Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastroesophageal and Hepatobiliary Cancers — A 2023 Post-ASCO GI Webcast

A CME/MOC-Accredited Virtual Event

Wednesday, March 8, 2023

5:00 PM – 6:00 PM ET

Consulting Clinical Investigators

Lipika Goyal, MD, MPhil

Zev Wainberg, MD, MSc

Faculty Panel

Eric H Lee, MD, PhD

Neil Morganstein, MD

Swati Vishwanathan, MD

Moderator

Neil Love, MD

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Consulting Clinical Investigators

Lipika Goyal, MD, MPhil
Director of Gastrointestinal Oncology
Stanford Cancer Center
Associate Professor
Stanford University School of Medicine
Palo Alto, California

Zev Wainberg, MD, MSc
Co-Director, GI Oncology Program
Director of Early Phase Clinical Research
Jonsson Comprehensive Cancer Center
UCLA School of Medicine
Los Angeles, California

Moderator
Neil Love, MD
Research To Practice

Faculty Panel

Eric H Lee, MD, PhD
Hematologist/Oncology and Research Director
Compassionate Cancer Care Medical Group
Fountain Valley, California

Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey

Swati Vishwanathan, MD
Attending Physician
Oncology/Hematology
United Hospital Center
WVU Medicine
Bridgeport, West Virginia

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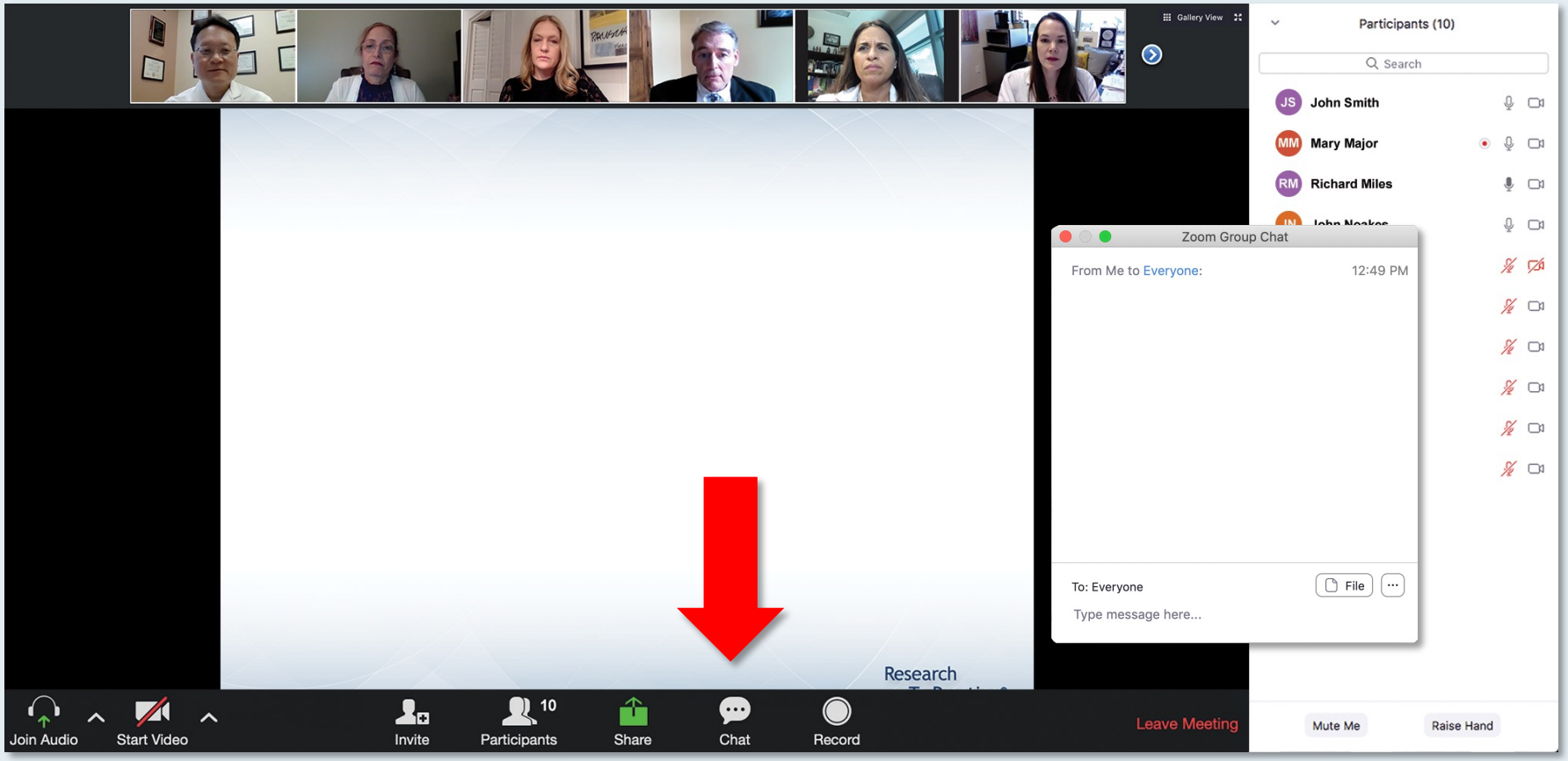
We Encourage Clinicians in Practice to Submit Questions



