Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Hepatobiliary Cancers

Thursday, May 4, 2023
5:00 PM – 6:00 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD

Moderator

Neil Love, MD

RTP Year in Review 2023

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Professor
Memorial Sloan Kettering Cancer Center
New York, New York

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Richard S Finn, MD
Professor, Department of Medicine, Division of Hematology/Oncology
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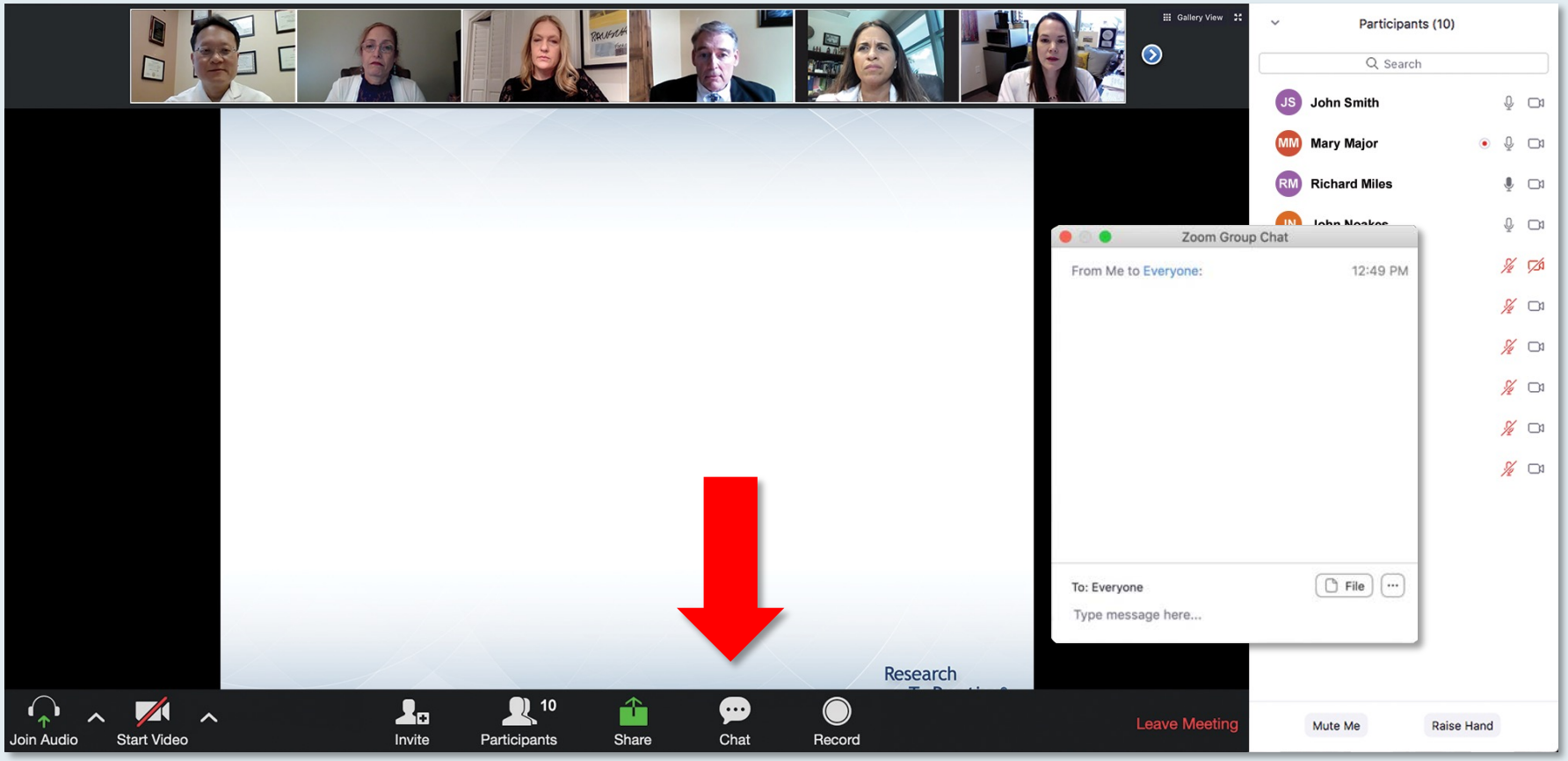
We Encourage Clinicians in Practice to Submit Questions



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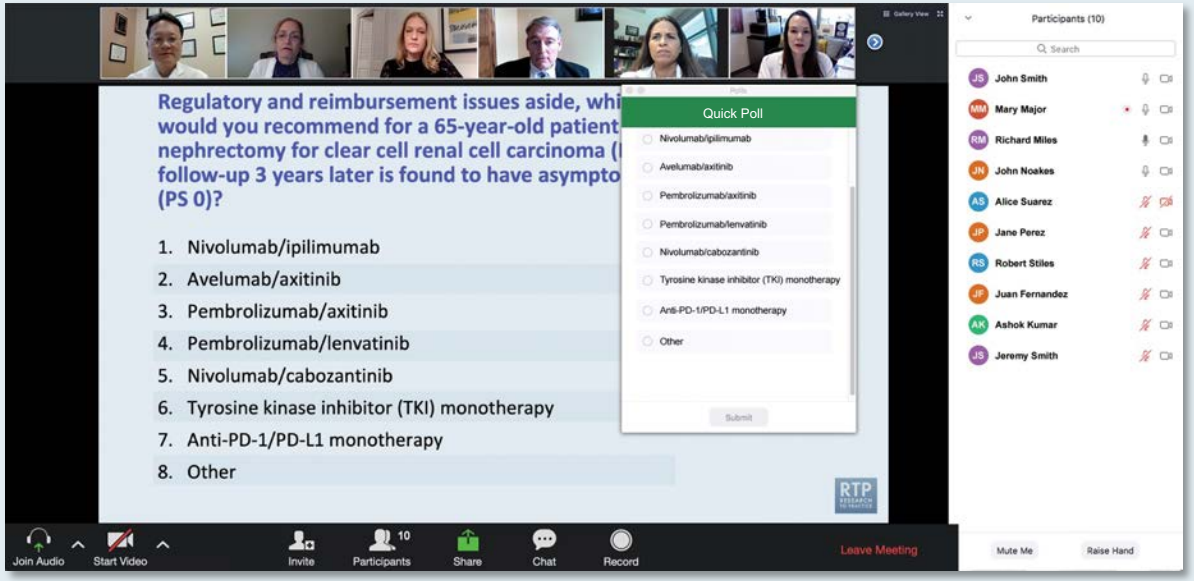

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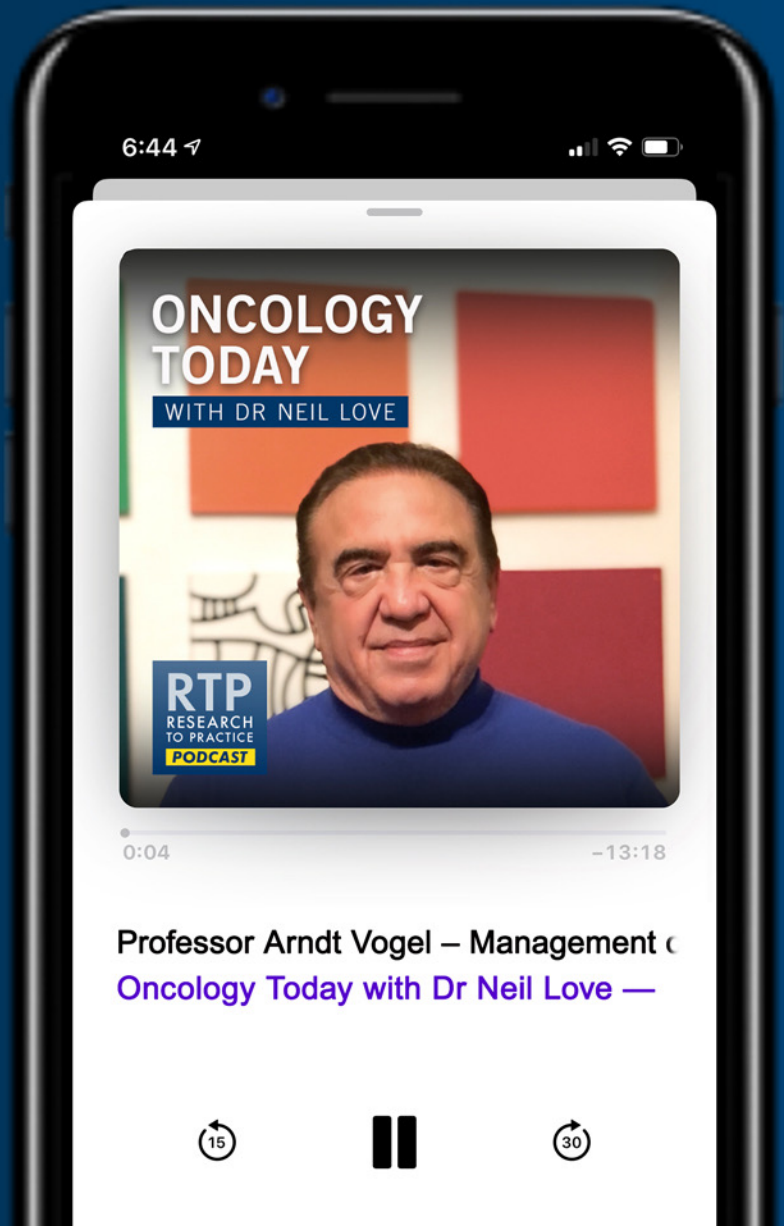

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Abou-Alfa — Disclosures

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Agenda

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MODULE 1: Hepatocellular Carcinoma

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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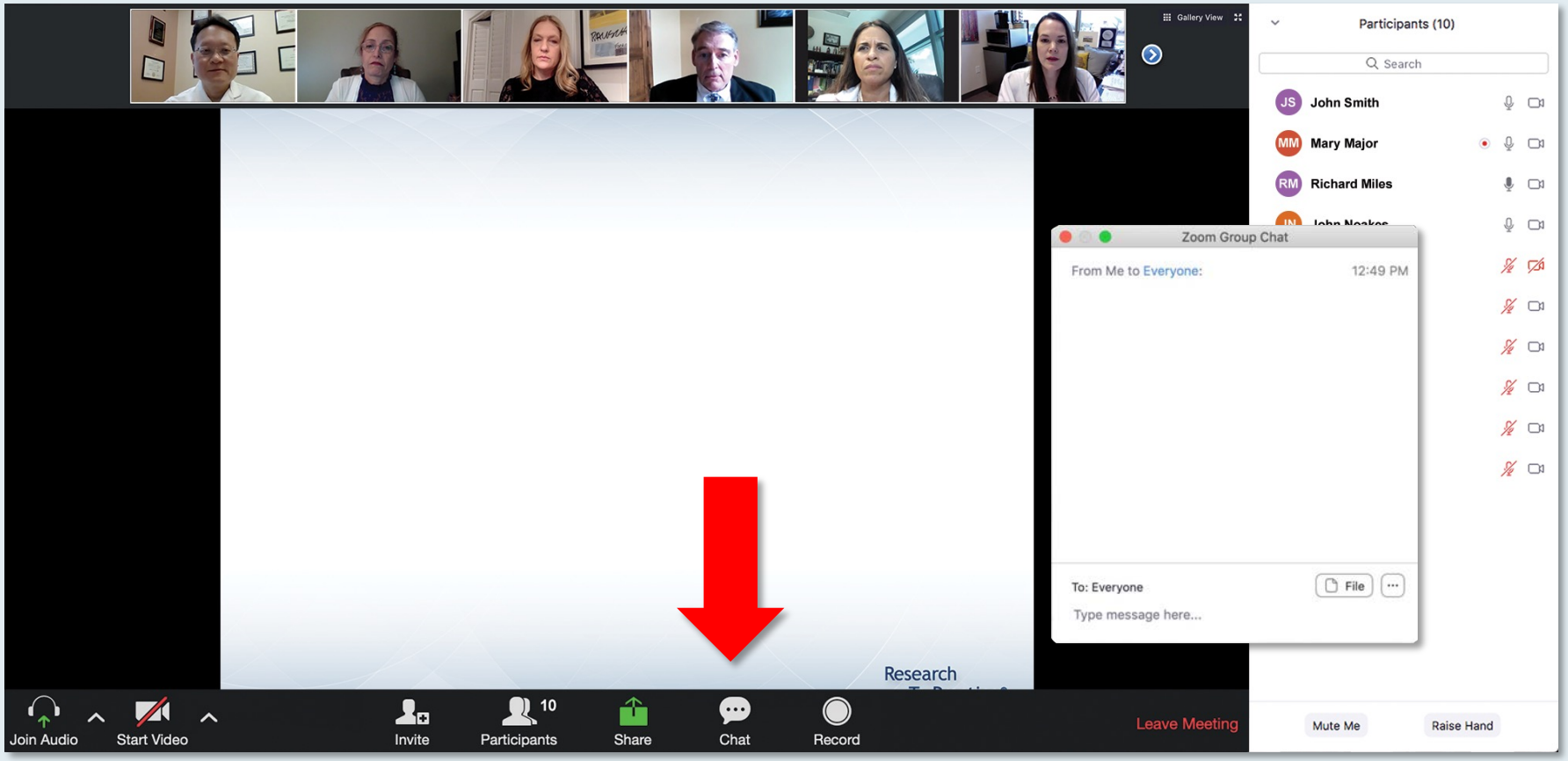

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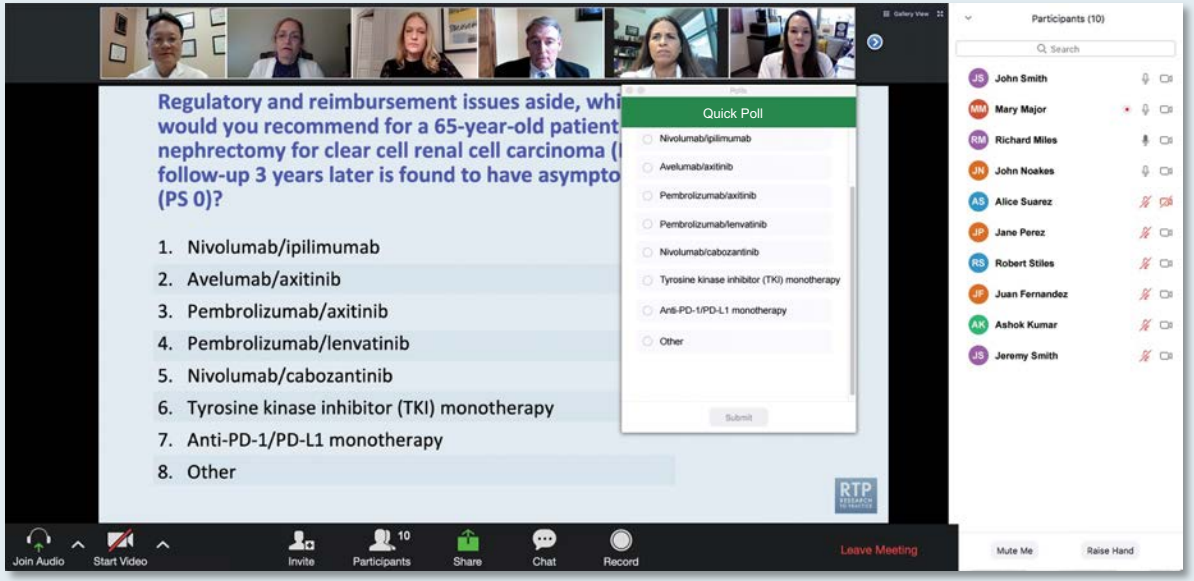

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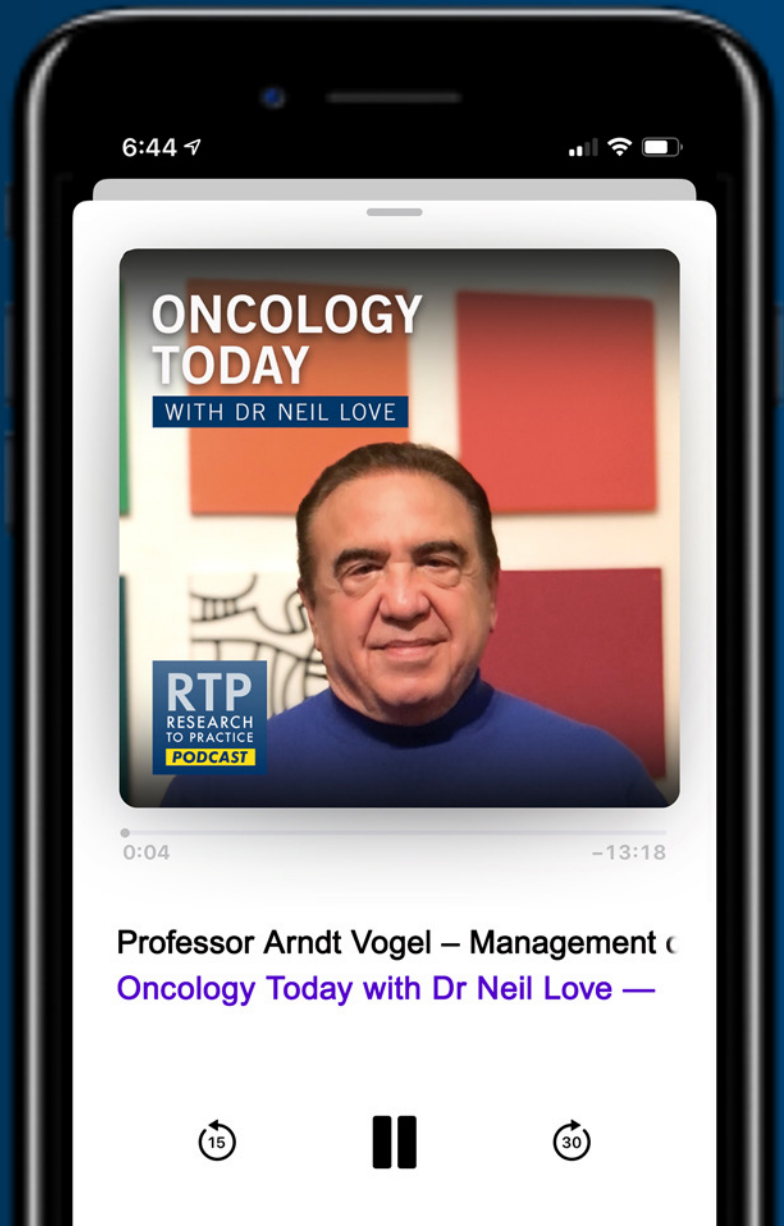

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- Cheng A-L et al. Updated efficacy and safety data from **IMbrave150**: **Atezolizumab** plus **bevacizumab** vs sorafenib for **unresectable** hepatocellular carcinoma. *J Hepatol* 2022;76(4):862-73.
- Abou-Alfa GK et al. **Tremelimumab** plus **durvalumab** in **unresectable** hepatocellular carcinoma. *NEJM Evid* 2022;1(8).
- Qin S et al. Final analysis of **RATIONALE-301**: Randomized, **phase III** study of **tislelizumab** versus sorafenib as **first-line** treatment for **unresectable** hepatocellular carcinoma. ESMO 2022;Abstract LBA36.

