What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Hybrid Symposium Series Held During the 49th Annual ONS Congress

Hepatobiliary Cancers

Saturday, April 27, 2024
6:00 AM – 7:30 AM

Faculty

Blanca Ledezma, MSN, NP, AOCNP
Stacey Stein, MD
Amanda K Wagner, APRN-CNP, AOCNP
Mark Yarchoan, MD

Moderator

Neil Love, MD

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Faculty

Blanca Ledezma, MSN, NP, AOCNP
UCLA Santa Monica Hematology/Oncology
Santa Monica, California

Stacey Stein, MD
Associate Professor of Medicine
Assistant Medical Director of the Clinical Trials Office
Yale Cancer Center
Yale School of Medicine
New Haven, Connecticut

Amanda K Wagner, APRN-CNP, AOCNP
GI Malignancies
The James Cancer Hospital
The Ohio State University
Columbus, Ohio

Mark Yarchoan, MD
Associate Professor of Medical Oncology
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Ms Ledezma — Disclosures

Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Lilly

Dr Stein — Disclosures

Advisory Committees	AbbVie Inc, Eisai Inc, Genentech, a member of the Roche Group
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Merck
Data and Safety Monitoring Boards/ Committees	Aethlon Medical Inc, Genentech, a member of the Roche Group

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Ms Wagner — Disclosures

No relevant conflicts of interest to disclose

Dr Yarchoan — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group
Co-Founder with Equity	Adventris Pharmaceuticals
Research Funding (to Johns Hopkins)	Bristol Myers Squibb, Exelixis Inc, Genentech, a member of the Roche Group, Incyte Corporation

Commercial Support

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Research To Practice NCPD Planning Committee Members, Staff and Reviewers

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

This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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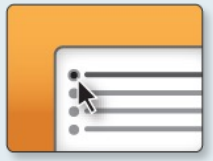
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

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

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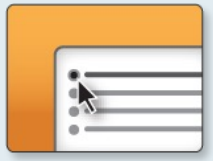
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

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

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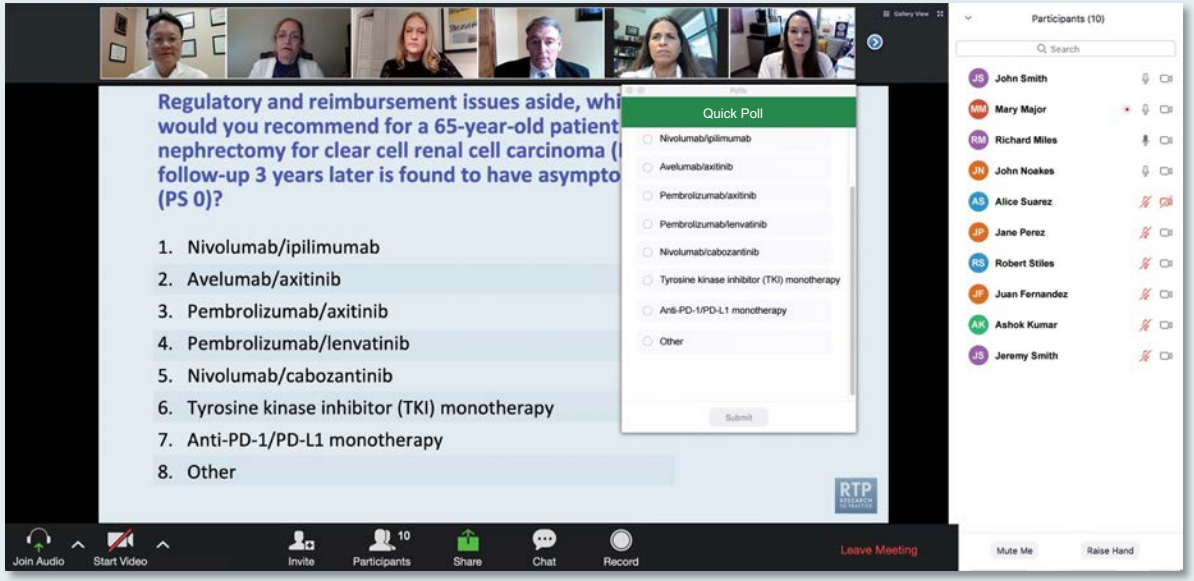
Clinicians, Please Complete the Pre- and Postmeeting Surveys



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About the Enduring Program

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

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“What I Tell My Patients”
Sixteenth Annual RTP-ONS NCPD Symposium Series

Wednesday April 24	**Hormone Receptor–Positive Breast Cancer** 6:00 PM – 8:00 PM ET
Thursday April 25	**Endometrial Cancer** 6:00 AM – 7:30 AM ET
	Antibody–Drug Conjugates 12:15 PM – 1:45 PM ET
	Chronic Lymphocytic Leukemia and Bispecific Antibodies in Lymphoma 6:00 PM – 8:00 PM ET
Friday April 26	**Head and Neck Cancer** 6:00 AM – 7:30 AM ET
	Non–Small Cell Lung Cancer with an EGFR Mutation 12:15 PM – 1:45 PM ET
	Ovarian Cancer 6:00 PM – 7:30 PM ET
Saturday April 27	**Hepatobiliary Cancers** 6:00 AM – 7:30 AM ET
	Myelofibrosis 12:15 PM – 1:45 PM ET
	Gastroesophageal and Colorectal Cancers 6:00 PM – 8:00 PM ET
Wednesday, May 1	**LIVE WEBINAR — Prostate Cancer** 7:00 PM – 8:00 PM ET

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Consulting Nurse Faculty

Jacqueline Broadway-Duren, PhD, DNP, APRN, FNP-BC
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Kathleen D Burns, RN, MSN, AGACNP-BC, OCN
City of Hope Comprehensive Cancer Center
Duarte, California

Sonia Glennie, ARNP, MSN, OCN
Swedish Cancer Institute Center for Blood Disorders
Seattle, Washington

Amy Goodrich, CRNP
The Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

Jessica Mitchell, APRN, CNP, MPH
Mayo Clinic College of Medicine and Science
Rochester, Minnesota

Tiffany A Richards, PhD, ANP-BC, AOCNP
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Kimberly A Spickes, MNSc, RN, APRN, OCN, ACNP-BC
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Ronald Stein, JD, MSN, NP-C, AOCNP
USC Norris Comprehensive Cancer Center
Los Angeles, California

https://www.ResearchToPractice.com/ONS2024Clips

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RTP RESEARCH TO PRACTICE

Agenda

Introduction

Part 1: Hepatocellular Carcinoma

Part 2: Biliary Tract Cancers

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Part 2: Biliary Tract Cancers

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Consulting Nursing Faculty Comments

Psychosocial impact, self-advocacy and spirituality

Kimberly A Spickes, MNSc, RN, APRN, OCN, ACNP-BC

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Agenda

Introduction

Part 1: Hepatocellular Carcinoma (HCC)

- Adjuvant Therapy for Early-Stage HCC
- Role of Immunotherapy in Intermediate-Stage HCC
- First-Line Therapy for Advanced HCC

Part 2: Biliary Tract Cancers

Agenda

Introduction

Part 1: Hepatocellular Carcinoma (HCC)

- **Adjuvant Therapy for Early-Stage HCC**
- Role of Immunotherapy in Intermediate-Stage HCC
- First-Line Therapy for Advanced HCC

Part 2: Biliary Tract Cancers

The Current and Future Use of Adjuvant Systemic Therapy for Early-Stage Hepatocellular Carcinoma (HCC)

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Long-term outcomes with traditional treatment approaches for early-stage HCC; clinical features that impart a high risk of disease recurrence**
- **Historical data with adjuvant therapeutic approaches, such as sorafenib, for patients with HCC**
- **Design, eligibility criteria and key endpoints of the Phase III IMbrave050 study of atezolizumab in combination with bevacizumab for patients with high-risk HCC after curative resection or ablation**
- **Improved recurrence-free survival with adjuvant atezolizumab/bevacizumab compared to active surveillance in the IMbrave050 trial; clinical and research implications**
- **Other ongoing Phase III studies evaluating adjuvant immune checkpoint inhibitor therapy for HCC**

Amanda K Wagner, APRN-CNP, AOCNP

What I tell my patients with earlier-stage HCC about the goals of adjuvant therapy and what to expect from it

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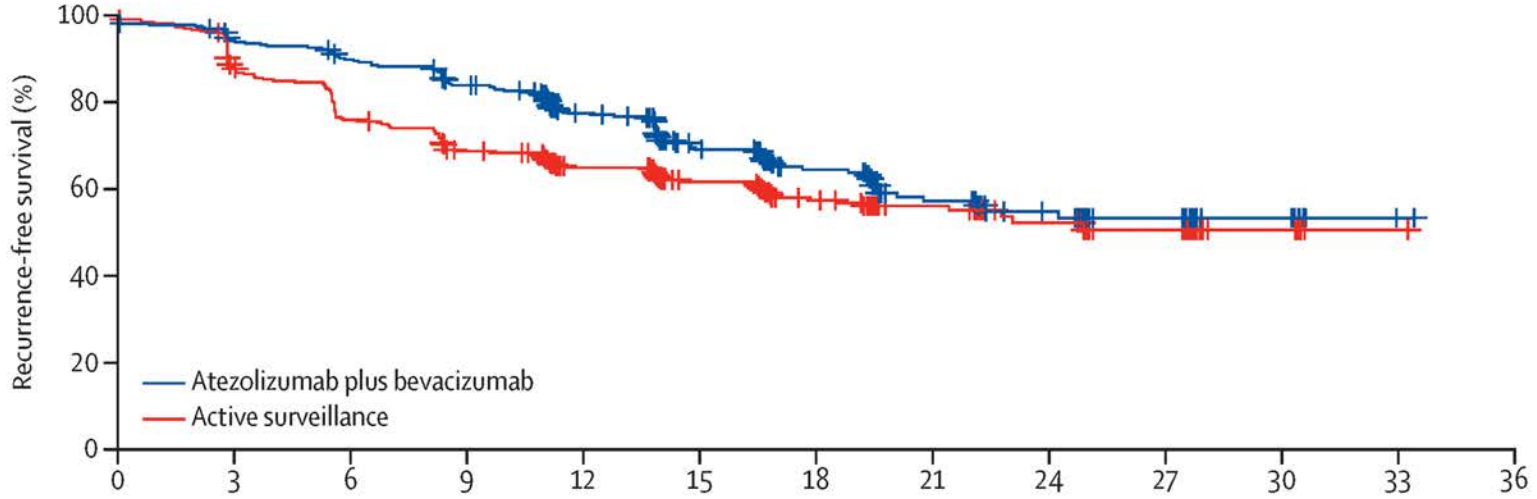
IMbrave050 Primary Endpoint: Recurrence-Free Survival by Independent Assessment

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



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

Qin S et al. *Lancet* 2023; 402: 1835–47

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- Adjuvant Therapy for Early-Stage HCC
- **Role of Immunotherapy in Intermediate-Stage HCC**
- First-Line Therapy for Advanced HCC

Part 2: Biliary Tract Cancers

The Potential Role of Immunotherapeutic Strategies for Intermediate-Stage HCC

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Historical outcomes associated with locoregional treatments, such as transarterial chemoembolization (TACE), for patients with intermediate-stage HCC**
- **Design, eligibility criteria and key efficacy and safety endpoints of the Phase III EMERALD-1 trial comparing durvalumab in combination with TACE with or without bevacizumab to TACE alone for patients with locoregional HCC not amenable to curative therapy**
- **Recently presented findings indicating a progression-free survival advantage with durvalumab, TACE and bevacizumab compared to TACE alone in the EMERALD-1 trial**
- **Potential clinical role of durvalumab with TACE and bevacizumab in therapy for intermediate-stage HCC**

Blanca Ledezma, MSN, NP, AOCNP

What I tell my patients with intermediate-stage HCC who are about to undergo TACE and those being considered for or enrolling on a trial evaluating TACE in combination with immunotherapy with or without bevacizumab

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ASCO Gastrointestinal Cancers Symposium

Abstract LBA432

EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization

Riccardo Lencioni*[1], Masatoshi Kudo[2], Joseph Erinjeri[3], Shukui Qin[4], Zhenggang Ren[5], Stephen L Chan[6], Yasuaki Arai[7], Jeong Heo[8], Anh Mai[9], Jose Escobar[10], Yamil Alonso Lopez Chuken[11], Jung-Hwan Yoon[12], Won Young Tak[13], Tanita Suttichaimongkol[14], Mohamed Bouattour[15], Shi-Ming Lin[16], Magdalena Żotkiewicz[17], Stephanie Udoye[18], Gordon J Cohen[18], **Bruno Sangro***[19]