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

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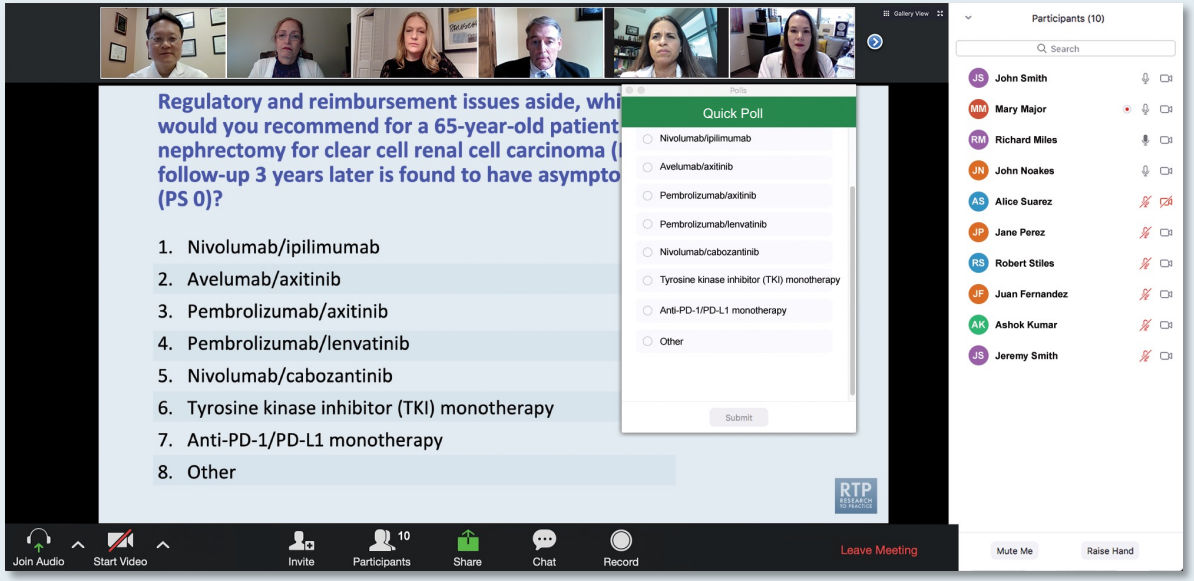
Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



Meet The Professor
Optimizing the Management of Colorectal Cancer

Wednesday, March 22, 2023
5:00 PM – 6:00 PM ET

Faculty

John Strickler, MD

Moderator

Neil Love, MD

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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Ovarian Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2023 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Sunday, March 26, 2023

11:45 AM – 1:15 PM ET

Faculty

Mansoor Raza Mirza, MD

Amit M Oza, MD

Richard T Penson, MD, MRCP

Moderator

Joyce F Liu, MD, MPH

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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Endometrial Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2023 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Monday, March 27, 2023

11:45 AM – 1:15 PM ET

Faculty

Robert L Coleman, MD

Matthew A Powell, MD

Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH

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

A Multitumor CME/MOC-Accredited Live Webinar Series

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Tuesday, April 4, 2023
5:00 PM – 6:00 PM ET

Faculty

Uma Borate, MD, MS

Andrew H Wei, MBBS, PhD

Moderator

Neil Love, MD

RTP Year in Review 2023

Meet The Professor

Optimizing the Management of ER-Positive and Triple-Negative Breast Cancer

Wednesday, April 12, 2023
5:00 PM – 6:00 PM ET

Faculty

Sara A Hurvitz, MD

Moderator

Neil Love, MD

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

A Multitumor CME/MOC-Accredited Live Webinar Series

Immunotherapy and Other Nontargeted Approaches for Lung Cancer

Thursday, April 13, 2023
5:00 PM – 6:00 PM ET

Faculty

Luis Paz-Ares, MD, PhD

Heather Wakelee, MD

Moderator

Neil Love, MD

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of Gastroesophageal Cancers

DR MANISH SHAH

WEILL CORNELL MEDICINE

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Neil Love, MD

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

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Dr Love — Disclosures

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Dr Goyal — Disclosures

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Dr Wainberg — Disclosures

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Data and Safety Monitoring Board/Committee	Daiichi Sankyo Inc, Pfizer Inc

Dr Lee — Disclosures

No relevant conflicts of interest to disclose.

Dr Morganstein — Disclosures

No relevant conflicts of interest to disclose.

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Dr Vishwanathan — Disclosures

No relevant conflicts of interest to disclose.

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Associate Professor
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Co-Director, GI Oncology Program
Director of Early Phase Clinical Research
Jonsson Comprehensive Cancer Center
UCLA School of Medicine
Los Angeles, California

Agenda

Module 1: Gastroesophageal Cancers — Dr Wainberg

Module 2: Hepatobiliary Cancers — Dr Goyal

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Agenda

Module 1: Gastroesophageal Cancers — Dr Wainberg

- Systemic therapy considerations for patients with HER2-negative localized gastroesophageal cancers
- First-line systemic therapy for patients with metastatic esophageal or gastric cancer
- Zolbetuximab/chemotherapy as first-line treatment for HER2-negative locally advanced unresectable or metastatic gastric/GEJ cancers
- Chemotherapy/trastuzumab/pembrolizumab as first-line therapy for HER2-positive metastatic gastric cancer
- Repeat tissue biopsy versus ctDNA testing for HER2-positive GI cancers after disease progression on first-line therapy
- Trastuzumab deruxtecan as second-line therapy for patients with HER2-positive gastric cancer; management of CNS disease

Systemic therapy considerations for patients with HER2-negative localized gastroesophageal cancers

Dr Zev Wainberg (Los Angeles, California)

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First-line systemic therapy for patients with metastatic esophageal or gastric cancer

Dr Zev Wainberg (Los Angeles, California)

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Zolbetuximab/chemotherapy as first-line treatment for HER2-negative locally advanced unresectable or metastatic gastric and gastroesophageal junction cancers

Dr Zev Wainberg (Los Angeles, California)

RTP RESEARCH TO PRACTICE

Chemotherapy/trastuzumab/pembrolizumab as first-line therapy for HER2-positive metastatic gastric cancer

Dr Zev Wainberg (Los Angeles, California)

RTP RESEARCH TO PRACTICE

Repeat tissue biopsy versus ctDNA testing for HER2-positive GI cancers after disease progression on first-line therapy

Dr Zev Wainberg (Los Angeles, California)

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Trastuzumab deruxtecan as second-line therapy for patients with HER2-positive gastric cancer; management of CNS disease

Dr Zev Wainberg (Los Angeles, California)

