose tumor radiation

Salem R et al. *Gastroenterology*. 2010;138:52-64.

Sato K et al. *Cardiovasc Intervent Radiol.* 2006;29(4):522-529.

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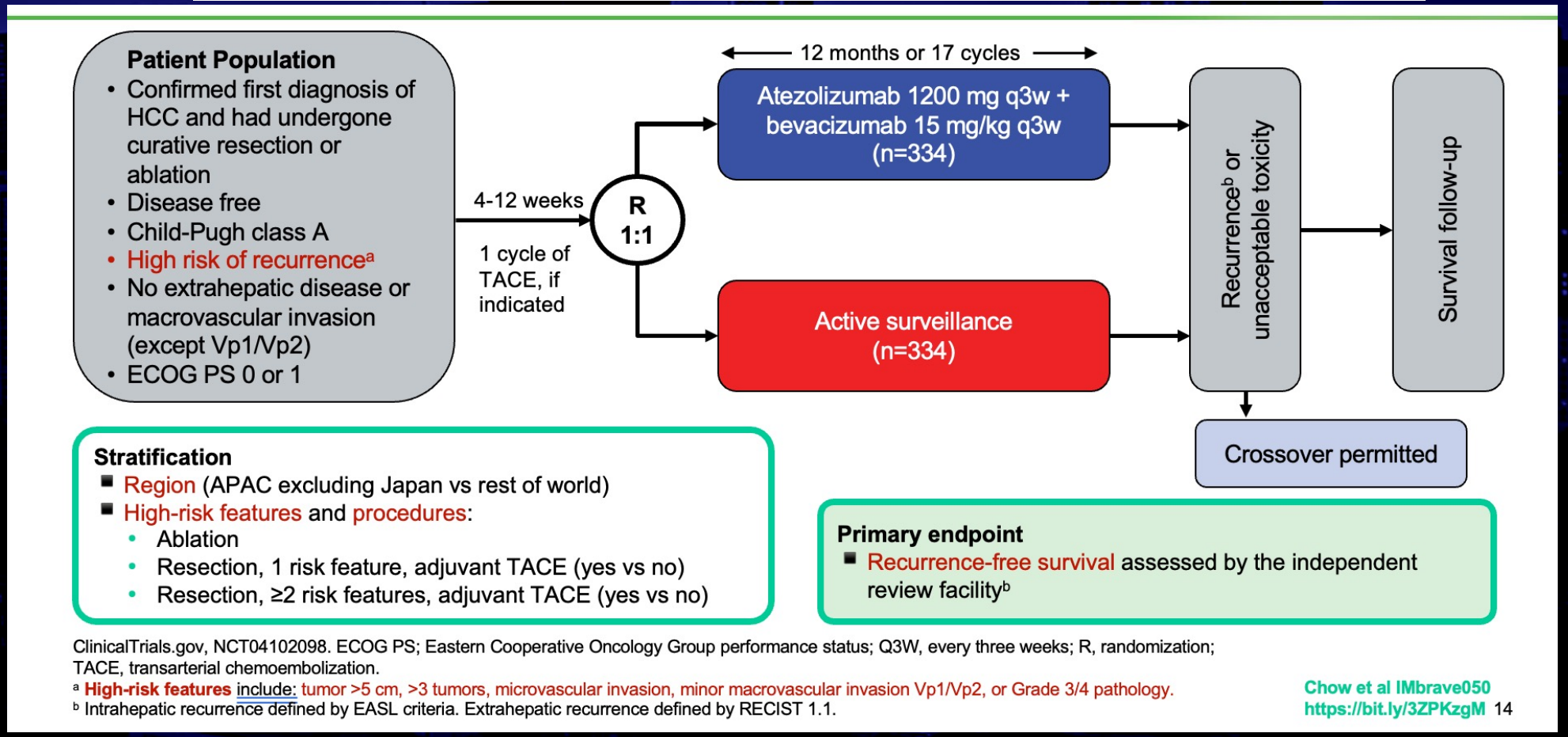
Summary of recent studies with Radiation Segmentectomy

RadSeg Study	Tumor Size (median)	Treated Volume (Median)	Median Dose (Perfused)	ORR% (CR%)	TTP	PFS	Grade ≥ 3 Toxicity (%)
RASER E Kim et al.	≤ 3 cm	153.6 mL	584 Gy	100% (90%)	Not reached	-	0
LEGACY Salem et al.	2.7 cm (1.0-8.1)	155 mL (19-1363)	410.1 Gy	88% (84%)	Not reached	40.7 mo	1.9%
Radseg vs resect De la Garza-Ramos et al.	2.5 cm	169 mL	361 Gy	98% (87%)	Not reached	-	1%
Radseg Intensification Montazeri et al.	2.3 cm (intensification)	250 mL	536 Gy	100% (89%)	-	-	-
RadSeg vs MWA Arndt et al.	≤ 4 cm	-	225.3 Gy to tumor	88% (88%)	57.8 mo (target)	59 mo (target)	9.1%
Boosted Y90 Large HC Kim et al.	7.6 cm	883 mL	241.6 Gy	100% (80%)	-	94.1% @ 1 yr local	0%
RadSeg vs sel TACE Padia et al.	3.2 cm	-	>200 Gy	97% (92%)	-	18.5 mo	3%
RS before transplant Toskich et al.	2.3 cm	175 mL	314 Gy	92% (76%)	-	-	0%

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

Shukui Qin*, Minshan Chen*, Ann-Lii Cheng*, Ahmed O Kaseb*, Masatoshi Kudo*, Han Chu Lee*, Adam C Yopp*, Jian Zhou, Lu Wang, Xiaoyu Wen, Jeong Heo, Won Young Tak, Shinichiro Nakamura, Kazushi Numata, Thomas Uguen, David Hsiehchen, Edward Cha, Stephen P Hack, Qinshu Lian, Ning Ma, Jessica H Spahn, Yulei Wang, Chun Wu, Pierce K H Chow*, for the IMbrave050 investigators†



ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; R, randomization; TACE, transarterial chemoembolization.

[a] **High-risk features** include: tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology.

[b] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.

Chow et al IMbrave050
https://bit.ly/3ZPKzgM 14

Qin et al. Lancet. 2023 Nov 18;402(10415):1835-1847. Kudo et al. ASCO 2023;Abstract 4002.

High Risk criteria by curative treatment

Curative treatment	Criteria for high risk of HCC recurrence
Resection	≤3 tumors, with **largest tumor >5 cm** regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) **≥4 tumors**, with largest tumor ≤5 cm regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) ≤3 tumors, with largest tumor ≤5 cm with **vascular invasion**,[a] and/or **poor tumor differentiation** (Grade 3 or 4)
Ablation[b]	1 tumor >2 cm but ≤5 cm Multiple tumors (≤4 tumors), all ≤5 cm

[a] Microvascular invasion or minor macrovascular portal vein invasion of the portal vein—Vp1/Vp2.
[b] Ablation must be radiofrequency ablation or microwave ablation.

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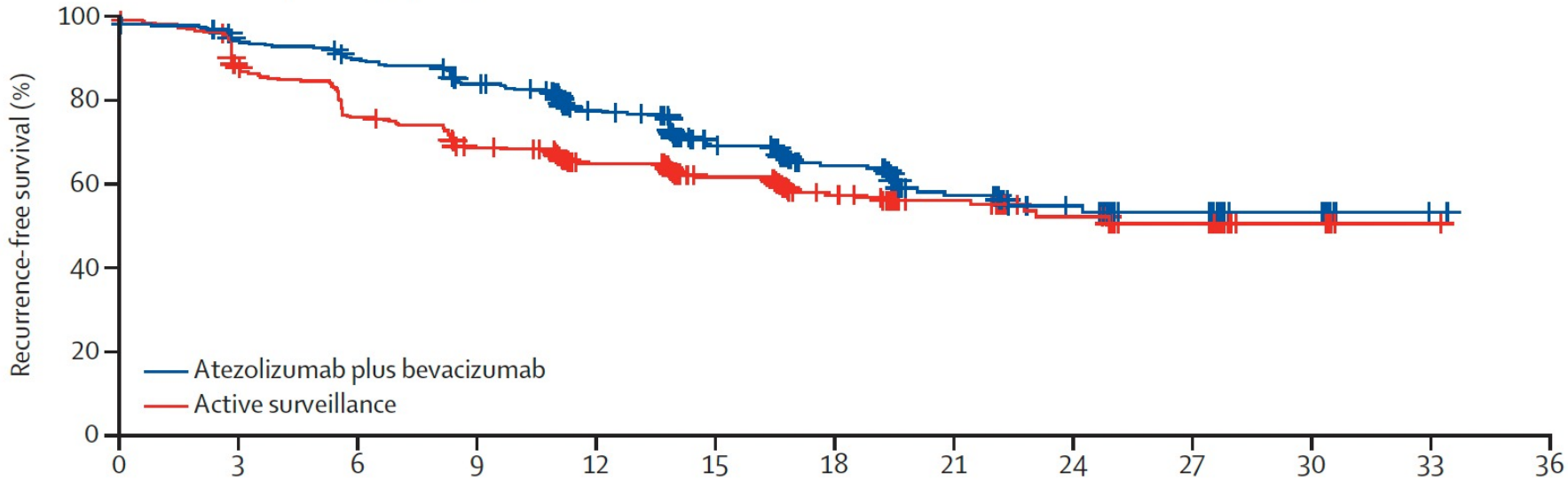
Primary endpoint: IRF RFS significantly improved with atezo/bev vs active surveillance

A

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)	
Patients with events, n (%)	110 (33%)	133 (40%)	
Median RFS, months (95% CI)	NE (22·1–NE)	NE (21·4–NE)	
12-month IRF-RFS event-free rate, % (95% CI)	78% (73–82)	65% (60–71)	
Stratified hazard ratio (adjusted 95% CI)			0·72 (0·53–0·98)
p value (log rank)			0·012



Number at risk (number censored)													
Atezolizumab plus bevacizumab	334 (0)	305 (10)	290 (12)	268 (15)	211 (53)	139 (105)	97 (139)	63 (164)	37 (188)	22 (202)	9 (215)	1 (223)	NE (NE)
Active surveillance	334 (0)	283 (12)	245 (12)	214 (20)	179 (44)	131 (84)	93 (114)	57 (148)	36 (166)	20 (181)	6 (195)	1 (200)	NE (NE)

Qin et al. Lancet. 2023 Nov 18;402(10415):1835-1847

Safety/Toxicities

	Atezolizumab plus bevacizumab (n=332)			Active surveillance (n=330)		
	Any grade	Grade 3 or 4	Grade 5	Any grade	Grade 3 or 4	Grade 5
Any adverse event	326 (98%)	136 (41%)	6 (2%)	205 (62%)	44 (13%)	1 (<1%)
Related adverse event	293 (88%)	116 (35%)	2 (<1%)	NA	NA	NA
Serious adverse event	80 (24%)	53 (16%)	6 (2%)	34 (10%)	26 (8%)	1 (<1%)
Related serious adverse event	44 (13%)	32 (10%)	2 (<1%)	NA	NA	NA
Adverse event leading to withdrawal from both atezolizumab and bevacizumab	29 (9%)	23 (7%)	0	NA	NA	NA
Adverse event leading to withdrawal from atezolizumab	31 (9%)	24 (7%)	0	NA	NA	NA
Adverse event leading to withdrawal from bevacizumab	62 (19%)	38 (11%)	0	NA	NA	NA

	Atezolizumab plus bevacizumab (n=332)			Active surveillance (n=330)		
	Any grade	Grade 3 or 4	Grade 5	Any grade	Grade 3 or 4	Grade 5
Adverse events (of any grade) with an incidence rate of at least 10% in either treatment group by preferred term						
Proteinuria	154 (46%)	29 (9%)	0	12 (4%)	0	0
Hypertension	127 (38%)	61 (18%)	0	10 (3%)	3 (1%)	0
Platelet count decreased	66 (20%)	15 (5%)	0	22 (7%)	4 (1%)	0
Aspartate aminotransferase increased	52 (16%)	3 (1%)	0	18 (5%)	2 (1%)	0
Alanine aminotransferase increased	47 (14%)	2 (1%)	0	18 (5%)	3 (1%)	0
Hypothyroidism	47 (14%)	0	0	1 (<1%)	0	0
Arthralgia	40 (12%)	1 (<1%)	0	8 (2%)	1 (<1%)	0
Pruritus	40 (12%)	1 (<1%)	0	3 (1%)	0	0
Rash	40 (12%)	0	0	1 (<1%)	0	0
Blood bilirubin increased	34 (10%)	1 (<1%)	0	23 (7%)	1 (<1%)	0
Pyrexia	34 (10%)	0	0	7 (2%)	0	0

Data are n (%). NA=not available.

Table 2: Safety summary for the safety-evaluable population

Qin et al. Lancet. 2023 Nov 18;402(10415):1835-1847

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IMbrave 050 conclusions

IMbrave050 is the first Phase 3 study of adjuvant treatment for HCC to demonstrate RFS improvement following curative intent resection or ablation

At the **prespecified interim analysis**, adjuvant atezolizumab + bevacizumab met its **primary endpoint** and showed a statistically significant and clinically meaningful improvement in IRF-assessed RFS vs active surveillance in patients with a high risk of HCC recurrence (HR, 0.72; 95% CI: 0.56, 0.98; *P*=0.012)

RFS benefit with atezolizumab + bevacizumab was **generally consistent across key clinical subgroups**

The **safety profile** of adjuvant atezolizumab + bevacizumab was generally consistent with that of each agent and with the underlying disease

Atezolizumab + bevacizumab may benefit patients with high-risk HCC as adjuvant treatment

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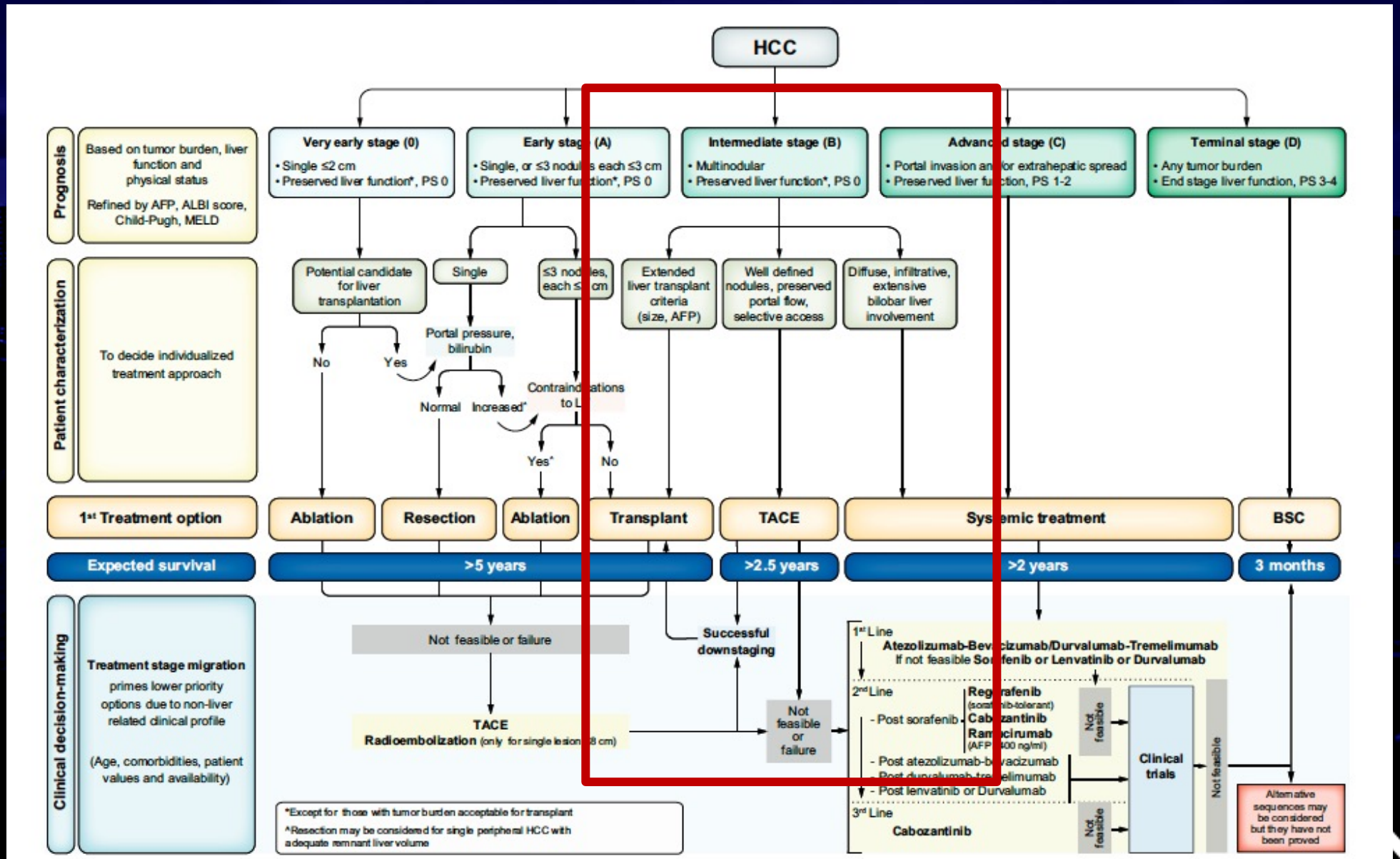
BCLC staging and treatment strategy



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Conventional Chemoembolization (cTACE, lipiodol TACE)

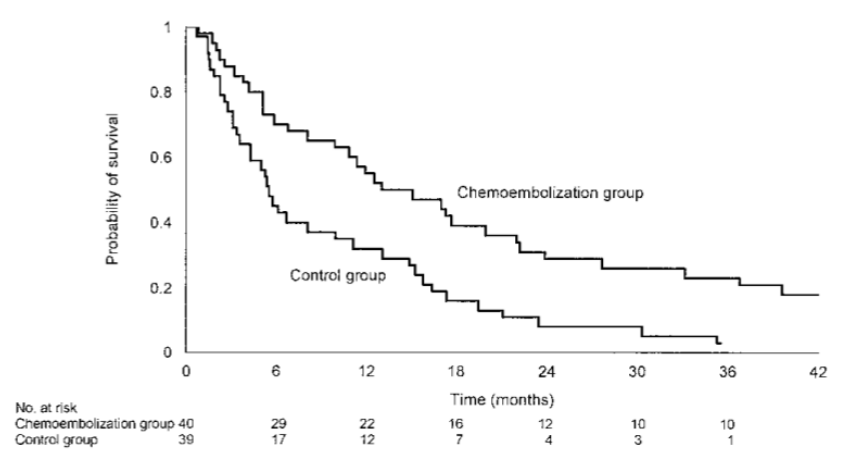


Fig. 2. Probability of survival in patients treated with chemoembolization and in patients of the control group (log-rank test, $P = .002$).

Lo et al. HEPATOLOGY, Vol. 35, No. 5, 2002

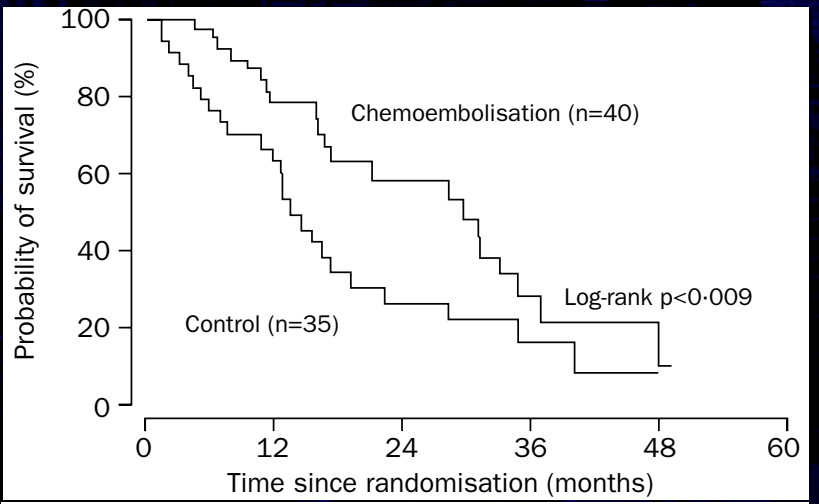
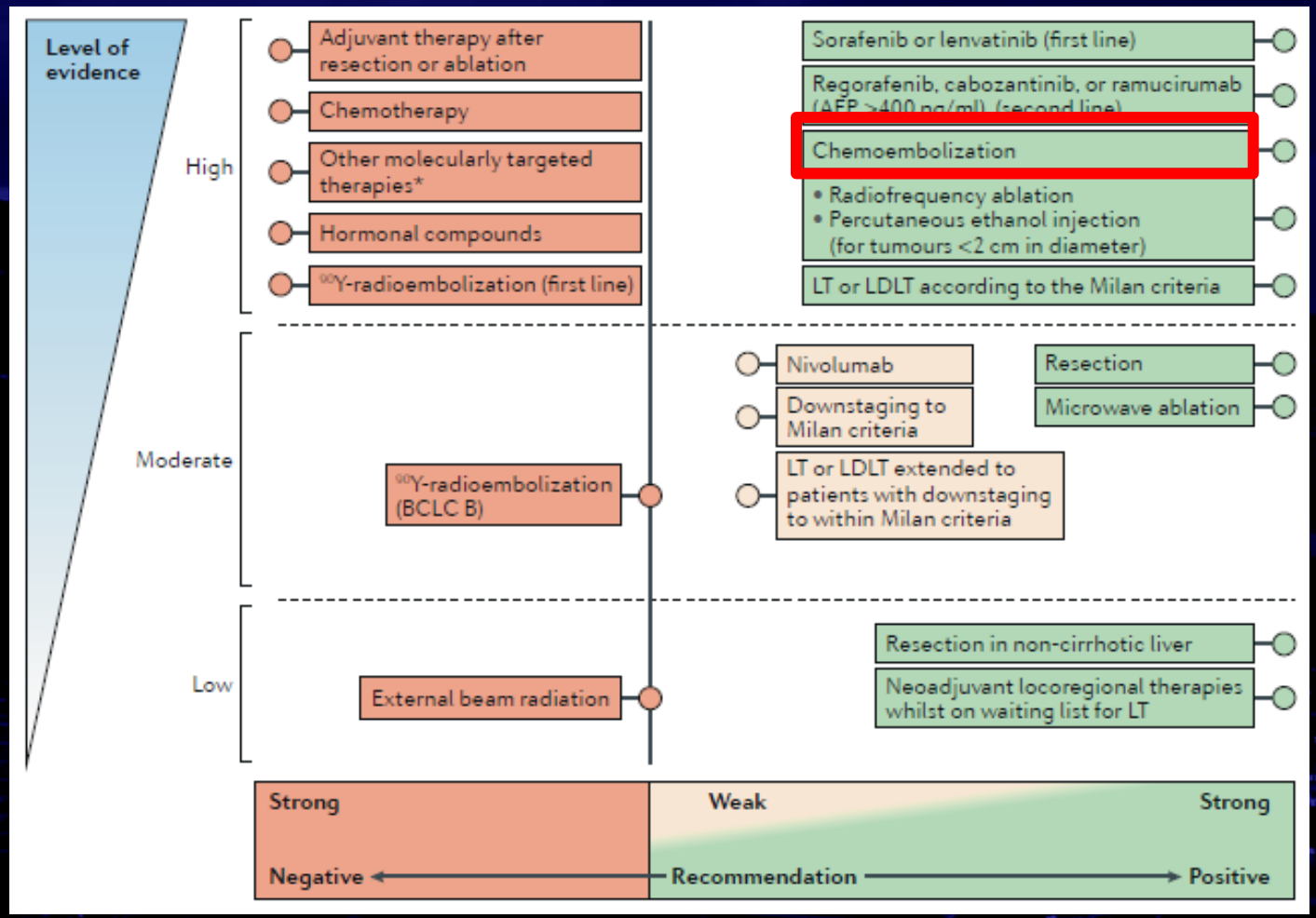