Key Data Sets

Ghassan Abou-Alfa, MD, MBA (Continued)

- Kelley RK et al. **Cabozantinib** plus **atezolizumab** versus sorafenib for **advanced** hepatocellular carcinoma (**COSMIC-312**): A multicentre, open-label, randomised, **phase 3** trial. *Lancet Oncol* 2022;23(8):995-1008.
- Finn RS et al. Primary results from the **phase III LEAP-002** study: **Lenvatinib** plus **pembrolizumab** versus lenvatinib as **first-line (1L)** therapy for **advanced** hepatocellular carcinoma (aHCC). ESMO 2022;Abstract LBA34.
- Rimini M et al. **Atezolizumab** plus **bevacizumab** versus lenvatinib or sorafenib in **non-viral unresectable** hepatocellular carcinoma: An international propensity score matching analysis. *ESMO Open* 2022;7(6):100591.
- El-Khoueiry AB et al. Safety and efficacy of **cabozantinib** for patients with **advanced** hepatocellular carcinoma who **advanced to Child-Pugh B** liver function at study week 8: A retrospective analysis of the **CELESTIAL** randomised controlled trial. *BMC Cancer* 2022;22(1):377.
- Freemantle N et al. **Quality of life** assessment of **cabozantinib** in patients with advanced hepatocellular carcinoma in the **CELESTIAL** trial. *Eur J Cancer* 2022;168:91-8.

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Ghassan Abou-Alfa, MD, MBA (Continued)

- Qin S et al. **Pembrolizumab** versus placebo as **second-line** therapy in patients from **Asia** with **advanced** hepatocellular carcinoma: A randomized, double-blind, phase III trial. *J Clin Oncol* 2023;41(7):1434-43.
- Melero I et al. **Nivolumab (NIVO)** plus **ipilimumab (IPI)** combination therapy in patients with **advanced** hepatocellular carcinoma (aHCC): **5-year** results from **CheckMate 040**. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-12.
- Yau T et al. **Nivolumab** plus **cabozantinib** with or without **ipilimumab** for **advanced** hepatocellular carcinoma: Results from **cohort 6** of the **CheckMate 040** trial. *J Clin Oncol* 2023;41(9):1747-57.
- Qin S et al. **Camrelizumab** (C) plus **rivoceranib** (R) vs. sorafenib (S) as **first-line** therapy for **unresectable** hepatocellular carcinoma (uHCC): A randomized, phase III trial. ESMO 2022; Abstract LBA35.
- NCT05301842: A **phase III**, randomized, open-label, sponsor-blinded, multicenter study of **durvalumab** in combination with **tremelimumab ± lenvatinib** given concurrently with **TACE** compared to TACE alone in patients with locoregional hepatocellular carcinoma (**EMERALD-3**)

Key Data Sets

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- Oh D-Y et al. **Durvalumab** plus **gemcitabine** and **cisplatin** in advanced **biliary tract** cancer. *NEJM Evid* 2022;1(8).
- Oh D et al. Updated overall survival (OS) from the **phase III TOPAZ-1** study of **durvalumab** (D) or placebo (PBO) plus **gemcitabine and cisplatin** (+ GC) in patients (pts) with advanced **biliary tract** cancer (BTC). ESMO 2022;Abstract 56P.
- He AR et al. Outcomes by primary tumour location in patients with advanced biliary tract cancer treated with **durvalumab** or placebo plus **gemcitabine and cisplatin** in the **phase 3 TOPAZ-1** study. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-1.
- Kelley RK et al. **Pembrolizumab** in combination with **gemcitabine and cisplatin** compared with gemcitabine and cisplatin alone for patients with advanced **biliary tract** cancer (**KEYNOTE-966**): a randomised, double-blind, placebo-controlled, **phase 3** trial. *Lancet* 2023 April 16;[Online ahead of print].
- Vogel A et al. **Pemigatinib** for **previously treated** locally advanced or metastatic **cholangiocarcinoma**: Final results from **FIGHT-202**. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-2.

Key Data Sets

Richard S Finn, MD (Continued)

- Bibeau K et al. Progression-free survival in patients with **cholangiocarcinoma** with or without **FGF/FGFR alterations**: A **FIGHT-202 post hoc** analysis of prior systemic therapy response. *JCO Precis Oncol* 2022;6:e2100414.
- Goyal L et al. **Futibatinib** for **FGFR2-rearranged intrahepatic cholangiocarcinoma**. *N Engl J Med* 2023;388(3):228-39.
- Goyal L et al. Updated results of the **FOENIX-CCA2 trial**: Efficacy and safety of **futibatinib** in **intrahepatic cholangiocarcinoma** (iCCA) harboring **FGFR2** fusions/rearrangements. ASCO 2022;Abstract 4009.
- Zymeworks announces positive topline data in the pivotal **HERIZON-BTC-01** trial of **zanidatamab** [press release]. December 19, 2022. Available at https://ir.zymeworks.com/news-releases/news-release-details/zymeworks-announces-positive-topline-data-pivotal-herizon-btc-01.
- Ohba A et al. **Trastuzumab deruxtecan** (T-DXd; DS-8201) in patients (pts) with **HER2-expressing** unresectable or recurrent **biliary tract** cancer (BTC): An investigator-initiated multicenter phase 2 study (**HERB** trial). ASCO 2022;Abstract 4006.

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Richard S Finn, MD (Continued)

- Carrizosa DR et al. **CRESTONE**: Initial efficacy and safety of **seribantumab** in solid tumors harboring **NRG1 fusions**. ASCO 2022;Abstract 3006.
- El-Khoueiry AB et al. **IMbrave151**: A phase 2, randomized, double-blind, placebo-controlled study of **atezolizumab** with or without **bevacizumab** in combination with **cisplatin plus gemcitabine** in patients with **untreated**, advanced **biliary tract** cancer. Gastrointestinal Cancers Symposium 2023;Abstract 491.
- Yoo C et al. Final results from the **NIFTY** trial, a phase IIb, randomized, open-label study of liposomal irinotecan (**nal-IRI**) plus fluorouracil (5-FU)/leucovorin **(LV)** in patients (pts) with **previously treated** metastatic **biliary tract** cancer (BTC). ESMO 2022;Abstract 55P.

Agenda

Prologue: Last Week

MODULE 1: Hepatocellular Carcinoma

MODULE 2: Biliary Tract Cancers

MODULE 3: Appendix

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- IMbrave050: Adjuvant atezolizumab/bevacizumab; BCLC revisions
- Immuno-oncology combinations as first-line systemic treatment for advanced hepatocellular carcinoma (HCC)
- Safety and efficacy of cabozantinib in HCC

MODULE 2: Biliary Tract Cancers

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IMbrave050: Adjuvant Atezolizumab/Bevacizumab; BCLC Revisions

- Chow et al. **IMbrave050**: **Phase 3** study of **adjuvant atezolizumab + bevacizumab** versus active surveillance in patients with hepatocellular carcinoma (HCC) at **high risk of disease recurrence** following resection or ablation. AACR 2023;Abstract CT003.
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IMbrave050: Phase 3 study of adjuvant atezolizumab + bevacizumab versus active surveillance in patients with hepatocellular carcinoma at high risk of disease recurrence following resection or ablation

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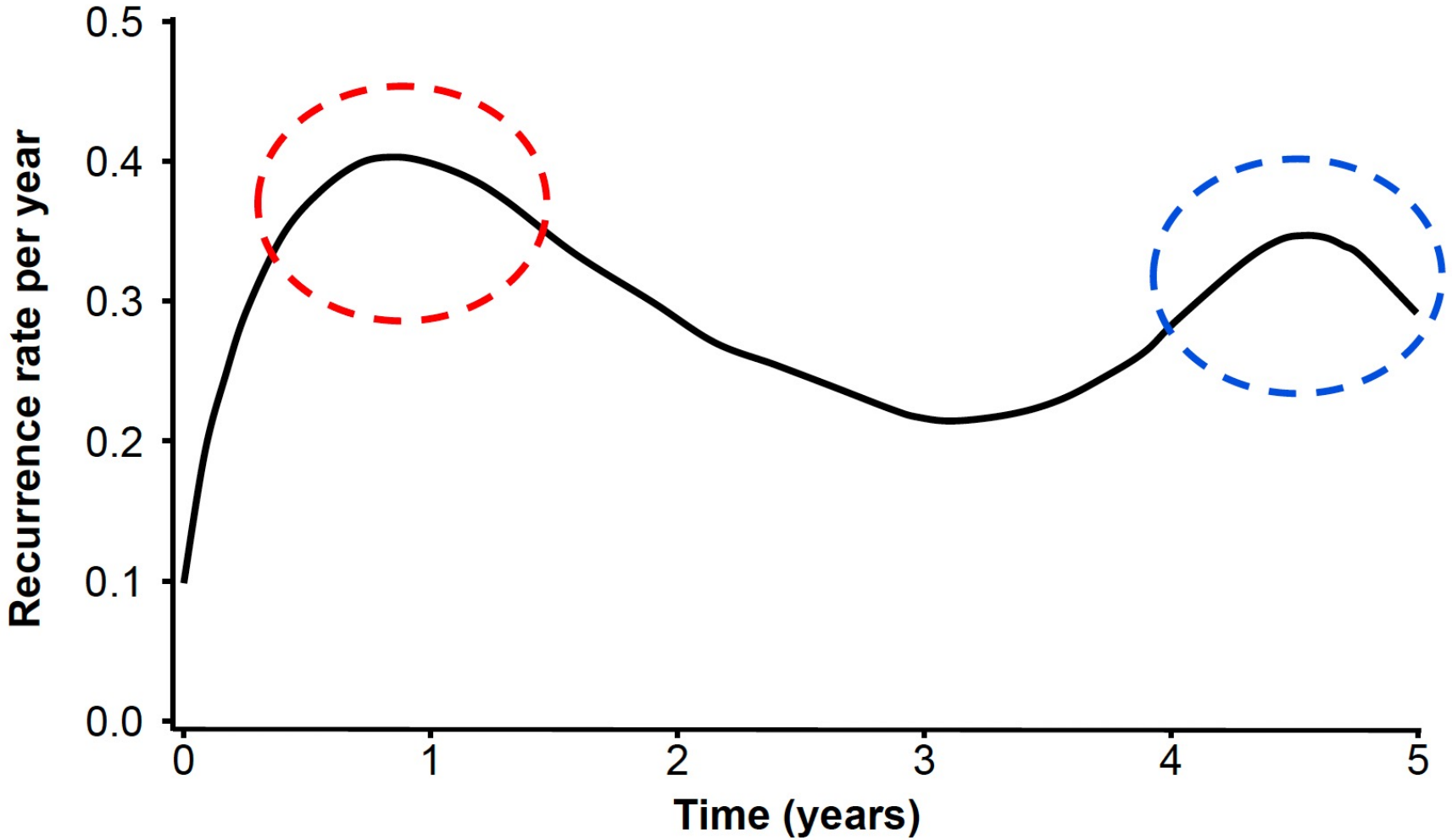
Bimodal recurrence after HCC resection

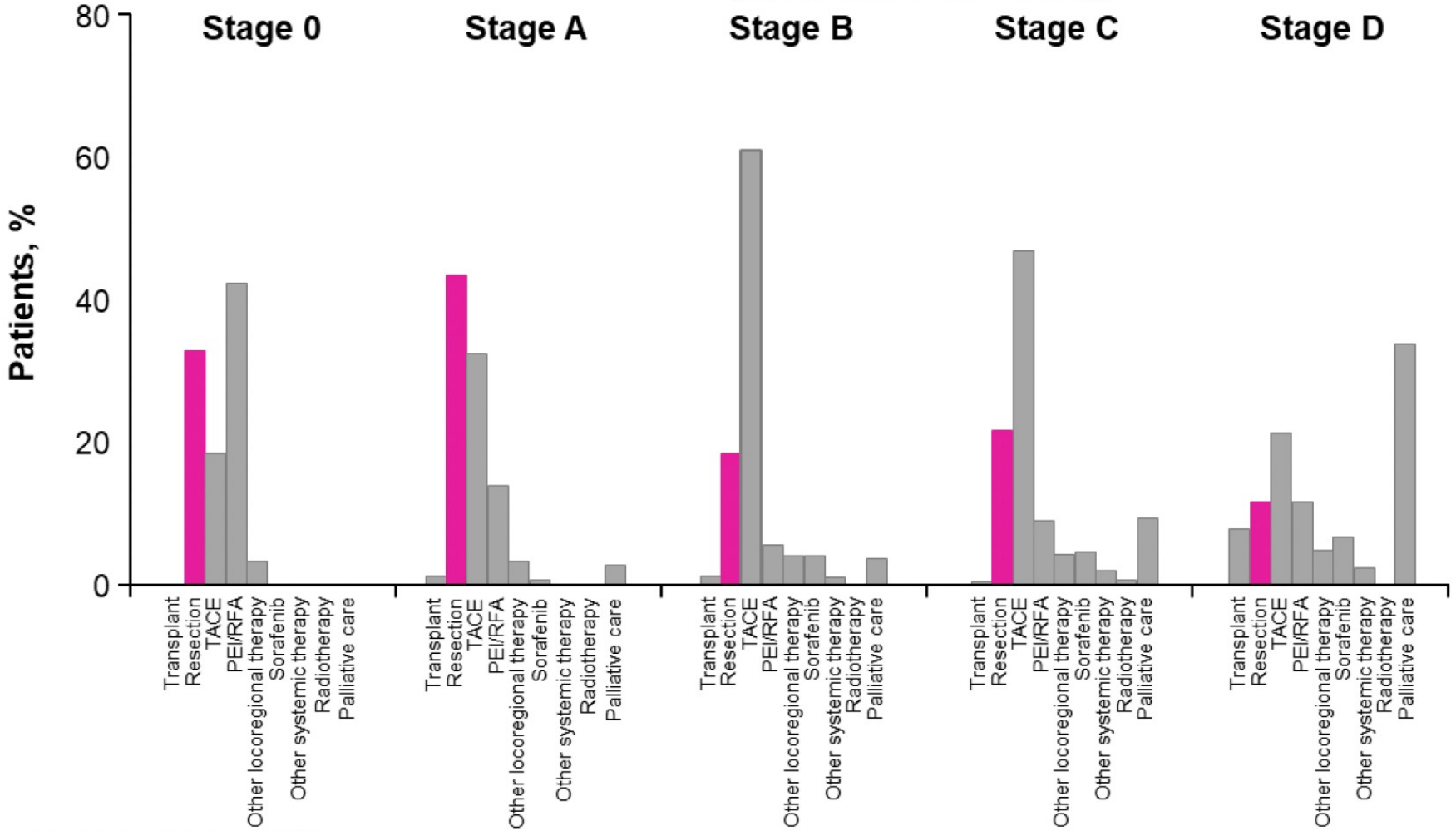


- Recurrence rate after resection peaks at around **1 year**, then gradually decreases over the next 2 years.[1] Current consensus is that these recurrences are from **micro-metastases**
- A second lower postoperative recurrence peak occurs at **4-5 years**[1]
- The second peak is currently understood to be due to **de novo tumors** associated with underlying liver disease[2]

1. Imamura et al. J Hepatol 2003. 2. Yao et al. Ann Surg Oncol 2022.

Resection is frequently used as first treatment for HCC with high-risk factors for recurrence