Agenda

Module 2: Hepatobiliary Cancers — Dr Goyal

- Tissue biopsy for patients with suspected hepatocellular carcinoma (HCC)
- Atezolizumab/bevacizumab versus durvalumab/tremelimumab as first-line therapy for HCC; disease etiology and response to treatment
- Liver-directed therapy in the era of effective novel systemic regimens
- First-line single-agent immunotherapy for patients with HCC
- Sequencing tyrosine kinase inhibitors for patients with HCC with and without contraindications to immunotherapy
- Perspective on positive top-line data from the IMbrave050 trial evaluating adjuvant atezolizumab/bevacizumab for high-risk HCC
- Survival benefit with durvalumab/gemcitabine/cisplatin for advanced biliary tract cancers (BTCs) in the TOPAZ-1 trial — A new standard?
- Spectrum of targetable genetic alterations in BTCs; novel FGFR2 inhibitors for cholangiocarcinoma

Tissue biopsy for patients with suspected hepatocellular carcinoma (HCC)

Dr Lipika Goyal (Palo Alto, California)

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Atezolizumab/bevacizumab versus durvalumab/tremelimumab as first-line therapy for HCC; disease etiology and response to treatment

Dr Lipika Goyal (Palo Alto, California)

Liver-directed therapy in the era of effective novel systemic regimens

Dr Lipika Goyal (Palo Alto, California)

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First-line single-agent immunotherapy for patients with HCC

Dr Lipika Goyal (Palo Alto, California)

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Sequencing tyrosine kinase inhibitors for patients with HCC with and without contraindications to immunotherapy

Dr Lipika Goyal (Palo Alto, California)

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Perspective on positive top-line data from the IMbrave050 trial evaluating adjuvant atezolizumab/bevacizumab for high-risk HCC

Dr Lipika Goyal (Palo Alto, California)

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Survival benefit with durvalumab/gemcitabine/cisplatin for advanced biliary tract cancers (BTCs) in the TOPAZ-1 trial — A new standard?

Dr Lipika Goyal (Palo Alto, California)

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Spectrum of targetable genetic alterations in BTCs; novel FGFR2 inhibitors for cholangiocarcinoma

Dr Lipika Goyal (Palo Alto, California)

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Thank you for joining us!

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

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

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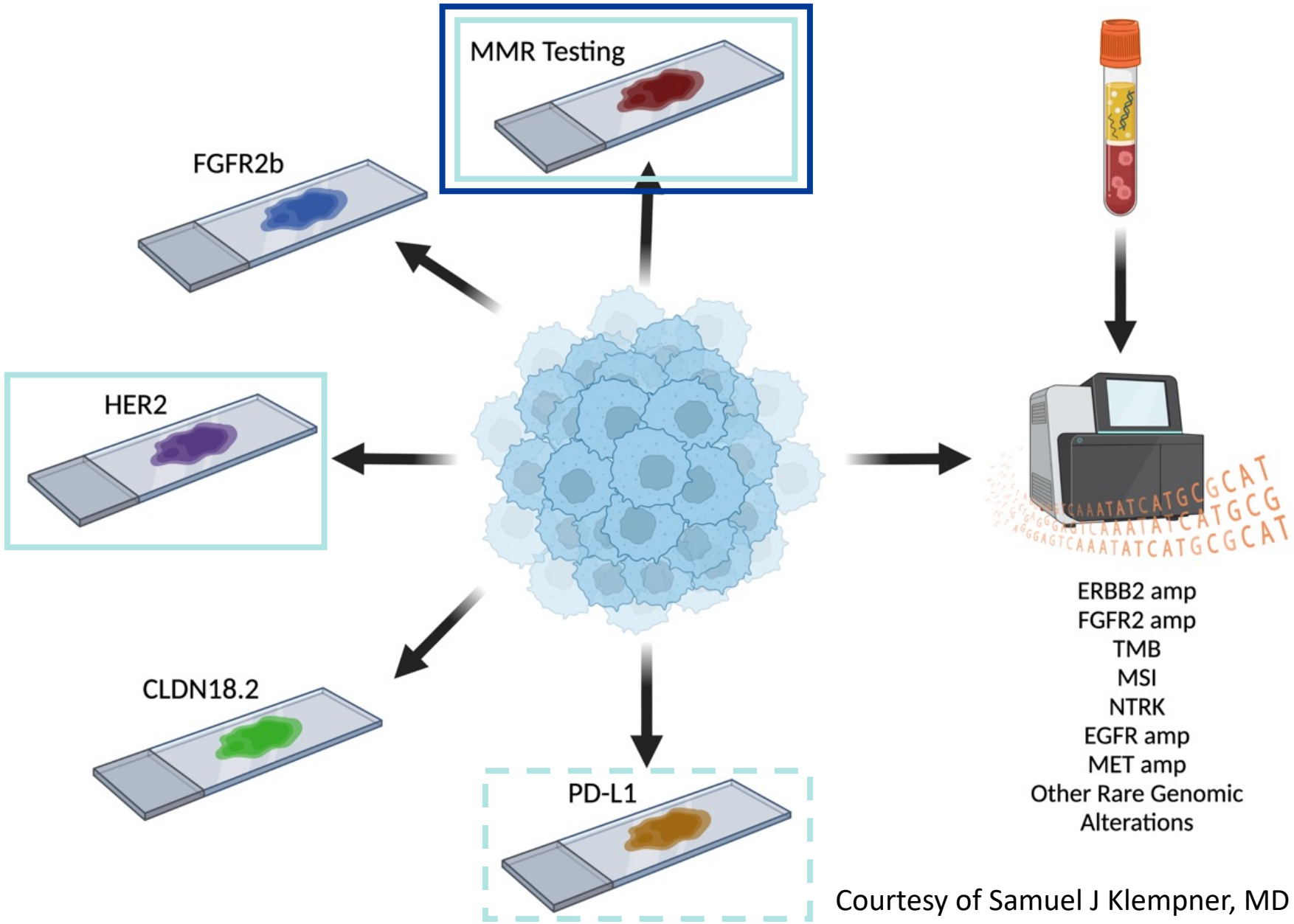
Supplementary Slides