Figure 3: **Survival curves of the chemoembolisation and control groups**

Llovet et al. THE LANCET • Vol. 359 • May 18, 2002



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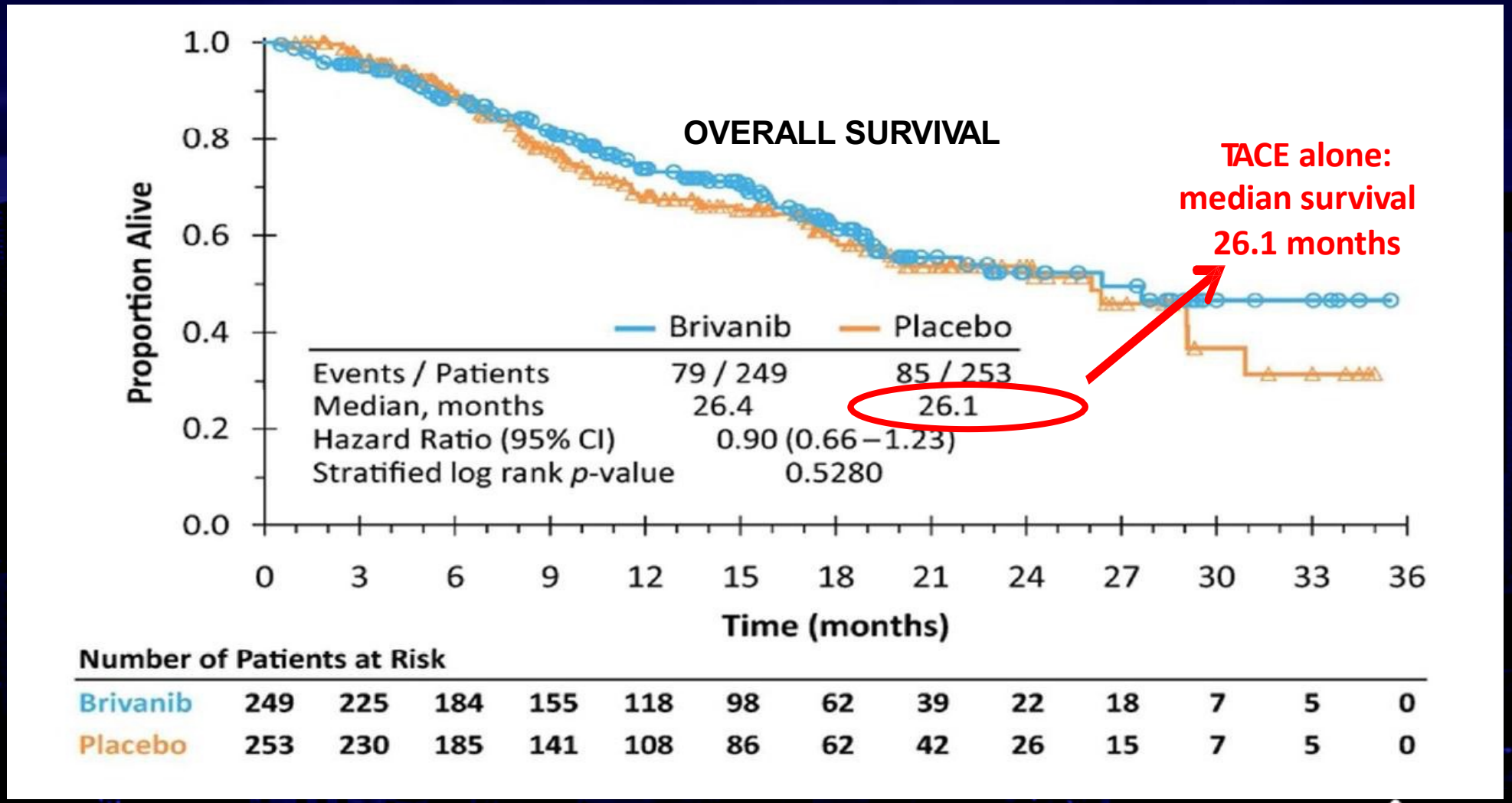
Brivanib as Adjuvant Therapy to TACE: A Phase III Randomized Controlled Clinical Trial



Kudo M et al. Hepatology 2014;60:697-707

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Negative Transarterial Trials +/- systemic therapy

Table 2 | **Outcomes of randomized controlled trials assessing intra-arterial therapies in HCC, 2009–2019**

Randomized controlled trial	Region	Experimental arms	End points	Outcomes	Ref.
Chemoembolization					
Okusaka et al. 2009	Japan	TAI (n = 82) vs cTACE (n = 79)	OS	22.3 months vs 21.2 months; P = 0.383	115
Kudo et al. 2011 (Post-TACE trial)	Japan, South Korea	cTACE (responders) plus sorafenib (n = 229) vs cTACE plus placebo (n = 229)	TTP[b]	5.4 months vs 3.7 months; HR 0.87 (95% CI 0.70–1.09); P = 0.252	116
Yu et al. 2014	China	TEA (n = 49) vs cTACE (n = 49)	OS	24.3 months vs 20.1 months; P = 0.513	117
Golfieri et al. 2014 (PRECISION ITALIA trial)	Italy	DEB-TACE (n = 89) vs cTACE (n = 88)	OS (2 years)	56.8% vs 55.4%; P = 0.949	118
Kudo et al. 2014 (BRISK-TA trial)	Global	cTACE or DEB-TACE plus brivanib (n = 249) vs cTACE plus placebo (n = 253)	OS	26.4 months vs 26.1 months; HR 0.90 (95% CI 0.66–1.23); P = 0.53	23
Lencioni et al. 2016 (SPACE trial)	Global	DEB-TACE plus sorafenib (n = 154) vs DEB-TACE plus placebo (n = 153)	TTP	5.6 months vs 5.5 months; HR 0.797 (95% CI 0.588–1.080); P = 0.072	22
Meyer et al. 2017 (TACE 2 trial)	UK	DEB-TACE plus sorafenib (n = 157) vs DEB-TACE plus placebo (n = 156)	PFS	7.8 months vs 7.7 months; HR 1.03 (95% CI 0.75–1.42); P = 0.85	21
Kudo et al. 2018 (ORIENTAL trial)	Japan, South Korea, Taiwan	cTACE plus orantinib (n = 445) vs cTACE plus placebo (n = 444)	OS	31.1 months vs 32.3 months; HR 1.090 (95% CI 0.878–1.352); P = 0.435	119
Ikeda et al. 2018	Japan	cTACE with miriplatin (n = 129) vs cTACE with epirubicin (n = 128)	OS	36.5 months vs 37.1 months; HR 1.01 (95% CI 0.73–1.40); P = 0.946	120
Kudo et al. 2019 (TACTICS trial)	Japan	cTACE plus sorafenib (n = 80) vs cTACE (n = 76)	mPFS[c]	25.2 months vs 13.5 months; HR 0.59 (95% CI 0.41–0.87); P = 0.006	121
Park et al. 2019 (STAH trial)[a]	South Korea	cTACE plus sorafenib (n = 170) vs sorafenib (n = 169)	OS	12.8 months vs 10.8 months; HR 0.91 (CI 0.69–1.21); P = 0.290	122
Transarterial radioembolization					
Salem et al. 2016	USA	TARE (n = 24) vs cTACE (n = 21)[d]	TTP	>26 months vs 6.8 months; HR 0.12 (95% CI 0.027–0.55); P = 0.001	127
Vilgrain et al. 2017 (SARAH trial)[a]	France	TARE (n = 237) vs sorafenib (n = 222)	OS	8 months vs 9.9 months; HR 1.15 (95% CI 0.94–1.41); P = 0.18	123
Chow et al. 2018 (SIRveNIB trial)[a]	Asia-Pacific	TARE (n = 182) vs sorafenib (n = 178)	OS	8.8 months vs 10.0 months; HR 1.12 (95% CI 0.9–1.4); P = 0.36)	124
Ricke et al. 2019 (SORAMIC trial)[a]	Europe, Turkey	TARE plus sorafenib (n = 216) vs sorafenib (n = 208)	OS	12.1 months vs 11.4 months; HR 1.01 (95% CI 0.81–1.25); P = 0.95	125
Intra-arterial chemotherapy					
Kudo et al. 2018 (SILIUS trial)[a]	Japan	HAIC plus sorafenib (n = 102) vs sorafenib (n = 103)	OS	11.8 months vs 11.5 months; HR 1.009 (95% CI 0.743–1.371); P = 0.95	126

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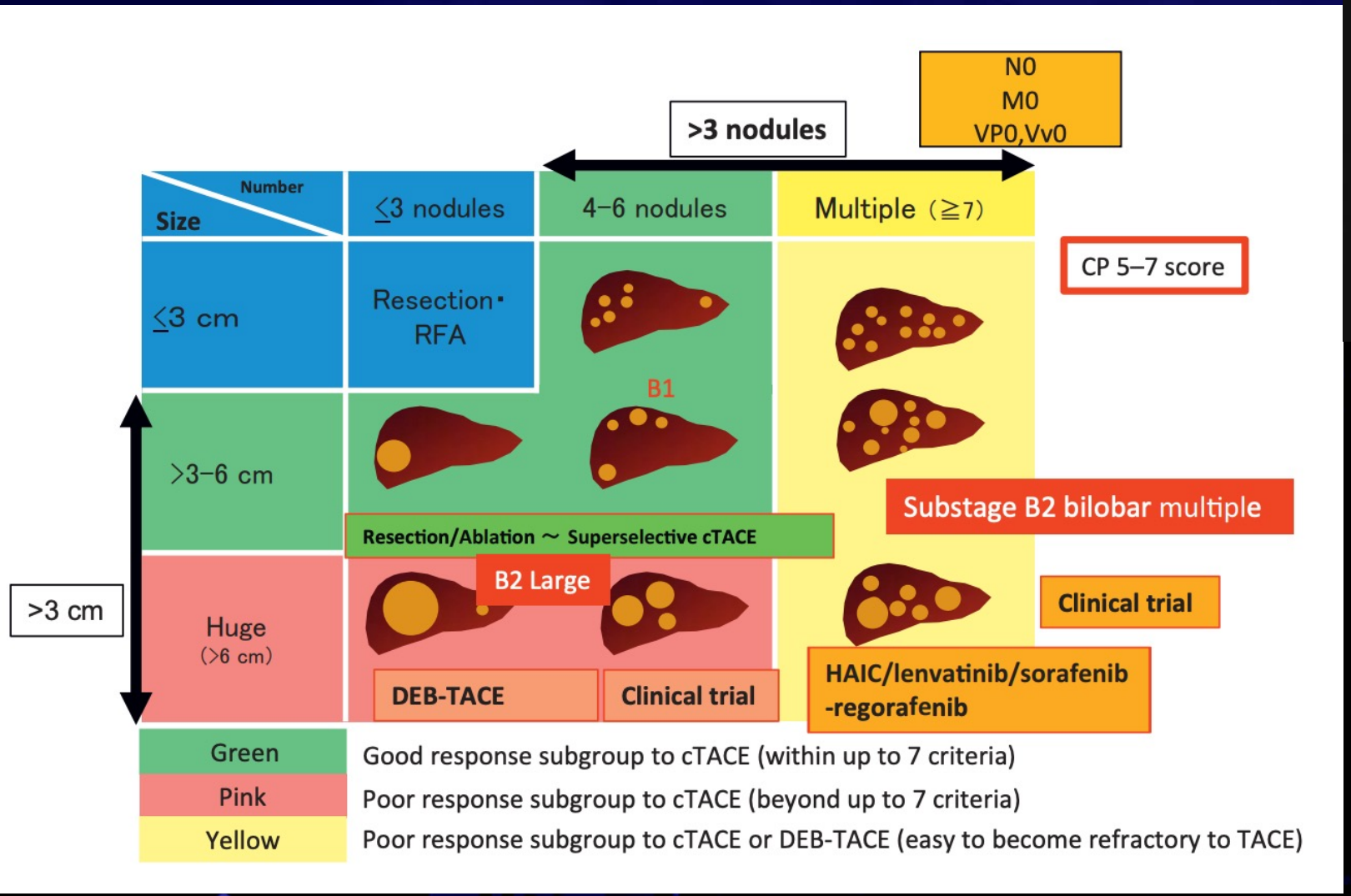
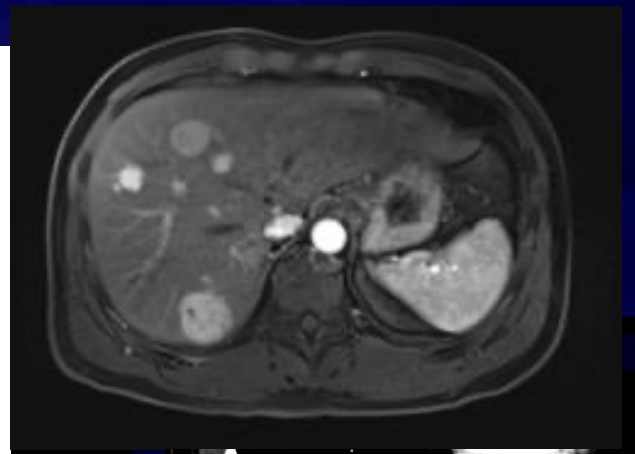
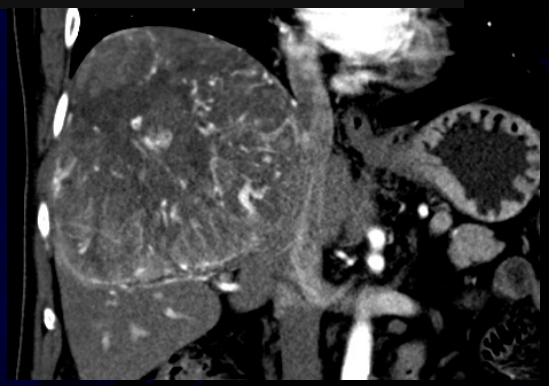
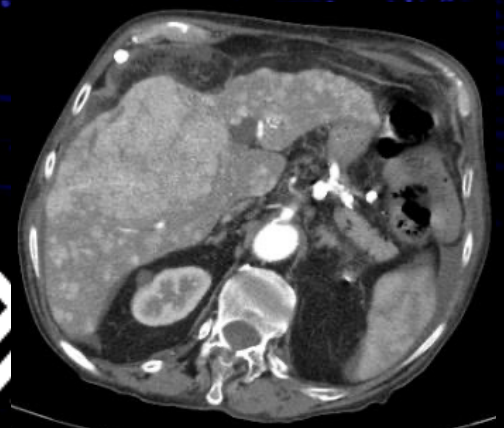
Heterogeneity and treatment strategy for intermediate-stage HCC









Kudo M. *Liver Cancer*. 2017;6:177-184.

EMERALD-1:
Durvalumab and TACE With or Without Bevacizumab

NCT03778957: Phase 3, Randomized, Double-blind, Placebo-controlled Study[1]

(N=724)[1]

Key Inclusion Criteria:[1]

- No evidence of extrahepatic disease
- Disease not amenable to curative surgery or transplantation or curative ablation, but disease amenable to TACE
- Child-Pugh class A to B7
- ECOG PS of 0 or 1
- Measurable disease by mRECIST criteria

Key Exclusion Criteria:[1]

- Any history of nephrotic or nephritic syndrome
- Clinically significant cardiovascular disease or history of arterioembolic event within 6 months prior to randomization
- Any prior or current evidence of coagulopathy or bleeding diathesis or patients who had any kind of surgery in the past 28 days (biopsies are exempt from this exclusion)
- History of abdominal fistula or GI perforation, nonhealed gastric ulcer that is refractory to treatment, or active GI bleeding within 6 months prior to enrollment
- Patients with Vp3 and Vp4 portal vein thrombosis on baseline imaging are excluded

Status: Active, not recruiting[1]

Randomization 1:1:1

ARM A[3]
TACE (DEB-TACE or cTACE) + Durvalumab 1500 mg IV Q4W[a]
Followed by:
Durvalumab 1120 mg IV Q3W **+ Placebo IV**

ARM B[3]
TACE (DEB-TACE or cTACE)+ Durvalumab 1500 mg IV Q4W[a]
Followed by:
Durvalumab 1120 mg IV **+ Bevacizumab** 15 mg/kg IV Q3W[b]

ARM C[3]
TACE (DEB-TACE or cTACE)
Followed by:
Placebo IV **+ Placebo** IV

Primary Outcome Measures:[1,2]

- PFS* (Arm B vs C)

Secondary Outcome Measures:[1,2]

- PFS¥ (Arm A vs C)
- OS
- QOL metrics
- PFS (by BICR using mRECIST)
- TTP, ORR, DoR, and DCR
- Safety

¥Assessed per BICR per RECIST 1.1

Stratification:

- Geographic region (Japan vs Asia [non-Japan] vs Other)
- Portal vein invasion (Vp1 or Vp2+/- Vp1)[3]
- TACE modality (DEB-TACE vs cTACE)

a: Durvalumab therapy will begin after at least 7 days following the initial TACE procedure.
b: Durvalumab +/- bevacizumab will begin after at least 14 days following the last TACE procedure

BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Group Performance Status; IV, intravenously; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q4W, every 4 weeks; QOL, quality of life; RECIST 1.1, Response Evaluation Criteria for Solid Tumors version 1.1; TACE, transarterial chemoembolization; TTP, time to progression.

1. ClinicalTrials.gov identifier: NCT03778957. Accessed September 2023. 2. Sangro B, et al. Ann Oncol. 2020; 31 (Suppl3): S202-S203. 3. Kudo M. Liver Cancer. 2019;8(4):221-238. doi:10.1159/000501501

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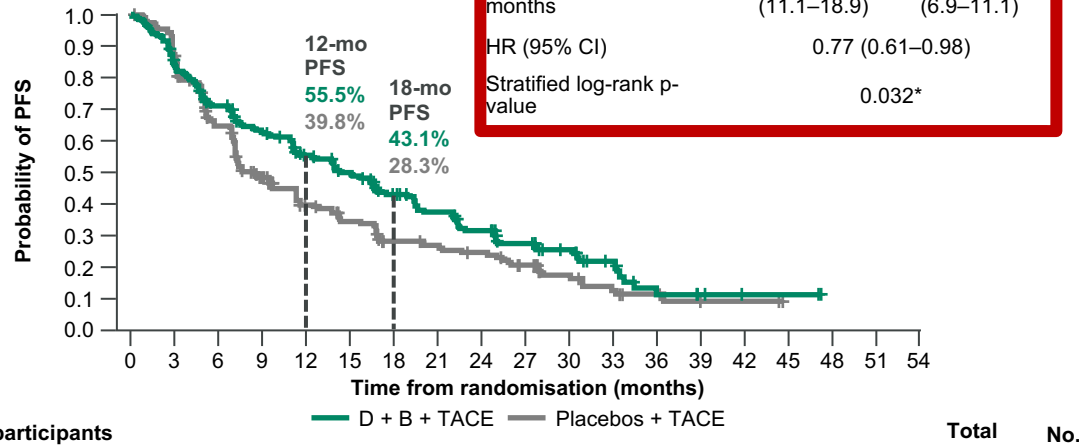
PFS with D + B + TACE versus placebos + TACE (RECIST 1.1 vs mRECIST)

PFS assessed by BICR per RECIST v1.1

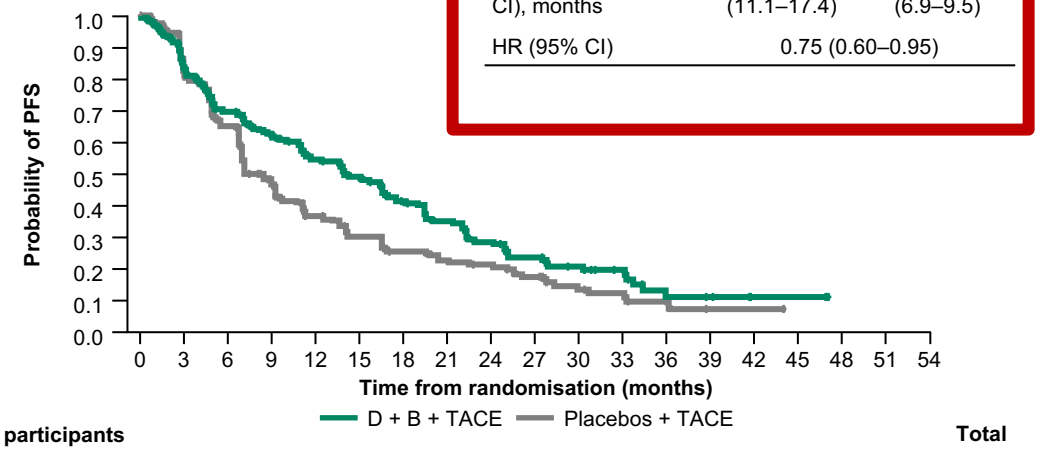
	D + B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	



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

PFS assessed by BICR per mRECIST

	D + B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	14.2 (11.1–17.4)	8.2 (6.9–9.5)
HR (95% CI)	0.75 (0.60–0.95)	



No. of participants at risk																				Total events
D + B + TACE	204	161	132	114	93	80	61	50	39	28	20	14	6	4	2	2	0	0	0	139
Placebos + TACE	205	159	122	81	58	46	37	32	29	22	13	9	4	1	1	0	0	0	0	154

Median (range) duration of follow-up in censored participants as assessed by BICR per RECIST v1.1, 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.
Median (range) duration of follow-up in censored participants as assessed by BICR per mRECIST, D + B + TACE 16.5 (0.03–47.1) months, placebos + TACE 9.2 (0.03–44.0) months.
*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; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolisation.

Sangro B, et al. Presented at EASL Liver Cancer Summit 2024. 22–24 February; Rotterdam, Netherlands.

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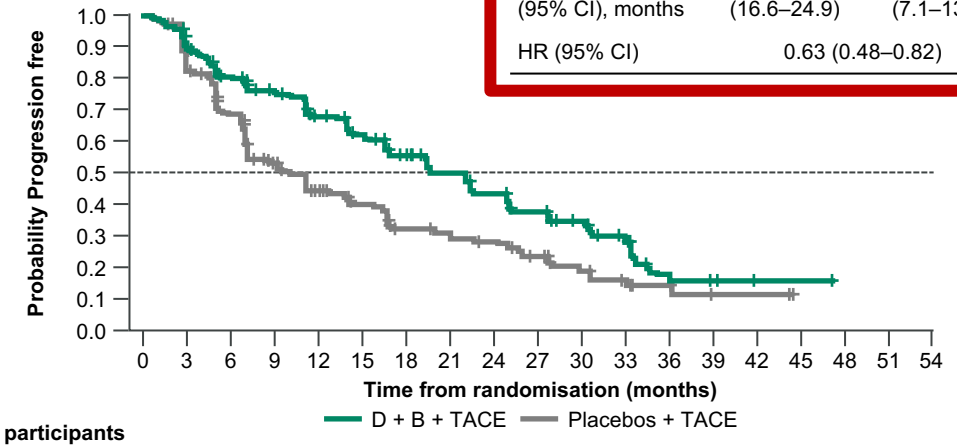
TTP with D + B + TACE versus placebos + TACE (RECIST 1.1 vs mRECIST)

TTP assessed by BICR per RECIST v1.1

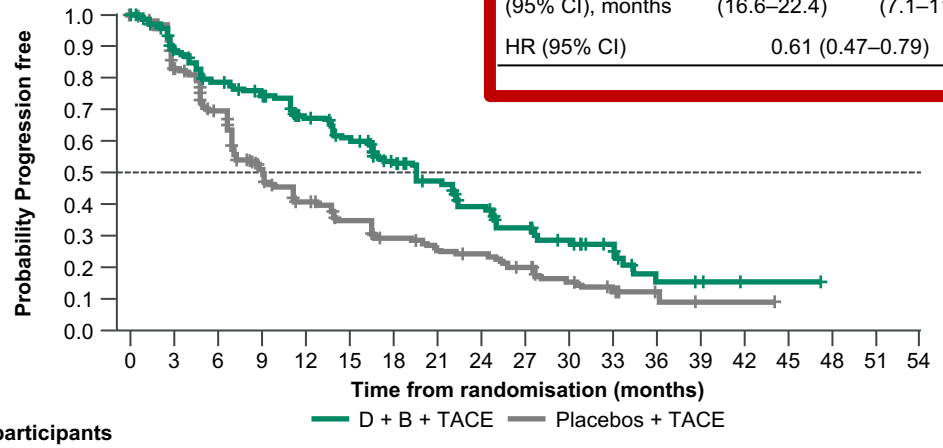
	D + B + TACE (n=204)	Placebos + TACE (n=205)
Median TTP (95% CI), months	22.0 (16.6–24.9)	10.0 (7.1–13.6)
HR (95% CI)	0.63 (0.48–0.82)	



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	99
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	132

TTP assessed by BICR per mRECIST

	D + B + TACE (n=204)	Placebos + TACE (n=205)
Median TTP (95% CI), months	19.4 (16.6–22.4)	9.2 (7.1–11.1)
HR (95% CI)	0.61 (0.47–0.79)	



No. of participants at risk																			Total events
D + B + TACE	204	161	132	114	93	80	61	50	39	28	20	14	6	4	2	2	0	0	0	102
Placebos + TACE	205	159	122	81	58	46	37	32	29	22	13	9	4	1	1	0	0	0	0	137

B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolisation; TTP, time to progression.