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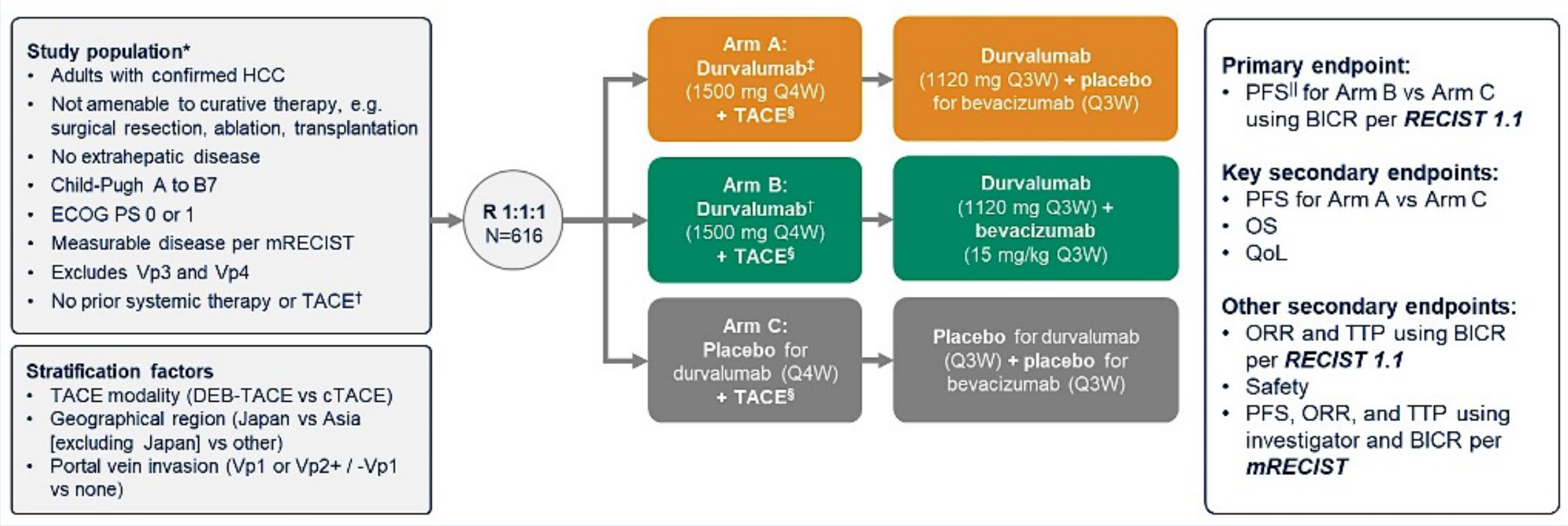
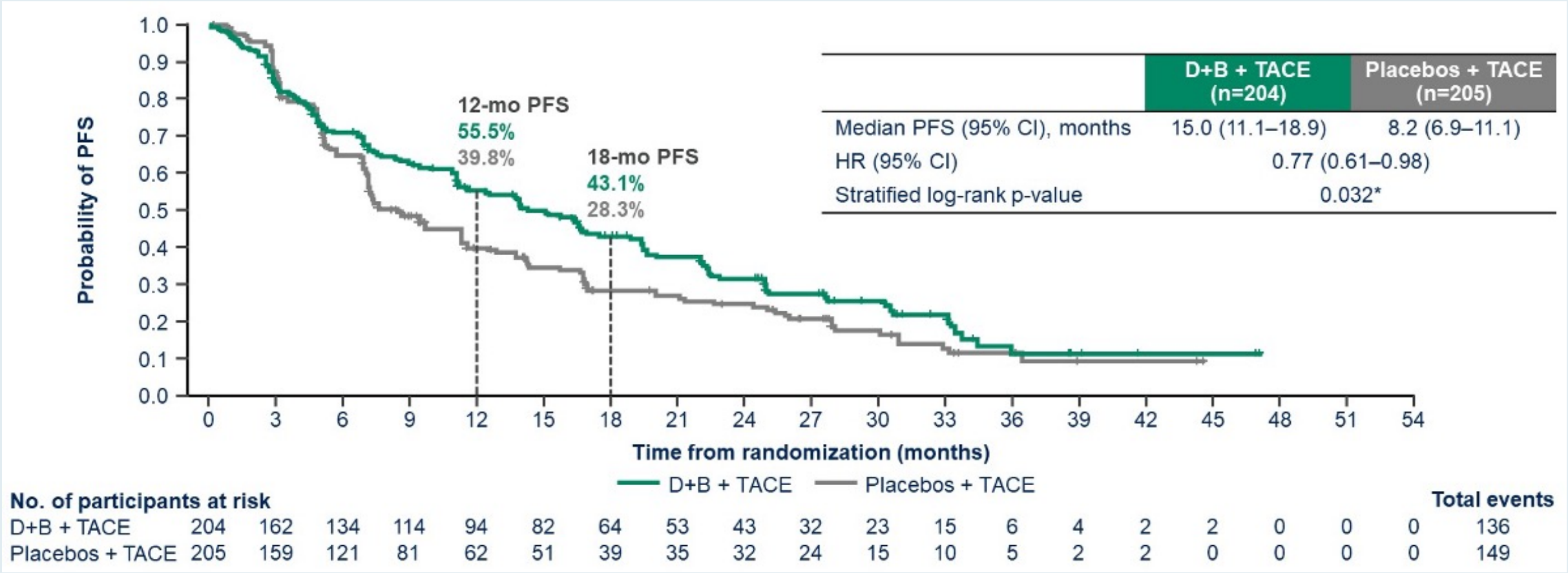
EMERALD-1: Phase III Study Design



TACE = transarterial chemoembolization

Lencioni R et al. Gastrointestinal Cancers Symposium 2024;Abstract LBA432.

EMERALD-1: Primary Endpoint Progression-Free Survival (PFS) with Durvalumab/Bevacizumab (D+B) and TACE Compared to Placebos and TACE



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

No. of participants at risk																			Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

Lencioni R et al. Gastrointestinal Cancers Symposium 2024;Abstract LBA432.

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EMERALD-1: Most Common Grade 3 or 4 Treatment-Emergent Adverse Events (AE)

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

Lencioni R et al. Gastrointestinal Cancers Symposium 2024;Abstract LBA432.

EMERALD-1: Author Conclusions

- **EMERALD-1 met the primary endpoint** and is the **first, global Phase 3 study** to demonstrate a statistically significant and clinically meaningful improvement in PFS with an immunotherapy and TACE-based regimen in unresectable HCC eligible for embolization
  - **Median PFS was 15.0 months with D+B + TACE and 8.2 months with placebos + TACE**
  - **PFS HR was 0.77, p=0.032**
- PFS benefit with D+B + TACE was generally consistent across key clinical subgroups
- The **safety profile was manageable** and consistent with the known safety profiles of TACE, durvalumab, and bevacizumab in unresectable HCC

Durvalumab plus **bevacizumab** in combination with **TACE** has the potential to set a new standard of care in **unresectable HCC eligible for embolization**

Lencioni R et al. Gastrointestinal Cancers Symposium 2024;Abstract LBA432.

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- Adjuvant Therapy for Early-Stage HCC
- Role of Immunotherapy in Intermediate-Stage HCC
- **First-Line Therapy for Advanced HCC**

Part 2: Biliary Tract Cancers

First-Line Therapy for Advanced HCC

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Biological rationale for combining anti-PD-1/PD-L1 and anti-VEGF antibodies for advanced HCC**
- **Long-term data with atezolizumab/bevacizumab as first-line therapy for unresectable HCC**
- **Selection of patients for up-front treatment with atezolizumab/bevacizumab**
- **Role of atezolizumab/bevacizumab in therapy for patients who would not have qualified for participation in the pivotal trial, such as those with Child-Pugh B disease**
- **Rationale for the combination of anti-PD-1/PD-L1 antibodies with anti-CTLA-4 antibodies for advanced HCC**

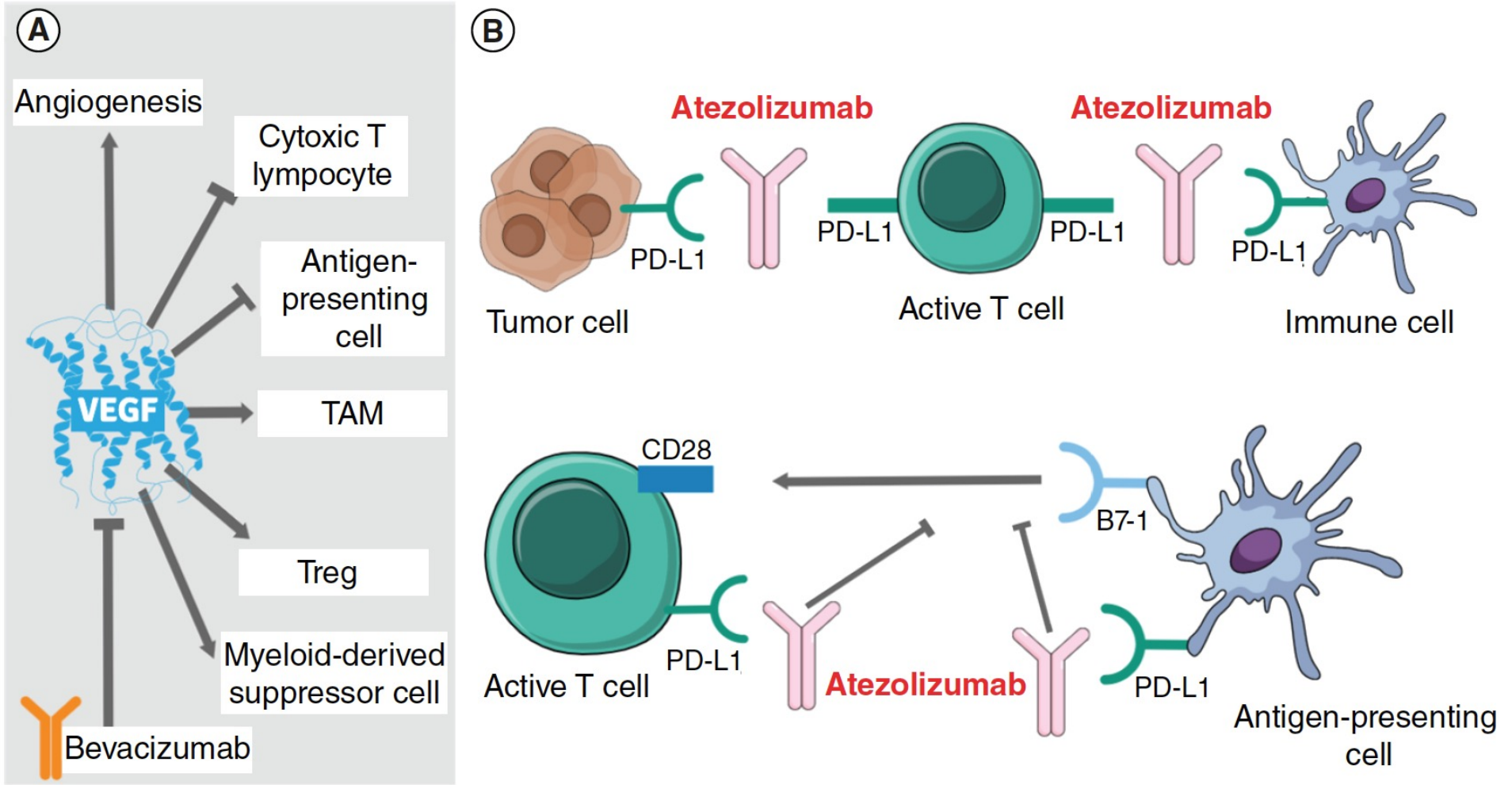
First-Line Therapy for Advanced HCC

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Long-term efficacy and safety outcomes, including updated overall survival results, reported with durvalumab/tremelimumab for previously untreated advanced HCC**
- **Advantages and disadvantages of dual immune checkpoint inhibitor therapy compared to other evidence-based front-line options for unresectable HCC**
- **Selection of patients for up-front durvalumab/tremelimumab**

Mechanism of Action of Atezolizumab and Bevacizumab



Liu X et al. *Future Oncol* 2021;17(17):2243-56.

Atezolizumab/Bevacizumab Regimen

Mechanism of action

- PD-L1 inhibitor
- Anti-VEGF monoclonal antibody

Indication in HCC

- For patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy

Recommended dose in HCC

- Atezolizumab: 840 mg IV q2wk, 1,200 mg IV q3wk or 1,680 mg IV q4wk
- Bevacizumab: 15 mg/kg IV q3wk

Key issues

- Screening for esophageal varices

Atezolizumab package insert, 4/2024.

Toxicities and Other Practical Considerations with Immune Checkpoint Inhibitor-Based Regimens for HCC

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Spectrum, incidence and severity of immune-related adverse events (AEs) and other toxicities observed with anti-PD-1/PD-L1 antibodies for HCC**
- **Effects on tolerability of administering anti-PD-1/PD-L1 antibodies in combination with other systemic therapies, such as anti-angiogenic agents or anti-CTLA-4 antibodies, for HCC**
- **Algorithms for monitoring and managing immune-related and other AEs with immune checkpoint inhibitors for patients with HCC**
- **Recommended dosing schedules for up-front atezolizumab/bevacizumab and durvalumab/tremelimumab**
- **Role, if any, for rechallenging with immune checkpoint inhibitor therapy after relapse on first-line atezolizumab/bevacizumab or durvalumab/tremelimumab**

Amanda K Wagner, APRN-CNP, AOCNP

What I tell my patients with advanced HCC who are about to start first-line therapy with durvalumab/tremelimumab

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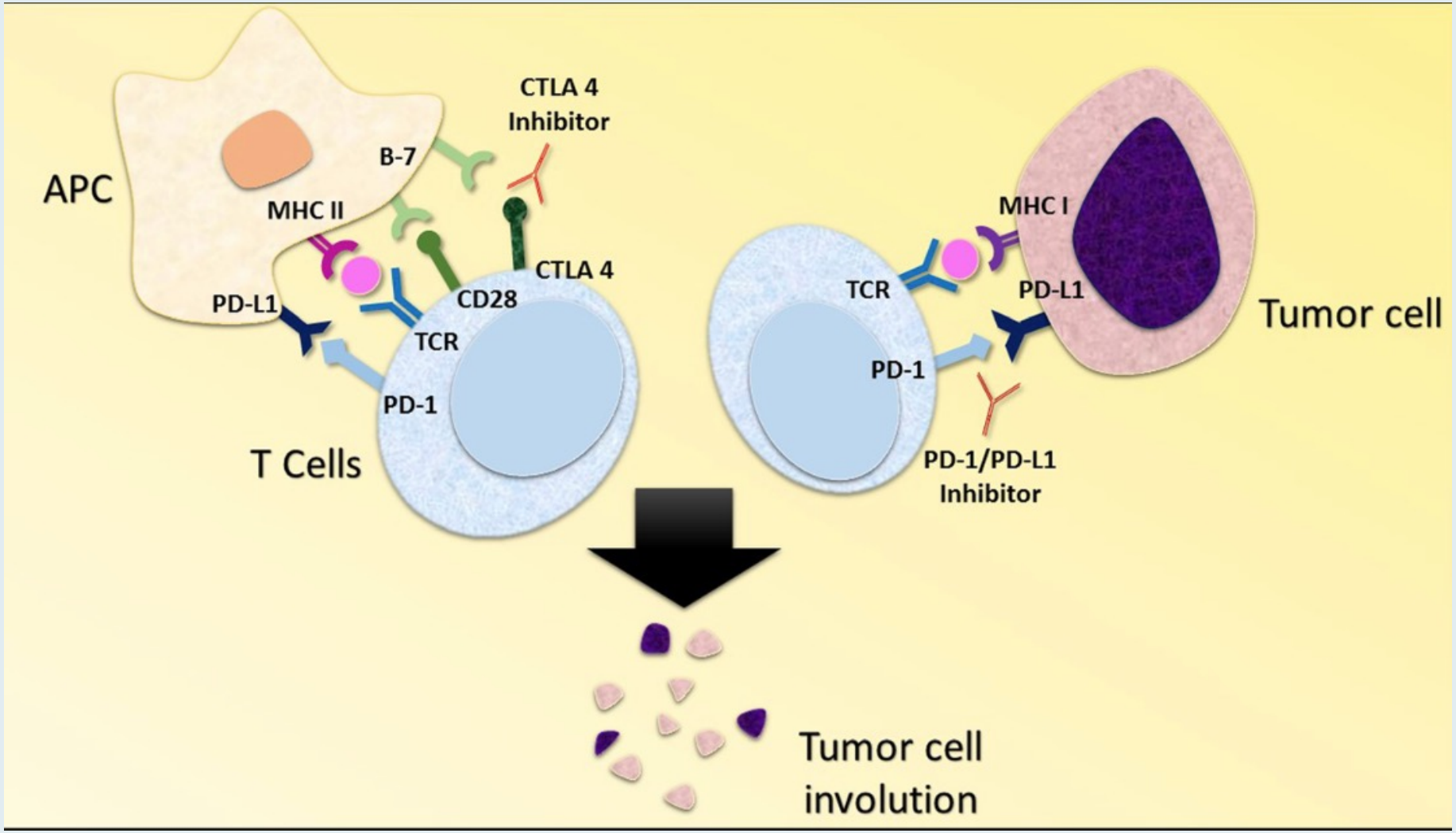
Mechanism of Action of Combined PD-1/PD-L1 and CTLA-4 Inhibitors



Chae YK et al. *J Immuno Ther* 2018;6(1):39.

