Meet The Professor
Optimizing the Management of Hepatobiliary Cancers

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

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This activity is supported by an educational grant from AstraZeneca Pharmaceuticals LP.

Dr Love — Disclosures

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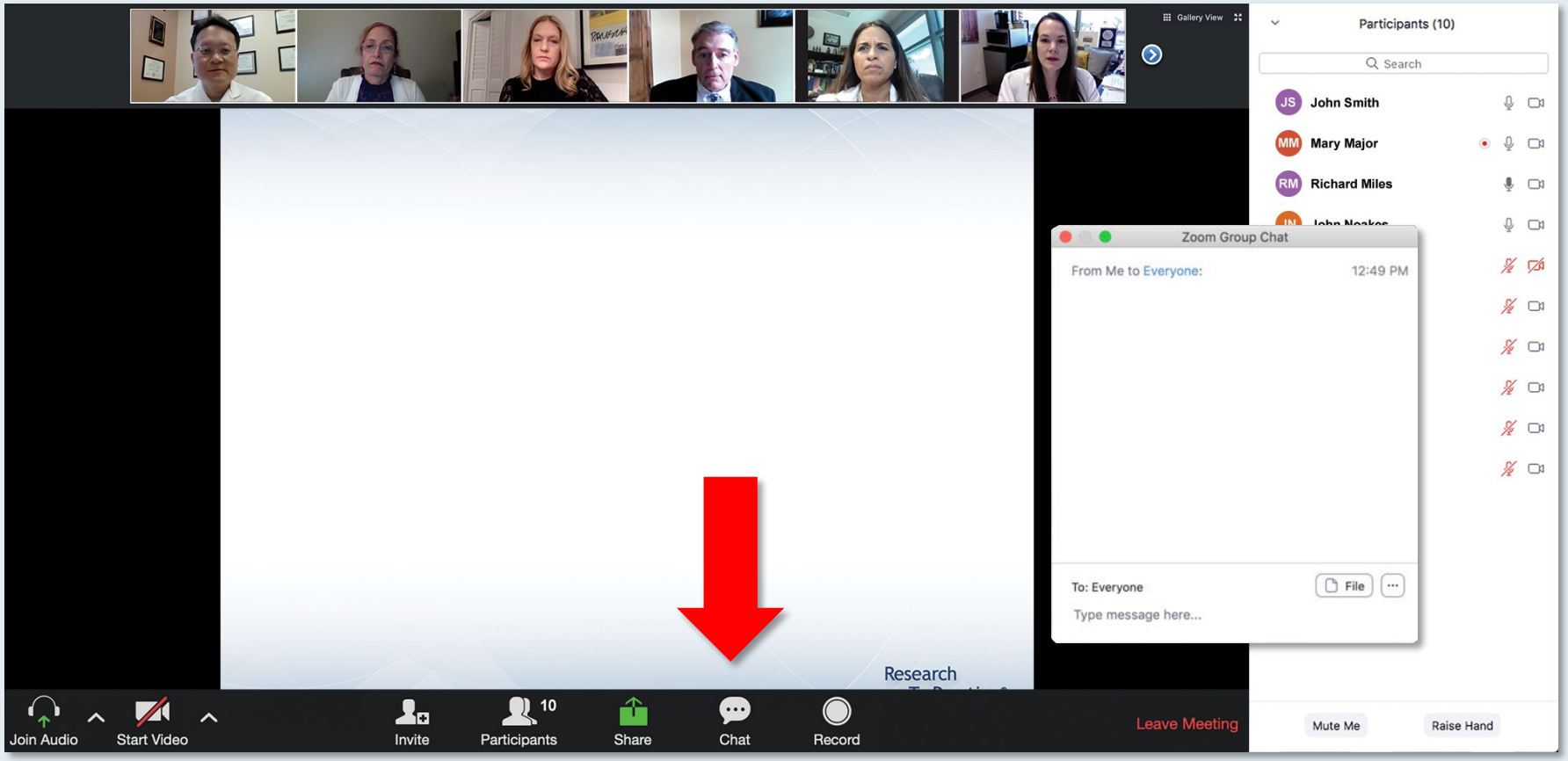

Feel free to submit questions now before the program begins and throughout the program.

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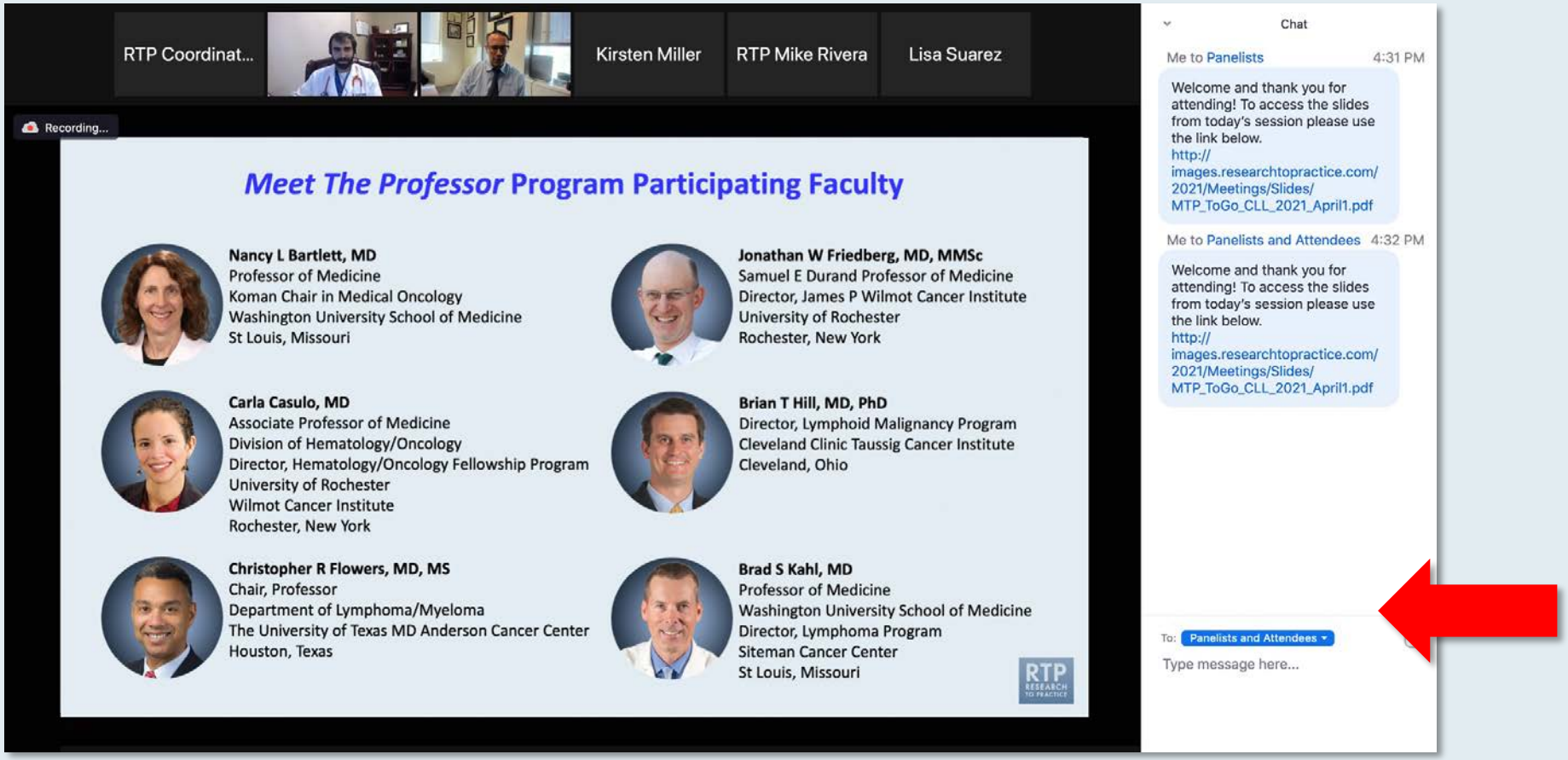
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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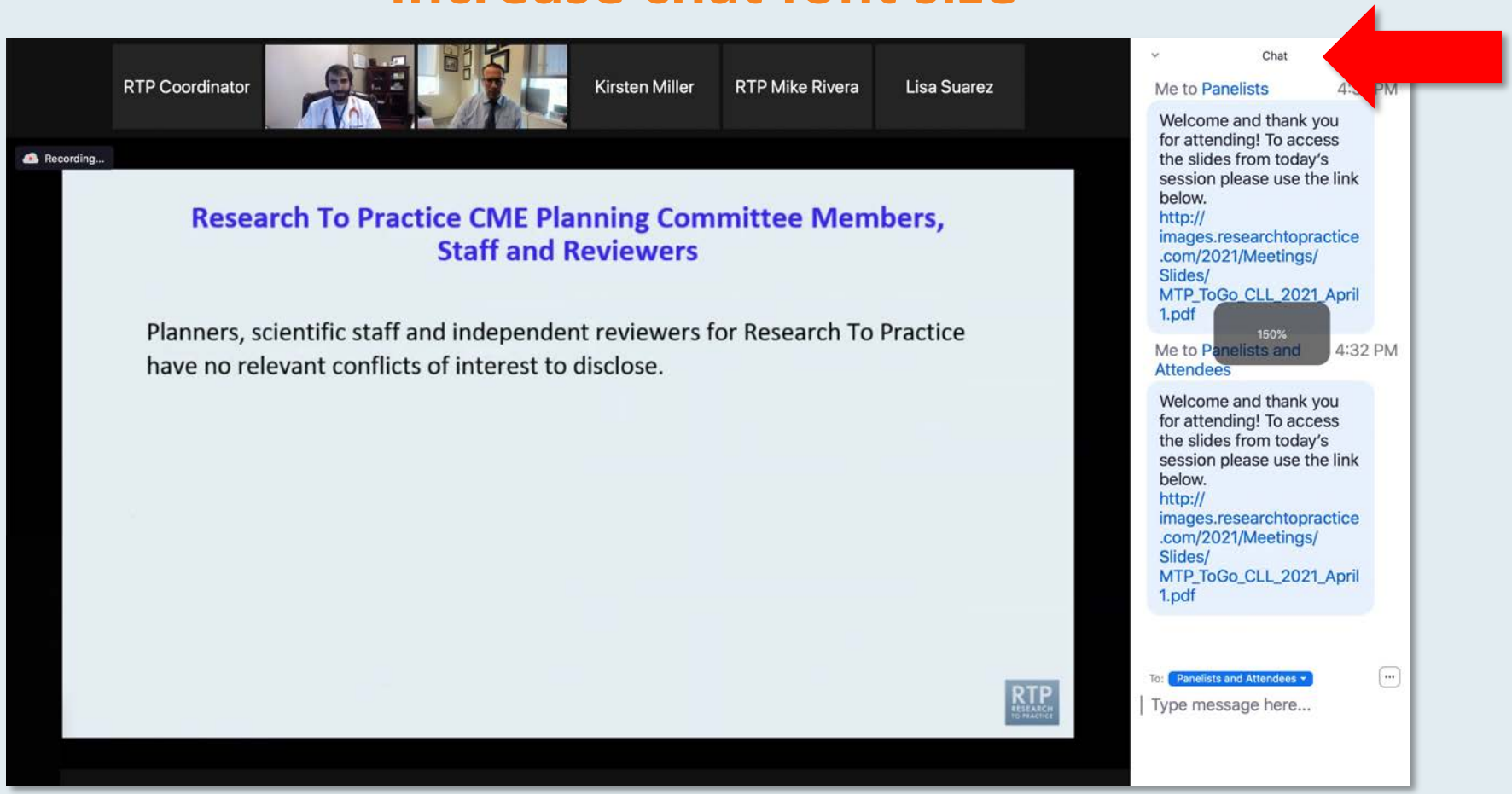

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of Cholangiocarcinoma and Other Biliary Tract Cancers

PROF JUAN VALLE
THE CHRISTIE NHS FOUNDATION TRUST

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WORLD PREMIERE OF AN ENDURING CME ACTIVITY

Oncology Today: Management of Unresectable Stage III Non-Small Cell Lung Cancer

Monday, August 1, 2022
5:00 PM – 6:00 PM ET

Faculty

Jeffrey Bradley, MD

David R Spigel, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

WORLD PREMIERE OF AN ENDURING CME ACTIVITY

Oncology Today:
The Use of T-DXd in HER2-Low Breast Cancer

Tuesday, August 2, 2022
5:00 PM – 6:00 PM ET

Faculty

Shanu Modi, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Ovarian Cancer

Wednesday, August 3, 2022
5:00 PM – 6:00 PM ET

Faculty

Prof Jonathan A Ledermann

Moderator

Neil Love, MD

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Recent Advances in Medical Oncology:
A daylong CME hybrid (live/online) event

Saturday, August 6, 2022

9:00 AM – 4:30 PM PT (12:00 PM – 7:30 PM ET)

Bellagio Las Vegas | Las Vegas, Nevada

Faculty

Neeraj Agarwal, MD
Harold J Burstein, MD, PhD
Ibiayi Dagogo-Jack, MD
Rafael Fonseca, MD
Brad S Kahl, MD
Rutika Mehta, MD, MPH
Craig Moskowitz, MD
Joyce O'Shaughnessy, MD
Krina Patel, MD, MSc
Philip A Philip, MD, PhD, FRCP
Suresh S Ramalingam, MD
Sandy Srinivas, MD

Moderator

Neil Love, MD

In Partnership with the American Oncology Network

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of Small Cell Lung Cancer

Thursday, August 11, 2022
5:00 PM – 6:00 PM ET

Faculty

Jacob Sands, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Wednesday, August 17, 2022
5:00 PM – 6:00 PM ET

Faculty

John Strickler, MD

Moderator

Neil Love, MD

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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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San Francisco, California

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Meet The Professor Program Participating Faculty

Ghassan Abou-Alfa, MD, MBA
Attending
Memorial Sloan Kettering Cancer Center
Professor
Weill Cornell College at Cornell University
New York, New York

MODERATOR
Neil Love, MD
Research To Practice

Robin K 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

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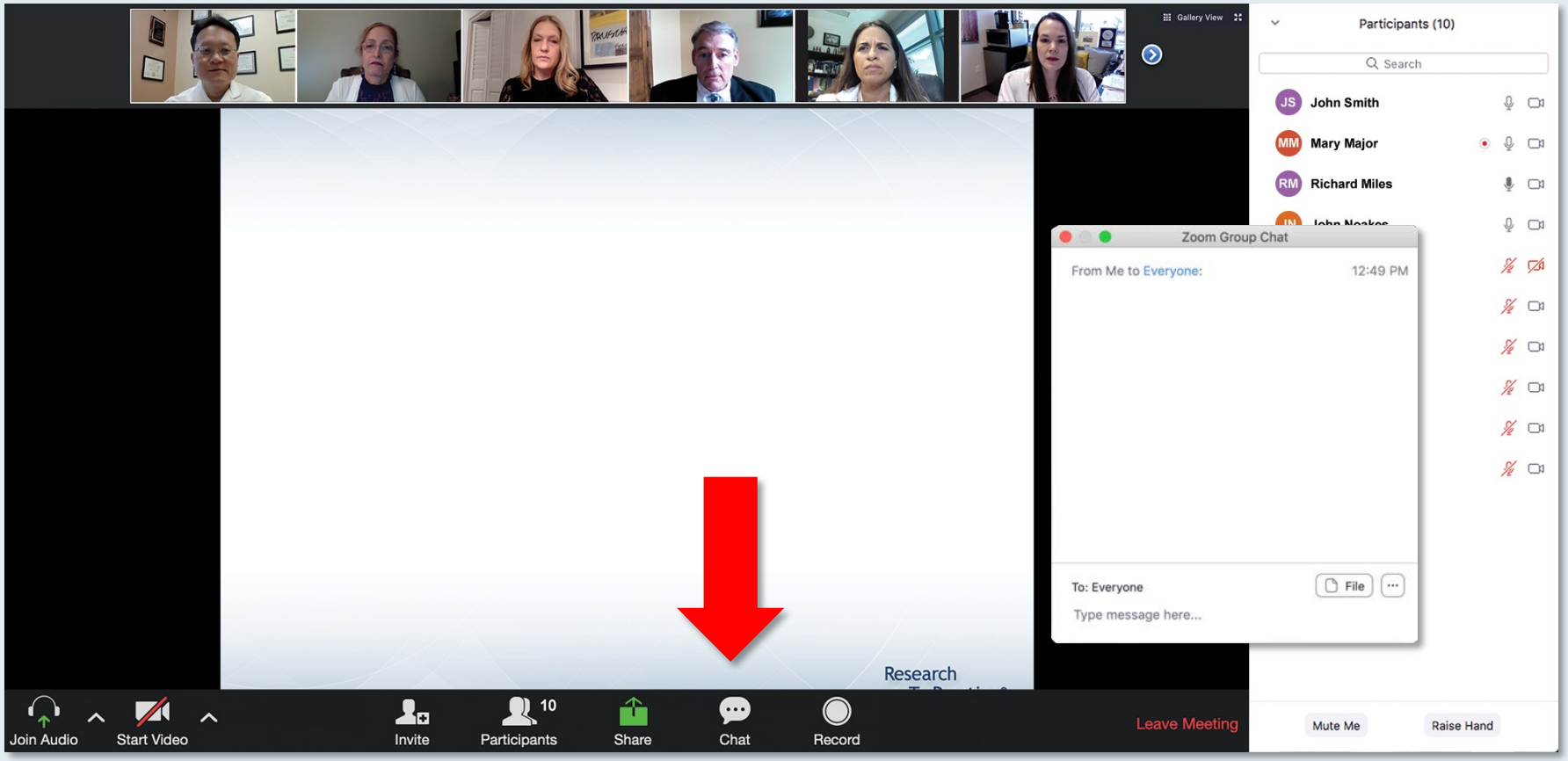

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Recent Advances and Real-World Implications in Medical Oncology

A Daylong Multitumor Educational Symposium
in Partnership with the American Oncology Network

Saturday, August 6, 2022

Breast Cancer

9:05 AM – 10:05 AM PT

Faculty

Harold J Burstein, MD, PhD
Joyce O'Shaughnessy, MD

Genitourinary Cancers

10:05 AM – 11:05 AM PT

Faculty

Neeraj Agarwal, MD
Sandy Srinivas, MD

Moderator

Neil Love, MD

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Recent Advances and Real-World Implications in Medical Oncology

A Daylong Multitumor Educational Symposium
in Partnership with the American Oncology Network

Saturday, August 6, 2022

Multiple Myeloma

11:20 AM – 12:20 PM PT

Faculty

Rafael Fonseca, MD
Krina Patel, MD, MSc

CLL and Lymphomas

12:55 PM – 1:55 PM PT

Faculty

Brad S Kahl, MD
Craig Moskowitz, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Recent Advances and Real-World Implications in Medical Oncology

A Daylong Multitumor Educational Symposium
in Partnership with the American Oncology Network

Saturday, August 6, 2022

Gastrointestinal Cancers

1:55 PM – 2:55 PM PT

Faculty

Rutika Mehta, MD, MPH
Philip A Philip, MD, PhD, FRCP

Lung Cancer

3:10 PM – 4:10 PM PT

Faculty

Ibiayi Dagogo-Jack, MD
Suresh S Ramalingam, MD

Moderator

Neil Love, MD

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

Minesh Dinubhai Patel, MD
Piedmont Cancer Institute
Peachtree City, Georgia

Jennifer L Dallas, MD
Novant Health Cancer Institute
Charlotte, North Carolina

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Northside Hospital Cancer Institute
Athens, Georgia

Shaachi Gupta, MD, MPH
Florida Cancer Specialists
Lake Worth, Florida

Liudmila N Schafer, MD
Saint Luke's Cancer Institute
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Pavel A Levin, MD, PhD
Texas Oncology-Pearland
Houston, Texas

John Yang, MD
Oncologist
Fall River, Massachusetts

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Meet The Professor with Dr Kelley

Introduction

MODULE 1: Hepatocellular Carcinoma

- Case Presentations
- Journal Club with Dr Kelley

MODULE 2: Biliary Tract Cancers

- Case Presentations
- Key Recent Data Sets; Journal Club with Dr Kelley

MODULE 3: Appendix of Key Publications

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MODULE 3: Appendix of Key Publications

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Nat Rev Dis Primers 2021;7(1):6.

PRIMER

Check for updates

Hepatocellular carcinoma

Josep M. Llovet[1,2,3]✉, *Robin Kate Kelley*[4], *Augusto Villanueva*[1], *Amit G. Singal*[5], *Eli Pikarsky*[6], *Sasan Roayaie*[7], *Riccardo Lencioni*[8,9], *Kazuhiko Koike*[10], *Jessica Zucman-Rossi*[11,12] and *Richard S. Finn*[13]

REVIEW ARTICLE
https://doi.org/10.1038/s43018-022-00357-2
Nat Cancer 2022;3(4):386-401.
nature cancer

Molecular pathogenesis and systemic therapies for hepatocellular carcinoma

Josep M. Llovet[1,2,3] ✉, Roser Pinyol[1], Robin K. Kelley[4], Anthony El-Khoueiry[5], Helen L. Reeves[6,7], Xin Wei Wang[8,9], Gregory J. Gores[10] and Augusto Villanueva[2]

N Engl J Med 2021;385(3):280-2.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Hepatocellular Carcinoma — Origins and Outcomes

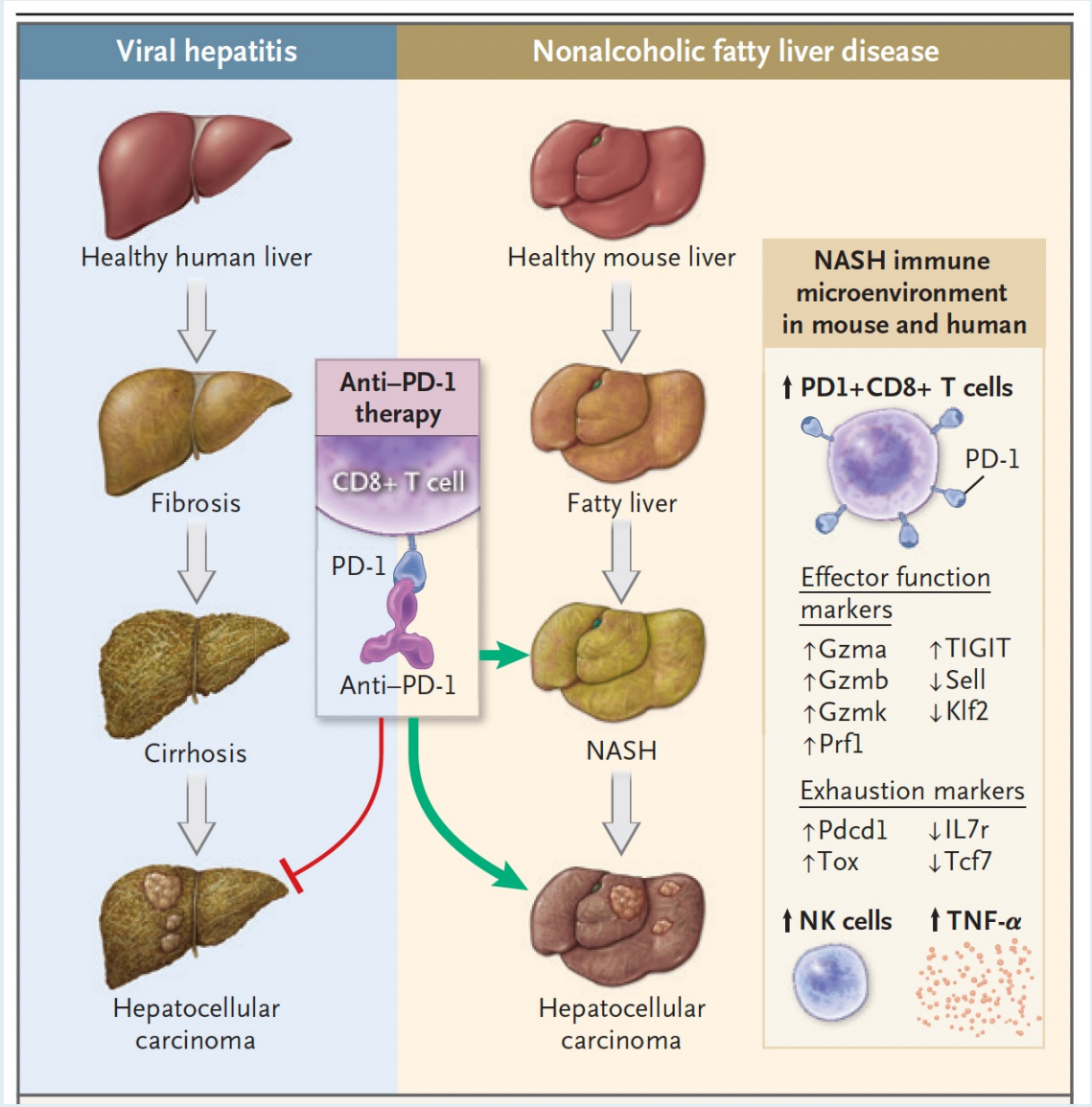
Robin K. Kelley, M.D., and Tim F. Greten, M.D.

Pfister D et al. *Nature* 2021;592:450-6.

Article

NASH limits anti-tumour surveillance in immunotherapy-treated HCC

PD-1 Inhibition for Hepatocellular Carcinoma in the Context of NASH



Kelley RK, Greten TF. *N Engl J Med* 2021;385(3):280-2.

Research Article
Hepatic and Biliary Cancer

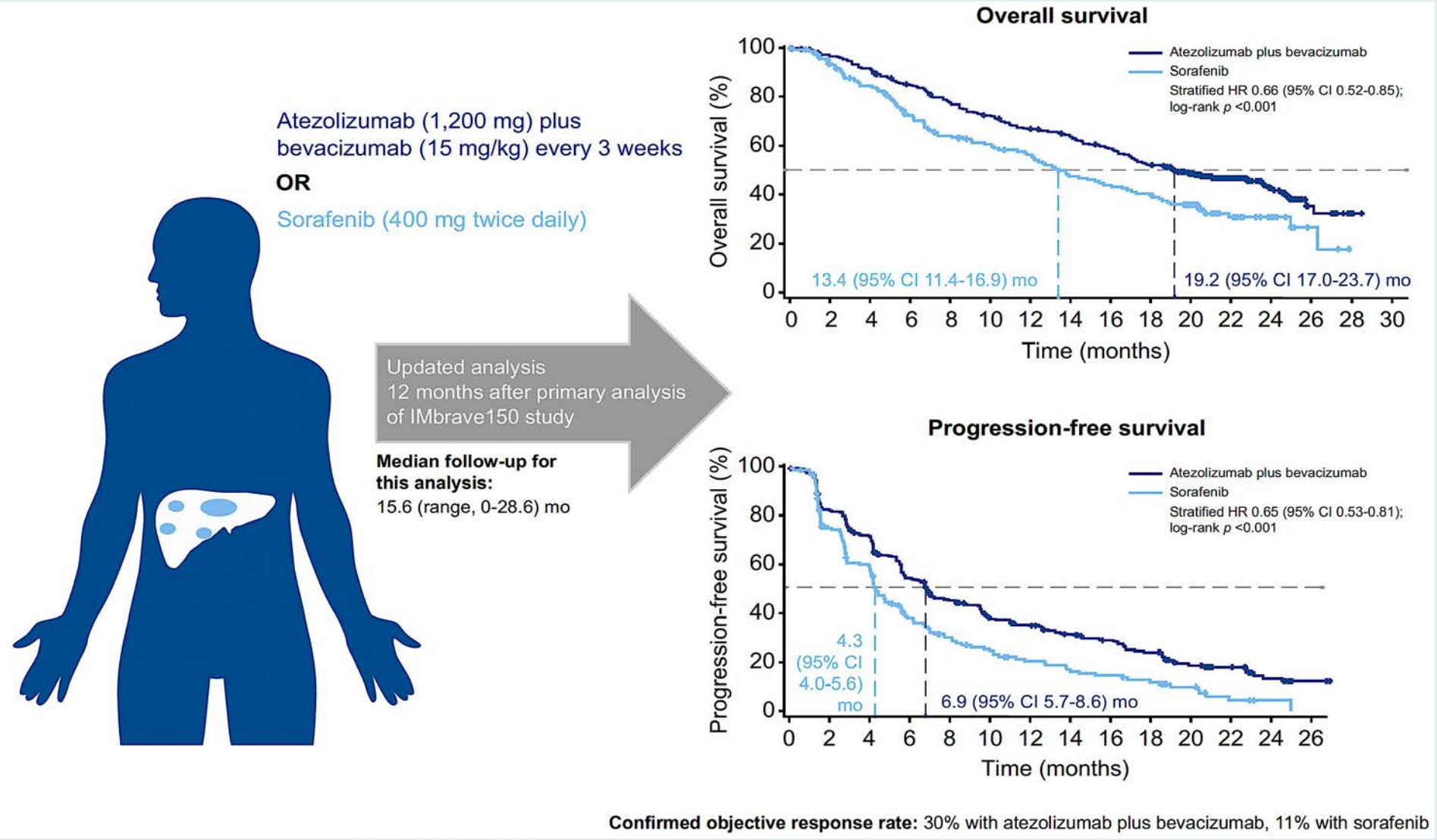
JOURNAL
OF HEPATOLOGY

Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab *vs.* sorafenib for unresectable hepatocellular carcinoma

Ann-Lii Cheng[1,*], Shukui Qin[2], Masafumi Ikeda[3], Peter R. Galle[4], Michel Ducreux[5], Tae-You Kim[6], Ho Yeong Lim[7], Masatoshi Kudo[8], Valeriy Breder[9], Philippe Merle[10], Ahmed O. Kaseb[11], Daneng Li[12], Wendy Verret[13], Ning Ma[14], Alan Nicholas[15], Yifan Wang[16], Lindong Li[17], Andrew X. Zhu[18,19], Richard S. Finn[20,*]

J Hepatol 2022;76(4):862-73.

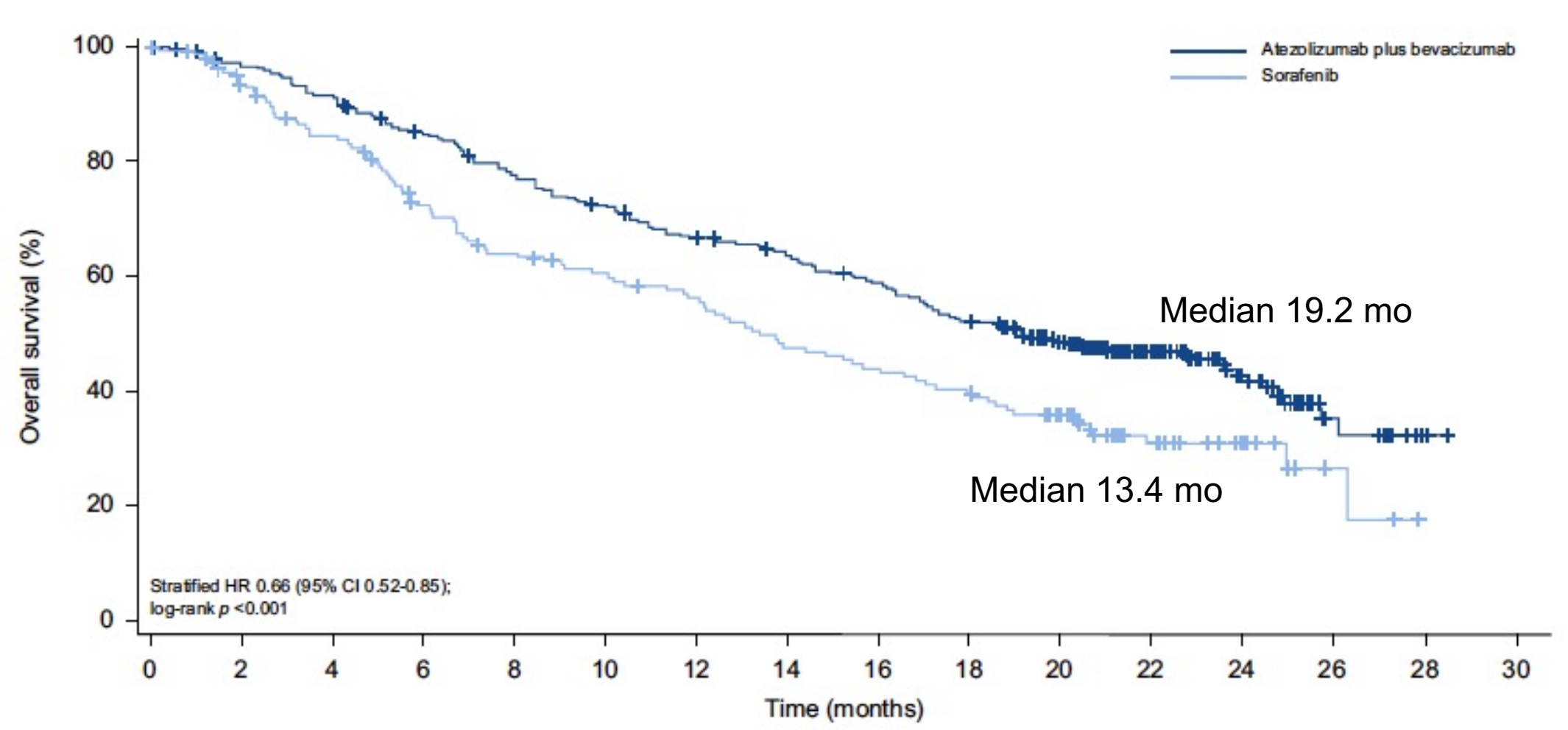
IMbrave150: Updated OS and PFS with Atezolizumab and Bevacizumab (Median Follow-Up = 15.6 Months)



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

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

IMbrave150: Updated OS with Atezolizumab and Bevacizumab (Median Follow-Up = 15.6 Months)



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

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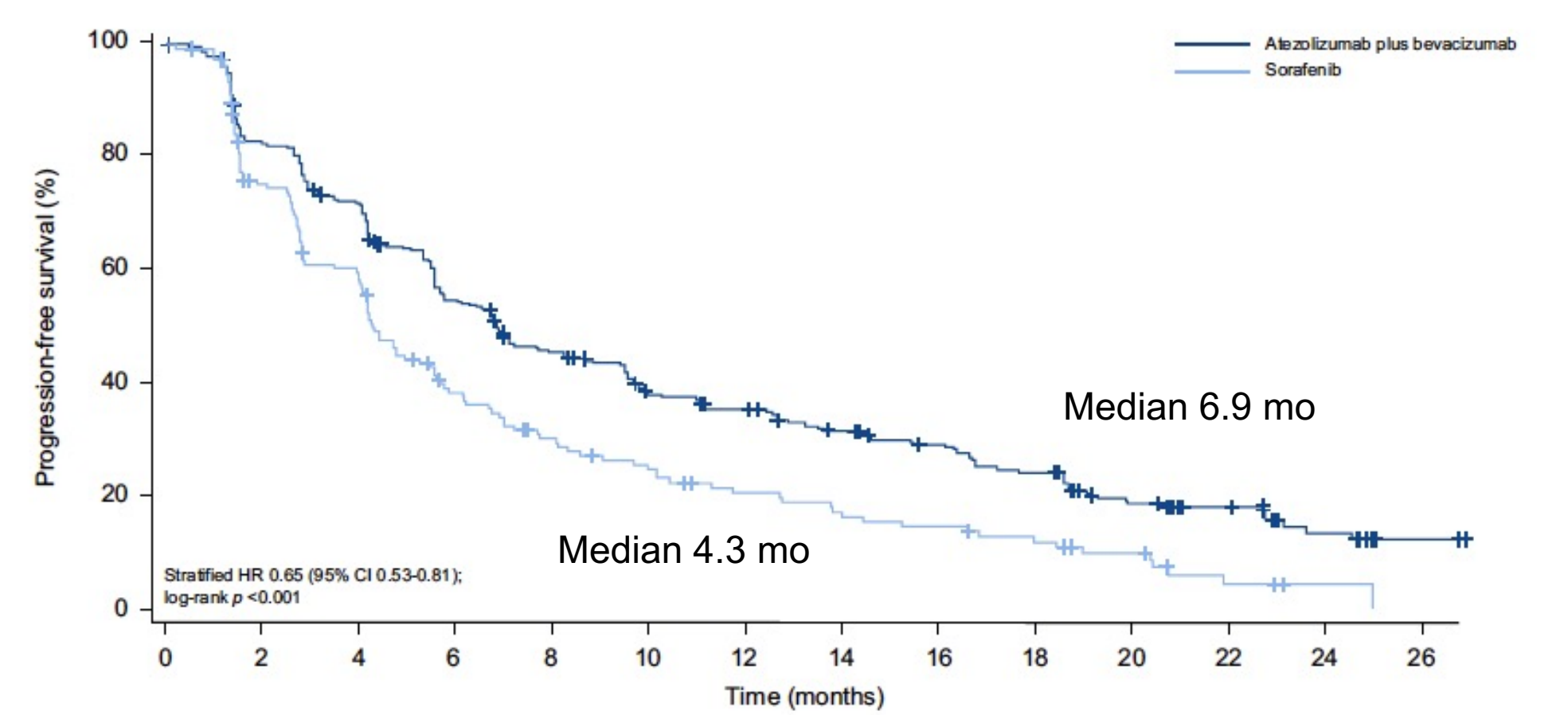

Cheng A-L et al. *J Hepatol* 2022;76(4):862-73.

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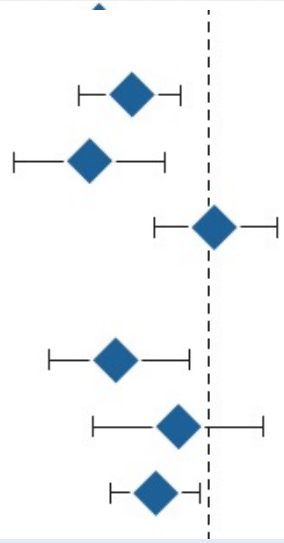
IMbrave150 Update: Subgroup Analysis of OS with Atezolizumab and Bevacizumab (Median Follow-Up = 15.6 Months)

Subgroup	Atezolizumab plus bevacizumab		Sorafenib		Hazard ratio for death (95% CI)
	Events/ patients	Median OS, months (95% CI)	Events/ patients	Median OS, months (95% CI)	
Etiology					
Hepatitis B	86/164	19.0 (16.1-NE)	46/76	12.4 (6.7-16.9)	0.58 (0.40-0.83)
Hepatitis C	31/72	24.6 (19.8-NE)	24/36	12.6 (7.4-18.4)	0.43 (0.25-0.73)
Non-viral	63/100	17.0 (11.7-22.8)	30/53	18.1 (11.7-26.3)	1.05 (0.68-1.63)
PD-L1 status					
TC or IC ≥1%	44/86	22.8 (17.0-NE)	24/36	12.6 (7.4-17.1)	0.52 (0.32-0.87)
TC and IC <1%	27/49	19.9 (13.9-NE)	17/28	15.4 (11.4-26.3)	0.81 (0.44-1.49)
Unknown	109/201	18.0 (16.1-24.0)	59/101	13.4 (9.7-18.6)	0.69 (0.50-0.94)



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

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ESMO WORLD CONGRESS ON Gastrointestinal Cancer 2022 | Abstract SO-14

Atezolizumab Plus bevacizumab versus lenvatinib or sorafenib in non-viral unresectable hepatocellular carcinoma: An international study

ANDREA CASADEI GARDINI and MARGHERITA RIMINI

SAN RAFFAELE HOSPITAL; MILAN

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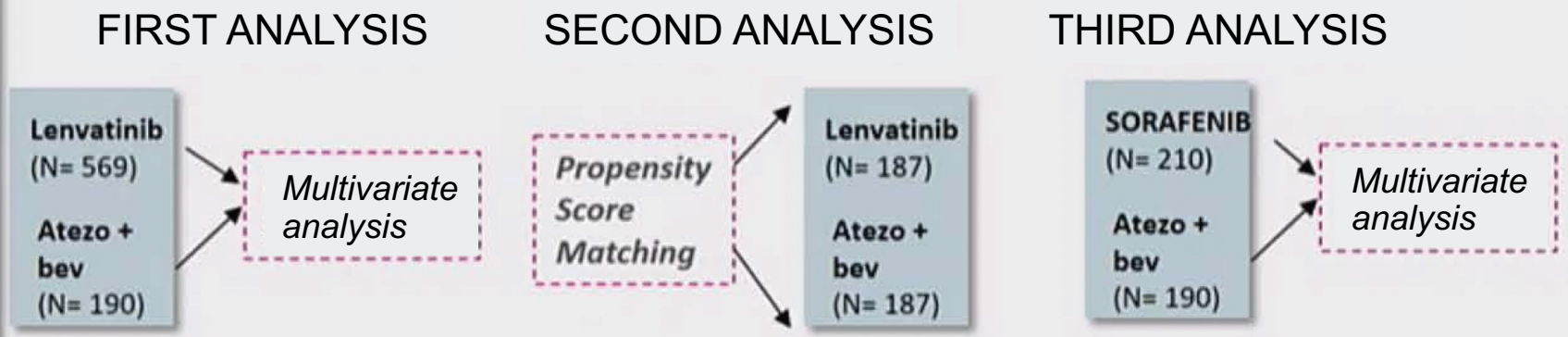
Study Design

- **Retrospective** data of patients treated in **1L WITH NO VIRAL ETIOLOGY**
- **BCLC-C or BCLC-B** (not eligible for LRT)
- **Common inclusion criteria** for the use of LEN or Atezo plus bev were applied
- The overall cohort included Western and Eastern patient populations from 36 centres in 4 countries (Italy, Japan, Republic of Korea, and United Kingdom)