Key Biomarkers to Know

Need to Know for ALL Advanced GEA

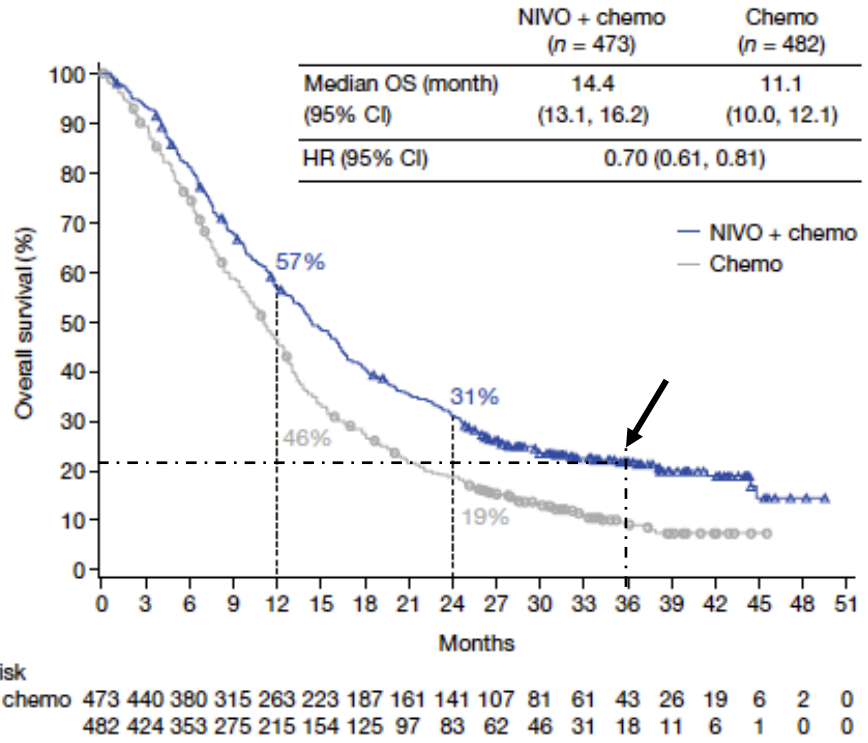
Should Know for Localized GEA



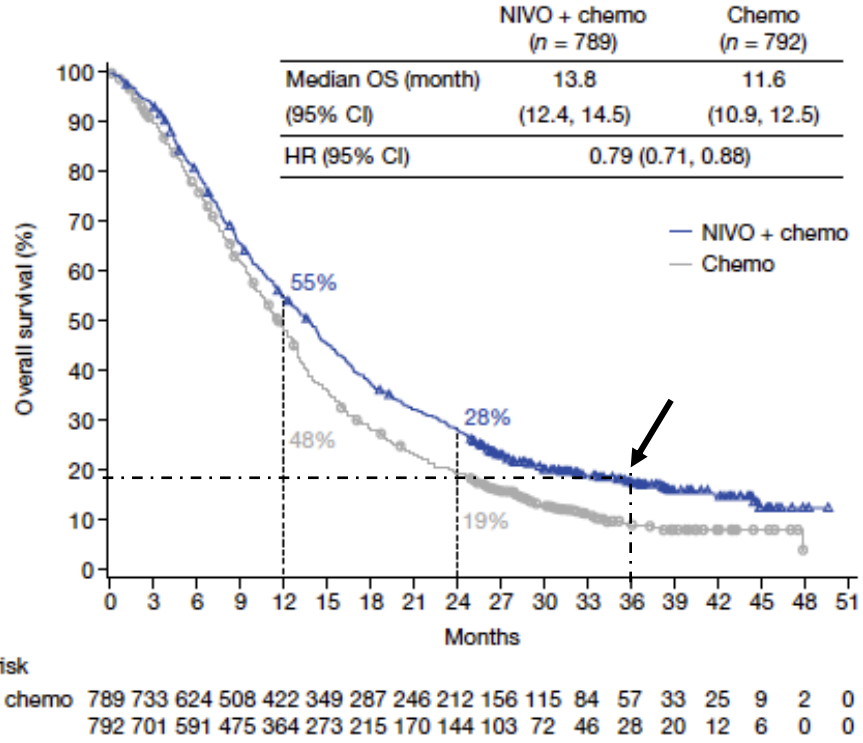
Courtesy of Samuel J Klempner, MD

Frontline Chemo-PD-1 is Here to Stay: CM-649

OS in CPS ≥ 5



OS in CPS All Randomized



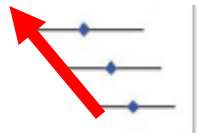
- CM-649 is a positive trial for CPS ≥ 5 (primary) and all randomized (secondary)
- 4/2021: Nivo FDA approved with 5FU/platinum for advanced/metastatic GEA, regardless of PD-L1
- 15% increase in G3-4 TRAEs (59% vs 44%) in nivo-chemo vs. chemo

Lancet 2021, Nature 2022

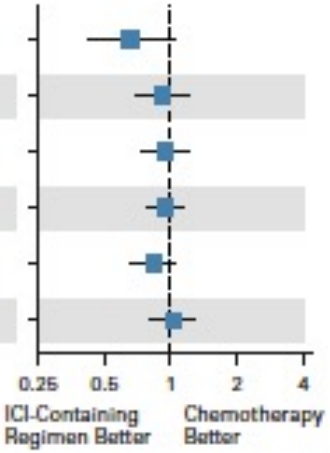
Courtesy of Samuel J Klempner, MD

PD-L1 Strata in Frontline Chemo-IO

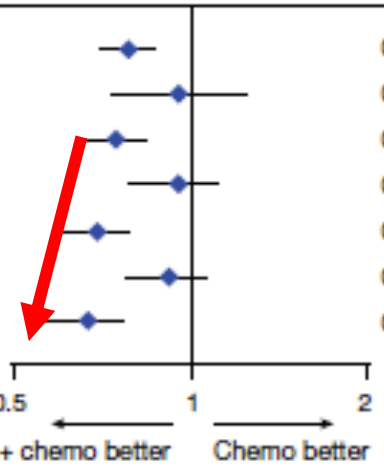
PD-L1 expression	CPS ≥10	146	142	0.56 (0.41-0.77)
	CPS ≥5	197	200	0.64 (0.49-0.84)
	CPS ≥1	275	271	0.73 (0.58-0.90)