Durvalumab/Tremelimumab Regimen

Mechanism of action

- PD-L1 inhibitor
- CTLA-4 inhibitor

Indication in HCC

- For adult patients with unresectable hepatocellular carcinoma (HCC)

Recommended dose in HCC

- Tremelimumab: Single priming dose of 300 mg (if weight 30 kg and more); single priming dose of 4 mg/kg (if weight less than 30 kg)
- Durvalumab: 1,500 mg Cycle 1/Day 1, followed by 1,500 mg as a single agent every 4 weeks (if weight 30 kg and more); 20 mg/kg Cycle 1/Day 1, followed by 20mg/kg as a single agent every 4 weeks (if weight less than 30 kg)

Durvalumab package insert, 6/2023; Tremelimumab package insert, 6/2023

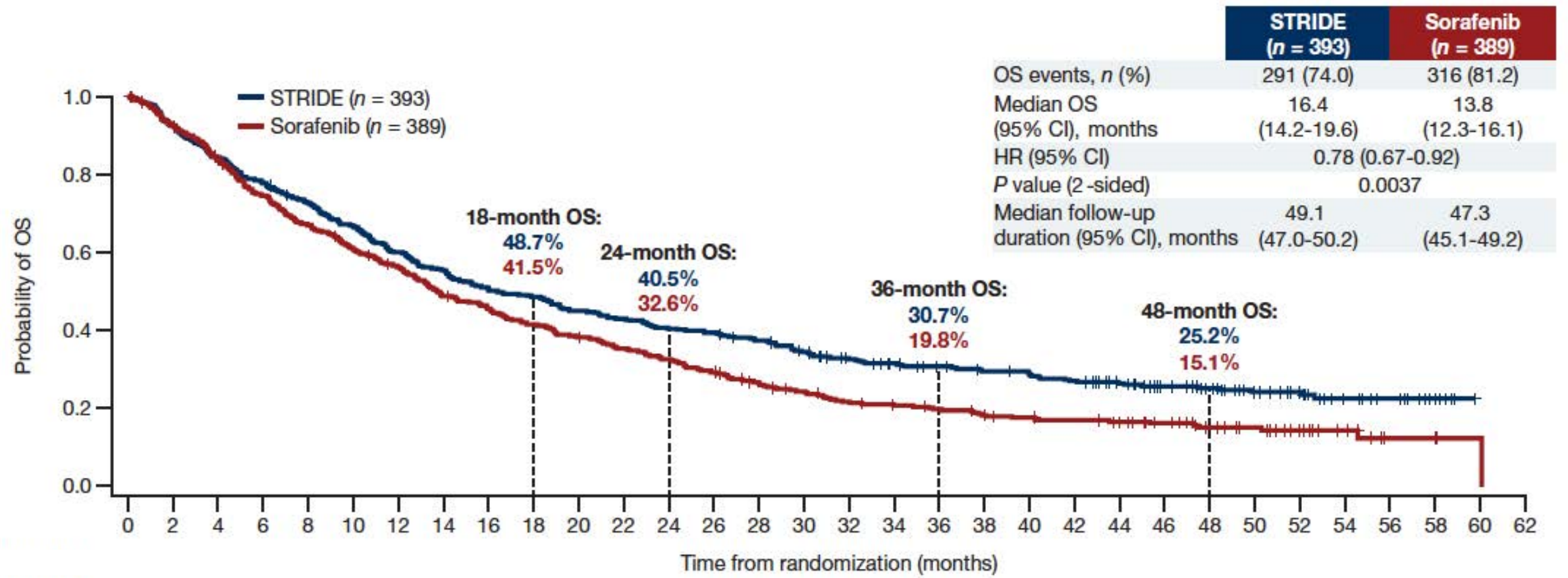
ORIGINAL ARTICLE

Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma

B. Sangro[1*], S. L. Chan[2], R. K. Kelley[3], G. Lau[4], M. Kudo[5], W. Sukeepaisarnjaroen[6], M. Yarchoan[7], E. N. De Toni[8], J. Furuse[9], Y. K. Kang[10], P. R. Galle[11], L. Rimassa[12,13], A. Heurgué[14], V. C. Tam[15], T. Van Dao[16], S. C. Thungappa[17], V. Breder[18], Y. Ostapenko[19], M. Reig[20], M. Makowsky[21], M. J. Paskow[22], C. Gupta[23], J. F. Kurland[21], A. Negro[21] & G. K. Abou-Alfa[24,25,26], for the HIMALAYA investigators†

Ann Oncol 2024 February 19;[Online ahead of print].

HIMALAYA 4-Year Updated Analysis: Overall Survival (OS) with STRIDE versus Sorafenib



	STRIDE (*n* = 393)	Sorafenib (*n* = 389)
OS events, *n* (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), months	16.4 (14.2-19.6)	13.8 (12.3-16.1)
HR (95% CI)	0.78 (0.67-0.92)	
P value (2-sided)	0.0037	
Median follow-up duration (95% CI), months	49.1 (47.0-50.2)	47.3 (45.1-49.2)

STRIDE = 300 mg of tremelimumab (1 dose) and 1,500 mg of durvalumab every 4 weeks

Sangro B et al. *Ann Oncol* 2024 February 19;[Online ahead of print].

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CheckMate 9DW Trial Evaluating Nivolumab with Ipilimumab Meets Primary Endpoint of Overall Survival for the First-Line Treatment of Advanced Hepatocellular Carcinoma

Press Release – March 20, 2024

"The Phase 3 CheckMate-9DW trial evaluating nivolumab plus ipilimumab as a first-line treatment for patients with advanced hepatocellular carcinoma (HCC) who have not received prior systemic therapy met its primary endpoint of improved overall survival (OS) compared to investigator's choice of sorafenib or lenvatinib at a pre-specified interim analysis.

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

https://news.bms.com/news/corporate-financial/2024/Bristol-Myers-Squibb-Announces-CheckMate--9DW-Trial-Evaluating-Opdivo-nivolumab-Plus-Yervoy-ipilimumab-Meets-Primary-Endpoint-of-Overall-Survival-for-the-First-Line-Treatment-of-Advanced-Hepatocellular-Carcinoma/default.aspx

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Agenda

Introduction

Part 1: Hepatocellular Carcinoma

Part 2: Biliary Tract Cancers (BTCs)

- Immunotherapy in the Management of Advanced BTCs
- Biomarker Testing Recommendations and the Use of FGFR Inhibitors for Advanced Cholangiocarcinoma
- Potential Role of HER2-Targeted Therapy for BTCs

Agenda

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Part 1: Hepatocellular Carcinoma

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- **Immunotherapy in the Management of Advanced BTCs**
- **Biomarker Testing Recommendations and the Use of FGFR Inhibitors for Advanced Cholangiocarcinoma**
- **Potential Role of HER2-Targeted Therapy for BTCs**

The Role of Anti-PD-1/PD-L1 Antibodies in the Management of Advanced BTCs

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Long-term outcomes achieved with historical approaches to up-front treatment for advanced BTCs**
- **Pivotal findings with the addition of durvalumab to first-line chemotherapy for advanced BTCs**
- **Published results with pembrolizumab combined with cisplatin/gemcitabine as first-line treatment for advanced BTCs**
- **Optimal integration into practice of up-front chemoimmunotherapeutic strategies for patients with advanced BTCs**

Durvalumab

Mechanism of action

- **PD-L1 inhibitor**

Indication in BTC

- **In combination with gemcitabine and cisplatin for locally advanced or metastatic biliary tract cancer (BTC)**

Recommended dose in BTC

- **Weight ≥30 kg: 1,500 mg every 3 weeks in combination with chemotherapy, and then 1,500 mg every 4 weeks as a single agent**
- **Weight <30 kg: 20 mg/kg every 3 weeks in combination with chemotherapy, and then 20 mg/kg every 4 weeks as a single agent**

Durvalumab package insert, 6/2023.

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Pembrolizumab

Mechanism of action

- **PD-1 inhibitor**

Indication in BTC

- **In combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC)**

Recommended dose in BTC

- **200 mg every 3 weeks or 400 mg every 6 weeks**

Pembrolizumab package insert, 3/2024.

Blanca Ledezma, MSN, NP, AOCNP

What I tell my patients with newly diagnosed metastatic biliary tract cancer who are about to receive chemoimmunotherapy

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Consulting Nursing Faculty Comments

Patient adherence to therapy, dose reductions, and oral medication conversion

Sonia Glennie, ARNP, MSN, OCN

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Part 2: Biliary Tract Cancers (BTCs)

- Immunotherapy in the Management of Advanced BTCs
- **Biomarker Testing Recommendations and the Use of FGFR Inhibitors for Advanced Cholangiocarcinoma**
- Potential Role of HER2-Targeted Therapy for BTCs

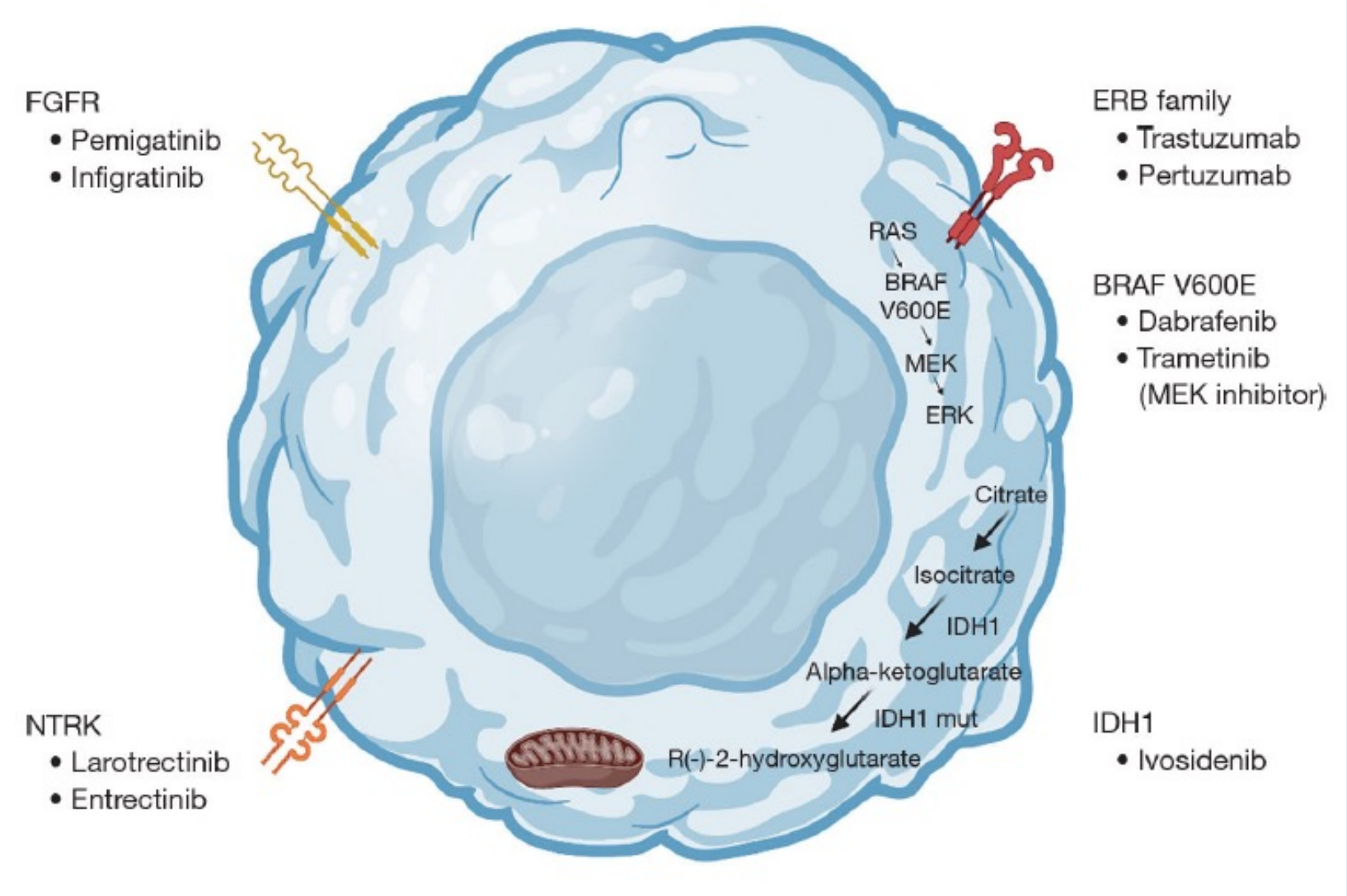
The Importance of Biomarker Testing in the Care of Patients with Advanced BTCs

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Spectrum and clinical relevance of genomic aberrations in patients with advanced BTCs**
- **Prevalence of targetable molecular alterations in various BTCs: Intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma versus gallbladder cancer**
- **Available platforms for and optimal timing of genomic evaluation**
- **Variable capacity of genetic testing methods to accurately identify different abnormalities**

Key Targets in Biliary Tract Cancers



LaPelusa M et al. *Chin Clin Oncol* 2023 April;12(2):14.