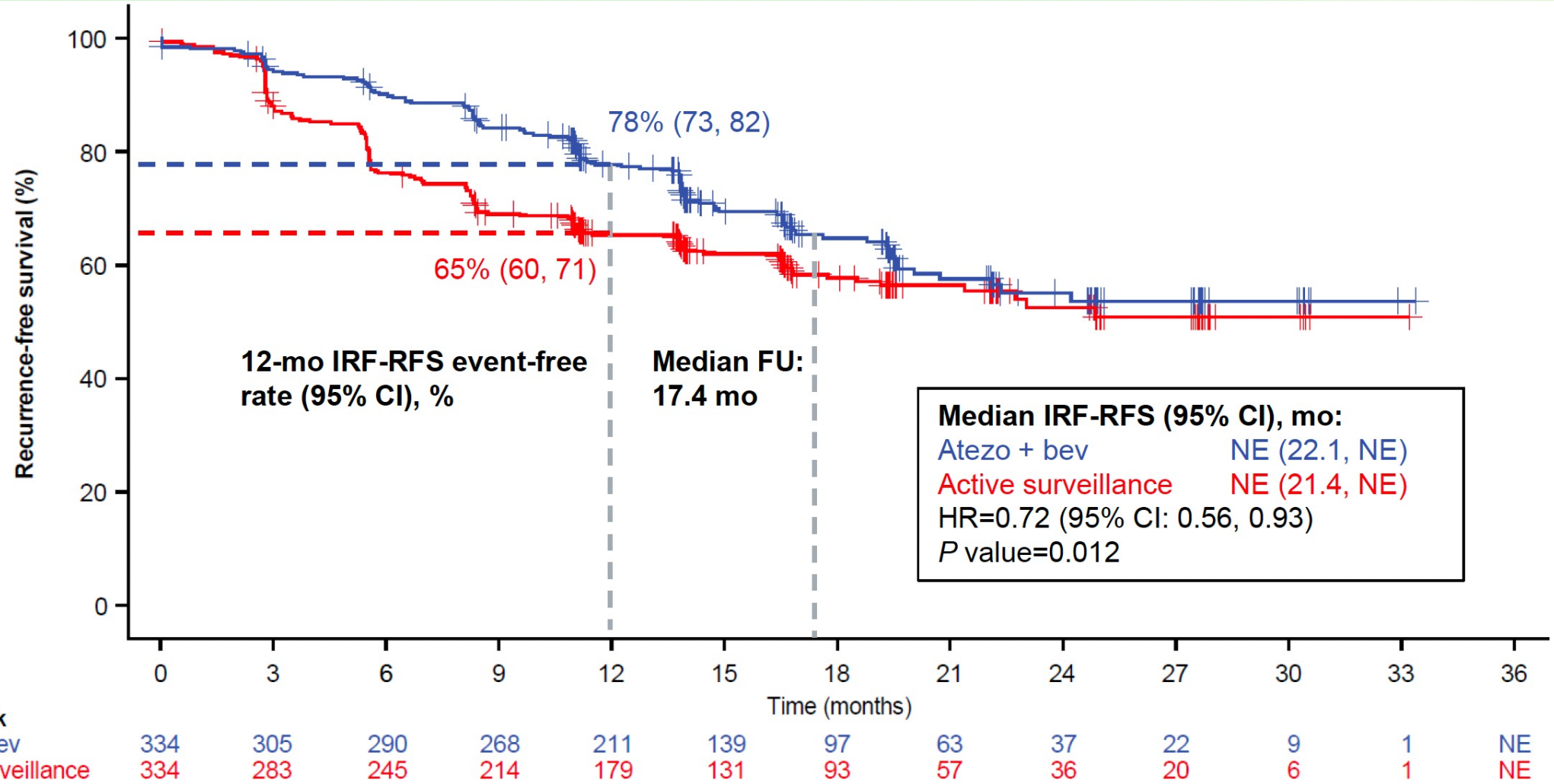
First recorded HCC treatment by BCLC stage (the BRIDGE study)[1]



- Globally, treatment practices include surgical resection for **high-risk patients** like those enrolled in IMbrave050

1. Park et al. Liver Int 2015.

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

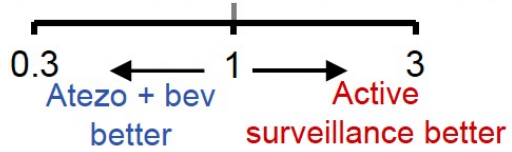


No. at risk													
Atezo + bev	334	305	290	268	211	139	97	63	37	22	9	1	NE
Active surveillance	334	283	245	214	179	131	93	57	36	20	6	1	NE

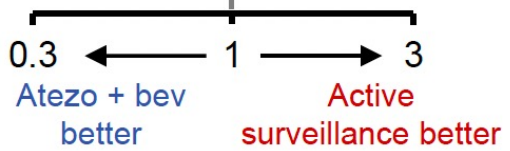
Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log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

IRF-assessed RFS subgroups

Baseline risk factors	No. of patients	Unstratified HR (95% CI)
All patients	668	0.74 (0.57, 0.95)
<65 years old	427	0.80 (0.58, 1.08)
≥65 years old	241	0.64 (0.41, 1.00)
Male	555	0.74 (0.56, 0.98)
Female	113	0.73 (0.38, 1.40)
Asian	545	0.75 (0.56, 0.99)
White	78	0.59 (0.28, 1.25)
Other race	45	0.91 (0.36, 2.29)
ECOG PS 0	527	0.65 (0.48, 0.87)
ECOG PS 1	141	1.13 (0.67, 1.91)
PD-L1 ≥1%	294	0.82 (0.55, 1.20)
PD-L1 <1%	270	0.62 (0.43, 0.91)
Unknown PD-L1	104	0.82 (0.39, 1.71)
1 high-risk feature[a]	311	0.74 (0.48, 1.14)
≥2 high-risk features[a]	274	0.77 (0.55, 1.08)
BCLC 0/A	569	0.78 (0.59, 1.04)
BCLC B	57	0.44 (0.18, 1.08)
BCLC C	42	0.73 (0.31, 1.73)



Baseline risk factors	No. of patients	Unstratified HR (95% CI)
Hepatitis B etiology	416	0.87 (0.63, 1.20)
Hepatitis C etiology	72	0.65 (0.30, 1.40)
Non-viral etiology	83	0.70 (0.34, 1.42)
Unknown etiology	97	0.45 (0.23, 0.89)
Resection	585	0.75 (0.58, 0.98)
Ablation	83	0.61 (0.26, 1.41)
In patients who underwent resection		
1 tumor	526	0.77 (0.58, 1.03)
>1 tumors	59	0.60 (0.28, 1.27)
Tumor size >5 cm	327	0.66 (0.48, 0.91)
Tumor size ≤5 cm	258	1.06 (0.65, 1.74)
mVI present	354	0.79 (0.56, 1.10)
mVI absent	231	0.69 (0.45, 1.06)
Poor tumor differentiation	245	0.76 (0.51, 1.12)
No poor tumor differentiation	340	0.74 (0.52, 1.07)
Received TACE	66	1.21 (0.57, 2.59)
Did not receive TACE	519	0.71 (0.53, 0.94)

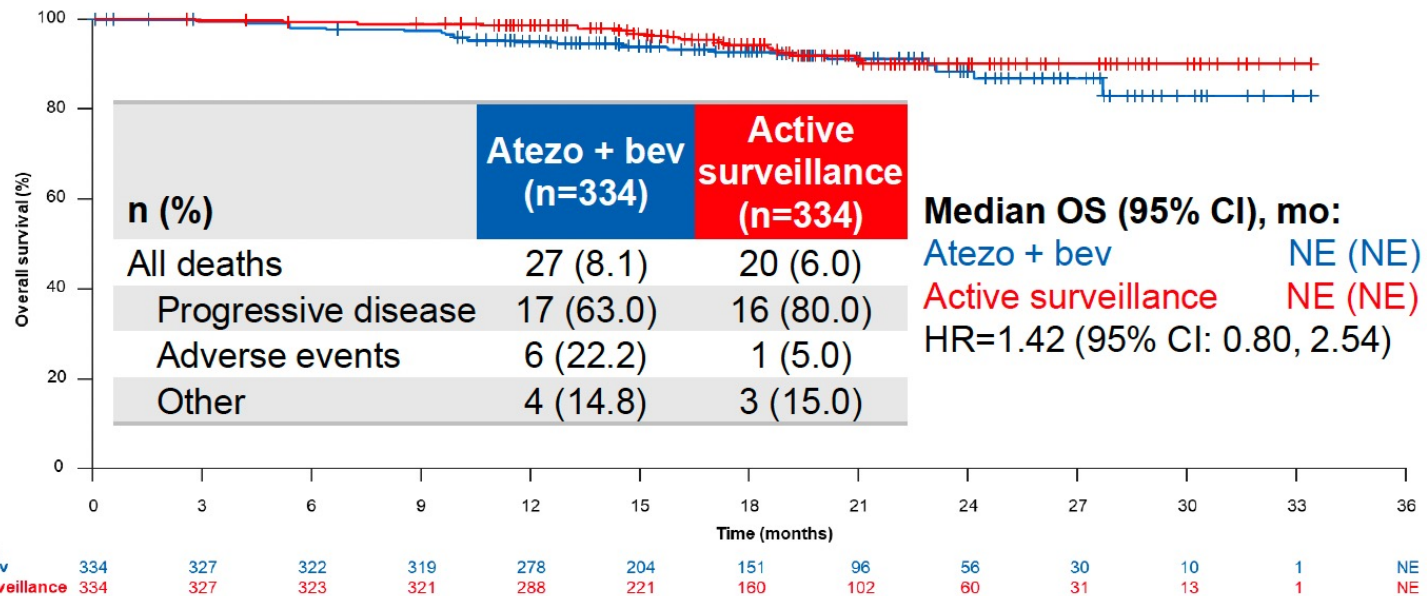


Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.
mVI, microvascular invasion. [a] Patients who underwent ablation were categorized as "not applicable."

IRF = independent review facility; RFS = relapse-free survival

Overall survival was highly immature

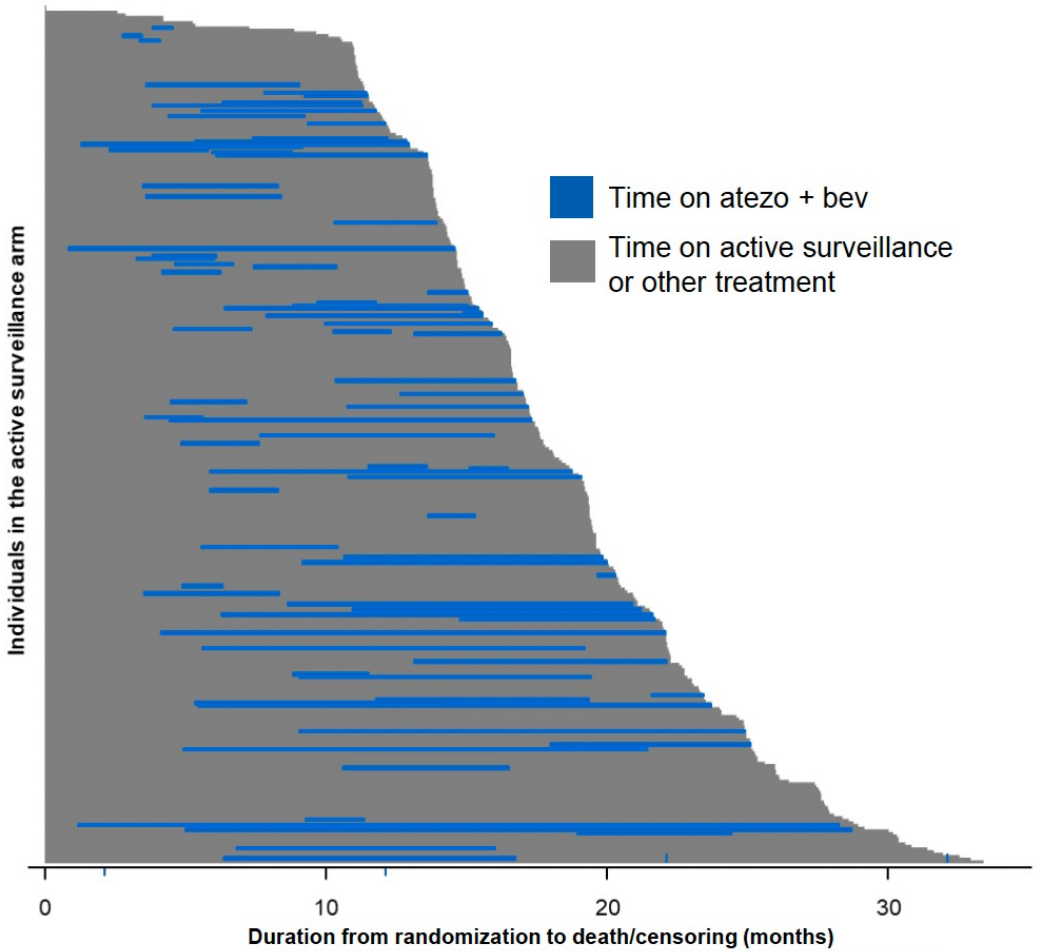
- **OS is highly immature, with a 7% event-patient ratio (n=47).** There were:
  - 7 more deaths in the atezo + bev arm (27 vs 20)
  - Similar number of deaths due to HCC recurrence
  - 3 COVID-19-related deaths within 1 year of randomization, all in the atezo + bev arm
- Patients in the active surveillance 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)

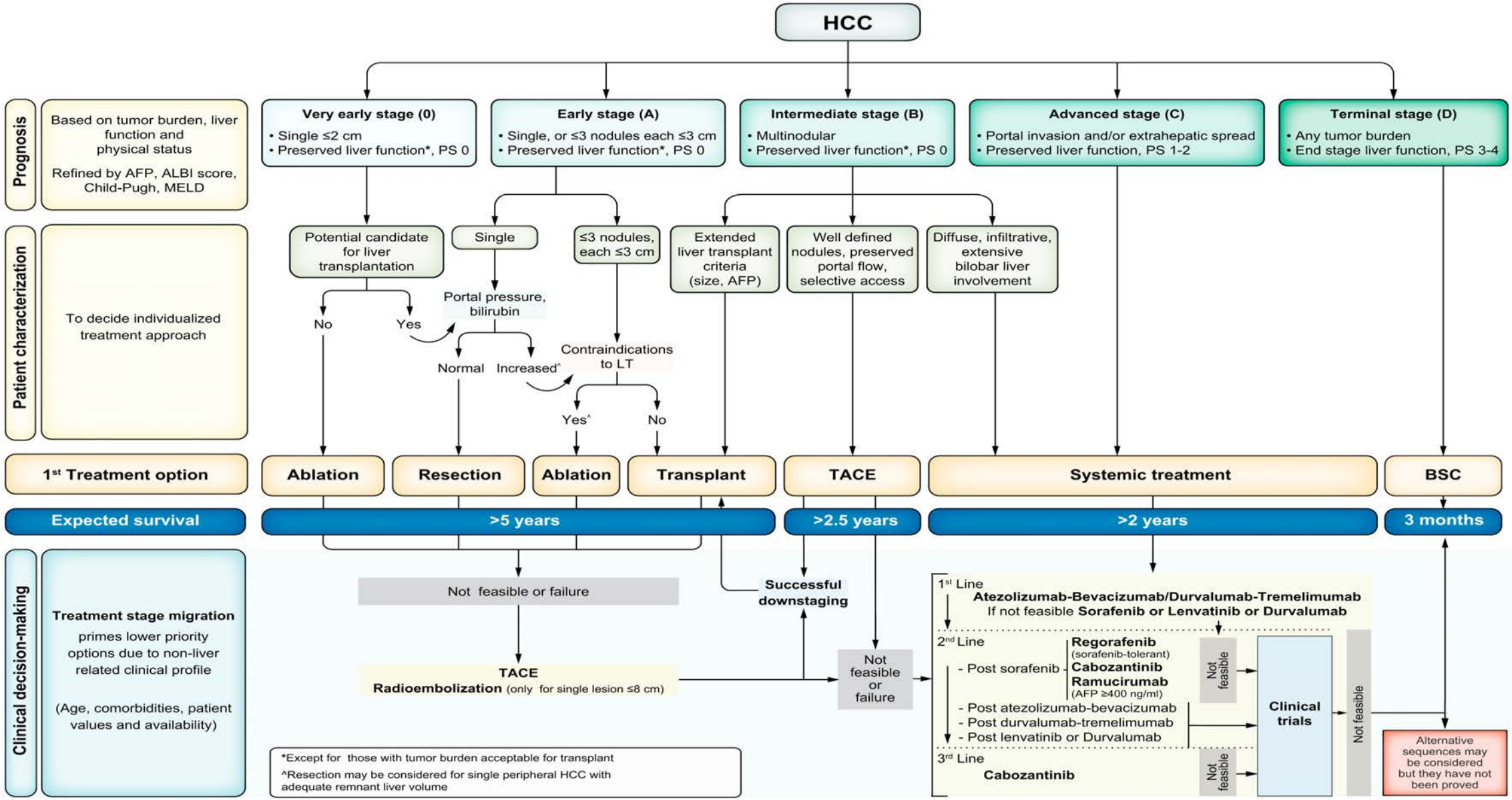
Of the 133 patients with an RFS event during active surveillance, **81 (61%) crossed over to atezo + bev**



Clinical cutoff: October 21, 2022. Median follow-up duration: 17.4 mo. NE, not estimable. HR is stratified.

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

BCLC Revised



Reig M et al. J Hepatol 2022;76(3):681-93.