Sangro B, et al. Presented at EASL Liver Cancer Summit 2024. 22–24 February; Rotterdam, Netherlands.

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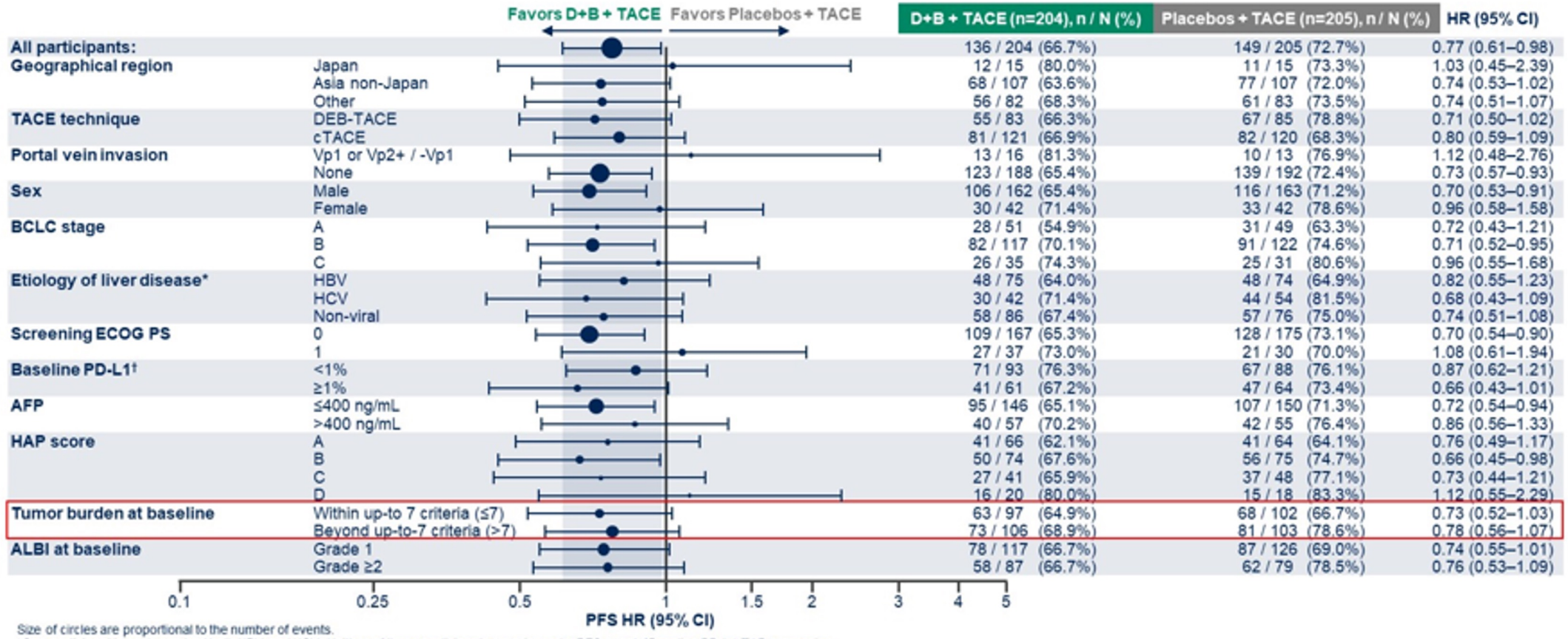
PFS with D+B + TACE versus placebo + TACE in key subgroups

PFS benefit was 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.

Lencioni R et al. ASCO GI 2024;Abstract LBA432.

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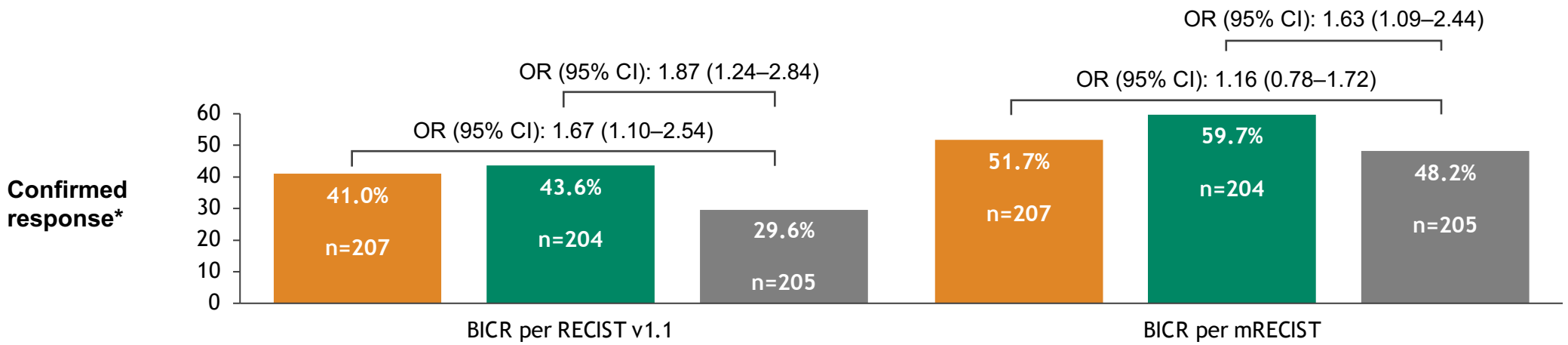
ORR (RECIST 1.1 vs mRECIST)



Participants with measurable disease at baseline	D + TACE (n=205)	D + B + TACE (n=202)	Placebos + TACE (n=203)	D + TACE (n=205)	D + B + TACE (n=201)	Placebos + TACE (n=199)
Complete response, n (%)	**3 (1.5)**	**6 (3.0)**	**5 (2.5)**	**51 (24.9)**	**61 (30.3)**	**42 (21.1)**
Partial response, n (%)	81 (39.5)	82 (40.6)	55 (27.1)	55 (26.8)	59 (29.4)	54 (27.1)
Stable disease ≥20 weeks, n (%)	42 (20.5)	45 (22.3)	63 (31.0)	17 (8.3)	10 (5.0)	26 (13.1)
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)	10.8 (6.4-26.4)	17.4 (11.1-30.9)	11.3 (5.7-24.8)

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

Sangro B, et al. Presented at EASL Liver Cancer Summit 2024. 22–24 February; Rotterdam, Netherlands.

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EMERALD-1 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

Lencioni R et al. ASCO GI 2024;Abstract LBA432.

Mount Sinai

EMERALD-1 safety: G3-4 TEAEs

AE, n (%)	D + TACE (n=232)	D+B + TACE (n=154)	Placebos + TACE (n=200)
Hypertension	5 (2.2)	9 (5.8)	1 (0.5)
Anemia	10 (4.3)	7 (4.5)	3 (1.5)
Acute kidney injury	4 (1.7)	6 (3.9)	0
Proteinuria	0	6 (3.9)	0
Post-embolization syndrome	8 (3.4)	5 (3.2)	8 (4.0)
Hepatic encephalopathy	1 (0.4)	5 (3.2)	3 (1.5)
Ascites	4 (1.7)	4 (2.6)	3 (1.5)
Hyponatremia	1 (0.4)	4 (2.6)	0
Esophageal varices hemorrhage	0	4 (2.6)	1 (0.5)

AEs occurring in ≥2% of participants by preferred term in any arm.
AE, adverse event; B, bevacizumab; D, durvalumab; TACE, transarterial chemoembolization; TEAE, treatment-emergent adverse event.

Lencioni R et al. ASCO GI 2024;Abstract LBA432.

Mount Sinai

Ongoing Combination Trials

RCT	Experimental Arm	Endpoint
LEAP-012	TACE vs TACE + Pembrolizumab/Lenvatinib	PFS per RECIST OS
EMERALD-3	TACE vs TACE + Durvalumab/Tremelimumab +/- Lenvatinib	PFS per RECIST (BICR)
EMERALD-Y90	TARE + Durvalumab/Bevacizumab	PFS per mRECIST
ROWAN	TARE + Durvalumab/Tremelimumab	ORR per mRECIST
REPLACE (formerly RENOTACE)	TACE/TARE vs Regorafenib + Pembrolizumab	PFS per mRECIST
KEYNOTE-937	Adjuvant Pembrolizumab vs placebo post resection or CR post-ablation	RFS OS

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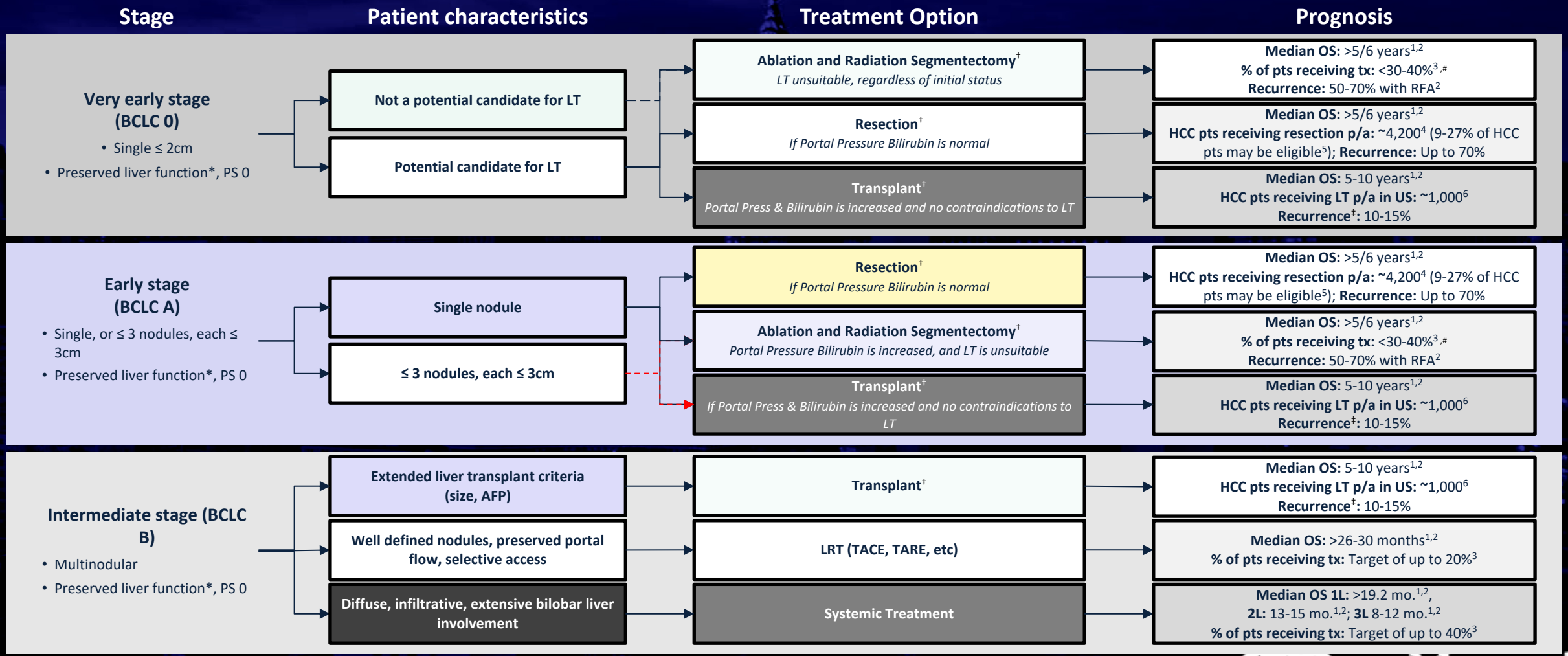
BCLC: HCC Treatment Pathways



Source(s): 1. Reig, Maria, et al. (2022) Journal of hepatology; 2. Llovet, J.M. et al. (2021) Nature Reviews Disease Primers; 3. EASL-EORTC Clinical Practice Guidelines 2012; 4. Gani, F. et al. (2019) HPB; 5. Yao, W. et al. (2020) Frontiers in Oncology; 6. OPTN/SRTR 2021 Annual data report

Note(s): *Except for those with tumor burden acceptable for LT; †If treatment fails or is deemed no longer feasible, TACE is used, followed by Systemic Treatment options; ‡Recurrence over a 5-year period; #Estimated that entirety of curative treatment options (LT, Resection and Ablation) account for up to 30-40% of patients

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Early and Intermediate HCC Management

- Liver Transplantation and Resection remain best “curative” treatment modalities
- BCLC A:
  - Thermal Ablation best utilized for unresectable hepatocellular carcinoma < 3 cm
  - Alternative for thermal ablation benefit from radiation segmentectomy up to 8 cm
    - High ORR, CR and CPN correlation
  - LRT for Bridging Therapy for Transplantation benefits from long TTP
  - IMbrave050 demonstrates benefit of atezo/bev adjuvant therapy for high risk patients with curative treatment
    - Definition of high risk: poorly differentiated, microvascular invasion, elevated AFP, infiltrative appearance
- BCLC B:
  - TACE’s principle is based on occlusion of feeding tumor vessels with drug
  - TARE’s principle is based on seeding the tumor with radioactive spheres and maintaining blood flow and oxygenation to the target to potentiate the effects of radiation
  - Downstaging Therapy for Transplantation offers best chance at curative transplantation
- Thoughts:
  - Potential combination of TACE/TARE and Immune Checkpoint Inhibitors
    - EMERALD-1 demonstrates longer PFS when TACE is combined with Durva/Bev vs TACE +/- durvalumab
    - Safety profile of EMERALD-1 consistent with previously reported SAEs from systemic therapy

Mount Sinai

Agenda

Module 1: Recent Developments in the Management of Early- and Intermediate-Stage Hepatocellular Carcinoma (HCC) — Dr Kim

Module 2: First-Line Therapy for Advanced HCC and Biliary Tract Cancers (BTCs) — Prof Vogel

Module 3: Integration of Targeted Therapy into the Management of Advanced BTCs — Dr Kelley

Consulting Faculty Comments

Choosing between atezolizumab/bevacizumab and durvalumab/tremelimumab (STRIDE regimen) as first-line therapy for advanced HCC

Dr Warren Brenner
(Boca Raton, Florida)

Dr Erik Rupard
(St George, Utah)

Dr Kimberly Ku
(Bloomington, Illinois)

Dr Neil Morganstein
(Summit, New Jersey)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

For a patient with HCC who received adjuvant atezolizumab/bevacizumab or TACE combined with durvalumab/bevacizumab and experienced disease recurrence, would you rechallenge with another immune checkpoint inhibitor-based strategy later in the treatment course?

QUESTIONS FOR THE FACULTY

What first-line therapy would you typically recommend for an otherwise healthy patient with advanced HCC and Child-Pugh B7 cirrhosis?

Consulting Faculty Comments

Use of immunotherapy as part of standard therapy for patients with advanced BTCs with and without concomitant autoimmune conditions

Dr Neil Morganstein (Summit, New Jersey)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

For patients with advanced BTCs, are there any situations in which you would not add either durvalumab or pembrolizumab to up-front chemotherapy?

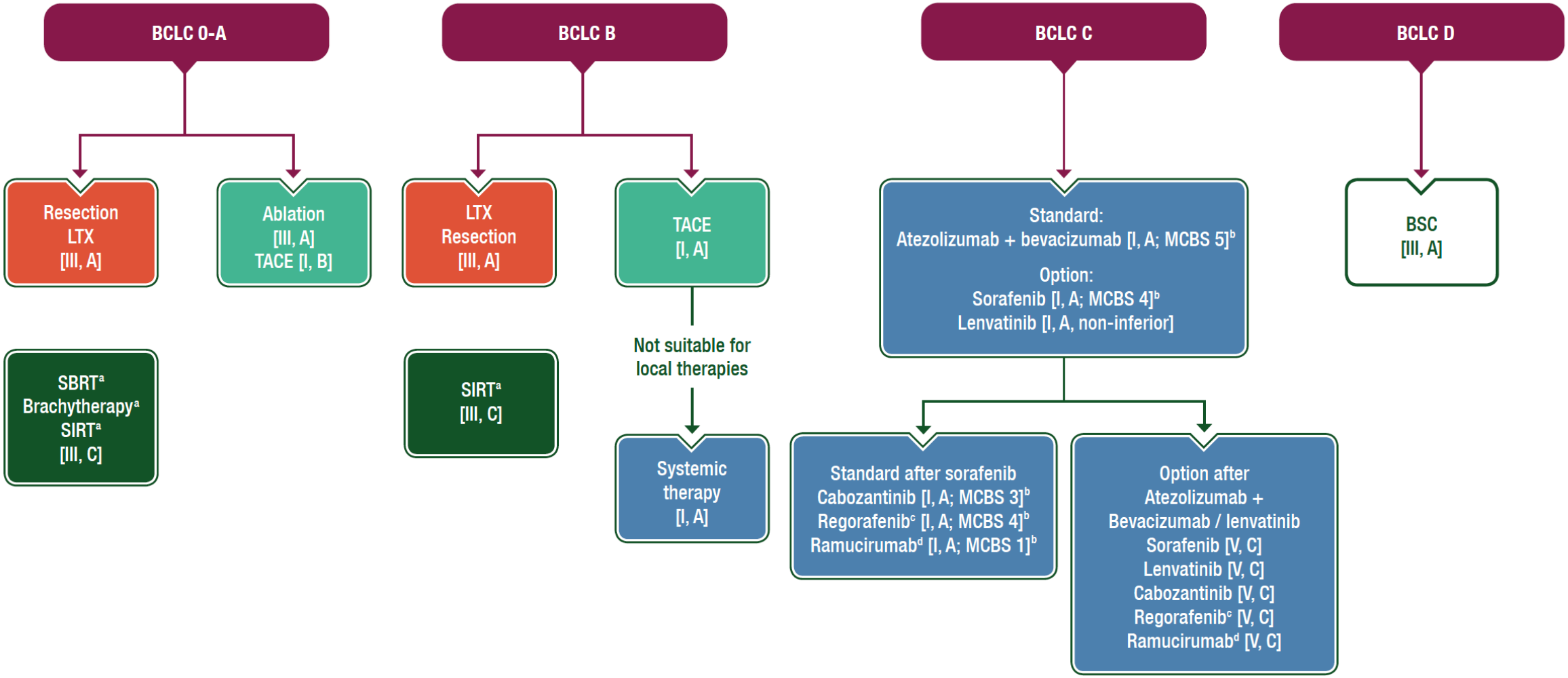
What first-line regimen do you generally employ for patients with actionable FGFR alterations?

First-Line Therapy for Advanced HCC and Biliary Tract Cancers (BTCs)