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	Trastuzumab deruxtecan	Multiple testing modalities available including immunohistochemistry and FISH for expression and amplification, tumor next-generation DNA sequencing for mutations

FISH = fluorescence in situ hybridization

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

The Role of FGFR Inhibitors in the Management of Advanced Cholangiocarcinoma

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Mechanistic similarities and differences between the approved FGFR inhibitors pemigatinib and futibatinib for advanced cholangiocarcinoma**
- **Principal findings with pemigatinib and with futibatinib for previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement**
- **Evidence-based selection and sequencing of pemigatinib and futibatinib for FGFR-altered cholangiocarcinoma**
- **Ongoing Phase III trials evaluating FGFR inhibition for patients with treatment-naïve cholangiocarcinoma**

Tolerability and Other Considerations with FGFR Inhibitors for Cholangiocarcinoma

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Comparative tolerability profiles of the approved FGFR inhibitors for cholangiocarcinoma; implications for therapeutic selection**
- **Pathophysiology of the ocular toxicities observed with pemigatinib and futibatinib; monitoring and management protocols**
- **Incidence and management of other common AEs reported with pemigatinib and futibatinib, such as hyperphosphatemia, nail changes, stomatitis, hand-foot syndrome and dry skin**
- **Role, if any, of rechallenging with an FGFR inhibitor for patients who have experienced disease progression on FGFR inhibitor therapy**

Amanda K Wagner, APRN-CNP, AOCNP

What I tell my patients with metastatic biliary tract cancer and an FGFR alteration about the mechanism of action of and side effects and tolerability issues with the FGFR inhibitors pemigatinib and futibatinib

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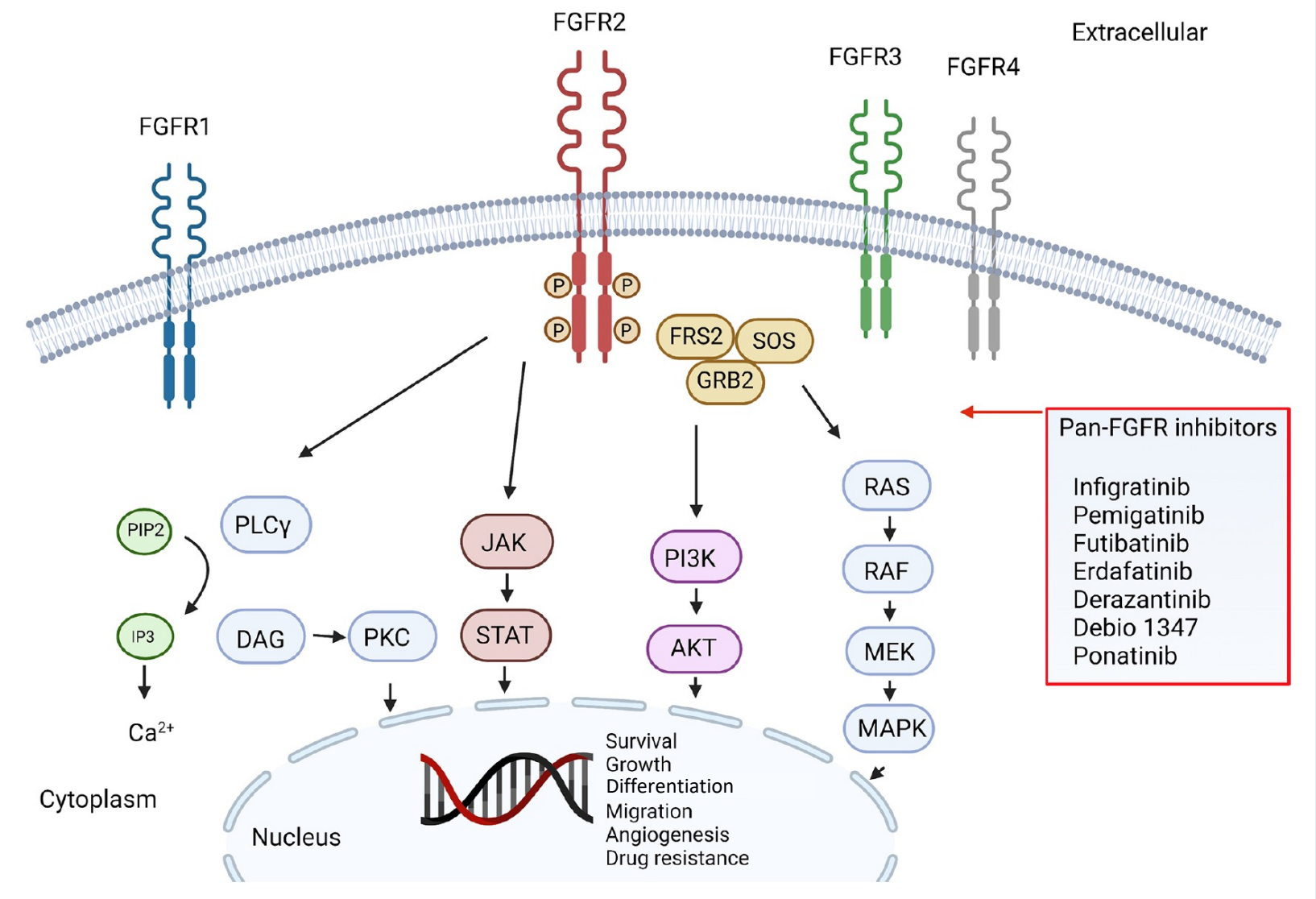
FGFR Inhibitors Mechanism of Action



Zugman M et al. *Front Oncol* 2022;12:860453.

Futibatinib

Mechanism of action

- **FGFR inhibitor**

Indication

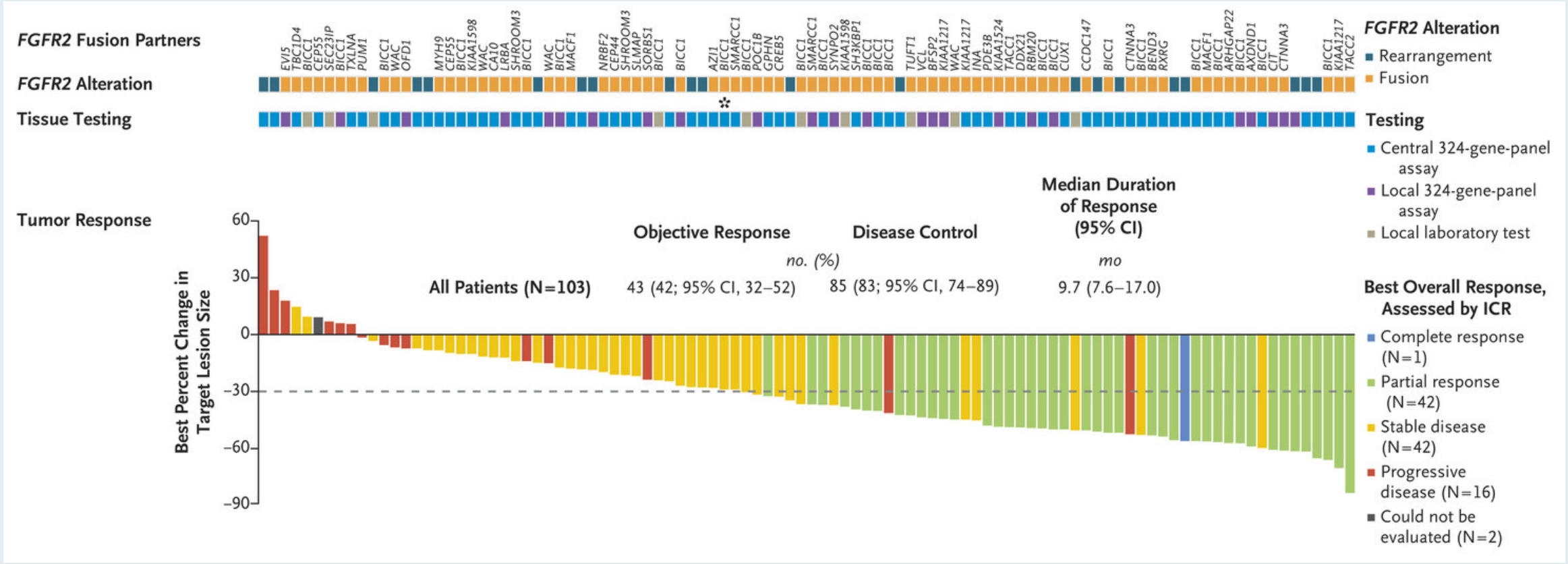
- **For patients with previously treated, unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangements**

Recommended dose

- **20 mg orally (five 4-mg tablets) once daily with or without food until disease progression or unacceptable toxicity**

Futibatinib package insert, 4/2024.

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



Median PFS: 9.0 mos
Median OS: 21.7 mos

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

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Pemigatinib

Mechanism of action

- **FGFR inhibitor**

Indication

- **For patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma harboring FGFR2 fusions or other rearrangements**

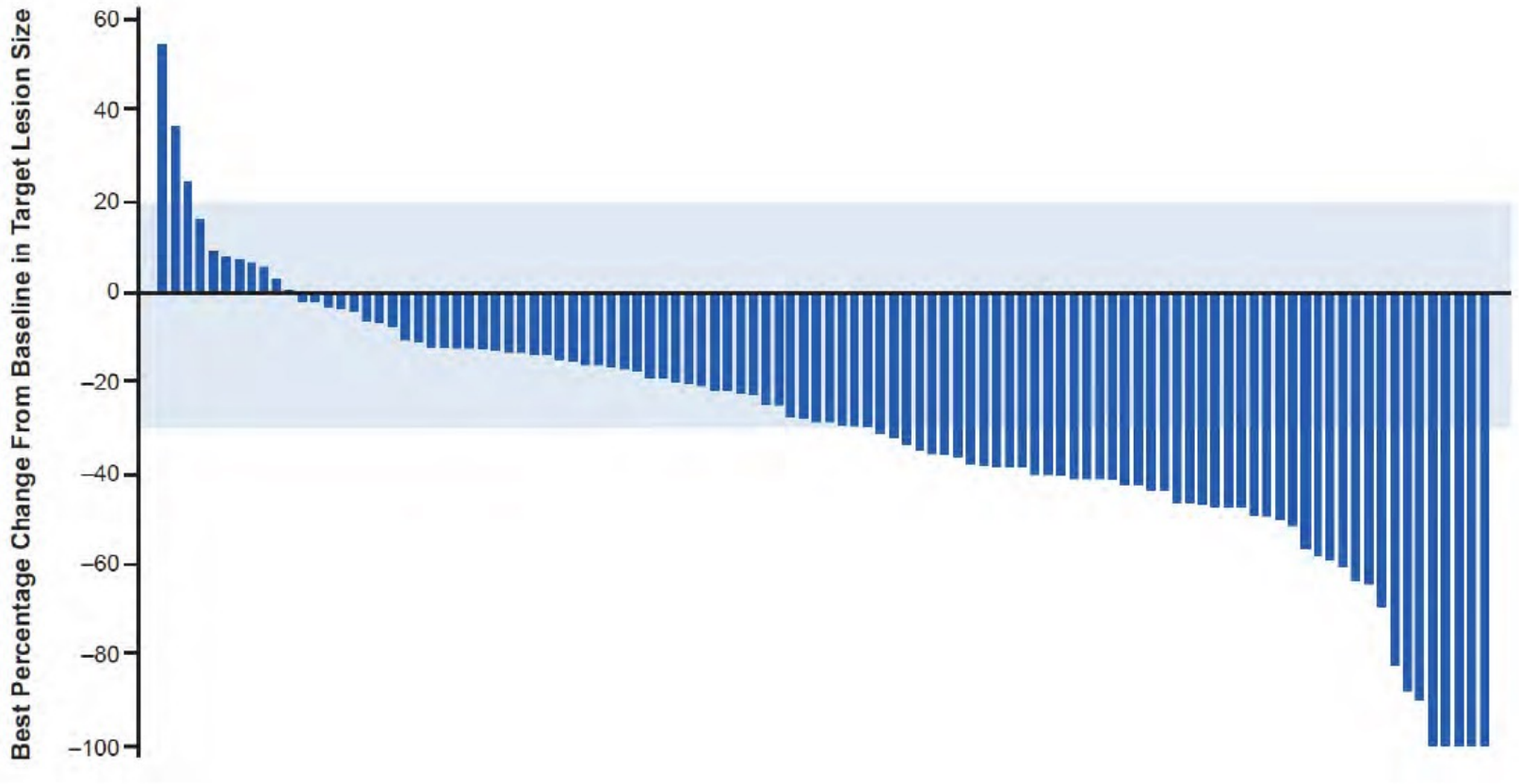
Recommended dose

- **13.5 mg orally once daily, with or without food, for 14 consecutive days followed by 7 days off therapy in 21-day cycles until disease progression or unacceptable toxicity**

Pemigatinib package insert, 6/2023.

FIGHT-202 Final Results: Best Percent 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.