Trial	Comparison	No.	Location	PD-L1 Expression	HR (95% CI)
KEYNOTE-590	Pembrolizumab plus chemotherapy *v* chemotherapy	54 *v* 46	Esophageal	CPS < 10	0.66 (0.42 to 1.04)
CheckMate-649	Nivolumab plus chemotherapy *v* chemotherapy	137 *v* 148	Gastric	CPS < 1	0.92 (0.70 to 1.23)
CheckMate-649	Nivolumab plus chemotherapy *v* chemotherapy	168 *v* 173	Gastric	CPS 1–4	0.95 (0.75 to 1.21)[a]
CheckMate-649	Nivolumab plus chemotherapy *v* chemotherapy	316 *v* 310	Gastric	CPS < 5	0.94 (0.78 to 1.13)
KEYNOTE-062	Pembrolizumab plus chemotherapy *v* chemotherapy	158 *v* 160	Gastric	CPS 1–9	0.84 (0.66 to 1.06)[a]
KEYNOTE-062	Pembrolizumab *v* chemotherapy	164 *v* 160	Gastric	CPS 1–9	1.03 (0.81 to 1.30)[a]



Population	Nivolumab plus chemotherapy	Chemotherapy	Unstratified HR for death (95% CI)
Overall (*n* = 1,581)	13.8	11.6	0.78 (0.70, 0.87)
PD-L1 CPS <1 (*n* = 265)	13.1	12.5	0.95 (0.73, 1.24)
PD-L1 CPS ≥1 (*n* = 1,297)	13.8	11.3	0.74 (0.66, 0.84)
PD-L1 CPS <5 (*n* = 607)	12.4	12.3	0.94 (0.79, 1.11)
PD-L1 CPS ≥5 (*n* = 955)	14.4	11.1	0.69 (0.60, 0.79)
PD-L1 CPS <10 (*n* = 795)	12.4	12.5	0.91 (0.78, 1.06)
PD-L1 CPS ≥10 (*n* = 767)	15.0	10.9	0.66 (0.56, 0.77)

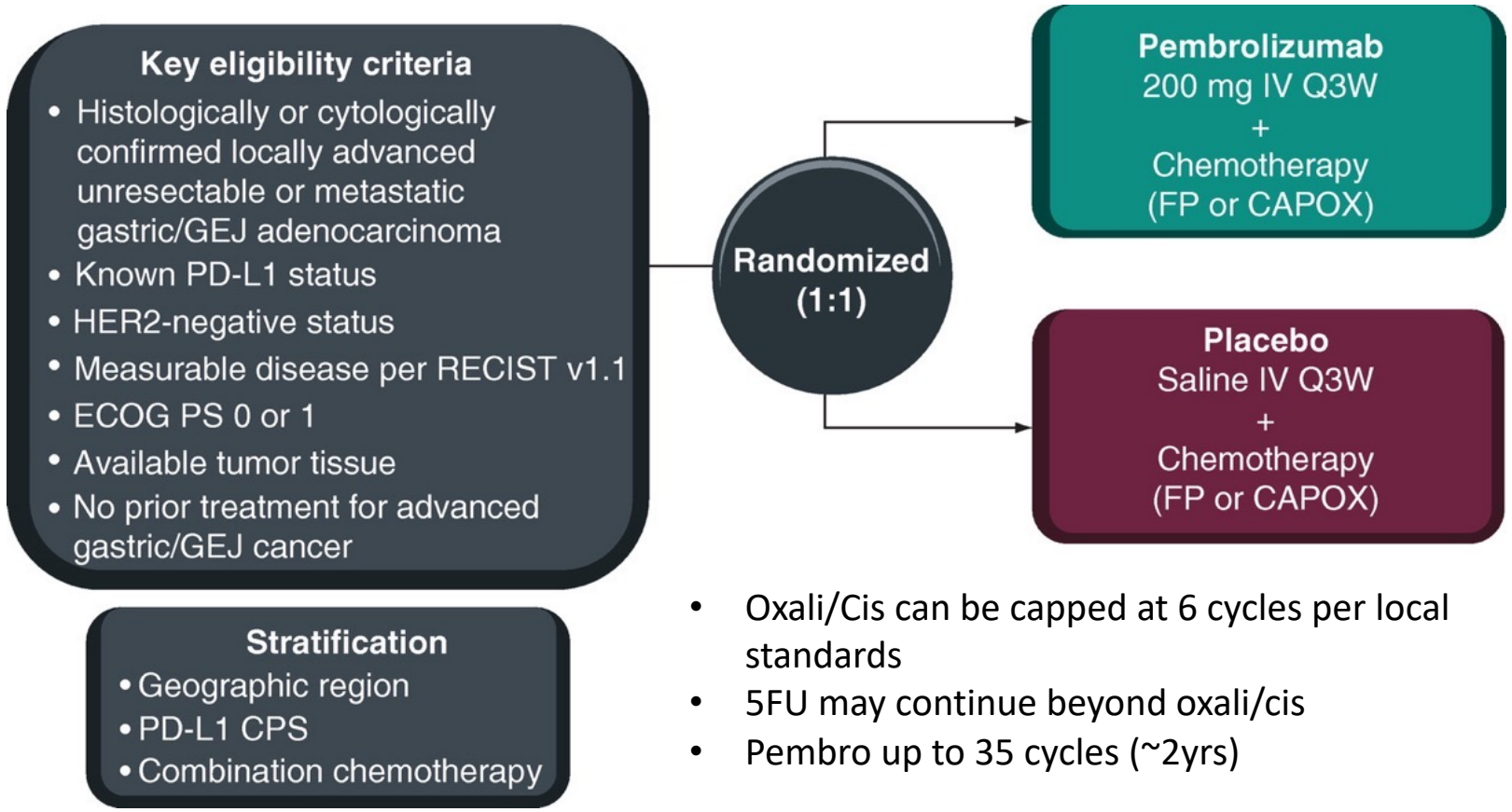


- Outside dMMR/MSI-H PD-L1 CPS expression is the best predictor of ICI benefit in frontline GEA
- The magnitude of benefit differs across PD-L1 CPS subgroups
- Risk/benefit should be discussed with all patients
- PD-L1 testing remains important