Arndt Vogel

Canada

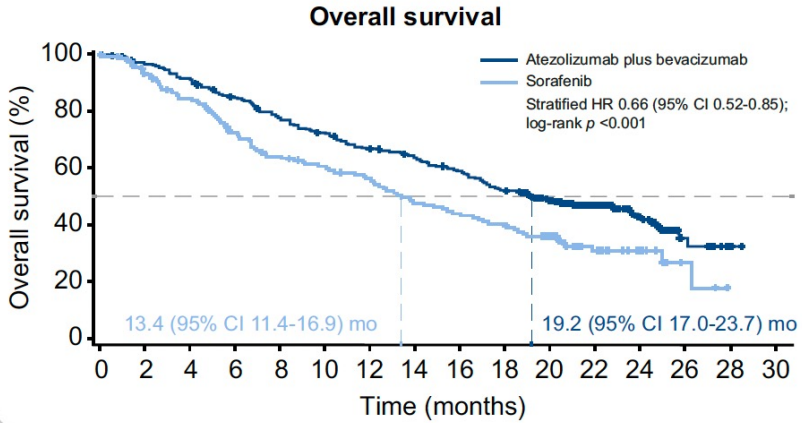
ESMO CLINICAL PRACTICE GUIDELINE HCC

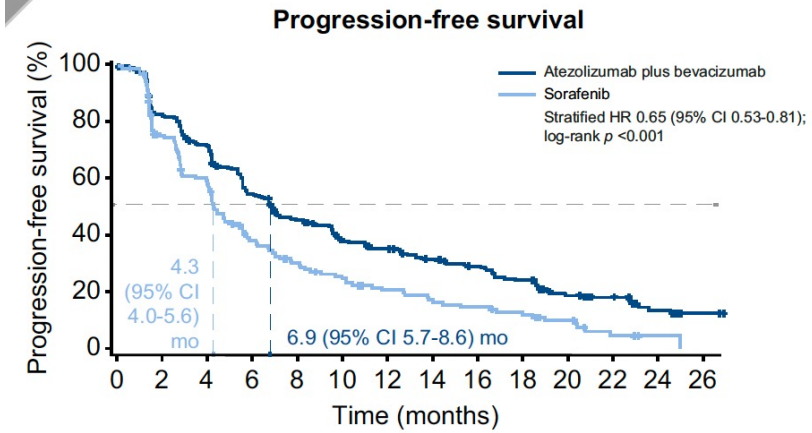


Vogel et al. ESMO CPG 2021, eUpdate

Efficacy of anti-PD-(L)1 & anti-VEGF ABs in 1st line phase III

IMbrave150

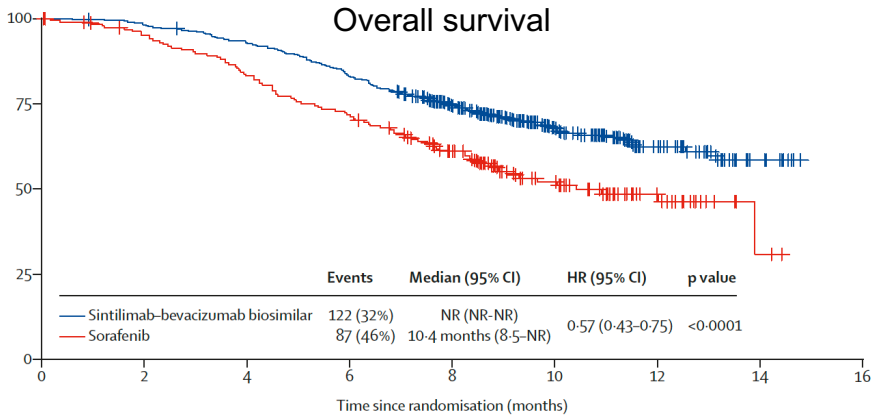


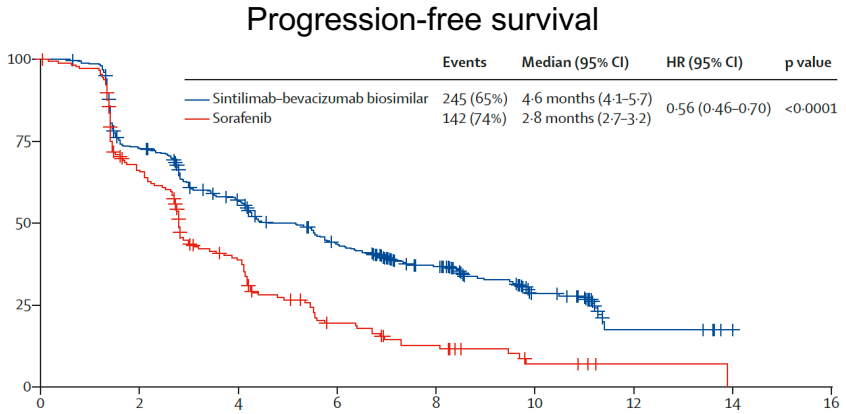


ORR: 30% vs 11%

Cheng AL et al., J Hepatol 2022

ORIENT-32



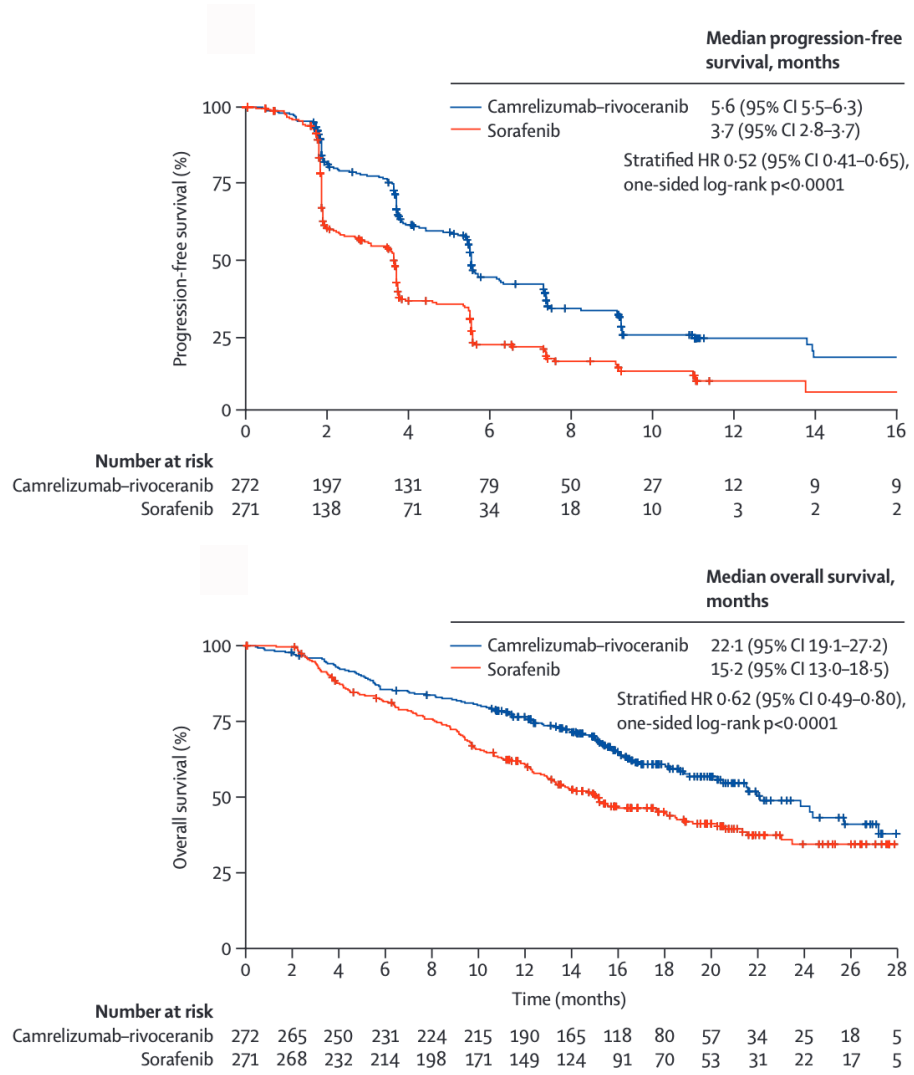


ORR: 21% vs 4%

Ren AL et al., Lancet Oncology 2021

Efficacy of anti-PD1 and VEGF-R TKI in first-line phase 3 trials

CARES-310: Camrelizumab + rivoceranib



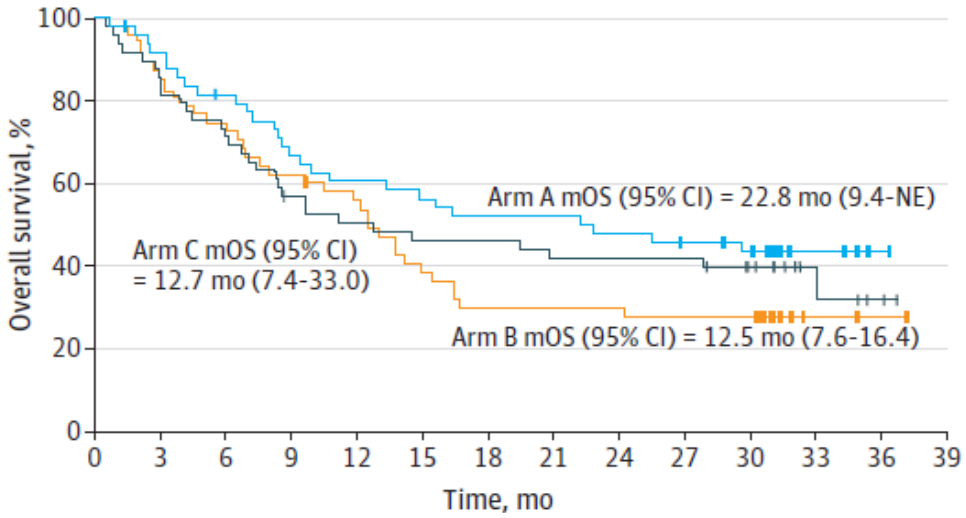
	Camrelizumab–rivoceranib (n=272)				Sorafenib (n=269)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-related adverse event	45 (17%)	193 (71%)	26 (10%)	1 (<1%)	128 (48%)	128 (48%)	12 (4%)	1 (<1%)
Hypertension	87 (32%)	100 (37%)	2 (1%)	0	76 (28%)	40 (15%)	0	0
Aspartate 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
Blood alkaline phosphatase increased	44 (16%)	3 (1%)	0	0	30 (11%)	3 (1%)	0	0
Conjugated blood bilirubin increased	34 (13%)	10 (4%)	2 (1%)	0	28 (10%)	6 (2%)	2 (1%)	0
Rash	40 (15%)	5 (2%)	0	0	47 (17%)	3 (1%)	0	0
Anaemia	41 (15%)	4 (1%)	0	0	19 (7%)	2 (1%)	0	0
Decreased appetite	39 (14%)	3 (1%)	0	0	31 (12%)	3 (1%)	0	0
Unconjugated blood bilirubin increased	33 (12%)	2 (1%)	0	0	20 (7%)	1 (<1%)	0	0
Hypoalbuminaemia	34 (13%)	0	0	0	21 (8%)	0	0	0
Weight decreased	28 (10%)	4 (1%)	0	0	33 (12%)	6 (2%)	0	0
Asthenia	29 (11%)	3 (1%)	0	0	15 (6%)	0	0	0
Haematuria	31 (11%)	0	0	0	12 (4%)	0	0	0
Nausea	31 (11%)	0	0	0	14 (5%)	0	0	0
Headache	28 (10%)	2 (1%)	0	0	4 (1%)	1 (<1%)	0	0
Blood lactate dehydrogenase increased	26 (10%)	1 (<1%)	0	0	29 (11%)	0	0	0
Lymphocyte count decreased	18 (7%)	8 (3%)	0	0	14 (5%)	3 (1%)	0	0
Amylase increased	15 (6%)	9 (3%)	1 (<1%)	0	6 (2%)	0	1 (<1%)	0
Hyponatraemia	13 (5%)	8 (3%)	0	0	8 (3%)	1 (<1%)	0	0
Lipase increased	7 (3%)	7 (3%)	6 (2%)	0	6 (2%)	4 (1%)	1 (<1%)	0
Hypophosphataemia	17 (6%)	2 (1%)	0	0	27 (10%)	12 (4%)	0	0
Upper gastrointestinal haemorrhage	2 (1%)	6 (2%)	0	0	0	0	0	0
Alopecia	4 (1%)	0	0	0	52 (19%)	0	0	0

Data are n (%). Treatment-related adverse events of grade 1–2 occurring in at least 10% of patients or of grade 3–5 occurring in at least 2% of patients in either group are reported.

Qin/Vogel Lancet 2023

Efficacy of anti-PD1 & anti-CTL4 in HCC

CheckMate 040: Nivolumab/Ipilimumab



Yau et al. JAMA Oncology 2020

CheckMate 9DW – presented @ASCO 2024

N=1084
HCC Histology
No prior therapy
Child Pugh A
ECOG PS 0/1

Randomisation 1:1

Nivolumab 1mg/kg + Ipilimumab 3mg/kg q3w x4
Followed by Nivolumab 240mg q4w

Lenvatinib 8/12mg OD or
Sorafenib 400mg BD

Arndt Vogel @ArndtVogel · 21. März

CheckMate-9DW Meets Primary Endpoint in 1st line HCC
👉Nivo/Ipi significantly improves OS
👉AtezoBev, DurvaTreme, CamRivo, now Nivo/Ipi... to be continued...
😅Could become an exciting year in HCC, more data in all stages to be reported
@myESMO @ILCAnews @EASLnews #livertwitter

Bristol Myers Squibb

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

03/20/2024

CATEGORY: Corporate/Financial News

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

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced the Phase 3 CheckMate -9DW trial evaluating *Opdivo* (nivolumab) plus *Yervoy* (ipilimumab) as a first-line treatment for patients with advanced hepatocellular carcinoma (HCC) who have not received prior systemic therapy met its primary endpoint of improved overall survival (OS) compared to investigator's choice of sorafenib or lenvatinib at a pre-specified interim analysis.

The dual immunotherapy combination of *Opdivo* plus *Yervoy* demonstrated a statistically significant and clinically meaningful improvement in OS compared to investigator's choice of sorafenib or lenvatinib. The safety profile for the combination of *Opdivo* plus *Yervoy* remained consistent with previously reported data and was manageable with established protocols, with no new safety signals identified.

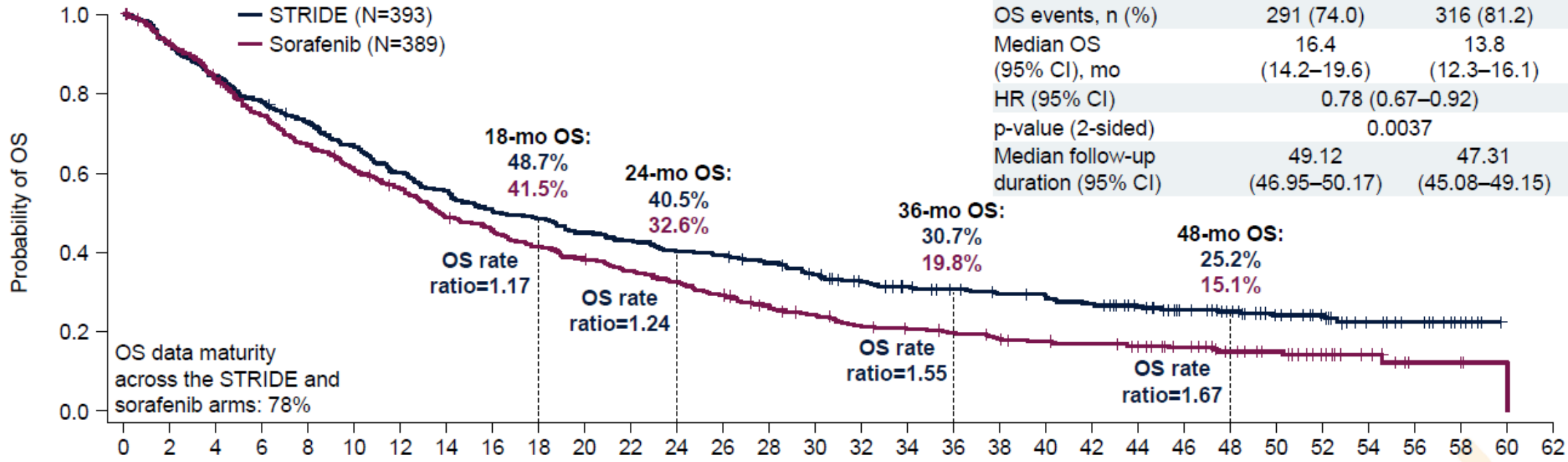
"Advanced stage liver cancer patients remain in need of additional treatment options that may help improve survival," said Dana Walker, M.D., M.S.C.E., vice president, global program lead, gastrointestinal and genitourinary cancers, Bristol Myers Squibb. "The overall survival benefit demonstrated by the combination of *Opdivo* plus *Yervoy* in the CheckMate -9DW trial demonstrates its potential to improve outcomes compared to well-established TKI treatment options."

3 46 105 5.575

Four-year updated overall survival for STRIDE versus sorafenib

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

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



Number at risk

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

OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. The 36-mo OS rate had a nominal 2-sided p-value of 0.0006.
Updated analysis data cut-off: 23 January 2023.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, month; MVI, macrovascular invasion; OS, overall survival; PS, performance status.

Sangro B et al. *Ann Oncol* 2024;35(5):448-457.

Four-year updated overall survival by response

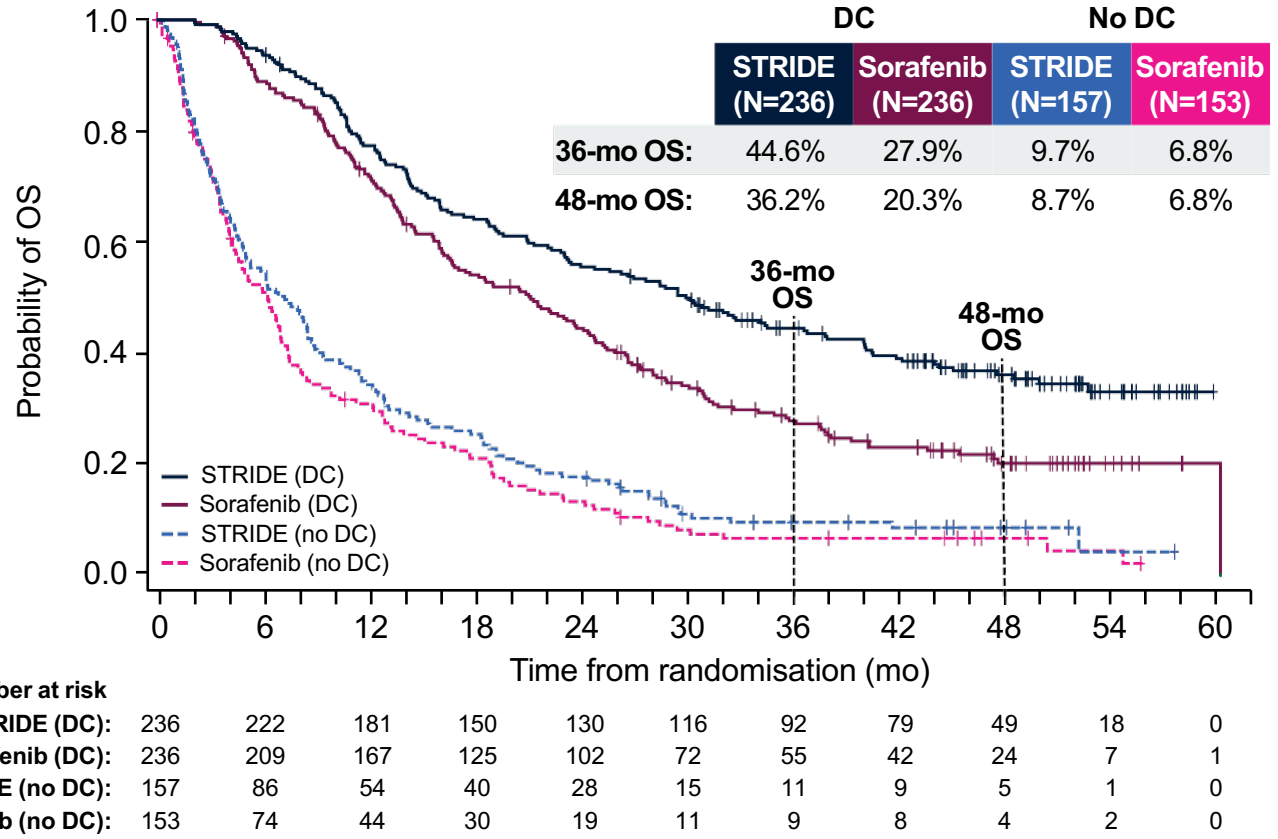
Long-term OS benefit was observed for participants treated with STRIDE, regardless of response

BOR in LTS*

	ITT[1]		LTS*	
	STRIDE (N=393)	Sorafenib (N=389)	STRIDE (N=103)	Sorafenib (N=64)
BOR, n (%)				
CR	12 (3.1)	0	12 (11.7)	0
PR	67 (17.0)	20 (5.1)	41 (39.8)	10 (15.6)
SD	157 (39.9)	216 (55.5)	39 (37.9)	45 (70.3)
PD	141 (35.9)	118 (30.3)	10 (9.7)	6 (9.4)
NE	16 (4.1)	35 (9.0)	1 (1.0)	3 (4.7)
DCR†, n (%)	**236 (60.1)**	**236 (60.7)**	**92 (89.3)**	**55 (85.9)**

OS rates were nearly 45% at 3 years and 36% at 4 years in participants who achieved disease control with STRIDE

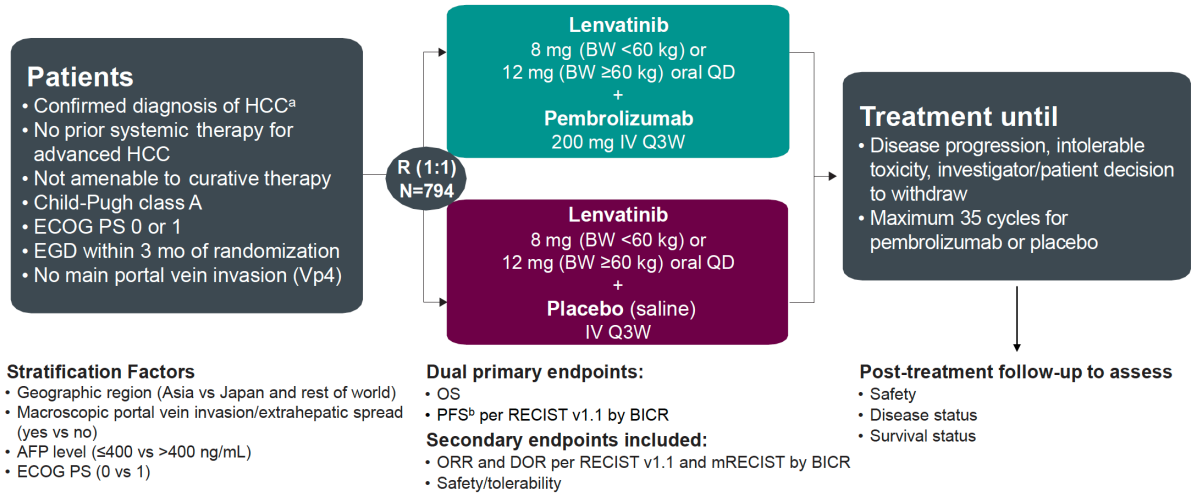
OS by disease control†

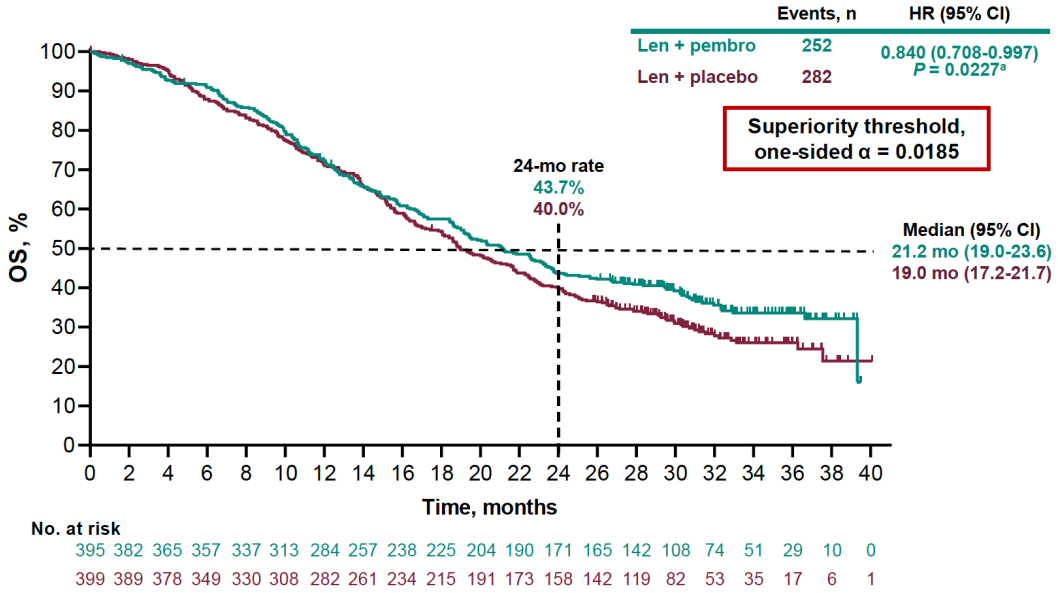


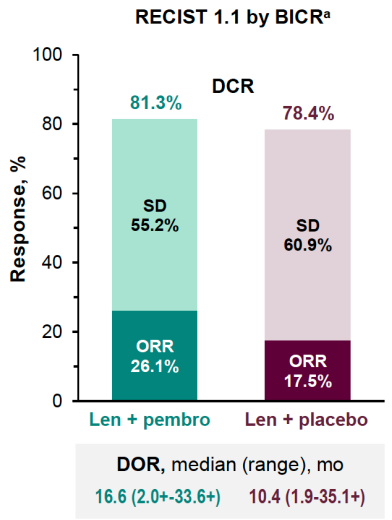
Sangro B et al. *Ann Oncol* 2024;35(5):448-457.