Efficacy of FDA-Approved FGFR Inhibitors for FGFR2 Fusion-Positive Cholangiocarcinoma

	Pemigatinib (N = 107)	Futibatinib (N = 67)
ORR	37.0%	42.0%
Disease control rate	82.0%	83.0%
Median progression-free survival	7.0 mo	9.0 mo
Median overall survival	17.5 mo	21.7 mo
Toxicities	Hyperphosphatemia, Alopecia, Diarrhea	Hyperphosphatemia, Diarrhea, Dry mouth

Vogel A et al. *ESMO GI* 2022;Abstract O-2; Goyal L et al. *N Engl J Med* 2023;388:228-39

Agenda

Introduction

Part 1: Hepatocellular Carcinoma

Part 2: Biliary Tract Cancers (BTCs)

- Immunotherapy in the Management of Advanced BTCs
- Biomarker Testing Recommendations and the Use of FGFR Inhibitors for Advanced Cholangiocarcinoma
- **Potential Role of HER2-Targeted Therapy for BTCs**

The Potential Role of HER2-Targeted Therapy for BTCs

Dr Stein
New Haven, Connecticut

Dr Yarchoan
Baltimore, Maryland

- **Incidence of HER2 overexpression in patients with BTCs**
- **Mechanism of action of the novel HER2-targeted bispecific antibody zanidatamab**
- **Recent pivotal trial findings with zanidatamab for previously treated advanced or metastatic HER2-positive BTCs**
- **Key efficacy and safety findings with trastuzumab deruxtecan for patients with previously treated HER2-positive BTCs**
- **Current off-protocol and potential future role of HER2-targeted therapy for advanced BTCs**

Blanca Ledezma, MSN, NP, AOCNP

What I tell my patients with advanced BTC about the importance of HER2 testing and potential therapy with trastuzumab deruxtecan

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FDA Grants Accelerated Approval to Trastuzumab Deruxtecan for Unresectable or Metastatic HER2-Positive Solid Tumors

Press Release – April 5, 2024

"On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. Efficacy was evaluated in 192 adult patients with previously treated unresectable or metastatic HER2-positive (IHC 3+) solid tumors who were enrolled in one of three multicenter trials: DESTINY-PanTumor02 (NCT04482309), DESTINY-Lung01 (NCT03505710), and DESTINY-CRC02 (NCT04744831). All three trials excluded patients with a history of interstitial lung disease (ILD)/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for active brain metastases or ECOG performance status >1. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The recommended fam-trastuzumab deruxtecan-nxki dosage for this indication is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. This tumor agnostic indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2

Trastuzumab Deruxtecan

Mechanism of action

- **Antibody-drug conjugate directed against HER2**

Indication

- **Unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options**

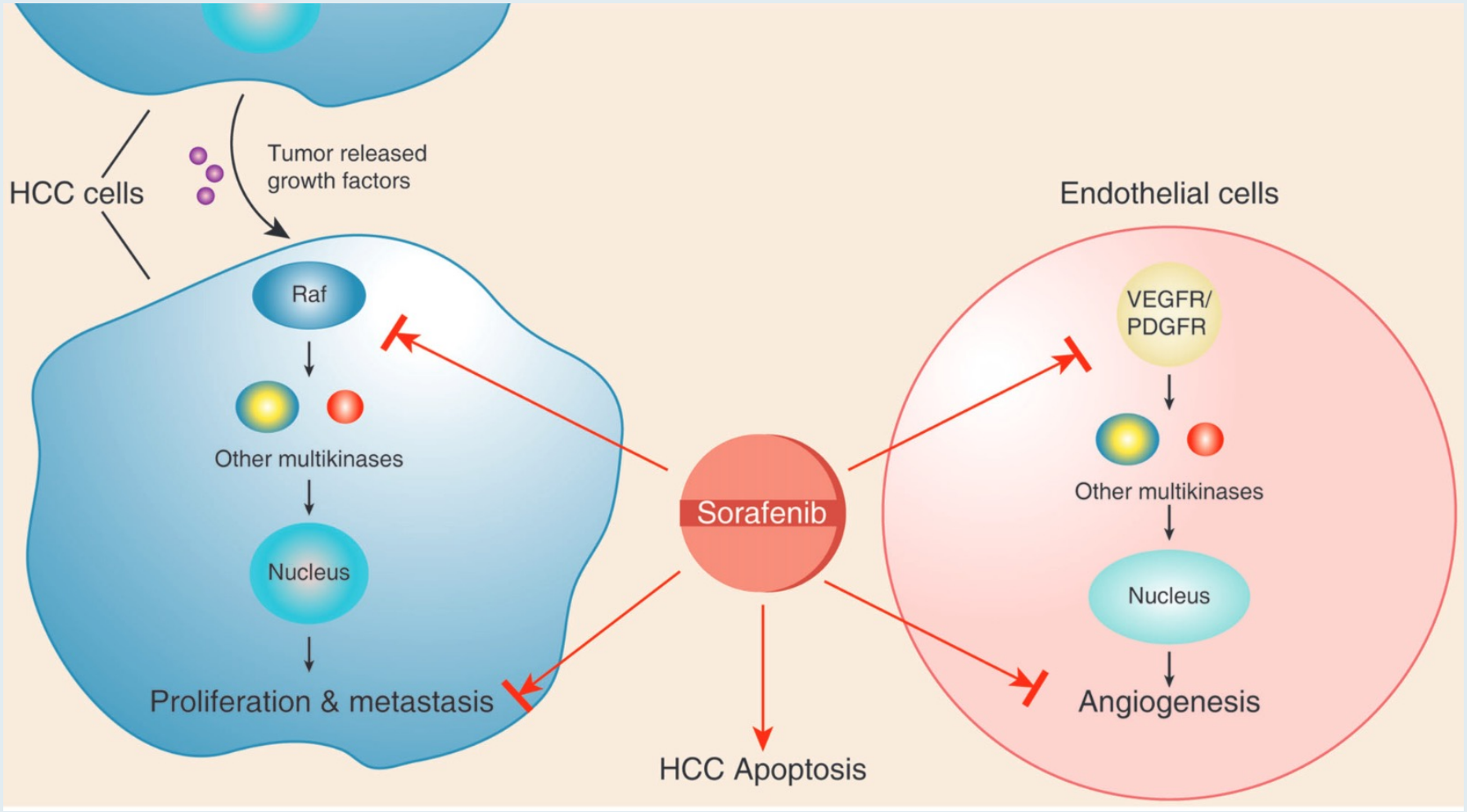
Key clinical trial

- **Phase II DESTINY-PanTumor02 trial evaluating trastuzumab deruxtecan in patients with HER2-expressing solid tumors**

Meric-Bernstam F et al. *J Clin Oncol* 2024;42(1):47-58.

APPENDIX

Mechanism of Action of Sorafenib



Daher S et al. *J Clin Transl Hepatol* 2018;6(1):69-78.

Sorafenib

Mechanism of action

- **Oral multikinase inhibitor**

Indication

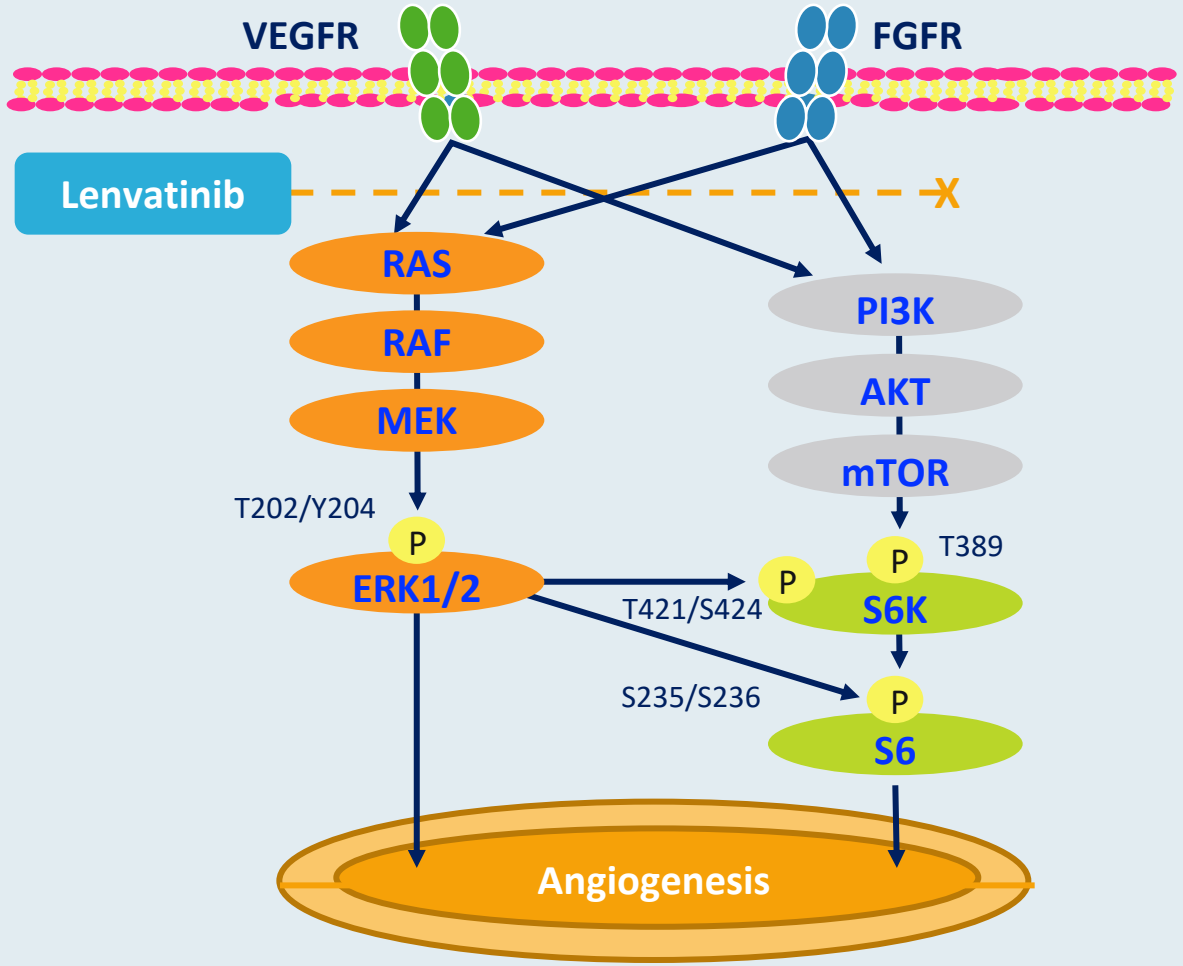
- **For patients with unresectable hepatocellular carcinoma**

Recommended dose

- **400 mg orally BID without food**

Sorafenib package insert, 8/2023.

Mechanism of Action of Lenvatinib



- Orally available inhibitor of multiple tyrosine kinases, including VEGF receptors, FGFR, RET, PDGFR and KIT
- Demonstrated promising radiographic response rates and survival results in Phase II and III trials in HCC

Finn RS et al. ASCO 2014;Abstract TPS4153; Stjepanovic N et al. *Biologics* 2014;8:129-39; Cheng AL et al. ASCO 2017;Abstract 4001; Ikeda K et al. *J Gastroenterol* 2017;52(4):512-9.

Lenvatinib

Mechanism of action

- Oral multikinase inhibitor

Indication

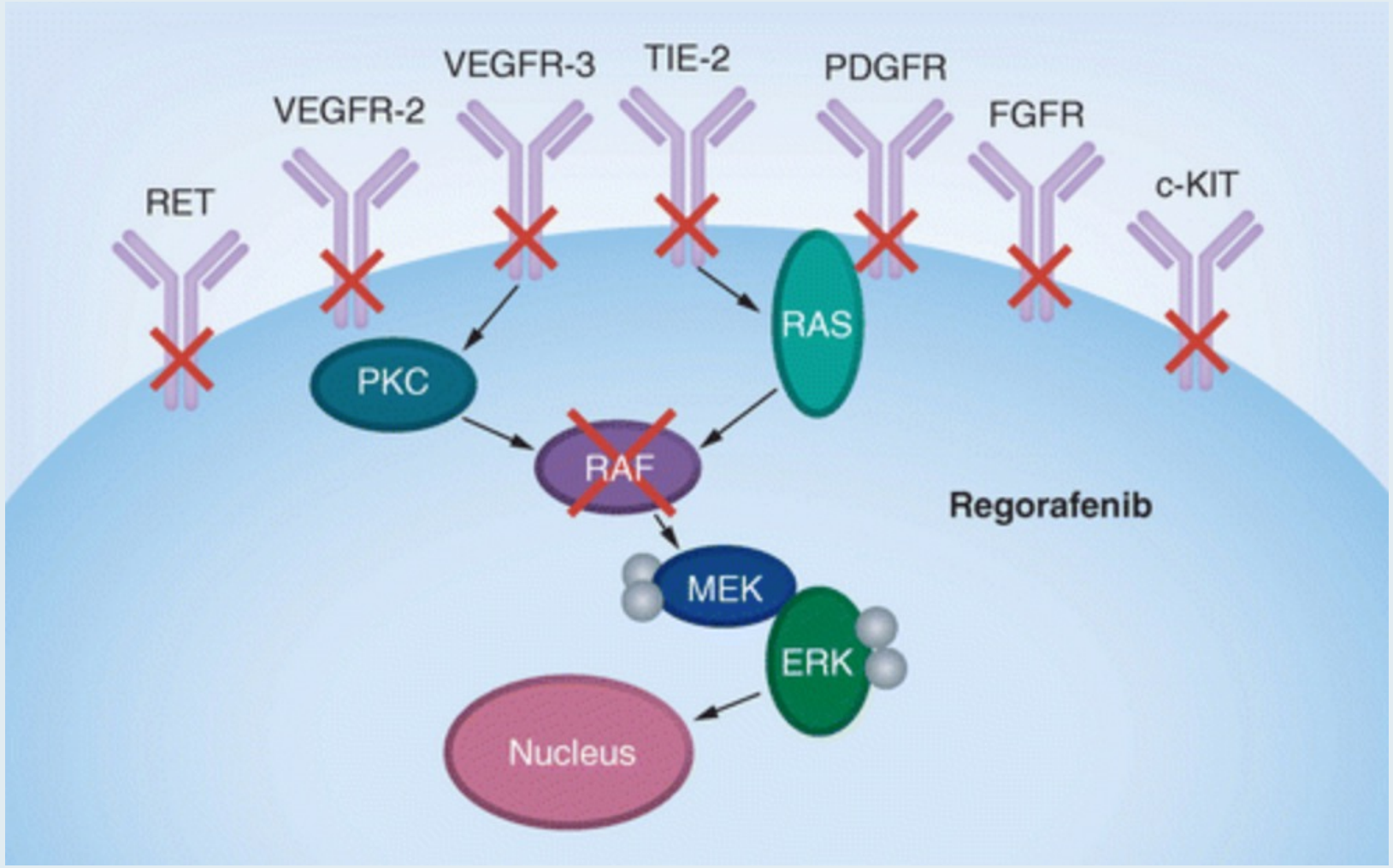
- As first-line therapy for patients with unresectable hepatocellular carcinoma

Recommended dose

- 12 mg orally once daily for patients of 60 kg or greater actual body weight
- 8 mg orally once daily for patients of less than 60 kg actual body weight

Lenvatinib package insert, 4/2024.

Mechanism of Action of Regorafenib



Cremolini C et al. *Future Med* 2013;2(5):411-17.