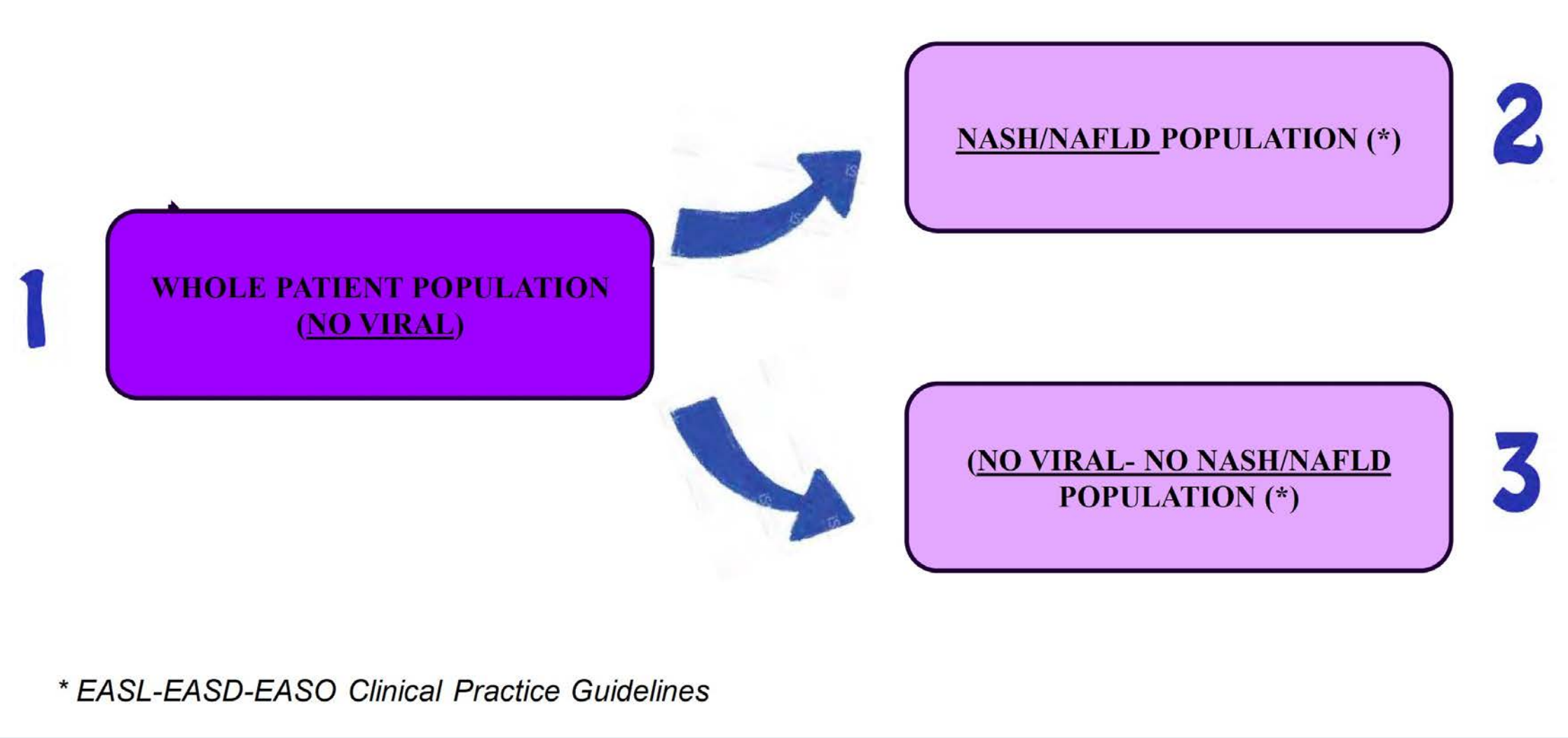


Endpoints

Effectiveness: OS, PFS

Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

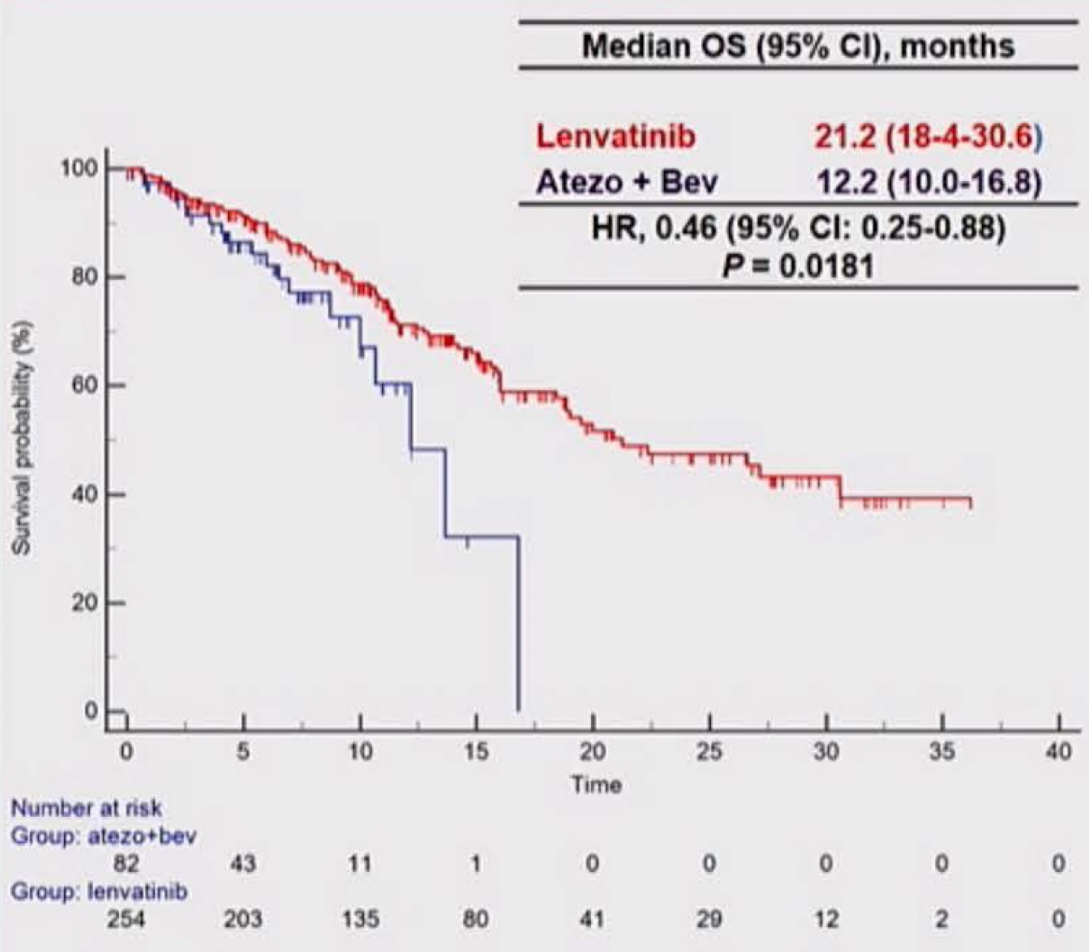
Study Design and Population

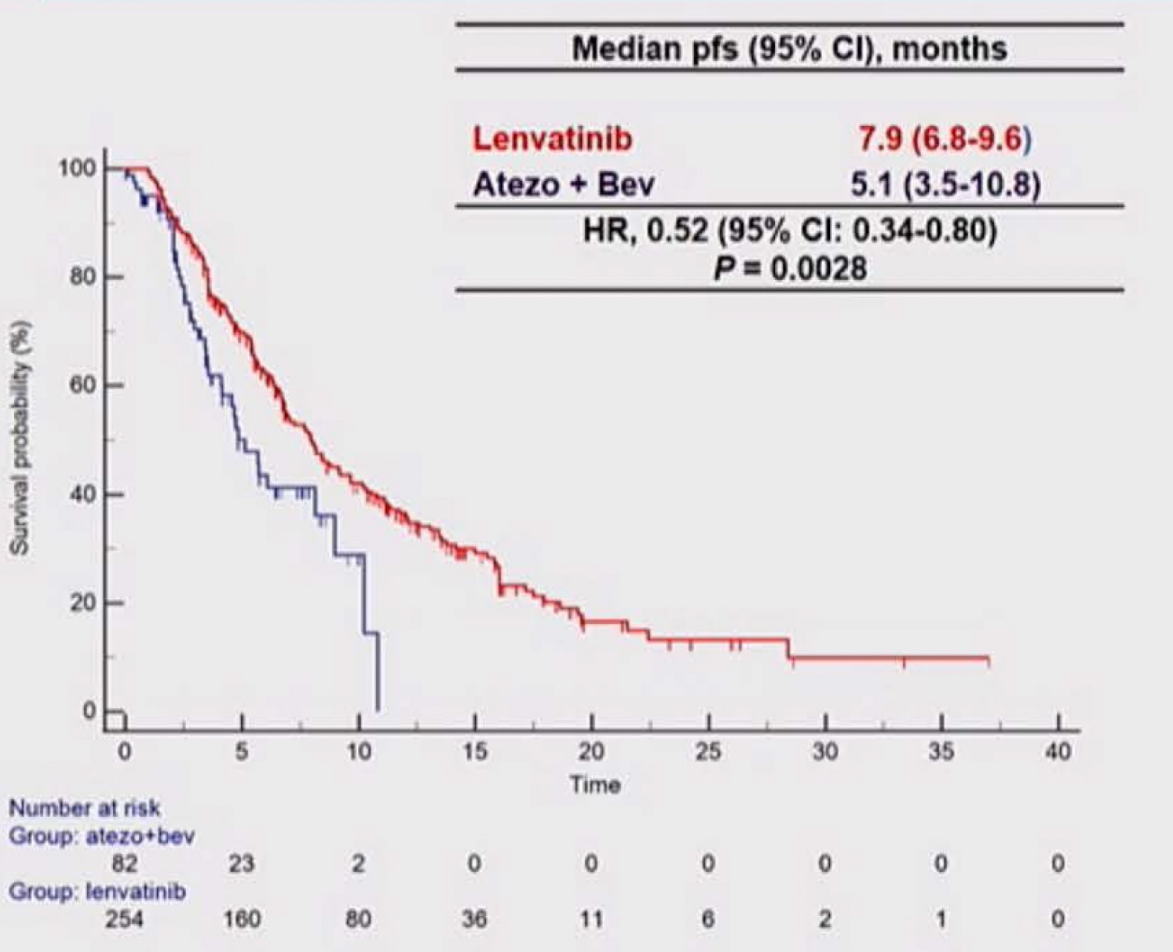


NASH = nonalcoholic steatohepatitis; NAFLD = nonalcoholic fatty liver disease

Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

Efficacy Results (First Study): NASH/NAFLD





Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

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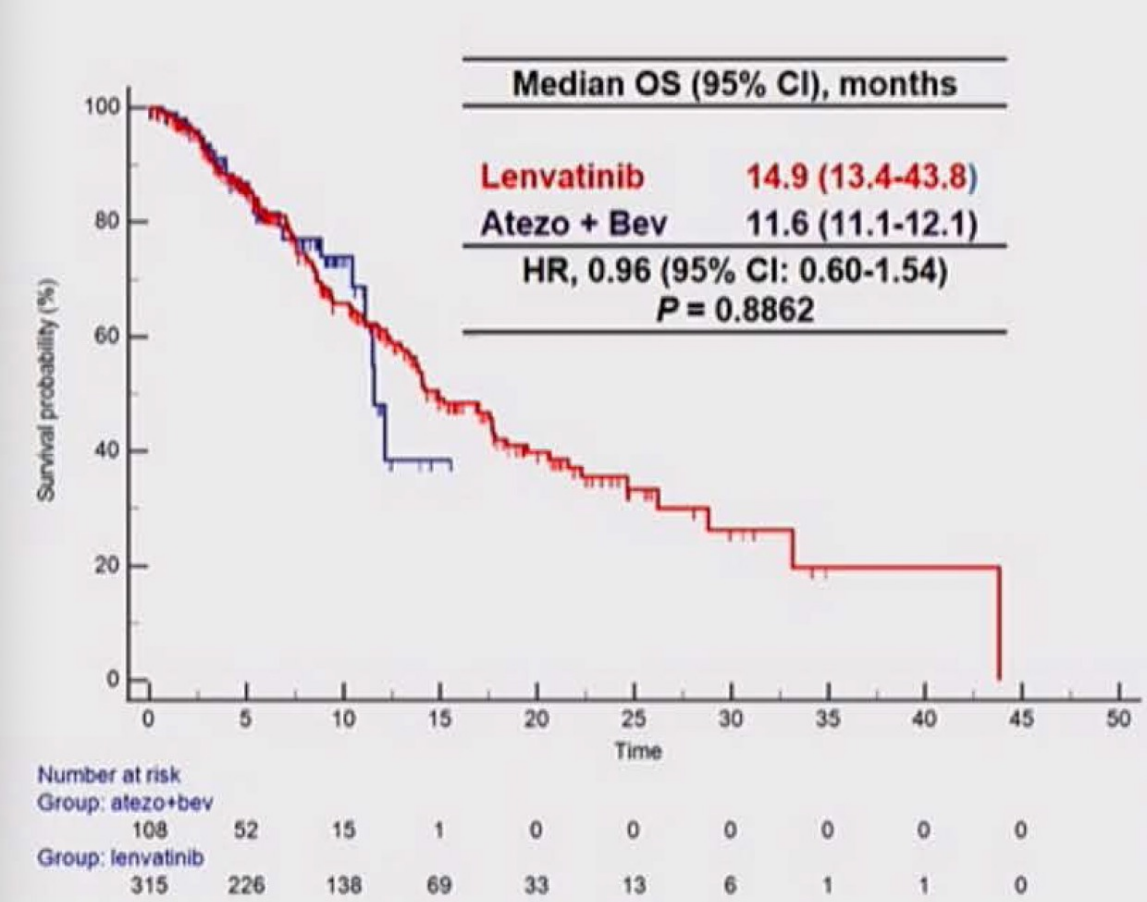
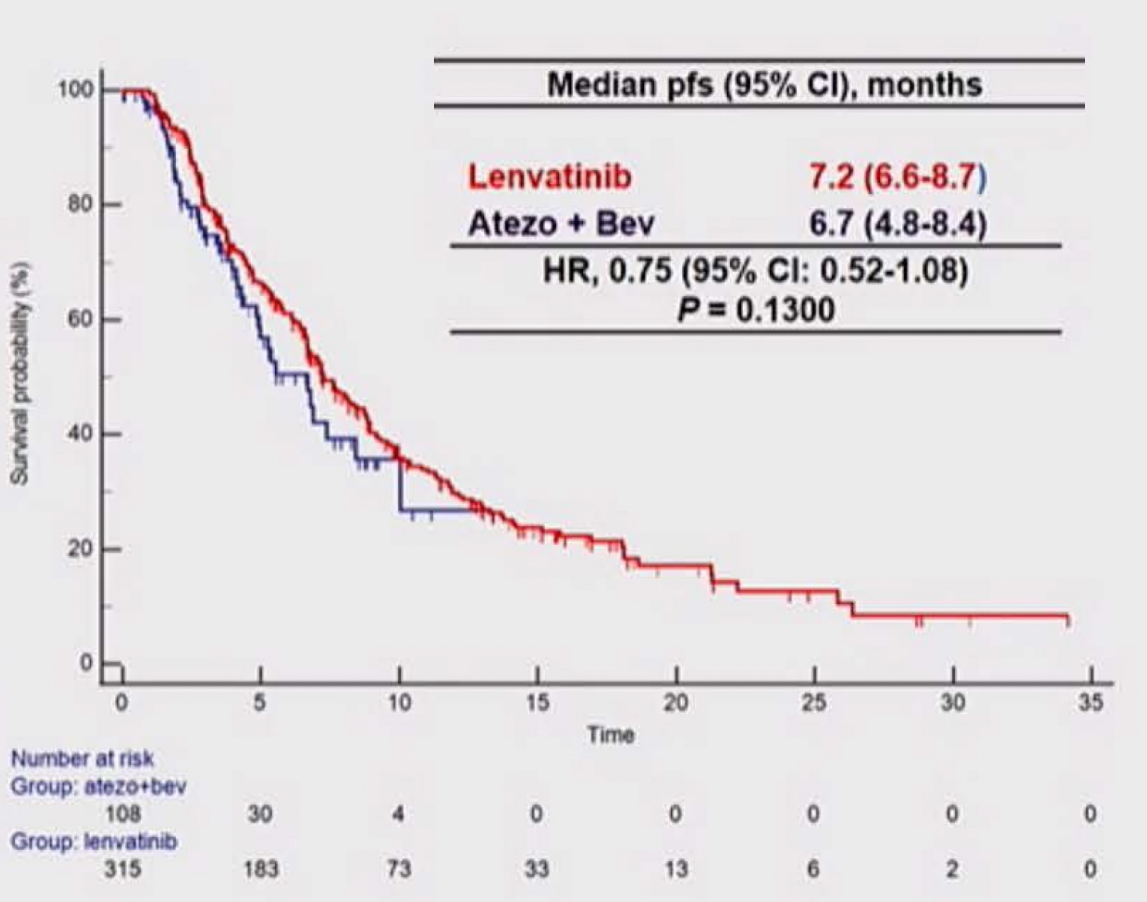
Clinical Outcomes in Nonviral, Non-NASH/NAFLD Population





Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

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ASCO 2022

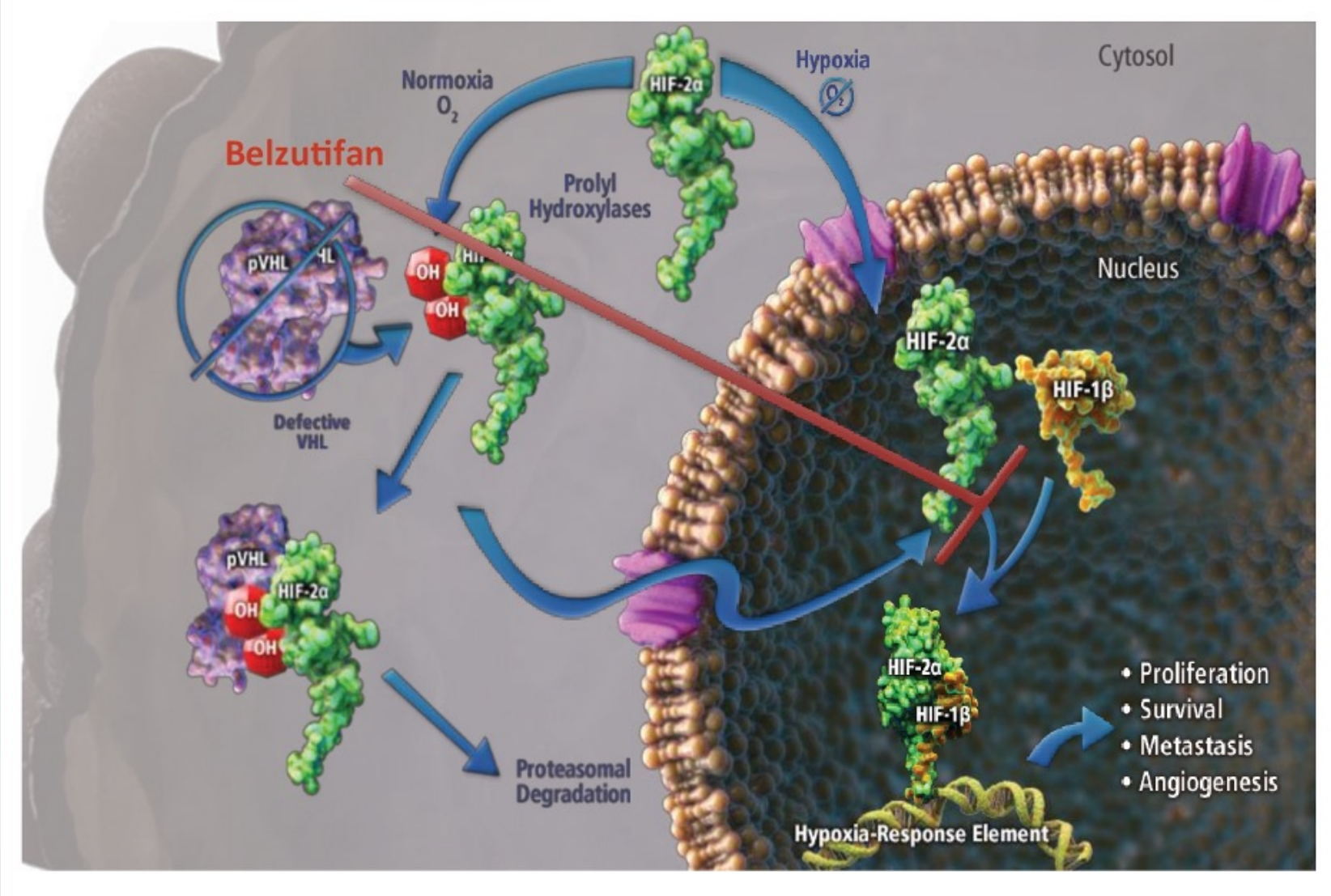
TPS4173

Phase 2 Open-Label Study of Pembrolizumab Plus Lenvatinib and Belzutifan in Patients With Advanced Solid Tumors

R.K. Kelley[1]; E. Van Cutsem[2]; M.S. Lee[3]; I. Wolf[4]; M. Fakih[5]; J. de Vos-Geelen[6]; V. Lee[7]; A. Vogel[8]; X.L. Wu[9]; F. Jin[9]; G.S. Naik[9]; E.M. O'Reilly[10]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Belzutifan Inhibition of HIF-2α Affects Downstream Pathways



Kelley RK et al. ASCO 2022;Abstract TPS4173.

Meet The Professor with Dr Kelley

Introduction

MODULE 1: Hepatocellular Carcinoma (HCC)

- Case Presentations
  - Dr Patel: An 84-year-old man with newly diagnosed HCC who has a PR with atezolizumab/bevacizumab
  - Dr Brenner: A 66-year-old man with HCC and lung metastases (AFP: 30,000) who receives front-line atezolizumab/bevacizumab
  - Dr Gupta: A 66-year-old man with metastatic HCC and rapid disease progression on first-line atezolizumab/bevacizumab
  - Dr Yang: A 78-year-old man with PMH of alcoholic cirrhosis and newly diagnosed multifocal HCC
  - Dr Schafer: An 82-year-old man with NASH liver cirrhosis and advanced HCC who develops proteinuria on atezolizumab/bevacizumab
- Journal Club with Dr Kelley

MODULE 2: Biliary Tract Cancers

- Case Presentations
- Key Recent Data Sets; Journal Club with Dr Kelley

MODULE 3: Appendix of Key Publications

RTP RESEARCH TO PRACTICE

Case Presentation: An 84-year-old man with newly diagnosed HCC who has a PR with atezolizumab/bevacizumab

Dr Minesh Patel (Peachtree City, Georgia)

RTP
RESEARCH
TO PRACTICE

Case Presentation: An 84-year-old man with newly diagnosed HCC who has a PR with atezolizumab/bevacizumab (continued)

Dr Minesh Patel (Peachtree City, Georgia)

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TO PRACTICE

ASCO Gastrointestinal Cancers Symposium 2022 | Abstract 379

Phase 3 randomized, open-label, multicenter study of tremelimumab and durvalumab as first-line therapy in patients with unresectable hepatocellular carcinoma: HIMALAYA

Ghassan K Abou-Alfa,[1,2*] Stephen L Chan,[3*] Masatoshi Kudo,[4*] George Lau,[5*] Robin Kate Kelley,[6] Junji Furuse,[7] Wattana Sukeepaisarnjaroen,[8] Yoon-Koo Kang,[9] Tu V Dao,[10] Enrico N De Toni,[11] Lorenza Rimassa,[12,13] Valery Breder,[14] Alexander Vasilyev,[15] Alexandra Heurgué,[16] Vincent C Tam,[17] Kabir Mody,[18] Satheesh Chiradoni Thungappa,[19] Philip He,[20] Alejandra Negro,[20] and Bruno Sangro[21]

[1]Department of Medicine, Memorial Sloan Kettering Center, New York, NY, USA; [2]Weill Medical College, Cornell University, New York, NY, USA; [3]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Sir Yue-Kong Pao Center for Cancer, The Chinese University of Hong Kong, Hong Kong, China; [4]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan; [5]Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong, China; [6]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA; [7]Department of Medical Oncology, Kyorin University Faculty of Medicine, Mitaka, Japan; [8]Department of Medicine, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand; [9]Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea; [10]Cancer Research and Clinical Trial Center, National Cancer Hospital, Hanoi, Vietnam; [11]Department of Medicine II, University Hospital, LMU Munich, Munich, Germany; [12]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [13]Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [14]Chemotherapy Department No17, N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [15]Railway Clinical Hospital, St. Petersburg, Russia; [16]Service d'Hépato-Gastro-entérologie, Hôpital Robert-Debré, Reims, France; [17]Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [18]Division of Hematology/Oncology, Department of Medicine, Mayo Clinic, Jacksonville, FL, USA; [19] Sri Venkateshwara Hospital, Bangalore, India; [20]AstraZeneca, Gaithersburg, MD, USA; [21]Liver Unit and HPB Oncology Area, Clinica Universidad de Navarra and CIBEREHD, Pamplona, Spain

*Drs Ghassan K Abou-Alfa, Stephen L Chan, Masatoshi Kudo, and George Lau contributed equally to this work.

PRESENTED BY: Ghassan K Abou-Alfa, MD, MBA

NEJM Evidence

Published June 6, 2022

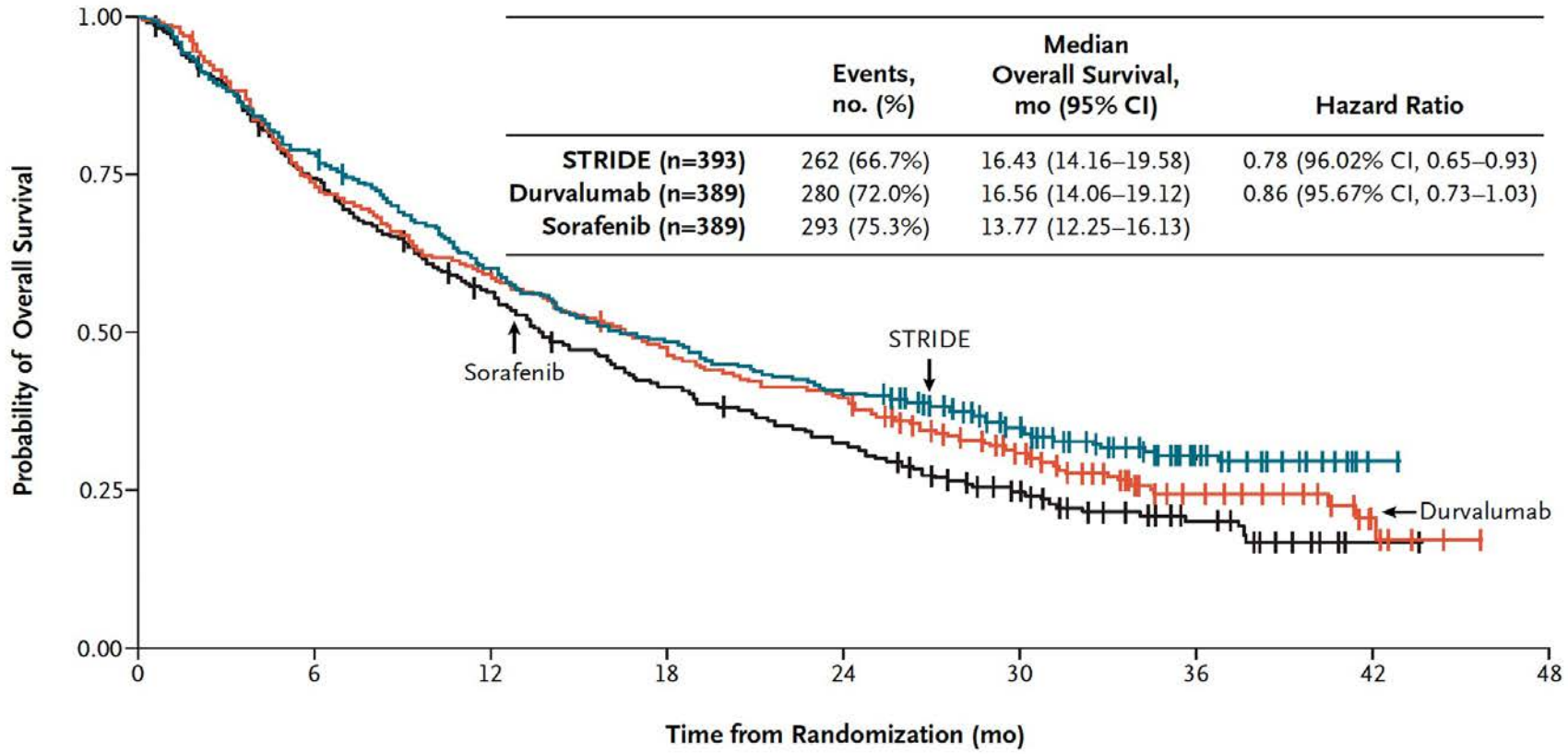
DOI: 10.1056/EVIDoa2100070

ORIGINAL ARTICLE

Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma

Ghassan K. Abou-Alfa, M.D., M.B.A.,[1,2] George Lau, M.D., F.R.C.P.,[3] Masatoshi Kudo, M.D., Ph.D.,[4] Stephen L. Chan, M.D.,[5] Robin Kate Kelley, M.D.,[6] Junji Furuse, M.D., Ph.D.,[7] Wattana Sukeepaisarnjaroen, M.D.,[8] Yoon-Koo Kang, M.D., Ph.D.,[9] Tu Van Dao, M.D., Ph.D.,[10] Enrico N. De Toni, M.D., Ph.D.,[11] Lorenza Rimassa, M.D.,[12,13] Valeriy Breder, M.D., Ph.D.,[14] Alexander Vasilyev, M.D.,[15] Alexandra Heurgué, M.D.,[16] Vincent C. Tam, M.D.,[17] Kabir Mody, M.D.,[18] Satheesh Chiradoni Thungappa, M.D.,[19] Yuriy Ostapenko, M.D.,[20] Thomas Yau, M.D.,[21] Sergio Azevedo, M.D.,[22] María Varela, M.D., Ph.D.,[23] Ann-Lii Cheng, M.D., Ph.D.,[24] Shukui Qin, M.D., Ph.D.,[25] Peter R. Galle, M.D., Ph.D.,[26] Sajid Ali, M.D.,[27] Michelle Marcovitz, Ph.D.,[27] Mallory Makowsky, Pharm.D.,[27] Philip He, Ph.D.,[27] John F. Kurland, Ph.D.,[27] Alejandra Negro, Ph.D.,[27] and Bruno Sangro, M.D., Ph.D.[28]

HIMALAYA: Overall Survival

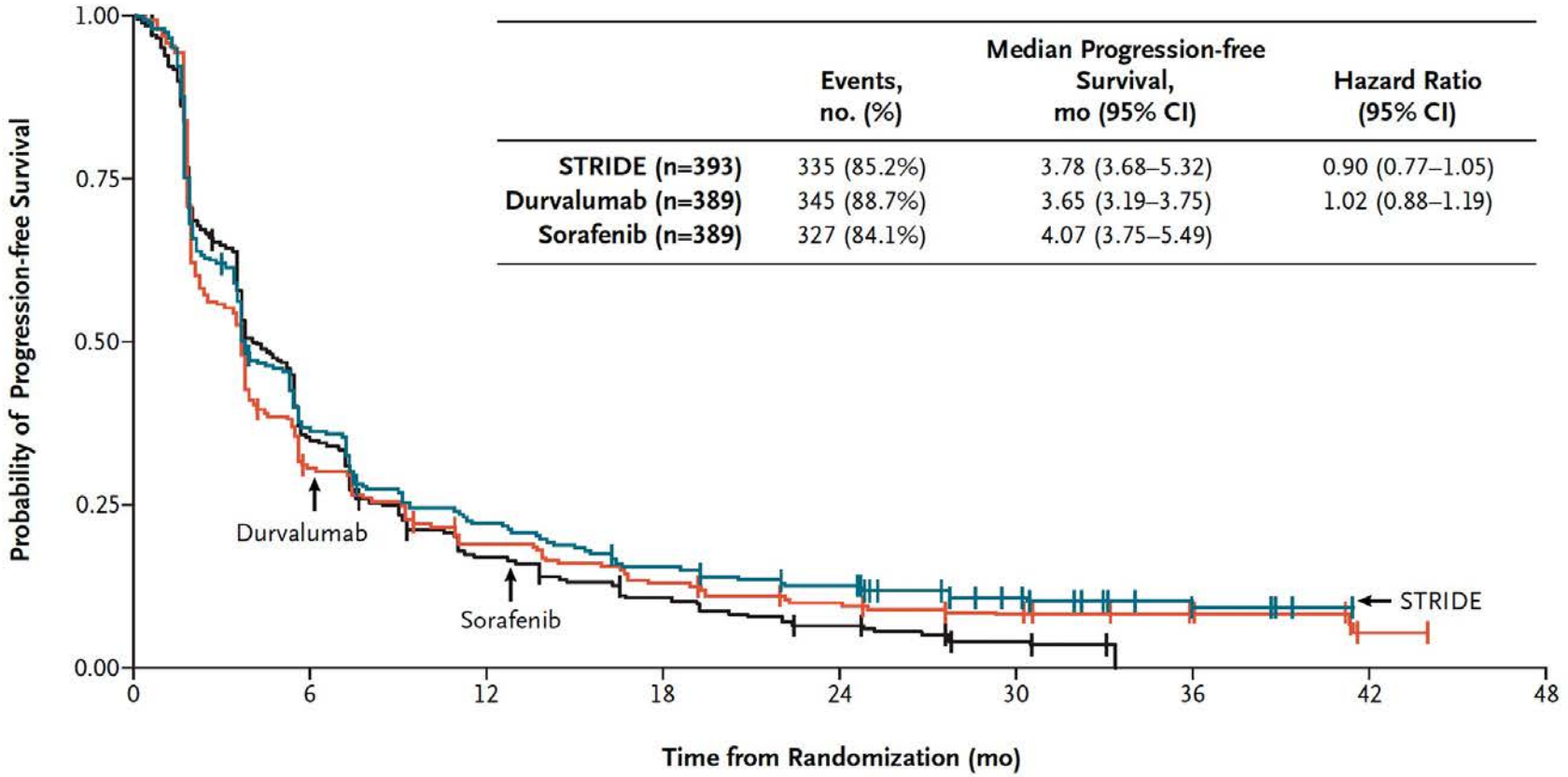


	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

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 G et al. *NEJM Evidence*, June 6, 2022.

HIMALAYA: Progression-Free Survival



	Events, no. (%)	Median Progression-free Survival, mo (95% CI)	Hazard Ratio (95% CI)
STRIDE (n=393)	335 (85.2%)	3.78 (3.68–5.32)	0.90 (0.77–1.05)
Durvalumab (n=389)	345 (88.7%)	3.65 (3.19–3.75)	1.02 (0.88–1.19)
Sorafenib (n=389)	327 (84.1%)	4.07 (3.75–5.49)	

No. at Risk									
STRIDE	393	135	81	55	43	26	7	0	0
Durvalumab	389	115	68	47	34	20	6	1	0
Sorafenib	389	118	53	31	18	6	0	0	0

Abou-Alfa G et al. *NEJM Evidence*, June 6, 2022.

HIMALAYA: Response Outcomes (Intent-to-Treat Population)

Parameter	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Response — no. (%)			
Objective†	79 (20.1)	66 (17.0)	20 (5.1)
Complete	12 (3.1)	6 (1.5)	0
Partial	67 (17.0)	60 (15.4)	20 (5.1)
Stable disease — no. (%)	157 (39.9)	147 (37.8)	216 (55.5)
Disease control rate — %	236 (60.1)	213 (54.8)	236 (60.7)
Duration of response — mo‡			
Median	22.34	16.82	18.43
IQR	8.54–NR	7.43–NR	6.51–25.99
Time to response — mo			
Median	2.17	2.09	3.78

Abou-Alfa G et al. *NEJM Evidence*, June 6, 2022.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

WORLD CONGRESS ON Gastrointestinal Cancer

2022 | Abstract O-5

O-5: Outcomes by baseline liver function in patients with unresectable hepatocellular carcinoma treated with tremelimumab and durvalumab in the Phase 3 HIMALAYA study

Arndt Vogel, MD

30 June 2022

Arndt Vogel, MD,[1] Stephen L Chan, MD,[2] Junji Furuse, MD, PhD,[3] Won Young Tak, MD, PhD,[4] Gianluca Masi, MD,[5] María Varela, MD, PhD,[6] Jee Hyun Kim, MD, PhD,[7] Suebpong Tanasanvimon, MD,[8] Maria Reig, MD, PhD,[9] Farshid Dayyani, MD, PhD,[10] Mallory Makowsky, PharmD,[11] Michelle Marcovitz, PhD,[11] Alejandra Negro, PhD,[11] Ghassan K Abou-Alfa, MD, MBA[12,13]

[1]Hannover Medical School, Hannover, Germany; [2]Sir Yue-Kong Pao Center for Cancer, The Chinese University of Hong Kong, Hong Kong, China; [3]Kyorin University Faculty of Medicine, Mitaka, Japan; [4]School of Medicine, Kyungpook National University, Daegu, Republic of Korea; [5]Pisa University, Pisa, Italy; [6]Hospital Universitario Central de Asturias, Universidad de Oviedo, Oviedo, Spain; [7]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea; [8]Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [9]Barcelona Clinic Liver Cancer (BCLC), Hospital Clinic de Barcelona, Barcelona University, Barcelona, Spain; [10]University of California, Irvine, CA, USA; [11]AstraZeneca, Gaithersburg, MD, USA; [12]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [13]Weill Medical College, Cornell University, New York, NY, USA

RTP RESEARCH TO PRACTICE

HIMALAYA: Response Outcomes in ALBI Grade Subgroups

Parameter	ALBI grade 1			ALBI grade 2/3			Full analysis set[1]		
	T300+D (n=217)	Durvalumab (n=198)	Sorafenib (n=203)	T300+D (n=175)	Durvalumab (n=191)	Sorafenib (n=186)	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* %	21.7	18.7	7.4	18.3	15.2	2.7	20.1	17.0	5.1
Median TTR‡ (IQR), mo	2.07 (1.84–3.94)	1.91 (1.81–3.98)	3.52 (1.84–5.49)	3.52 (1.91–5.40)	3.65 (1.94–3.94)	9.10 (7.79–11.01)	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Median DoR,†‡ (IQR), mo	22.34 (8.71–NR)	23.26 (7.43–NR)	22.06 (6.51–25.99)	26.55 (7.43–NR)	13.83 (7.43–27.43)	12.25 (7.69–NR)	22.34 (8.54–NR)	16.82 (7.43–NR)	18.43 (6.51–25.99)

- Similar to the full analysis set[1]:
  - ORR was higher for T300+D and durvalumab than for sorafenib in both ALBI subgroups
  - Median TTR was shorter for T300+D and durvalumab than for sorafenib in both ALBI subgroups

ORR = overall response rate; TTR = time to response; DoR = duration of response

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

HIMALAYA: Safety for T300 + D versus Sorafenib in ALBI Grade Subgroups

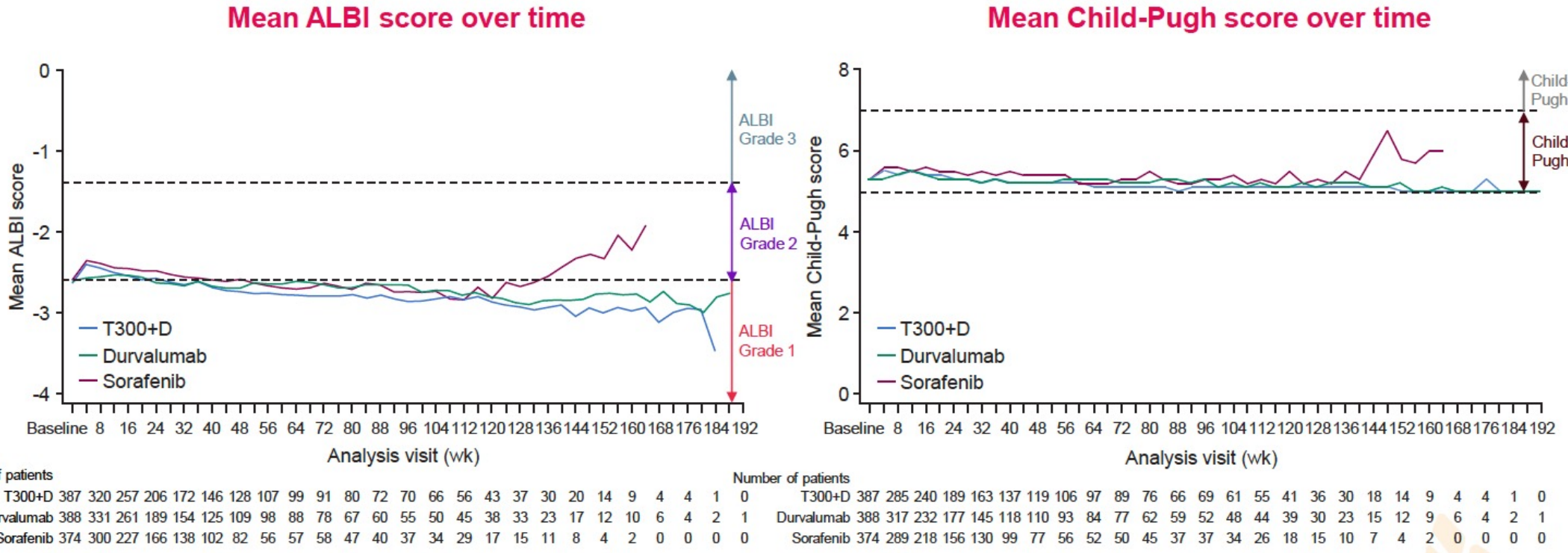
Patients with an event, n (%)	ALBI grade 1		ALBI grade 2/3		Safety analysis set[1]	
	T300+D (n=216)	Sorafenib (n=197)	T300+D (n=171)	Sorafenib (n=177)	T300+D (n=388)	Sorafenib (n=374)
Any TEAE	210 (97.2)	187 (94.9)	167 (97.7)	170 (96.0)	378 (97.4)	357 (95.5)
Any TRAE	166 (76.9)	168 (85.3)	127 (74.3)	149 (84.2)	294 (75.8)	317 (84.8)
Any grade 3/4 TEAE	111 (51.4)	102 (51.8)	85 (49.7)	94 (53.1)	196 (50.5)	196 (52.4)
Any grade 3/4 TRAE	59 (27.3)	76 (38.6)	41 (24.0)	62 (35.0)	100 (25.8)	138 (36.9)
Any TEAE leading to death	8 (3.7)	11 (5.6)	22 (12.9)	16 (9.0)	30 (7.7)	27 (7.2)
Any TRAE leading to death	5 (2.3)	1 (0.5)	4 (2.3)	2 (1.1)	9 (2.3)	3 (0.8)
Any serious TEAE	89 (41.2)	49 (24.9)	68 (39.8)	62 (35.0)	157 (40.5)	111 (29.7)
Any serious TRAE	44 (20.4)	15 (7.6)	24 (14.0)	20 (11.3)	68 (17.5)	35 (9.4)
Any TEAE leading to discontinuation	27 (12.5)	20 (10.2)	26 (15.2)	43 (24.3)	53 (13.7)	63 (16.8)
Any TRAE leading to discontinuation	20 (9.3)	15 (7.6)	12 (7.0)	26 (14.7)	32 (8.2)	41 (11.0)
Any immune-mediated TEAE	94 (43.5)	20 (10.2)	45 (26.3)	10 (5.6)	139 (35.8)	30 (8.0)

- In contrast to sorafenib, T300+D had a similar safety profile in both ALBI subgroups, similar to the safety analysis set[1]

TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

HIMALAYA: Liver Function Over Time in the Study Population



- Mean ALBI scores remained stable over time for T300+D and durvalumab; similar trends were observed in Child-Pugh scores

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

original reports

Safety, Efficacy, and Pharmacodynamics of Tremelimumab Plus Durvalumab for Patients With Unresectable Hepatocellular Carcinoma: Randomized Expansion of a Phase I/II Study

Robin Kate Kelley, MD[1]; Bruno Sangro, MD, PhD[2]; William Harris, MD[3]; Masafumi Ikeda, MD, PhD[4]; Takuji Okusaka, MD, PhD[5]; Yoon-Koo Kang, MD, PhD[6]; Shukui Qin, MD, PhD[7]; David W.-M. Tai, MD[8]; Ho Yeong Lim, MD[9]; Thomas Yau, MD[10]; Wei-Peng Yong, MD[11]; Ann-Lii Cheng, MD, PhD[12]; Antonio Gasbarrini, MD[13]; Silvia Damian, MD[14]; Jordi Bruix, MD[15]; Mitesh Borad, MD[16]; Johanna Bendell, MD[17]; Tae-You Kim, MD[18]; Nathan Standifer, PhD[19]; Philip He, PhD[20]; Mallory Makowsky, PharmD[20]; Alejandra Negro, PhD[20]; Masatoshi Kudo, MD, PhD[21]; and Ghassan K. Abou-Alfa, MD, MBA[22,23]

J Clin Oncol 2021;39(27):2991-3001.

Poster 4087

ASCO 2021

T cell receptor pharmacodynamics associated with survival and response to tremelimumab (T) in combination with durvalumab (D) in patients (pts) with unresectable hepatocellular carcinoma (uHCC)

Patricia McCoon,[1] Young S. Lee,[2] R. Kate Kelley,[3] Violeta Beleva Guthrie,[2] Song Wu,[2] Stephanie A. Bien,[4] Alejandra Negro,[5] Philip He,[5] John Kurland,[5] Carl Barrett,[1] Fernanda Pilataxi,[5] Steven Ching,[5] Ghassan K. Abou-Alfa[6]

Poster 4074

ASCO 2022

Patient-reported outcomes from the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma

Bruno Sangro,[1] Peter R Galle,[2] Robin Kate Kelley,[3] Chaiyut Charoentum,[4] Enrico N De Toni,[5] Yuriy Ostapenko,[6] Jeong Heo,[7] Ann-Lii Cheng,[8] Arndt Vogel,[9] Michelle Marcovitz,[10] Jayne Abraham,[11] Nikunj Patel,[10] Alejandra Negro,[10] Ghassan K Abou-Alfa[12,13]

Case Presentation: A 66-year-old man with HCC and lung metastases (AFP: 30,000) who receives front-line atezolizumab/bevacizumab

Dr Warren Brenner (Boca Raton, Florida)

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Case Presentation: A 66-year-old man with metastatic HCC and rapid disease progression on first-line atezolizumab/bevacizumab

Dr Shaachi Gupta (Lake Worth, Florida)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 78-year-old man with PMH of alcoholic cirrhosis and newly diagnosed multifocal HCC

Dr John Yang (Fall River, Massachusetts)

RTP RESEARCH TO PRACTICE

Case Presentation: An 82-year-old man with NASH liver cirrhosis and advanced HCC who develops proteinuria on atezolizumab/bevacizumab

Dr Liudmila Schafer (Kansas City, Missouri)

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TO PRACTICE

Meet The Professor with Dr Kelley

Introduction

MODULE 1: Hepatocellular Carcinoma

- Case Presentations
- Journal Club with Dr Kelley

MODULE 2: Biliary Tract Cancers

- Case Presentations
- Key Recent Data Sets; Journal Club with Dr Kelley

MODULE 3: Appendix of Key Publications

Poster 436

Gastrointestinal Cancers Symposium 2022.

Safety and efficacy of durvalumab plus bevacizumab in unresectable hepatocellular carcinoma: results from the Phase 2 Study 22 (NCT02519348)

Ho Yeong Lim,[1] Jeong Heo,[2] Tae-You Kim,[3] David W M Tai,[4] Yoon-Koo Kang,[5] George Lau,[6] Masatoshi Kudo,[7] Won Young Tak,[8] Magdalena Watras,[9] Sajid Ali,[10] Alejandra Negro,[11] Ghassan K Abou-Alfa,[12,13] R Kate Kelley[14]*

Lancet Oncol 2022;23:77-90.

Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial

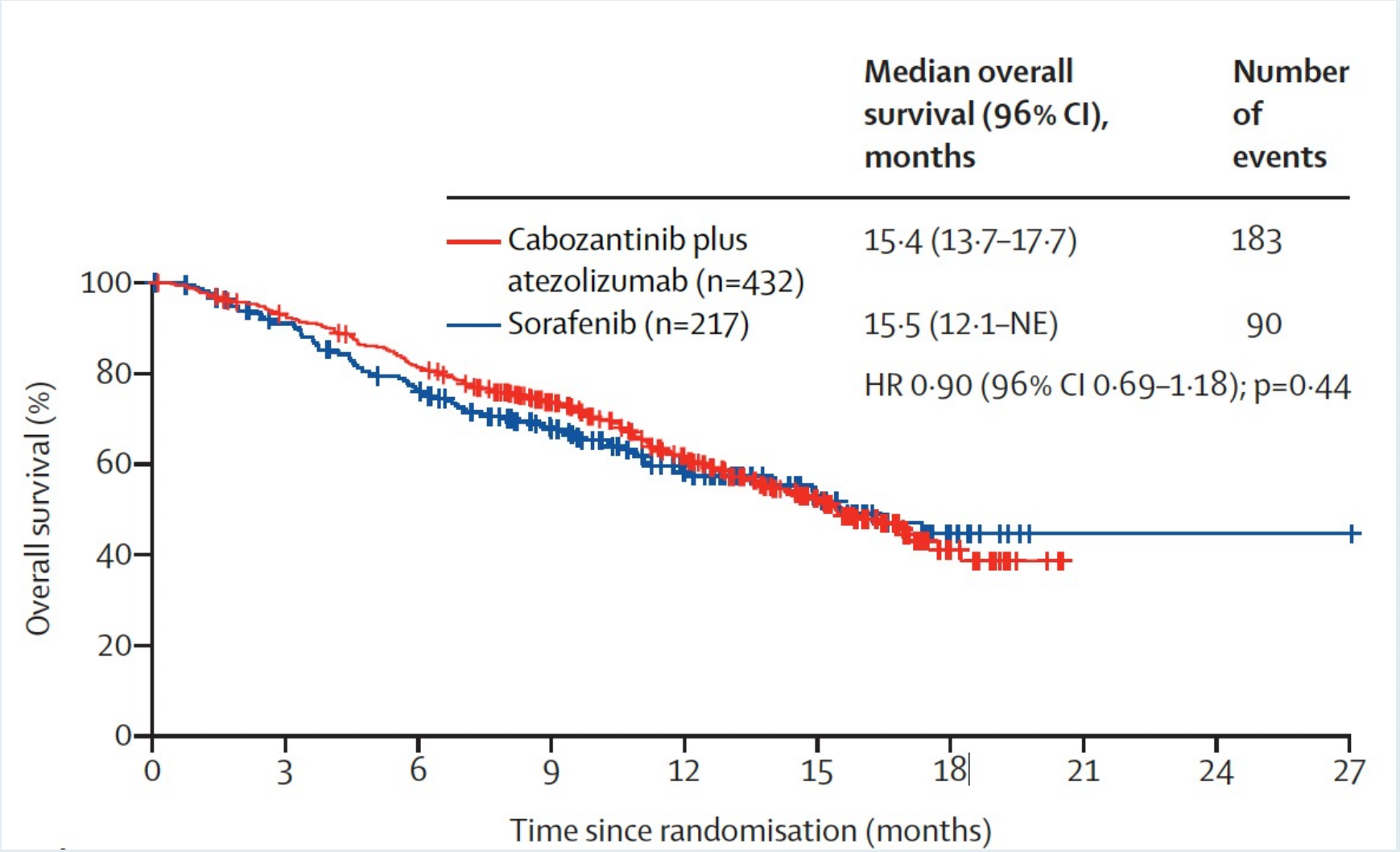
Thomas Yau, Joong-Won Park, Richard S Finn, Ann-Lii Cheng, Philippe Mathurin, Julien Edeline, Masatoshi Kudo, James J Harding, Philippe Merle, Olivier Rosmorduc, Lucjan Wyrwicz, Eckart Schott, Su Pin Choo, Robin Kate Kelley, Wolfgang Sieghart, Eric Assenat, Renata Zaucha, Junji Furuse, Ghassan K Abou-Alfa, Anthony B El-Khoueiry, Ignacio Melero, Damir Begic, Gong Chen, Jaclyn Neely, Tami Wisniewski, Marina Tschaika, Bruno Sangro

Lancet Oncology 2022;[Online ahead of print].

Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial

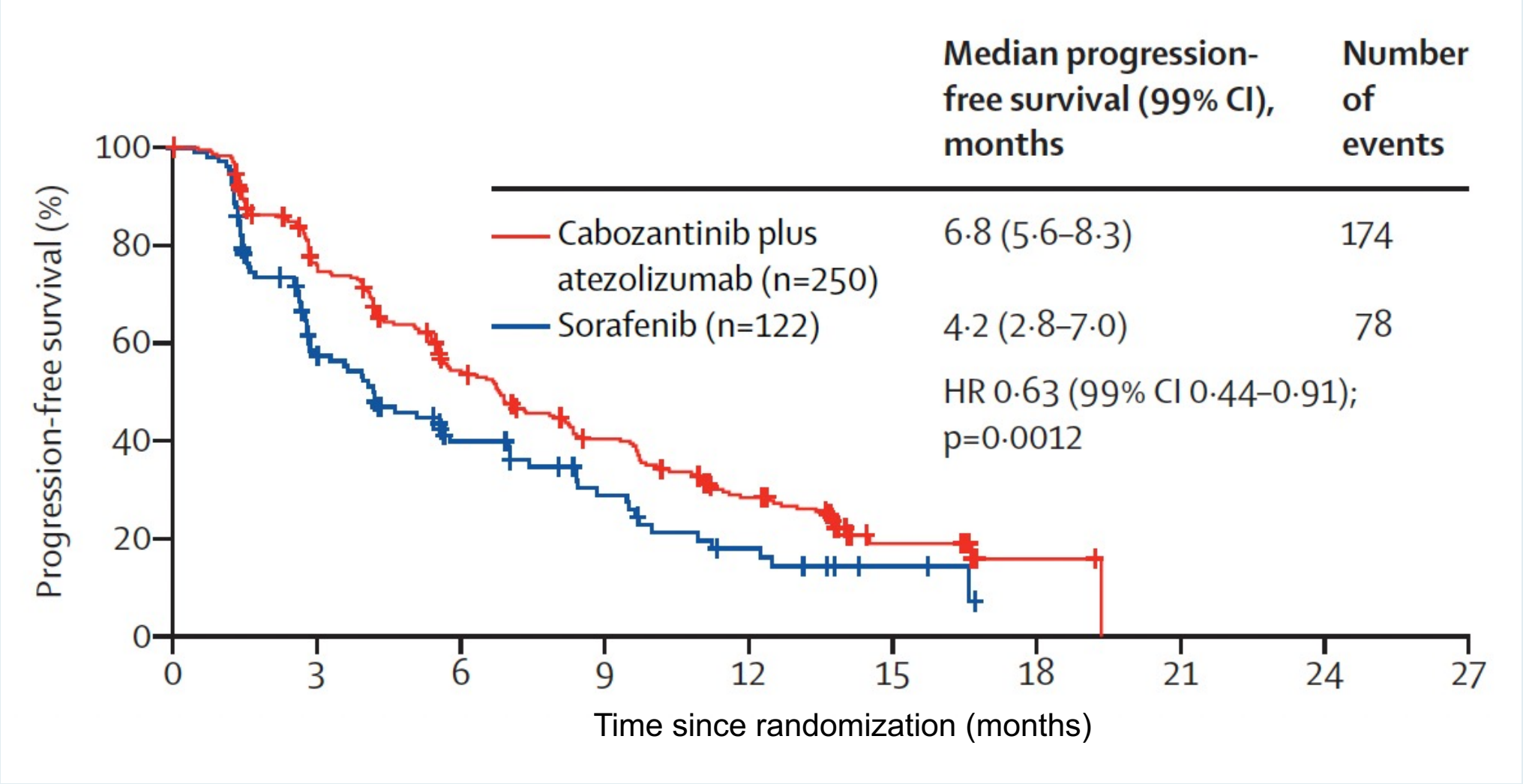
Robin Kate Kelley, Lorenza Rimassa*, Ann-Lii Cheng, Ahmed Kaseb, Shukui Qin, Andrew X Zhu, Stephen L Chan, Tamar Melkadze, Wattana Sukeepaisarnjaroen, Valery Breder, Gontran Verset, Edward Gane, Ivan Borbath, Jose David Gomez Rangel, Baek-Yeol Ryoo, Tamta Makharadze, Philippe Merle, Fawzi Benzaghou, Kamalika Banerjee, Saswati Hazra, Jonathan Fawcett, Thomas Yau*

COSMIC-312: Overall Survival in the ITT Population (Interim Analysis)



Kelley RK et al. *Lancet Oncol* 2022;[Online ahead of print].

COSMIC-312: Progression-Free Survival in the ITT Population (Final Analysis)



Kelley RK et al. *Lancet Oncol* 2022;[Online ahead of print].

Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of hepatocellular carcinoma

Tim F Greten [1], Ghassan K Abou-Alfa,[2,3] Ann-Lii Cheng,[4] Austin G Duffy,[5] Anthony B. El-Khoueiry,[6] Richard S Finn,[7] Peter R Galle,[8] Lipika Goyal,[9] Aiwu Ruth He,[10] Ahmed O Kaseb,[11] Robin Kate Kelley,[12] Riccardo Lencioni,[13,14] Amaia Lujambio,[15] Donna Mabry Hrones,[1] David J Pinato [16], Bruno Sangro,[17,18] Roberto I Troisi,[19] Andrea Wilson Woods,[20] Thomas Yau,[21] Andrew X Zhu,[9,22] Ignacio Melero [17,23,24]

J Immunother Cancer 2021;9(9):e002794.

Meet The Professor with Dr Kelley

Introduction

MODULE 1: Hepatocellular Carcinoma

- Case Presentations
- Journal Club with Dr Kelley

MODULE 2: Biliary Tract Cancers

- Case Presentations
- Key Recent Data Sets; Journal Club with Dr Kelley

MODULE 3: Appendix of Key Publications

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NEJM Evidence

Published June 1, 2022

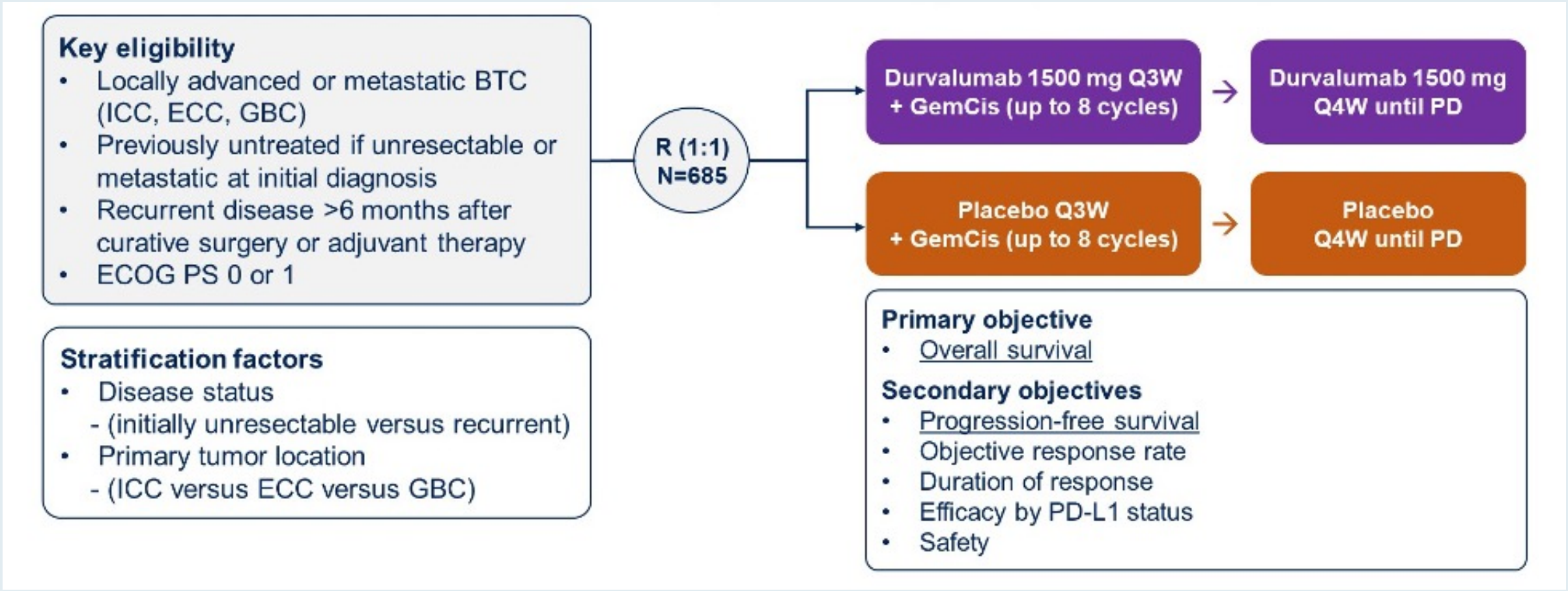
DOI: 10.1056/EVIDoa2200015

ORIGINAL ARTICLE

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

Do-Youn Oh, M.D., Ph.D.,[1] Aiwu Ruth He, M.D., Ph.D.,[2] Shukui Qin, M.D.,[3] Li-Tzong Chen, M.D., Ph.D.,[4,5,6] Takuji Okusaka, M.D., Ph.D.,[7] Arndt Vogel, M.D.,[8] Jin Won Kim, M.D., Ph.D.,[9] Thatthan Suksomboon charoen, M.D.,[10] Myung Ah Lee, M.D., Ph.D.,[11] Masayuki Kitano, M.D., Ph.D.,[12] Howard Burris, M.D.,[13] Mohamed Bouattour, M.D.,[14] Suebpong Tanasanvimon, M.D.,[15] Mairéad G. McNamara, M.B., Ph.D.,[16] Renata Zaucha, M.D., Ph.D.,[17] Antonio Avallone, M.D.,[18] Benjamin Tan, M.D.,[19] Juan Cundom, M.D.,[20] Choong-kun Lee, M.D., Ph.D.,[21] Hidenori Takahashi, M.D., Ph.D.,[22] Masafumi Ikeda, M.D., Ph.D.,[23] Jen-Shi Chen, M.D.,[24] Julie Wang, Ph.D.,[25] Mallory Makowsky, Pharm.D.,[25] Nana Rokutanda, M.D., Ph.D.,[25] Philip He, Ph.D.,[25,26] John F. Kurland, Ph.D.,[25] Gordon Cohen, M.D., M.P.H.,[25] and Juan W. Valle, M.D.[16]

TOPAZ-1 Phase III Trial Schema

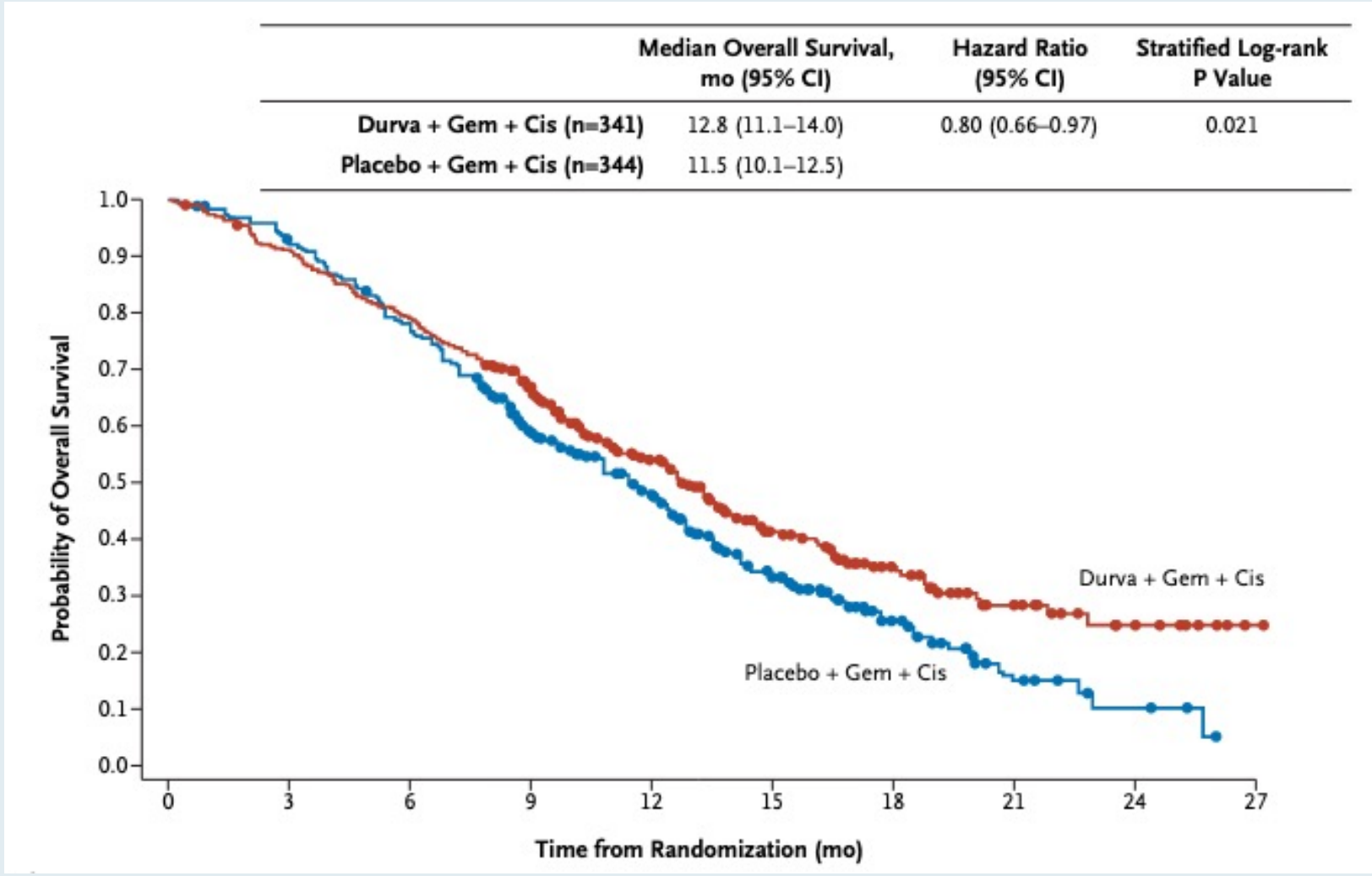


BTC = biliary tract cancer

Oh D-Y et al. Gastrointestinal Cancers Symposium 2022;Abstract 378.

TOPAZ-1: Primary Overall Survival Endpoint with Durvalumab and Gemcitabine/Cisplatin for Advanced Biliary Tract Cancer

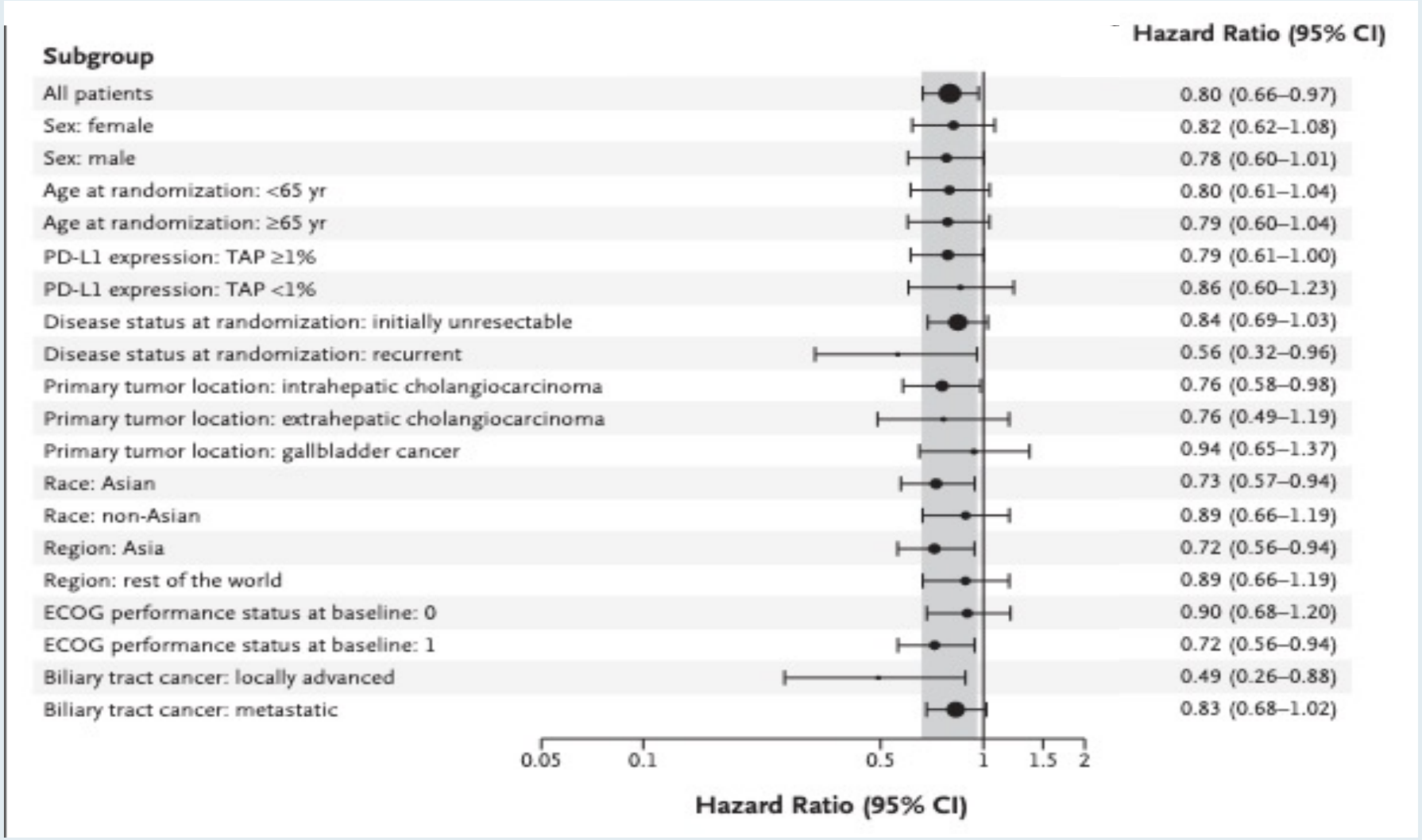
	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		



Oh D-Y et al. *NEJM Evidence*, June 1, 2022.

RTP RESEARCH TO PRACTICE

TOPAZ-1: Overall Survival Subgroup Analysis



Oh D-Y et al. *NEJM Evidence*, June 1, 2022.

TOPAZ-1: Adverse Event Summary

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=338)	Placebo plus Gemcitabine and Cisplatin (n=342)
Adverse events — no. (%)		
Any grade	336 (99.4)	338 (98.8)
Serious	160 (47.3)	149 (43.6)
Grade 3 or 4	256 (75.7)	266 (77.8)
Leading to discontinuation of any study treatment	44 (13.0)	52 (15.2)
Leading to death	12 (3.6)	14 (4.1)
Treatment-related adverse events — no. (%)		
Any grade	314 (92.9)	308 (90.1)
Serious	53 (15.7)	59 (17.3)
Grade 3 or 4	212 (62.7)	222 (64.9)
Leading to discontinuation of any study treatment	30 (8.9)	39 (11.4)
Leading to death*	2 (0.6)	1 (0.3)

Oh D-Y et al. *NEJM Evidence*, June 1, 2022.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

WORLD CONGRESS ON Gastrointestinal Cancer

2022 | Abstract O-1

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

Aiwu Ruth He, MD, PhD

29 June 2022

Aiwu Ruth He, MD, PhD,[1] Juan W Valle, MD,[2] Choong-kun Lee, MD, PhD,[3] Masafumi Ikeda, MD, PhD,[4] Piotr Potemski, MD, PhD,[5] Chigusa Morizane, MD, PhD,[6] Juan Cundom, MD,[7] David Tougeron, MD, PhD,[8] Farshid Dayyani, MD, PhD,[9] Nana Rokutanda, MD, PhD,[10] Julia Xiong, PhD,[11,] Magdalena Watras, MSc,[12] Gordon Cohen, MD, MPH,[10] Do-Youn Oh, MD, PhD[13]*

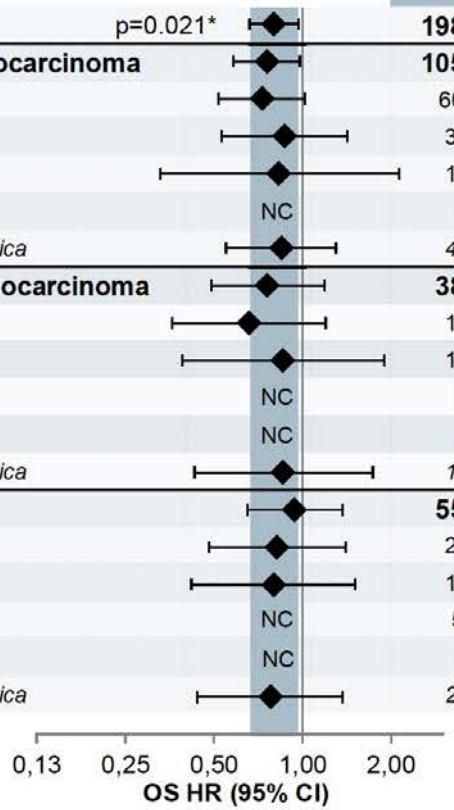
RTP RESEARCH TO PRACTICE

TOPAZ-1: OS by Primary Tumor Location and Region

OS HRs were <1, favouring durvalumab, across primary tumour locations

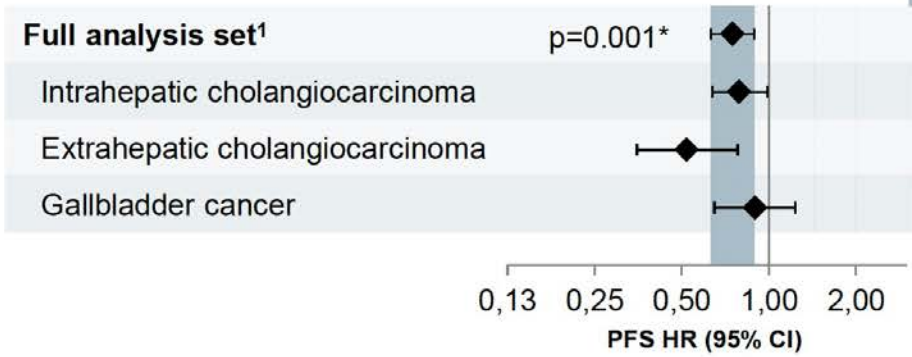
- OS benefit with durvalumab was consistent in patients with ICC and ECC, and in patients with GBC in Asia, Europe, and North America

	Durvalumab + GemCis (N=341)		Placebo + GemCis (N=344)		OS HR† (95% CI)
	Events, n/N (%)	Median OS (95% CI), mo	Events, n/N (%)	Median OS (95% CI), mo	
Full analysis set[1] p=0.021*	**198/341 (58.1)**	**12.8 (11.1–14.0)**	**226/344 (65.7)**	**11.5 (10.1–12.5)**	**0.80 (0.66–0.97)‡**
Intrahepatic cholangiocarcinoma	**105/190 (55.3)**	**13.5 (11.9–15.1)**	**126/193 (65.3)**	**11.5 (9.8–12.8)**	**0.76 (0.58–0.98)§**
Asia	60/100 (60.0)	13.0 (9.8–14.6)	81/111 (73.0)	11.4 (9.2–12.5)	0.73 (0.52–1.02)§
Europe	31/61 (50.8)	13.5 (9.5–18.8)	35/61 (57.4)	14.0 (8.0–18.3)	0.87 (0.53–1.42)§
North America	11/21 (52.4)	15.1 (6.8–NC)	9/18 (50.0)	13.3 (5.3–NC)	0.83 (0.33–2.12)§
South America	3/8 (37.5)	NR (2.3–NC)	1/3 (33.3)	NR (8.0–NC)	NC‖
Europe + North America	*42/82 (51.2)*	*13.7 (10.9–18.1)*	*44/79 (55.7)*	*13.6 (8.5–17.7)*	*0.85 (0.55–1.30)§*
Extrahepatic cholangiocarcinoma	**38/66 (57.6)**	**12.7 (9.8–16.6)**	**42/65 (64.6)**	**12.1 (7.8–14.4)**	**0.76 (0.49–1.19)§**
Asia	18/35 (51.4)	16.6 (12.6–NC)	27/42 (65.3)	12.8 (7.7–17.3)	0.66 (0.36–1.20)§
Europe	14/23 (60.9)	9.1 (8.7–NC)	12/19 (63.2)	14.4 (7.0–NC)	0.86 (0.39–1.90)§
North America	5/6 (83.3)	11.0 (0.9–NC)	3/4 (75.0)	9.6 (3.4–NC)	NC‖
South America	1/2 (50.0)	NR (10.0–NC)	0	NC	NC‖
Europe + North America	*19/29 (65.5)*	*9.8 (8.7–16.2)*	*15/23 (65.2)*	*12.1 (7.0–14.4)*	*0.86 (0.43–1.73)§*
Gallbladder cancer	**55/85 (64.7)**	**10.7 (8.9–13.2)**	**58/86 (67.4)**	**11.0 (8.7–12.8)**	**0.94 (0.65–1.37)§**
Asia	25/43 (58.1)	13.3 (9.0–20.1)	29/43 (67.4)	12.6 (8.4-17.7)	0.82 (0.48–1.40)§
Europe	18/24 (75.0)	9.6 (5.2–11.1)	22/27 (81.5)	8.1 (4.9–11.0)	0.80 (0.42–1.51)§
North America	5/10 (50.0)	12.2 (2.6–NC)	4/6 (66.7)	10.2 (5.7–NC)	NC‖
South America	7/8 (87.5)	8.1 (0.9–NC)	3/10 (30.0)¶	NR (2.0–NC)	NC‖
Europe + North America	*23/34 (67.6)*	*10.3 (6.6–12.2)*	*26/33 (78.8)*	*8.7 (6.0–11.0)*	*0.78 (0.44–1.37)§*



He AR et al. ESMO World Congress on Gastrointestinal Cancer;Abstract O-1.

TOPAZ-1: PFS by Primary Tumor Location



	Durvalumab + GemCis (N=341)		Placebo + GemCis (N=344)		PFS HR† (95% CI)
	Events, n/N (%)	Median PFS (95% CI), mo	Events, n/N (%)	Median PFS (95% CI), mo	
Full analysis set[1]	**229/341 (67.2)**	**7.2 (6.7–7.4)**	**252/344 (73.3)**	**5.7 (5.6–6.7)**	**0.75 (0.63–0.89)‡**
Intrahepatic cholangiocarcinoma	154/190 (81.1)	7.3 (6.5–7.5)	167/193 (86.5)	6.0 (5.6–7.2)	0.79 (0.64–0.99)§
Extrahepatic cholangiocarcinoma	50/66 (75.8)	7.6 (6.9–9.1)	55/65 (84.6)	5.7 (5.4–7.2)	0.52 (0.35–0.78)§
Gallbladder cancer	72/85 (84.7)	6.1 (5.5–7.2)	75/86 (87.2)	5.6 (4.2–7.2)	0.90 (0.65–1.24)§

- PFS HR was statistically significant in the full analysis set for durvalumab plus GemCis versus placebo plus GemCis

He AR et al. ESMO World Congress on Gastrointestinal Cancer;Abstract O-1.

TOPAZ-1: ORR and DoR by Primary Tumor Location

	Full analysis set (N=684)[1]		Intrahepatic cholangiocarcinoma (N=383)		Extrahepatic cholangiocarcinoma (N=131)		Gallbladder cancer (N=171)	
	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=343)	Durvalumab + GemCis (n=190)	Placebo + GemCis (n=193)	Durvalumab + GemCis (n=66)	Placebo + GemCis (n=65)*	Durvalumab + GemCis (n=85)	Placebo + GemCis (n=86)
ORR,† %	**26.7**	**18.7**	24.7	15.5	28.8	15.6	29.4	27.9
ORR OR (95% CI)	**1.60 (1.11–2.31)**		1.79 (1.07–2.97)		2.18 (0.92–5.16)		1.08 (0.55–2.09)	
Median TTR, mo	**1.6**	**2.7**	2.8	2.7	1.4	2.6	1.4	2.7
Median DoR,‡ mo	**6.4**	**6.2**	6.0	6.0	8.9	6.2	6.0	6.6
DoR ≥9 mo, %	**32.6**	**25.3**	28.3	24.0	43.3	23.3	33.2	27.5
DoR ≥12 mo, %	**26.1**	**15.0**	18.9	12.0	43.3	23.3	27.6	16.5

- ORR benefit for durvalumab plus GemCis was consistent and durable across primary tumour locations

ORR = objective response rate; DoR = duration of response; OR = odds ratio; TTR = time to response

He AR et al. ESMO World Congress on Gastrointestinal Cancer;Abstract O-1.

Meet The Professor with Dr Kelley

Introduction

MODULE 1: Hepatocellular Carcinoma

- Case Presentations
- Journal Club with Dr Kelley

MODULE 2: Biliary Tract Cancers

- Case Presentations
  - Dr Rudolph: A 71-year-old woman with metastatic pancreaticobiliary cancer thought to be intrahepatic cholangiocarcinoma
  - Dr Levin: A 49-year-old woman with intrahepatic cholangiocarcinoma and micrometastases in portal lymph nodes
  - Dr Dallas: A 66-year-old man with metastatic cholangiocarcinoma who has stable disease on gemcitabine (NGS: MSS, PIK3CA, KRAS G12A)
  - Dr Patel: A 72-year-old man with metastatic cholangiocarcinoma with PD on chemoimmunotherapy and Y-90 (NGS: PD-L1 10%, PTEN mutation, MYC alteration)
- Key Recent Data Sets; Journal Club with Dr Kelley

MODULE 3: Appendix of Key Publications

RTP RESEARCH TO PRACTICE

Case Presentation: A 71-year-old woman with metastatic pancreaticobiliary cancer thought to be intrahepatic cholangiocarcinoma

Dr Priya Rudolph (Athens, Georgia)

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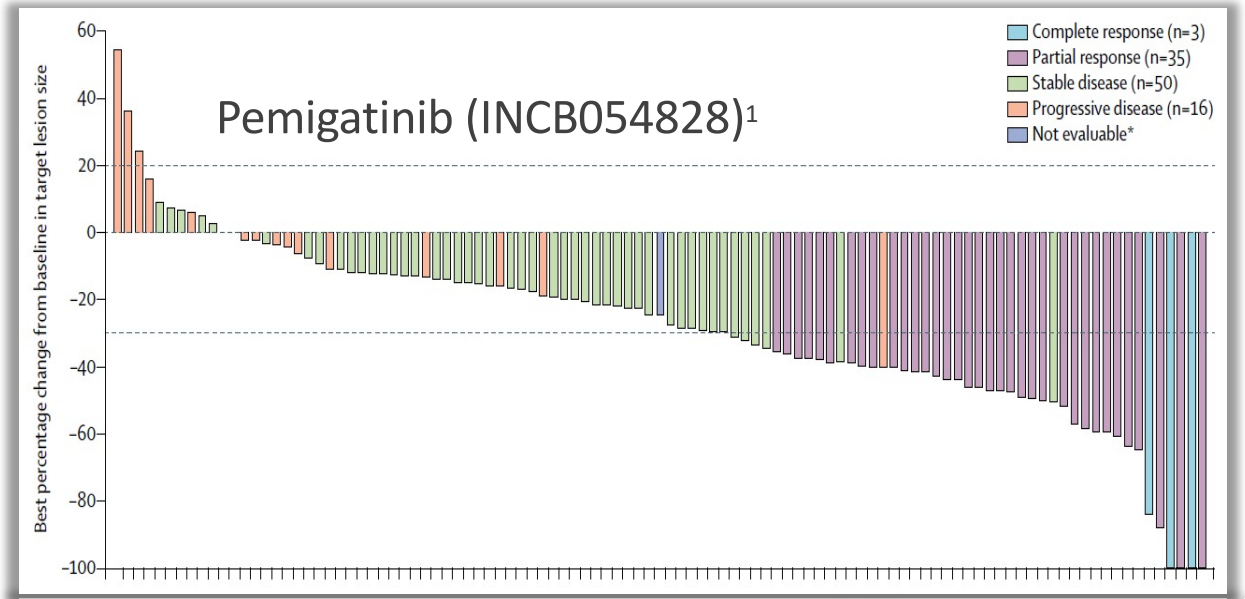
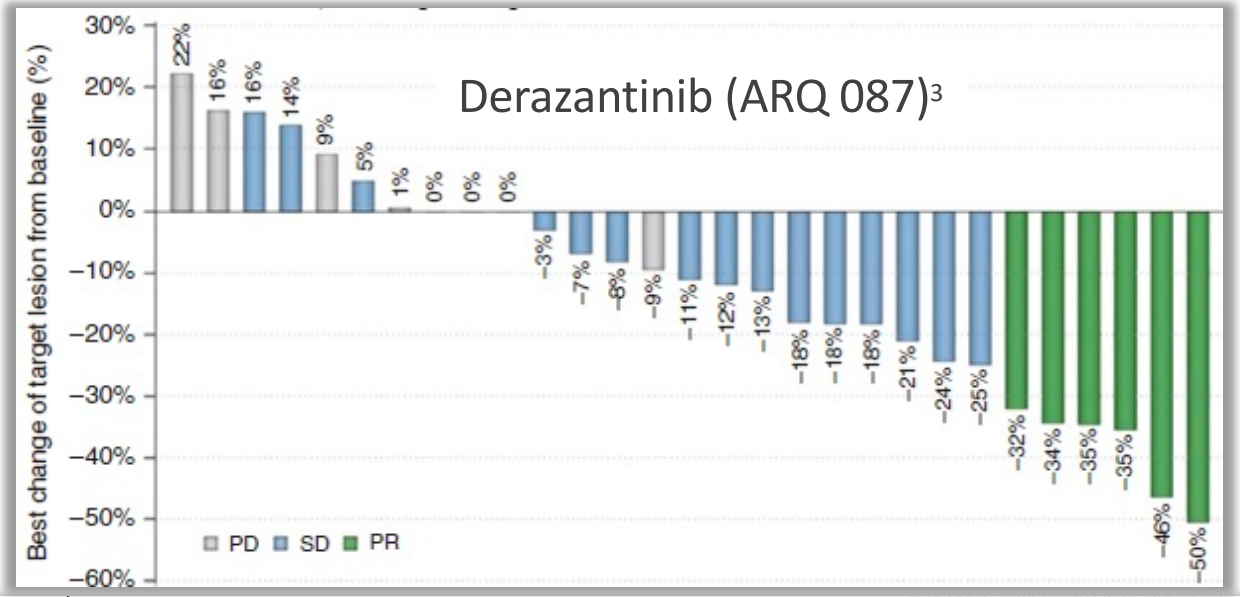
TO PRACTICE

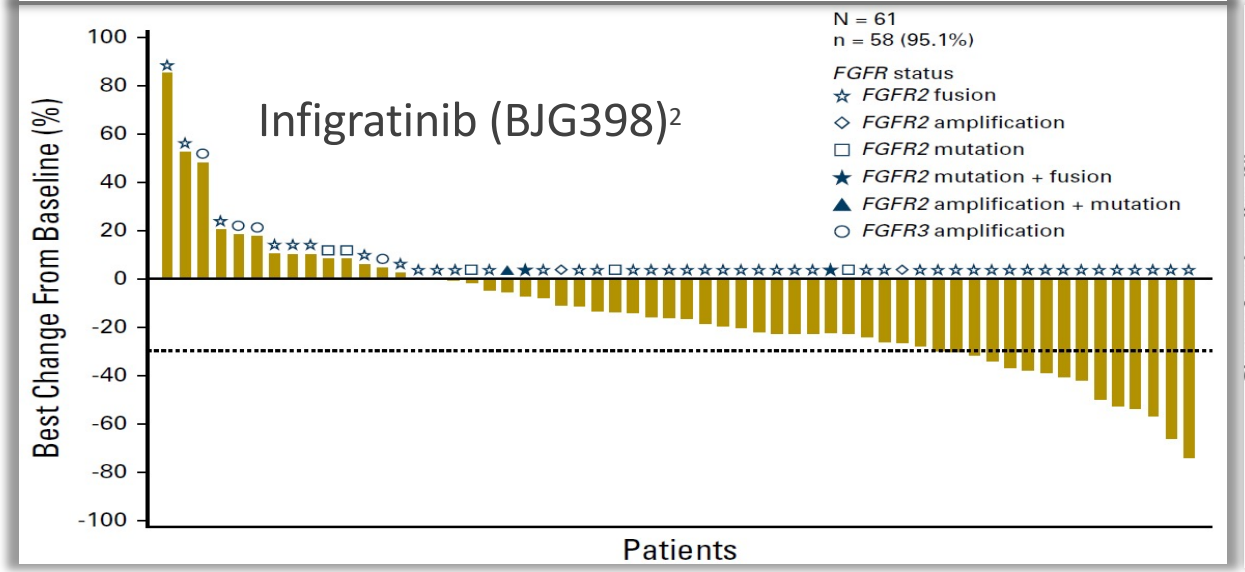
Do you generally offer anti-PD-1/PD-L1 monotherapy to a patient with biliary tract cancer who experiences disease progression on first-line gemcitabine/cisplatin, and would your decision be dependent on PD-L1 status?

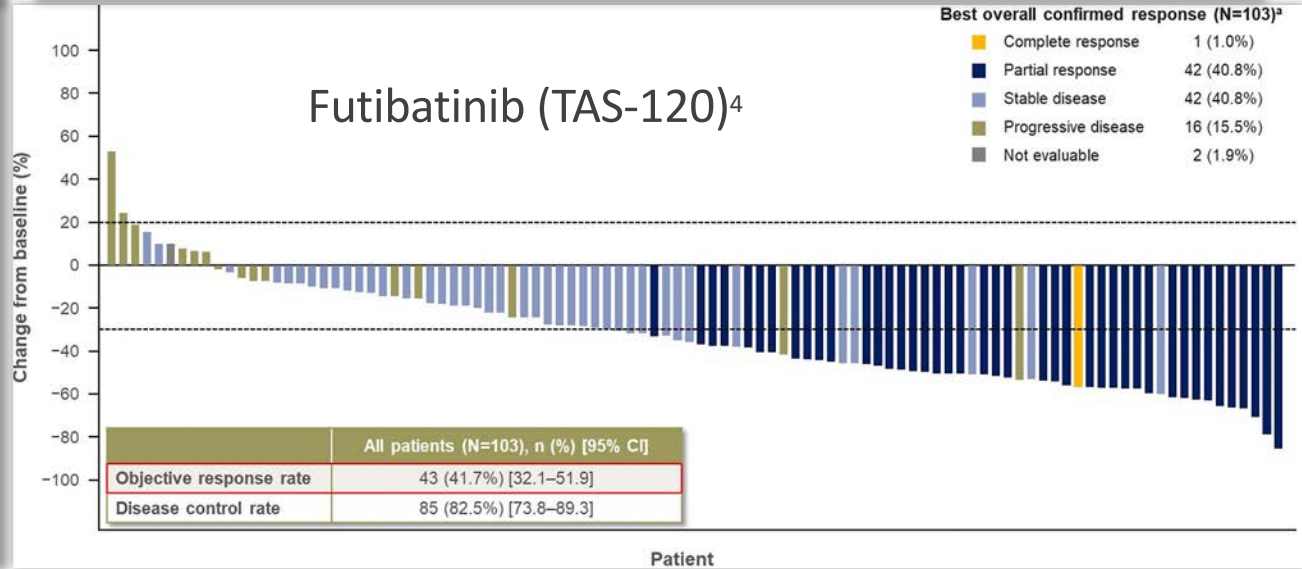
1. Yes, for a patient with high PD-L1
2. Yes, independent of PD-L1 status
3. No, I would not offer anti-PD-1/PD-L1 monotherapy in this setting
4. I'm not sure

Multiple FGFR2-targeted agents









1. Abou Alfa et al. *Lancet Oncol* 2020;21(5):671-684; 2. Javle et al *J Clin Oncol* 2018;36(3):276-282; 3. Mazzaferro et al *Br J Cancer* 2019;120(2):165-171; 4. Goyal et al ASCO 2022 abstr 4009

Courtesy of Professor Juan W Valle, MD

Case Presentation: A 49-year-old woman with intrahepatic cholangiocarcinoma and micrometastases in portal lymph nodes

Dr Pavel Levin (Houston, Texas)

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Case Presentation: A 66-year-old man with metastatic cholangiocarcinoma who has stable disease on gemcitabine (NGS: MSS, PIK3CA, KRAS G12A)

Dr Jennifer Dallas (Charlotte, North Carolina)

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RESEARCH
TO PRACTICE

Case Presentation: A 72-year-old man with metastatic cholangiocarcinoma with PD on chemoimmunotherapy and Y-90 (NGS: PD-L1 10%, PTEN mutation, MYC alteration)

Dr Minesh Patel (Peachtree City, Georgia)

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RESEARCH
TO PRACTICE

Multimodal Profiling of Biliary Tract Cancers to Detect Potentially Actionable Biomarkers and Differences in Immune Signatures Between Subtypes

Mody K et al.

Gastrointestinal Cancers Symposium 2021;Abstract 4023.

Final Results from ClarIDHy, a Global, Phase 3, Randomized, Double-Blind Study of Ivosidenib (IVO) versus Placebo (PBO) in Patients (pts) with Previously Treated Cholangiocarcinoma (CCA) and an Isocitrate Dehydrogenase 1 (IDH1) Mutation

Abou-Alfa GK et al.

ASCO 2021;Abstract 4069.

Prevalence of Germline Mutations and Homologous Recombination Deficiency (HRD) in a Real-World Biliary Tract Cancer (BTC) Cohort

Kelley RK et al.

Gastrointestinal Cancers Symposium 2022;Abstract 476.

The Journal of Molecular Diagnostics, Vol. 24, No. 4, April 2022

the Journal of Molecular Diagnostics

jmdjournal.org

Validation and Characterization of *FGFR2* Rearrangements in Cholangiocarcinoma with Comprehensive Genomic Profiling

Ian M. Silverman,* Meijuan Li,† Karthikeyan Murugesan,† Melanie A. Krook,‡ Milind M. Javle,§ Robin K. Kelley,¶ Mitesh J. Borad,‖ Sameek Roychowdhury,‡ Wei Meng,† Bahar Yilmazel,† Coren Milbury,† Shantanu Shewale,† Luis Feliz,** Timothy C. Burn,* and Lee A. Albacker†

J Gastrointest Oncol 2022;13(2):822-32.

Original Article

Biliary cancer brain metastases: a multi-institution case series with case reports

Samuel R. Falkson[1#^], Karen Zhang[2#], Hriday P. Bhambhvani[1], Jennifer L. Wild[2], Ann Griffin[2], Robin K. Kelley[2], Melanie Hayden Gephart[1]

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RTP
RESEARCH
TO PRACTICE

First-Line Treatment for Advanced Hepatocellular Carcinoma (HCC)

FDA-Approved Systemic Therapy for Advanced HCC

Sorafenib

First Line

Lenvatinib

Atezolizumab + bevacizumab

Durvalumab/tremelimumab*

Second Line and Beyond

Regorafenib

Nivolumab†

Pembrolizumab‡

Cabozantinib

Ramucirumab

Nivolumab + ipilimumab‡

* Positive Phase III trial

† Accelerated approval withdrawn

‡ Accelerated approval

RTP RESEARCH TO PRACTICE

FDA-Approved Anti-VEGF-Directed Monotherapy for HCC

Approved line of therapy	Agent	Study	Primary outcomes
First line	**Sorafenib**[1]	Sorafenib vs placebo (N = 602) Phase III SHARP trial	TTP 4.1 mo vs 4.9 mo mOS 10.7 mo vs 7.9 mo
	Lenvatinib[2]	Lenvatinib vs sorafenib (N = 954) Phase III REFLECT trial	mPFS 7.4 mo vs 3.7 mo mOS 13.6 mo vs 12.3 mo
Second line	**Regorafenib**[3]	Regorafenib vs placebo (N = 573) Phase III RESORCE trial	mPFS 3.1 mo vs 1.5 mo mOS 10.7 mo vs 7.9 mo
	Cabozantinib[4]	Cabozantinib vs placebo (N = 707) Phase III CELESTIAL trial	mPFS 5.2 mo vs 1.9 mo mOS 10.2 mo vs 8.0 mo
	Ramucirumab[5]	Ramucirumab vs placebo (N = 565) Phase III REACH-2 trial	mPFS 2.8 mo vs 1.6 mo mOS 8.5 mo vs 7.3 mo

TTP = time to progression; mPFS = median progression-free survival; mOS = median overall survival

[1] Llovet JM et al. *N Engl J Med* 2008;359(4):378-90; [2] Kudo M et al. *Lancet* 2018;391(10126):1163-73; [3] Bruix J et al. *Lancet* 2017;389(10064):56-66; [4] Abou-Alfa GK et al. *N Engl J Med* 2018;379(1):54-63; [5] Zhu AX et al. *Lancet Oncol* 2019;20(2):282-96.

Research Article
Hepatic and Biliary Cancer

JOURNAL
OF HEPATOLOGY

Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab *vs.* sorafenib for unresectable hepatocellular carcinoma

Ann-Lii Cheng[1,*], Shukui Qin[2], Masafumi Ikeda[3], Peter R. Galle[4], Michel Ducreux[5], Tae-You Kim[6], Ho Yeong Lim[7], Masatoshi Kudo[8], Valeriy Breder[9], Philippe Merle[10], Ahmed O. Kaseb[11], Daneng Li[12], Wendy Verret[13], Ning Ma[14], Alan Nicholas[15], Yifan Wang[16], Lindong Li[17], Andrew X. Zhu[18,19], Richard S. Finn[20,*]

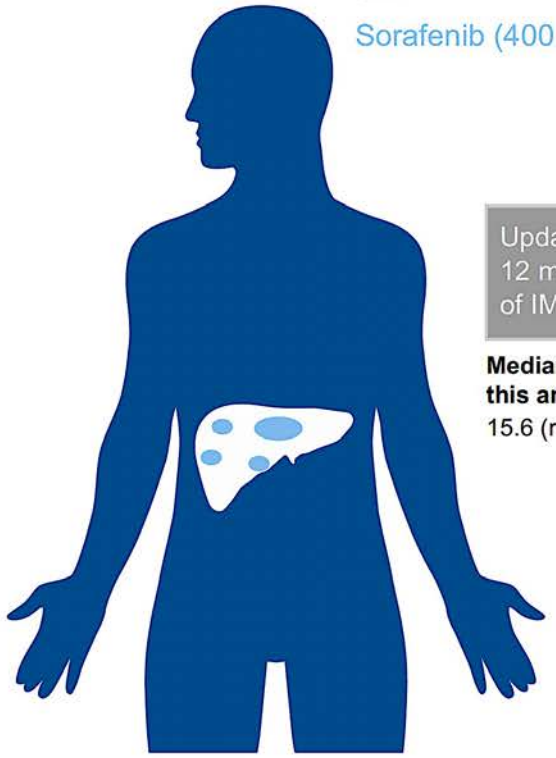
J Hepatol 2022;76(4):862-73.