Courtesy of Ghassan Abou-Alfa, MD, MBA

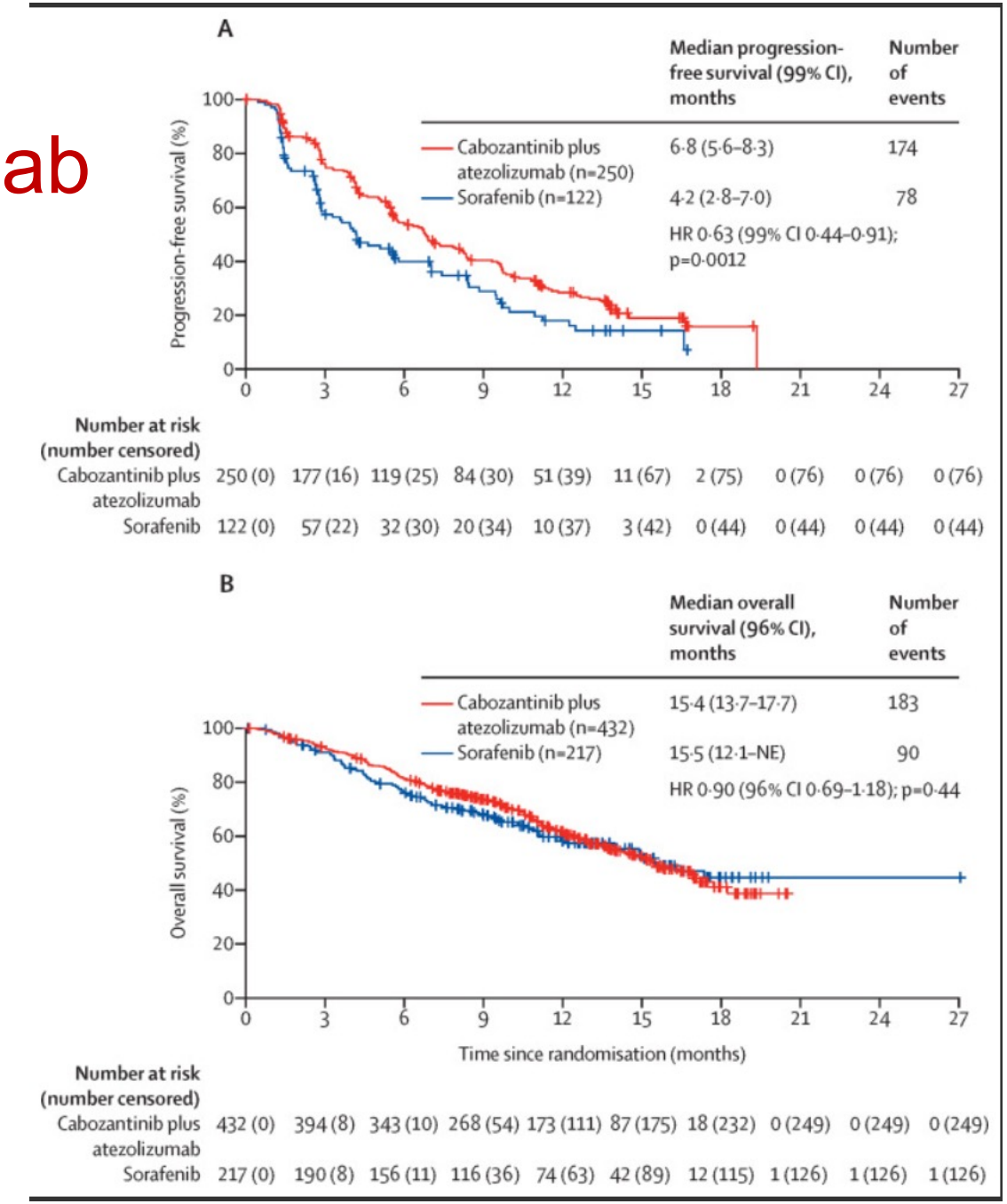
“Prospective translational studies should evaluate the role of ATB-mediated gut dysbiosis as a proposed mechanism underlying the adverse outcome in immunotherapy recipients.”

Fulgenzi CAM et al. Gastrointestinal Cancers Symposium 2023;Abstract 597.

Immuno-Oncology Combinations as First-Line Systemic Treatment for Advanced HCC

- Cheng A-L et al. Updated efficacy and safety data from **IMbrave150**: **Atezolizumab** plus **bevacizumab** vs sorafenib for **unresectable** hepatocellular carcinoma. *J Hepatol* 2022;76(4):862-73.
- Abou-Alfa GK et al. **Tremelimumab** plus **durvalumab** in **unresectable** hepatocellular carcinoma. *NEJM Evid* 2022;1(8).
- Qin S et al. Final analysis of **RATIONALE-301**: Randomized, **phase III** study of **tislelizumab** versus sorafenib as **first-line** treatment for **unresectable** hepatocellular carcinoma. ESMO 2022;Abstract LBA36.
- Kelley RK et al. **Cabozantinib** plus **atezolizumab** versus sorafenib for **advanced** hepatocellular carcinoma (**COSMIC-312**): A multicentre, open-label, randomised, **phase 3** trial. *Lancet Oncol* 2022;23(8):995-1008.
- Finn RS et al. Primary results from the **phase III LEAP-002** study: **Lenvatinib** plus **pembrolizumab** versus lenvatinib as **first-line (1L)** therapy for **advanced** hepatocellular carcinoma (aHCC). ESMO 2022;Abstract LBA34.
- Rimini M et al. **Atezolizumab** plus **bevacizumab** versus lenvatinib or sorafenib in **non-viral unresectable** hepatocellular carcinoma: An international propensity score matching analysis. *ESMO Open* 2022;7(6):100591.

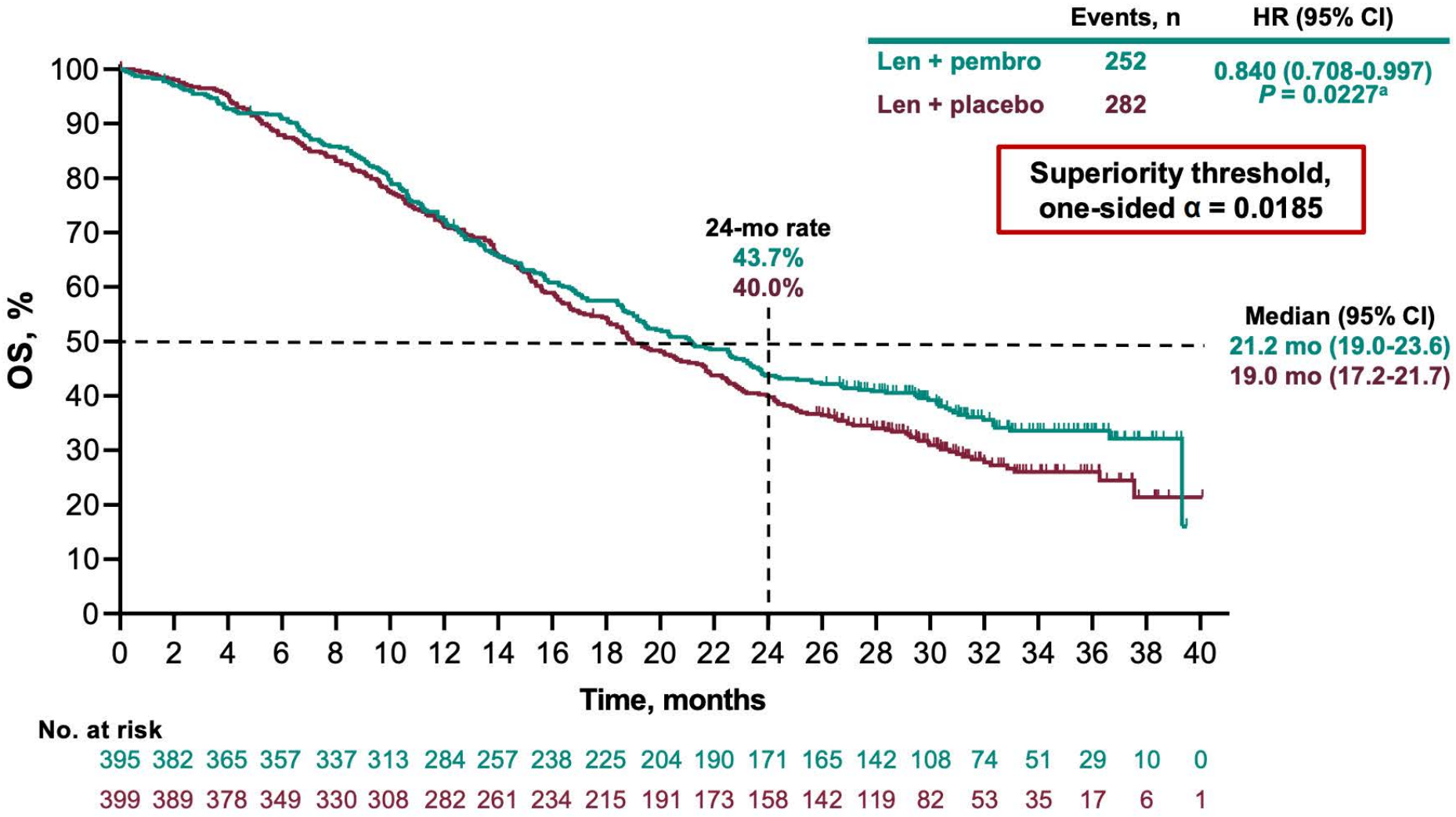
Cabozantinib plus Atezolizumab versus Sorafenib



Kelley RK et al. Lancet Oncol 2022;23(8):995-1008.

Courtesy of Ghassan Abou-Alfa, MD, MBA

LEAP-002



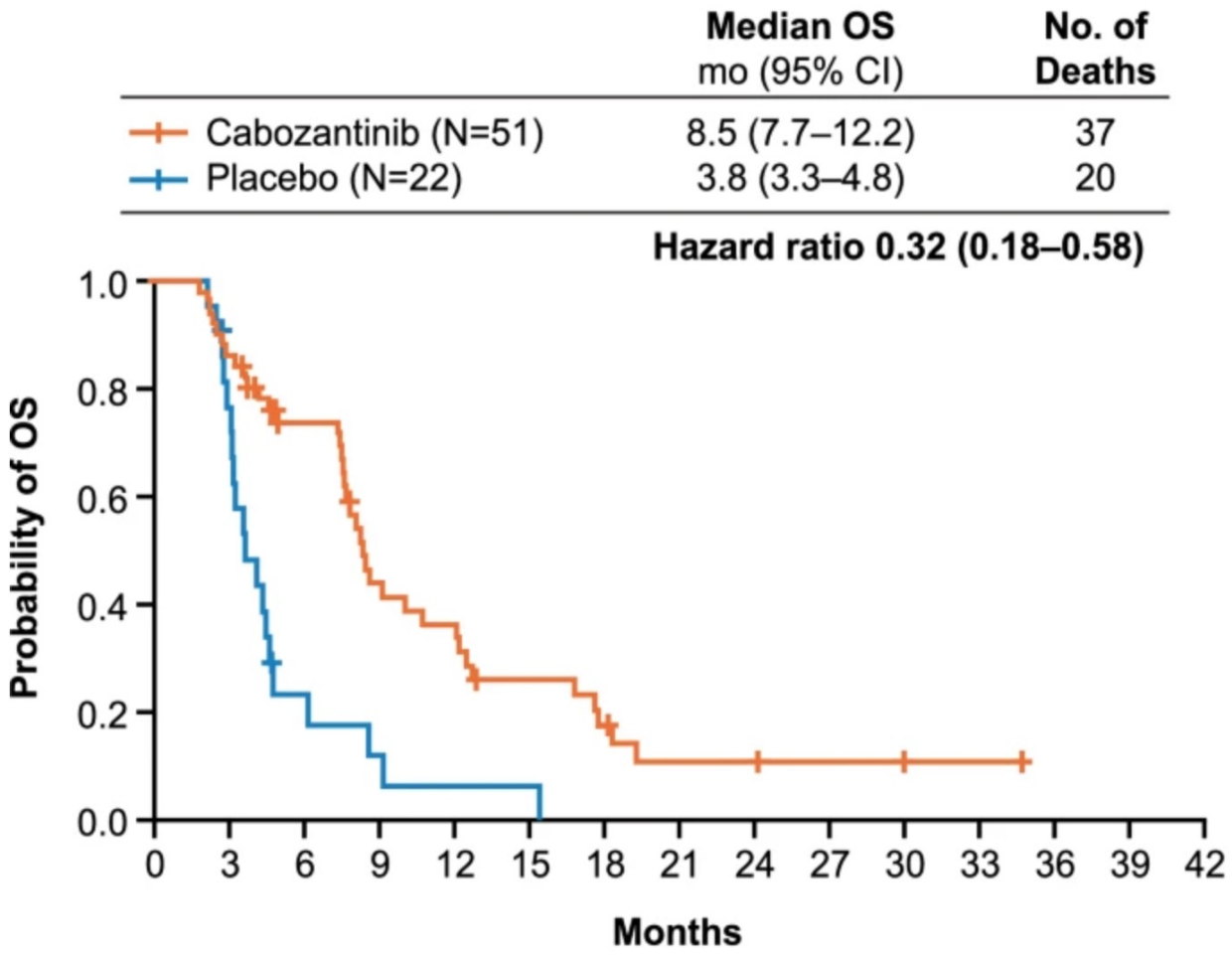
Finn RS et al. ESMO 2022;Abstract LBA34.

Courtesy of Ghassan Abou-Alfa, MD, MBA

Safety and Efficacy of Cabozantinib in HCC

- El-Khoueiry AB et al. Safety and efficacy of **cabozantinib** for patients with **advanced** hepatocellular carcinoma who **advanced to Child-Pugh B** liver function at study week 8: A retrospective analysis of the **CELESTIAL** randomised controlled trial. *BMC Cancer* 2022;22(1):377.
- Freemantle N et al. **Quality of life** assessment of **cabozantinib** in patients with advanced hepatocellular carcinoma in the **CELESTIAL** trial. *Eur J Cancer* 2022;168:91-8.

Cabozantinib and Worsening Child Pugh Score



	Patients with Child–Pugh B at Week 8, *n*	Patients with available BCDM-determined Child–Pugh score points, *n* [a]	Child–Pugh score (Week 8) *n* (%) [b]		
			7 points	8 points	9 points
Cabozantinib	51	42	26 (51)	11 (22)	3 (6)
Placebo	22	21	11 (50)	3 (14)	5 (23)

El-Khoueiry AB et al. BMC Cancer 2022;22(1):377.

Courtesy of Ghassan Abou-Alfa, MD, MBA

Cabozantinib and Quality of life in Patients with Advanced HCC

Dimension	Cabozantinib, mean (SD)	Placebo, mean (SD)	Difference (cabozantinib minus placebo)	Lower 95% CI	Upper 95% CI	*p*
Mobility	1.89 (0.95)	1.54 (0.81)	1.24	1.14	1.34	<0.0001
Self-care	1.45 (0.79)	1.25 (0.62)	1.14	1.04	1.24	0.0033
Usual activities	1.93 (0.95)	1.63 (0.87)	1.20	1.10	1.30	<0.0001
Pain/discomfort	2.18 (0.94)	1.93 (0.91)	1.13	1.06	1.21	0.0005
Anxiety/depression	1.62 (0.81)	1.53 (0.72)	1.07	0.99	1.16	0.1104

Freemantle N et al. Eur J Cancer 2022;168:91-8.

Courtesy of Ghassan Abou-Alfa, MD, MBA

Other Important Papers

- Qin S et al. **Pembrolizumab** versus placebo as **second-line** therapy in patients from **Asia** with **advanced** hepatocellular carcinoma: A randomized, double-blind, phase III trial. *J Clin Oncol* 2023;41(7):1434-43.
- Melero I et al. **Nivolumab (NIVO)** plus **ipilimumab (IPI)** combination therapy in patients with **advanced** hepatocellular carcinoma (aHCC): **5-year** results from **CheckMate 040**. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-12.
- Yau T et al. **Nivolumab** plus **cabozantinib** with or without **ipilimumab** for **advanced** hepatocellular carcinoma: Results from **cohort 6** of the **CheckMate 040** trial. *J Clin Oncol* 2023;41(9):1747-57.
- Qin S et al. **Camrelizumab** (C) plus **rivoceranib** (R) vs. sorafenib (S) as **first-line** therapy for **unresectable** hepatocellular carcinoma (uHCC): A randomized, phase III trial. ESMO 2022; Abstract LBA35.
- NCT05301842: A **phase III**, randomized, open-label, sponsor-blinded, multicenter study of **durvalumab** in combination with **tremelimumab ± lenvatinib** given concurrently with **TACE** compared to TACE alone in patients with locoregional hepatocellular carcinoma (**EMERALD-3**)

Agenda

Prologue: Last Week

MODULE 1: Hepatocellular Carcinoma

MODULE 2: Biliary Tract Cancers

- Prologue: Anatomic biology of biliary tract cancers (BTC)
- IOs with chemotherapy as first-line systemic treatment for metastatic BTC
- Overview of targeted therapies for BTC
- FGFR inhibitors in BTC
- Other targeted therapies
  - Anti-HER2 therapies in BTC
  - Seribantumab