RTP RESEARCH TO PRACTICE

Regorafenib

Mechanism of action

- **Oral multikinase inhibitor**

Indication

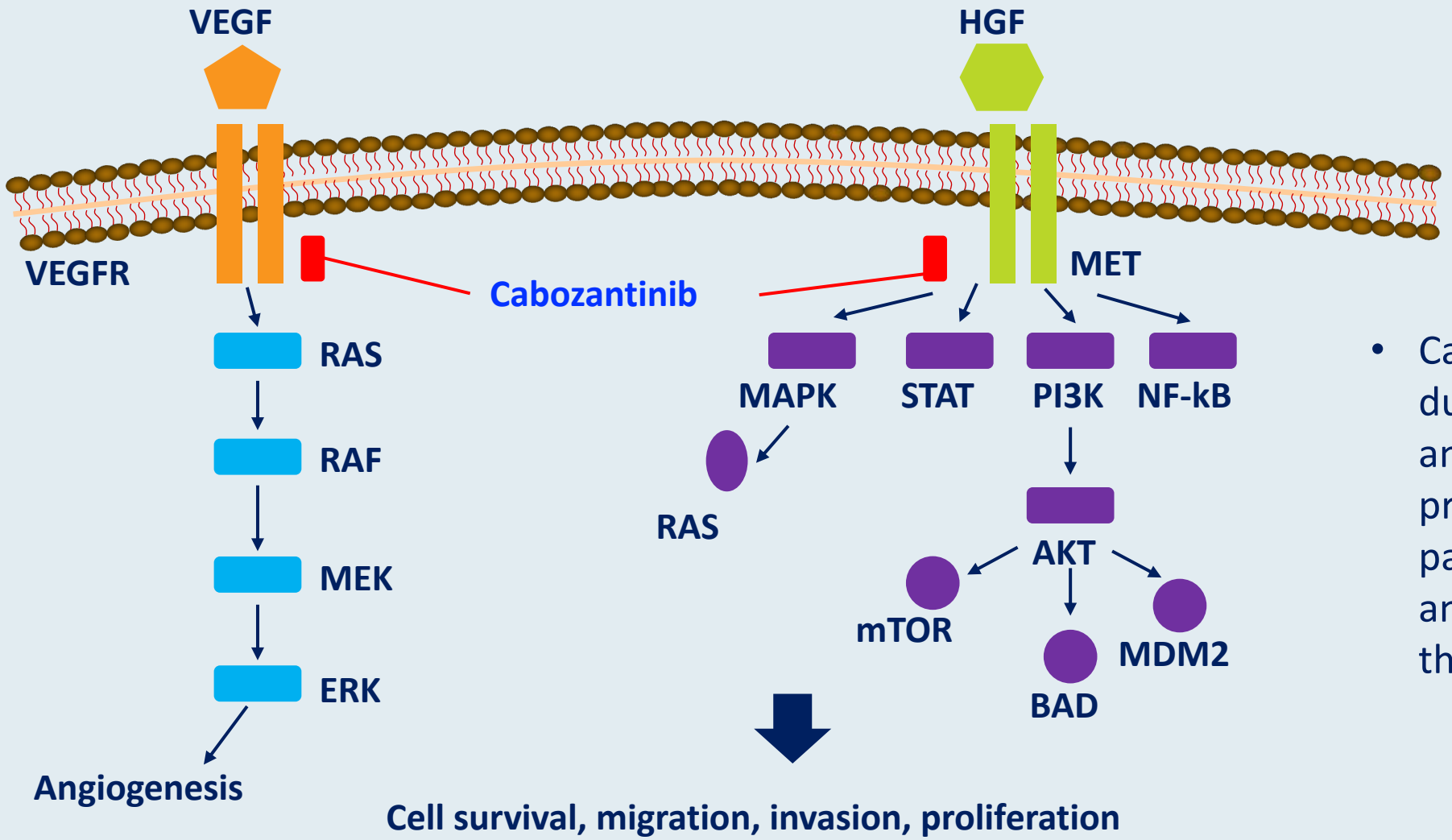
- **For patients with hepatocellular carcinoma who have previously received sorafenib**

Recommended dose

- **160 mg orally once daily for the first 21 days of each 28-day cycle**

Regorafenib package insert, 12/2020.

Mechanism of Action of Cabozantinib



- Cabozantinib provides dual inhibition of MET and VEGFR-2, thereby preventing the MET pathway from acting as an alternative pathway in the development of VEGF

Cabozantinib

Mechanism of action

- Oral multikinase inhibitor

Indication

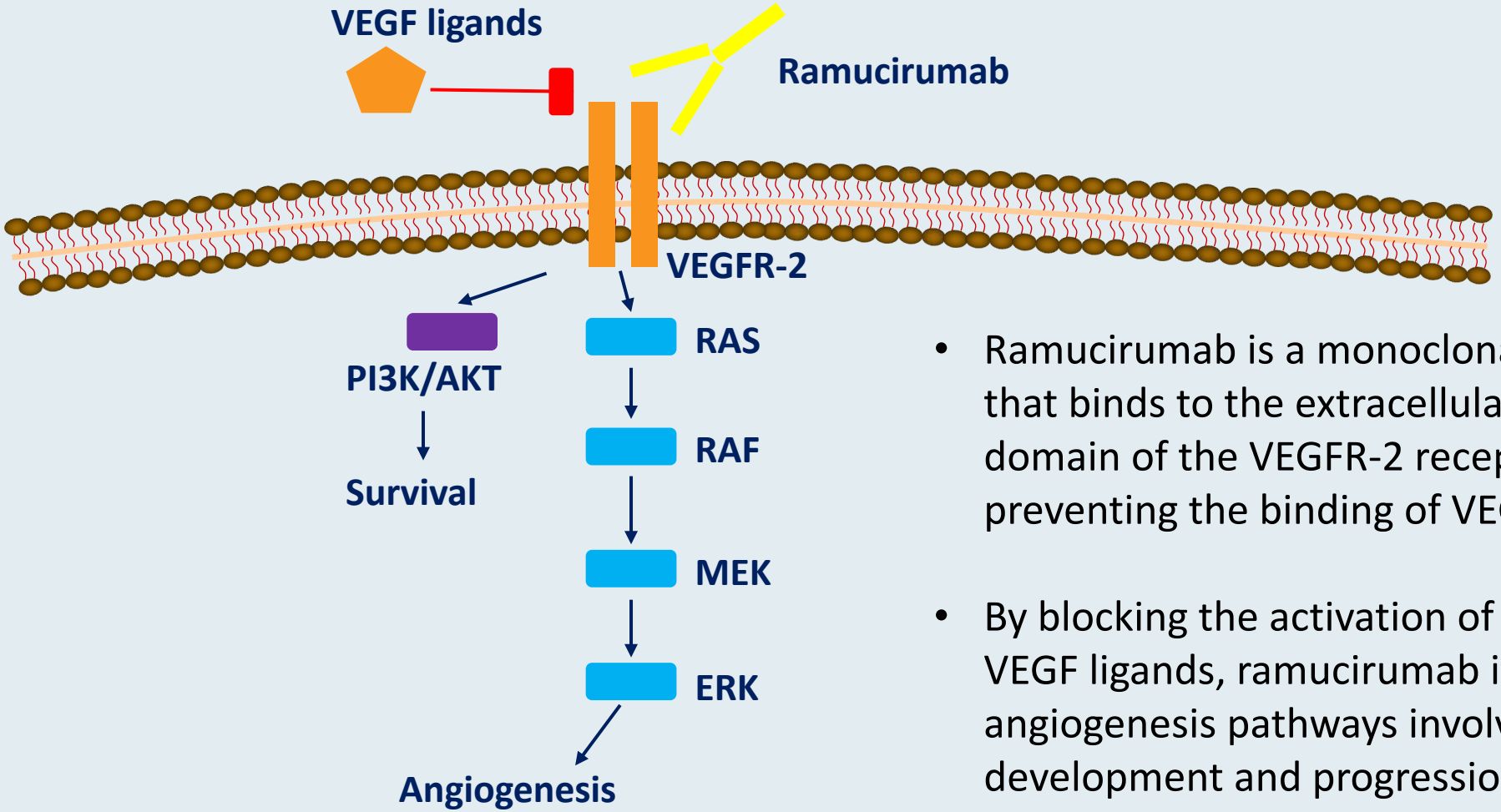
- For patients with hepatocellular carcinoma who have previously received sorafenib

Recommended dose

- 60 mg once daily without food until disease progression or unacceptable toxicity

Cabozantinib prescribing information, 1/2021.

Mechanism of Action of Ramucirumab



- Ramucirumab is a monoclonal antibody that binds to the extracellular binding domain of the VEGFR-2 receptor, preventing the binding of VEGF ligands
- By blocking the activation of VEGFR-2 by VEGF ligands, ramucirumab inhibits the angiogenesis pathways involved in the development and progression of cancer

Ramucirumab

Mechanism of action

- **Anti-VEGFR-2 monoclonal antibody**

Indication

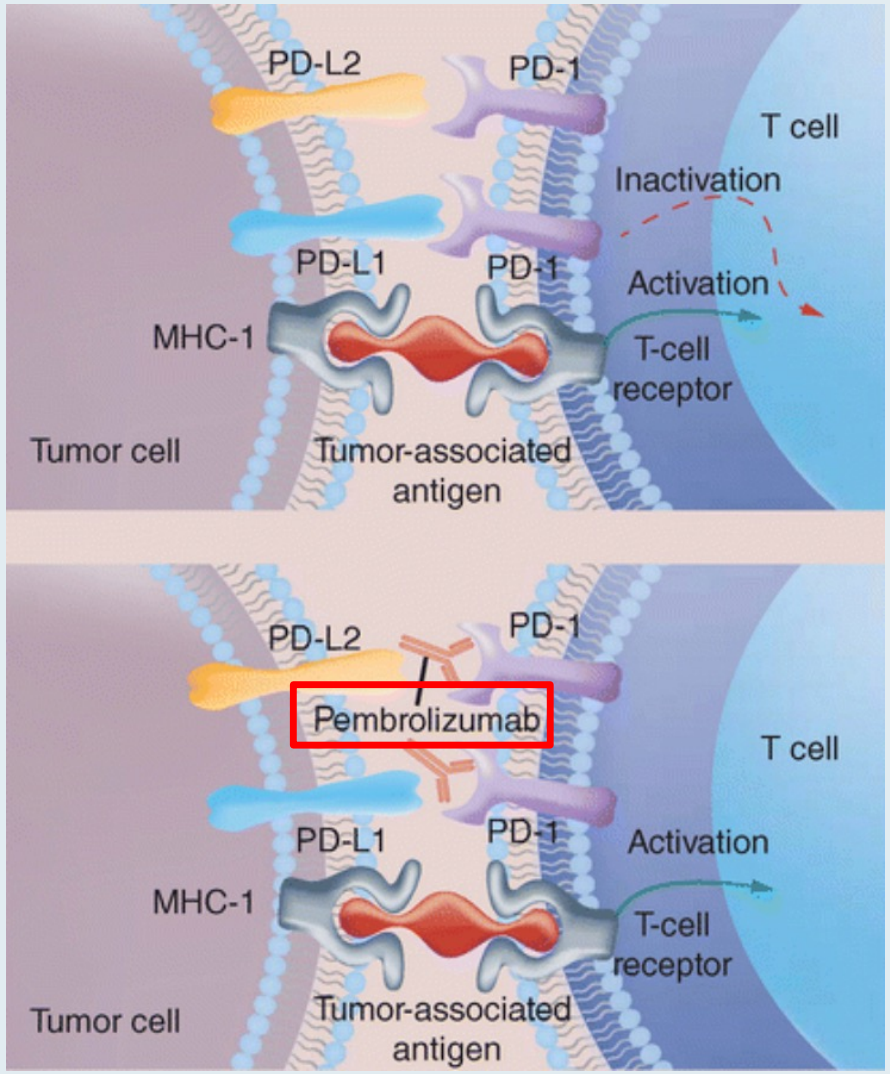
- **For patients with hepatocellular carcinoma who have an alpha fetoprotein level of ≥400 ng/mL and have previously received sorafenib**

Recommended dose

- **8 mg/kg IV infusion every 2 weeks**

Ramucirumab package insert, 3/2022.

Pembrolizumab Mechanism of Action



Reck M. *Immunotherapy* 2017;10(2):93-105.

RTP RESEARCH TO PRACTICE

FGFR2 Inhibition

FDA Grants Accelerated Approval to Futibatinib for Cholangiocarcinoma

Press Release – September 30, 2022

"…the Food and Drug Administration granted accelerated approval to futibatinib for adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements.

Efficacy was evaluated in TAS-120-101 (NCT02052778), a multicenter, open-label, single-arm trial that enrolled 103 patients with previously treated, unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma harboring a FGFR2 gene fusion or other rearrangement. The presence of FGFR2 fusions or other rearrangements was determined using next generation sequencing testing. Patients received 20 mg of futibatinib orally once daily until disease progression or unacceptable toxicity.

The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR) as determined by an independent review committee according to RECIST v1.1. ORR was 42% (95% Confidence Interval [CI]: 32, 52); all 43 responders achieved partial responses. The median DoR was 9.7 months (95% CI: 7.6, 17.1)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-futibatinib-cholangiocarcinoma

The NEW ENGLAND JOURNAL of MEDICINE

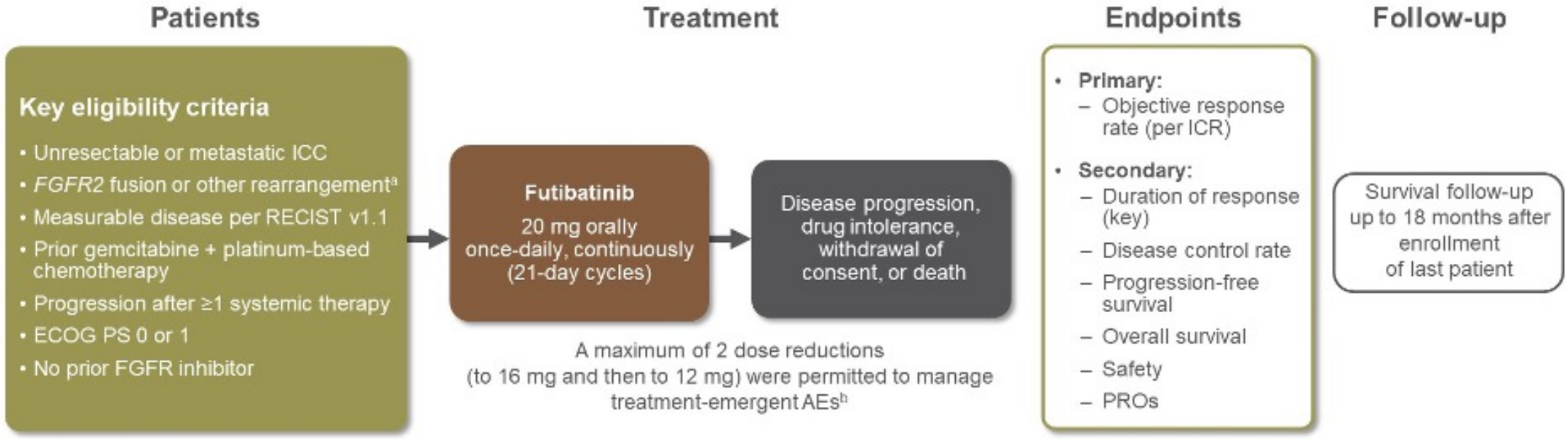
ORIGINAL ARTICLE

Futibatinib for *FGFR2*-Rearranged Intrahepatic Cholangiocarcinoma

L. Goyal, F. Meric-Bernstam, A. Hollebecque, J.W. Valle, C. Morizane, T.B. Karasic, T.A. Abrams, J. Furuse, R.K. Kelley, P.A. Cassier, H.-J. Klümpen, H.-M. Chang, L.-T. Chen, J. Tabernero, D.-Y. Oh, A. Mahipal, M. Moehler, E.P. Mitchell, Y. Komatsu, K. Masuda, D. Ahn, R.S. Epstein, A.-B. Halim, Y. Fu, T. Salimi, V. Wacheck, Y. He, M. Liu, K.A. Benhadji, and J.A. Bridgewater, for the FOENIX-CCA2 Study Investigators*

N Engl J Med 2023;388;228-39.