IMbrave150: Updated OS and PFS with Atezolizumab and Bevacizumab (Median Follow-Up = 15.6 Months)

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

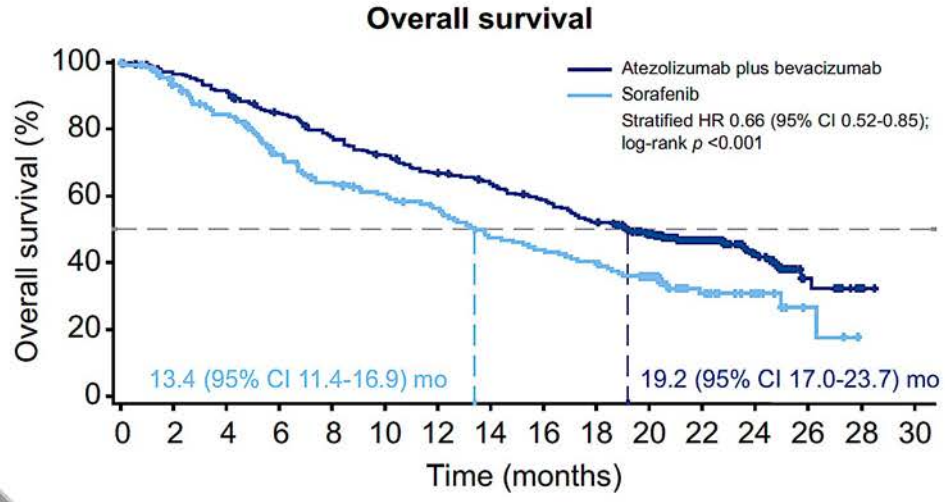
OR

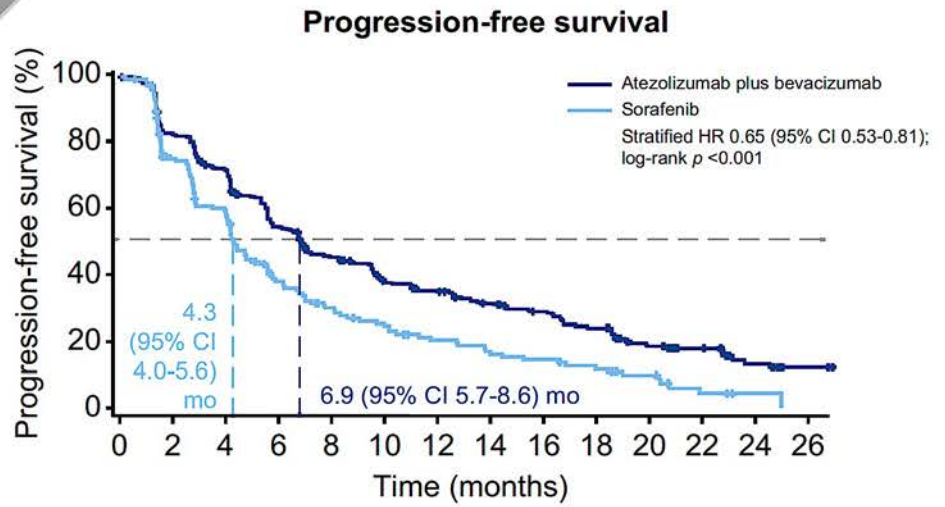
Sorafenib (400 mg twice daily)



Updated analysis
12 months after primary analysis of IMbrave150 study

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



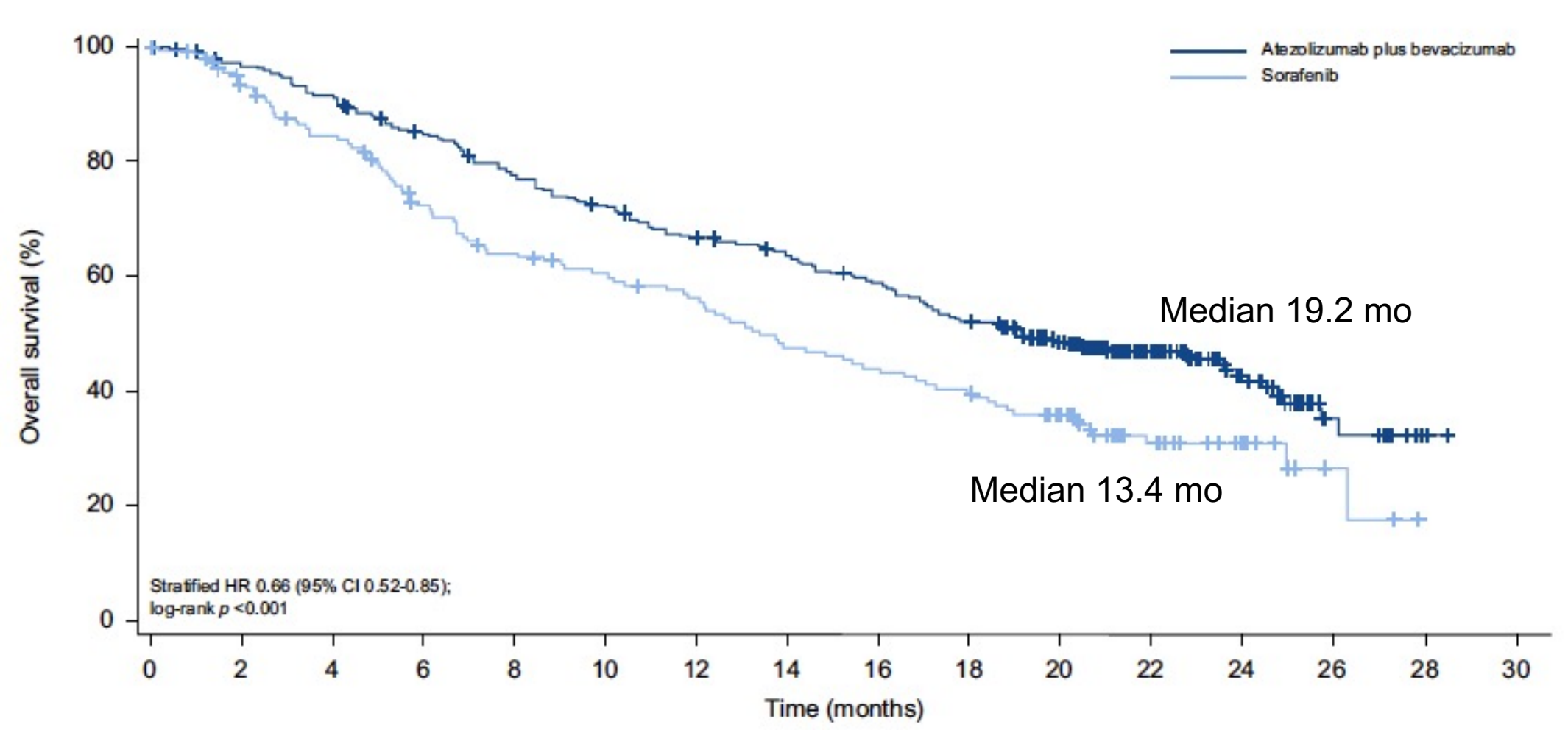


Confirmed objective response rate: 30% with atezolizumab plus bevacizumab, 11% with sorafenib

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

RTP RESEARCH TO PRACTICE

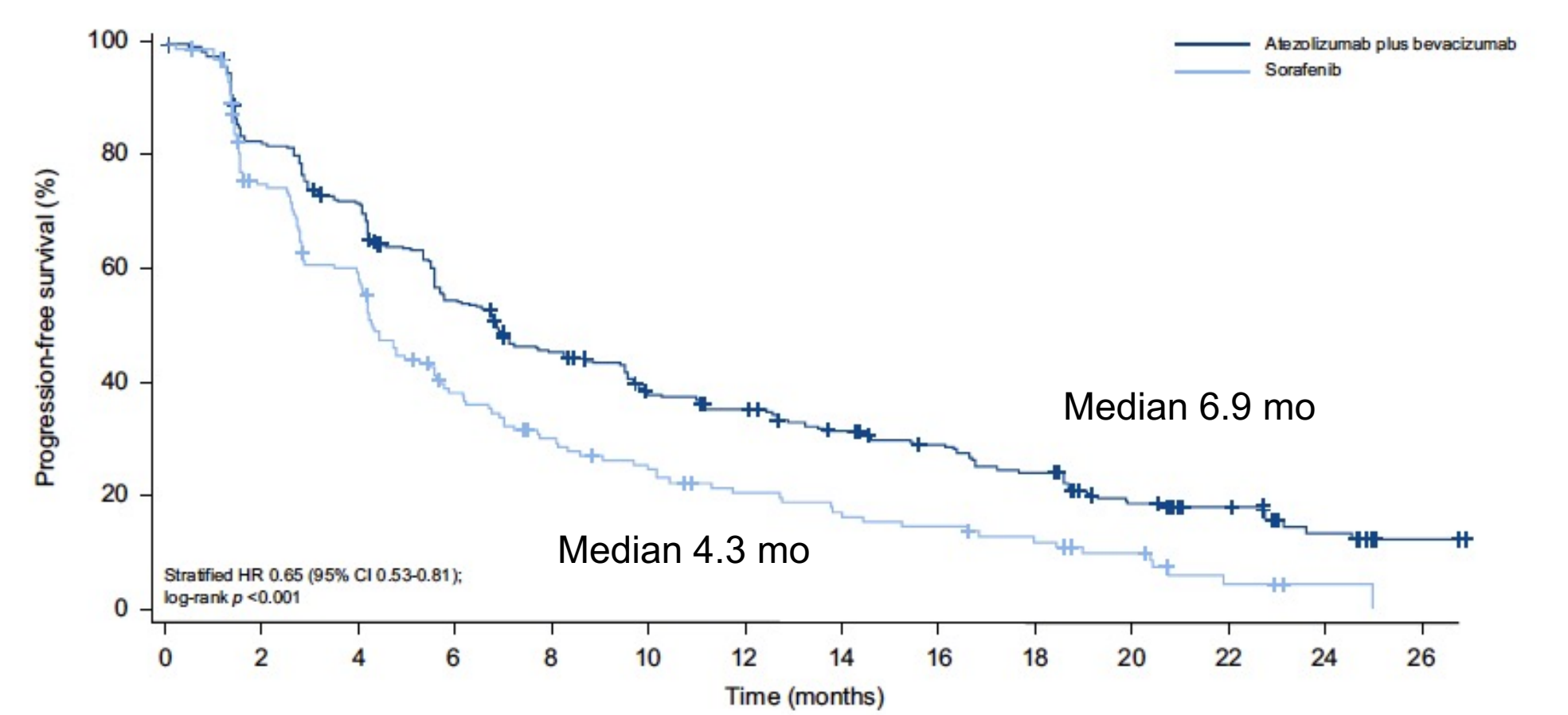
IMbrave150: Updated OS with Atezolizumab and Bevacizumab (Median Follow-Up = 15.6 Months)



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

RTP RESEARCH TO PRACTICE

IMbrave150: Updated PFS with Atezolizumab and Bevacizumab (Median Follow-Up = 15.6 Months)

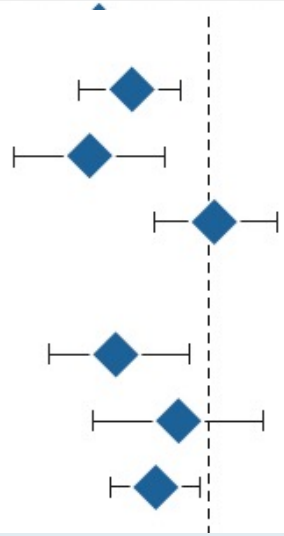


Cheng A-L et al. *J Hepatol* 2022;76(4):862-73.

RTP RESEARCH TO PRACTICE

IMbrave150 Update: Subgroup Analysis of OS with Atezolizumab and Bevacizumab (Median Follow-Up = 15.6 Months)

Subgroup	Atezolizumab plus bevacizumab		Sorafenib		Hazard ratio for death (95% CI)
	Events/ patients	Median OS, months (95% CI)	Events/ patients	Median OS, months (95% CI)	
Etiology					
Hepatitis B	86/164	19.0 (16.1-NE)	46/76	12.4 (6.7-16.9)	0.58 (0.40-0.83)
Hepatitis C	31/72	24.6 (19.8-NE)	24/36	12.6 (7.4-18.4)	0.43 (0.25-0.73)
Non-viral	63/100	17.0 (11.7-22.8)	30/53	18.1 (11.7-26.3)	1.05 (0.68-1.63)
PD-L1 status					
TC or IC ≥1%	44/86	22.8 (17.0-NE)	24/36	12.6 (7.4-17.1)	0.52 (0.32-0.87)
TC and IC <1%	27/49	19.9 (13.9-NE)	17/28	15.4 (11.4-26.3)	0.81 (0.44-1.49)
Unknown	109/201	18.0 (16.1-24.0)	59/101	13.4 (9.7-18.6)	0.69 (0.50-0.94)



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

RTP RESEARCH TO PRACTICE

ESMO WORLD CONGRESS ON Gastrointestinal Cancer 2022 | Abstract SO-14

Atezolizumab Plus bevacizumab versus lenvatinib or sorafenib in non-viral unresectable hepatocellular carcinoma: An international study

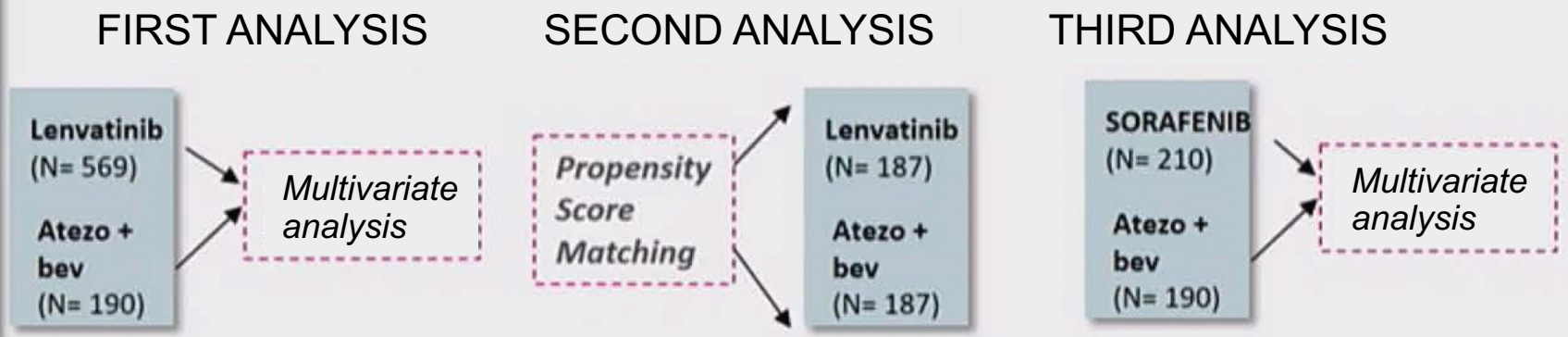
ANDREA CASADEI GARDINI and MARGHERITA RIMINI

SAN RAFFAELE HOSPITAL; MILAN

RTP RESEARCH TO PRACTICE

Study Design

- **Retrospective** data of patients treated in **1L WITH NO VIRAL ETIOLOGY**
- **BCLC-C or BCLC-B** (not eligible for LRT)
- **Common inclusion criteria** for the use of LEN or Atezo plus bev were applied
- The overall cohort included Western and Eastern patient populations from 36 centres in 4 countries (Italy, Japan, Republic of Korea, and United Kingdom)

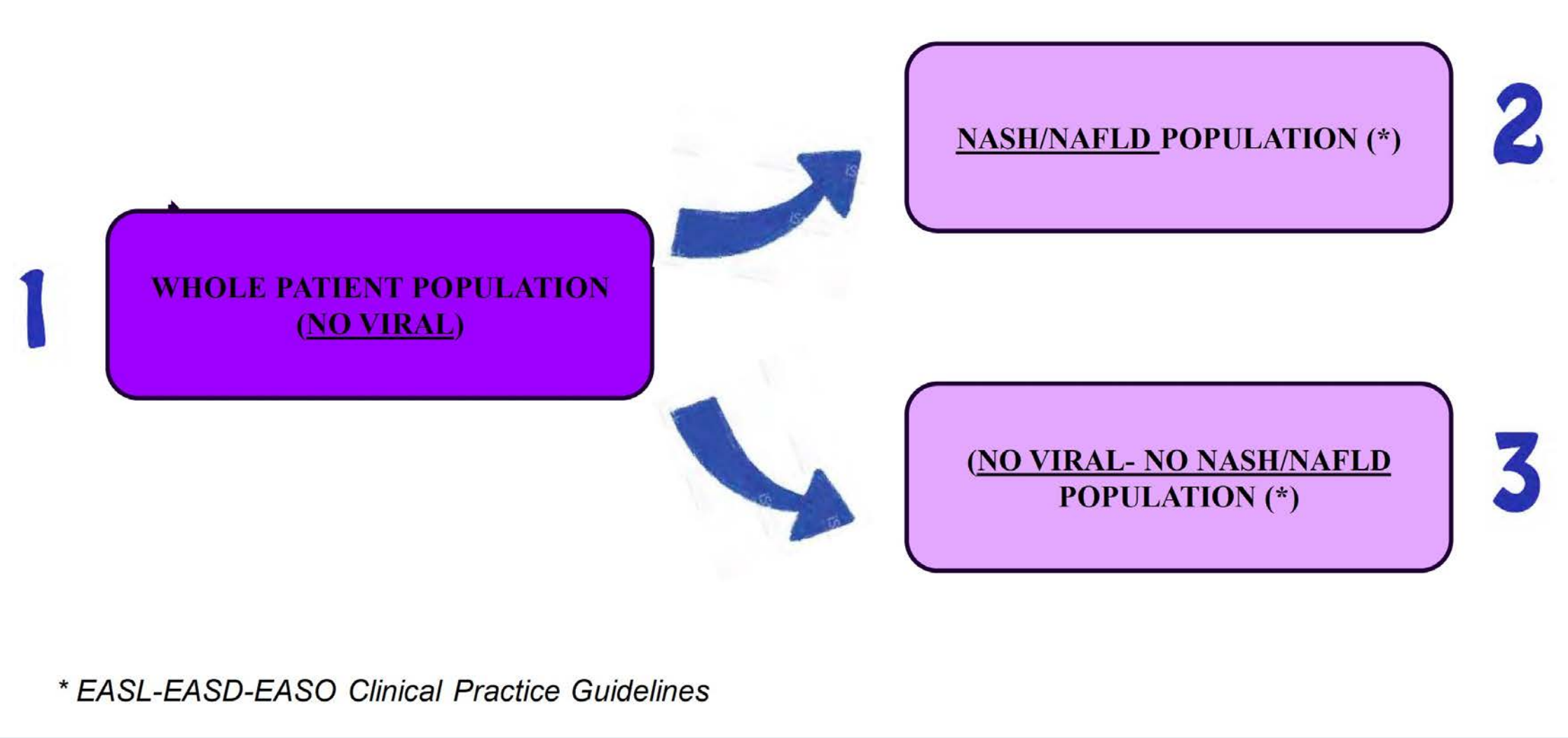


Endpoints

Effectiveness: OS, PFS

Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

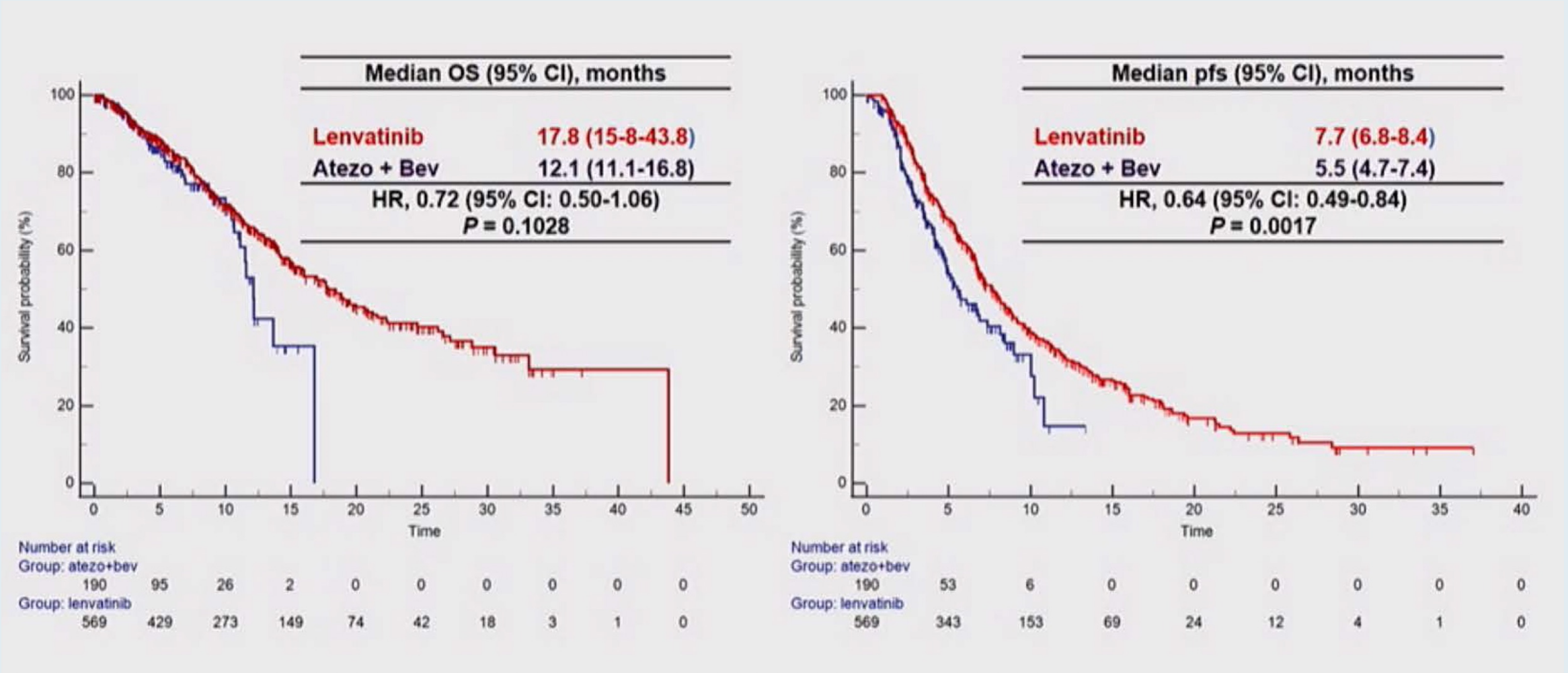
Study Design and Population



NASH = nonalcoholic steatohepatitis; NAFLD = nonalcoholic fatty liver disease

Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

Efficacy Results (First Study): ALL Population No Viral



Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

RTP RESEARCH TO PRACTICE

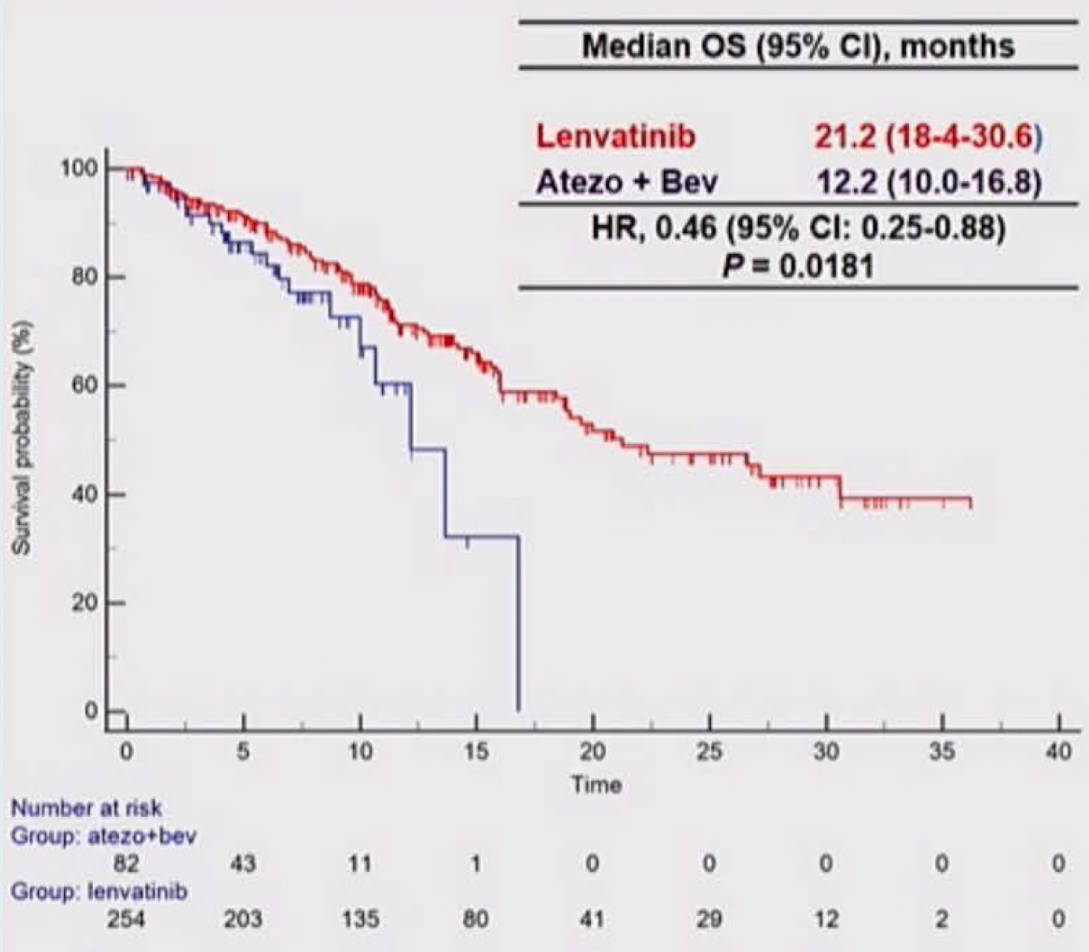
Clinical Outcomes in Whole Patient Population

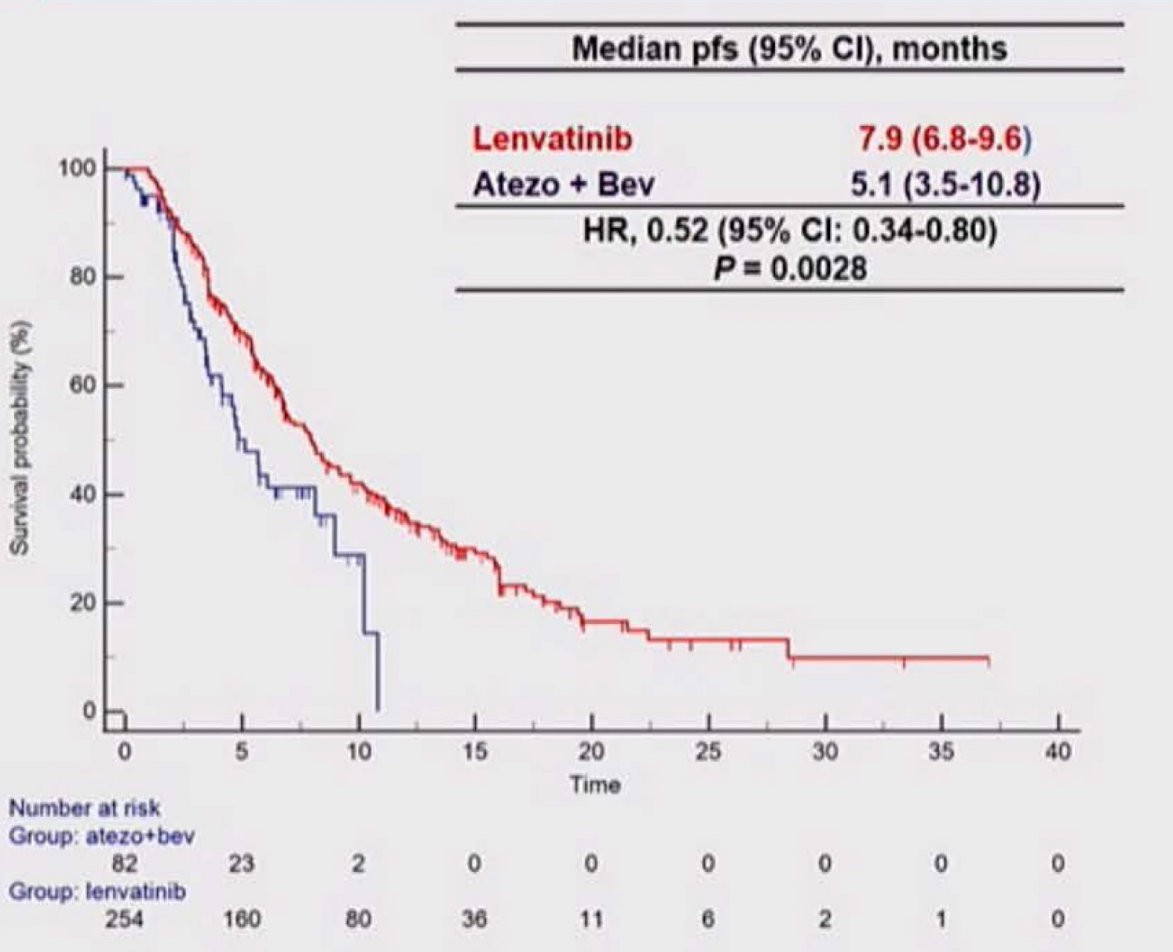
	whole patients population	
	Univariate	Multivariate
	HR (95% IC);	HR (95% IC);
Treatment arm **Atezolizumab plus bevacizumab** **Lenvatinib**		1 0.65 (0.44-0.95) 0.0268
Gender **Male** **Female**	1 0.73 (0.54-0.99) 0.0430	1 0.74 (0.50-1.09) 0.1240
Age **<75** **>75**	1 0.94 (0.73-1.20) 0.6035	
Previously Surgery **Yes** **No**	1 1.50 (1.16-1.94) 0.0021	1 1.78 (1.26-2.14) 0.0072
Previously Radiofrequency **Yes** **No**	1 0.87 (0.63-1.21) 0.6932	
Previously TACE **Yes** **No**	1 1.44 (1.12-1.84) 0.0038	1 1.70 (0.89-1.98) 0.6591
Child pugh **A** **B**	1 2.19 (1.45-3.33) 0.0002	1 1.36 (0.83-2.01) 0.4270
BCLC **B** **C**	**1** **1.60 (1.25-2.05)** **0.0002**	**1** **1.47 (1.07-2.01)** **0.0167**
ECOG **0** **>0**	1 0.92 (0.67-1.26) 0.5913	
Macrovascular invasion **Yes** **No**	1 0.63 (0.46-0.87) 0.0048	
AFP **<400** **>400**	1 1.69 (1.26-2.28) 0.0005	1 1.08 (0.77-1.51) 0.6487
NLR **<3** **>3**	1 2.02 (1.51-2.70) <0.0001	1.66 (1.24-2.22) 0.0005
ALBI **1** **2**	1 5.20 (3.19-8.47) <0.0001	1 1.94 (1.22-3.08) 0.0045
Aspartate aminotransferase AST	1.00 (1.00-1.00) 0.0033	1.01 (1.00-1.01) 0.0001
Alanine aminotransferase (ALT)	1.00 (0.99-1.00) 0.0202	

Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

RTP RESEARCH TO PRACTICE

Efficacy Results (First Study): NASH/NAFLD

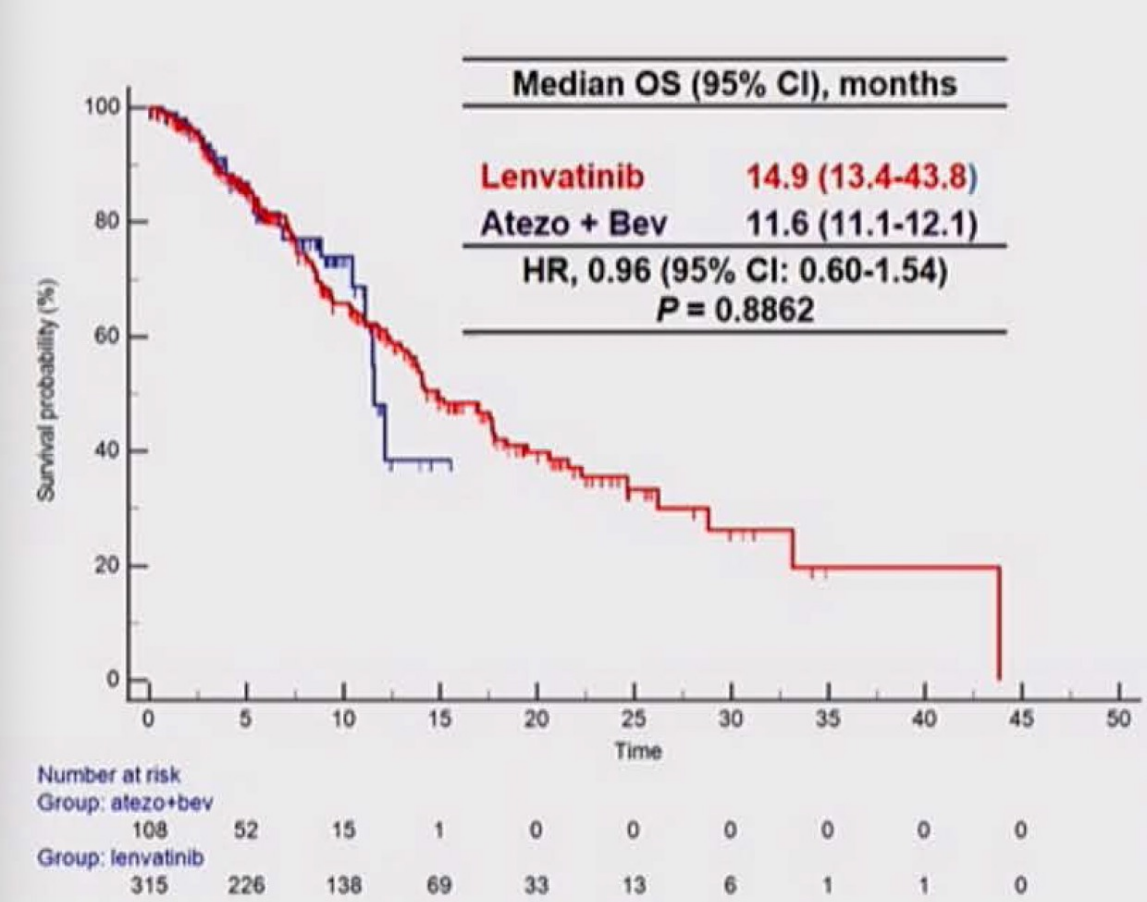


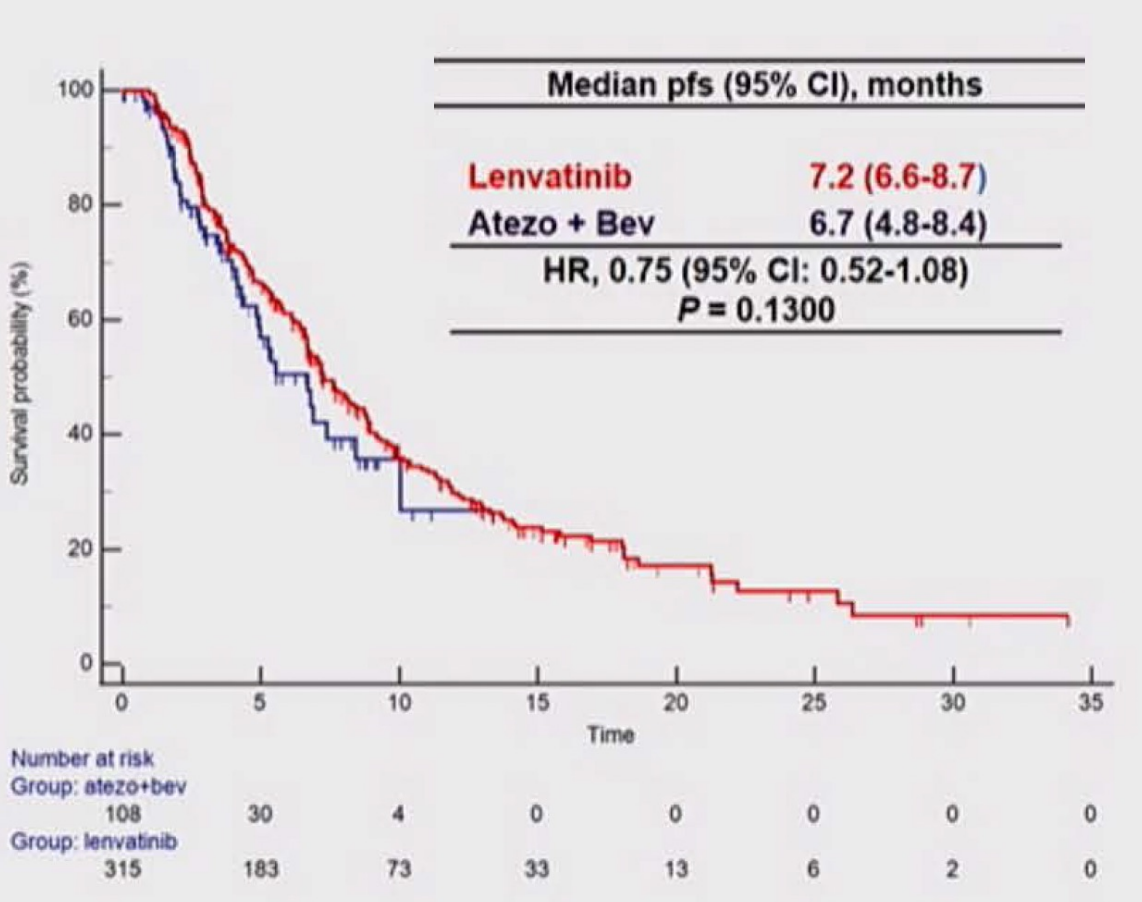


Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

RTP RESEARCH TO PRACTICE

Clinical Outcomes in Nonviral, Non-NASH/NAFLD Population





Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

RTP RESEARCH TO PRACTICE

Conclusion

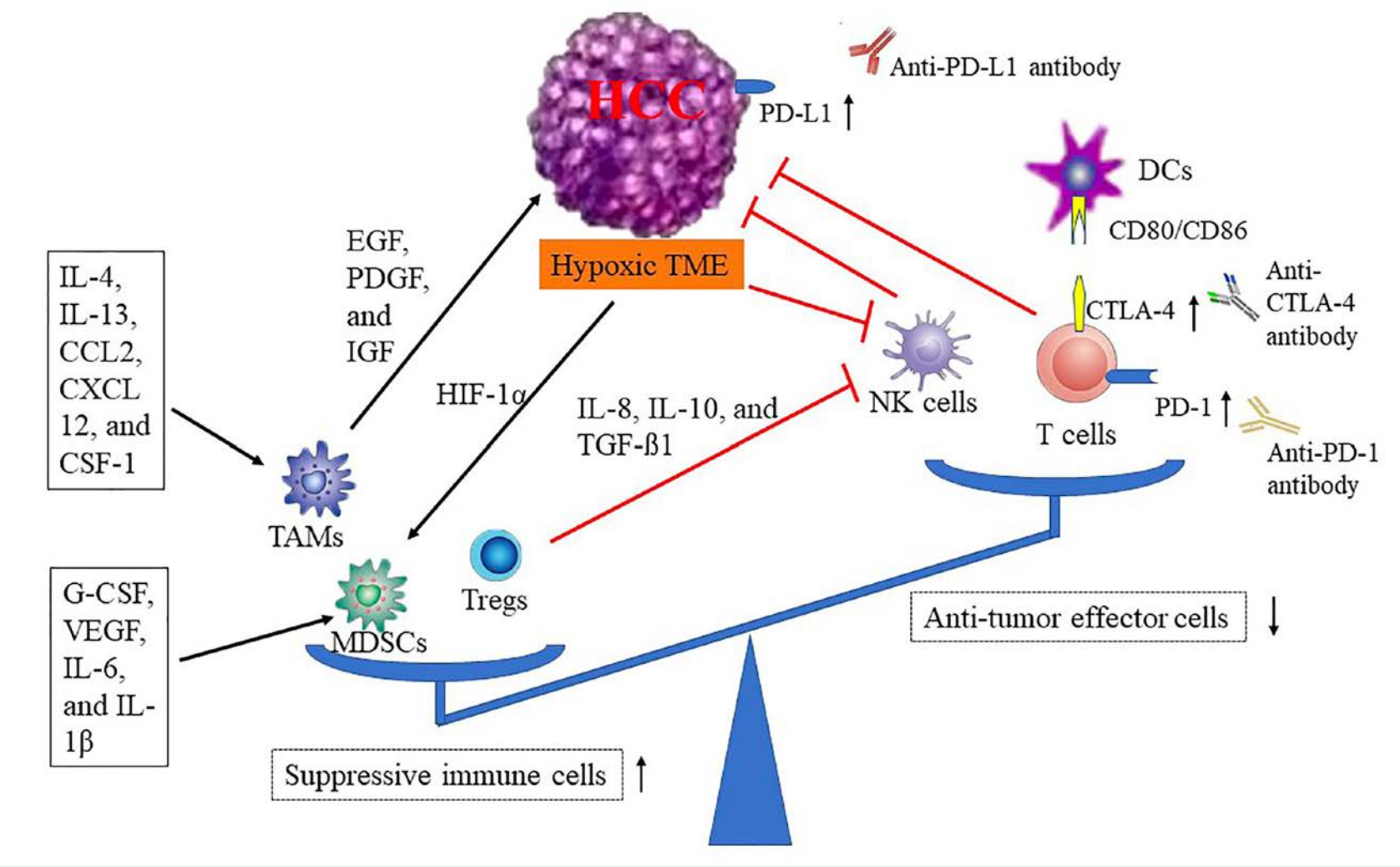
- The present analysis conducted on a large number of non-viral HCC patients showed for the first time an association with a better outcome of lenvatinib compared to atezolizumab plus bevacizumab, in particular in patients with NAFLD/NASH-related HCC.

- In light of the lack of level I evidence comparing lenvatinib to atezolizumab and bevacizumab our study adds important and novel evidence highlighting the clinical impact of underlying etiology as a factor influencing outcome from treatment of advanced HCC patients.

- Future large prospective trials are needed to validate our results and to deepen the potential role of etiology in the clinical management of these patients.

Gardini AC, Rimini M. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract SO-14.

Increase in Immune Checkpoint Proteins in the Tumor Microenvironment of HCC: Rationale for Targeting PD-1/PD-L1 and CTLA-4



Due to the differences in timing, location, and nonoverlapping effects between the PD-1/PD-L1 and CTLA-4 signaling pathways, combination therapy concurrently targeting these 2 immune checkpoints may achieve synergistic effects in the treatment of HCC

Xing R et al. *Front Immunol* 2021;12:783236.

NEJM Evidence

Published June 6, 2022

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ORIGINAL ARTICLE

Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma

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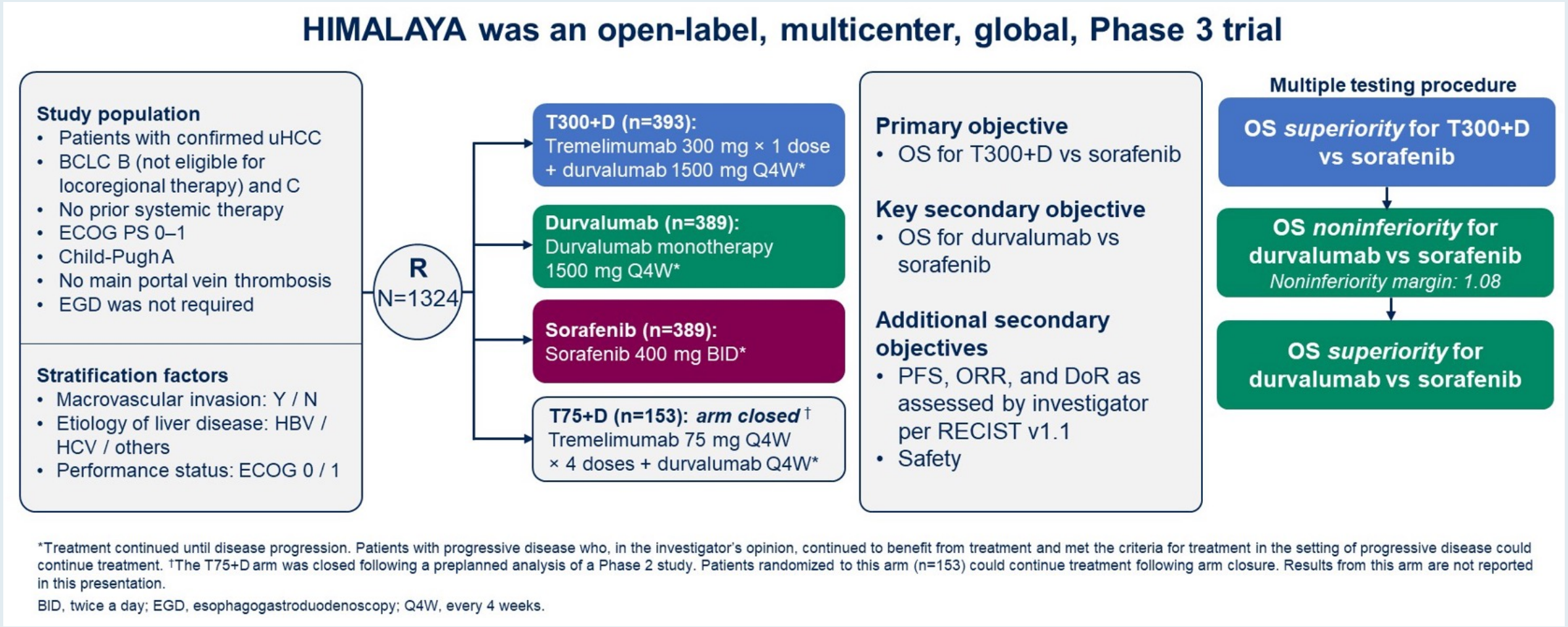
HIMALAYA Phase III Trial Schema

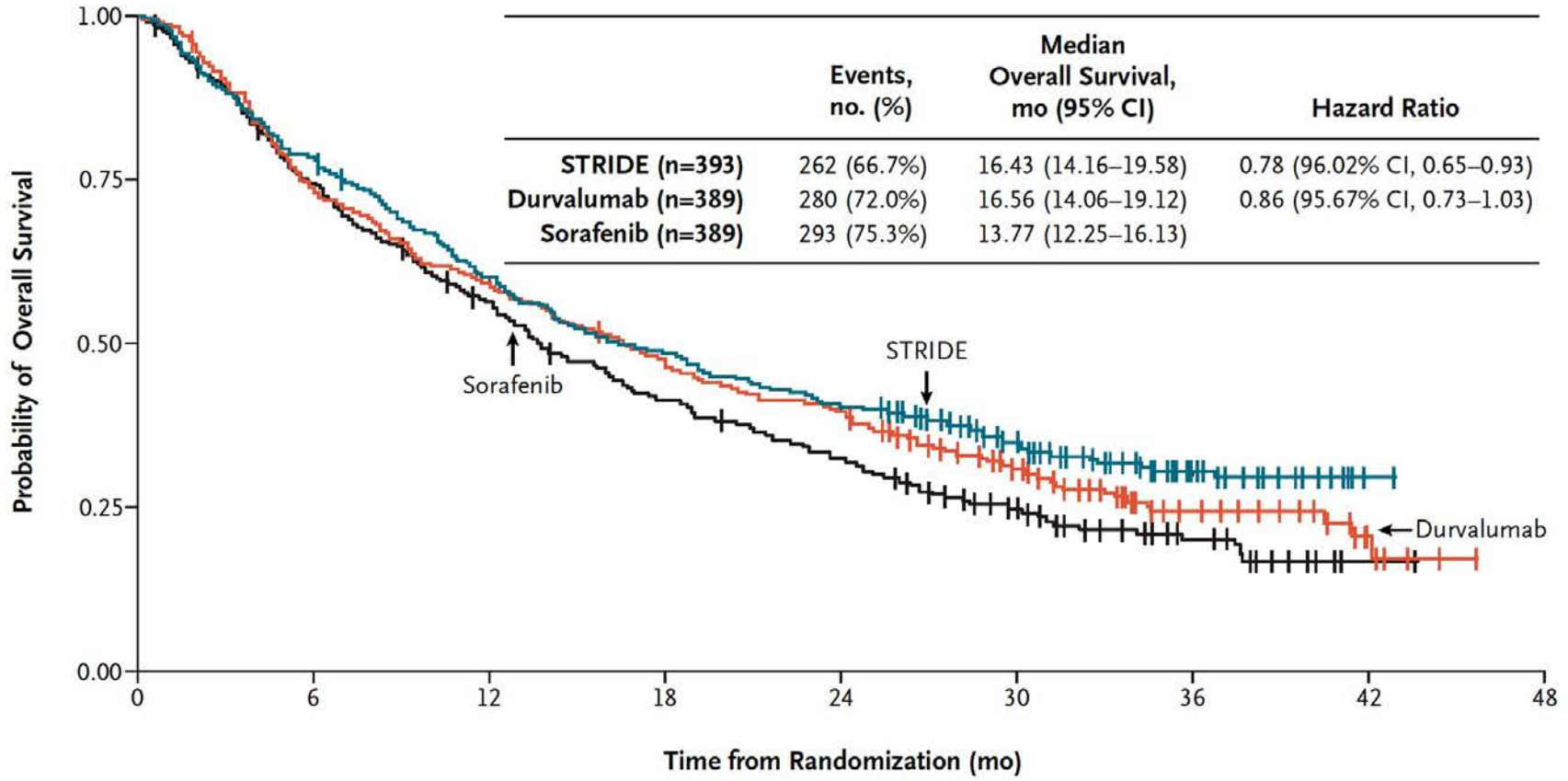


*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.