ESMO 9/2021, JCO 2022, Nature 2022

Courtesy of Samuel J Klempner, MD

Other Chemo-IO Approaches: KEYNOTE-859



- Oxali/Cis can be capped at 6 cycles per local standards
- 5FU may continue beyond oxali/cis
- Pembro up to 35 cycles (~2yrs)

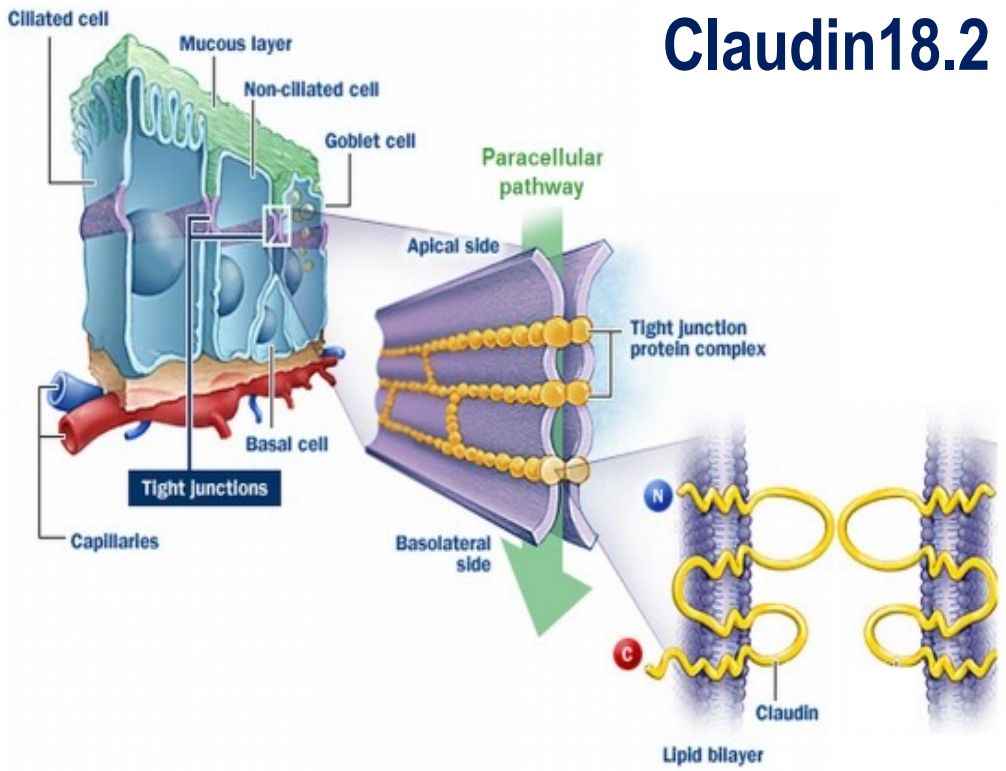
- Sample size = 1,579pts
- Primary Endpoint = OS
- Secondary = PFS, ORR, DOR

11/22/2022: Press release that KN-859 met OS in all randomized, and that PFS and ORR were improved vs chemo

Courtesy of Samuel J Klempner, MD

CLAUDIN18.2 – A NOVEL TARGET

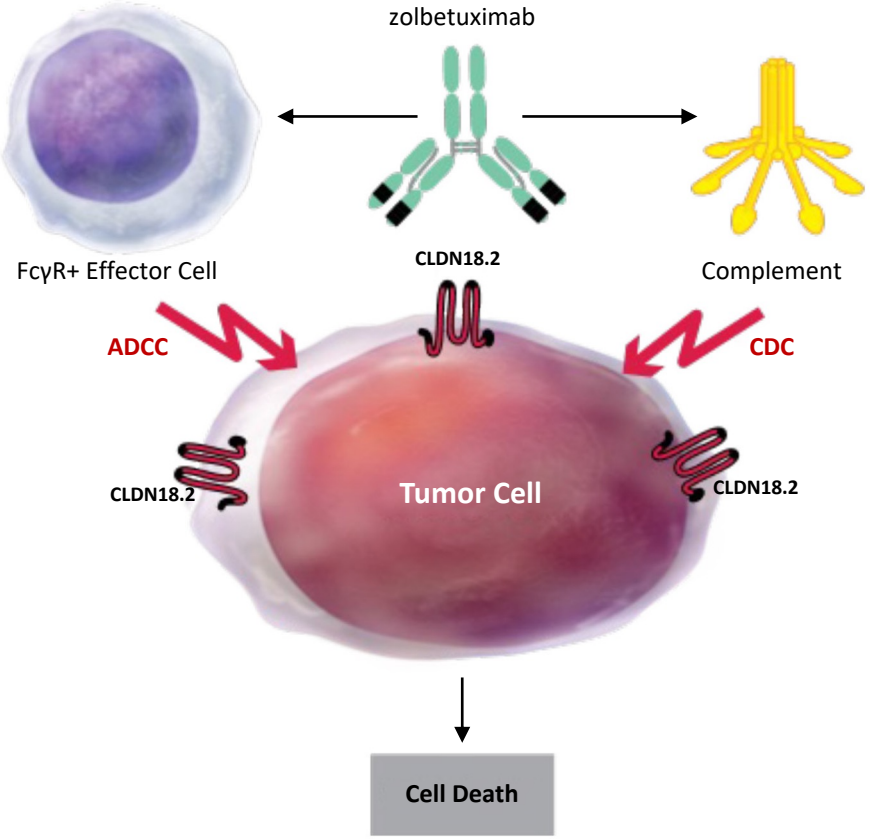
Claudin18.2



- Member of the claudin family
- Major structural component of tight junctions
- Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except: stomach mucosa, but with limited accessibility