FOENIX-CCA2 (TAS-120-101): 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: Select Treatment-Related Adverse Events with Futibatinib for Intrahepatic Cholangiocarcinoma

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

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

FDA Grants Accelerated Approval to Pemigatinib for Cholangiocarcinoma with an FGFR2 Rearrangement or Fusion

Press Release – April 17, 2020

"…the Food and Drug Administration granted accelerated approval to pemigatinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.

The FDA also approved the FoundationOne® CDX as a companion diagnostic for patient selection.

Efficacy was investigated in FIGHT-202 (NCT02924376), a multicenter open-label single-arm trial, in 107 patients with locally advanced unresectable or metastatic cholangiocarcinoma whose disease had progressed on or after at least one prior therapy and had an FGFR2 gene fusion or rearrangement (clinical trial assay performed at a central laboratory). Patients received pemigatinib, 13.5 mg orally, once daily for 14 consecutive days, followed by 7 days off therapy.

The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) determined by an independent review committee using RECIST 1.1. Among the 107 patients, the ORR was 36% (95% CI: 27%, 45%), including 3 complete responses. The median DOR was 9.1 months with responses lasting ≥ 6 months in 24 of the 38 (63%) responding patients and ≥ 12 months in 7 (18%) patients."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pemigatinib-cholangiocarcinoma-fgfr2-rearrangement-or-fusion

RTP RESEARCH TO PRACTICE

2022 | Abstract O-2

O-2

#575

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

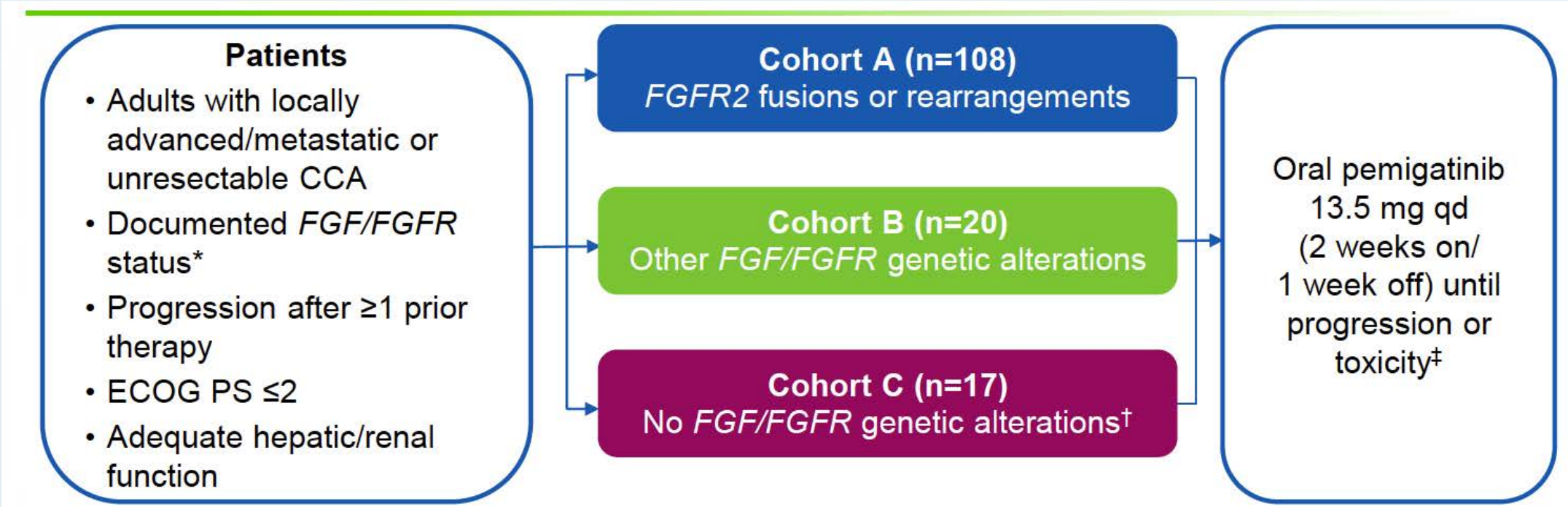
Pemigatinib for Previously Treated Locally Advanced or Metastatic Cholangiocarcinoma: Final Results From FIGHT-202

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]

RTP RESEARCH TO PRACTICE

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

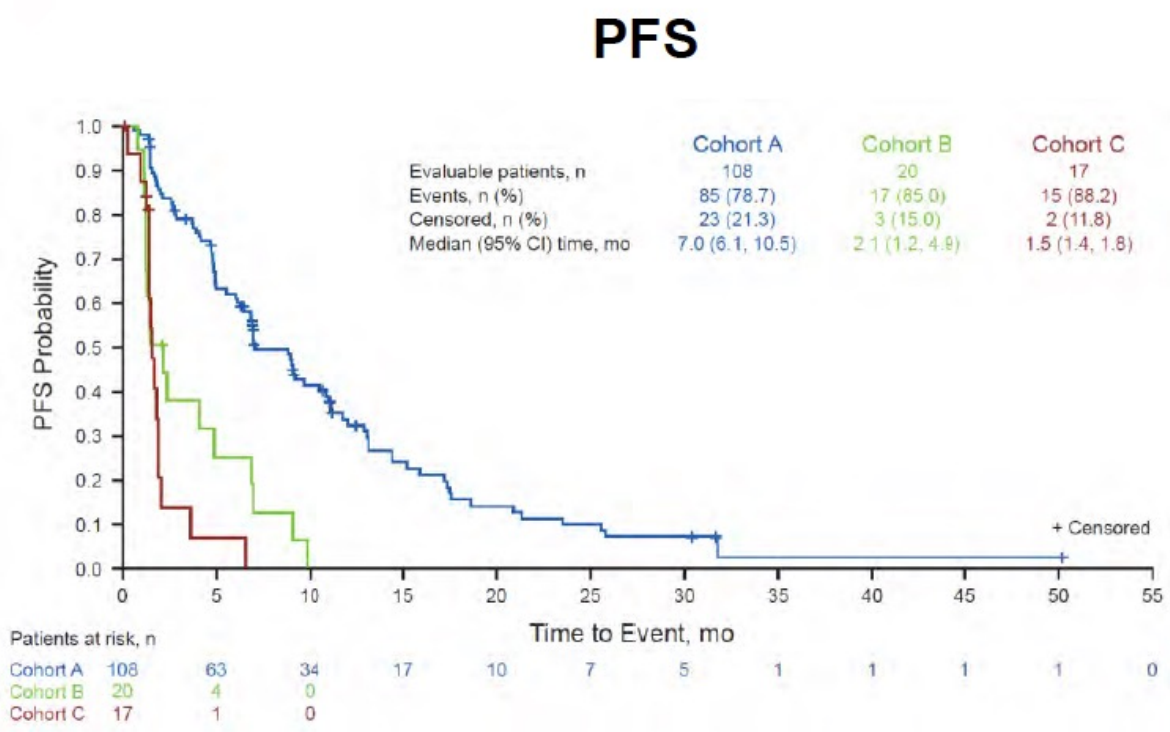
Parameter	Cohort A (n=108)	Cohort B (n=20)	Cohort C (n=17)
Duration of follow-up, median (range), mo	42.9 (19.9–52.2)	47.5 (43.7–51.1)	51.9 (49.5–53.7)
ORR,* % (95% CI)	37 (28, 47)	0 (0, 17)	0 (0, 20)
DCR,† % (95% CI)	82 (74, 89)	40 (19, 64)	18 (4, 43)
Best overall response, %			
Complete response	3	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)	—	—

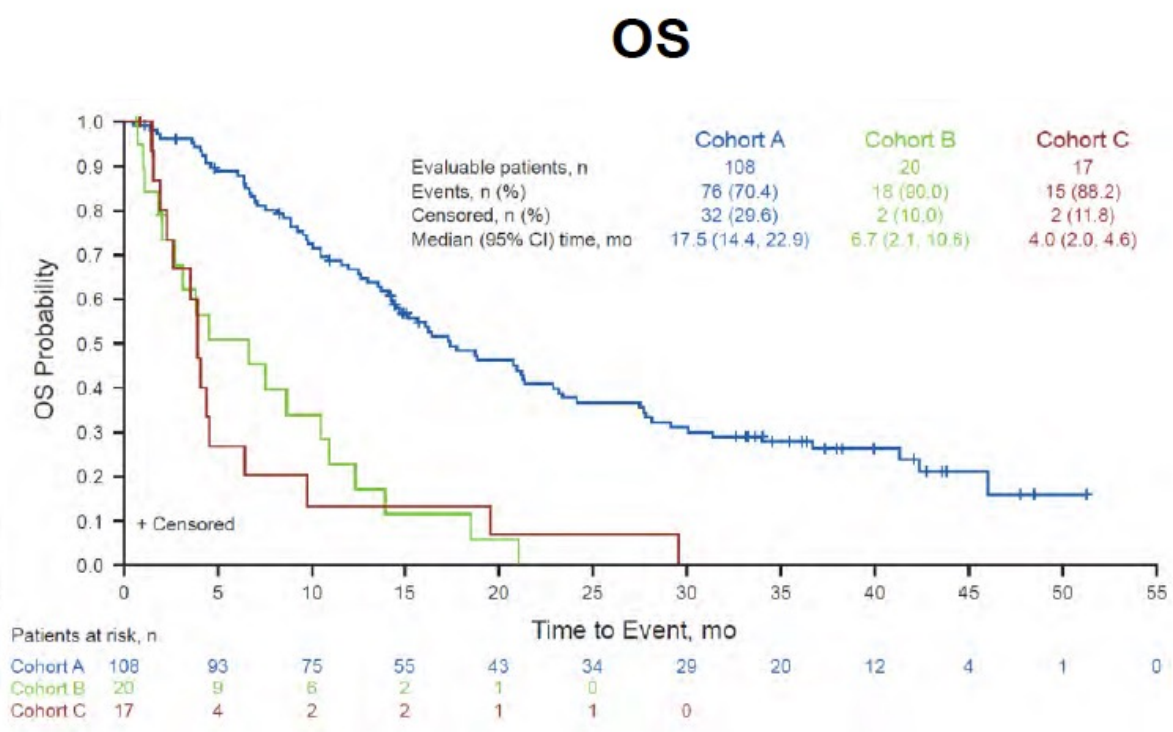
DCR, disease control rate; DOR, duration of response; ORR, objective response rate.

*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: PFS and OS in 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.

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.

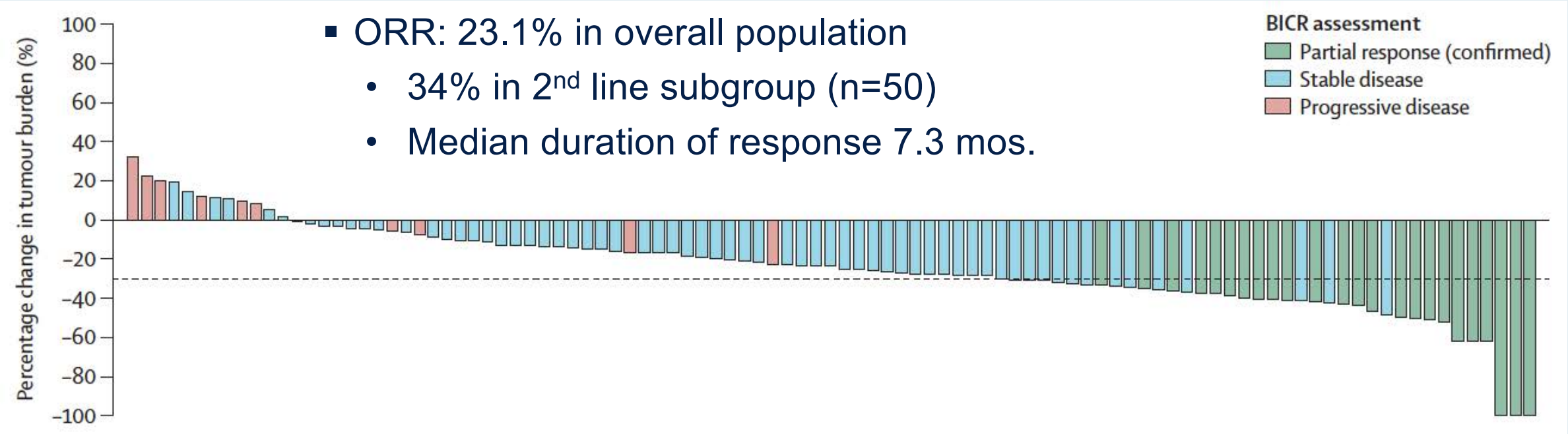
Lancet Gasteroenterol Hepatol 2021;6(10):803-15.

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 in 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 mos.



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.