Abou-Alfa GK et al. Gastrointestinal Cancers Symposium 2022;Abstract 379.

HIMALAYA: Overall Survival

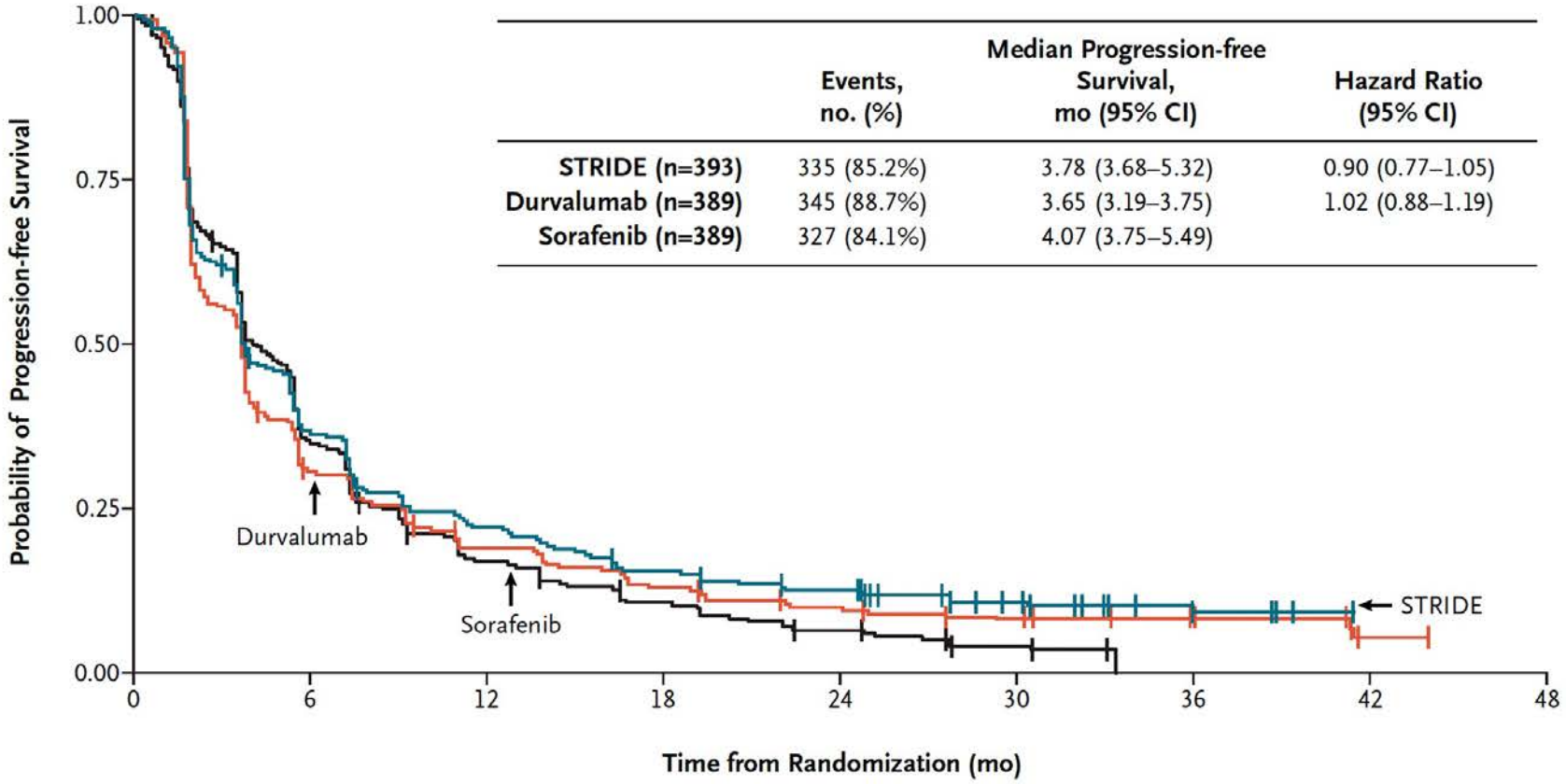


	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

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 G et al. *NEJM Evidence*, June 6, 2022.

HIMALAYA: Progression-Free Survival



	Events, no. (%)	Median Progression-free Survival, mo (95% CI)	Hazard Ratio (95% CI)
STRIDE (n=393)	335 (85.2%)	3.78 (3.68–5.32)	0.90 (0.77–1.05)
Durvalumab (n=389)	345 (88.7%)	3.65 (3.19–3.75)	1.02 (0.88–1.19)
Sorafenib (n=389)	327 (84.1%)	4.07 (3.75–5.49)	

No. at Risk									
STRIDE	393	135	81	55	43	26	7	0	0
Durvalumab	389	115	68	47	34	20	6	1	0
Sorafenib	389	118	53	31	18	6	0	0	0

Abou-Alfa G et al. *NEJM Evidence*, June 6, 2022.

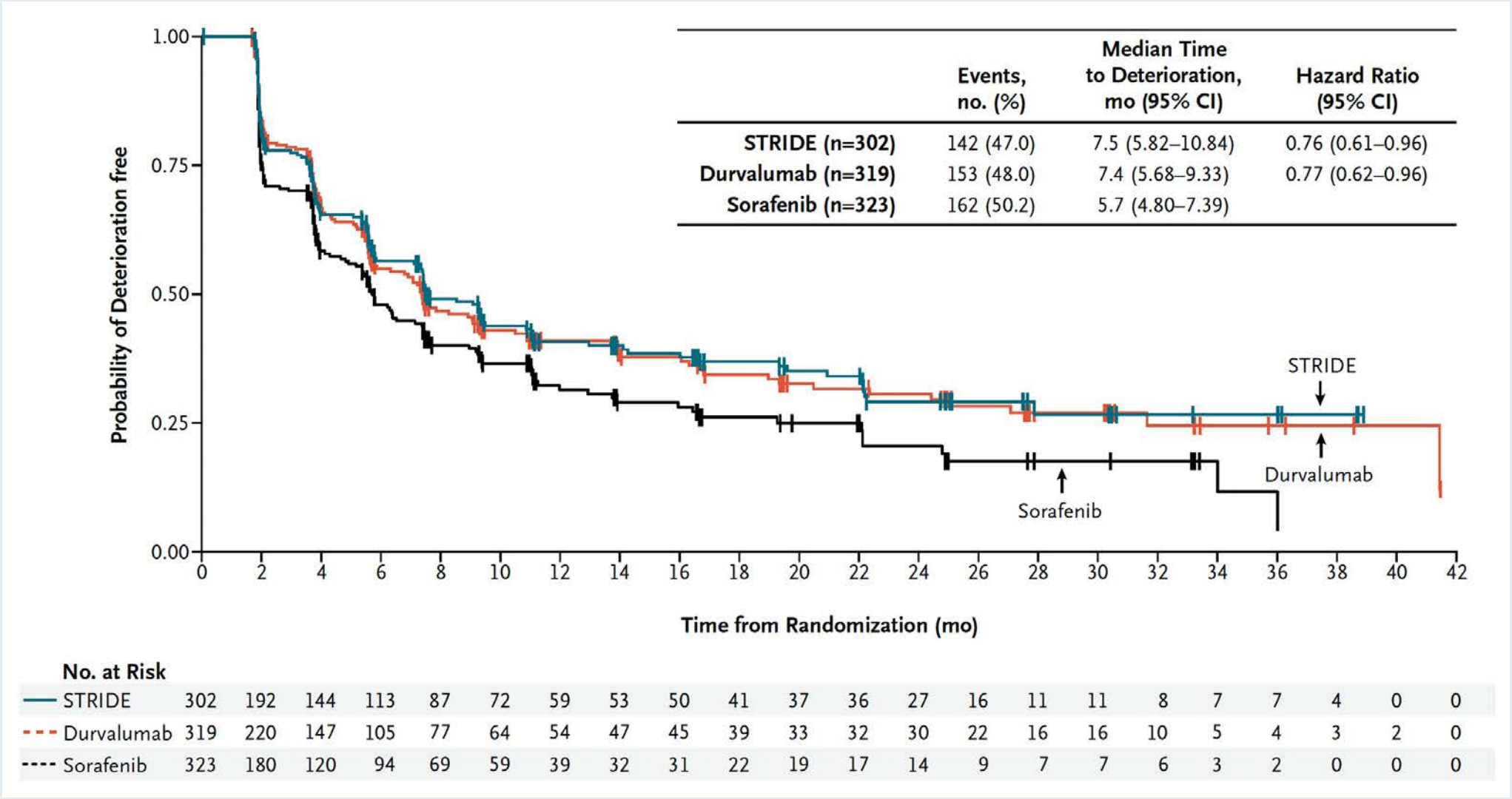
RTP RESEARCH TO PRACTICE

HIMALAYA: Response Outcomes (Intent-to-Treat Population)

Parameter	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Response — no. (%)			
Objective†	79 (20.1)	66 (17.0)	20 (5.1)
Complete	12 (3.1)	6 (1.5)	0
Partial	67 (17.0)	60 (15.4)	20 (5.1)
Stable disease — no. (%)	157 (39.9)	147 (37.8)	216 (55.5)
Disease control rate — %	236 (60.1)	213 (54.8)	236 (60.7)
Duration of response — mo‡			
Median	22.34	16.82	18.43
IQR	8.54–NR	7.43–NR	6.51–25.99
Time to response — mo			
Median	2.17	2.09	3.78

Abou-Alfa G et al. *NEJM Evidence*, June 6, 2022.

HIMALAYA: Time to Deterioration of Global Health Status or Quality of Life



	Events, no. (%)	Median Time to Deterioration, mo (95% CI)	Hazard Ratio (95% CI)
STRIDE (n=302)	142 (47.0)	7.5 (5.82–10.84)	0.76 (0.61–0.96)
Durvalumab (n=319)	153 (48.0)	7.4 (5.68–9.33)	0.77 (0.62–0.96)
Sorafenib (n=323)	162 (50.2)	5.7 (4.80–7.39)	

No. at Risk																						
STRIDE	302	192	144	113	87	72	59	53	50	41	37	36	27	16	11	11	8	7	7	4	0	0
Durvalumab	319	220	147	105	77	64	54	47	45	39	33	32	30	22	16	16	10	5	4	3	2	0
Sorafenib	323	180	120	94	69	59	39	32	31	22	19	17	14	9	7	7	6	3	2	0	0	0

Abou-Alfa G et al. *NEJM Evidence*, June 6, 2022.

HIMALAYA: Summary of Treatment-Related Adverse Events

Event	STRIDE (n=388)	Durvalumab (n=388)	Sorafenib (n=374)	T75+D (n=152)
Any	294 (75.8)	202 (52.1)	317 (84.8)	106 (69.7)
Any serious	68 (17.5)	32 (8.2)	35 (9.4)	28 (18.4)
Grade 3 or 4	100 (25.8)	50 (12.9)	138 (36.9)	32 (21.1)
Leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)	13 (8.6)
Leading to dose delay	83 (21.4)	54 (13.9)	144 (38.5)	42 (27.6)
Leading to death	9 (2.3)†	0	3 (0.8)‡	2 (1.3)
Grade 3 or 4 immune-mediated	49 (12.6)	24 (6.2)	9 (2.4)	18 (11.8)
Any immune-mediated leading to death	6 (1.5)§	0	0	0
Grade 3 or 4 hepatic SMQ	23 (5.9)	20 (5.2)	17 (4.5)	15 (9.9)

Abou-Alfa G et al. *NEJM Evidence*, June 6, 2022.

RTP RESEARCH TO PRACTICE

HIMALAYA: Select Treatment-Emergent Adverse Events

Event	STRIDE (n=388)		Durvalumab (n=388)		Sorafenib (n=374)		T75+D (N=152)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Diarrhea	103 (26.5)	17 (4.4)	58 (14.9)	6 (1.5)	167 (44.7)	16 (4.3)	32 (21.1)	4 (2.6)
Constipation	36 (9.3)	0	42 (10.8)	0	35 (9.4)	0	12 (7.9)	1 (0.7)
Abdominal pain	46 (11.9)	5 (1.3)	37 (9.5)	4 (1.0)	63 (16.8)	12 (3.2)	26 (17.1)	3 (2.0)
Nausea	47 (12.1)	0	37 (9.5)	0	53 (14.2)	0	14 (9.2)	0
Pruritus	89 (22.9)	0	56 (14.4)	0	24 (6.4)	1 (0.3)	27 (17.8)	0
Rash	87 (22.4)	6 (1.5)	40 (10.3)	1 (0.3)	51 (13.6)	4 (1.1)	27 (17.8)	0
Alopecia	2 (0.5)	0	5 (1.3)	0	53 (14.2)	0	1 (0.7)	0
Palmar-plantar erythrodysesthesia syndrome	3 (0.8)	0	1 (0.3)	0	174 (46.5)	34 (9.1)	3 (2.0)	1 (0.7)
Aspartate aminotransferase increased	48 (12.4)	20 (5.2)	56 (14.4)	26 (6.7)	24 (6.4)	12 (3.2)	16 (10.5)	10 (6.6)
Alanine aminotransferase increased	36 (9.3)	10 (2.6)	44 (11.3)	12 (3.1)	20 (5.3)	7 (1.9)	10 (6.6)	5 (3.3)

Abou-Alfa G et al. *NEJM Evidence*, June 6, 2022.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

WORLD CONGRESS ON Gastrointestinal Cancer

2022 | Abstract O-5

O-5: Outcomes by baseline liver function in patients with unresectable hepatocellular carcinoma treated with tremelimumab and durvalumab in the Phase 3 HIMALAYA study

Arndt Vogel, MD

30 June 2022

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RTP RESEARCH TO PRACTICE

HIMALAYA: Exploratory Liver Function Analysis

Liver function assessments

- Child-Pugh score
- ALBI score, calculated as: log10(bilirubin) × 0.66 − albumin × 0.085

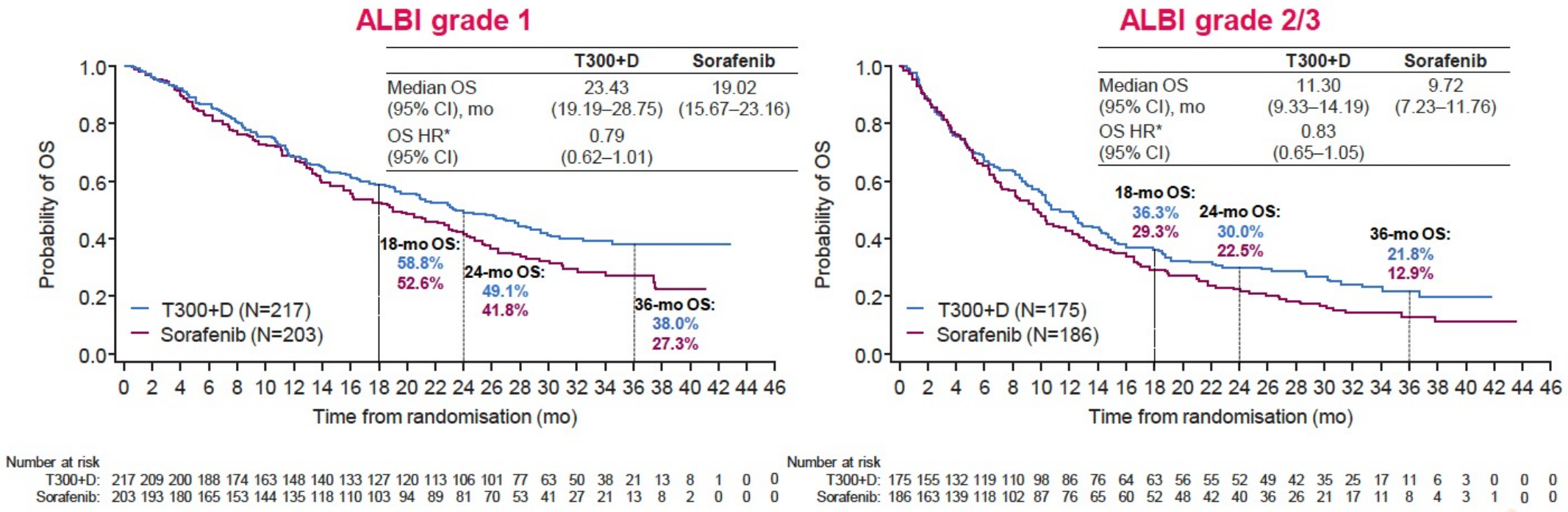
OS, ORR, DoR, TTR, and safety outcomes were assessed by baseline ALBI score

- Baseline ALBI score subgroups:

ALBI grade 1	score ≤−2.60	*Lowest risk group*
ALBI grade 2	score >−2.60 to ≤−1.39	*Intermediate risk group*
ALBI grade 3*	score >−1.39	*Highest risk group*

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

HIMALAYA: OS for T300 + D versus Sorafenib by ALBI Grade



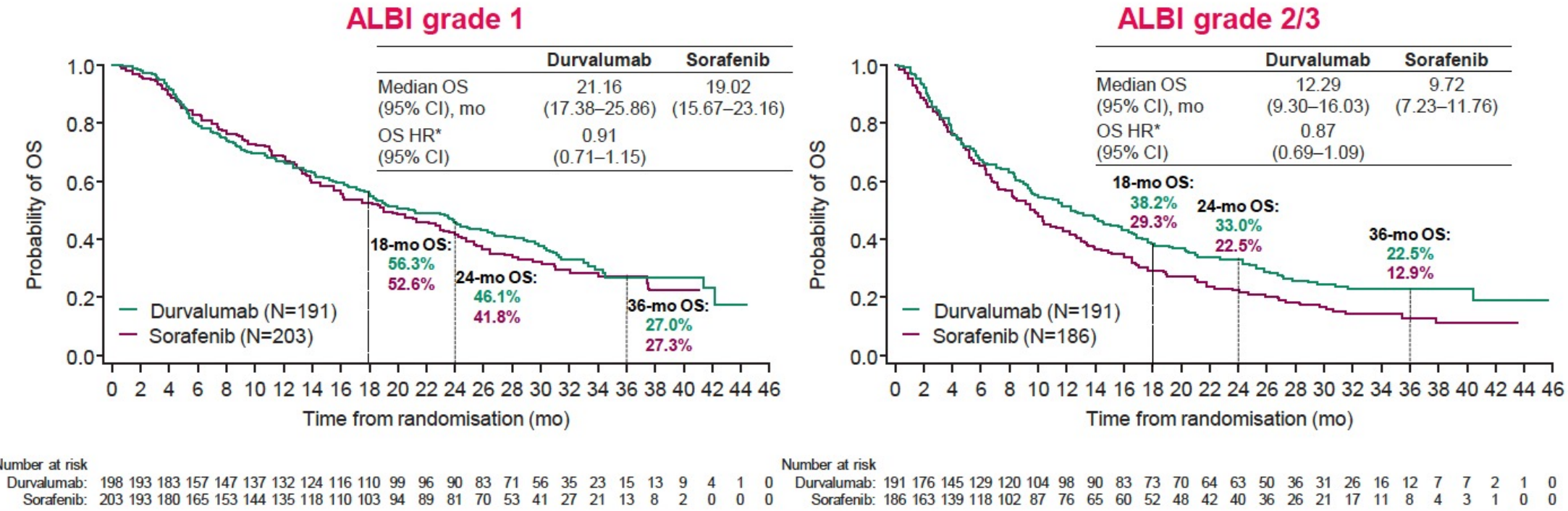
- OS HRs for T300+D versus sorafenib in the ALBI grade 1 and ALBI grade 2/3 subgroups were generally consistent with the full analysis set (0.78; 96% CI, 0.65–0.93)[1]
- ALBI grade 1 was associated with longer survival than ALBI grade 2/3, regardless of treatment arm

OS = overall survival; T300 + D = 300-mg priming dose of tremelimumab and regular schedule of durvalumab; HR = hazard ratio

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

RTP RESEARCH TO PRACTICE

HIMALAYA: OS for Durvalumab versus Sorafenib by ALBI Grade



- OS HRs for durvalumab versus sorafenib in the ALBI grade 1 and ALBI grade 2/3 subgroups were generally consistent with the full analysis set (0.86; 96% CI, 0.73–1.03)[1]
- ALBI grade 1 was associated with longer survival than ALBI grade 2/3, regardless of treatment arm

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

HIMALAYA: Response Outcomes in ALBI Grade Subgroups

Parameter	ALBI grade 1			ALBI grade 2/3			Full analysis set[1]		
	T300+D (n=217)	Durvalumab (n=198)	Sorafenib (n=203)	T300+D (n=175)	Durvalumab (n=191)	Sorafenib (n=186)	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* %	21.7	18.7	7.4	18.3	15.2	2.7	20.1	17.0	5.1
Median TTR‡ (IQR), mo	2.07 (1.84–3.94)	1.91 (1.81–3.98)	3.52 (1.84–5.49)	3.52 (1.91–5.40)	3.65 (1.94–3.94)	9.10 (7.79–11.01)	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Median DoR,†‡ (IQR), mo	22.34 (8.71–NR)	23.26 (7.43–NR)	22.06 (6.51–25.99)	26.55 (7.43–NR)	13.83 (7.43–27.43)	12.25 (7.69–NR)	22.34 (8.54–NR)	16.82 (7.43–NR)	18.43 (6.51–25.99)

- Similar to the full analysis set[1]:
  - ORR was higher for T300+D and durvalumab than for sorafenib in both ALBI subgroups
  - Median TTR was shorter for T300+D and durvalumab than for sorafenib in both ALBI subgroups

ORR = overall response rate; TTR = time to response; DoR = duration of response

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

HIMALAYA: Safety for T300 + D versus Sorafenib in ALBI Grade Subgroups

Patients with an event, n (%)	ALBI grade 1		ALBI grade 2/3		Safety analysis set[1]	
	T300+D (n=216)	Sorafenib (n=197)	T300+D (n=171)	Sorafenib (n=177)	T300+D (n=388)	Sorafenib (n=374)
Any TEAE	210 (97.2)	187 (94.9)	167 (97.7)	170 (96.0)	378 (97.4)	357 (95.5)
Any TRAE	166 (76.9)	168 (85.3)	127 (74.3)	149 (84.2)	294 (75.8)	317 (84.8)
Any grade 3/4 TEAE	111 (51.4)	102 (51.8)	85 (49.7)	94 (53.1)	196 (50.5)	196 (52.4)
Any grade 3/4 TRAE	59 (27.3)	76 (38.6)	41 (24.0)	62 (35.0)	100 (25.8)	138 (36.9)
Any TEAE leading to death	8 (3.7)	11 (5.6)	22 (12.9)	16 (9.0)	30 (7.7)	27 (7.2)
Any TRAE leading to death	5 (2.3)	1 (0.5)	4 (2.3)	2 (1.1)	9 (2.3)	3 (0.8)
Any serious TEAE	89 (41.2)	49 (24.9)	68 (39.8)	62 (35.0)	157 (40.5)	111 (29.7)
Any serious TRAE	44 (20.4)	15 (7.6)	24 (14.0)	20 (11.3)	68 (17.5)	35 (9.4)
Any TEAE leading to discontinuation	27 (12.5)	20 (10.2)	26 (15.2)	43 (24.3)	53 (13.7)	63 (16.8)
Any TRAE leading to discontinuation	20 (9.3)	15 (7.6)	12 (7.0)	26 (14.7)	32 (8.2)	41 (11.0)
Any immune-mediated TEAE	94 (43.5)	20 (10.2)	45 (26.3)	10 (5.6)	139 (35.8)	30 (8.0)

- In contrast to sorafenib, T300+D had a similar safety profile in both ALBI subgroups, similar to the safety analysis set[1]

TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

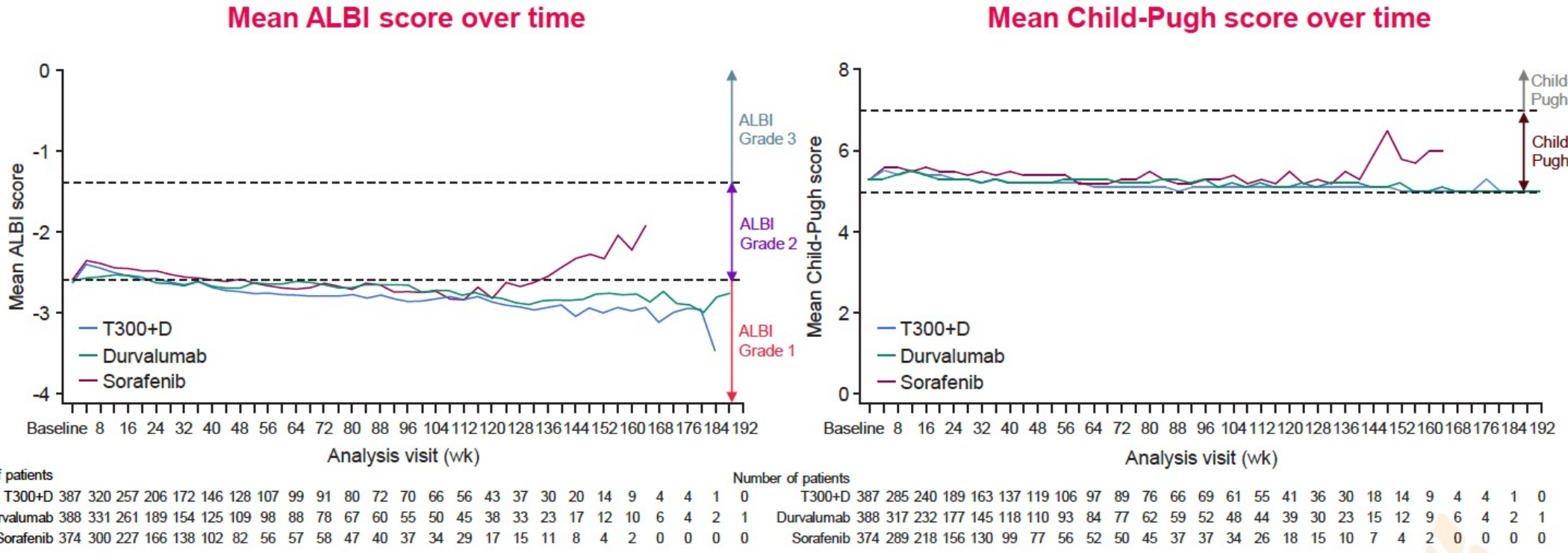
HIMALAYA: Safety for Durvalumab versus Sorafenib in ALBI Grade Subgroups

Patients with an event, n (%)	ALBI grade 1		ALBI grade 2/3		Safety analysis set[1]	
	Durvalumab (n=198)	Sorafenib (n=197)	Durvalumab (n=190)	Sorafenib (n=177)	Durvalumab (n=388)	Sorafenib (n=374)
Any TEAE	171 (86.4)	187 (94.9)	174 (91.6)	170 (96.0)	345 (88.9)	357 (95.5)
Any TRAE	99 (50.0)	168 (85.3)	103 (54.2)	149 (84.2)	202 (52.1)	317 (84.8)
Any grade 3/4 TEAE	63 (31.8)	102 (51.8)	81 (42.6)	94 (53.1)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	17 (8.6)	76 (38.6)	33 (17.4)	62 (35.0)	50 (12.9)	138 (36.9)
Any TEAE leading to death	6 (3.0)	11 (5.6)	20 (10.5)	16 (9.0)	26 (6.7)	27 (7.2)
Any TRAE leading to death	0	1 (0.5)	0	2 (1.1)	0	3 (0.8)
Any serious TEAE	48 (24.2)	49 (24.9)	67 (35.3)	62 (35.0)	115 (29.6)	111 (29.7)
Any serious TRAE	14 (7.1)	15 (7.6)	18 (9.5)	20 (11.3)	32 (8.2)	35 (9.4)
Any TEAE leading to discontinuation	10 (5.1)	20 (10.2)	22 (11.6)	43 (24.3)	32 (8.2)	63 (16.8)
Any TRAE leading to discontinuation	4 (2.0)	15 (7.6)	12 (6.3)	26 (14.7)	16 (4.1)	41 (11.0)
Any immune-mediated TEAE	25 (12.6)	20 (10.2)	39 (20.5)	10 (5.6)	64 (16.5)	30 (8.0)

- Durvalumab had a similar safety profile in both ALBI subgroups, similar to the safety analysis set[1]

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

HIMALAYA: Liver Function Over Time in the Study Population



- Mean ALBI scores remained stable over time for T300+D and durvalumab; similar trends were observed in Child-Pugh scores

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

HIMALAYA: Conclusions

In this exploratory analysis from the Phase 3 HIMALAYA study:

- The STRIDE (T300+D) regimen and durvalumab monotherapy showed favourable benefit-risk profiles compared with sorafenib, irrespective of baseline ALBI grade
- Improvement in overall survival and duration of response with the STRIDE (T300+D) regimen versus sorafenib was consistent across ALBI subgroups
- Liver function was stable over time for patients who remained on the study in either the STRIDE (T300+D) or durvalumab groups
- Safety in both ALBI subgroups was generally consistent with the full analysis set[1]
- ALBI grade is prognostic of response with the STRIDE (T300+D) regimen, durvalumab monotherapy, or sorafenib
- These results support the use of the STRIDE (T300+D) regimen as a new treatment option in patients with unresectable HCC

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-5.

Select Ongoing Phase III Trials of Combination Therapy for Locoregional HCC

Study	N	Eligibility	Randomization arms	Est primary completion
EMERALD-1	724	Child-Pugh A-B7 Not amenable to curative surgery, transplant or ablation	• TACE + durvalumab • TACE + durvalumab + bevacizumab • TACE + placebo	September 2022
EMERALD-2	877	Child-Pugh score of 5-6 High risk of recurrence after curative resection or ablation	• Durvalumab + bevacizumab q3wk • Durvalumab + placebo q3wk • Durvalumab + placebo q2wk	June 2023
EMERALD-3	525	Child-Pugh A Not amenable to curative surgery, transplant or ablation	• TACE + durvalumab + tremelimumab + lenvatinib • TACE + durvalumab + tremelimumab • TACE	October 2025

TACE = transarterial chemoembolization

www.clinicaltrials.gov. Accessed June 2022.

Lancet Oncol 2022;[Online ahead of print].

Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial

Robin Kate Kelley, Lorenza Rimassa*, Ann-Lii Cheng, Ahmed Kaseb, Shukui Qin, Andrew X Zhu, Stephen L Chan, Tamar Melkadze, Wattana Sukeepaisarnjaroen, Valery Breder, Gontran Verset, Edward Gane, Ivan Borbath, Jose David Gomez Rangel, Baek-Yeol Ryoo, Tamta Makharadze, Philippe Merle, Fawzi Benzaghou, Kamalika Banerjee, Saswati Hazra, Jonathan Fawcett, Thomas Yau*

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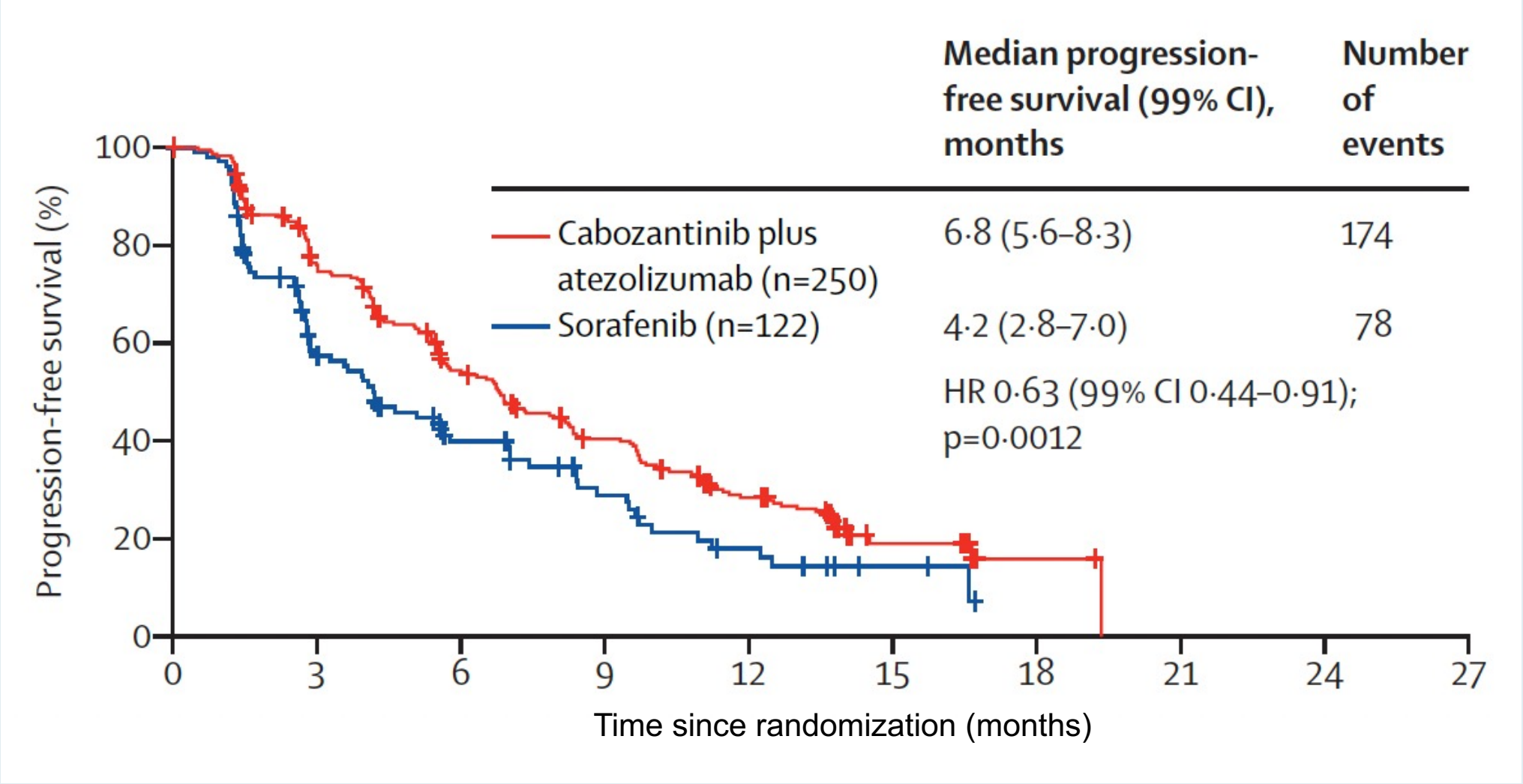
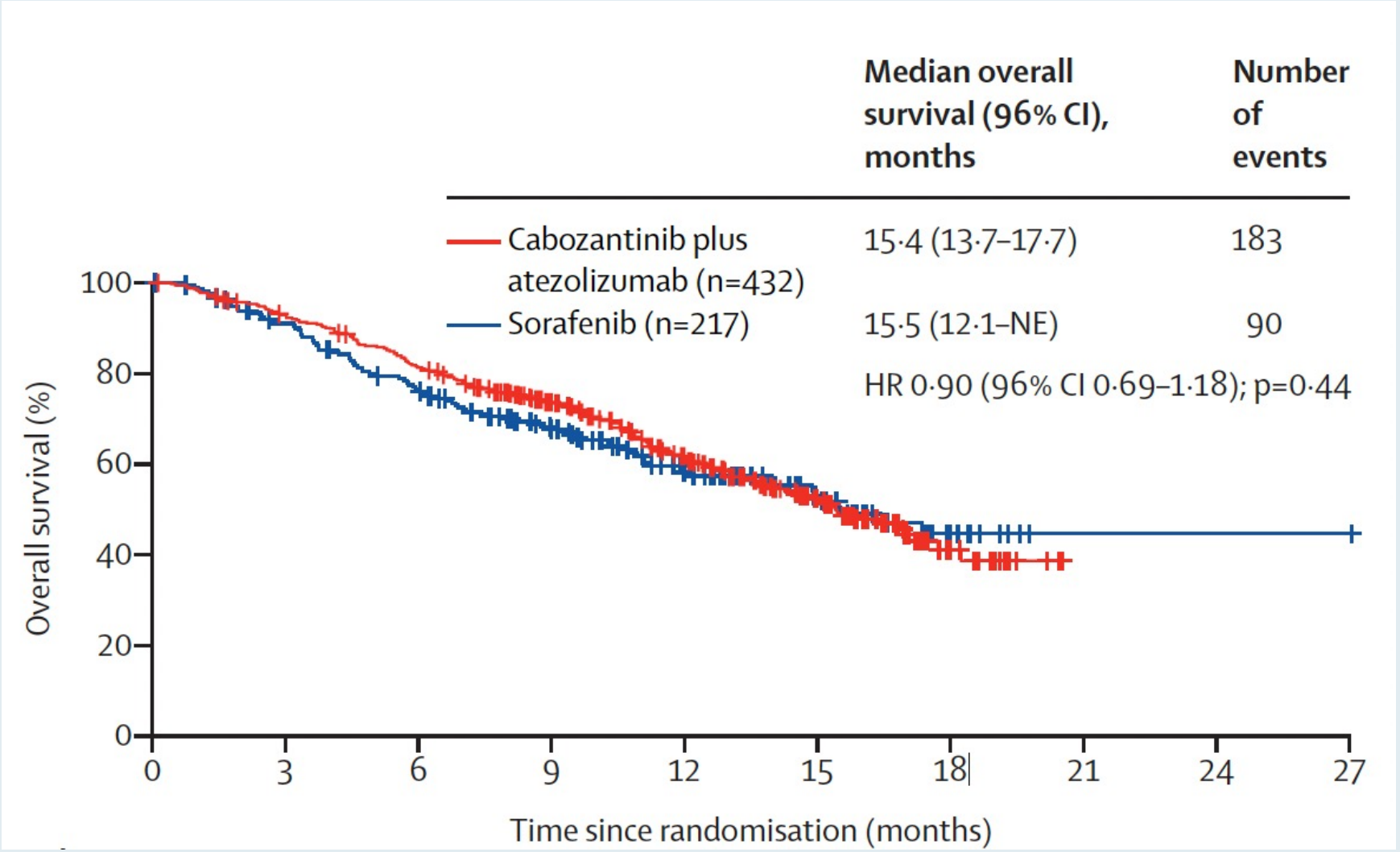
RTP RESEARCH TO PRACTICE

COSMIC-312: Progression-Free Survival in the ITT Population (Final Analysis)



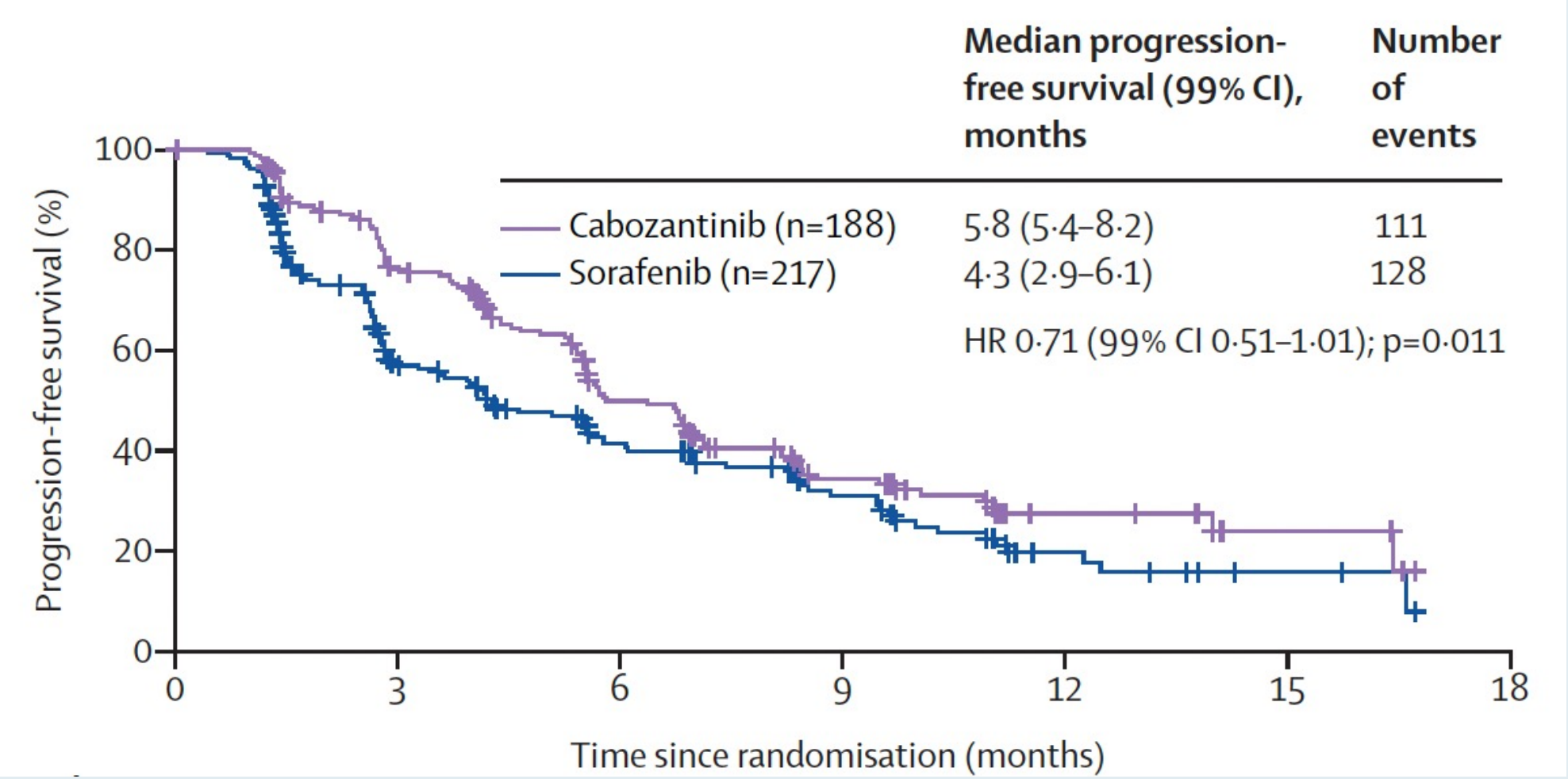
Kelley RK et al. *Lancet Oncol* 2022;[Online ahead of print].

COSMIC-312: Overall Survival in the ITT Population (Interim Analysis)



Kelley RK et al. *Lancet Oncol* 2022;[Online ahead of print].

COSMIC-312: Interim Analysis of PFS for Cabozantinib versus Sorafenib



Kelley RK et al. *Lancet Oncol* 2022;[Online ahead of print].

COSMIC-312: Tumor Response by Blinded Independent Review Committee

	Progression-free survival ITT population		ITT population		
	Cabozantinib plus atezolizumab (n=250)	Sorafenib (n=122)	Cabozantinib plus atezolizumab (n=432)	Sorafenib (n=217)	Cabozantinib (n=188)
Objective response, n (%, 95% CI)	32 (13%, 8·9–17·6)	6 (5%, 1·8–10·4)	47 (11%, 8·1–14·2)	8 (4%, 1·6–7·1)	12 (6%, 3·3–10·9)
Best overall response					
Complete response	1 (<1%)	0	1 (<1%)	0	0
Partial response	31 (12%)	6 (5%)	46 (11%)	8 (4%)	12 (6%)
Stable disease	172 (69%)	71 (58%)	290 (67%)	132 (61%)	145 (77%)
Progressive disease	32 (13%)	26 (21%)	61 (14%)	44 (20%)	20 (11%)
Unable to evaluate or missing	12 (5%)	19 (16%)	29 (7%)	32 (15%)	8 (4%)
No measurable disease	2 (1%)	0	5 (1%)	1 (<1%)	3 (2%)
Disease control*	204 (82%)	77 (63%)	337 (78%)	140 (65%)	157 (84%)
Median time to response (IQR), months	4·1 (2·5–8·4)	3·5 (1·5–4·5)	4·0 (2·6–8·3)	3·5 (2·1–4·4)	4·2 (2·1–5·6)
Median duration of response (95% CI), months	12·4 (9·8–NE)	8·4 (3·0–NE)	10·6 (7·1–12·7)	8·8 (3·0–NE)	15·1 (4·4–NE)
Median time to progression (95% CI), months	7·1 (6·3–8·5)	4·2 (2·9–7·0)	7·0 (6·7–8·3)	4·6 (3·6–6·1)	6·8 (5·6–8·2)

Data are n (%) unless otherwise indicated. ITT=intention-to-treat. NE=not estimable. RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1. *Disease control was defined as the proportion of patients with a complete response, partial response, or stable disease (post-hoc analysis). BIRC=blinded independent radiology committee.