MODULE 3: Appendix

Agenda

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MODULE 3: Appendix

2023 Year in Review: Biliary Cancers

Richard S. Finn, MD
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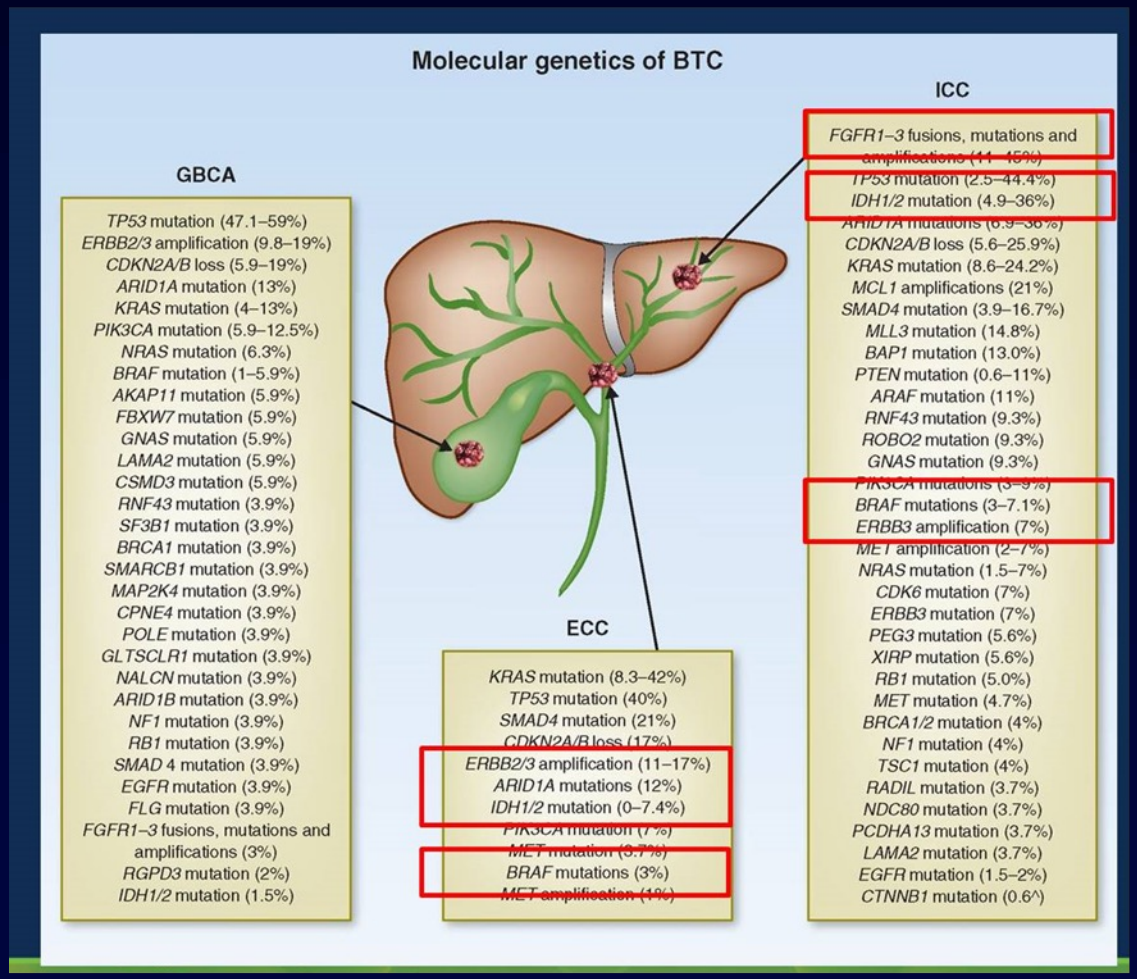
Geffen School of Medicine at UCLA

BTC: a heterogenous group of tumors



Targeted Therapy for Biliary Tract Cancers

Recommend molecular profiling for advanced disease

	Intrahepatic	Extrahepatic	Gallbladder	Comments
% BRAF substitution	5	3	1	36% RR; 75% DCR with BRAF/MEK inhibition[1]
% KRAS substitution	22	42	11	
% PI3KCA substitution	5	7	14	
% FGFR2 fusions / FGFR1-3 alterations	10-15	0	3	FGFR2 fusions: 20-40% ORR; ~80% DCR with FGFR1-3 inhibitors[2]
% IDH 1/2 substitution	15-20	0	0	+ RP3 data; IDH1 inhibitor ~60% DCR[2]
% MSI-H / dMMR	1-3	1-3	1-3	PD1 inhibitors: 30-50% RR[2]
% ERBB2 amplification	3-4	11	16	HER2 directed therapy: ~40% RR[3]
% ARID1A Alterations	18	12	13	Rationale for Checkpoint inhibition, BET, EZH2, PARP inhibitors

1. Wainberg et al, ASCO GI 2019
2. Harris et al, Semin Oncol 2018
3. Javle et al, ASCO GI 2017

Courtesy of Richard S Finn, MD

IOs with Chemotherapy as First-Line Treatment for Metastatic BTC

- Oh D-Y et al. **Durvalumab** plus **gemcitabine** and **cisplatin** in advanced **biliary tract** cancer. *NEJM Evid* 2022;1(8).
- Oh D et al. Updated overall survival (OS) from the **phase III TOPAZ-1** study of **durvalumab** (D) or placebo (PBO) plus **gemcitabine and cisplatin** (+ GC) in patients (pts) with advanced **biliary tract** cancer (BTC). ESMO 2022;Abstract 56P.
- He AR et al. Outcomes by primary tumour location in patients with advanced biliary tract cancer treated with **durvalumab** or placebo plus **gemcitabine and cisplatin** in the **phase 3 TOPAZ-1** study. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-1.
- Kelley RK et al. **Pembrolizumab** in combination with **gemcitabine and cisplatin** compared with gemcitabine and cisplatin alone for patients with advanced **biliary tract** cancer (**KEYNOTE-966**): a randomised, double-blind, placebo-controlled, **phase 3** trial. *Lancet* 2023 April 16:[Online ahead of print].

Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial

Robin Kate Kelley, Makoto Ueno*, Changhoon Yoo, Richard S Finn, Junji Furuse, Zhenggang Ren, Thomas Yau, Heinz-Josef Klümpen, Stephen L Chan, Masato Ozaka, Chris Verslype, Mohamed Bouattour, Joon Oh Park, Olga Barajas, Uwe Pelzer, Juan W Valle, Li Yu, Usha Malhotra, Abby B Siegel, Julien Edeline, Arndt Vogel*, on behalf of the KEYNOTE-966 Investigators†*

Lancet 2023;[Online ahead of print].

KEYNOTE-966

Added value of this study

“To our knowledge, KEYNOTE-966 is the first placebo-controlled study of a PD-1 inhibitor and the second study of a PD-1 or PD-L1 checkpoint inhibitor to show a statistically significant improvement in overall survival and a manageable safety profile in patients with advanced biliary tract cancer. KEYNOTE-966 offers key findings beyond those of TOPAZ-1, owing to its larger population, enrolment of a greater proportion of participants outside of Asia, the continuation of gemcitabine until disease progression, and more complete ascertainment of important clinical biomarkers such as hepatitis B and C viral status, all of which might affect the generalizability of outcomes to a global patient population.”

KEYNOTE-966 (continued)

Implications of all the available evidence

"Results of KEYNOTE-966 add to the body of evidence supporting the efficacy and safety of adding immune checkpoint inhibitors targeting PD-1 and PD-L1 to standard-of-care chemotherapy in the treatment of patients with biliary tract cancer. The statistically significant, clinically meaningful overall survival benefit observed in the absence of new safety signals supports the combination of pembrolizumab, gemcitabine, and cisplatin as a potential new first-line treatment option for patients with unresectable locally advanced or metastatic biliary tract cancer."

FGFR Inhibitors in BTC

- Vogel A et al. **Pemigatinib** for **previously treated** locally advanced or metastatic **cholangiocarcinoma**: Final results from **FIGHT-202**. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-2.
- Bibeau K et al. Progression-free survival in patients with **cholangiocarcinoma** with or without **FGF/FGFR alterations**: A **FIGHT-202 post hoc** analysis of prior systemic therapy response. *JCO Precis Oncol* 2022;6:e2100414.
- Goyal L et al. **Futibatinib** for **FGFR2-rearranged intrahepatic cholangiocarcinoma**. *N Engl J Med* 2023;388(3):228-39.
- Goyal L et al. Updated results of the **FOENIX-CCA2 trial**: Efficacy and safety of **futibatinib** in **intrahepatic cholangiocarcinoma** (iCCA) harboring **FGFR2** fusions/rearrangements. ASCO 2022;Abstract 4009.

FIGHT-202

- Pemigatinib oral selective FGFR 1,2,3 inhibitor
- 13.5 mg qD, 2 weeks on 1 off
- FIGHT-202 open label single arm Phase 2 study in previously treated CCA, primary endpoint ORR
- ORR 37% in patients with FGFR2 fusions/gene rearrangements (n=108)
  - DOR 9.1 months
  - PFS 7.0 mos, OS 17.5 mos
- TEAEs- hyperphosphatemia, alopecia, diarrhea, fatigue
- Exploratory analysis for this 108 patients, PFS to front-line was 5.5 mos (less than second-line pemigatinib)

Vogel A et al. ESMO GI 2022; Abstract O-2.

Courtesy of Richard S Finn, MD

Futibatinib

- Highly selective FGFR 1-4 inhibitor, irreversible, 20 mg daily
- FOENIX-CCA2 study, single arm phase 2 in patients with FGFR2 fusions/ rearrangements (n=103)
- ORR 41.7 %, mDOR 9.5 mos, mPFS 8.9 mos
- Mature mOS 20.0 mos
- TEAEs- hyperphosphatemia, alopecia, dry mouth, diarrhea

Goyal L et al. ASCO 2022;Abstract 4009.

Courtesy of Richard S Finn, MD

Anti-HER2 Therapies in BTC

- Zymeworks announces positive topline data in the pivotal **HERIZON-BTC-01** trial of **zanidatamab** [press release]. December 19, 2022. Available at https://ir.zymeworks.com/news-releases/news-release-details/zymeworks-announces-positive-topline-data-pivotal-herizon-btc-01.
- Ohba A et al. **Trastuzumab deruxtecan** (T-DXd; DS-8201) in patients (pts) with **HER2-expressing** unresectable or recurrent **biliary tract** cancer (BTC): An investigator-initiated multicenter phase 2 study (**HERB** trial). ASCO 2022;Abstract 4006.

HER2 Targeting: second line studies

- HERIZON-BTC-01 trial, phase 2b (n~87), single agent
  - Zanidatamab, HER2 bispecific antibody against 2 different domains of HER2
  - ORR 41.3%, mDOR 12.9 mos in second line
  - Amplified or IHC 2 and 3+
  - No new safety signals (GI and infusion reactions)
- HERB trial, phase 2, single arm, trastuzumab deruxtecan
  - 30 pts (22 HER2 positive, 8 HER2 low)
  - ORR HER2 + 36.4 %, HER2 low 12.5%, All 30%
  - PFS HER2+ 5.1 mos, HER2 low 3.5 mos
  - TEAEs – hematologic, pneumonitis

HERIZON-BTC-01 press release, December 19, 2022; Ohba A et al.ASCO 2022;Abstract 4006.

Courtesy of Richard S Finn, MD

Seribantumab

- Carrizosa DR et al. **CRESTONE**: Initial efficacy and safety of **seribantumab** in solid tumors harboring **NRG1 fusions**. ASCO 2022;Abstract 3006.

Seribantumab

- Fully human anti-HER3 mAb, IV q3weeks
- Competes with NRG-1 to bind to HER3
- NRG fusions, rare, 0.2% of solid tumors
- CRESTONE: ph2 study in solid tumors with NRG fusions, n=35
- Included 2 patients with CCA
- ORR overall study 33%, 36% in NSCLC, mDOR not reached

Carrizosa DR et al. ASCO 2022;Abstract 3006.

Courtesy of Richard S Finn, MD

Other Important Papers

- El-Khoueiry AB et al. **IMbrave151**: A phase 2, randomized, double-blind, placebo-controlled study of **atezolizumab** with or without **bevacizumab** in combination with **cisplatin plus gemcitabine** in patients with **untreated**, advanced **biliary tract** cancer. Gastrointestinal Cancers Symposium 2023;Abstract 491.
- Yoo C et al. Final results from the **NIFTY** trial, a phase IIb, randomized, open-label study of liposomal irinotecan (**nal-IRI**) plus fluorouracil (5-FU)/leucovorin **(LV)** in patients (pts) with **previously treated** metastatic **biliary tract** cancer (BTC). ESMO 2022;Abstract 55P.

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Hepatocellular Carcinoma

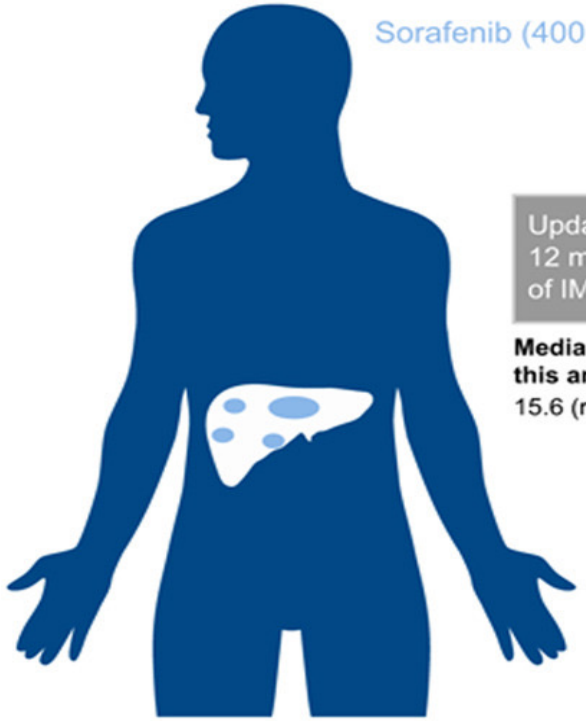
IMbrave150 One Year Update

IMbrave150: Atezolizumab plus bevacizumab versus sorafenib in patients with unresectable HCC

Atezolizumab (1,200 mg) plus bevacizumab (15 mg/kg) every 3 weeks

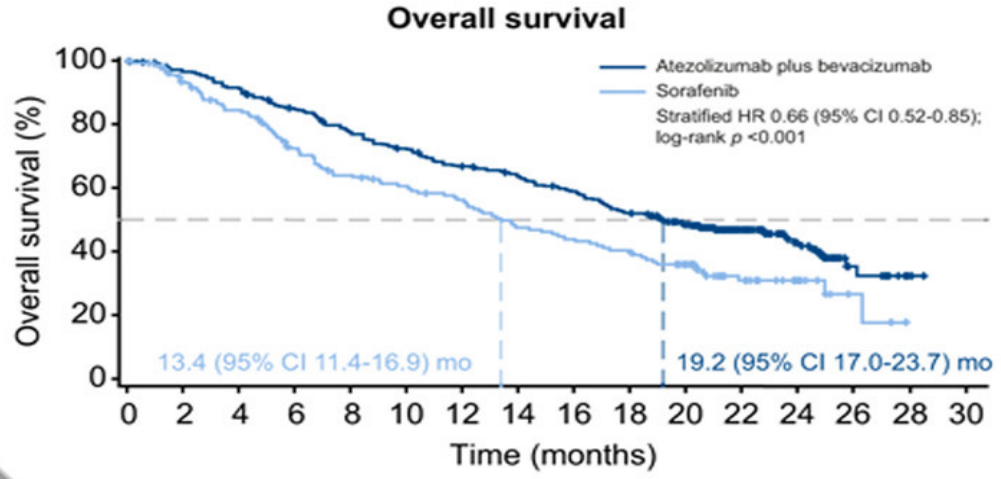
OR

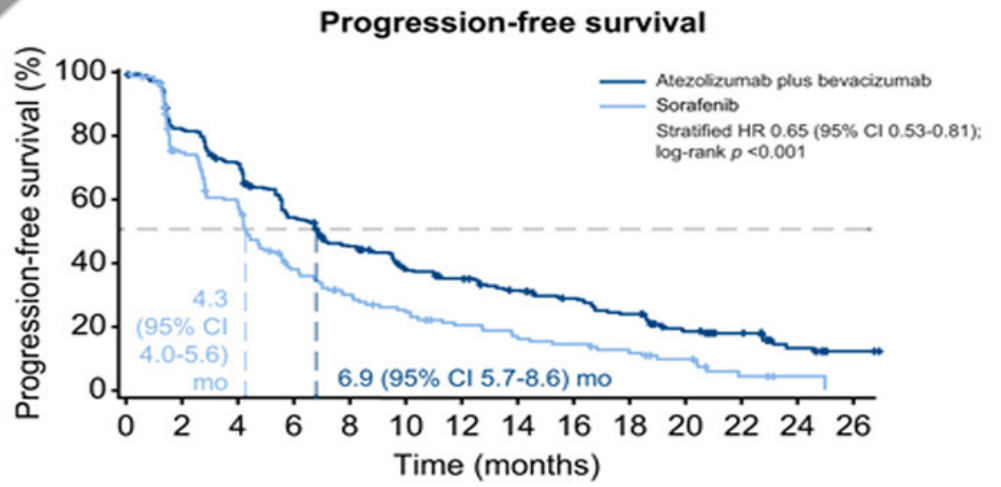
Sorafenib (400 mg twice daily)



Updated analysis
12 months after primary analysis of IMbrave150 study

Median follow-up for this analysis:
15.6 (range, 0-28.6) mo





Confirmed objective response rate: 30% with atezolizumab plus bevacizumab, 11% with sorafenib

Cheng A-L et al. J Hepatol 2022;76(4):862-73.

Courtesy of Ghassan Abou-Alfa, MD, MBA

IMbrave050

Phase III global, multicenter, open-label, randomized study evaluating the efficacy and safety of adjuvant atezolizumab plus bevacizumab, compared with active surveillance, in people with HCC at high risk of recurrence (determined by the size and number of cancerous lesions and the histopathology results, if available) after surgical resection or ablation with curative intent.