Trastuzumab Deruxtecan (T-DXd)

2023 ASCO ANNUAL MEETING

Abstract LBA3000

DESTINY-PanTumor02

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

Funda Meric-Bernstam

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 5, 2023

Additional authors: Vicky Makker, Ana Oaknin, Do-Yo
Kyung Hae Jung, Iwona Ługowska, Luis Manso, Arán
Daniil Stroyakovskiy, Chiedozie Anoka, Yan Ma, Soha

On behalf of the DESTINY-PanTumor02

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Funda Meric-Bernstam, MD

J Clin Oncol 2024;42(1):47-58

Original Reports | Gynecologic Cancer

Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

Funda Meric-Bernstam, MD[1]; Vicky Makker, MD[2,3]; Ana Oaknin, MD[4]; Do-Youn Oh, MD[5]; Susana Banerjee, PhD[6]; Antonio González-Martín, MD[7]; Kyung Hae Jung, MD[8]; Iwona Ługowska, MD[9]; Luis Manso, MD[10]; Aránzazu Manzano, MD[11]; Bohuslav Melichar, MD[12]; Salvatore Siena, MD[13]; Daniil Stroyakovskiy, MD[14]; Anitra Fielding, MBChB[15]; Yan Ma, MSc[16]; Soham Puvvada, MD[15]; Norah Shire, PhD[15]; and Jung-Yun Lee, MD[17]

RTP RESEARCH TO PRACTICE

DESTINY-PanTumor02: Phase II Basket Trial Schema

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd
5.4 mg/kg
q3w

n≈40 per cohort planned

(Cohorts with no objective responses in the first 15 patients were to be closed)

- **Cervical cancer**
- **Endometrial cancer**
- **Ovarian cancer**
- **Biliary tract cancer**
- **Pancreatic cancer**
- **Bladder cancer**
- **Other tumors**[b]

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

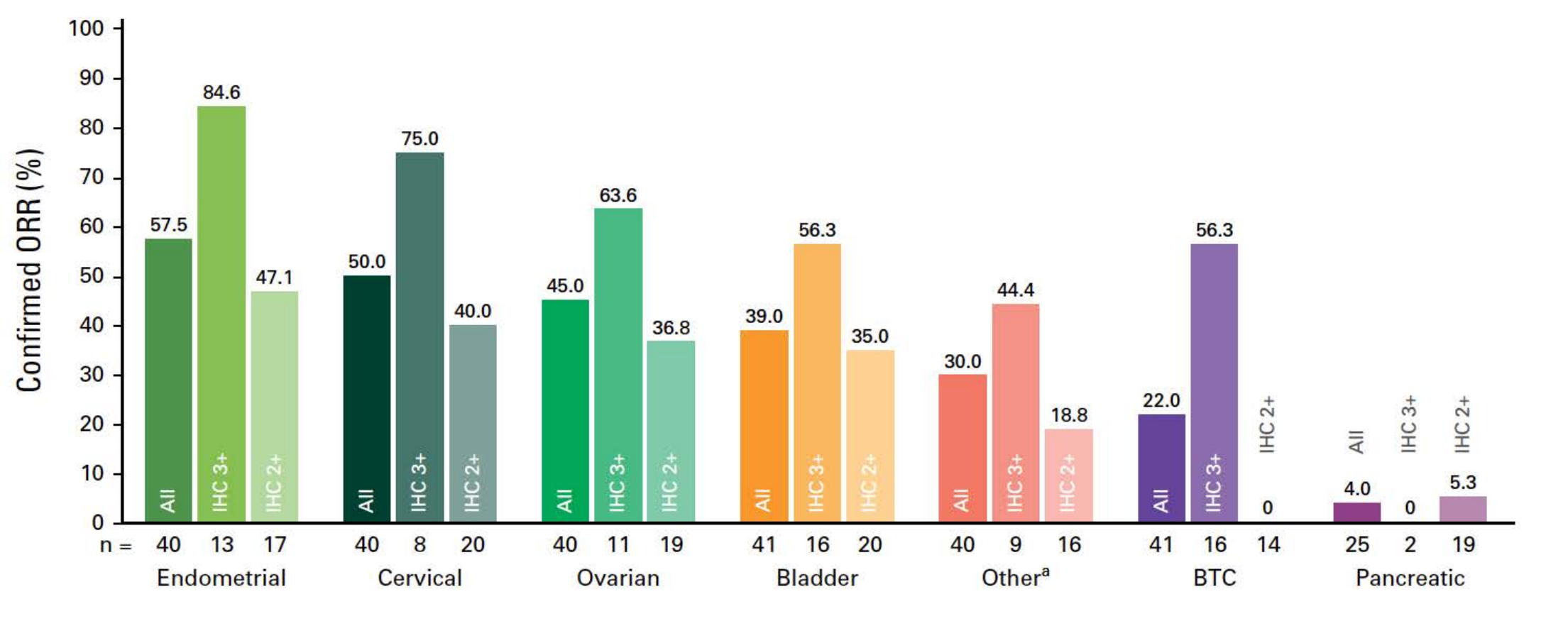
- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

Meric-Bernstam F et al. ASCO 2023;Abstract LBA3000; Meric-Bernstam F et al. *J Clin Oncol* 2024;42(1):47-58.

DESTINY-PanTumor02: Objective Response Rate by HER2 Status



Meric-Bernstam F et al. ASCO 2023;Abstract LBA3000; Meric-Bernstam F et al. *J Clin Oncol* 2024;42(1):47-58.

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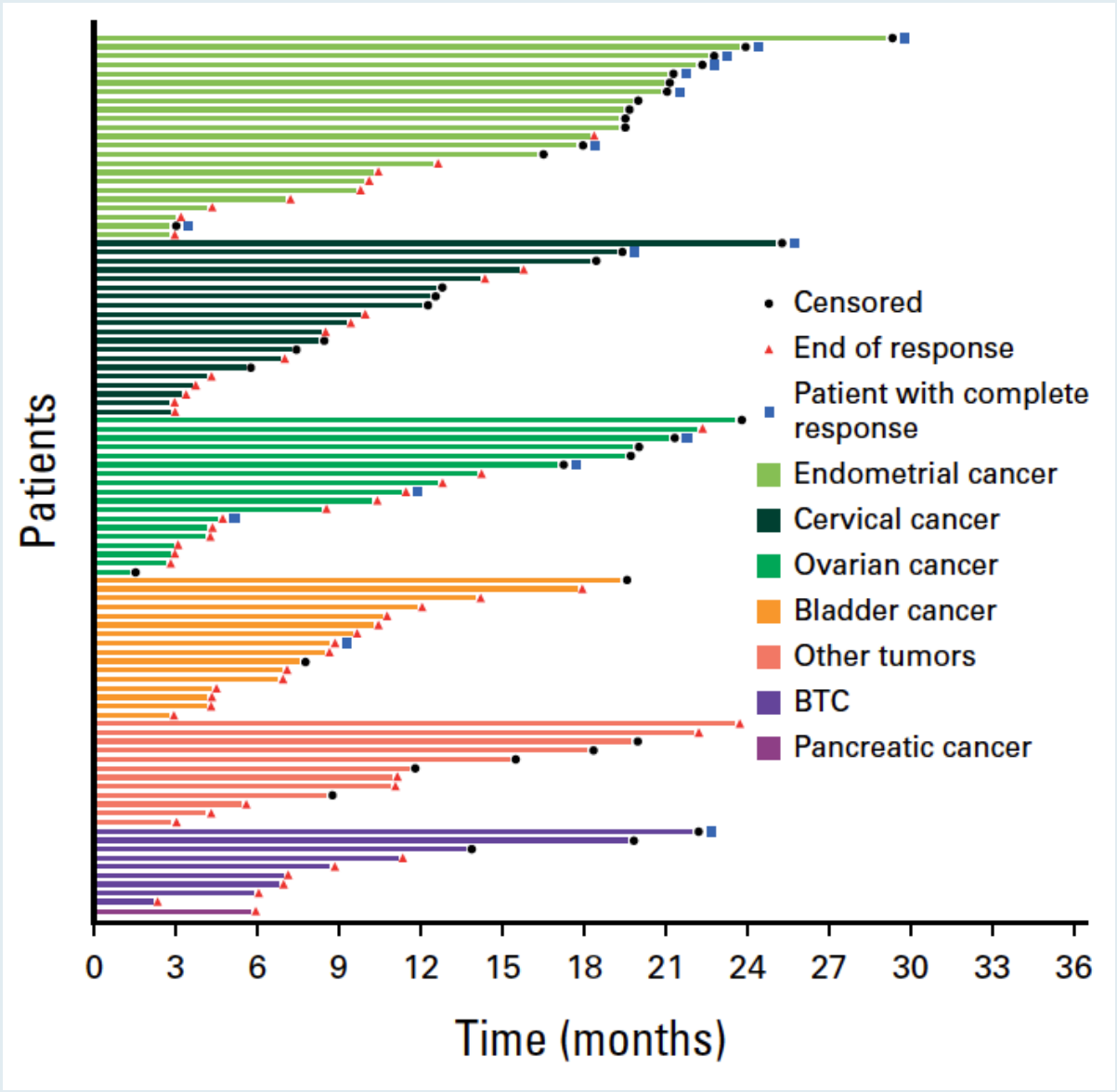
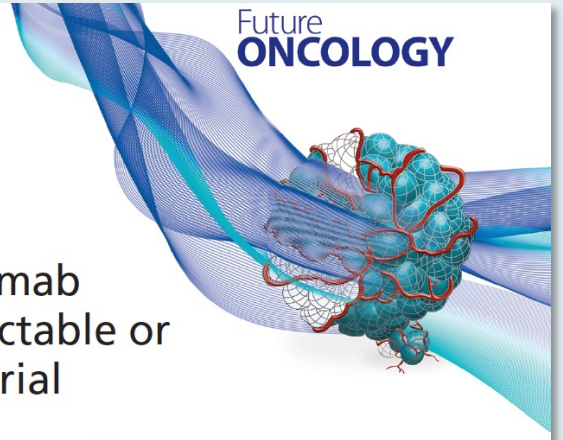
DESTINY-PanTumor02: Duration of Response



Meric-Bernstam F et al. *J Clin Oncol* 2024;42(1):47-58.

Future Oncol 2022 Jun;18(19):2351-60



Multicenter phase II trial of trastuzumab deruxtecan for HER2-positive unresectable or recurrent biliary tract cancer: HERB trial

Akihiro Ohba[1], Chigusa Morizane*[,1], Makoto Ueno[2], Satoshi Kobayashi[2], Yasuyuki Kawamoto[3], Yoshito Komatsu[4], Masafumi Ikeda[5], Mitsuhito Sasaki[5], Naohiro Okano[6], Junji Furuse[6], Nobuyoshi Hiraoka[7], Hiroshi Yoshida[7], Aya Kuchiba[8], Ryo Sadachi[8], Kenichi Nakamura[9], Naoko Matsui[9], Yoshiaki Nakamura[10], Wataru Okamoto[11], Takayuki Yoshino[10] & Takuji Okusaka[1]

2022 ASCO ANNUAL MEETING

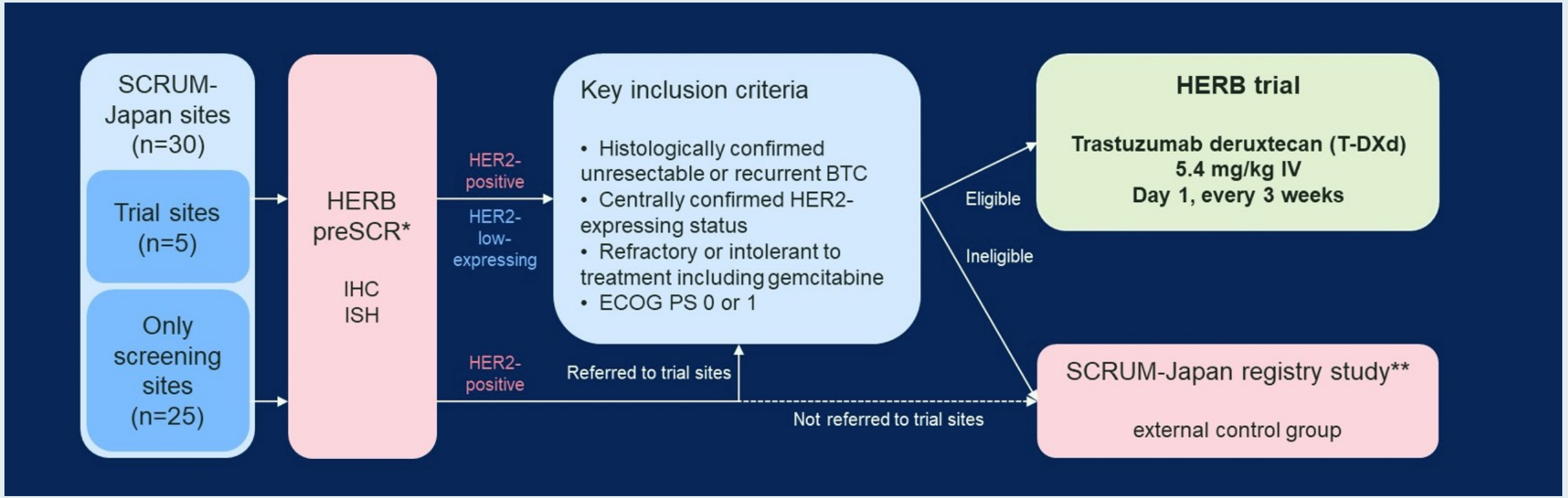
Abstract 4006

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. *Future Oncol* 2022 Jun;18(19):2351-60; ASCO 2022;Abstract 4006.

RTP RESEARCH TO PRACTICE

HERB Primary Endpoint: Confirmed Objective Response Rate by BICR with T-DXd in BTC

- Tumor response

*: P =0.01

	HER2-positive (n=22)	HER2-low-expressing (n=8)	All pts (n=30)
Confirmed ORR (90% CI)	**36.4% (19.6-56.1)***	12.5% –	30.0% –
(95% CI)	(17.2–59.3)	(0.3–52.7)	(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 BTC

	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 in BTC

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/Pneumonitis with T-DXd in BTC

	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.

What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Hybrid Symposium Series Held During the 49th Annual ONS Congress

Hepatobiliary Cancers

Saturday, April 27, 2024
6:00 AM – 7:30 AM

Faculty

Blanca Ledezma, MSN, NP, AOCNP
Stacey Stein, MD
Amanda K Wagner, APRN-CNP, AOCNP
Mark Yarchoan, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Hybrid Symposium Series Held During the 49th Annual ONS Congress

Myelofibrosis

Saturday, April 27, 2024
12:15 PM – 1:45 PM

Faculty

Ilene Galinsky, NP
Andrew T Kuykendall, MD
Sara M Tinsley-Vance, PhD, APRN, AOCN
Abdulraheem Yacoub, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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

To Claim NCPD Credit

In-person attendees: Please refer to the program syllabus for the NCPD credit link or QR code.

Virtual attendees: The NCPD credit link is posted in the chat room.

NCPD/ONCC credit information will be emailed to each participant within 1 to 2 business days.

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