Kelley RK et al. *Lancet Oncol* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

COSMIC-312: Select Adverse Events

	Cabozantinib plus atezolizumab (n=429)				Sorafenib (n=207)				Cabozantinib (n=188)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	104 (24%)	245 (57%)	28 (7%)	51 (12%)	87 (42%)	84 (41%)	11 (5%)	23 (11%)	44 (23%)	101 (54%)	12 (6%)	30 (16%)
Diarrhoea	190 (44%)	18 (4%)	0	0	93 (45%)	4 (2%)	0	0	91 (48%)	12 (6%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	148 (34%)	35 (8%)	0	0	75 (36%)	17 (8%)	0	0	66 (35%)	16 (9%)	0	0
Aspartate aminotransferase increased	92 (21%)	37 (9%)	0	0	22 (11%)	7 (3%)	1 (<1%)	0	43 (23%)	18 (10%)	0	0
Alanine aminotransferase increased	89 (21%)	35 (8%)	3 (1%)	0	17 (8%)	5 (2%)	1 (<1%)	0	43 (23%)	12 (6%)	0	0
Decreased appetite	109 (25%)	7 (2%)	0	0	37 (18%)	4 (2%)	0	0	69 (37%)	9 (5%)	0	0
Fatigue	91 (21%)	15 (3%)	0	0	25 (12%)	8 (4%)	0	0	52 (28%)	7 (4%)	0	0
Hypertension	63 (15%)	37 (9%)	0	0	21 (10%)	17 (8%)	0	0	32 (17%)	23 (12%)	0	0

Kelley RK et al. *Lancet Oncol* 2022;[Online ahead of print].

Selection and Sequencing of Therapies for Relapsed/Refractory HCC

FDA-Approved Anti-VEGF-Directed Monotherapy for HCC

Approved line of therapy	Agent	Study	Primary outcomes
First line	Sorafenib[1]	Sorafenib vs placebo (N = 602) Phase III SHARP trial	TTP 4.1 mo vs 4.9 mo mOS 10.7 mo vs 7.9 mo
	Lenvatinib[2]	Lenvatinib vs sorafenib (N = 954) Phase III REFLECT trial	mPFS 7.4 mo vs 3.7 mo mOS 13.6 mo vs 12.3 mo
Second line	**Regorafenib[3]**	Regorafenib vs placebo (N = 573) Phase III RESORCE trial	mPFS 3.1 mo vs 1.5 mo mOS 10.7 mo vs 7.9 mo
	Cabozantinib[4]	Cabozantinib vs placebo (N = 707) Phase III CELESTIAL trial	mPFS 5.2 mo vs 1.9 mo mOS 10.2 mo vs 8.0 mo
	Ramucirumab[5]	Ramucirumab vs placebo (N = 565) Phase III REACH-2 trial	mPFS 2.8 mo vs 1.6 mo mOS 8.5 mo vs 7.3 mo

TTP = time to progression; mPFS = median progression-free survival ; mOS = median overall survival

[1] Llovet JM et al. *N Engl J Med* 2008;359(4):378-90; [2] Kudo M et al. *Lancet* 2018;391(10126):1163-73; [3] Bruix J et al. *Lancet* 2017;389(10064):56-66; [4] Abou-Alfa GK et al. *N Engl J Med* 2018;379(1):54-63; [5] Zhu AX et al. *Lancet Oncol* 2019;20(2):282-96.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

WORLD CONGRESS ON Gastrointestinal Cancer

2022 | Abstract SO-12

Nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma: 5-year results from CheckMate 040

Ignacio Melero,[1] Thomas Yau,[2] Yoon-Koo Kang,[3] Tae-You Kim,[4] Armando Santoro,[5] Bruno Sangro,[6] Masatoshi Kudo,[7] Ming-Mo Hou,[8] Ana Matilla,[9] Francesco Tovoli,[10] Jennifer Knox,[11] Aiwu Ruth He,[12] Bassel El-Rayes,[13] Mirelis Acosta-Rivera,[14] Ho Yeong Lim,[15] Samira Soleymani,[16] Jin Yao,[16] Jaclyn Neely,[16] Marina Tschaika,[16] Chiun Hsu,[17] Anthony B. El-Khoueiry[18]

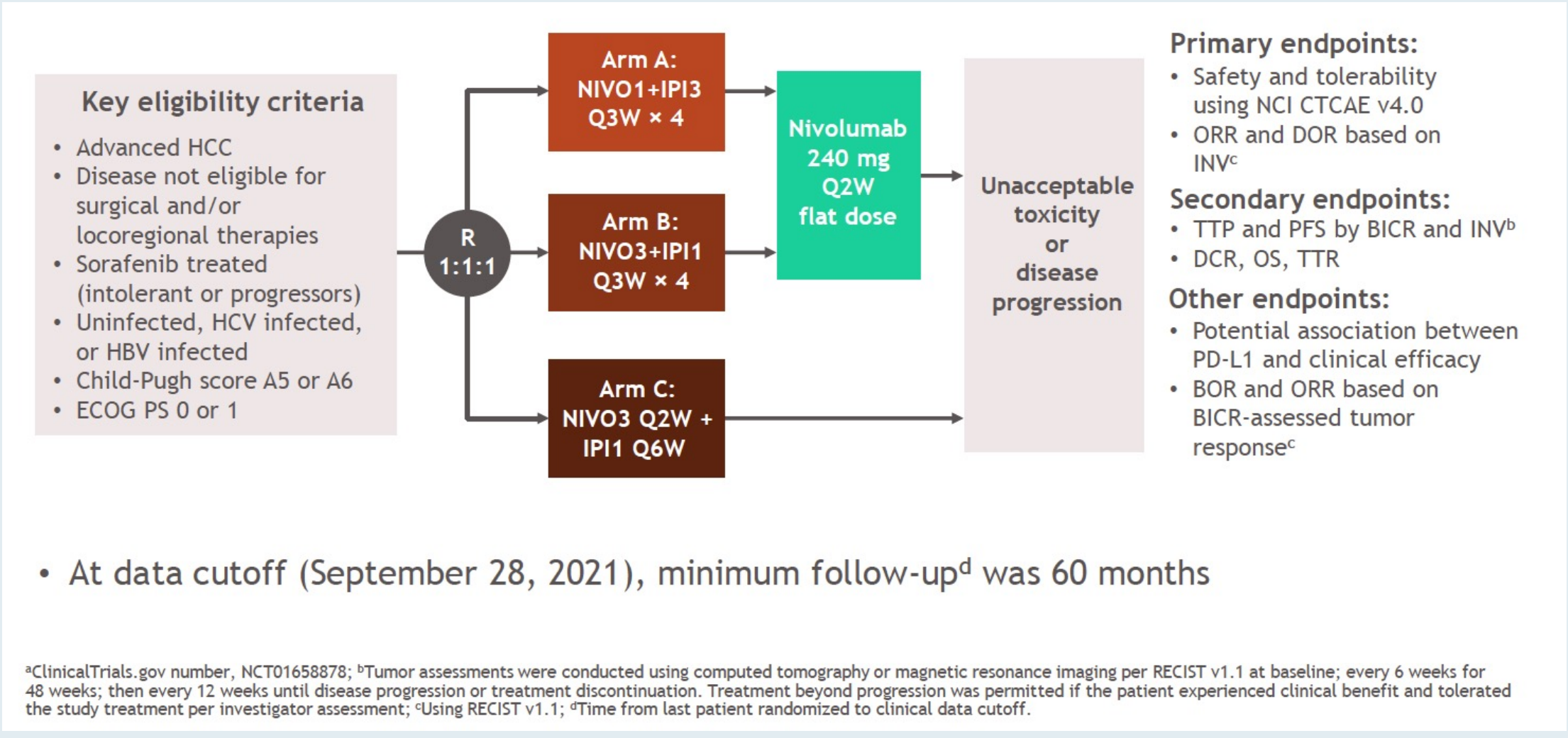
[1]Clinica Universidad de Navarra and CIBERONC, Pamplona, Spain; [2]University of Hong Kong, Hong Kong, China; [3]University of Ulsan, Seoul, South Korea; [4]Seoul National University, Seoul, South Korea; [5]Humanitas University and IRCCS Humanitas Research Hospital - Humanitas Cancer Center, Rozzano, Italy; [6]Clinica Universidad de Navarra-CCUN and CIBEREHD, Pamplona, Spain; [7]Kindai University Faculty of Medicine, Osaka, Japan; [8]Chang Gung Memorial Hospital, Taipei, Taiwan; [9]Hospital General Universitario Gregorio Marañón CIBEREHD, Madrid, Spain; [10]University of Bologna, Bologna, Italy; [11]Princess Margaret Cancer Centre, Toronto, ON, Canada; [12]Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA; [13]University of Alabama at Birmingham, AL, USA; [14]Fundacion de Investigacion, San Juan, Puerto Rico; [15]School of Medicine, Sungkyunkwan University, Korea; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]National Taiwan University Hospital, Taipei, Taiwan; [18]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Abstract Number SO-12

Primary publication: Yau T, et al. *JAMA Oncol* 2020;6:e204564.

RTP RESEARCH TO PRACTICE

CheckMate 040: Phase I/II Study Design



- At data cutoff (September 28, 2021), minimum follow-up[d] was 60 months

[a]ClinicalTrials.gov number, NCT01658878; [b]Tumor assessments were conducted using computed tomography or magnetic resonance imaging per RECIST v1.1 at baseline; every 6 weeks for 48 weeks; then every 12 weeks until disease progression or treatment discontinuation. Treatment beyond progression was permitted if the patient experienced clinical benefit and tolerated the study treatment per investigator assessment; [c]Using RECIST v1.1; [d]Time from last patient randomized to clinical data cutoff.

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

CheckMate 040: 5-Year Efficacy Results

	Arm A NIVO1+IPI3 Q3W (n = 50)		Arm B NIVO3+IPI1 Q3W (n = 49)		Arm C NIVO3 Q2W + IPI1 Q6W (n = 49)	
	INV	BICR	INV	BICR	INV	BICR
ORR per RECIST v1.1, % (95% CI)[a,b]	34 (21-49)	32 (20-47)	27 (15-41)	31 (18-45)	29 (17-43)	31 (18-45)
CR, n (%)	1 (2)	4 (8)	1 (2)	3 (6)	0	1 (2)
PR, n (%)	16 (32)	12 (24)	12 (24)	12 (24)	14 (29)	14 (29)
SD, n (%)	15 (30)	9 (18)	9 (18)	5 (10)	8 (16)	9 (18)
Non-CR/non-PD, n (%)	NA	2 (4)	NA	1 (2)	NA	0
PD, n (%)	16 (32)	20 (40)	24 (49)	24 (49)	22 (45)	21 (43)
TTR, median (range), months	2.6 (1.2-12.8)	2.0 (1.1-12.8)	2.6 (1.2-4.1)	2.6 (1.2-5.5)	1.6 (1.2-5.5)	2.7 (1.2-8.7)
DOR, median (95% CI), months	51.2 (12.6-NE)	17.5 (8.3-NE)	15.2 (7.1-NE)	22.2 (4.4-NE)	21.7 (4.2-NE)	16.6 (4.3-NE)
DCR, % (95% CI)[c]	64 (49-77)	54 (39-68)	45 (31-60)	43 (29-58)	45 (31-60)	49 (34-64)
DDC, median (95% CI), months[d]	NA	16.6 (8.2-28.4)	NA	16.5 (7.0-55.3)	NA	11.5 (5.5-23.2)
PFS, median (95% CI), months	6.8 (2.7-16.4)	3.9 (2.6-8.3)	2.7 (1.4-4.2)	1.6 (1.3-6.9)	2.7 (1.4-4.4)	2.6 (1.3-4.5)

- After a minimum follow-up of 60 months, outcomes were consistent with the primary analysis[1]
- Durable responses were achieved across the treatment arms

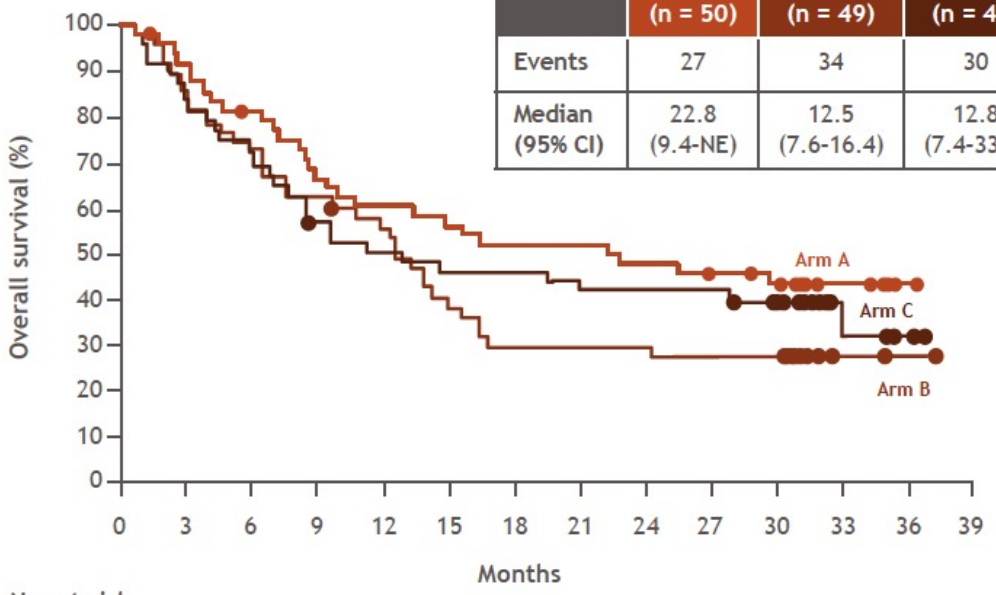
INV = investigator; BICR = blinded independent central review

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

CheckMate 040: 5-Year Overall Survival

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)

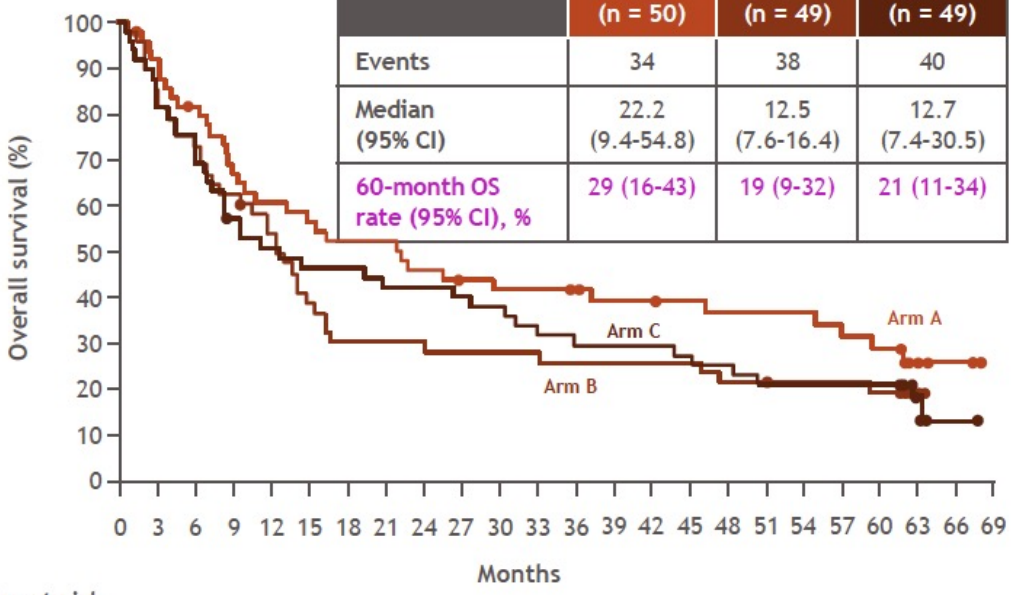


No. at risk

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

[a]Median follow-up, 30.7 months; [b]Median follow-up, 62.6 months; minimum follow-up, 60 months. 1. Yau T, et al. *JAMA Oncol* 2020;6:e204564.

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

original reports

Safety, Efficacy, and Pharmacodynamics of Tremelimumab Plus Durvalumab for Patients With Unresectable Hepatocellular Carcinoma: Randomized Expansion of a Phase I/II Study

Robin Kate Kelley, MD[1]; Bruno Sangro, MD, PhD[2]; William Harris, MD[3]; Masafumi Ikeda, MD, PhD[4]; Takuji Okusaka, MD, PhD[5]; Yoon-Koo Kang, MD, PhD[6]; Shukui Qin, MD, PhD[7]; David W.-M. Tai, MD[8]; Ho Yeong Lim, MD[9]; Thomas Yau, MD[10]; Wei-Peng Yong, MD[11]; Ann-Lii Cheng, MD, PhD[12]; Antonio Gasbarrini, MD[13]; Silvia Damian, MD[14]; Jordi Bruix, MD[15]; Mitesh Borad, MD[16]; Johanna Bendell, MD[17]; Tae-You Kim, MD[18]; Nathan Standifer, PhD[19]; Philip He, PhD[20]; Mallory Makowsky, PharmD[20]; Alejandra Negro, PhD[20]; Masatoshi Kudo, MD, PhD[21]; and Ghassan K. Abou-Alfa, MD, MBA[22,23]

J Clin Oncol 2021;39(27):2991-3001.

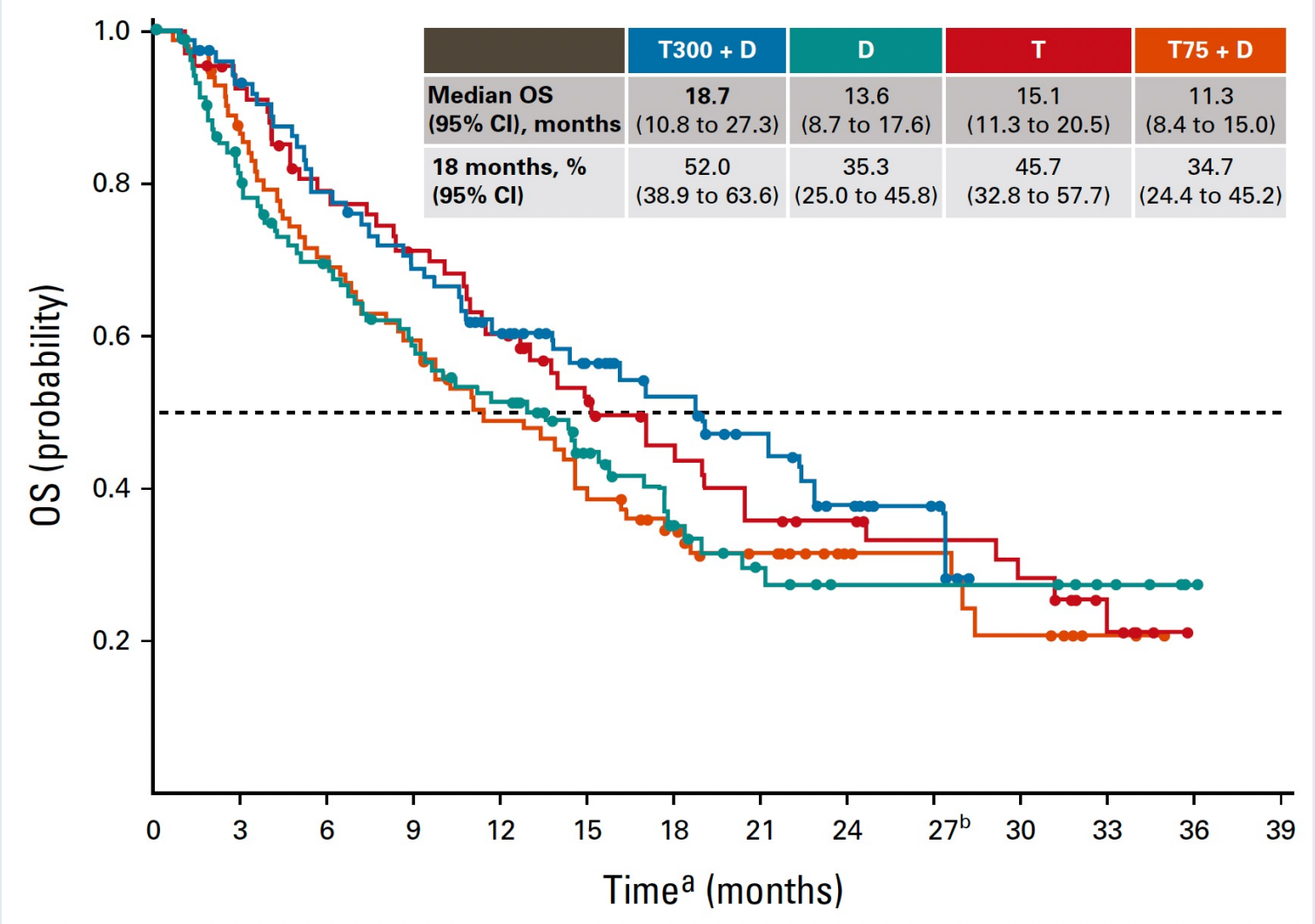
Durvalumab and Tremelimumab Alone or in Combination for Progressive HCC After Prior Sorafenib: Response Outcomes

Outcome	T300 + D (n = 75)	Durvalumab (n = 104)	Tremelimumab (n = 69)	T75 + D (n = 84)
ORR	24%	11%	7%	10%
CR	1%	0	0	2%
PR	17%	11%	5%	6%
SD	16%	28%	29%	23%
Disease control rate	34%	39%	34%	31%
Median DoR	Not reached	11 mo	24 mo	13 mo
Median PFS	2.2 mo	2.1 mo	2.7 mo	1.9 mo

ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; DoR = duration of response; PFS = progression-free survival

Kelley RK et al. *J Clin Oncol* 2021;39(27):2991-3001.

Durvalumab and Tremelimumab Alone or in Combination for Progressive HCC After Prior Sorafenib: Overall Survival



Kelley RK et al. *J Clin Oncol* 2021;39(27):2991-3001.

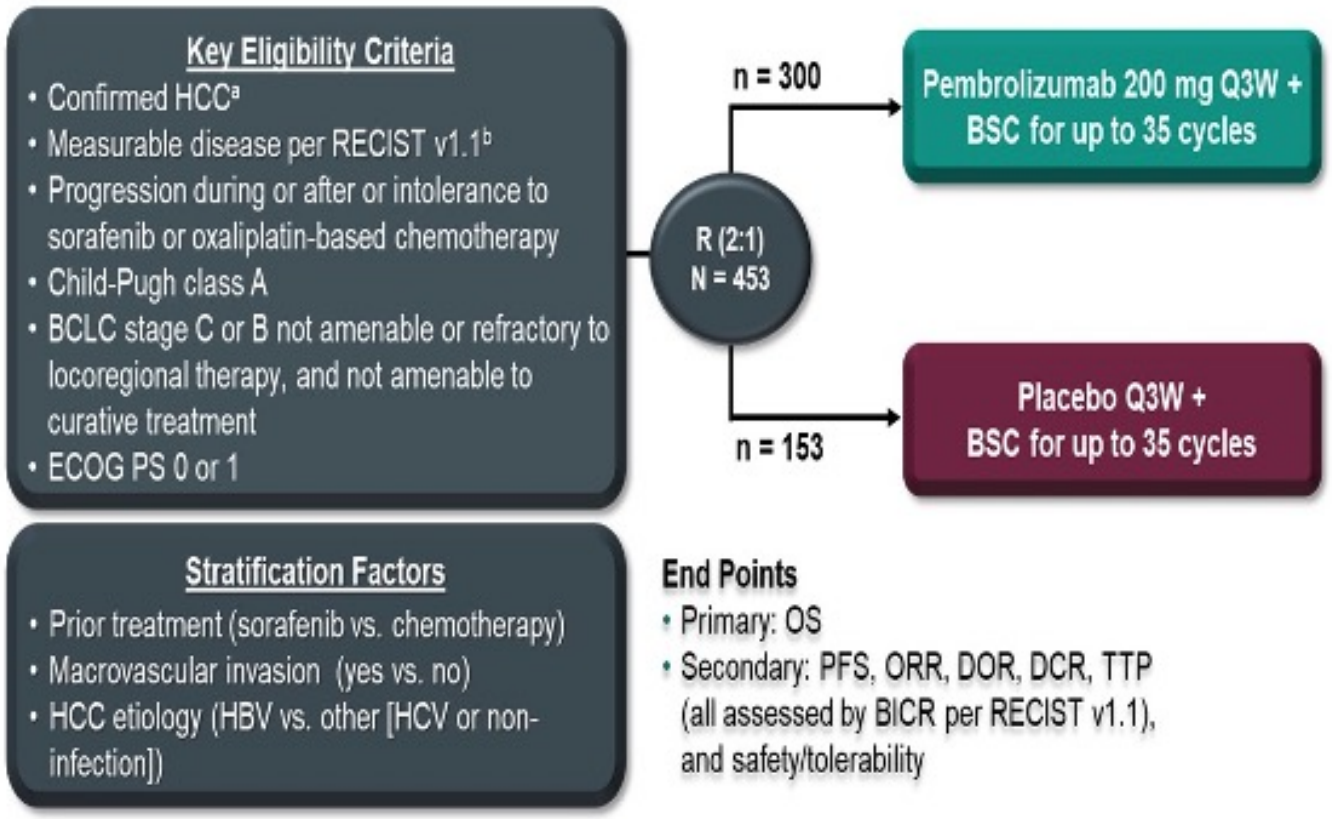
RTP RESEARCH TO PRACTICE

Pembrolizumab Plus Best Supportive Care Versus Placebo Plus Best Supportive Care as Second-line Therapy in Patients in Asia With Advanced Hepatocellular Carcinoma: Phase 3 KEYNOTE-394 Study

Shukui Qin, MD[1]; Zhendong Chen, MD[2]; Weijia Fang, MD[3]; Zhenggang Ren, MD[4]; Ruocai Xu, MD[5]; Baek-Yeol Ryoo, MD[6]; Zhiqiang Meng, MD[7]; Yuxian Bai, MD[8]; Xiaoming Chen, MD[9,10]; Xiufeng Liu, MD[1]; Juxiang Xiao, MD[11]; Gwo Fuang Ho, MRCP, MBChB[12]; Yimin Mao, MD[13]; Xin Wang, MD[14]; Jieer Ying, MD[15]; Jianfeng Li, MD[16]; Wen Yan Zhong, PhD[17]; Yu Zhou, MD[17]; Abby B. Siegel, MD[18]; Chunyi Hao, MD[19]

Gastrointestinal Cancers Symposium 2022;Abstract 383.

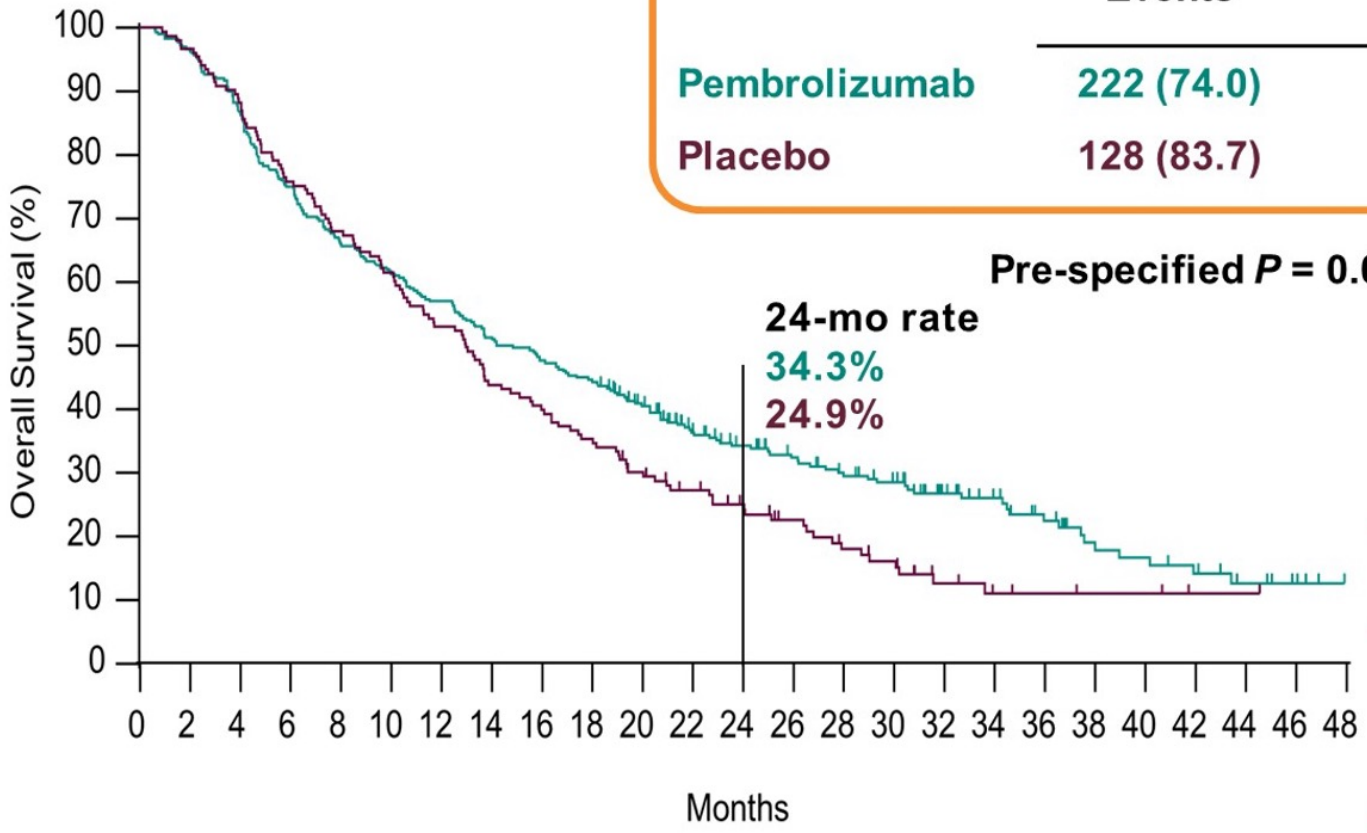
KEYNOTE-394 Study Design and Statistical Considerations



- Overall Type I error = 0.025 controlled across testing of OS, PFS, and ORR[1]
  - Initial allocation PFS = 0.002; OS = 0.023
  - Re-allocated per multiplicity strategy specified in the protocol among 3 endpoints above
- Per protocol, there were 2 interim and 1 final analysis for OS and 1 interim and 1 final analysis for PFS and ORR
  - Interim analysis for PFS and ORR at the time of OS 1st interim analysis
  - Final analysis at the time of OS 2nd interim analysis
- Efficacy boundaries
  - *P* = 0.0193 for OS (final analysis cutoff, June 30, 2021, based on 350 observed events)
  - *P* = 0.0134 for PFS and *P* = 0.0091 for ORR (at 2nd interim cutoff, June 30, 2020; only if OS criteria met)

Qin S et al. Gastrointestinal Cancers Symposium 2022;Abstract 383.

KEYNOTE-394: Overall Survival



	Events	OS, median (95% CI), mo	HR (95% CI)	*P*[a]
Pembrolizumab	222 (74.0)	14.6 (12.6-18.0)	0.79 (0.63-0.99)	*0.0180*
Placebo	128 (83.7)	13.0 (10.5-15.1)		

Pre-specified *P* = 0.0193 required for statistical significance

Post-Study Systemic Anticancer Therapy

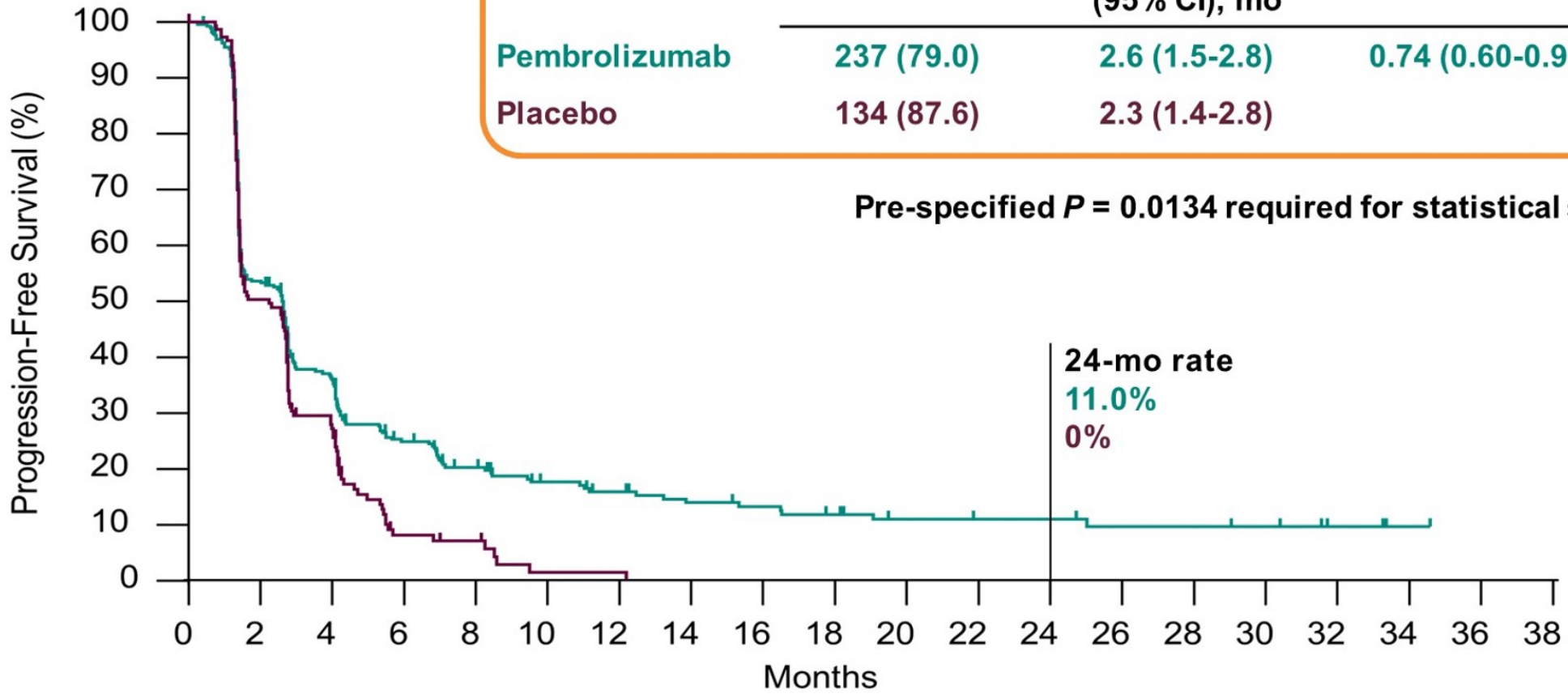
	Pembrolizumab n = 300	Placebo n = 153
Any post-study systemic anticancer therapy	152 (50.7)	102 (66.7)
PD-1 inhibitor or PD-L1 inhibitor[b]	62 (20.7)	43 (28.1)

Qin S et al. Gastrointestinal Cancers Symposium 2022;Abstract 383.

KEYNOTE-394: Progression-Free Survival

	Events	PFS, median (95% CI), mo	HR (95% CI)	*P*[a]
Pembrolizumab	237 (79.0)	2.6 (1.5-2.8)	0.74 (0.60-0.92)	*0.0032*
Placebo	134 (87.6)	2.3 (1.4-2.8)		

Pre-specified *P* = 0.0134 required for statistical significance



Qin S et al. Gastrointestinal Cancers Symposium 2022;Abstract 383.

RTP RESEARCH TO PRACTICE

KEYNOTE-394: Objective Response

	Pembrolizumab n = 300	Placebo n = 153
ORR (CR + PR), % (95% CI)	12.7 (9.1-17.0)	1.3 (0.2-4.6)
Estimated treatment difference, (95% CI; *P*[a])	11.4 (6.7-16.0); *<0.0001*	
Best overall response, n (%)		
CR	6 (2.0)	1 (0.7)
PR	32 (10.7)	1 (0.7)
SD	115 (38.3)	70 (45.8)
Sustained SD[b]	26 (8.7)	8 (5.2)
PD	129 (43.0)	72 (47.1)
Not evaluable	10 (3.3)	1 (0.7)
Not assessable[c]	8 (2.7)	8 (5.2)
DOR,[d] median (range), mo	23.9 (2.8 to 32.0+)	5.6 (3.0+ to 5.6)

Pre-specified *P* = 0.0091 required for statistical significance

Qin S et al. Gastrointestinal Cancers Symposium 2022;Abstract 383.

KEYNOTE-394: Adverse Event (AE) Summary

n (%)	Pembrolizumab n = 299	Placebo n = 153
All-cause AEs		
Any	283 (94.6)	147 (96.1)
Grade 3-5	157 (52.5)	50 (32.7)
Led to discontinuation	38 (12.7)	12 (7.8)
Led to death	10 (3.3)	2 (1.3)
Treatment-related AEs		
Any	200 (66.9)	76 (49.7)
Grade 3-5[a]	43 (14.4)	9 (5.9)
Led to discontinuation	12 (4.0)	1 (0.7)
Led to death	3 (1.0)	0

n (%)	Pembrolizumab n = 299	Placebo n = 153
Immune-mediated AEs[b]		
Any	54 (18.1)	16 (10.5)
Grade 3-5	9 (3.0)	0
Led to discontinuation	5 (1.7)	0
Led to death[c]	1 (0.3)	0
Immune-mediated hepatitis[c,d]	5 (1.7)	0

Qin S et al. Gastrointestinal Cancers Symposium 2022;Abstract 383.

Current Treatment Strategies for Advanced Biliary Tract Cancers

RTP
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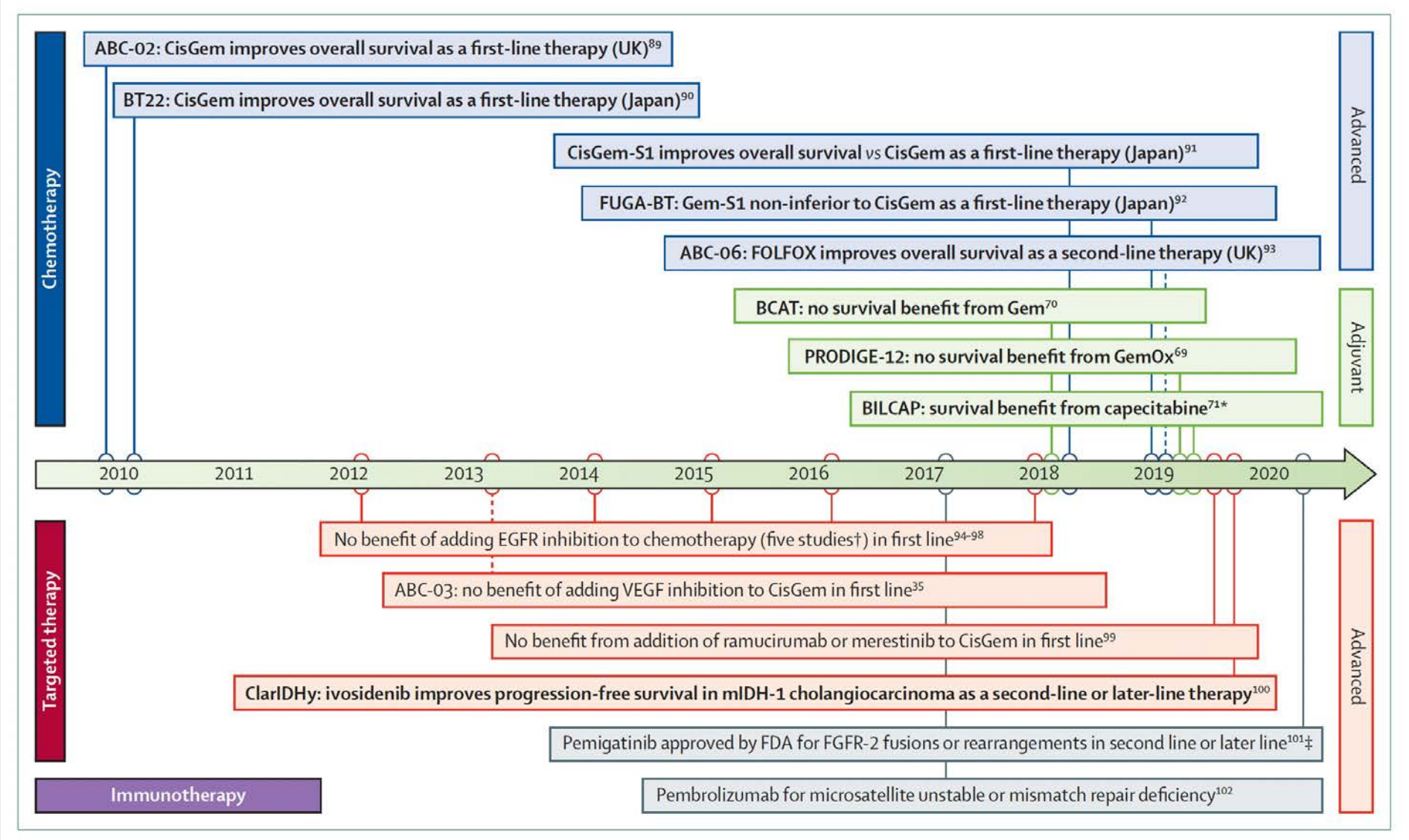
Timeline of Developments in Systemic Therapy of Biliary Tract Cancer



Valle JW et al. *Lancet* 2021;397(10272):428-44.

RTP RESEARCH TO PRACTICE

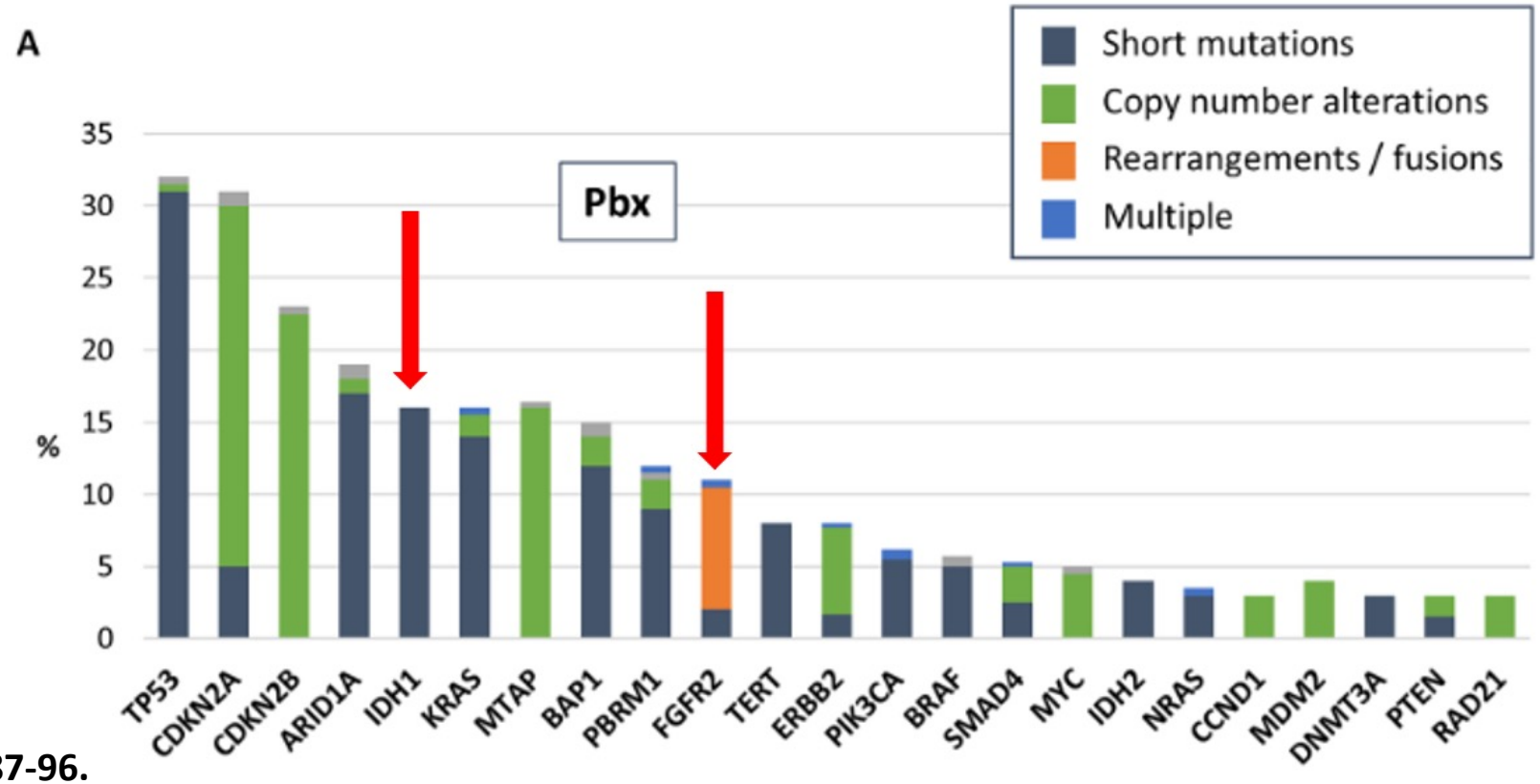
Therapeutic Targets and Approach to Molecular Profiling for Biliary Tract Cancers

Target	Frequency	Targeted agents	Molecular test
IDH1	***13%*** of intrahepatic cholangiocarcinomas	Ivosidenib	Tumor next-generation DNA sequencing or targeted sequencing for hotspot mutations in coding region of IDH1
FGFR pathway	**20%** of intrahepatic cholangiocarcinomas	Erdafitinib; futibatinib; infigratinib; pemigatinib	Tumor next-generation DNA sequencing including FGFR2 intronic region, targeted RNAseq or FISH testing for FGFR2 translocation
BRAF	**5%** of intrahepatic cholangiocarcinomas	Dabrafenib with trametinib; vemurafenib	Tumor next-generation DNA sequencing or targeted sequencing for hotspot mutations in coding region of BRAF
MSI-high or MMR deficiency	**2%** of biliary tract cancers	Pembrolizumab	Multiple testing modalities available: PCR, immunohistochemistry or tumor next-generation DNA sequencing
ERBB2 (HER2)	***15%-20%*** gallbladder cancer; extrahepatic cholangiocarcinomas		Multiple testing modalities available including immunohistochemistry and FISH for expression and amplification, tumor next-generation DNA sequencing for mutations

Valle JW et al. *Lancet* 2021;397(10272):428-44.

Emerging Targets in Cholangiocarcinoma: Focus on FGFR2 and IDH1

- Mutation profiling of N=1632 iCCA using Foundation Medicine panel
  - n=1048 with primary tumor biopsy (PbX)
  - *FGFR2* fusion or rearrangement: 9%
  - *IDH1* mutation: 16%



Israel MA et al. *Oncologist* 2021;26(9):787-96.

RTP RESEARCH TO PRACTICE

FGFR Inhibitor Efficacy in FGFR2 Fusion-Positive Cholangiocarcinoma

	Pemigatinib* (N = 107)	Infigratinib* (N = 108)	Futibatinib (N = 67)	Derazantinib (N = 29)
ORR	35.5%	23.1%	37.3%	20.7%
DCR	82.2%	84.3%	82.1%	82.8%
mPFS	6.9 mo	7.3 mo	7.2 mo	5.7 mo
mOS	21.1 mo	12.2 mo	NR	NR
Toxicities	Hyperphosphatemia, alopecia, diarrhea	Hyperphosphatemia, stomatitis, fatigue	Hyperphosphatemia, diarrhea, dry mouth	Hyperphosphatemia, fatigue, ocular

* FDA approved

Abou-Alfa GK et al. *Lancet Oncol* 2020;21(5):671-84; Javle M et al. Gastrointestinal Cancers Symposium 2021; Goyal L et al. ASCO 2020; Mazzaferro V et al. *Br J Cancer* 2019;120(2):165-71.