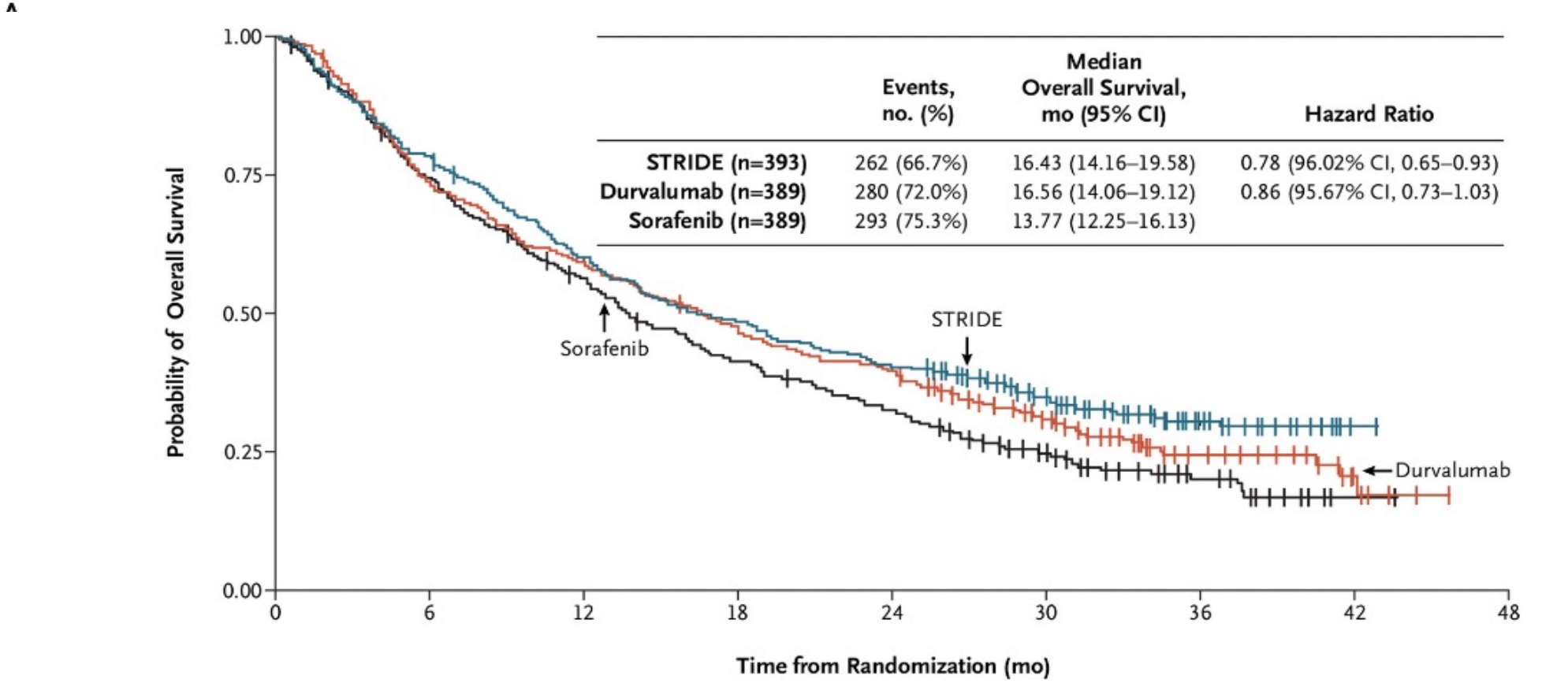
Overall survival data were immature at the time of interim analysis and follow-up will continue to the next analysis. Safety was consistent with the known safety profile of each therapeutic agent and with the underlying disease.

Results from the IMbrave050 study will be discussed with health authorities, including the U.S. Food and Drug Administration and the European Medicines Agency, and presented at an upcoming medical meeting.

https://www.gene.com/media/press-releases/14981/2023-01-18/genentechs-tecentriq-plus-avastin-is-the

Courtesy of Ghassan Abou-Alfa, MD, MBA

HIMALAYA OS for Durvalumab + Tremelimumab 300 mg vs Sorafenib and Durvalumab vs Sorafenib



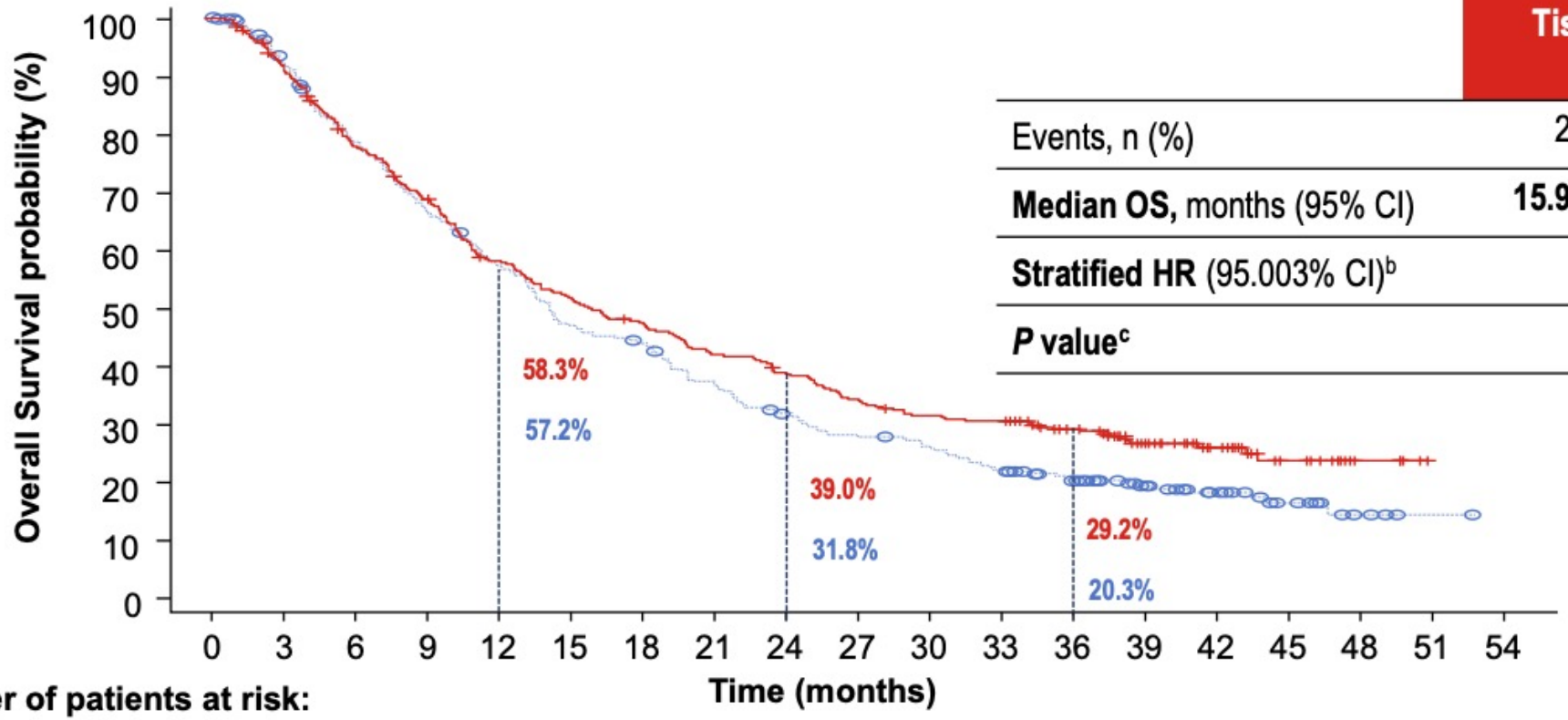
	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

No. at Risk									
STRIDE	393	308	235	190	158	98	32	1	0
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

Abou-Alfa GK et al. NEJM Evidence. Published June 6, 2022. DOI:https://doi.org/10.1056/EVIDoa2100070

Courtesy of Ghassan Abou-Alfa, MD, MBA

Tislelizumab vs Sorafenib Primary Endpoint: OS



	Tislelizumab (n=342)	Sorafenib (n=332)
Events, n (%)	242 (70.8)	255 (76.8)
Median OS, months (95% CI)	**15.9** (13.2, 19.7)	**14.1** (12.6, 17.4)
Stratified HR (95.003% CI)[b]	**0.85** (0.712, 1.019)	
***P* value**[c]	**0.0398**	

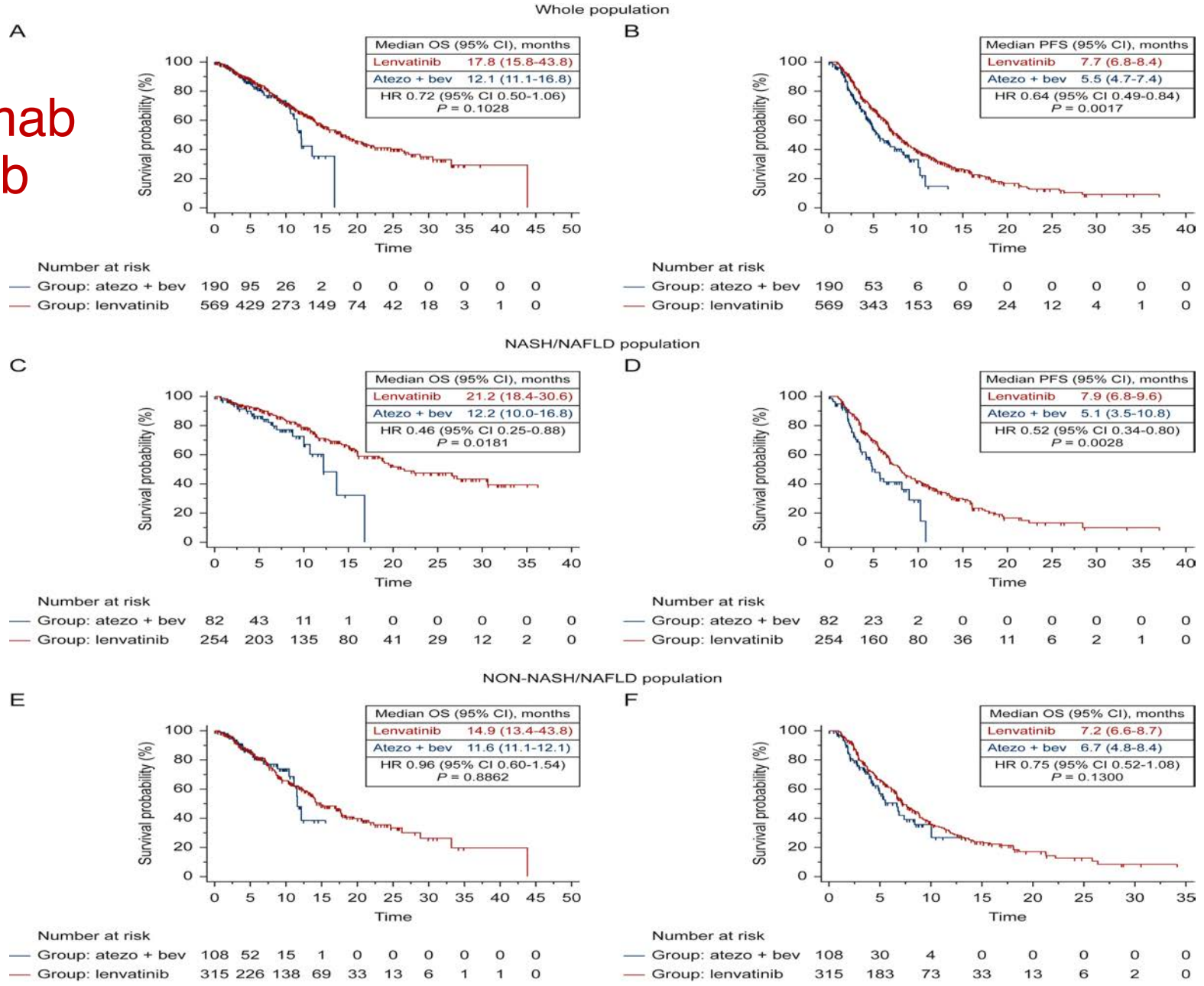
Number of patients at risk:

Tislelizumab	342	307	259	228	191	170	155	137	126	111	101	98	77	53	33	18	4	0	0
Sorafenib	332	291	247	208	179	147	136	113	96	84	77	66	52	39	29	13	4	1	0

Qin S et al. ESMO 2022;Abstract LBA36.

Courtesy of Ghassan Abou-Alfa, MD, MBA

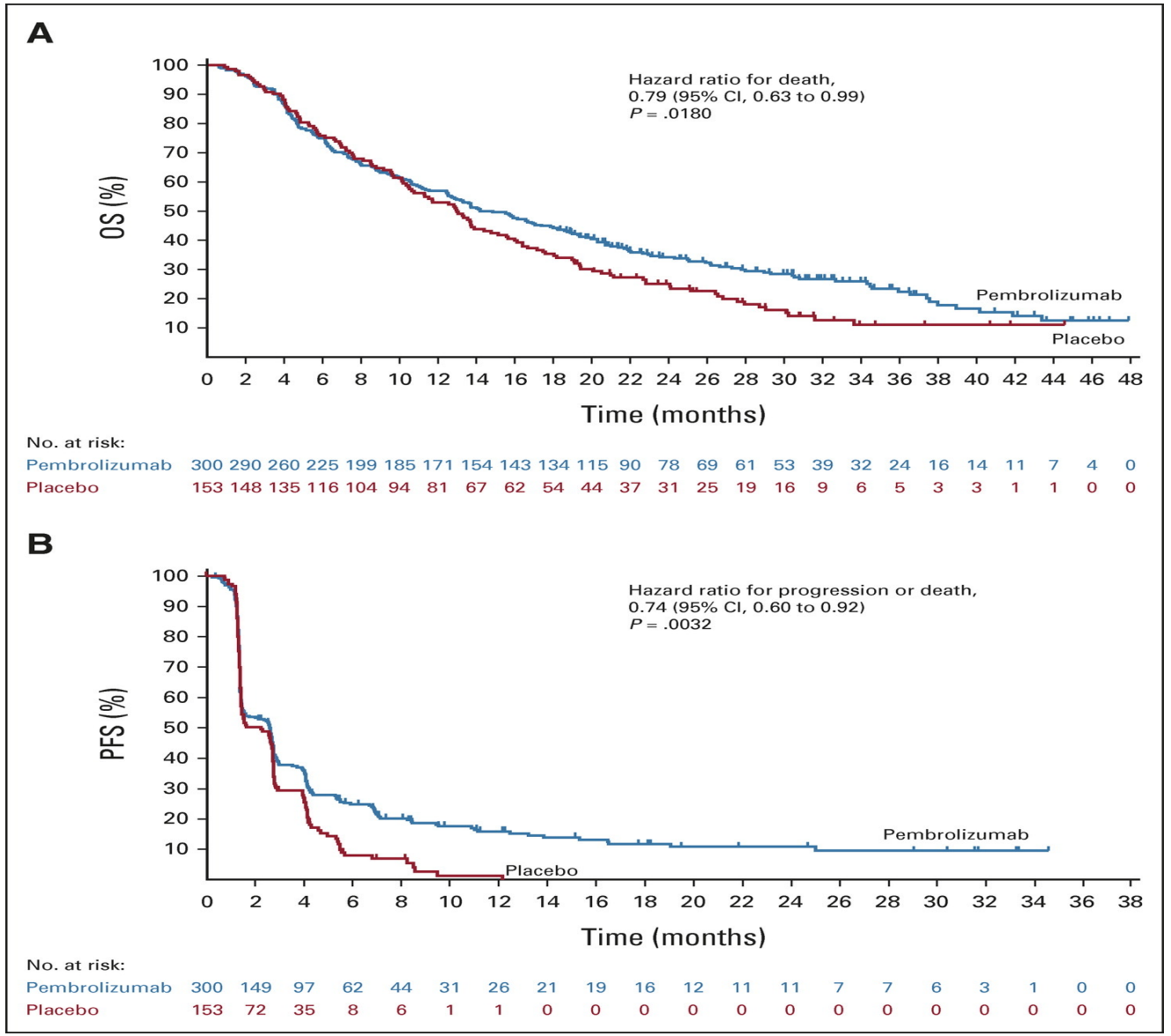
Atezolizumab plus Bevacizumab versus Lenvatinib or Sorafenib



Rimini M et al. ESMO Open 2022;7(6):100591.

Courtesy of Ghassan Abou-Alfa, MD, MBA

Second-line Pembrolizumab versus Placebo in Patients from Asia with Advanced HCC



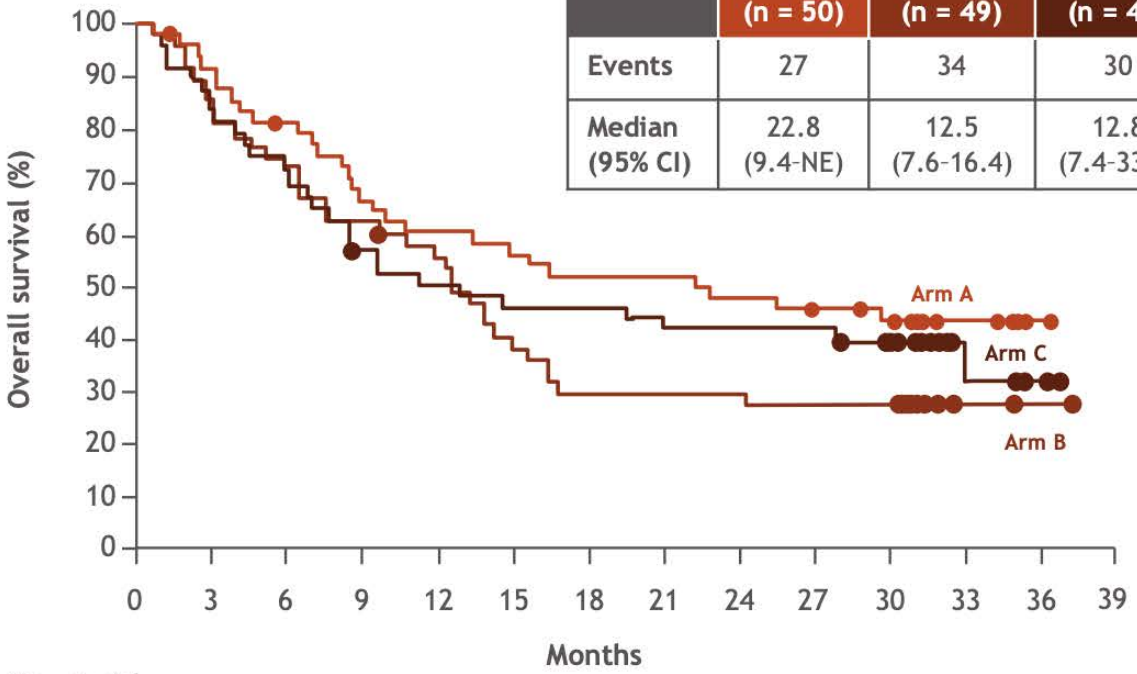
Qin S et al. J Clin Oncol 2023;41(7):1434-43.