Courtesy of Florian Lordick, MD, PhD

Mechanism of Action of Zolbetuximab



Sahin U et al. *Ann Oncol.* 2021 May;32(5):609-619

SPOTLIGHT – STUDY DESIGN

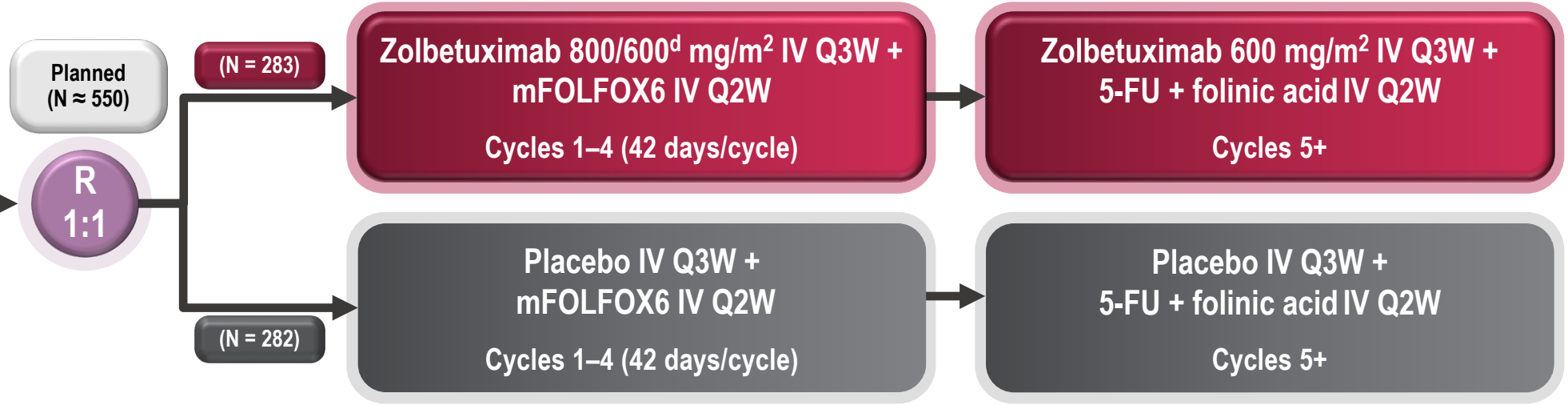
Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial

Key Eligibility Criteria

- Previously untreated LA unresectable or mG/GEJ adenocarcinoma
- CLDN18.2+ (moderate-to-strong CLDN18 staining in ≥75% of tumor cells)[b]
- HER2–[c]
- ECOG PS 0–1

Stratification Factors

- Region (Asia vs non-Asia)
- Number organs w/ metastases (0–2 vs ≥3)
- Prior gastrectomy (yes vs no)



Primary End Point

- PFS[e]

Key Secondary End Points

- OS
- TTCD in GHS/QoL, PF, and OG25-Pain

Secondary End Points

- ORR[e]
- DOR[e]
- Safety
- PROs

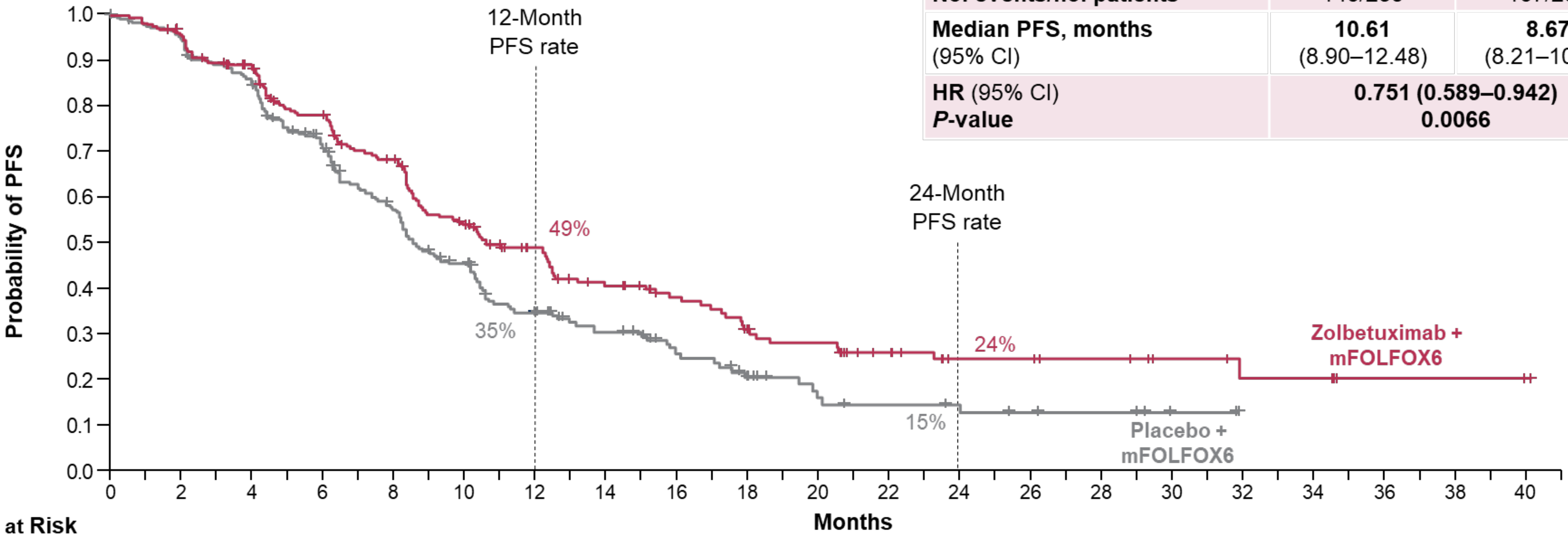
[a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; [e]Per RECIST v1.1 by independent review committee.