Lancet Gasteroenterol Hepatol 2021;6(10):803-15.

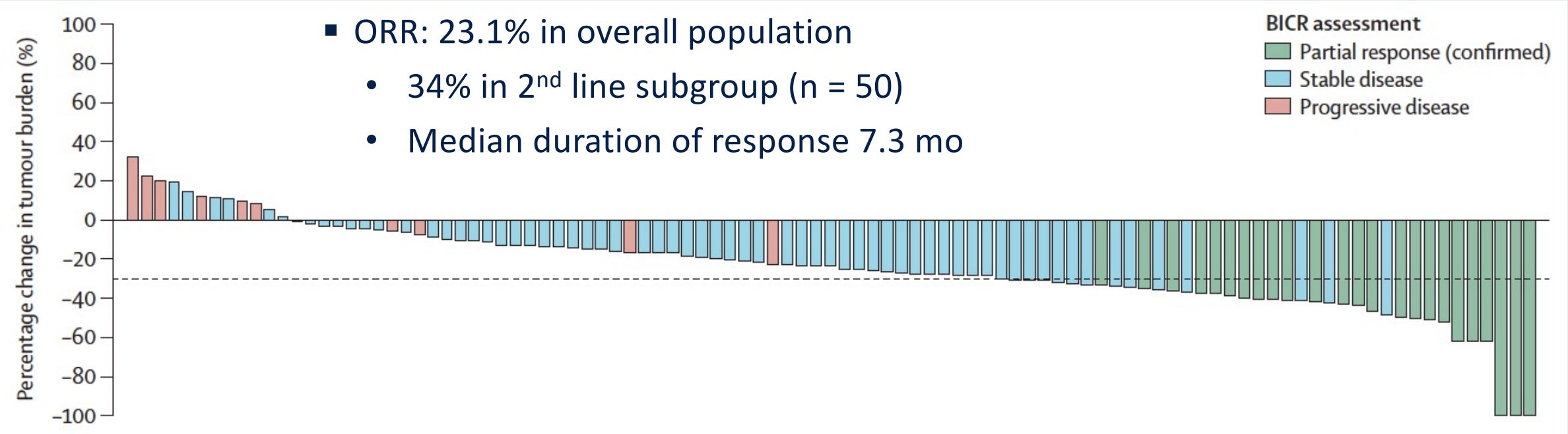
Articles

Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with *FGFR2* fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study

Milind Javle, Sameek Roychowdhury, Robin Kate Kelley, Saeed Sadeghi, Teresa Macarulla, Karl Heinz Weiss, Dirk-Thomas Waldschmidt, Lipika Goyal, Ivan Borbath, Anthony El-Khoueiry, Mitesh J Borad, Wei Peng Yong, Philip A Philip, Michael Bitzer, Surbpong Tanasanvimon, Ai Li, Amit Pande, Harris S Soifer, Stacie Peacock Shepherd, Susan Moran, Andrew X Zhu, Tanios S Bekaii-Saab, Ghassan K Abou-Alfa

Phase II Study of Infigratinib for Advanced or Metastatic Cholangiocarcinoma Harboring FGFR2 Fusions or Rearrangements

- ORR: 23.1% in overall population
  - 34% in 2nd line subgroup (n = 50)
  - Median duration of response 7.3 mo



Javle M et al. *Lancet Gasteroenterol Hepatol* 2021;6(10):803-15.

RTP RESEARCH TO PRACTICE

Infigratinib for Advanced or Metastatic Cholangiocarcinoma: Adverse Events in ≥20% of Patients

	Treatment-emergent adverse events					Treatment-related adverse events of any grade
	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	
Any adverse event	8 (7%)	29 (27%)	61 (56%)	9 (8%)	107 (99%)	104 (96%)
Hyperphosphataemia	37 (34%)	35 (32%)	11 (10%)	0	83 (77%)	80 (74%)
Stomatitis	29 (27%)	14 (13%)	16 (15%)	0	59 (55%)	55 (51%)
Fatigue	21 (19%)	18 (17%)	4 (4%)	0	43 (40%)	31 (29%)
Alopecia	34 (31%)	7 (6%)	0	0	41 (38%)	35 (32%)
Dry eye	25 (23%)	11 (10%)	1 (1%)	0	37 (34%)	34 (31%)
Palmar-plantar erythrodysaesthesia syndrome	11 (10%)	18 (17%)	7 (6%)	0	36 (33%)	35 (32%)
Arthralgia	22 (20%)	12 (11%)	0	0	34 (31%)	31 (29%)
Dysgeusia	27 (25%)	7 (6%)	0	0	34 (31%)	28 (26%)
Constipation	22 (20%)	9 (8%)	1 (1%)	0	32 (30%)	10 (9%)
Dry mouth	24 (22%)	3 (3%)	0	0	27 (25%)	23 (21%)
Hypercalcaemia	13 (12%)	8 (7%)	5 (5%)	1 (1%)	27 (25%)	17 (16%)
Blood creatinine concentration increased	19 (18%)	7 (6%)	0	0	26 (24%)	17 (16%)
Diarrhoea	17 (16%)	6 (6%)	3 (3%)	0	26 (24%)	19 (18%)
Dry skin	23 (21%)	2 (2%)	0	0	25 (23%)	22 (20%)
Decreased appetite	16 (15%)	7 (6%)	1 (1%)	0	24 (22%)	16 (15%)
Hypophosphataemia	6 (6%)	4 (4%)	13 (12%)	1 (1%)	24 (22%)	10 (9%)
Blurred vision	13 (12%)	10 (9%)	0	0	23 (21%)	20 (19%)
AST concentration increased	18 (17%)	3 (3%)	2 (2%)	0	23 (21%)	10 (9%)
Vomiting	16 (15%)	6 (6%)	1 (1%)	0	23 (21%)	14 (13%)

Javle M et al. *Lancet Gasteroenterol Hepatol* 2021;6(10):803-15.

2022 | Abstract O-2

O-2

#575

Presented at the 2022 ESMO World Congress on Gastrointestinal Cancer; 29 June–2 July, 2022; Barcelona, Spain

Pemigatinib for Previously Treated Locally Advanced or Metastatic Cholangiocarcinoma: Final Results From FIGHT-202

Arndt Vogel, MD

Arndt Vogel, MD,[1] Vaibhav Sahai, MBBS, MS,[2] Antoine Hollebecque, MD,[3] Gina M. Vaccaro, MD,[4] Davide Melisi, MD, PhD,[5] Raed M. Al Rajabi, MD,[6] Andrew S. Paulson, MD,[7] Mitesh J. Borad, MD,[8] David Gallinson, DO,[9] Adrian G. Murphy, MD,[10] Do-Youn Oh, MD, PhD,[11] Efrat Dotan, MD,[12] Daniel V. Catenacci, MD,[13] Eric Van Cutsem, MD, PhD,[14] Christine F. Lihou, BS,[15] Huiling Zhen, PhD,[15] Luisa Veronese, MD,[16] Ghassan K. Abou-Alfa, MD[17]

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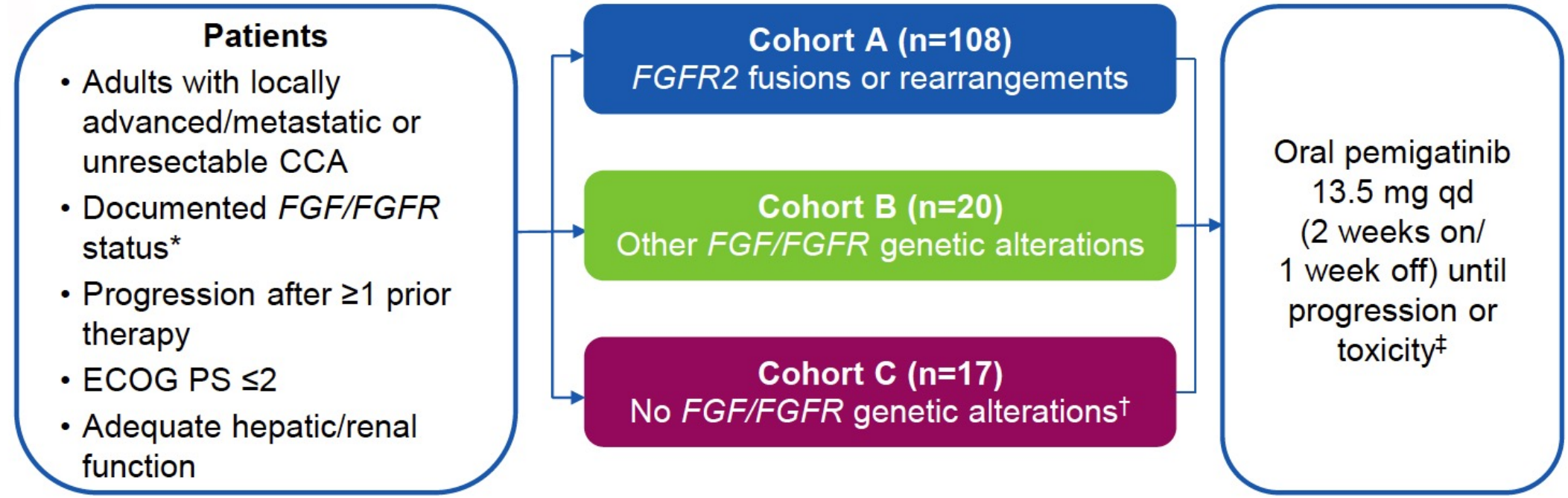
FIGHT-202 Trial Schema



- Primary endpoint: ORR§ in cohort A (confirmed by independent central review)
- Secondary endpoints: ORR§ in cohorts A/B combined, B, and C; DOR/DCR/PFS/OS/safety in all cohorts

CCA, cholangiocarcinoma; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; qd, once daily.

*Patients prescreened for *FGF/FGFR* status, documented either centrally (FoundationOne®, Foundation Medicine), based on local assessment, or an existing Foundation Medicine report. Retrospective central confirmation of locally documented *FGF/FGFR* status was required. †United States only. ‡The efficacy population included all patients with centrally confirmed *FGF/FGFR* status who received ≥1 pemigatinib dose; the safety population included all patients who received ≥1 pemigatinib dose. §ORR was defined as the percentage of patients with complete response (disappearance of all target lesions) or partial response (≥30% decrease in sum of the longest diameters of target lesions).

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-2.

FIGHT-202 Final Results: Response to Pemigatinib

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)	—	—

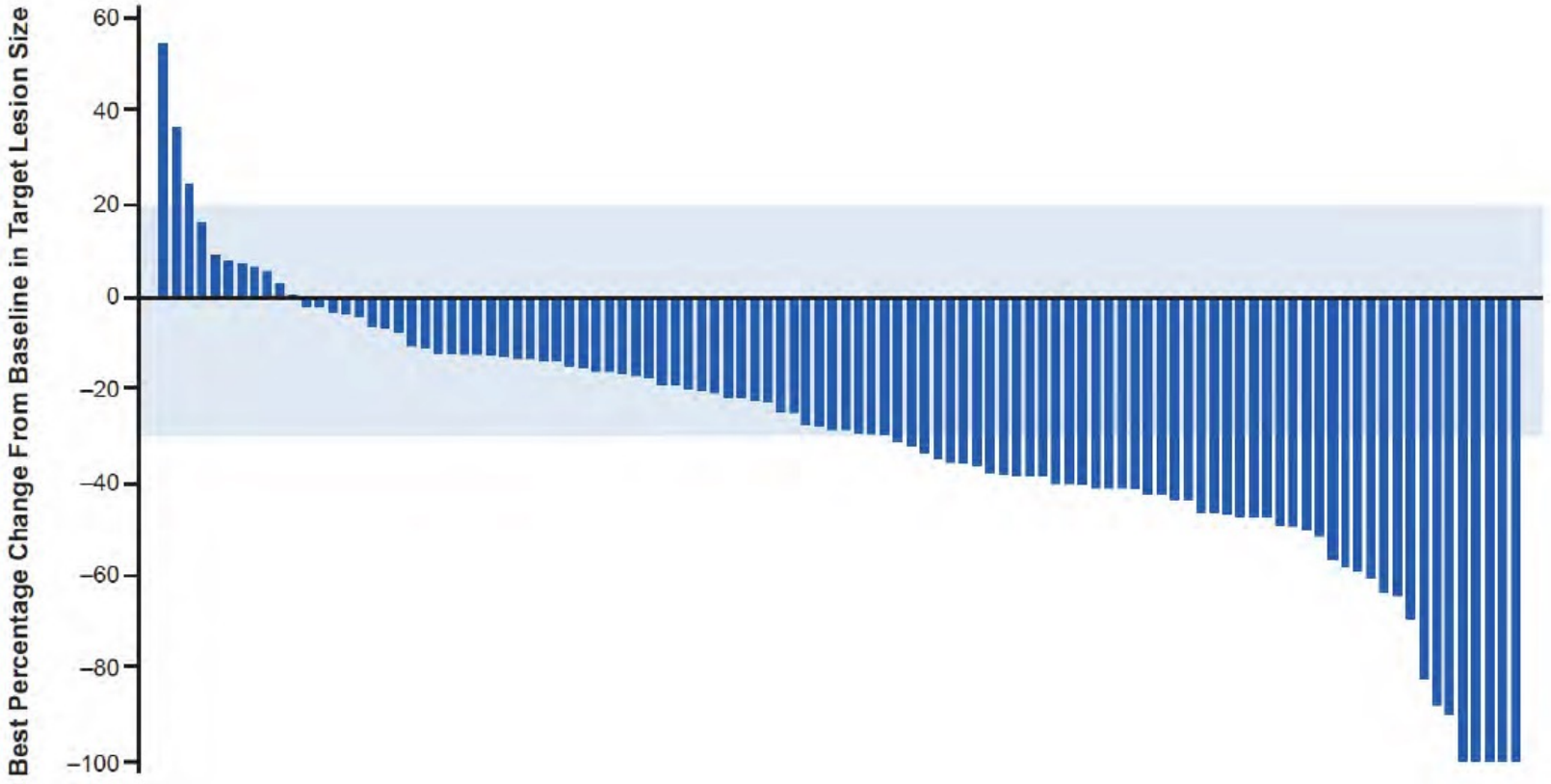
DCR, disease control rate; DOR, duration of response; ORR, objective response rate.

*ORR is complete response + partial response; †DCR is complete response + partial response + stable disease.

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-2.

FIGHT-202 Final Results: Best Percentage Change from Baseline in Target Lesion Size in Cohort A

- Among 104 evaluable patients, median best percentage change from baseline in the sum of target lesion diameters was –28.4% (range, –100% to +55%)

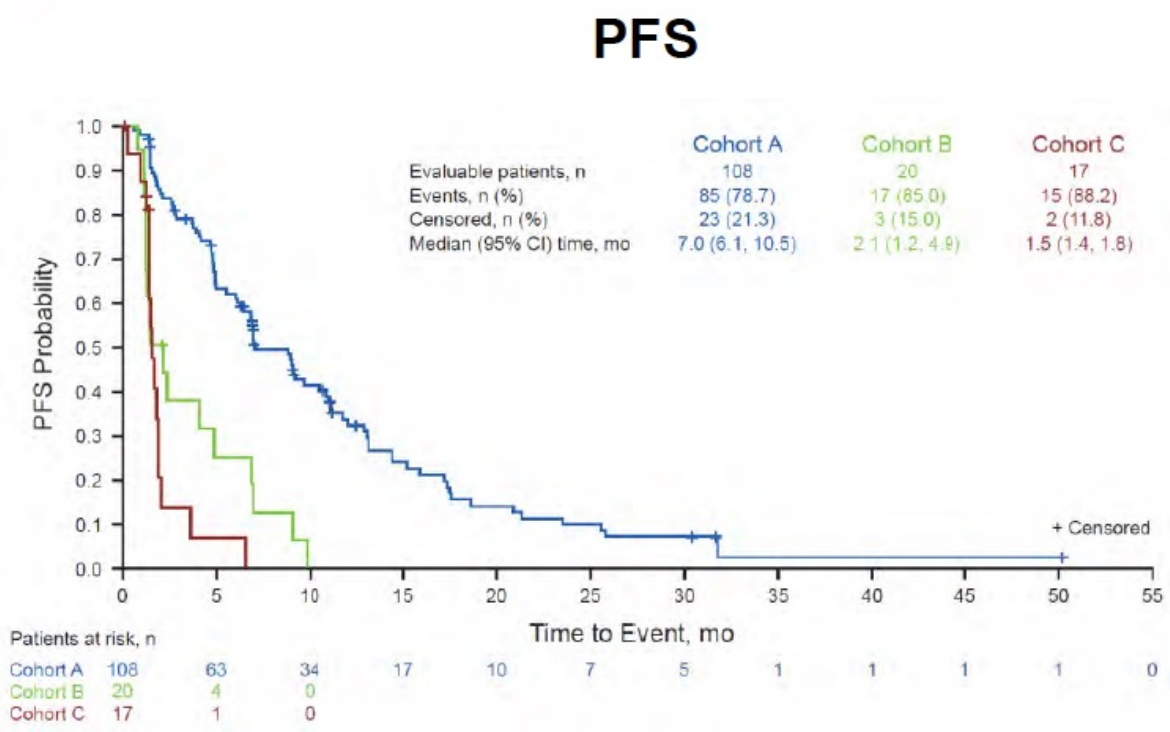


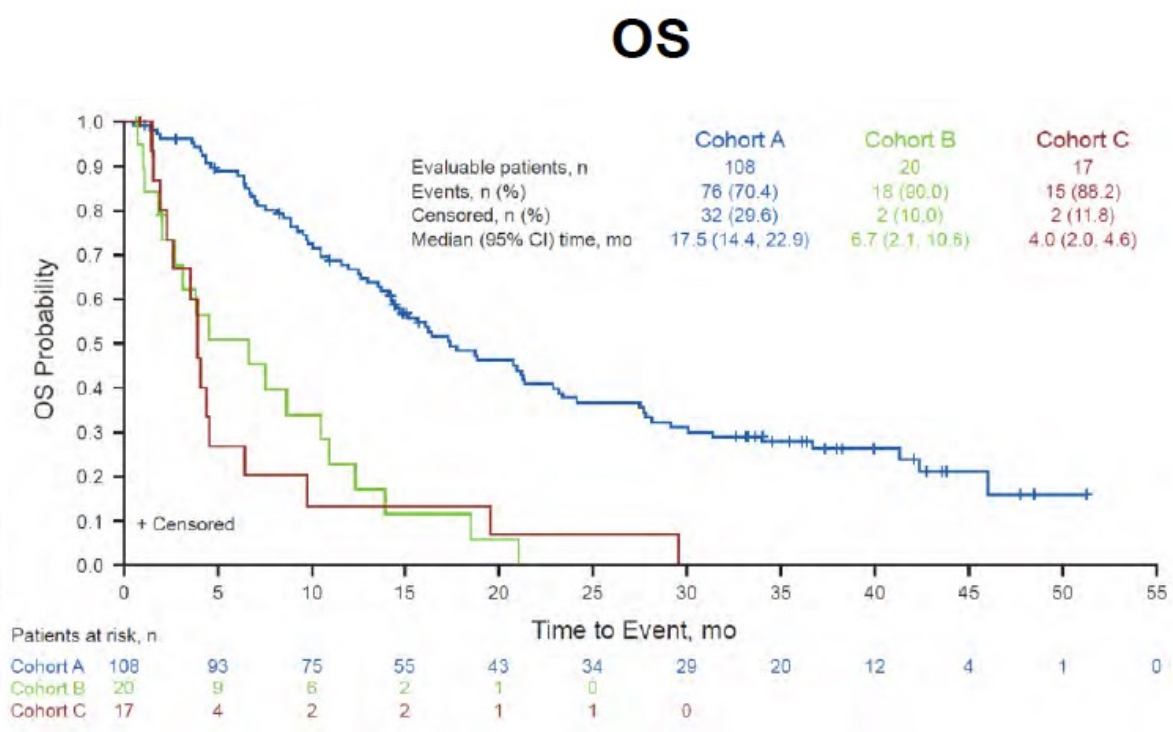
Lower limit of blue shading indicates criterion for partial response (≥30% decrease in sum of target lesion diameters).

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-2.

RTP RESEARCH TO PRACTICE

FIGHT-202 Final Results: PFS and OS for All Patients





- 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)

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-2.

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FIGHT-202: TEAEs Occurring in ≥25% of Patients

Event	Cohort A (n=108)		Cohort B (n=20)		Cohort C (n=17)		Total (N=147)*	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any TEAE, %	100	67	100	75	100	76	100	69
Hyperphosphatemia	56	0	65	0	71	0	59	0
Alopecia	59	0	20	0	18	0	50	0
Diarrhoea	54	4	25	0	35	6	48	3
Fatigue	46	5	25	0	53	18	44	5
Nausea	43	3	35	0	41	0	41	2
Stomatitis	43	9	30	0	18	0	38	7
Constipation	43	1	25	0	12	0	37	1
Dysgeusia	42	0	15	0	18	0	36	0
Decreased appetite	31	1	40	5	41	6	34	2
Dry mouth	39	0	25	0	6	0	34	0
Arthralgia	34	6	25	10	12	0	30	6
Vomiting	33	2	15	0	24	0	29	1
Dry eye	35	0	5	0	6	0	28	1

- The safety profile remained consistent with the primary publication[1]; no new safety signals were observed

TEAE, treatment-emergent adverse event.

*The total includes 2 patients for whom *FGF/FGFR* status could not be centrally determined; the 2 patients were not assigned to a cohort and were evaluated for safety but not for efficacy.

1. Abou-Alfa GH, et al. *Lancet Oncol.* 2020;21(5):671-684.

Vogel A et al. ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-2.

FDA Accepts for Priority Review Futibanib's New Drug Application for Cholangiocarcinoma

Press Release: March 30, 2022

"The US Food and Drug Administration (FDA) has accepted for priority review the New Drug Application (NDA) for futibatinib in the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma (CCA) harboring FGFR2 gene rearrangements, including gene fusions. Futibatinib is an investigational, oral, potent, selective and irreversible small-molecule inhibitor of FGFR1, 2, 3 and 4. The FDA provided an anticipated Prescription Drug User Fee Act (PDUFA) action date of September 30, 2022.

The NDA is based on data from the pivotal Phase 2b FOENIX-CCA2 trial in 103 patients with locally advanced or metastatic unresectable intrahepatic (inside the liver) CCA, harboring FGFR2 gene rearrangements including fusions who had received one or more prior lines of systemic therapy. Patients in the trial received futibatinib 20 mg once daily until disease progression or unacceptable toxicity. The trial's primary endpoint was an objective response rate (ORR), which was 41.7% as assessed by independent central review. The key secondary endpoint of duration of response (DOR) demonstrated a median of 9.7 months (72% of responses ≥6 months). Common treatment-related adverse events (TRAEs) in the trial were hyperphosphatemia (85%), alopecia (33%) and dry mouth (30%). The only serious adverse reaction reported in more than one patient enrolled in the FOENIX-CCA2 trial was migraine (1.9%)."

https://www.prnewswire.com/news-releases/us-food-and-drug-administration-fda-accepts-for-priority-review-taiho-oncologys-new-drug-application-for-futibatinib-for-cholangiocarcinoma-301513278.html?tc=eml_cleartime

RTP RESEARCH TO PRACTICE

Updated Results of the FOENIX-CCA2 Trial: Efficacy and Safety of Futibatinib in Intrahepatic Cholangiocarcinoma Harboring *FGFR2* Fusions/Rearrangements

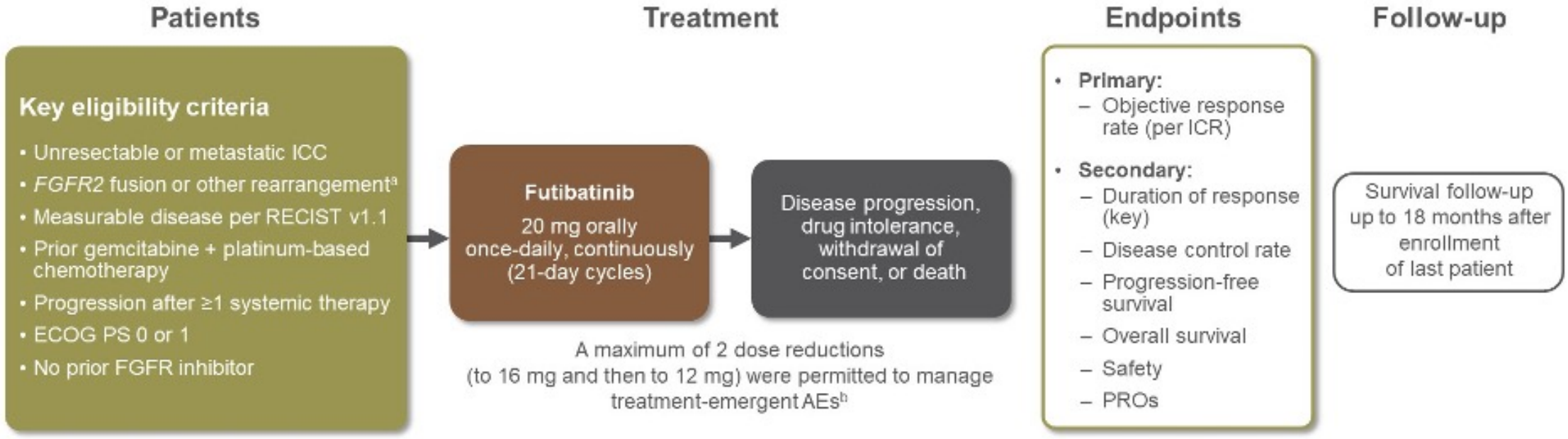
Lipika Goyal,[1] Funda Meric-Bernstam,[2] Antoine Hollebecque,[3] Chigusa Morizane,[4] Juan W. Valle,[5] Thomas B. Karasic,[6] Thomas A. Abrams,[7] Robin Kate Kelley,[8] Philippe Cassier,[9] Junji Furuse,[10] Heinz-Josef Klümpen,[11] Heung-Moon Chang,[12] Li-Tzong Chen,[13] Yoshito Komatsu,[14] Kunihiro Masuda,[15] Daniel Ahn,[16] Kate Li,[17] Karim A. Benhadji,[17] Volker Wacheck,[17] John A. Bridgewater[18]

[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Gustave Roussy, Drug Development Department (DITEP), F-94805, Villejuif, France; [4]National Cancer Center Hospital, Tokyo, Japan; [5]University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [6]Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [7]Dana-Farber Cancer Institute, Boston, MA, USA; [8]University of California, San Francisco, CA, USA; [9]Centre Léon-Bérard, Lyon, France; [10]Kyorin University, Faculty of Medicine, Tokyo, Japan; [11]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; [12]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [13]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan; [14]Hokkaido University Hospital Cancer Center, Hokkaido, Japan; [15]Tohoku University Graduate School of Medicine, Miyagi, Japan; [16]Mayo Clinic, Phoenix, AZ, USA; [17]Taiho Oncology, Inc., Princeton, NJ, USA; [18]UCL Cancer Institute, London, UK

ASCO 2022;Abstract 4009.

RTP RESEARCH TO PRACTICE

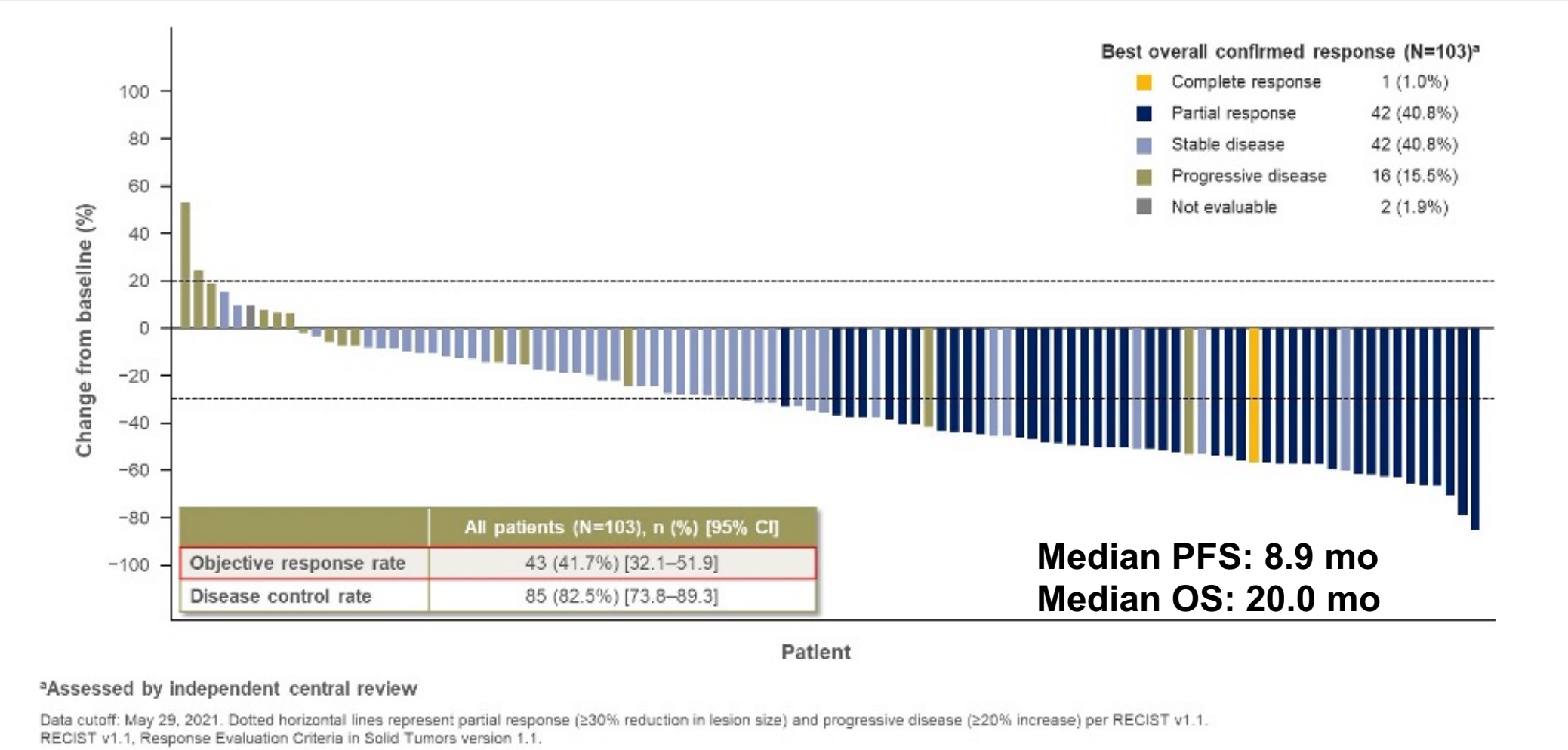
FOENIX-CCA2: Phase II Study Design



- At the time of the final data cutoff (May 29, 2021), median follow-up was 25.0 months, and 96/103 patients (93%) had discontinued treatment
- The median number of treatment cycles was 13.0, for a median treatment duration of 9.1 months

Goyal L et al. ASCO 2022;Abstract 4009.

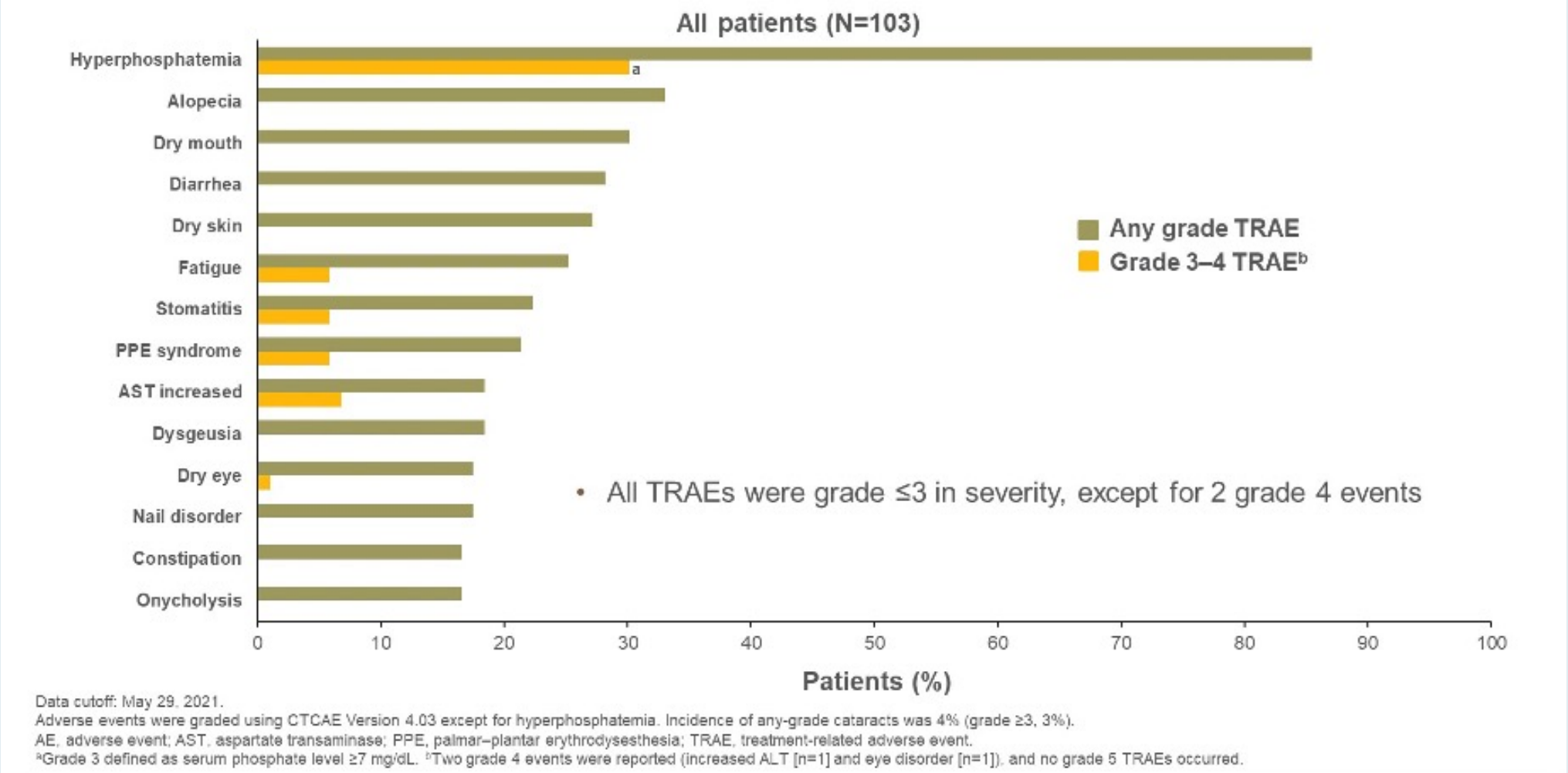
FOENIX-CCA2: Phase II Study of Futibatinib for Intrahepatic Cholangiocarcinoma with FGFR2 Fusions/Rearrangements



Goyal L et al. ASCO 2022;Abstract 4009.

RTP RESEARCH TO PRACTICE

FOENIX-CCA2: Most Common (≥15%) Treatment-Related Adverse Events (TRAEs) with Futibatinib for Intrahepatic Cholangiocarcinoma



Goyal L et al. ASCO 2022;Abstract 4009.

RTP RESEARCH TO PRACTICE

FOENIX-CCA2: Adverse Events (AEs) of Special Interest with Futibatinib for Intrahepatic Cholangiocarcinoma

AE of special interest by group term	Safety population (N=103), n (%)		
	Any grade[a]	Grade 3	Grade 4
Hyperphosphatemia[b]	94 (91)	32 (31)	0
Nail toxicities[c]	54 (52)	2 (2)	0
Increased ALT and AST[d]	28 (27)	12 (12)	1 (1)
Palmar–plantar erythrodysesthesia (PPE) syndrome	23 (22)	6 (6)	0
Rash[e]	9 (9)	0	0
Retinal disorders[f]	8 (8)	0	0

- One AE of special interest led to treatment discontinuation (PPE syndrome, grade 1)
- Hyperphosphatemia was manageable with phosphate-lowering therapy and dose modification
  - Median time to resolution of grade 3 hyperphosphatemia was 7.0 days (range, 2.0–26.0 days)

Goyal L et al. ASCO 2022;Abstract 4009.

Ongoing Phase III Studies of FGFR Inhibitors for Advanced Cholangiocarcinoma

Study	N	Eligibility	Randomization arms	Est primary completion
FIGHT-302	434	• Previously untreated • Unresectable and/or metastatic • FGFR2 rearrangement	• Pemigatinib • Gemcitabine + cisplatin	March 2027
PROOF	300	• Previously untreated • Unresectable and/or metastatic • FGFR2 fusion/translocation	• Infigratinib • Gemcitabine + cisplatin	January 2026
FOENIX-CCA3	216	• Previously untreated • Unresectable and/or metastatic • FGFR2 rearrangement	• Futibatinib • Gemcitabine + cisplatin	April 2025

www.clinicaltrials.gov. Accessed June 2022.

Research

JAMA Oncology | Original Investigation

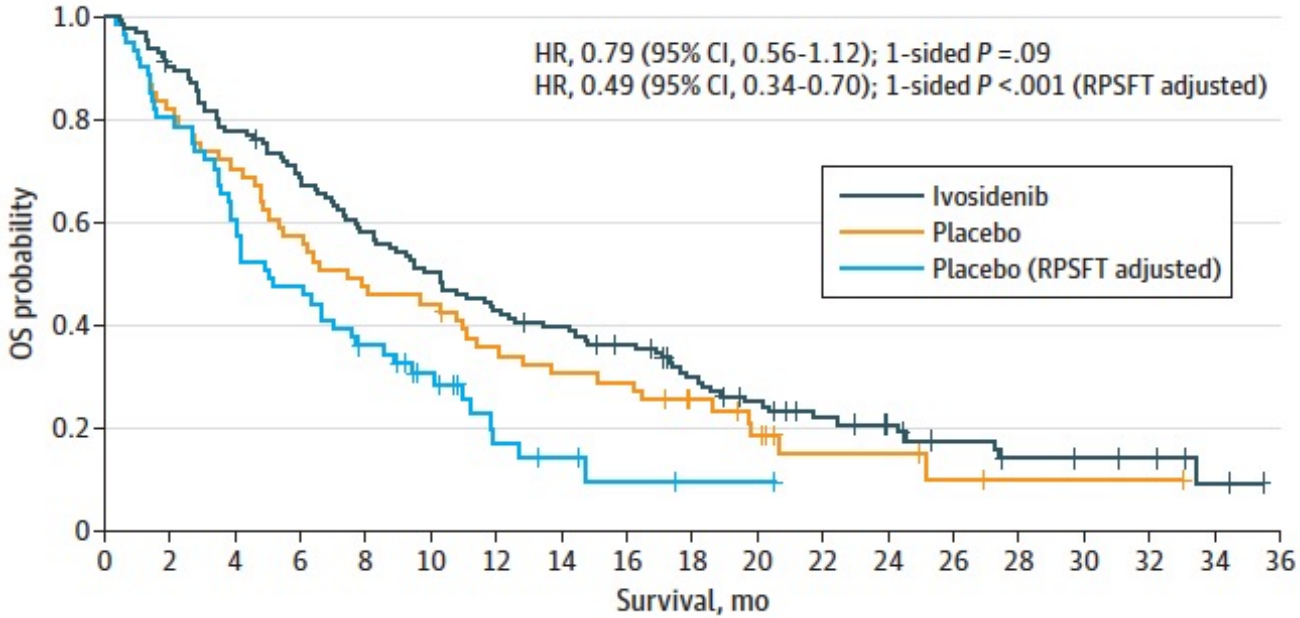
Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With *IDH1* Mutation

The Phase 3 Randomized Clinical ClarIDHy Trial

Andrew X. Zhu, MD, PhD; Teresa Macarulla, MD; Milind M. Javle, MD; R. Kate Kelley, MD; Sam J. Lubner, MD; Jorge Adeva, MD; James M. Cleary, MD; Daniel V. T. Catenacci, MD; Mitesh J. Borad, MD; John A. Bridgewater, PhD; William P. Harris, MD; Adrian G. Murphy, MD; Do-Youn Oh, MD; Jonathan R. Whisenant, MD; Maeve A. Lowery, MD; Lipika Goyal, MD; Rachna T. Shroff, MD; Anthony B. El-Khoueiry, MD; Christina X. Chamberlain, PhD; Elia Aguado-Fraile, PhD; Sung Choe, PhD; Bin Wu, PhD; Hua Liu, PhD; Camelia Gliser, BS; Shuchi S. Pandya, MD; Juan W. Valle, MD; Ghassan K. Abou-Alfa, MD

JAMA Oncol 2021;7(11):1669-77.

ClarIDHy: Final Overall Survival (OS) with Ivosidenib for Advanced Cholangiocarcinoma with an IDH1 Mutation



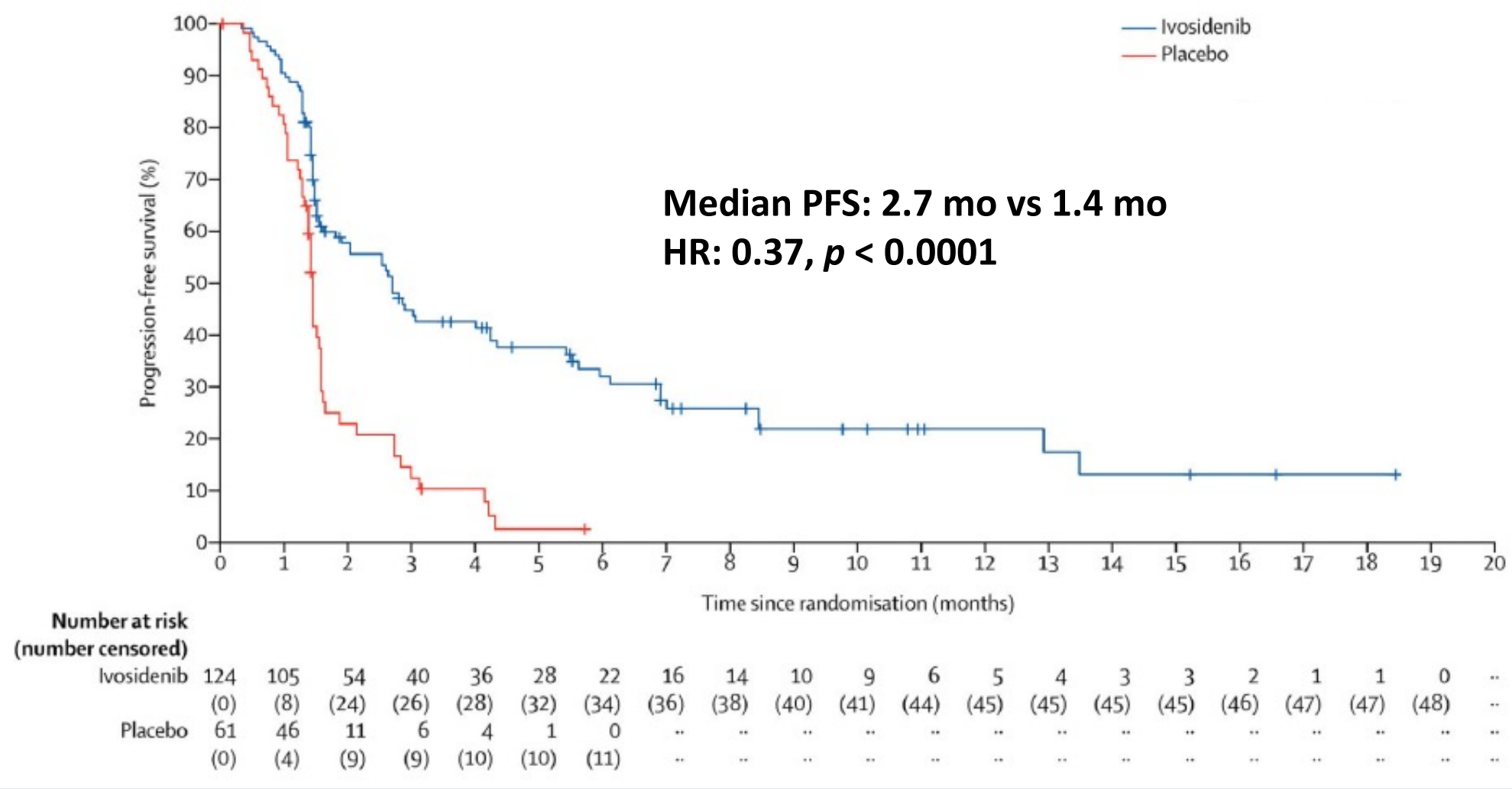
No. at risk

Ivosidenib	126	113	97	85	72	62	53	48	42	32	25	18	14	10	7	6	5	2
Placebo	61	50	43	35	29	27	21	18	17	12	8	4	4	2	1	1	1	
Placebo (RPSFT adjusted)	61	49	37	29	21	14	6	4	2	1	1							

Treatment group	Events/patients, No.	OS, median (95% CI), mo
Ivosidenib	100/126	10.3 (7.8-12.4)
Placebo	50/61	7.5 (4.8-11.1)
Placebo adjusted by RPSFT	49/61	5.1 (3.8-7.6)

Zhu AX et al. *JAMA Oncol* 2021;7(1):1669-77.

ClarIDHy: Progression-Free Survival (PFS) with Ivosidenib for Advanced Cholangiocarcinoma with an IDH1 Mutation



Abou-Alfa GK et al. *Lancet Oncol* 2020;21(6):796-807.

RTP RESEARCH TO PRACTICE

ClarIDHy: Select Adverse Events

Adverse Event	Ivosidenib (n = 121)			Placebo (n = 59)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Diarrhea	33%	2%	0	24%	2%	0
Fatigue	23%	3%	0	15%	0	0
Ascites	13%	7%	0	8%	7%	0
Electrocardiogram QT prolonged	8%	1%	0	2%	0	0
ALT increased	7%	2%	0	2%	0	0
AST increased	6%	5%	0	3%	2%	0
Hyponatremia	5%	3%	2%	2%	8%	2%
Blood bilirubin increased	4%	6%	0	5%	2%	0

Abou-Alfa GK et al. *Lancet Oncol* 2020;21(6):796-807.

Dabrafenib/Trametinib Combination Granted Accelerated Approval for a Tumor-Agnostic Indication for Solid Tumors with BRAF V600E Mutation

Press Release: June 23, 2022

"The US Food and Drug Administration (FDA) granted accelerated approval for dabrafenib + trametinib for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. In accordance with the Accelerated Approval Program, continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

The FDA approval was based on clinical efficacy and safety demonstrated in three clinical trials. In the Phase II ROAR (Rare Oncology Agnostic Research) basket study and the NCI-MATCH Subprotocol H study, dabrafenib + trametinib resulted in overall response rates of up to 80% in patients with BRAF V600E solid tumors, including high- and low-grade glioma, biliary tract cancer and certain gynecological and gastrointestinal cancers. An additional study (Study X2101) demonstrated the clinical benefit and acceptable safety profile of dabrafenib + trametinib in pediatric patients.