Courtesy of Ghassan Abou-Alfa, MD, MBA

NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses) 5 years Follow-Up

Primary analysis[1,a]

	Arm A (n = 50)	Arm B (n = 49)	Arm C (n = 49)
Events	27	34	30
Median (95% CI)	22.8 (9.4-NE)	12.5 (7.6-16.4)	12.8 (7.4-33.0)

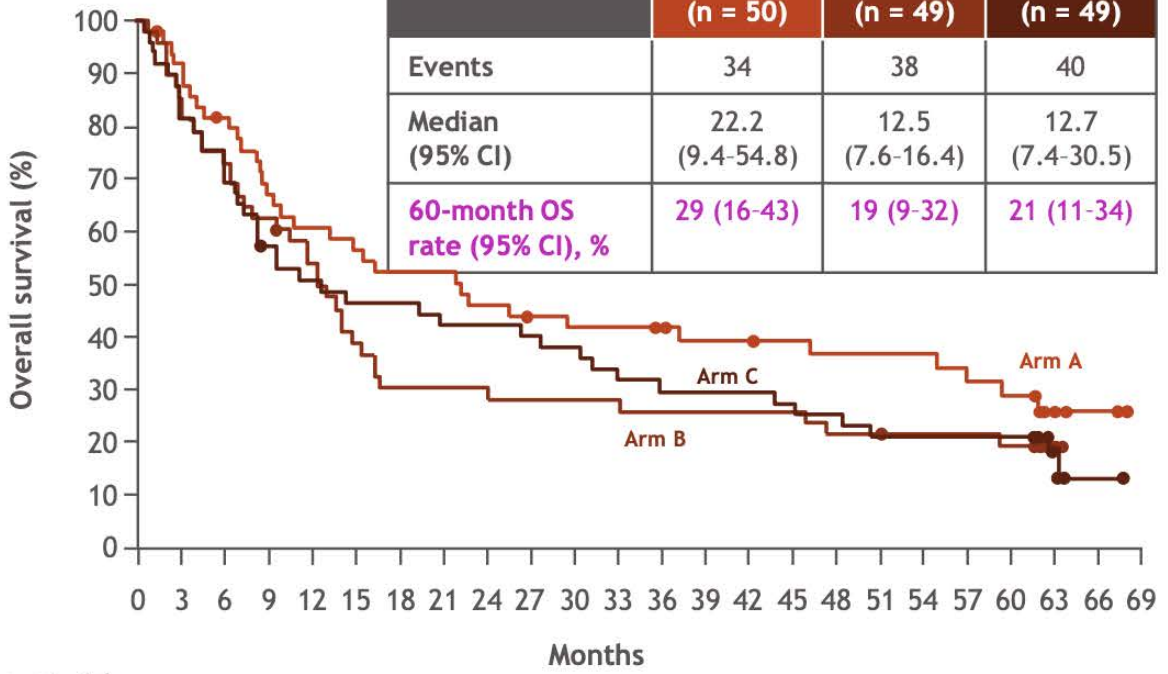


No. at risk

Arm A (NIVO1+IPI3 Q3W)	50	45	39	32	29	27	25	25	23	21	19	7	2	0
Arm B (NIVO3+IPI1 Q3W)	49	41	36	30	26	18	14	14	14	13	13	2	1	0
Arm C (NIVO3 Q2W + IPI1 Q6W)	49	42	36	27	24	22	22	20	20	20	15	4	2	0

Long-term follow-up[b]

	Arm A (n = 50)	Arm B (n = 49)	Arm C (n = 49)
Events	34	38	40
Median (95% CI)	22.2 (9.4-54.8)	12.5 (7.6-16.4)	12.7 (7.4-30.5)
60-month OS rate (95% CI), %	29 (16-43)	19 (9-32)	21 (11-34)



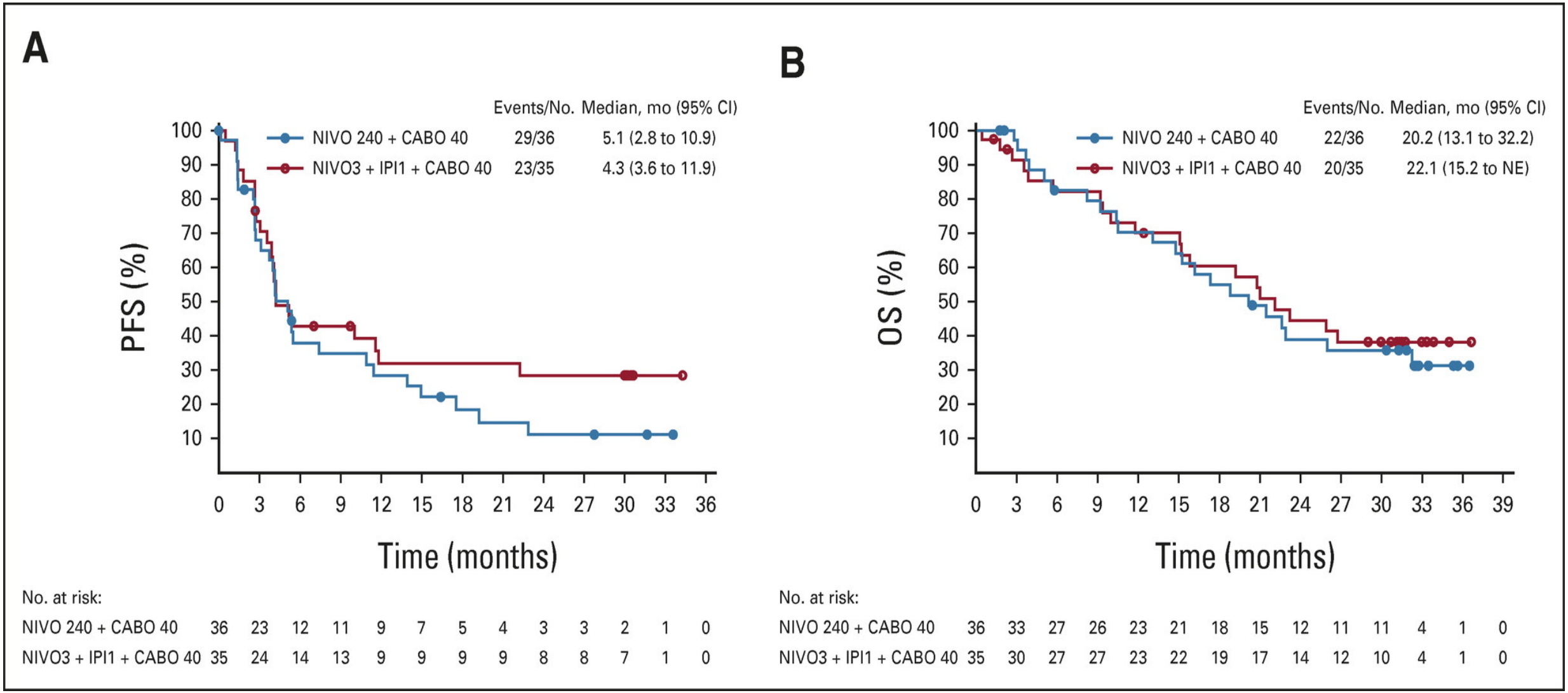
No. at risk

Arm A (NIVO1+IPI3 Q3W)	50	45	39	32	29	27	25	25	22	20	19	19	18	16	16	15	14	14	14	12	11	4	2	0
Arm B (NIVO3+IPI1 Q3W)	49	41	36	30	26	18	14	14	14	13	13	12	12	12	12	12	10	10	9	9	8	2	0	0
Arm C (NIVO3 Q2W + IPI1 Q6W)	49	42	36	27	24	22	22	20	20	19	18	15	14	14	14	13	12	10	10	10	10	4	1	0

Melero I et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-12.

Courtesy of Ghassan Abou-Alfa, MD, MBA

Nivolumab plus Cabozantinib +/- Ipilimumab



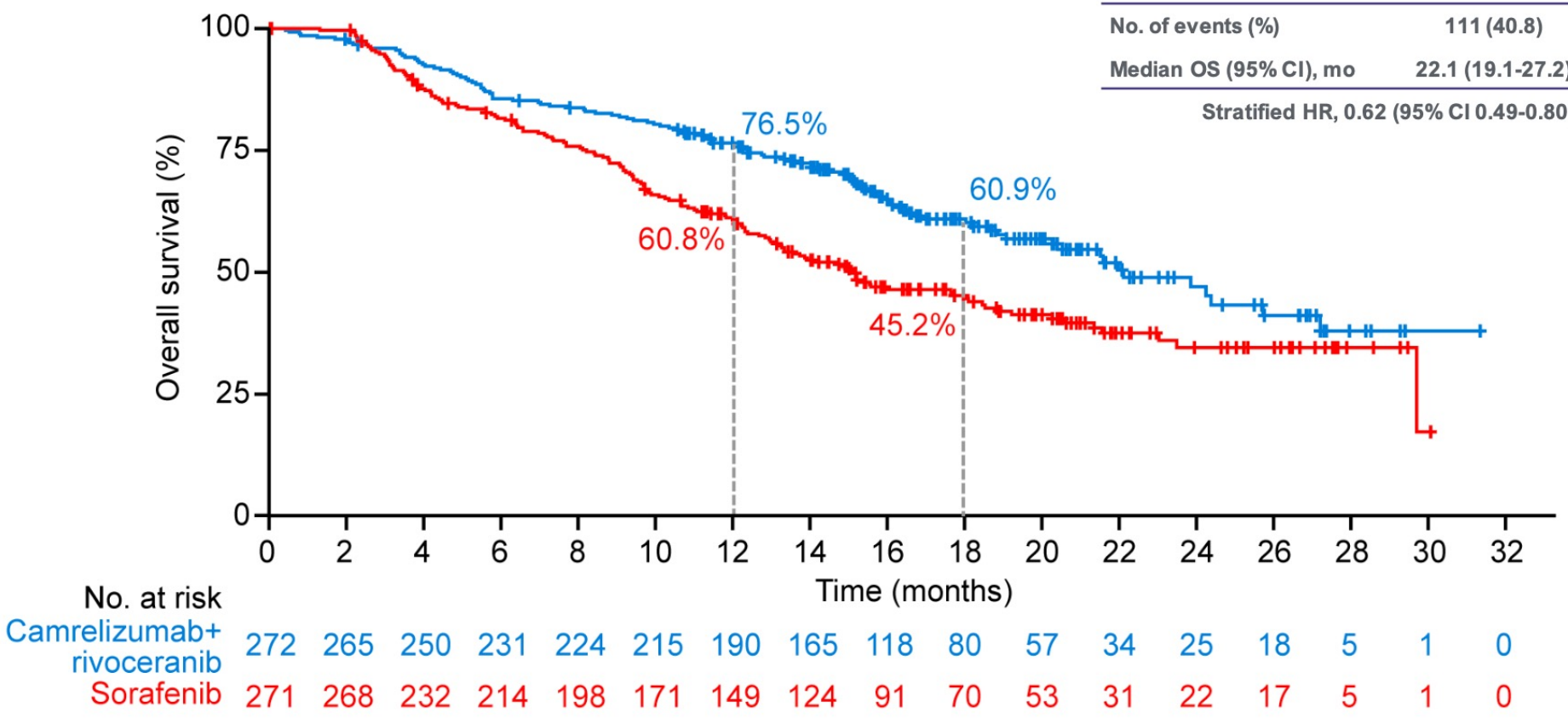
Yau T et al. J Clin Oncol 2023;41(9):1747-57.

Courtesy of Ghassan Abou-Alfa, MD, MBA

Camrelizumab plus Rivoceranib v Sorafenib

	Camrelizumab + rivoceranib	Sorafenib
No. of events (%)	111 (40.8)	151 (55.7)
Median OS (95% CI), mo	22.1 (19.1-27.2)	15.2 (13.0-18.5)

Stratified HR, 0.62 (95% CI 0.49-0.80)*, p <0.0001†



Qin S, et al., ESMO Paris 2022

Courtesy of Ghassan Abou-Alfa, MD, MBA

AFRICA LIVER CANCER GUIDELINES
2021 • VIRTUAL

First Line Systemic Therapy

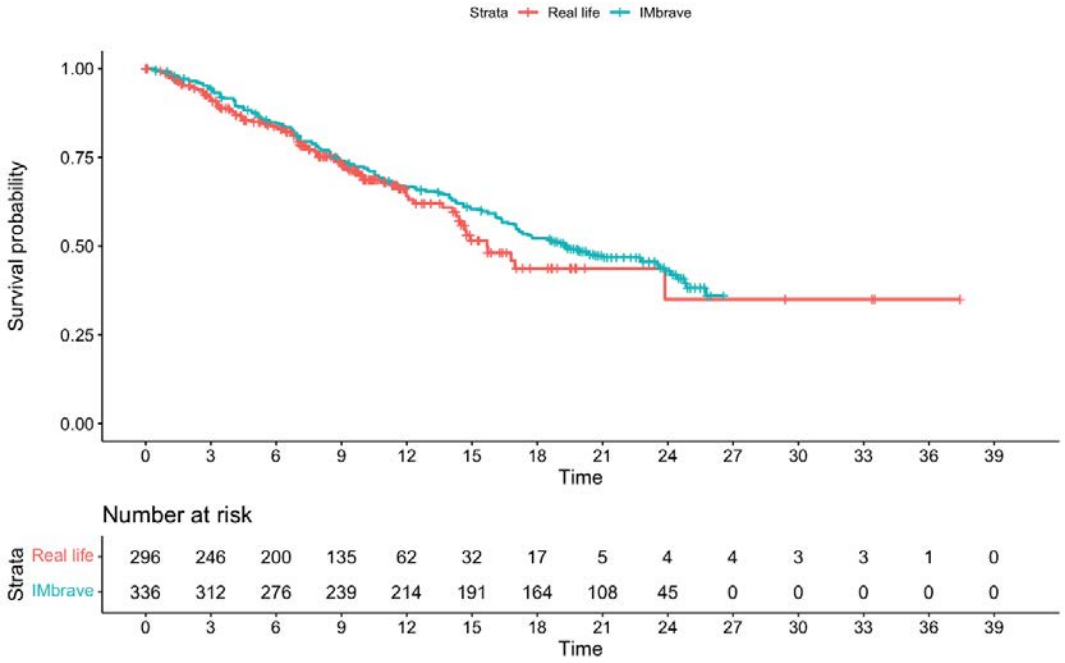
Regions	n	Sorafenib	Lenvatinib	Atezolizumab plus bevacizumab	Doxorubicin	FOLFOX	Don't use any (availability, cost)
North South	167	84%	11%	11%	5%	2%	3%
East West	127	66%	2%	4%	13%	1%	8%
Central	30	27%	0	7%	10%	10%	47%

Abou-Alfa, GK , et al. AORTIC, Senegal, Dakkar, Nov 7, 2021

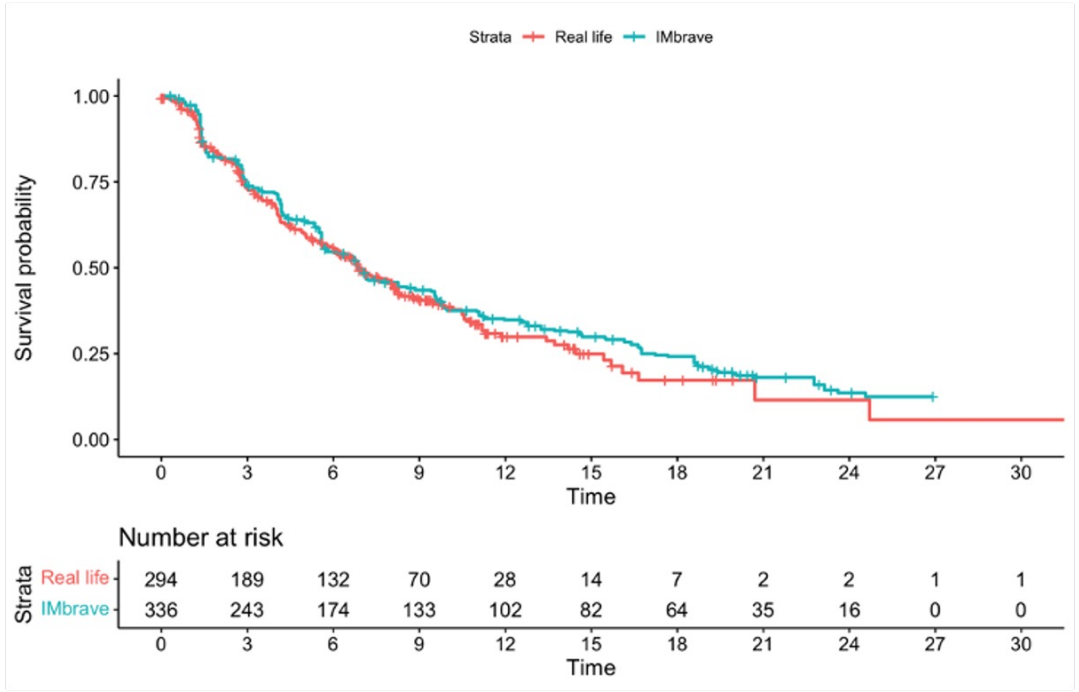
Courtesy of Ghassan Abou-Alfa, MD, MBA

Memorial Sloan Kettering Cancer Center

Atezolizumab plus Bevacizumab AB-Real International Study



AB-Real	IMbrave150
mOS: 15.74 months (95%CI: 14.4-NA)	mOS: 19.20 months (95%CI: 17.0-23.7)
HR: 0.87 (95%CI: 0.67-1.13; p=0.3)	



AB-Real	IMbrave150
mPFS: 6.91 (95%CI: 6.1-8.3)	mPFS: 6.91 months (95%CI: 5.7- 8.6)
HR: 0.90 (95%CI: 0.74-1.10; p=0.3)	