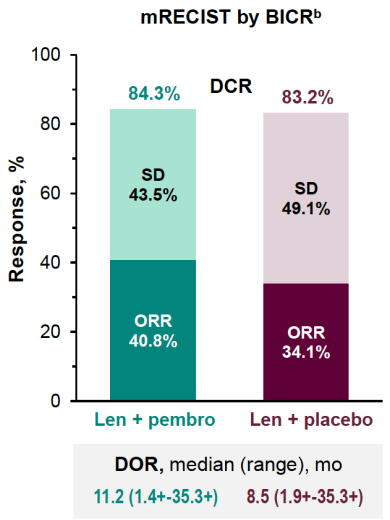
Efficacy of anti-PD1 and TKIs in HCC

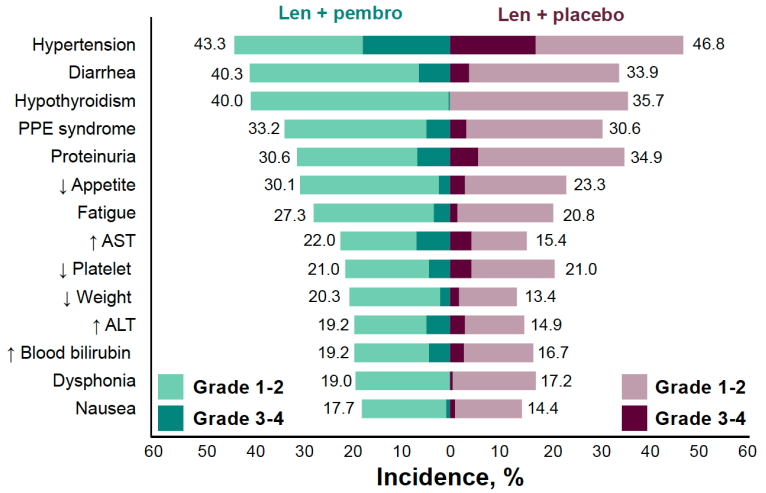
LEAP-002





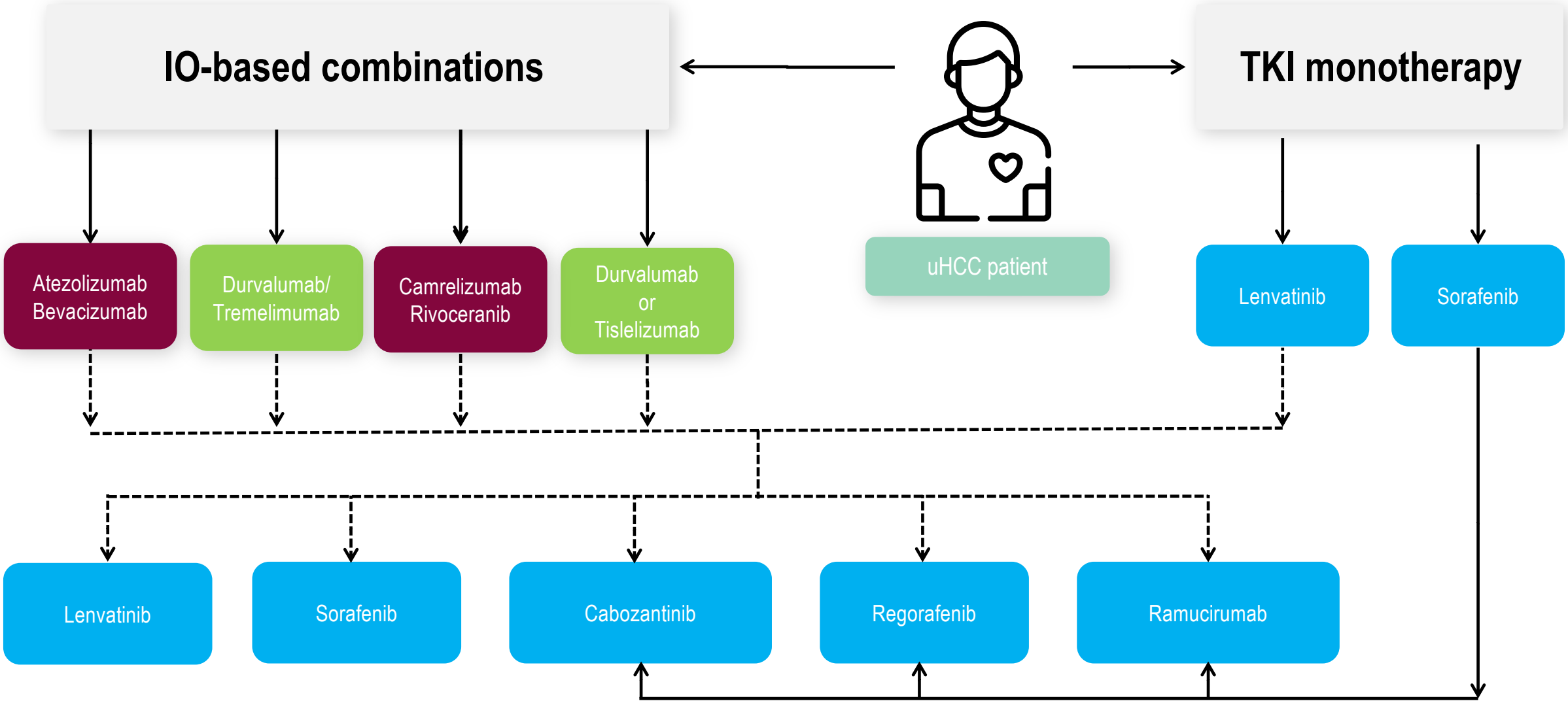






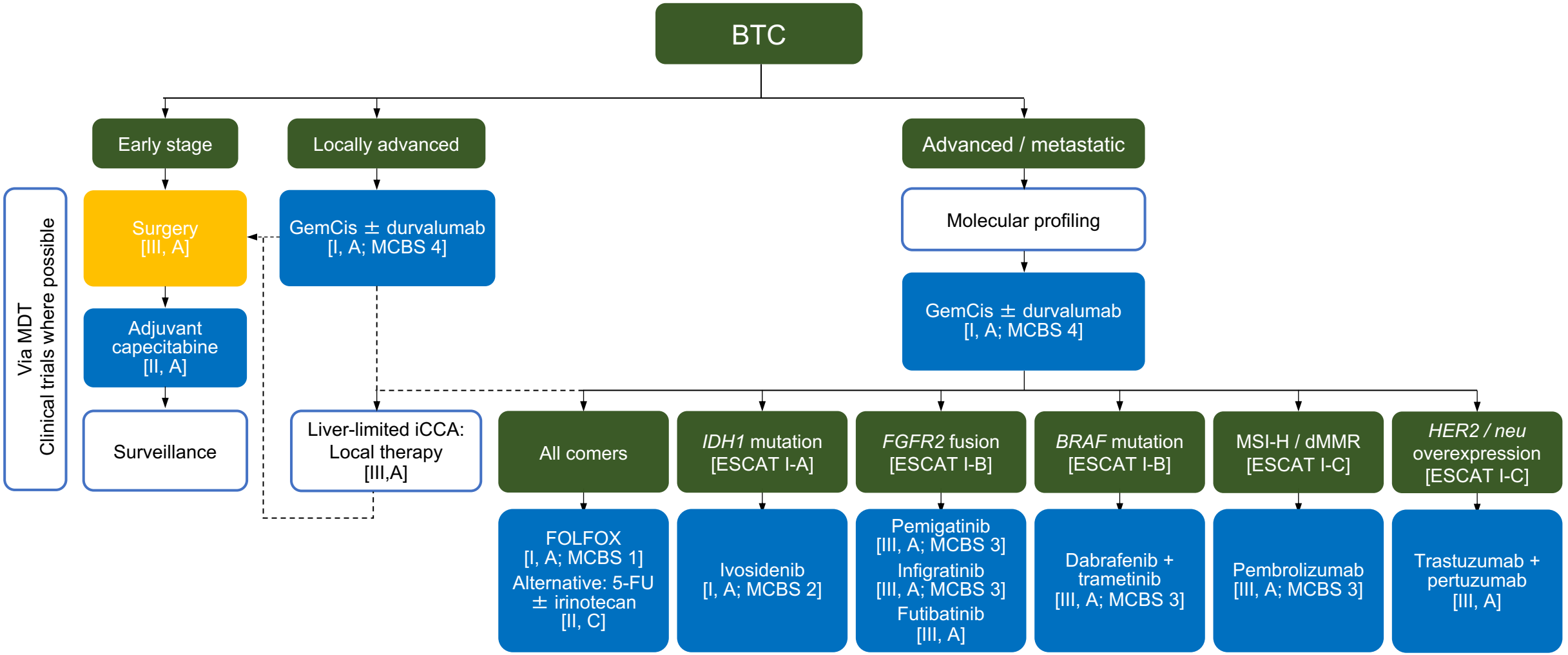
Finn RS et al. ESMO 2022;Abstract LBA34.

How should we best sequence systemic therapy?



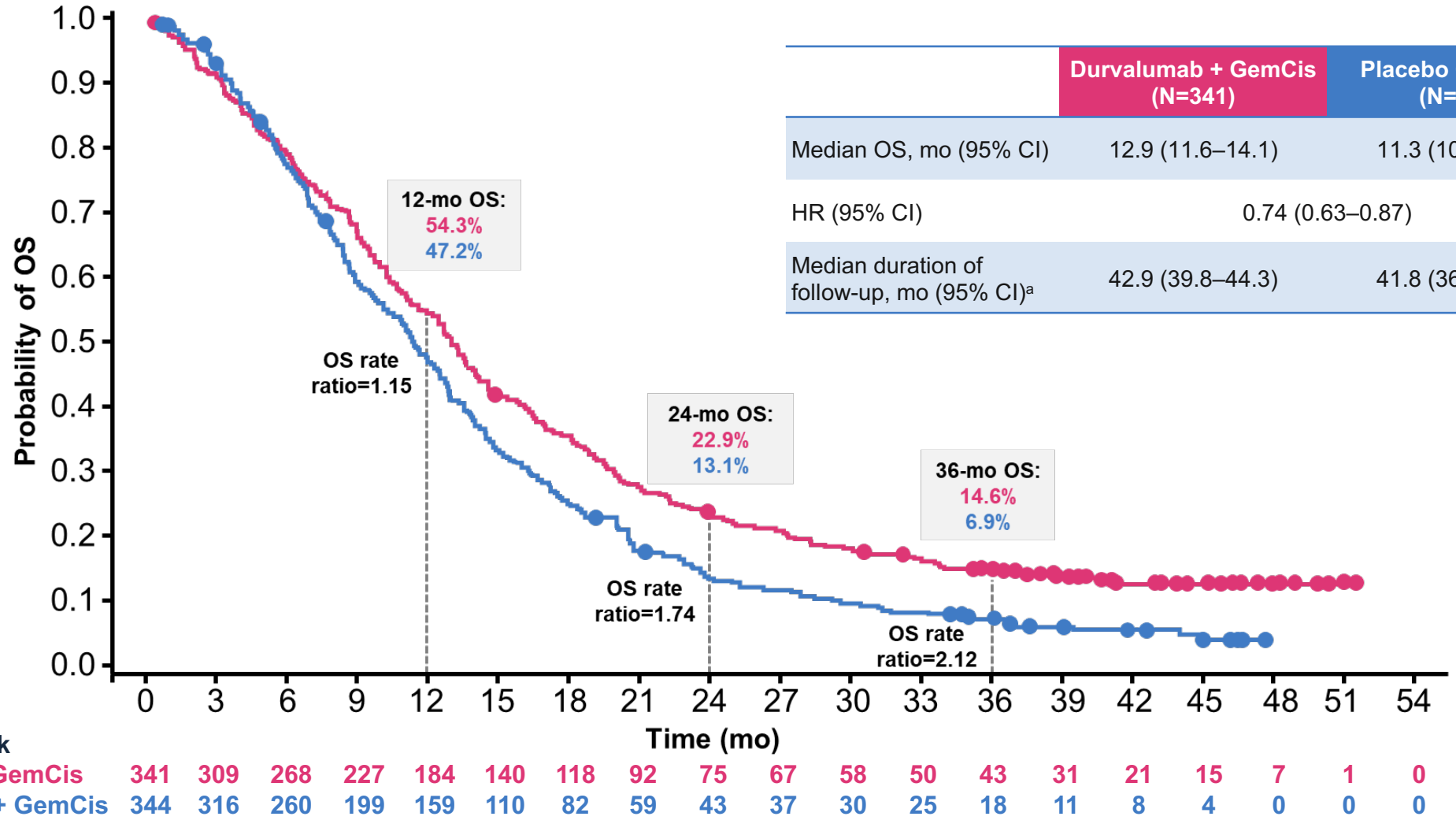
Modifiziert nach Vogel et al. Lancet 2022

ESMO 2023 Clinical Practice Guidelines



Vogel A, et al. Ann Oncol 2023

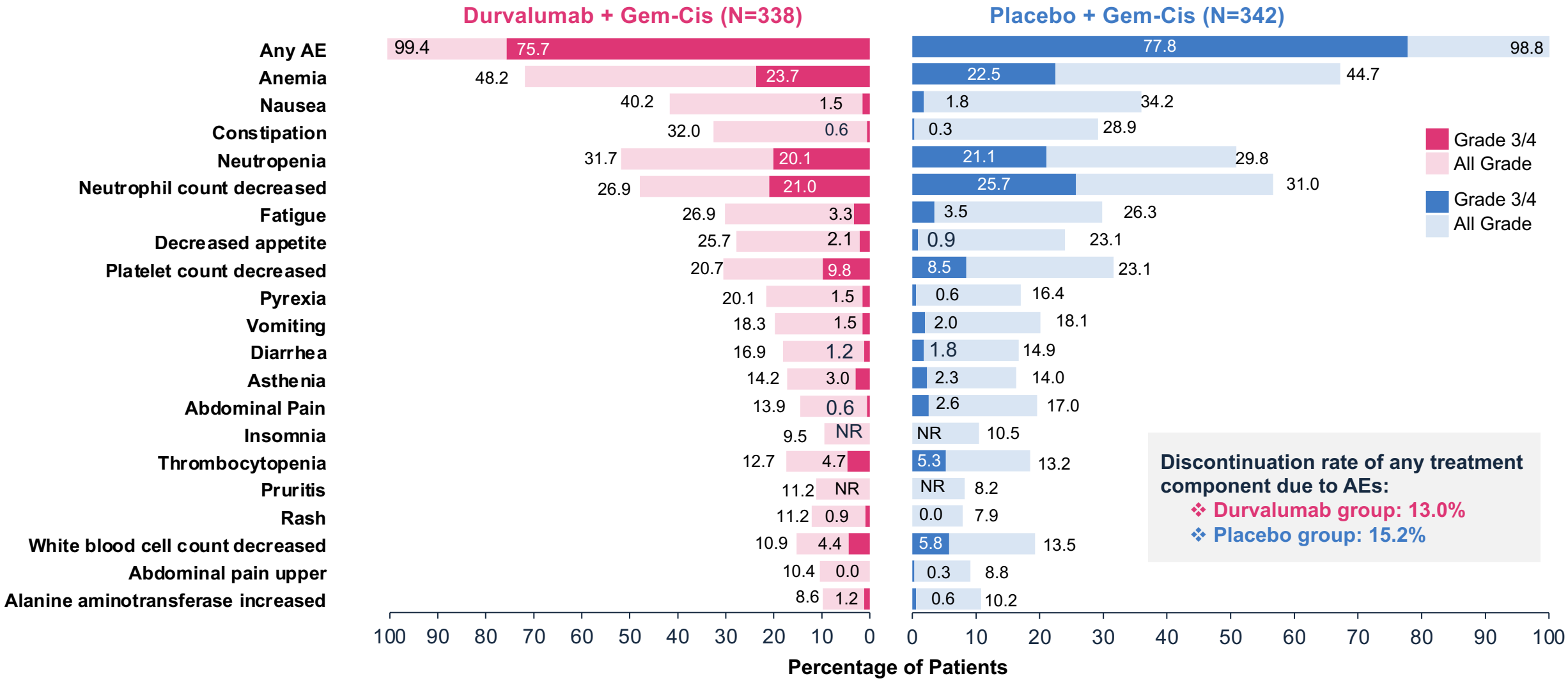
TOPAZ-1: Overall Survival (3-Year Update)



	Durvalumab + GemCis (N=341)	Placebo + GemCis (N=344)
Median OS, mo (95% CI)	12.9 (11.6–14.1)	11.3 (10.1–12.5)
HR (95% CI)	0.74 (0.63–0.87)	
Median duration of follow-up, mo (95% CI)[a]	42.9 (39.8–44.3)	41.8 (36.7–46.2)

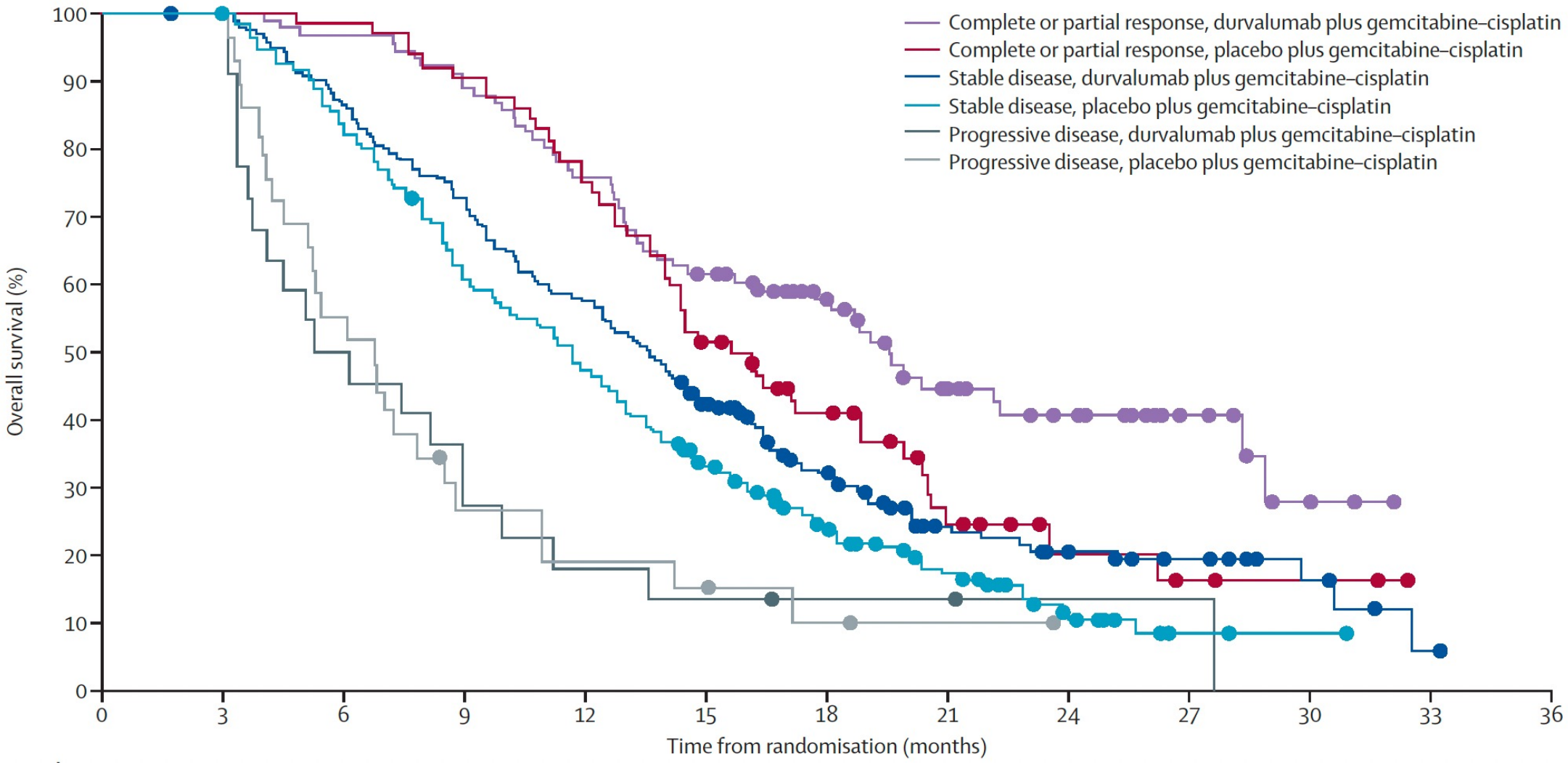
1. Oh D-Y, et al. Presented at Cholangiocarcinoma Foundation 2024 Annual Conference, Salt Lake City, UT, April 17–19, 2024.

TOPAZ-1: AEs of any Grade ≥10% in Either Treatment Arm (Primary Analysis)[1]



1. Oh D-Y, et. al. *NEJM Evid.* 2022;1(8).

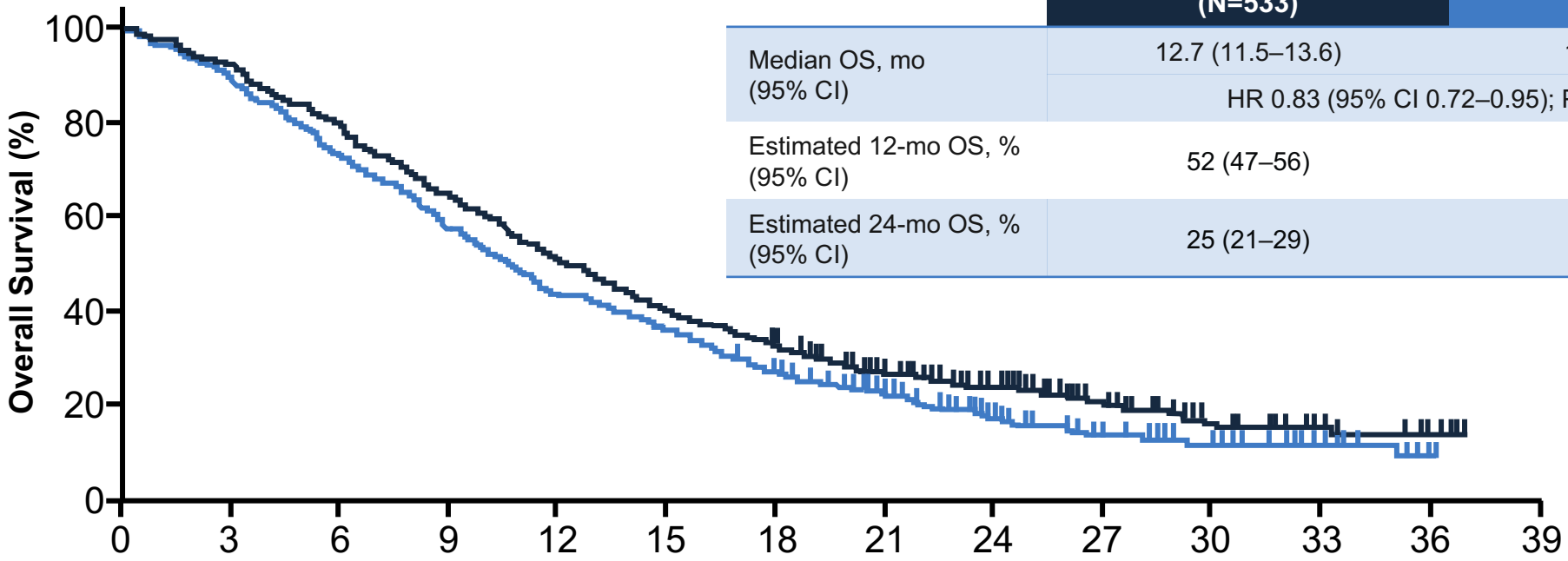
TOPAZ-1: OS by Best Objective Response



Oh D-Y, et al. Lancet Gastroenterol Hepatol 2024; Published Online May 29, 2024.

KEYNOTE-966: Overall Survival (Final Analysis)

	Pembrolizumab + GemCis (N=533)	Placebo + GemCis (N=536)
Median OS, mo (95% CI)	12.7 (11.5–13.6)	10.9 (9.9–11.6)
	HR 0.83 (95% CI 0.72–0.95); P=0.0034	
Estimated 12-mo OS, % (95% CI)	52 (47–56)	44 (40–48)
Estimated 24-mo OS, % (95% CI)	25 (21–29)	18 (15–22)



No. at risk (no. censored)														
Pembro + GemCis	533 (0)	496 (0)	430 (0)	350 (0)	275 (0)	217 (0)	175 (1)	122 (26)	88 (50)	46 (83)	21 (100)	11 (109)	5 (114)	0 (119)
Placebo + GemCis	536 (0)	483 (1)	394 (1)	313 (1)	236 (1)	195 (1)	148 (3)	97 (30)	59 (49)	32 (65)	20 (74)	10 (84)	1 (92)	0 (93)

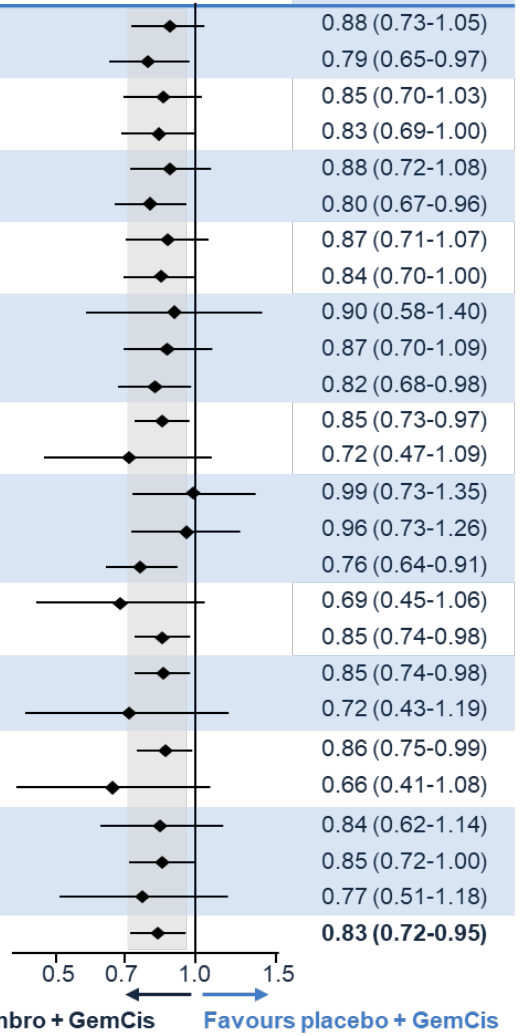
Median follow-up at final analysis, defined as time from random assignment to the Dec 15, 2022, data cutoff, was 25.6 months (IQR 21.7-30.4).

BTC, biliary tract cancer; CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; IQR, interquartile range; mo, months; NS, not significant; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. Kelley RK, et al. *Lancet.* 2023;401:1853-1865.

KEYNOTE-966: Overall Survival by Subgroup

		Pembro + GemCis (n/N)	Placebo + GemCis (n/N)	HR (95% CI)
Age (years)	<65	210/269	242/298	0.88 (0.73-1.05)
	≥65	204/264	201/238	0.79 (0.65-0.97)
Sex	Female	200/253	220/264	0.85 (0.70-1.03)
	Male	214/280	223/272	0.83 (0.69-1.00)
Geographical Region	Asia	185/242	201/244	0.88 (0.72-1.08)
	Not Asia	229/291	242/292	0.80 (0.67-0.96)
ECOG PS	0	186/258	177/228	0.87 (0.71-1.07)
	1	227/274	266/308	0.84 (0.70-1.00)
Smoking status	Current	42/56	38/49	0.90 (0.58-1.40)
	Former	160/205	160/191	0.87 (0.70-1.09)
	Never	212/272	244/295	0.82 (0.68-0.98)
Antibiotic use within 1 month of study start	No	364/471	403/493	0.85 (0.73-0.97)
	Yes	50/62	40/43	0.72 (0.47-1.09)
Site of origin	Extrahepatic	78/98	83/105	0.99 (0.73-1.35)
	Gallbladder	102/115	104/118	0.96 (0.73-1.26)
	Intrahepatic	234/320	256/313	0.76 (0.64-0.91)
Disease status	Locally advanced	37/60	52/66	0.69 (0.45-1.06)
	Metastatic	377/473	391/470	0.85 (0.74-0.98)
Biliary stent or drain	No	388/500	406/495	0.85 (0.74-0.98)
	Yes	26/33	37/41	0.72 (0.43-1.19)
Previous chemotherapy	No	382/483	408/488	0.86 (0.75-0.99)
	Yes	32/50	35/48	0.66 (0.41-1.08)
PD-L1 combined positive score	<1	86/113	87/110	0.84 (0.62-1.14)
	≥1	287/363	309/365	0.85 (0.72-1.00)
	Unknown	41/57	47/61	0.77 (0.51-1.18)
Overall		**414/533**	**443/536**	**0.83 (0.72-0.95)**



1. Kelley RK, et al. *Lancet*. 2023;401:1853-1865.

KEYNOTE-966: Safety Results

	Pembrolizumab + GemCis (N=529)		Placebo + GemCis (N=534)	
AEs from any cause, N (%)	524 (99)		532 (<100)	
Maximum toxicity Grade 3 or 4, N (%)	420 (79)		400 (75)	
Potentially immune-mediated AEs, N (%)	117 (22)		69 (13)	
AEs leading to death, N (%)	31 (6)		49 (9)	
AEs leading to discontinuation of ≥1 study drug, N (%)	138 (26)		122 (23)	
Discontinuation of all study drugs, N (%)	35 (7)		39 (7)	
AEs occurring in ≥30% of participants in either study group				
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
Decreased neutrophil count (%)	63	49	61	47
Anemia (%)	61	29	59	29
Nausea (%)	44	2	46	2
Decreased platelet count (%)	40	18	40	20
Fatigue (%)	36	6	32	4
Constipation (%)	36	<1	36	1

- AE profile of pembrolizumab + GemCis was as expected based on the known profiles of treatment components
- Potentially immune-mediated AEs were more common in the pembrolizumab group

Other AEs occurring in ≥15% of participants in either study group: decreased appetite, decreased white blood cell count, pyrexia, vomiting, diarrhea, abdominal pain, rash, increased AST, increased ALT, hypomagnesemia, pruritus, asthenia, and peripheral edema

1. Kelley RK, et al. *Lancet*. 2023;401:1853-1865. 2. Pembrolizumab Product Monograph. April 12, 2024.

Agenda

Module 1: Recent Developments in the Management of Early- and Intermediate-Stage Hepatocellular Carcinoma (HCC) — Dr Kim

Module 2: First-Line Therapy for Advanced HCC and Biliary Tract Cancers (BTCs) — Prof Vogel

Module 3: Integration of Targeted Therapy into the Management of Advanced BTCs — Dr Kelley

Consulting Faculty Comments

Use of immunotherapy for patients with hyperbilirubinemia; choosing between FGFR inhibitors

Dr Gigi Chen (Pleasant Hill, California)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

For patients with actionable FGFR abnormalities, how do you decide whether to use pemigatinib or futibatinib?