The safety profile of dabrafenib + trametinib observed in these studies was consistent with the known safety profile in other approved indications."

https://www.novartis.com/news/media-releases/novartis-tafinlar-mekinist-receives-fda-approval-first-tumor-agnostic-indication-braf-v600e-solid-tumors

RTP RESEARCH TO PRACTICE

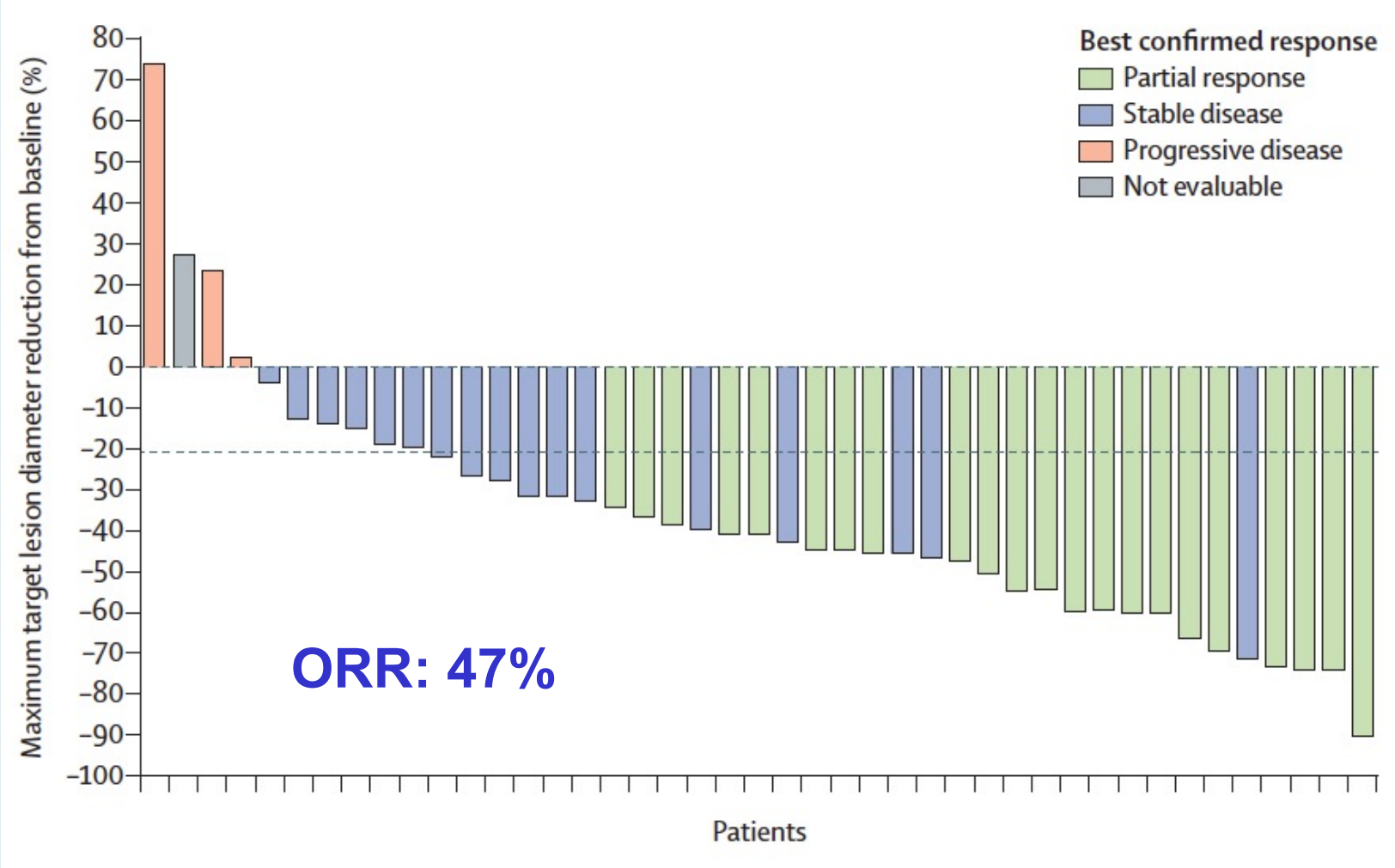
Articles

Dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial

Vivek Subbiah, Ulrik Lassen, Elena Élez, Antoine Italiano, Giuseppe Curigliano, Milind Javle, Filippo de Braud, Gerald W Prager, Richard Greil, Alexander Stein, Angelica Fasolo, Jan H M Schellens, Patrick Y Wen, Kert Viele, Aislyn D Boran, Eduard Gasal, Paul Burgess, Palanichamy Ilankumaran, Zev A Wainberg

***Lancet Oncol* 2020;21(9):1234-43.**

ROAR Phase II Basket Trial: Dabrafenib/Trametinib Combination for Cholangiocarcinoma with a BRAF V600E Mutation



Subbiah V et al. *Lancet Oncol* 2020;21(9):1234-43.

RTP RESEARCH TO PRACTICE

ROAR Phase II Basket Trial: Select Adverse Events with Dabrafenib/Trametinib for Cholangiocarcinoma with a BRAF V600E Mutation

	Grade 1-2	Grade 3	Grade 4
Increased gamma-glutamyltransferase	7 (16%)	5 (12%)	0
Pyrexia	26 (60%)	3 (7%)	0
Decreased WBC count	7 (16%)	3 (7%)	0
Hypertension	2 (5%)	3 (7%)	0
Hyperglycemia	6 (14%)	2 (5%)	0

Subbiah V et al. *Lancet Oncol* 2020;21(9):1234-43.

RTP RESEARCH TO PRACTICE

Future Directions in the Management of Biliary Tract Cancers

NEJM Evidence

Published June 1, 2022

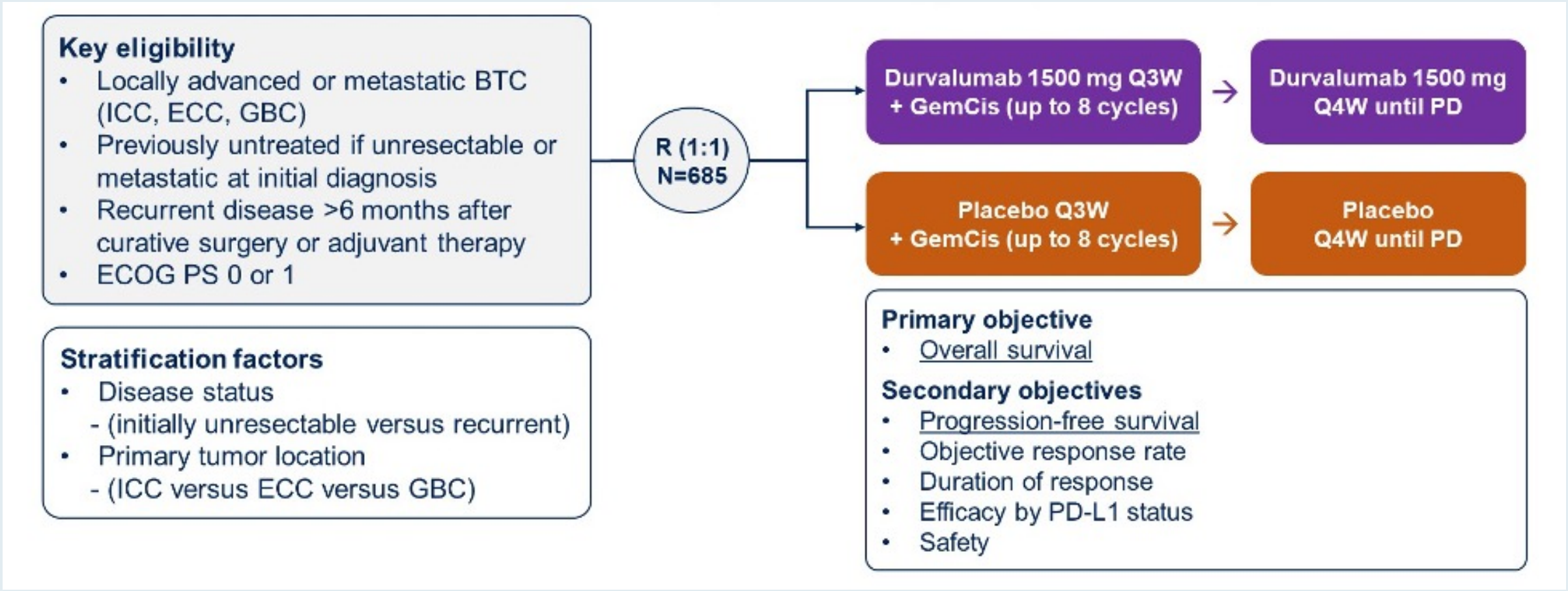
DOI: 10.1056/EVIDoa2200015

ORIGINAL ARTICLE

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

Do-Youn Oh, M.D., Ph.D.,[1] Aiwu Ruth He, M.D., Ph.D.,[2] Shukui Qin, M.D.,[3] Li-Tzong Chen, M.D., Ph.D.,[4,5,6] Takuji Okusaka, M.D., Ph.D.,[7] Arndt Vogel, M.D.,[8] Jin Won Kim, M.D., Ph.D.,[9] Thatthan Suksomboon charoen, M.D.,[10] Myung Ah Lee, M.D., Ph.D.,[11] Masayuki Kitano, M.D., Ph.D.,[12] Howard Burris, M.D.,[13] Mohamed Bouattour, M.D.,[14] Suebpong Tanasanvimon, M.D.,[15] Mairéad G. McNamara, M.B., Ph.D.,[16] Renata Zaucha, M.D., Ph.D.,[17] Antonio Avallone, M.D.,[18] Benjamin Tan, M.D.,[19] Juan Cundom, M.D.,[20] Choong-kun Lee, M.D., Ph.D.,[21] Hidenori Takahashi, M.D., Ph.D.,[22] Masafumi Ikeda, M.D., Ph.D.,[23] Jen-Shi Chen, M.D.,[24] Julie Wang, Ph.D.,[25] Mallory Makowsky, Pharm.D.,[25] Nana Rokutanda, M.D., Ph.D.,[25] Philip He, Ph.D.,[25,26] John F. Kurland, Ph.D.,[25] Gordon Cohen, M.D., M.P.H.,[25] and Juan W. Valle, M.D.[16]

TOPAZ-1 Phase III Trial Schema

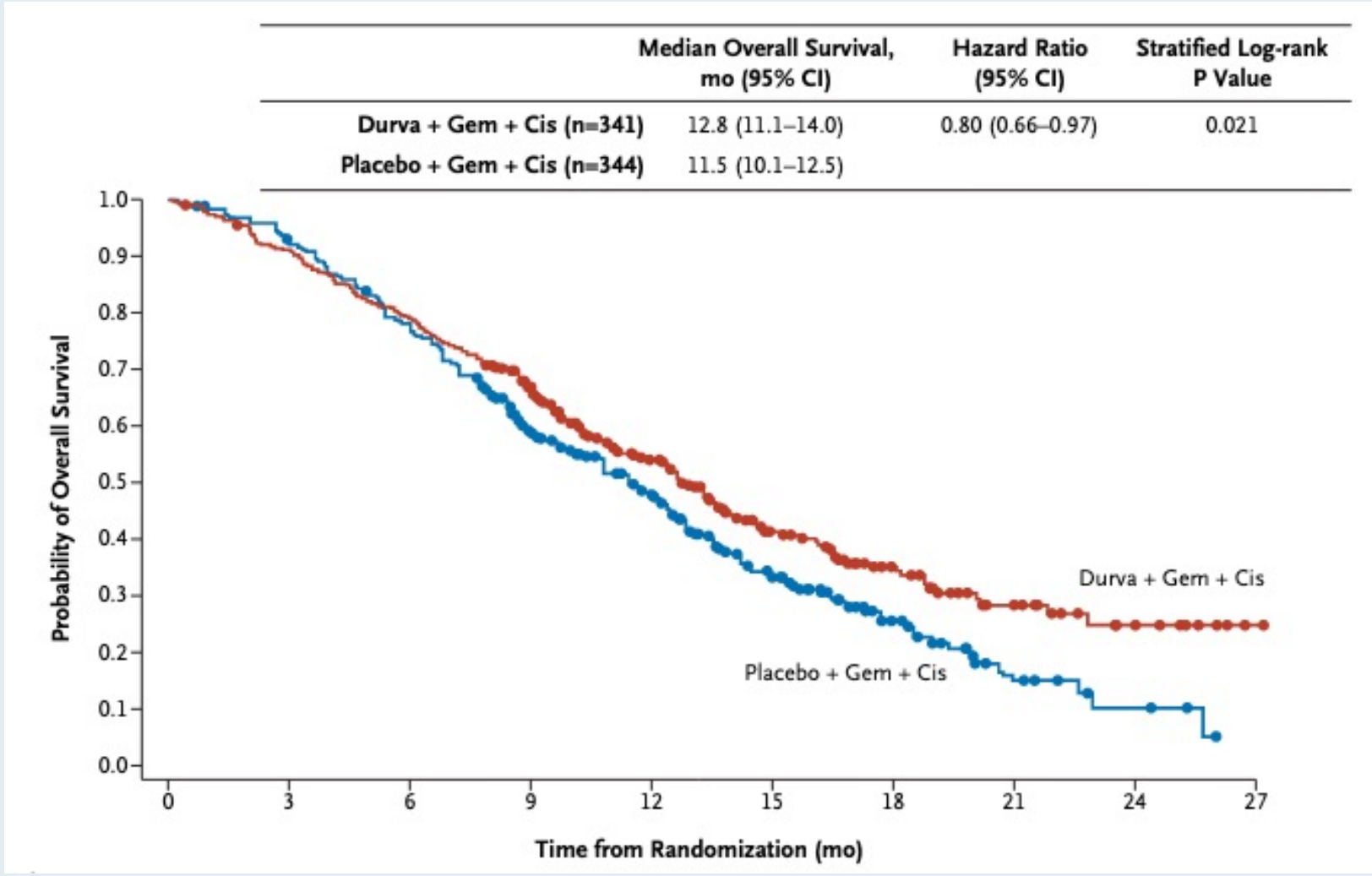


BTC = biliary tract cancer

Oh D-Y et al. Gastrointestinal Cancers Symposium 2022;Abstract 378.

TOPAZ-1: Primary Overall Survival Endpoint with Durvalumab and Gemcitabine/Cisplatin for Advanced Biliary Tract Cancer

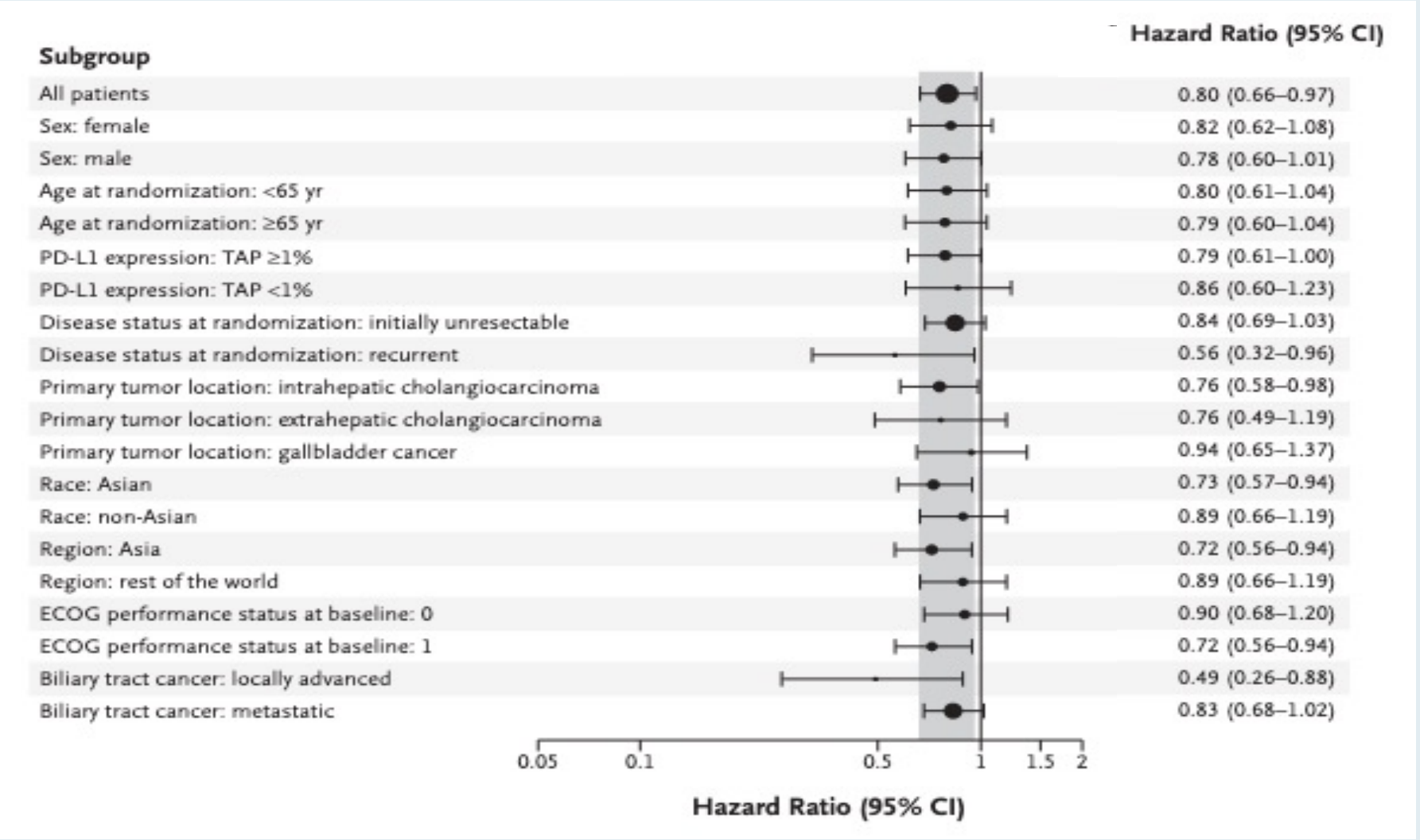
	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		



Oh D-Y et al. *NEJM Evidence*, June 1, 2022.

RTP RESEARCH TO PRACTICE

TOPAZ-1: Overall Survival Subgroup Analysis



Oh D-Y et al. *NEJM Evidence*, June 1, 2022.

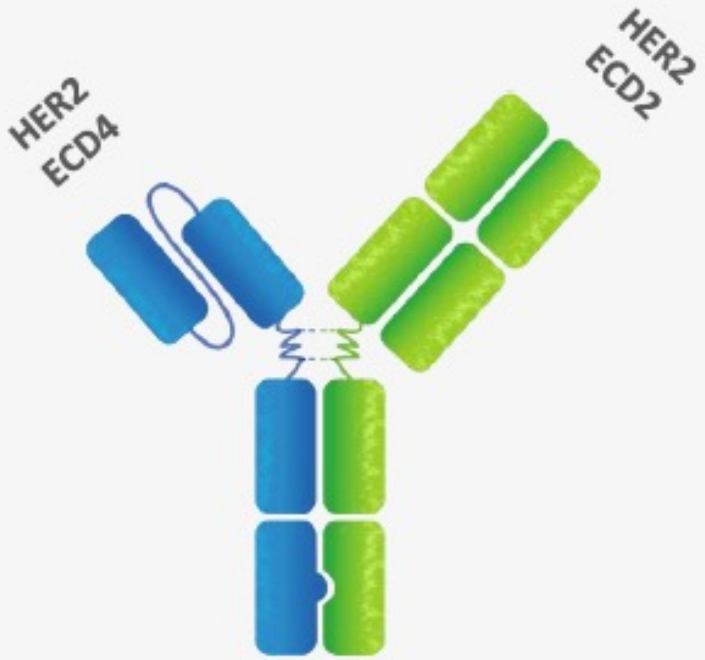
TOPAZ-1: Adverse Event Summary

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=338)	Placebo plus Gemcitabine and Cisplatin (n=342)
Adverse events — no. (%)		
Any grade	336 (99.4)	338 (98.8)
Serious	160 (47.3)	149 (43.6)
Grade 3 or 4	256 (75.7)	266 (77.8)
Leading to discontinuation of any study treatment	44 (13.0)	52 (15.2)
Leading to death	12 (3.6)	14 (4.1)
Treatment-related adverse events — no. (%)		
Any grade	314 (92.9)	308 (90.1)
Serious	53 (15.7)	59 (17.3)
Grade 3 or 4	212 (62.7)	222 (64.9)
Leading to discontinuation of any study treatment	30 (8.9)	39 (11.4)
Leading to death*	2 (0.6)	1 (0.3)

Oh D-Y et al. *NEJM Evidence*, June 1, 2022.

Zanidatamab: A Bispecific HER2-Targeted Antibody

- A biparatopic antibody that simultaneously binds two distinct sites on HER2: ECD4 (targeted by trastuzumab) and ECD2 (targeted by pertuzumab)
- Unique binding results in multiple mechanisms of action of zanidatamab that lead to improved binding, clustering, and receptor internalization and downregulation, inhibition of ligand-dependent and -independent proliferation, and potent activation of antibody-dependent cellular cytotoxicity



ECD=extracellular domain

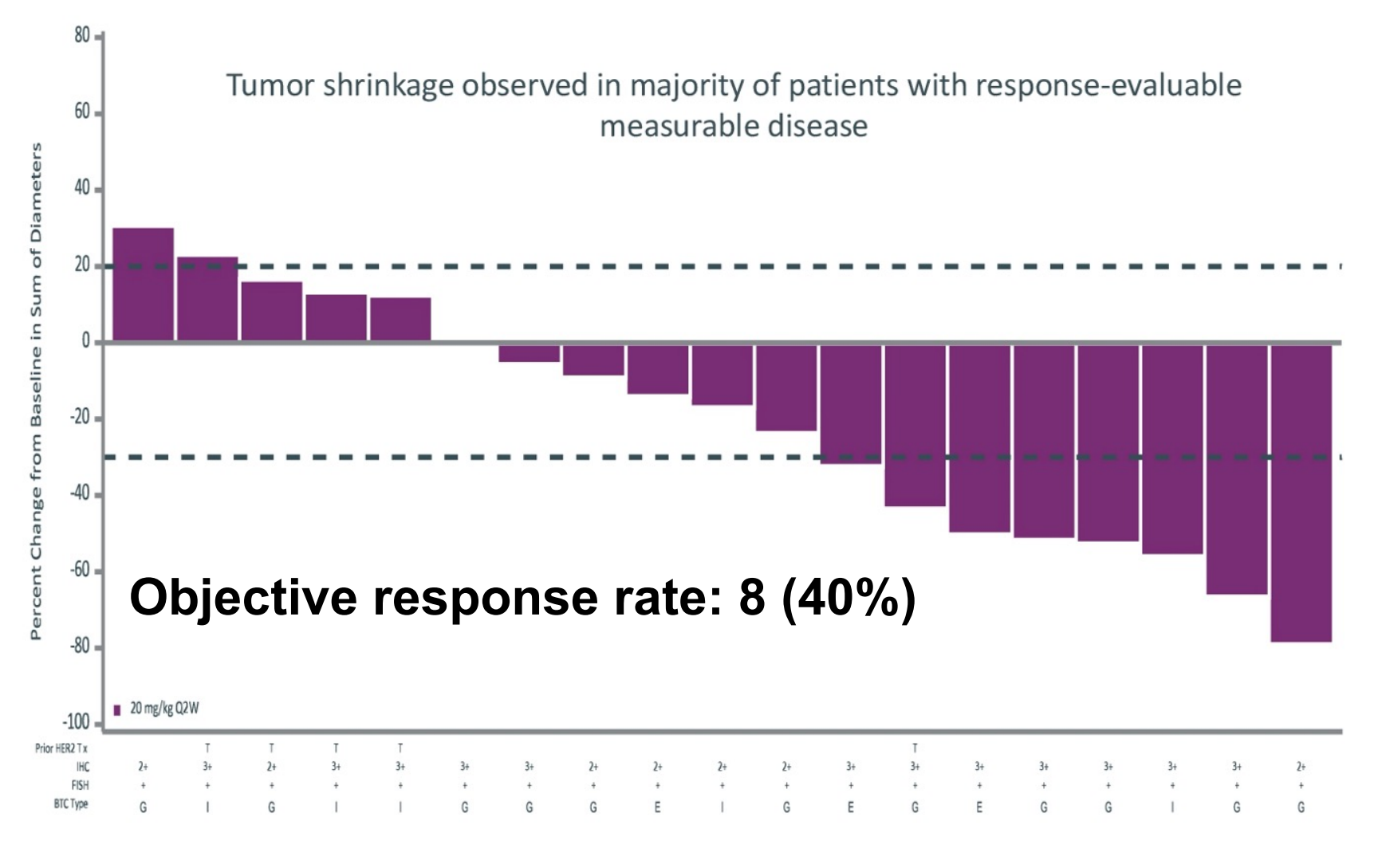
Pant S et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS352.

Zanidatamab (ZW25) in HER2-Positive Biliary Tract Cancer (BTC): Results from a Phase I Study

Meric-Bernstam F et al.

Gastrointestinal Cancers Symposium 2021;Abstract 299.

Antitumor Activity of Zanidatamab in a Phase I Study for Advanced Biliary Tract Cancer



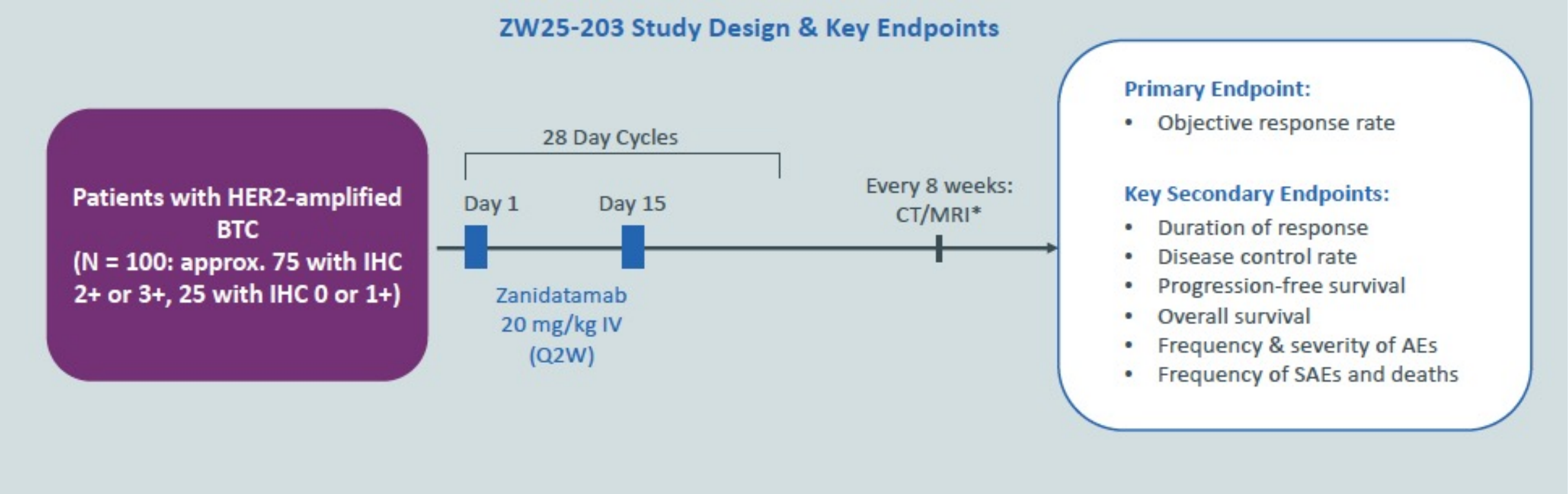
Meric-Bernstam F et al. Gastrointestinal Cancers Symposium 2021;Abstract 299.

Adverse Events (AEs) Associated with Zanidatamab in a Phase I Study for Advanced Biliary Tract Cancer

	N = 21
Patients with treatment-emergent AEs	21 (100%)
Patients with zanidatamab-related AEs (≥15% of patients)	
Any AE	15 (71%)
Diarrhea	9 (43%)
Infusion-related reaction	7 (33%)

Meric-Bernstam F et al. Gastrointestinal Cancers Symposium 2021;Abstract 299.

HERIZON-BTC-01 (ZW25-203): Phase IIb Study of Zanidatamab Monotherapy for Advanced or Metastatic HER2-Amplified Biliary Tract Cancer



Pant S et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS352.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

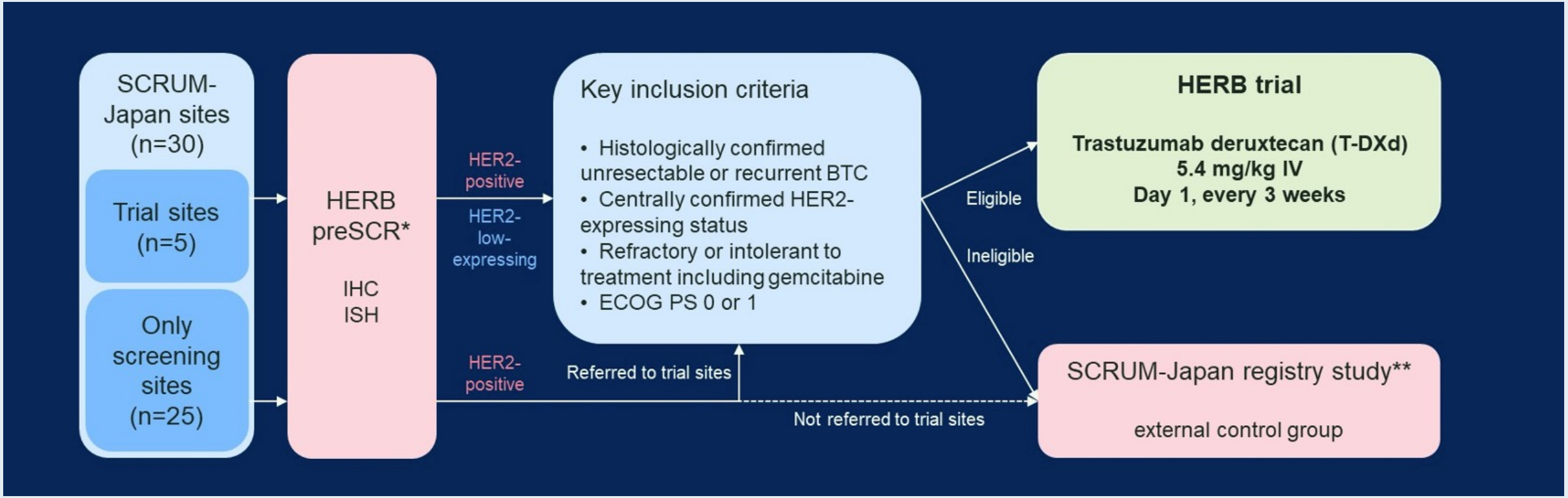
Abstract 4006.

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)

Akihiro Ohba[1], Chigusa Morizane[1], Yasuyuki Kawamoto[2], Yoshito Komatsu[2], Makoto Ueno[3], Satoshi Kobayashi[3], Masafumi Ikeda[4], Mitsuhito Sasaki[4], Junji Furuse[5], Naohiro Okano[5], Nobuyoshi Hiraoka[1], Hiroshi Yoshida[1], Aya Kuchiba[1], Ryo Sadachi[1], Kenichi Nakamura[1], Naoko Matsui[1], Yoshiaki Nakamura[4], Wataru Okamoto[6], Takayuki Yoshino[4], Takuji Okusaka[1]

[1]National Cancer Center Hospital, [2]Hokkaido University Hospital, [3]Kanagawa Cancer Center, [4]National Cancer Center Hospital East, [5]Kyorin University Faculty of Medicine, [6]Hiroshima University Hospital

HERB: A Phase II Study of Trastuzumab Deruxtecan (T-DXd) for HER2-Expressing Biliary Tract Cancer



Ohba A et al. ASCO 2022;Abstract 4006.

HERB Primary Endpoint: Confirmed Objective Response Rate (ORR) by Blinded Independent Central Review with T-DXd for Biliary Tract Cancer

- Tumor response

*: P =0.01

	HER2-positive (n=22)	HER2-low-expressing (n=8)	All pts (n=30)
Confirmed ORR (90% CI) (95% CI)	**36.4% (19.6-56.1)*** (17.2–59.3)	12.5% – (0.3–52.7)	30.0% – (14.7–49.4)
Confirmed DCR (95% CI)	81.8% (59.7–94.8)	75.0% (34.9–96.8)	80.0% (61.4–92.3)
Confirmed best response, n (%)			
CR	2 (9.1)	0 (0)	2 (6.7)
PR	6 (27.3)	1 (12.5)	7 (23.3)
SD	10 (45.5)	5 (62.5)	15 (50.0)
PD	3 (13.6)	1 (12.5)	4 (13.3)
NE	1 (4.5)	1 (12.5)	2 (6.7)

- Best percentage change

Ohba A et al. ASCO 2022;Abstract 4006.

HERB Secondary Endpoints: Progression-Free Survival (PFS) and Overall Survival (OS) with T-DXd for Biliary Tract Cancer

	HER2-positive disease (n = 22)	HER2-low expressing disease (n = 8)
Median PFS	5.1 mo	3.5 mo
6-month PFS rate	40.9%	0
Median OS	7.1 mo	8.9 mo
6-month OS rate	63.6%	75.0%

Ohba A et al. ASCO 2022;Abstract 4006.

HERB: Treatment-Emergent Adverse Events with T-DXd for Biliary Tract Cancer

Event	Any grade, n (%)	Grade ≥ 3, n (%)
Anemia	22 (68.8)	17 (53.1)
Neutrophil count decreased	18 (56.3)	10 (31.3)
White blood cell count decreased	18 (56.3)	10 (31.3)
Platelet count decreased	14 (43.8)	3 (9.4)
Nausea	14 (43.8)	0 (0)
Alopecia	13 (40.6)	0 (0)
Anorexia	12 (37.5)	1 (3.1)
Lymphocyte count decreased	11 (34.4)	7 (21.9)
Fatigue / Malaise	11 (34.4)	0 (0)
Interstitial lung disease / Pneumonitis	8 (25.0)	4 (12.5)
Hypoalbuminemia	7 (21.9)	1 (3.1)
Vomiting	7 (21.9)	0 (0)
Mucositis oral	5 (15.6)	0 (0)

Ohba A et al. ASCO 2022;Abstract 4006.

HERB: Interstitial Lung Disease (ILD)/Pneumonitis with T-DXd for Biliary Tract Cancer

	ILDs (n=8)*
Grade, n (%) 1 2 3 5	 3 (37.5) 1 (12.5) 2 (25.0) 2 (25.0)
Median time to onset (range), days	124 (35–247)**
Median Age (range), years	73 (51–75)
Sex, female, n (%)	3 (37.5)
Number of prior regimens, n (%) 1 ≥ 2	 4 (50.0) 4 (50.0)
HER2 status of IHC/ISH, n (%) 3+/+ 2+/+	 5 (62.5) 3 (37.5)
Lung metastasis, n (%)	3 (37.5)
Smoking history, n (%)	3 (37.5)
Biliary drainage, n (%)	4 (50.0)

Ohba A et al. ASCO 2022;Abstract 4006.

ASCO Gastrointestinal Cancers Symposium

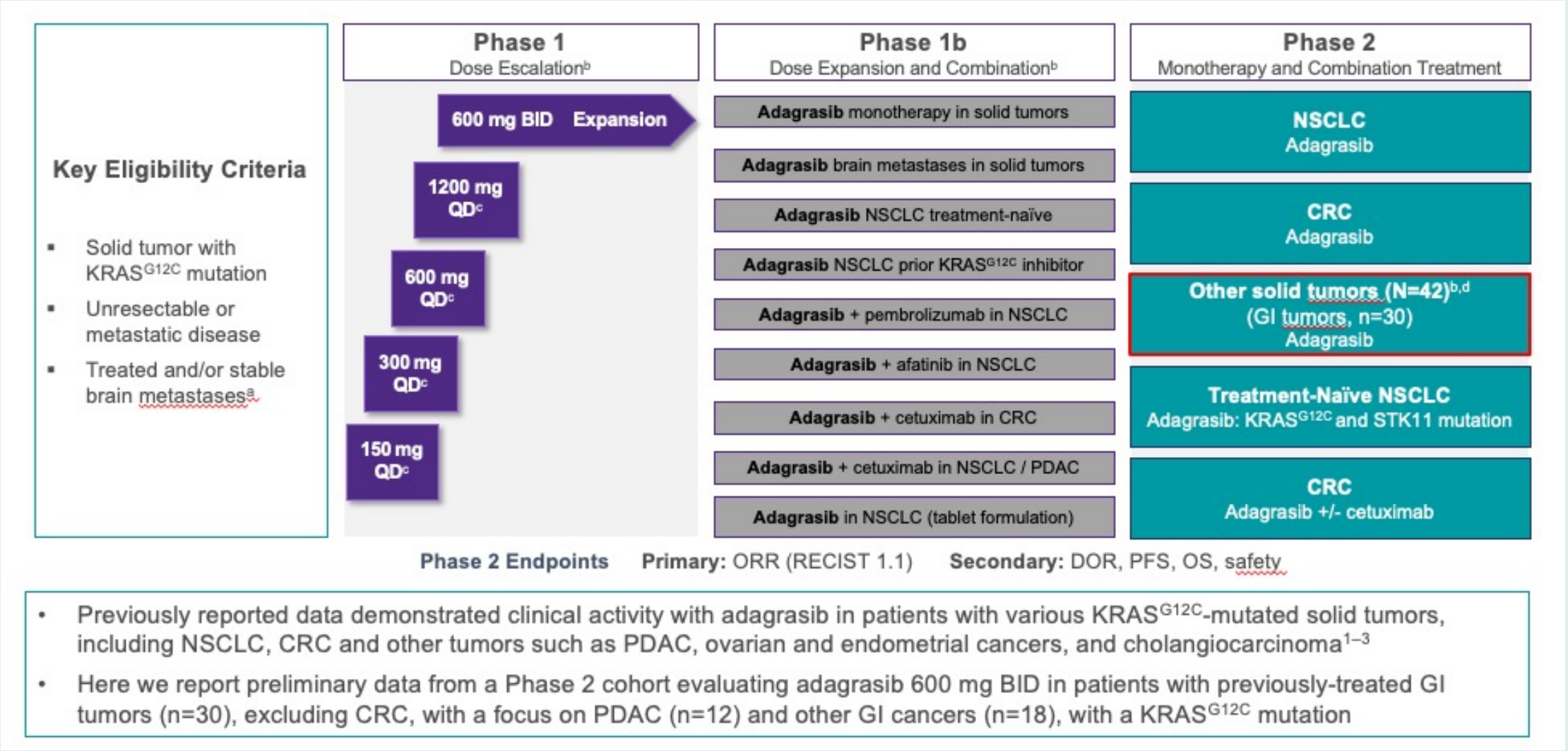
Abstract 519.

KRYSTAL-1: Updated Activity and Safety of Adagrasib (MRTX849) in Patients (Pts) With Unresectable or Metastatic Pancreatic Cancer (PDAC) and Other Gastrointestinal (GI) Tumors Harboring a KRAS^{G12C} Mutation

TS Bekaii-Saab[1], AI Spira[2], R Yaeger[3], GL Buchschacher Jr.[4], AJ McRee[5], JK Sabari[6], ML Johnson[7], M Barve[8], N Hafez[9], K Velastegui[10], JG Christensen[10], T Kheoh[10], H Der-Torossian[10], SM Gadgeel[11]

[1]Department of Medical Oncology and Hematology, Mayo Clinic, Scottsdale, Arizona, USA; [2]Virginia Cancer Specialists, Fairfax, Virginia, NEXT Oncology, Virginia, US Oncology Research, The Woodlands, Texas, USA; [3]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA; [4]Kaiser Permanente Southern California, Los Angeles, California, USA; [5]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA; [6]Perlmutter Cancer Center, New York University Langone Health, New York, New York, USA; [7]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, USA; [8]Mary Crowley Cancer Research, Dallas, Texas, USA; [9]Yale Cancer Center, New Haven, Connecticut, USA; [10]Mirati Therapeutics, Inc., San Diego, California, USA; [11]Henry Ford Cancer Institute/Henry Ford Health System, Detroit, Michigan, USA

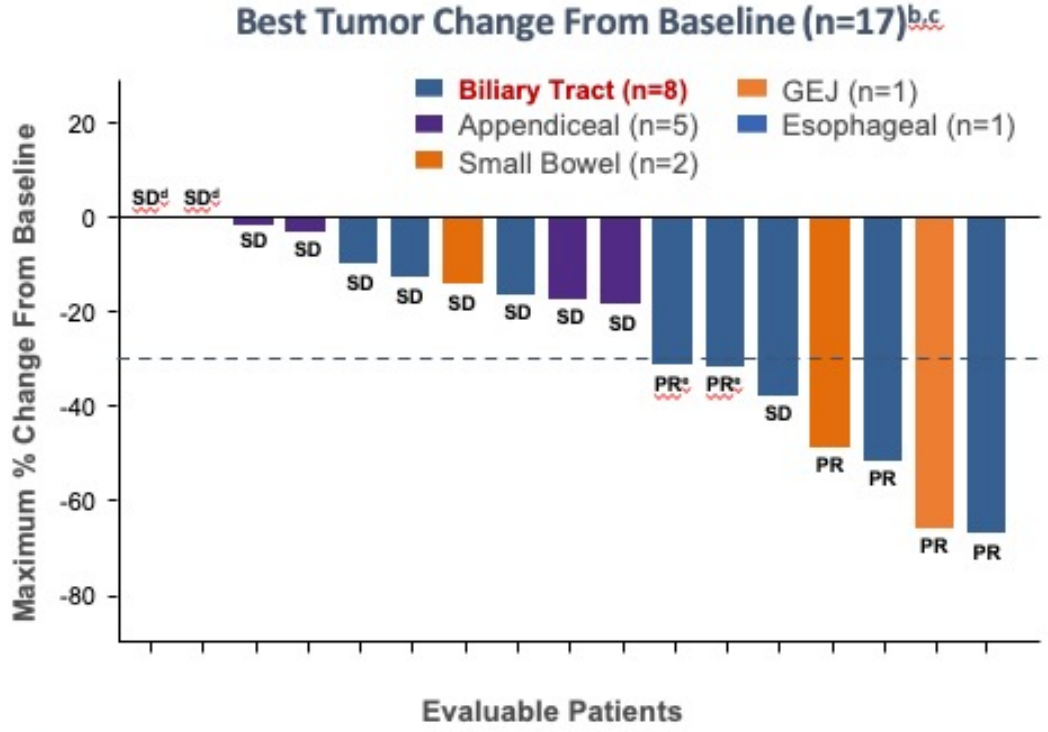
KRYSTAL-1: Trial Schema

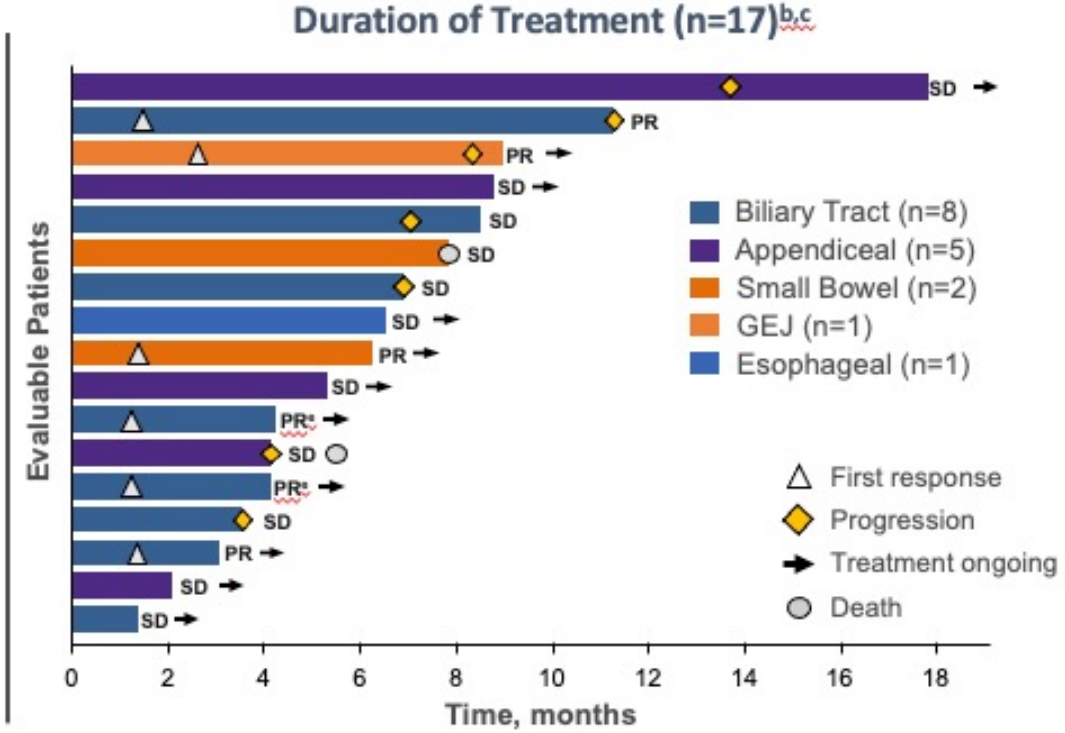


- Previously reported data demonstrated clinical activity with adagrasib in patients with various KRAS^{G12C}-mutated solid tumors, including NSCLC, CRC and other tumors such as PDAC, ovarian and endometrial cancers, and cholangiocarcinoma[1–3]
- Here we report preliminary data from a Phase 2 cohort evaluating adagrasib 600 mg BID in patients with previously-treated GI tumors (n=30), excluding CRC, with a focus on PDAC (n=12) and other GI cancers (n=18), with a KRAS^{G12C} mutation

Bekaii-Saab TS et al. Gastrointestinal Cancers Symposium 2022;Abstract 519.

KRYSTAL-1: Best Tumor Change from Baseline and Duration of Treatment with Adagrasib for Other Gastrointestinal Tumors





- Response rate:
  - **Biliary tract cancer: 50% (4/8), including 2 unconfirmed PRs**
  - GEJ and small bowel cancer: 1 PR each
- DCR: 100% (17/17 patients)

- Median TTR: 1.3 months
- Median DOR: 7.85 months
- Median PFS: 7.85 months (95% CI 6.90–11.30)
- Treatment ongoing in 65% (11/17) of patients

Bekaii-Saab TS et al. Gastrointestinal Cancers Symposium 2022;Abstract 519.

WORLD PREMIERE OF AN ENDURING CME ACTIVITY

Oncology Today: Management of Unresectable Stage III Non-Small Cell Lung Cancer

Monday, August 1, 2022
5:00 PM – 6:00 PM ET

Faculty

Jeffrey Bradley, MD

David R Spigel, MD

Moderator

Neil Love, MD

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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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