Fulgenzi C, et al. ILCA Madrid September 4, 2022

Courtesy of Ghassan Abou-Alfa, MD, MBA

EMERALD-3

POPULATION

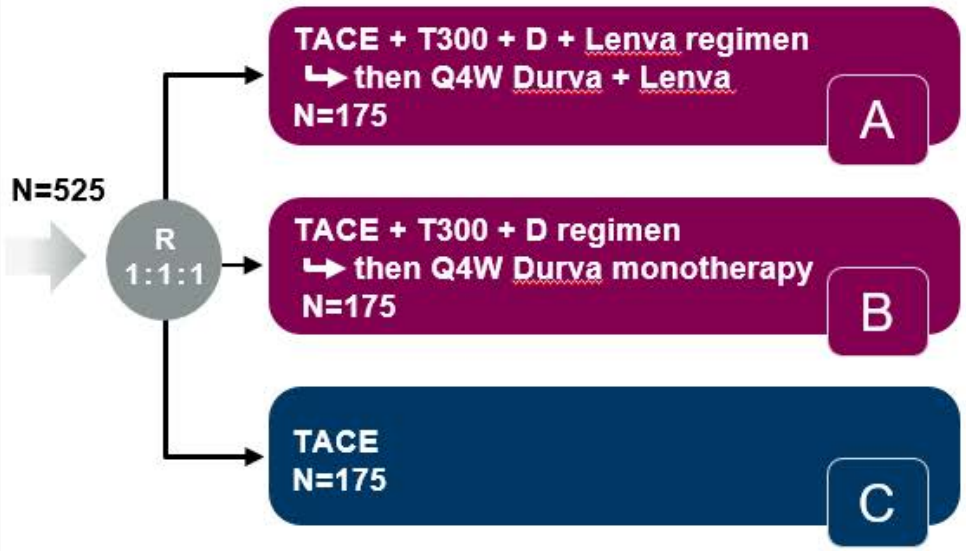
- Pathologically or radiologically confirmed HCC
- Unsuitable for curative treatment e.g. surgical resection, transplantation, ablation
- No prior systemic therapy
- No extrahepatic disease
- Child-Pugh class A
- ECOG: 0 or 1
- Exclude Vp3 and Vp4

Stratification factors

- Region (Japan vs. Asia without Japan vs. rest of world)
- Prior Palliative LR therapy (1>6m vs. 1≤6m vs. none))
- Baseline tumor burden (> up to 7 vs ≤ up to 7)

TREATMENT

Open label, Phase-3, multi-center study



ENDPOINTS

Primary Endpoint:
PFS (RECIST 1.1 by BICR)

Secondary Endpoints:
OS, ORR, Landmark OS, PROs, Safety

Dosing:

- Treme 300mg + Durva 1500mg IV on Cycle 1 Day 1(C1D1) for one dose
- Followed by Durva Q4W until progression
- Lenvatinib will start Day 1 (D1=first day of systemic therapy) and continue daily

TACE modalities :

- cTACE, DEB-TACE

Courtesy of Ghassan Abou-Alfa, MD, MBA

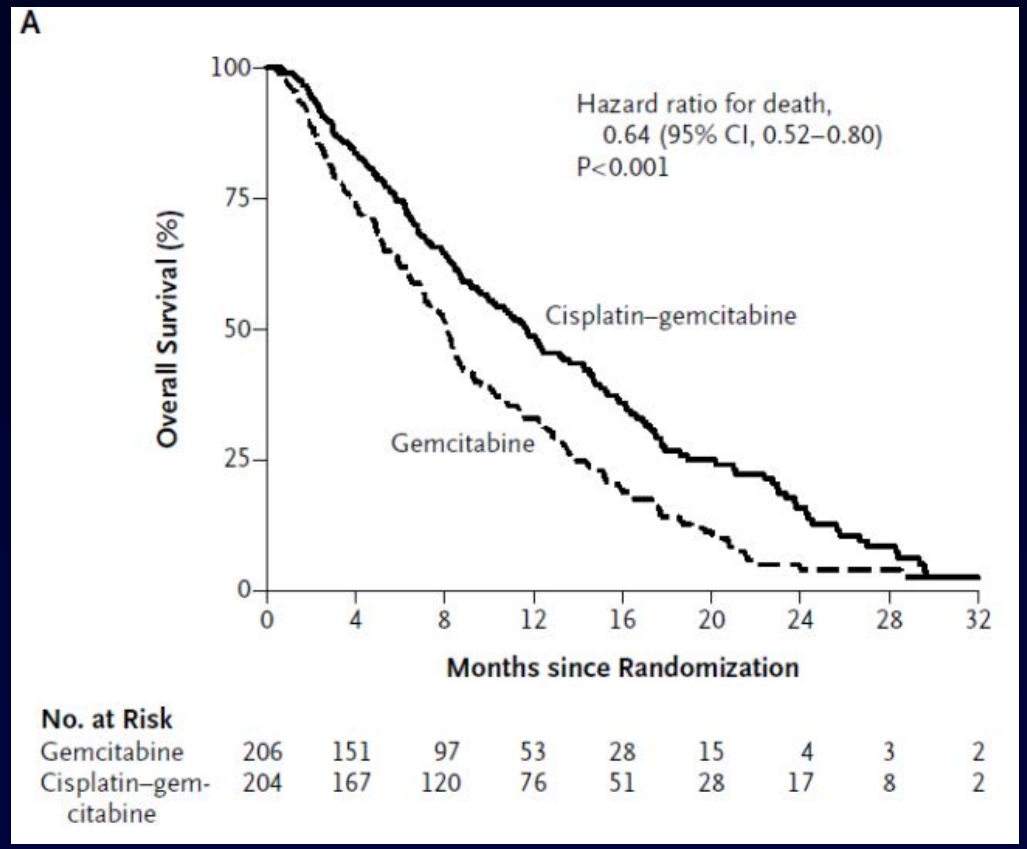
Biliary Tract Cancers

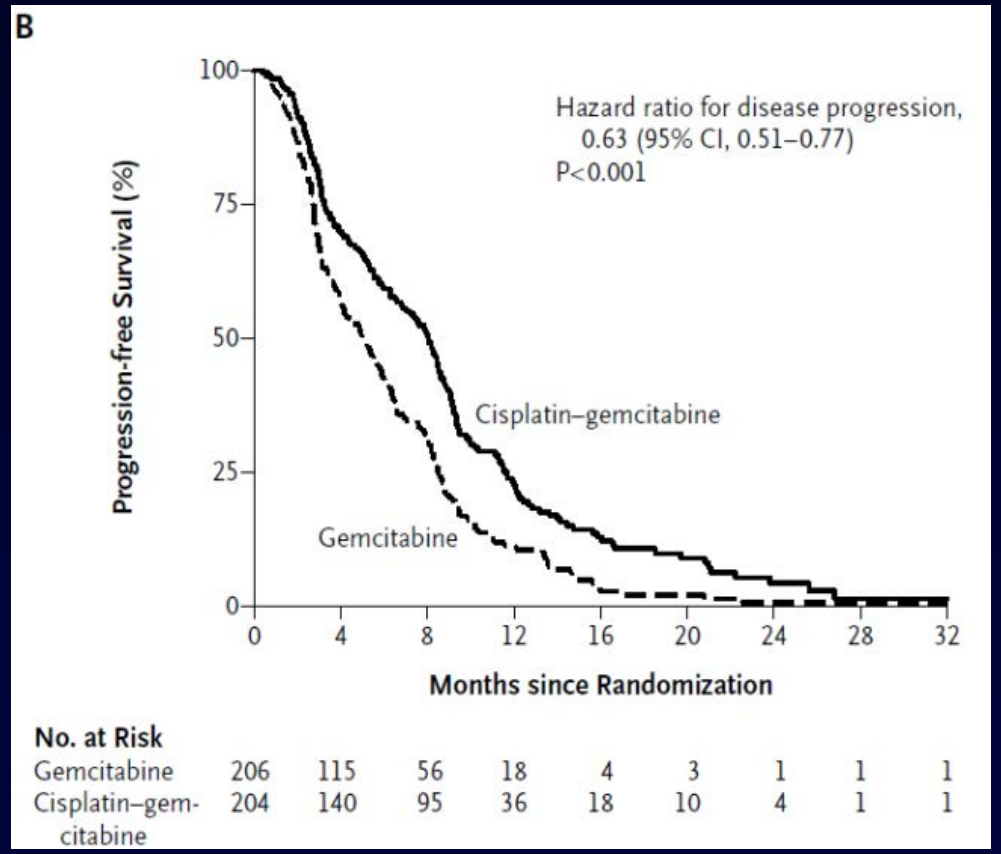
Overview

- IO
  - Practice changing: TOPAZ and KEYNOTE-966
  - Of interest: IMbrave151
- Molecular Targeted Therapy
  - FGFR2 targeting: FIGHT-202, Futibatinib
  - HER2 targeting: HERIZON-BTC-01, Trastuzumab deruxtecan
  - NRG1 fusions
- Second line chemotherapy update: NIFTY trial

Courtesy of Richard S Finn, MD

Gemcitabine and cisplatin the SOC for >10 years





OS: 11.7 v 8.1 mos

PFS: 8.0 v 5.0 mos

ORR: 26.1% v 15.5%

Valle NEJM 2010

Courtesy of Richard S Finn, MD

TOPAZ-1:

- Randomized placebo-controlled Phase 3 study:
  - Gem cis durvalumab vs gem cis placebo (n=685)
  - Primary endpoint: Improved OS: 11.5 to 12.8 mos (HR: 0.80)
  - Secondary endpoints: PFS 5.7 to 7.2 mos (HR: 0.75)
  - ORR 26.7% vs 18.7%, mDOR similar (6.6 v 6.2 mos) but tail
  - No new AEs
  - Max chemo cycles of 8, mostly Asian population
  - Updates: at 24 mos: 23.6 % alive vs 11.5%, benefit regardless of ORR, primary tumor location

Oh D et al. NEJM Evid 2022;1(8); Oh D et al. ESMO 2022; Abstract 56P; He AR at al. ESMO GI Abstract 0-1.

Courtesy of Richard S Finn, MD

KEYNOTE-966

- Randomized placebo-controlled Phase 3 study:
  - Gem cis pembro vs gem cis placebo (n>1000)
  - Primary endpoint: Improved OS: 10.9 to 12.7 mos (HR 0.83)
  - Secondary endpoints: PFS 5.6 to 6.5 (HR 0.86 NS)
  - ORR 28% and 29%, DOR longer with pembro 6.8 to 8.3 mos with tail
  - No new AEs
  - Max number of cycles cis 8, pembro 35, gem up to MD
  - Asian 45%, non-Asian 55%

Kelley RK et al. Lancet 2023;Apr 16 [epub ahead of print].

Courtesy of Richard S Finn, MD

IMbrave151

- Placebo controlled, blinded, randomized phase 2
  - Atezo bev + gem cis vs Atezo-placebo +gem cis
  - Primary endpoint: PFS 7.9 to 8.3 mos HR 0.76 NS
  - Secondary endpoints: ORR 24.1 vs 25.3
  - DOR longer with atezo-bev NE vs 5.8 mos HR 0.22
  - mOS NE vs 11.4 HR 0.74 NS
  - No new safety signals

El-Khoueiry A et al. ASCO GI 2023; Abstract 491.

Courtesy of Richard S Finn, MD

NIFTY trial: Phase 2b open-label study

- Liposomal irinotecan (nal-IRI) plus 5FU/LV vs 5fu lv alone after cis-gem (second line)
- Primary endpoint: PFS BICR 1.7 to 4.2 mos HR 0.61
- ORR: 2.3% vs 19.3%
- mOS 5.3 to 8.6 mos HR 0.68
- Typical chemotherapy AEs

Yoo C et al. ESMO 2022 Abstract 55P.

Courtesy of Richard S Finn, MD

Conclusions

- Front-line gem-cis +IO is standard of care based on 2 phase 3 studies (durva or pembro)
- Molecular profiling is a must for all patients
  - FDA approved agents for FGFR2 alterations, IDH mutations, and BRAF mutations
  - Early signals of activity for new HER2 directed therapies
- For patients without genomic alterations, second-line chemotherapy appropriate
  - FOLFOX or nal-IRI

Courtesy of Richard S Finn, MD

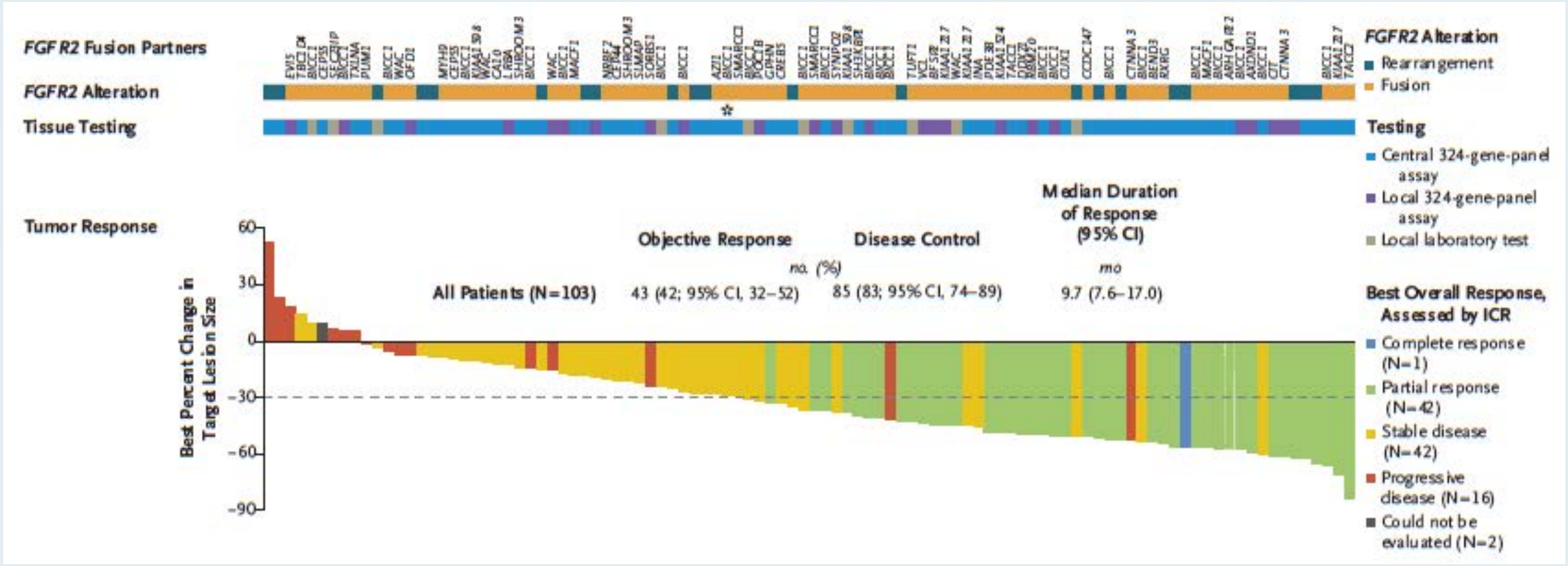
FIGHT-202: A Post Hoc Analysis of PFS in Patients with Cholangiocarcinoma with or without FGF or FGFR Alterations

Therapy	*FGFR2* Fusions/Rearrangements (n = 107)	Other *FGF/FGFR* Alterations (n = 20)	No *FGF/FGFR* Alterations (n = 18)
Prior first-line therapy			
Evaluable patients, No.	102	19	16
Median PFS (95% CI), months	5.5 (4.0 to 8.0)	4.4 (2.7 to 7.1)	2.8 (1.6 to 11.3)
Gemcitabine plus cisplatin, No.	69	12	13
Median PFS (95% CI), months	5.7 (4.6 to 9.1)	3.9 (1.6 to 6.4)	2.8 (1.6 to 17.7)
Not gemcitabine plus cisplatin, No.	33	7	3
Median PFS (95% CI), months	4.1 (2.3 to 6.5)	7.4 (3.1 to 14.0)	5.1 (1.3 to 5.5)
Prior second-line therapy			
Evaluable patients, No.	39	8	6
Median PFS (95% CI), months	4.2 (3.0 to 5.3)	3.0 (1.1 to 9.9)	5.9 (2.4 to 12.5)
Pemigatinib second-line therapy			
Evaluable patients, No.	65	12	12
Median PFS (95% CI), months	7.0 (4.9 to 11.1)	2.1 (1.2 to 6.9)	1.7 (1.2 to 2.0)

Bibeau K et al. *JCO Precis Oncol* 2022;6:e2100414.

RTP RESEARCH TO PRACTICE

FOENIX-CCA2: A Phase II Study of Futibatinib for Intrahepatic Cholangiocarcinoma with FGFR2 Fusions or Rearrangements



Median PFS: 9.0 mo
Median OS: 21.7 mo

Goyal L et al. *N Engl J Med* 2023;388(3):228-39.

RTP RESEARCH TO PRACTICE

FOENIX-CCA2: Select Treatment-Related Adverse Events with Futibatinib for Intrahepatic Cholangiocarcinoma

Event (%)	All patients (N = 103)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	99	8	34	56	1
Hyperphosphatemia	85	10	46	30	0
Dry mouth	30	27	3	0	0
Palmar-plantar erythrodysesthesia syndrome	21	3	14	5	0
Increased aspartate aminotransferase level	18	11	1	7	0
Increased alanine aminotransferase level	15	5	5	4	1

Goyal L et al. *N Engl J Med* 2023;388(3):228-39.

RTP RESEARCH TO PRACTICE

Oncology Today with Dr Neil Love — HER2-Positive Metastatic Breast Cancer

A CME/MOC-Accredited Virtual Event

Wednesday, May 17, 2023
5:00 PM – 6:00 PM ET

Faculty

Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

CME and MOC credit information will be emailed to each participant within 5 business days.

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