For patients who experience disease progression on one FGFR inhibitor, do you typically try the other?

QUESTIONS FOR THE FACULTY

What are the most common toxicities reported with pemigatinib and futibatinib?

Which of these do you believe are most detrimental to patient quality of life?

Consulting Faculty Comments

Sequencing of trastuzumab deruxtecan in the treatment algorithm for patients with BTCs

Dr Warren Brenner (Boca Raton, Florida)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Are you generally conducting HER2 assessment for your patients with BTCs? If so, when do you test?

Where in the treatment course are you typically offering trastuzumab deruxtecan (T-DXd) to your patients with advanced BTCs?

QUESTIONS FOR THE FACULTY

What is zanidatamab? Do you believe this agent will soon be endorsed for patients with HER2-positive BTCs?

If zanidatamab becomes available, how will you select between it and T-DXd? Will you likely use these agents in sequence?

Consulting Faculty Comments

Therapeutic approach to combined HCC-cholangiocarcinoma

Dr Erik Rupard (St George, Utah)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

In general, how do you approach the treatment of patients with mixed hepatocellular cholangiocarcinoma?

UCSF Helen Diller Family Comprehensive Cancer Center

Integration of Targeted Therapy into the Management of Advanced Biliary Tract Cancers

Katie Kelley, MD
Professor of Clinical Medicine
University of California, San Francisco

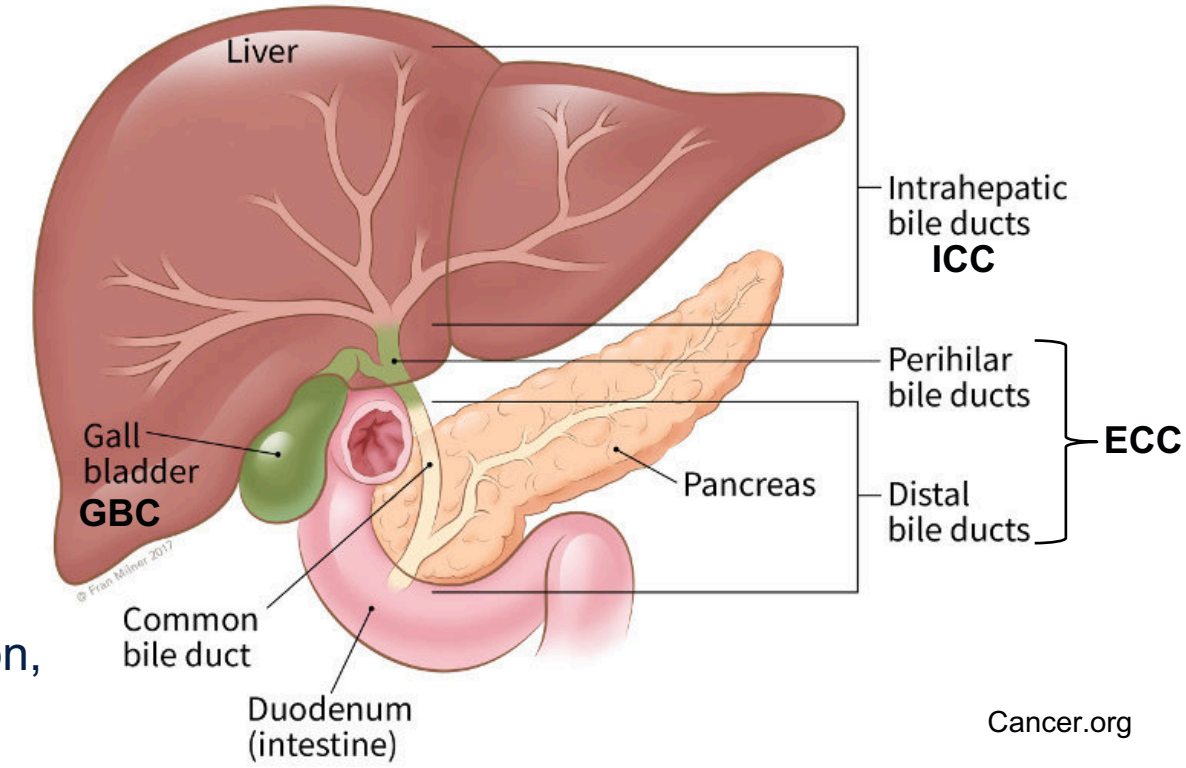
Outline

- Background on molecular alterations in advanced biliary tract cancers (BTC)
- Targeting FGFR2 alterations in cholangiocarcinoma (CCA)
  - Pemigatinib and futibatinib; new agents on horizon
- Targeting HER2 in BTC
  - Zanidatamab: Bispecific HER2-targeting antibody
    - HERIZON-BTC-01
  - T-DXd: Antibody-drug conjugate
    - HERB and DESTINY-PanTumor02 trials
- Summary and future directions

Background on Biliary Tract Cancers (BTC)

- Uncommon tumors with rising incidence worldwide[1-4]
  - Global age-standardized incidence rate (ASIR) 2.7 per 100,000 in 2017[1]
- Heterogeneous anatomy
  - Gallbladder (GBC)
  - Cholangiocarcinoma (CCA)
    - Intrahepatic CCA (ICC)
    - Extrahepatic CCA (ECC)

- Heterogeneous etiology and biology
  - Risk factors include viral hepatitis, fluke infection, fatty liver, hereditary, autoimmunity, idiopathic
  - Molecular heterogeneity of tumor and microenvironment



Cancer.org

1. Wu et al. J Dig Dis 2022;23(3); 2. Clements et al. J Hepatol 2020;72:95-103;
3. Koshiol et al. BMC Cancer 2022;22(1):1178; 4. seer.cancer.gov

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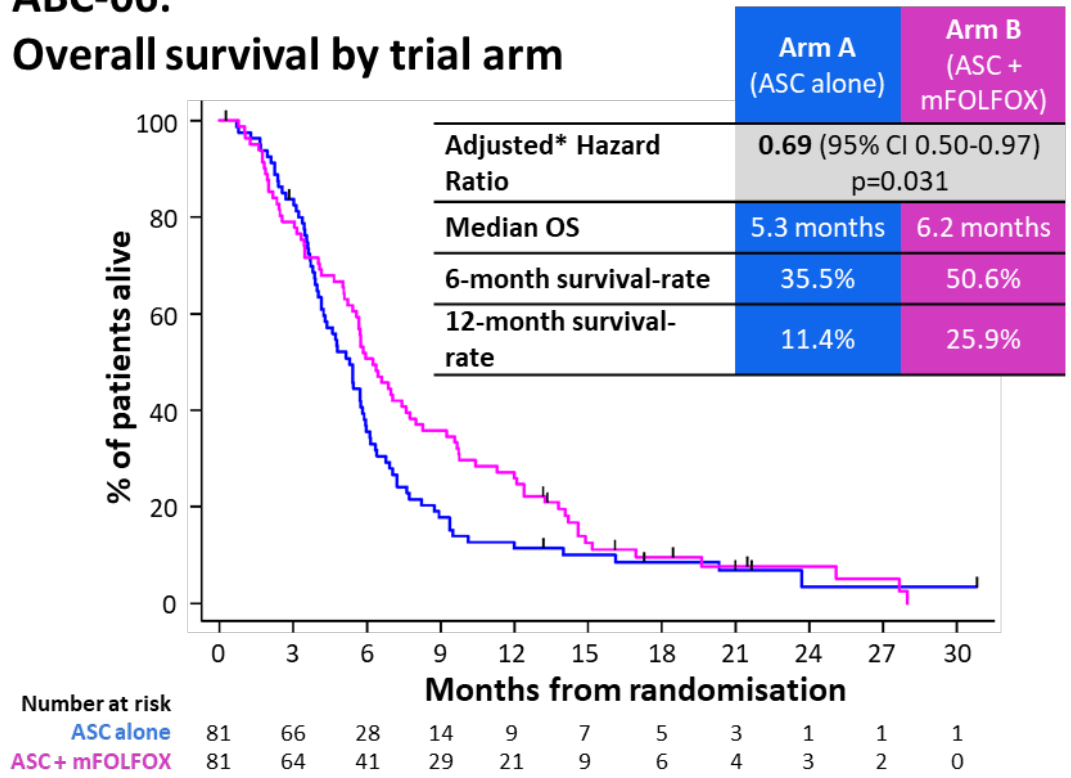
Advanced BTC: ≥2nd Line Systemic Therapy Options

- Before 2019: No established 2nd line therapy after GEM+CIS
- 2019: ABC-06 trial of FOLFOX vs ASC showed improved PFS and OS for FOLFOX
  - mOS 6.2 vs. 5.3 mos for FOLFOX vs ASC
  - mPFS 4.0 months for FOLFOX arm
  - ORR 5% for FOLFOX arm
- Other regimens such as FOLFIRI, 5-FU/nal-IRI, capecitabine, GEM/*nab*-paclitaxel are commonly used based upon phase 2 data

ABC-06:
Overall survival by trial arm



Lamarca et al, Lancet Oncol 2021;22(5)

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Beyond Chemotherapy: Molecular Targets Vary by Anatomic Subsite of BTC

Intrahepatic cholangiocarcinoma (ICC)

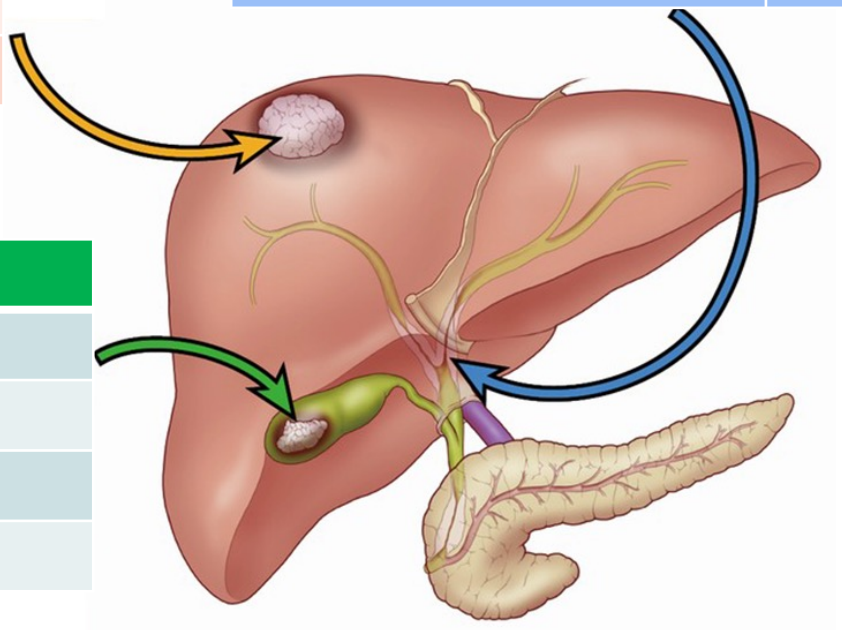
Targetable gene	Prevalence, %
FGFR2 (fusions)	10
IDH1/2	15
ERBB2/HER2 (amp./IHC)	4-5

Extrahepatic cholangiocarcinoma (ECC)

Targetable gene	Prevalence, %
ERBB2/HER2 (amp./IHC)	17-19
PRKACA and *PRKACB*	9
ARID1A	5-12

Gallbladder cancer (GBC)

Targetable gene	Prevalence, %
EGFR	4-13
ERBB2/HER2 (amp./IHC)	19-31
PTEN	0-4
PIK3CA	6-13



Overall

MSI-high/dMMR ~1-3%
BRAF V600E 1-5%
***ERBB2* mut. ≤ 10%**
NTRK, RET, others rare

Jain A, Javle M. J Gastrointest Oncol 2016;7(5); Valle et al. Cancer Discovery 2017; Ju et al. Am J Clin Pathol 2020;153(5): 598-604; Banales et al. Nat Rev Gastroenterol Hepatol 2020;17(9); Hiraoka et al. Hum Path 2020;105:9-19

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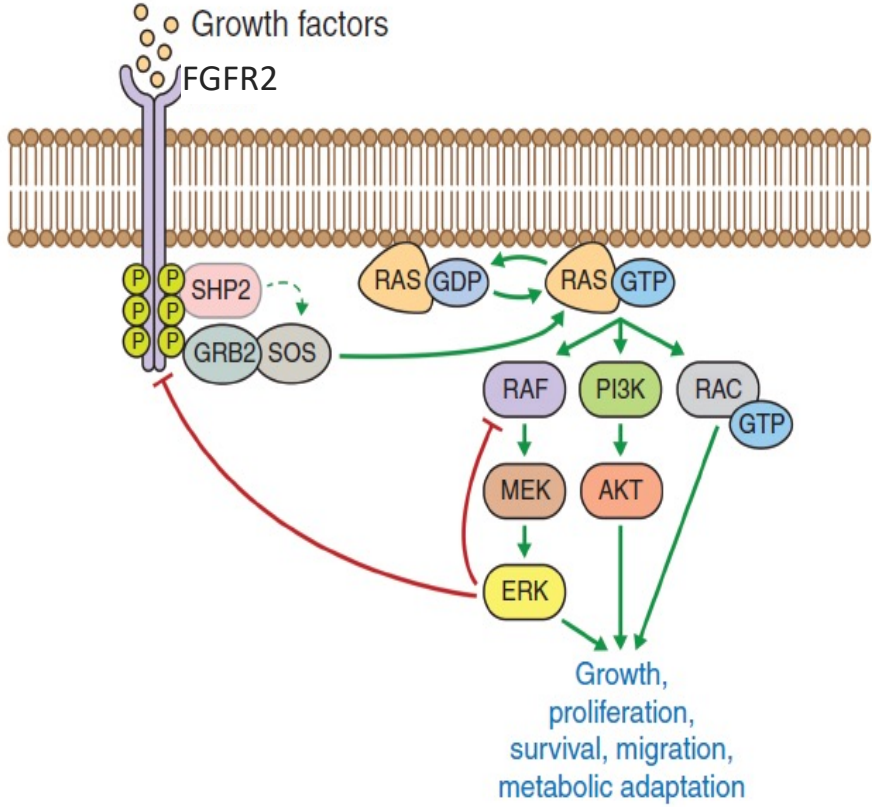
FGFR2 Fusions and Rearrangements in CCA

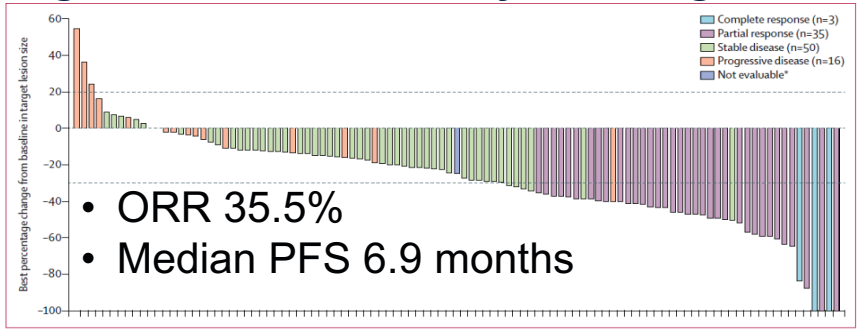
- Present in ~10% of intrahepatic CCA, rare in other locations
  - Kinase domain of *FGFR2* fused in-frame to a known 3' partner gene (fusions) or to unidentified partner gene (rearrangements)
- Produce chimeric constitutively active FGFR2 kinase
- Can be inhibited by:
  - ATP-competitive pan-FGFR inhibitors:
    - Infigratinib, pemigatinib, erdafitinib, others
    - TYRA-200
  - Non-ATP-competitive covalent pan-FGFR inhibitors
    - Futibatinib
    - KIN-3248
  - FGFR2-selective covalent inhibitors
    - RLY-4008

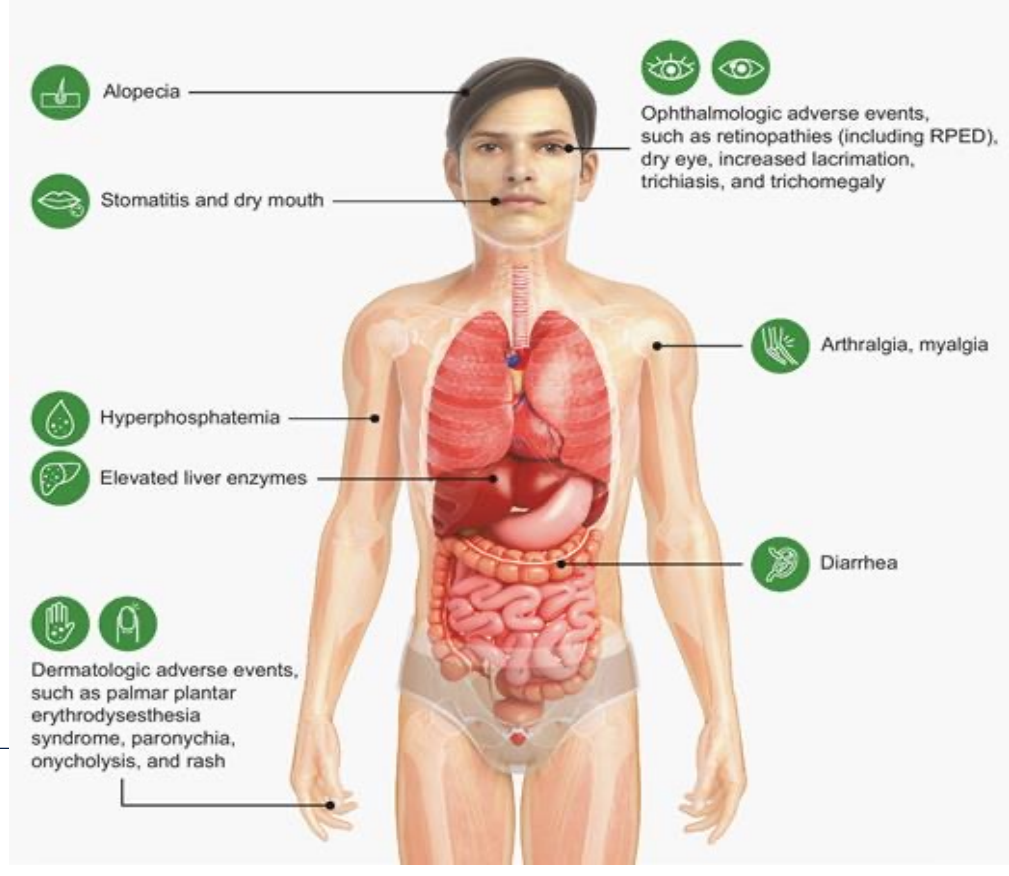


ATP-Competitive FGFR Inhibition in CCA with *FGFR2* Rearrangements

- Studied in ≥2nd line advanced BTC, non-randomized trials
- ATP-competitive inhibitors of FGFR1-3>4:
  - Pemigatinib[1]
    - Accelerated approval from USFDA in 2020 for ICC with *FGFR2* rearrangement
  - Infigratinib[2]
    - ORR 23%, median PFS 7.3 mos.
    - Accelerated approval from USFDA in 2021; distribution discontinued by manufacturer 2023
- Class toxicities[3] include: Hyperphosphatemia, stomatitis, palmar-plantar erythrodysesthesia, ophthalmologic toxicities

Fight-202: Phase 2 Study of Pemigatinib





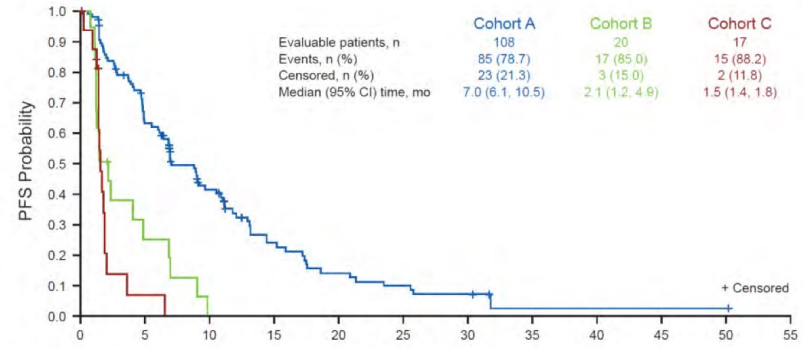
1. Abou-Alfa et al. Lancet Oncol 2020;21:671-84; 2. Javle et al. Lancet Gastroenterol Hepatol 2021;6; 3. Meric-Bernstam et al. Clin Cancer Res 2024;30(8):1466-77

Pemigatinib in *FGFR2*-Rearranged CCA

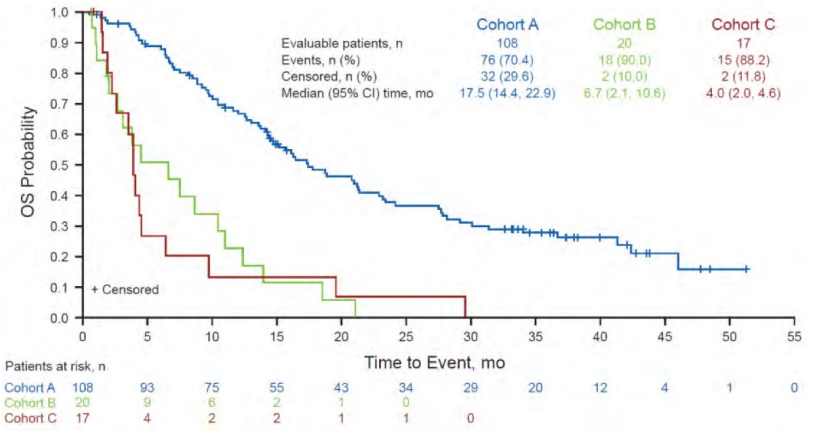
Parameter	Cohort A (n=108)	Cohort B (n=20)	Cohort C (n=17)
Duration of follow-up, median (range), mo	42.9 (19.9–52.2)	47.5 (43.7–51.1)	51.9 (49.5–53.7)
ORR,* % (95% CI)	37 (28, 47)	0 (0, 17)	0 (0, 20)
DCR,† % (95% CI)	82 (74, 89)	40 (19, 64)	18 (4, 43)
Best overall response, %			
Complete response	3	0	0
Partial response	34	0	0
Stable disease	45	40	18
Progressive disease	15	35	65
Not evaluable	3	25	18
DOR, median (95% CI), mo	9.1 (6.0, 14.5)	—	—

- Median PFS in cohort A was 7.0 months (95% CI: 6.1, 10.5)
- Median OS in cohort A was 17.5 months (95% CI: 14.4, 22.9)

PFS



OS



- Received accelerated approval from USFDA in April 2020.

Abou-Alfa et al. Lancet Oncol. 2020;21(5):671-684.
Voget et al. ESMO GI 2022.

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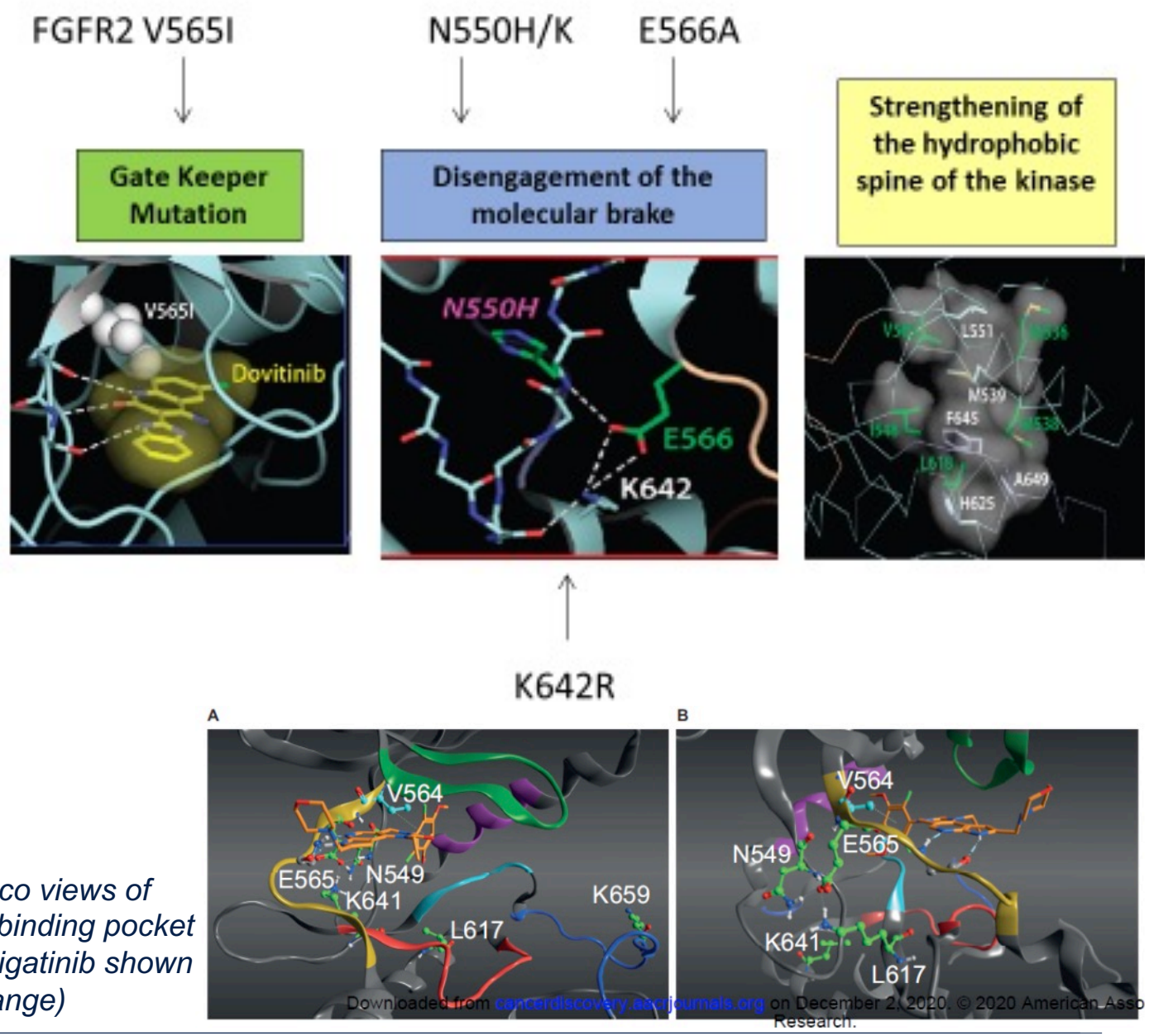
Acquired Resistance to FGFR2 Inhibition Limits Duration of Response

- Acquired, polyclonal secondary *FGFR2* kinase domain point mutations cause acquired resistance to ATP-competitive inhibitors
  - Gatekeeper residue mutations
  - Molecular brake mutations
  - Mutations that destabilize inactive conformation in other ways
- Covalent inhibitors (e.g. **RLY-4008, futibatinib)** show activity against some common resistance mutations
  - Other agents are in development



In silico views of ATP-binding pocket (pemigatinib shown in orange)

Goyal et al. Cancer Discov 2017;7(3):252-63; Hollebecque et al. ESMO 2019; Silverman et al. Cancer Discov 2021;11(2):326-339

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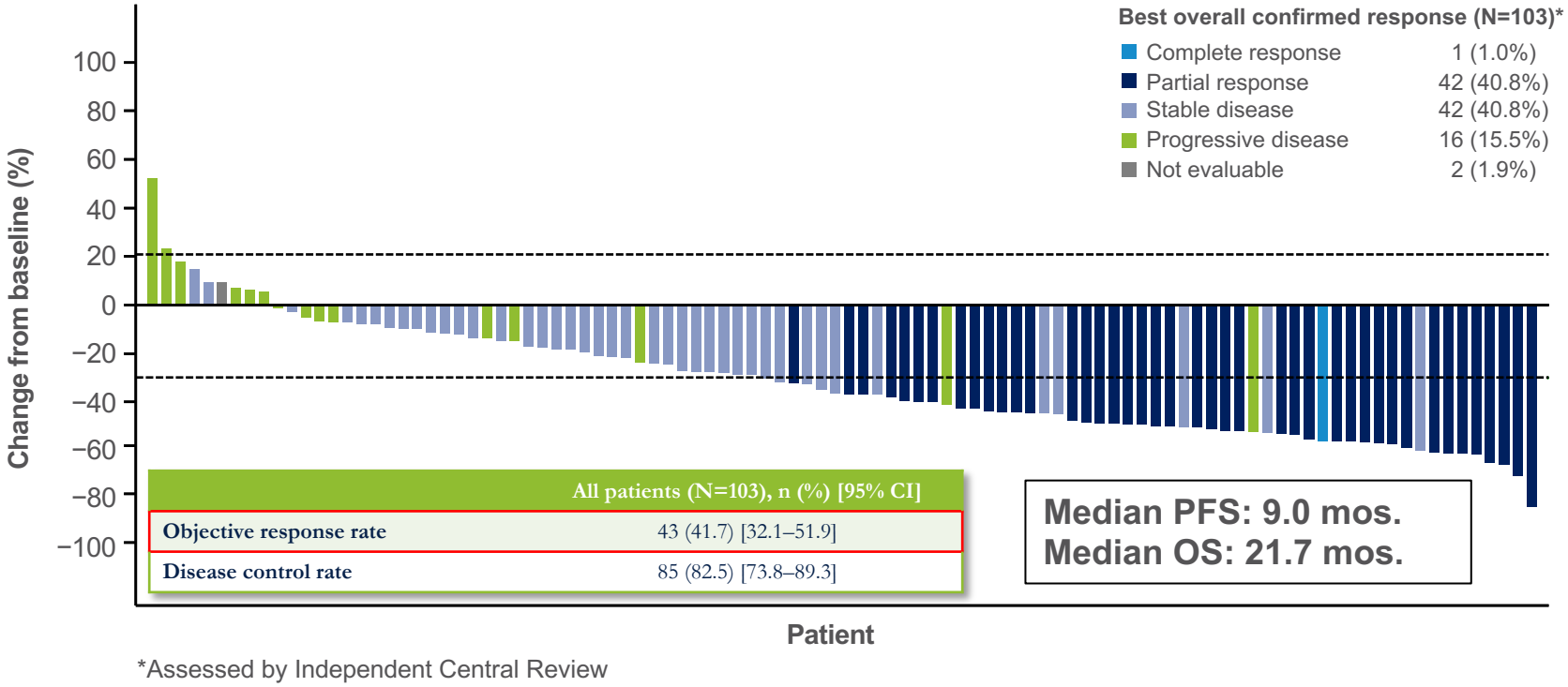
Futibatinib in *FGFR2*-Rearranged CCA



*Assessed by Independent Central Review

Data cutoff: October 1, 2020. Dotted horizontal lines represent partial response (≥30% reduction in lesion size) and progressive disease (≥20% increase) per RECIST v1.1.
CI, confidence interval; iCCA, intrahepatic cholangiocarcinoma; ICR, independent central review; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

- Received accelerated approval from USFDA in September 2022

Goyal et al. AACR 2021; Goyal et al. NEJM 2023

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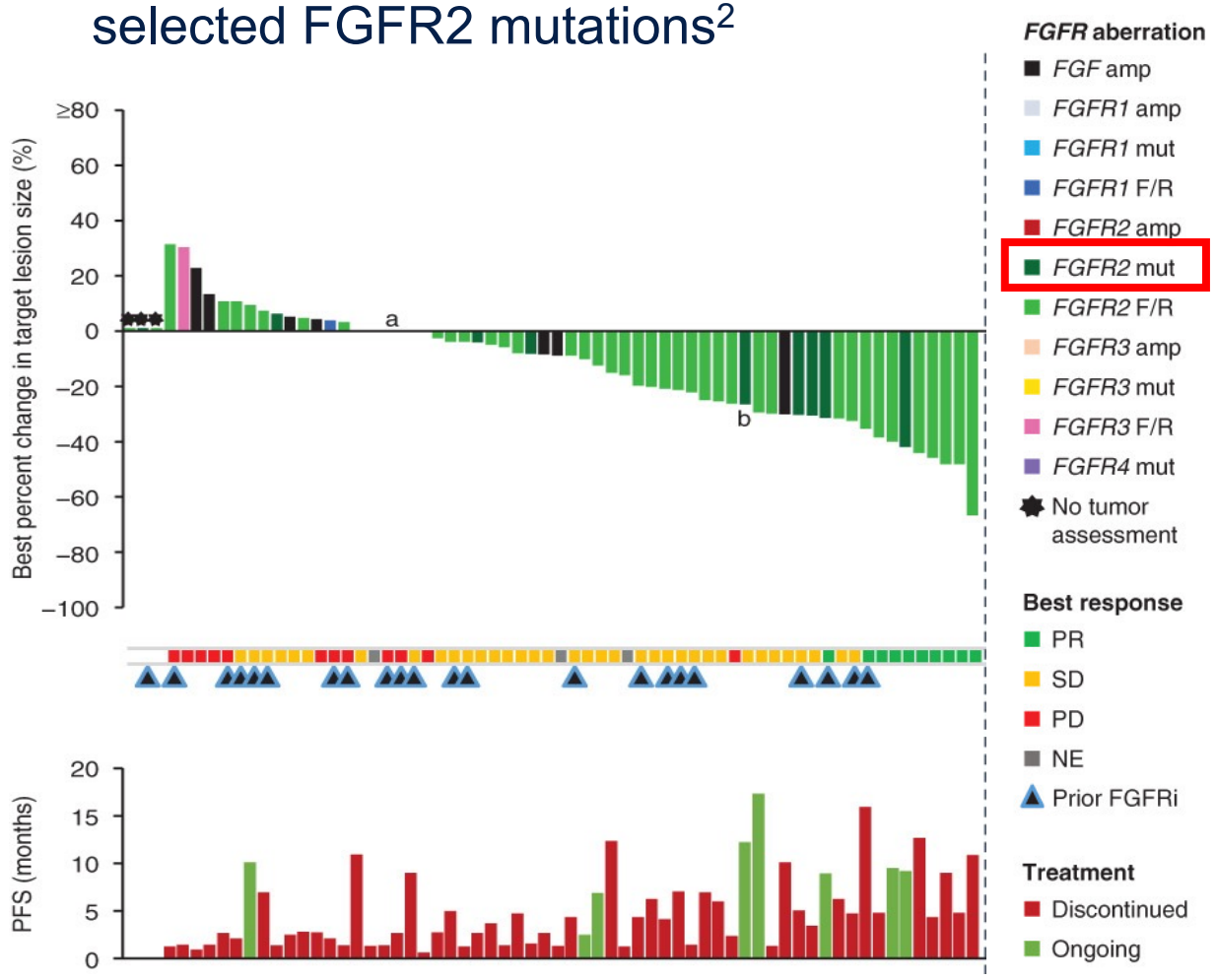
Do pan-FGFR inhibitors have activity in other FGFR2 alterations?

- Pemigatinib has limited activity in other FGF/FGFR2 alterations or WT[1]

Table 2. Primary and secondary efficacy outcomes

	FGFR2 fusions or rearrangements (n=107)	Other *FGF/FGFR* alterations (n=20)	No *FGF/FGFR* alterations (n=18)
Proportion of patients with an objective response	35·5% (26·5 to 45·4)	0	0
Best overall response*			
Complete response	3 (2·8%)	0	0
Partial response	35 (32·7%)	0	0
Stable disease	50 (46·7%)	8 (40·0%)	4 (22·2%)
Progressive disease	16 (14·9%)	7 (35·0%)	11 (61·1%)
Not evaluable	3 (2·8%)	5 (25·0%)	3 (16·7%)
Progression-free survival			
Patients with events	71 (66%)	17 (85%)	16 (89%)
Patients censored	36 (34%)	3 (15%)	2 (11%)
Median, months	6·9 (6·2 to 9·6)	2·1 (1·2 to 4·9)	1·7 (1·3 to 1·8)
Overall survival†			
Patients with events	40 (37%)	16 (80%)	14 (78%)
Patients censored	67 (63%)	4 (20%)	4 (22%)
Median overall survival, months	21·1 (14·8 to not estimable)	6·7 (2·1 to 10·6)	4·0 (2·3 to 6·5)

- Futibatinib has some activity in CCA with selected FGFR2 mutations[2]



1. Abou-Alfa et al. Lancet Oncol 2020;21:671-84; 2. Meric-Bernstam et al. Cancer Discovery 2022;12(2):402-15

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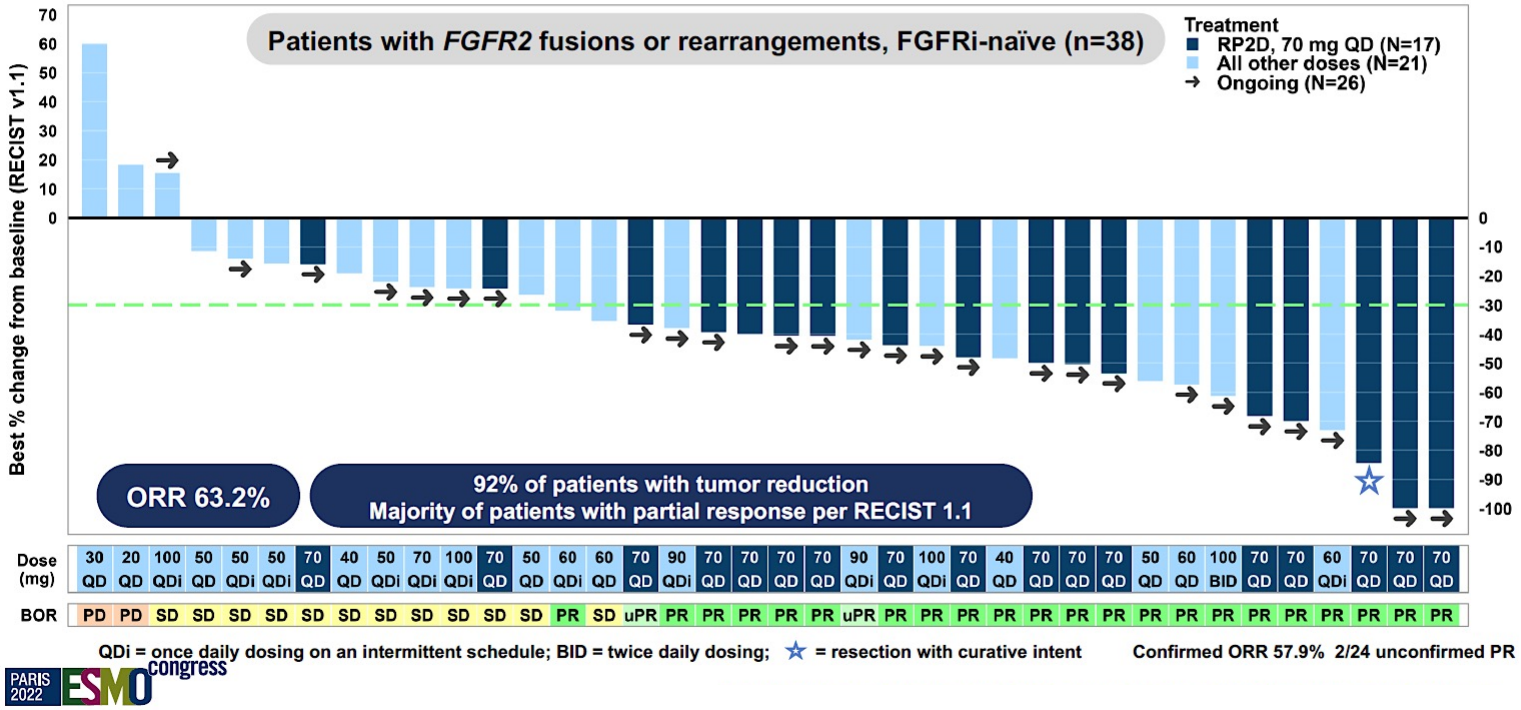
Phase 1/2 Trial of RLY-4008

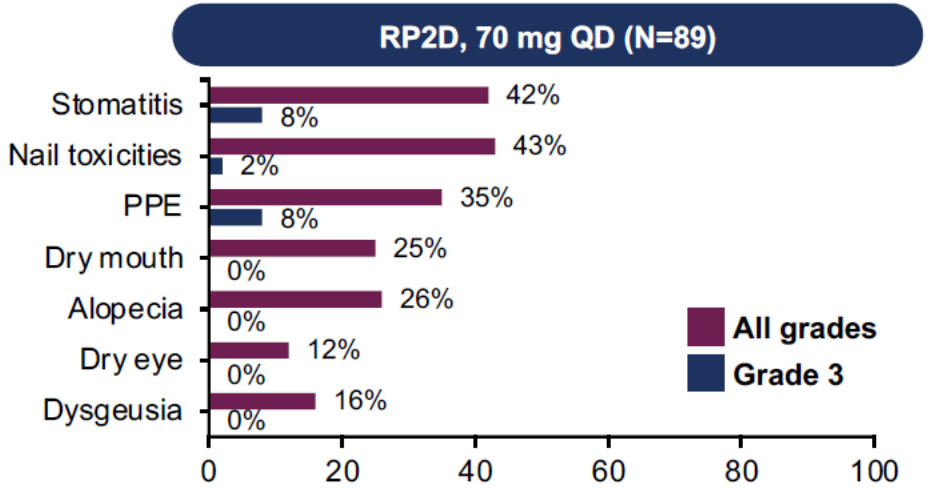
- RLY-4008 is an oral, highly selective FGFR2 inhibitor
- Active against common FGFR2 kinase domain resistance mutations

Radiographic Tumor Regression and Response per RECIST 1.1 Across All Doses

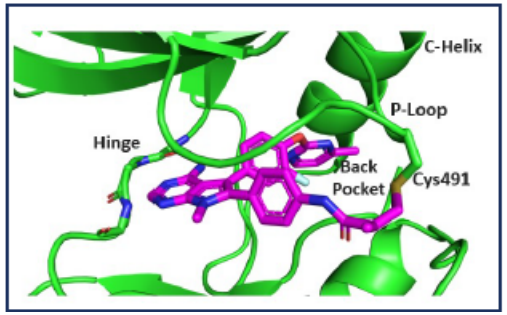


PARIS 2022 ESMO congress

Treatment-Related Adverse Events (TRAEs) ≥ 15%



RLY-4008 Structure



Goyal et al. AACR-NCI-EORTC 2021; Hollebeque et al. ESMO 2022, LBA12

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Tinengotinib in Patients with Advanced Solid Tumors Harboring Actionable FGFR1-3 Alterations

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
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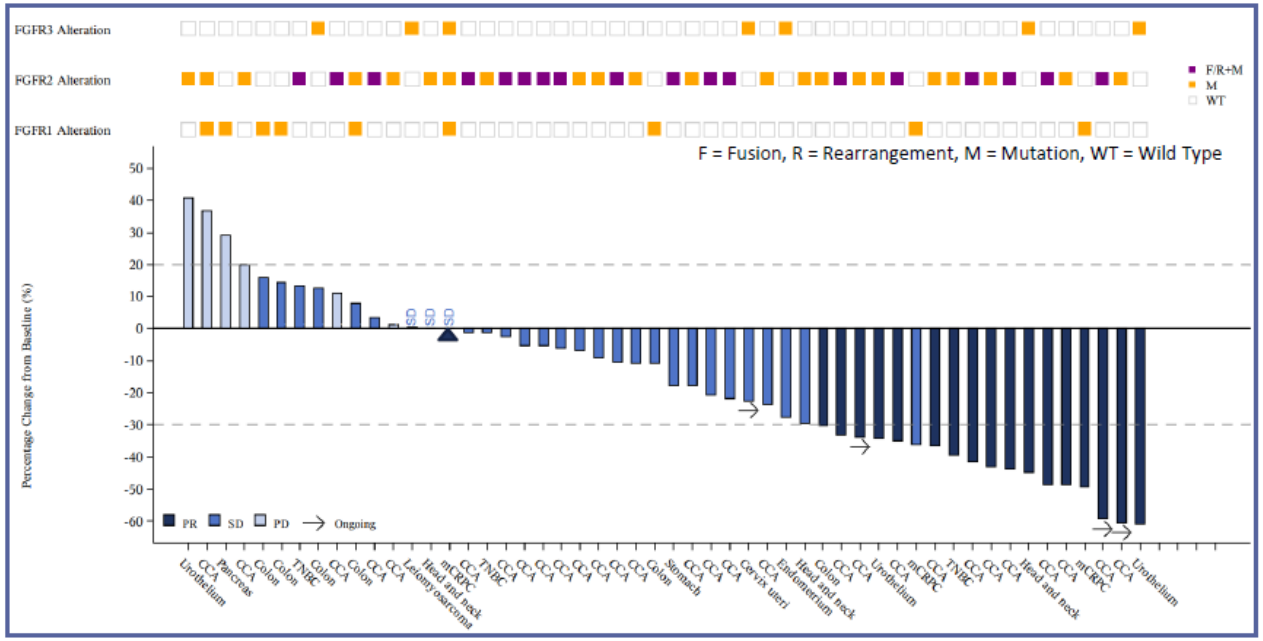
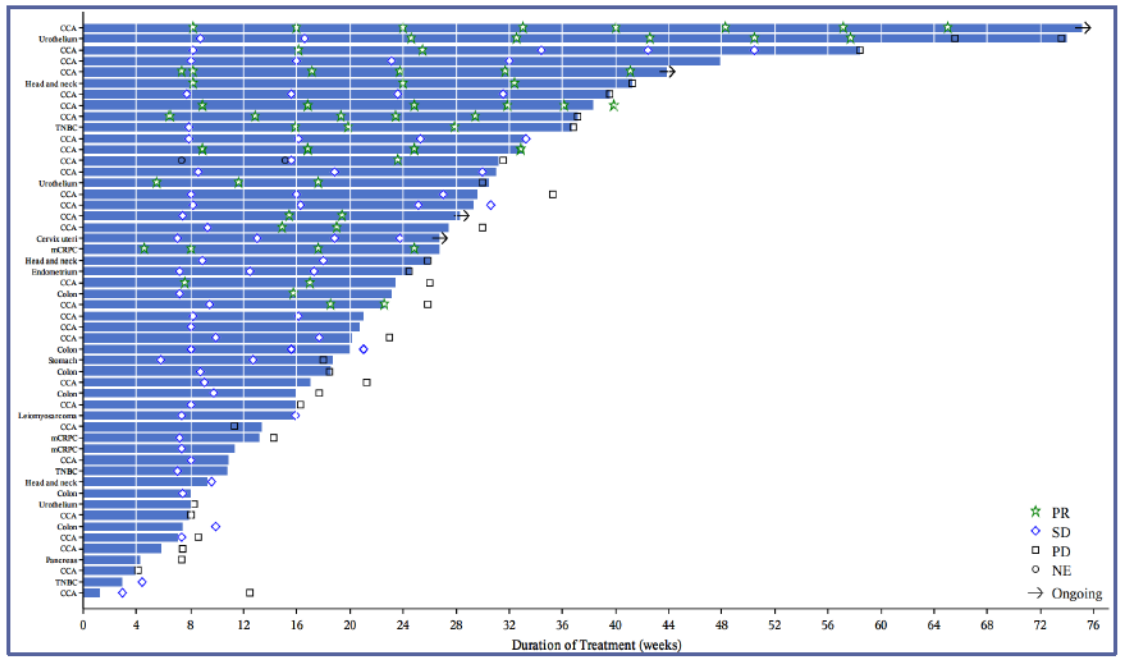
Figure 1. Waterfall plot for all efficacy-evaluable patients (N=52)



▲ mCRPC patient with FGFR1/2/3 mutation had no target lesions, and the best response was SD.

Figure 2. Swimming plot for all efficacy-evaluable patients (N=52)



51 pts (29 CCA). ORR 33%. DCR 88%. Median PFS 6.9 months. Median DOR 6.7 months.

Of the 51, 24 pts had prior FGFRi. ORR 38%. DCR 88%. Median PFS 6.0 months.

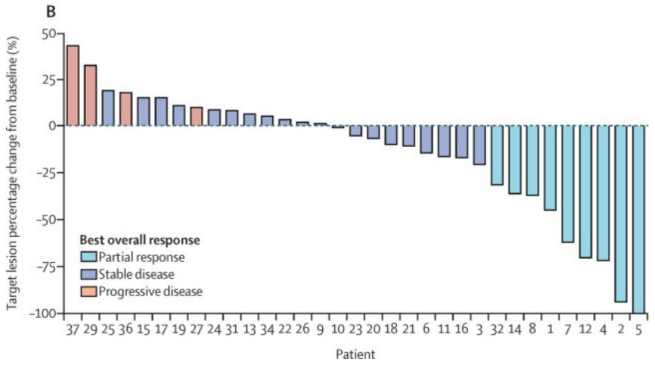
Piha-Paul, et al., AACR 2024

HER2 Overexpression and/or Amplifications are seen in 10-15% of Biliary Tract Cancers

Trastuzumab/Pertuzumab
(2 monoclonal antibodies)

MyPathway (N=39)
HER2 3+ by IHC, *HER2:CEP17* >2.0 or HER2 CN>6.0 by FISH/CISH, or HER2 amp by NGS

ORR: 23%
DoR: 10.8 months

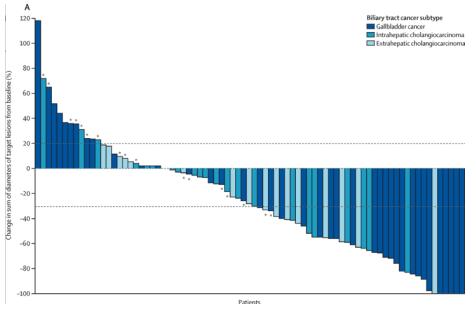


Javle, et al. *Lancet Onc*, 2021

Zanidatamab
(bi-specific antibody)

HERIZON-BTC-01 (n=80)
HER2 2+ or 3+ by IHC

ORR: 41.3%
DoR: 12.9 months
ORR 51.6%/5.6% for IHC 3+/2+

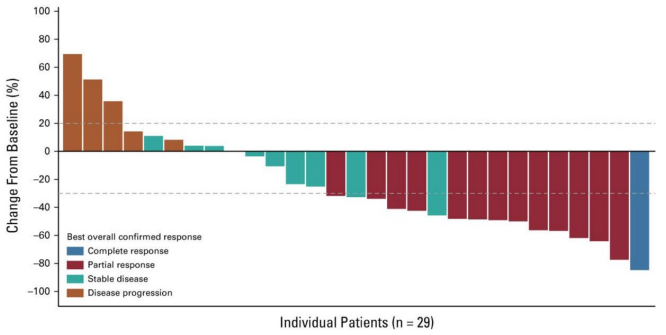


Harding, et al. *Lancet Onc*, 2023

Trastuzumab/Tucatinib
(monoclonal Ab/small molecule)

SGNTUC-019 (n=30)
HER2 3+ by IHC, *HER2:CEP17* >2.0 or HER2 CN>6.0 by FISH/CISH, or HER2 amp by NGS

ORR: 46.7%
DoR: 6.0 months

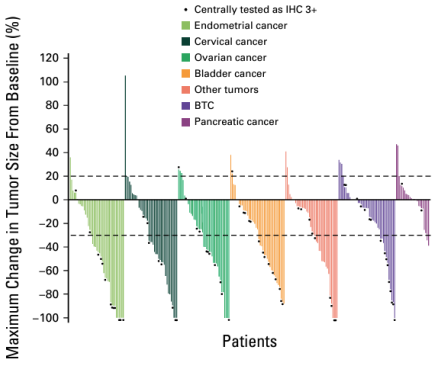


Nakamura, et al. *JCO*, 2023

Trastuzumab-deruxtecan
(antibody drug conjugate)

DESTINY-PanTumor 02
(n=41 with BTC)
HER2 2+ or 3+ by IHC

ORR: 22%
DOR: 8.6 months
ORR 56.3%/0% for IHC 3+/2+

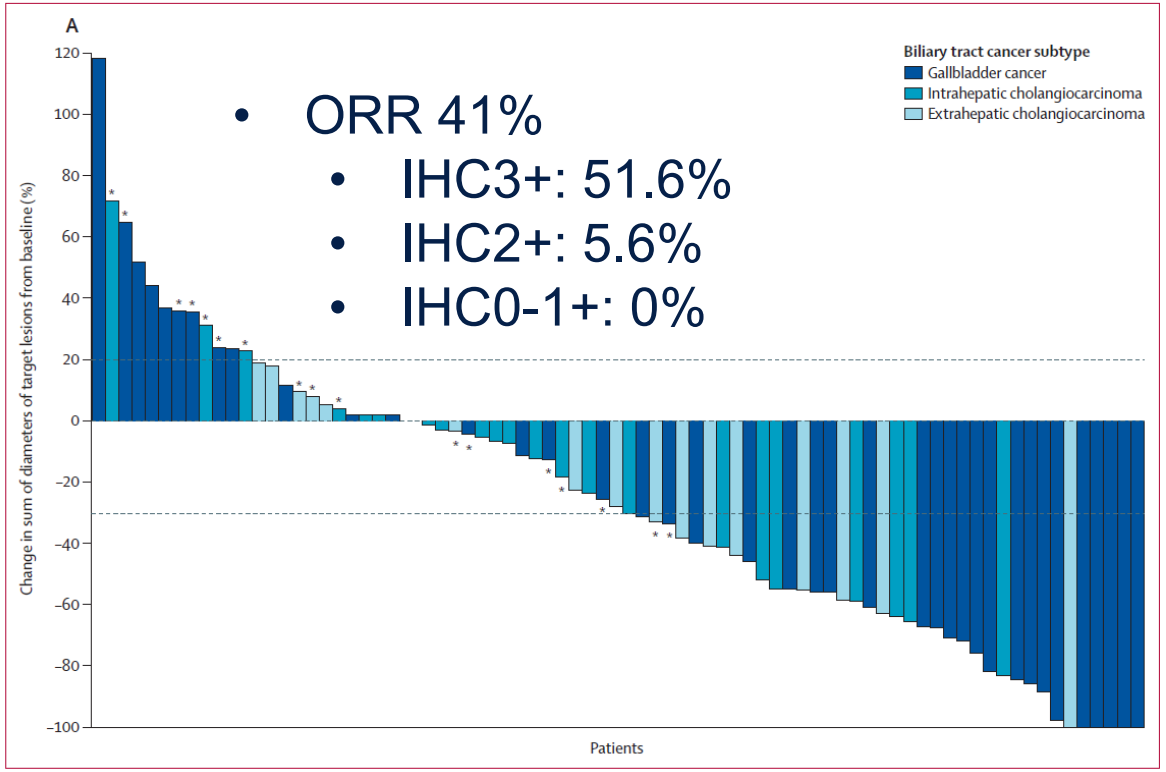


Meric-Bernstam, et al. *JCO,* 2024

Slide courtesy Dr. Lipika Goyal

Zanidatamab in Advanced BTC

- Bispecific mAb targeting 2 distinct HER2 epitopes
  - Dimerization, juxtamembrane domains
  - Causes receptor internalization and downregulation
- HERIZON-BTC trial:
  - N=87 HER2 amplified (*HER2*/chr17 ratio ≥2.0)
    - IHC3+ n=62
    - IHC2+ n=18
    - IHC0-1+ n=7
  - Key TRAE: Diarrhea (37%), infusion reactions (33%)
    - TRAE Grade 3: Diarrhea (5%), reduced EF (3%), anemia (2%)



Harding et al. Lancet Oncol 2023;24:772-82

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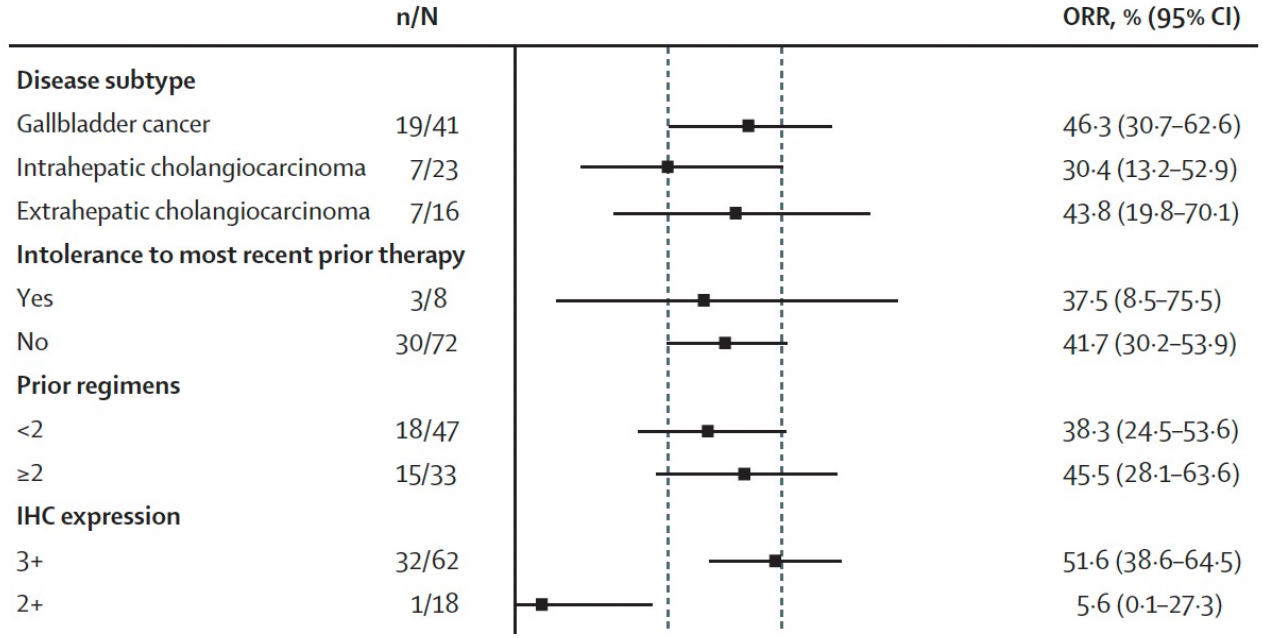
Zanidatamab in Advanced BTC: Efficacy Data

	Independent central review assessment (n=80)	Investigator assessment (n=80)
Confirmed objective response rate, n (%; 95% CI)	33 (41·3%; 30·4–52·8)	33 (41·3%; 30·4–52·8)
Confirmed best overall response		
Complete response	1 (1%)	4 (5%)
Partial response	32 (40%)	29 (36%)
Stable disease	22 (28%)	21 (26%)
Progressive disease	24 (30%)	25 (31%)
Not evaluable*	1 (1%)	1 (1%)
Median time to first response (95% CI), months, months†	1·8 (1·7–2·0)	1·8 (1·8–2·0)
Range	1·6–5·5	1·6–3·7
Duration of response, months†		
Median (95% CI)	12·9 (6·0–not estimable)	11·1 (5·6–14·1)
Range	1·5–16·9+	1·9–15·0+
Had event	11/33 (33%)	17/33 (52%)
Censored	22/33 (67%)	16/33 (49%)



Progression-free survival, months§		
Median (95% CI)	5·5 (3·7–7·2)	5·4 (3·6–7·2)
Range	0·3–18·5+	0·3–18·5+
Had event	54/80 (68%)	62/80 (78%)
Censored	26/80 (33%)	18/80 (23%)

Harding et al. Lancet Oncol 2023;24:772-82

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Zanidatamab in Advanced BTC: Safety Data

	Grade 1–2	Grade 3
Any adverse event	47 (54%)	16 (18%)
Diarrhoea	28 (32%)	4 (5%)
Infusion-related reaction	28 (32%)	1 (1%)
Ejection fraction decreased	5 (6%)	3 (3%)
Nausea	7 (8%)	1 (1%)
Alanine aminotransferase increased	6 (7%)	0
Aspartate aminotransferase increased	5 (6%)	1 (1%)
Vomiting	6 (7%)	0
Fatigue	5 (6%)	0
Anaemia	2 (2%)	2 (2%)
Hypokalaemia	1 (1%)	1 (1%)
Platelet count decreased	1 (1%)	1 (1%)
Blood bilirubin increased	0	1 (1%)
Enteritis	0	1 (1%)
Lipase increased	0	1 (1%)
Oral candidiasis	0	1 (1%)
Pneumonitis	0	1 (1%)
Stomatitis	0	1 (1%)

Harding et al. Lancet Oncol 2023;24:772-82

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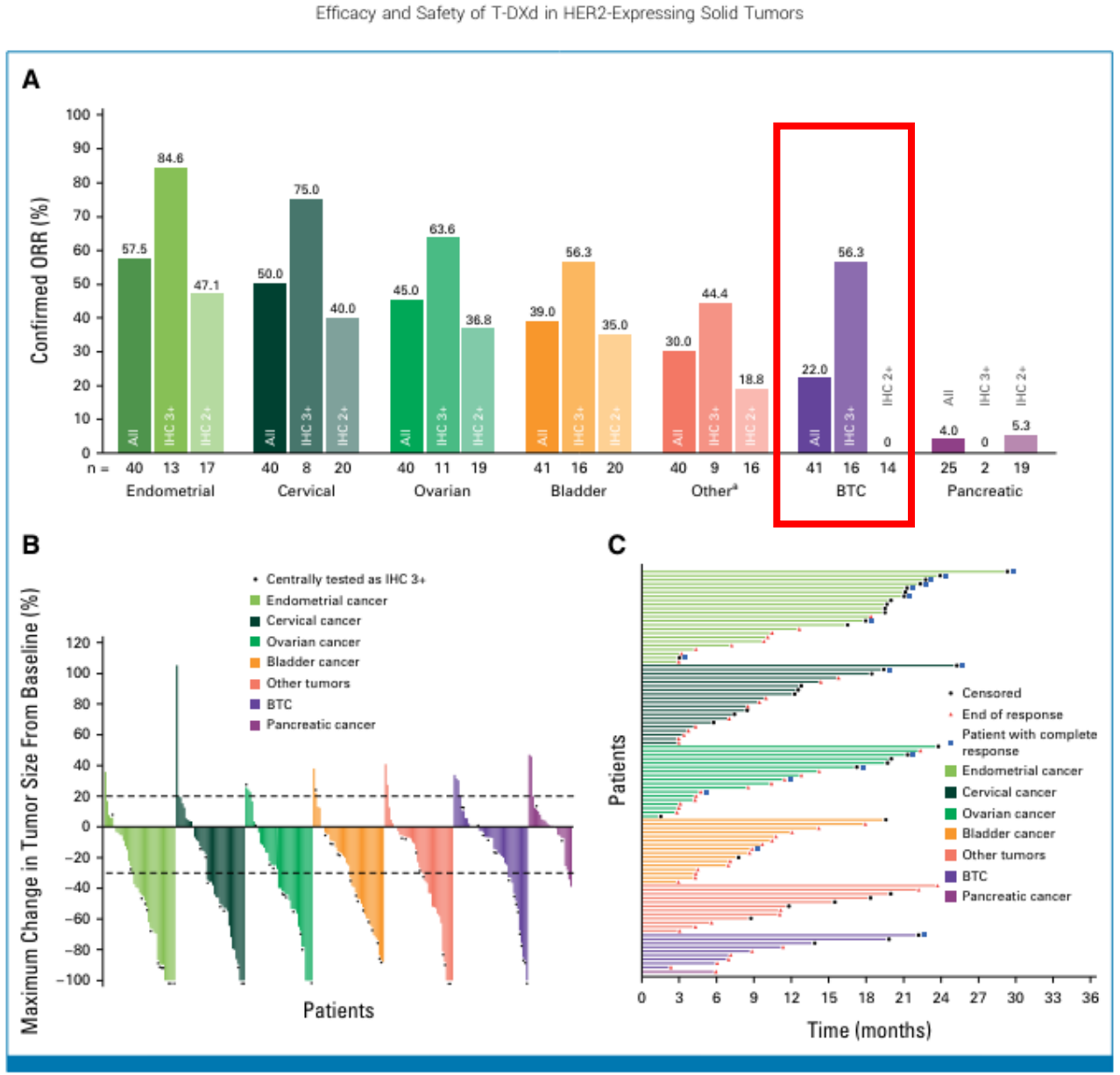
Trastuzumab Deruxtecan

- HERB trial[1,2]: Trastuzumab deruxtecan (T-DXd) in HER2+ advanced BTC
  - N=32: 24 HER2+, 8 HER2-low
  - ORR 36.4% in HER2+ (IHC 3+ or 2+/ISH+)
  - ORR 12.5% in HER2-low
  - Interstitial lung disease (ILD) in 25%
- DESTINY-PanTumor02[3]:
  - N=41 advanced BTC HER2+ (3+ or 2+ by IHC)
  - ORR 22% overall BTC
    - IHC3+ 56%
    - IHC2+ 0%
  - ILD 10.5%

FDA granted tumor-agnostic accelerated approval for T-DXd in patients with HER2 IHC3+ tumors in April 2024.



1. Ohba et al. Future Oncol 2022;18(19); 2. Ohba et al. ASCO 2022, Abstract 4006; 3. Meric-Bernstam et al. J Clin Oncol 2023;42(1)

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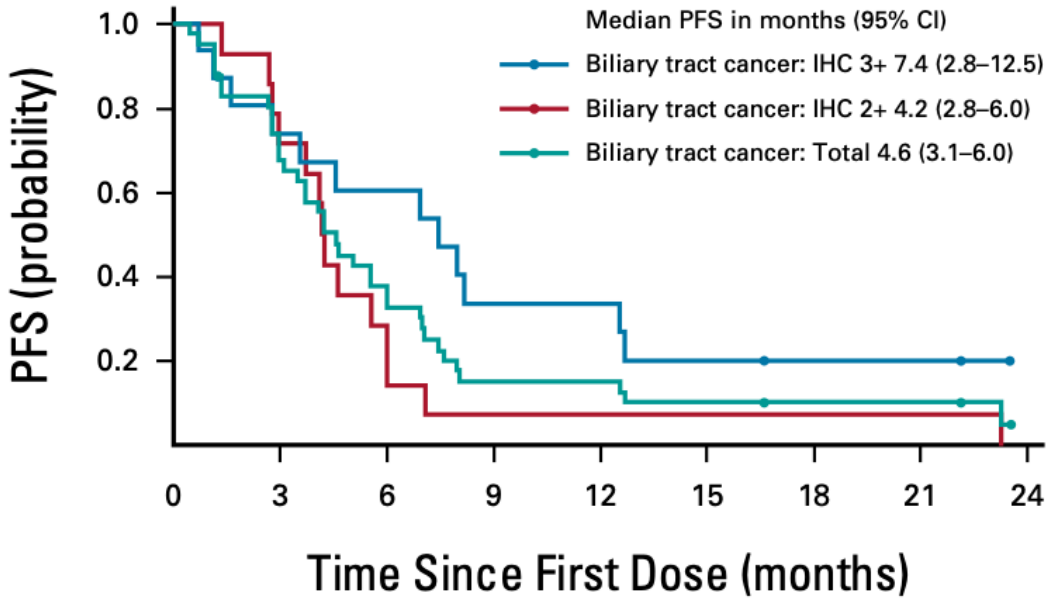
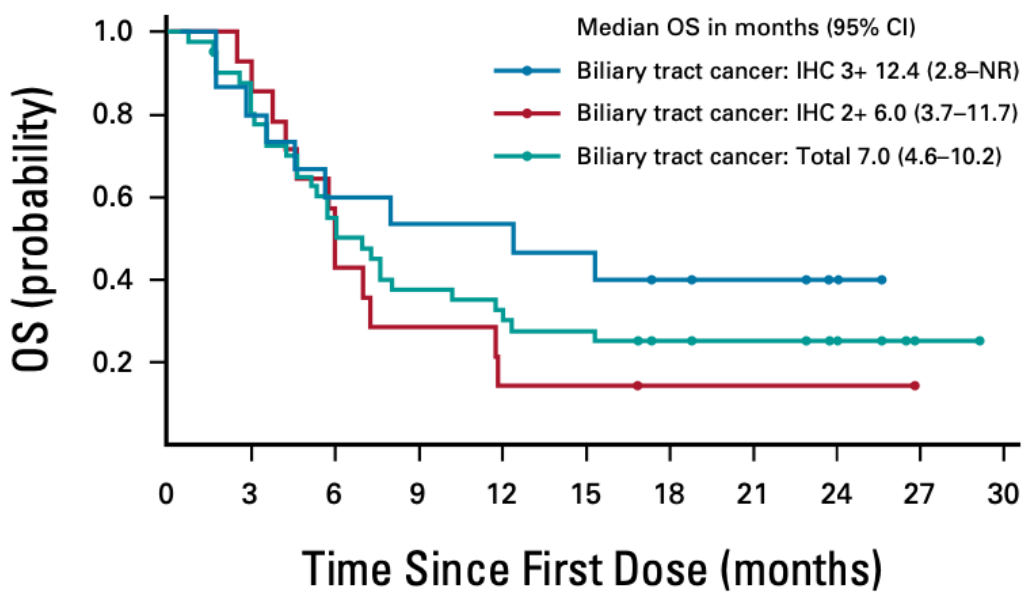
T-DXd in BTC: PFS and OS



No. at risk:

Biliary tract cancer: IHC 3+	16	11	9	5	5	3	2	2	0
Biliary tract cancer: IHC 2+	14	10	3	1	1	1	1	1	0
Biliary tract cancer: Total	41	27	14	6	6	4	3	3	0



No. at risk:

Biliary tract cancer: IHC 3+	16	12	9	8	8	7	5	4	1	0
Biliary tract cancer: IHC 2+	14	12	7	4	2	2	1	1	1	0
Biliary tract cancer: Total	41	32	21	15	12	11	8	7	4	1	0

Meric-Bernstam et al. J Clin Oncol 2023;42(1)

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T-DXd in BTC: Safety Profile

Adverse Event	Biliary Tract Cancer (n = 41)
Drug-related adverse events, No. (%)	33 (80.5)
Grade ≥3	16 (39.0)
Serious adverse events	5 (12.2)
Leading to discontinuation	5 (12.2)
Leading to dose modification[a]	13 (31.7)
Associated with death	0
Most common drug-related adverse events (>10% of total patients), No. (%)	
Nausea	19 (46.3)
Anemia	10 (24.4)
Diarrhea	8 (19.5)
Fatigue	9 (22.0)
Vomiting	9 (22.0)
Neutropenia	9 (22.0)
Decreased appetite	7 (17.1)
Asthenia	6 (14.6)
Alopecia	9 (22.0)
Thrombocytopenia	5 (12.2)

Meric-Bernstam et al. J Clin Oncol 2023;42(1)

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Summary of FDA-Approved Targeted Therapies in Advanced ≥2nd Line BTC in 2024

Full approval based upon randomized, phase 3 study in BTC:

- *IDH1* mutation: ivosidenib

Accelerated approvals based on phase 2 studies in BTC:

- *FGFR2* rearrangement/fusion: pemigatinib, futibatinib

Tumor-agnostic approvals:

- *BRAF* V600E: dabrafenib+trametinib
- MSI/TMB high: pembrolizumab, dostarlimab
- *NTRK* fusion: entrectinib, larotrectinib
- *RET* fusion: selpercatinib
- *ERBB2*/HER2 IHC3+: T-DXd

All patients with advanced BTC should have comprehensive molecular profiling including coverage of FGFR2 fusions/ rearrangements and HER2 IHC.

Targeted therapies have substantially improved outcomes for patients with tumors harboring molecular targets in BTC. Tumor profiling with NGS and HER2 IHC are now a standard of care.

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Second Opinion: Investigators Discuss How They Apply Available Clinical Research in the Care of Patients with Non-Small Cell Lung Cancer with an EGFR Mutation

A CME Symposium Held in Conjunction with the 2024 ASCO® Annual Meeting

Friday, May 31, 2024

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Jonathan W Goldman, MD
Corey J Langer, MD
Joel W Neal, MD, PhD
Zofia Piotrowska, MD, MHS
Joshua K Sabari, MD

Moderator

Helena Yu, MD

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