Courtesy of Florian Lordick, MD, PhD

Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

SPOTLIGHT – PROGRESSION-FREE SURVIVAL

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	146/283	167/282
Median PFS, months (95% CI)	**10.61** (8.90–12.48)	**8.67** (8.21–10.28)
HR (95% CI) *P*-value	**0.751 (0.589–0.942)** **0.0066**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	263	254	232	226	190	187	148	143	108	102	84	78	59	56	53	43	40	33	28	28	21	19	17	12	12	12	10	10	9	7	7	5	5	5	2	2	2	2	2	1	0
Placebo + mFOLFOX6	282	273	260	237	226	183	168	136	122	91	83	60	56	43	40	38	26	25	19	14	12	9	9	9	8	7	6	5	5	4	2	2	0	0	0	0	0	0	0	0	0	0

- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

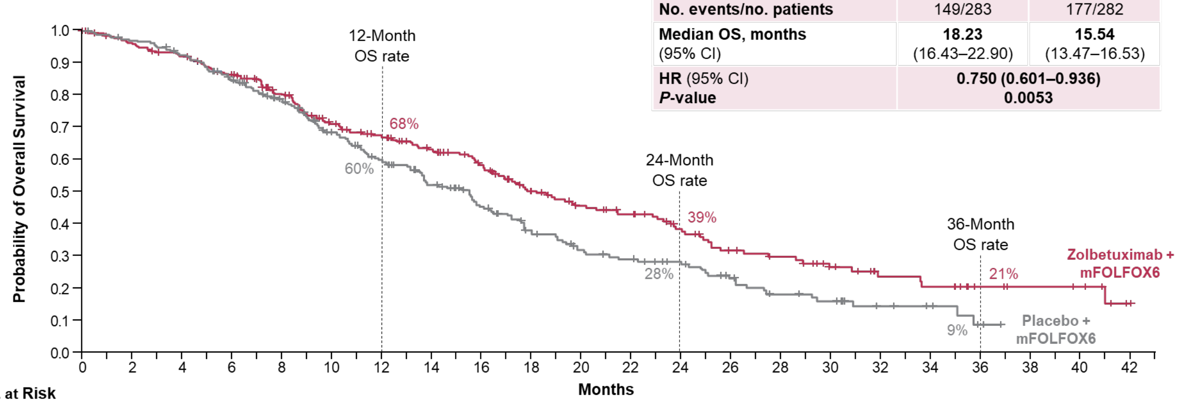
Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).
[a]Per RECIST version 1.1.

Courtesy of Florian Lordick, MD, PhD

Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

SPOTLIGHT – OVERALL SURVIVAL

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	**18.23** (16.43–22.90)	**15.54** (13.47–16.53)
HR (95% CI) *P*-value	**0.750 (0.601–0.936)** **0.0053**	

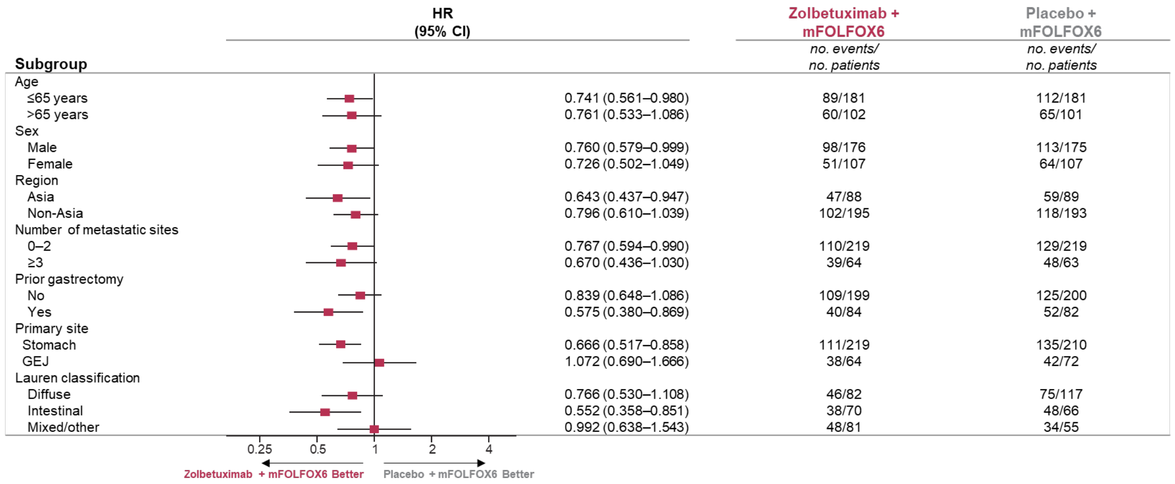


No. at Risk

Zolbetuximab + mFOLFOX6	283	270	264	255	251	241	233	217	196	178	164	152	146	135	125	117	107	93	83	75	70	67	62	58	49	42	34	32	30	27	23	20	15	15	13	13	9	8	7	7	6	4	1	0
Placebo + mFOLFOX6	282	277	271	266	253	242	224	210	197	183	164	152	139	129	108	101	85	77	64	60	49	42	40	36	34	30	25	21	18	17	15	9	8	7	6	5	2	0	0	0	0	0	0	0

- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 22.14 months (zolbetuximab + mFOLFOX6) vs 20.93 months (placebo + mFOLFOX6).



- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 across most subgroups

Data cutoff: September 9, 2022.

Courtesy of Florian Lordick, MD, PhD

Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

SPOTLIGHT – OVERALL RESPONSE RATE

	Zolbetuximab + mFOLFOX6 (N = 211)	Placebo + mFOLFOX6 (N = 211)
Patients[a], n	128	131
ORR[b], % (95% CI)	60.7 (53.72–67.30)	62.1 (55.17–68.66)
BOR[c,d], n (%)		
CR	12 (5.7)	7 (3.3)
PR	116 (55.0)	124 (58.8)
SD	45 (21.3)	52 (24.6)
PD	14 (6.6)	14 (6.6)
Median DOR[b], months, (95% CI)	8.51 (6.80–10.25)	8.11 (6.47–11.37)
3rd quartile, months (95% CI)	29.9 (10.41–NE)	15.5 (13.27–NE)

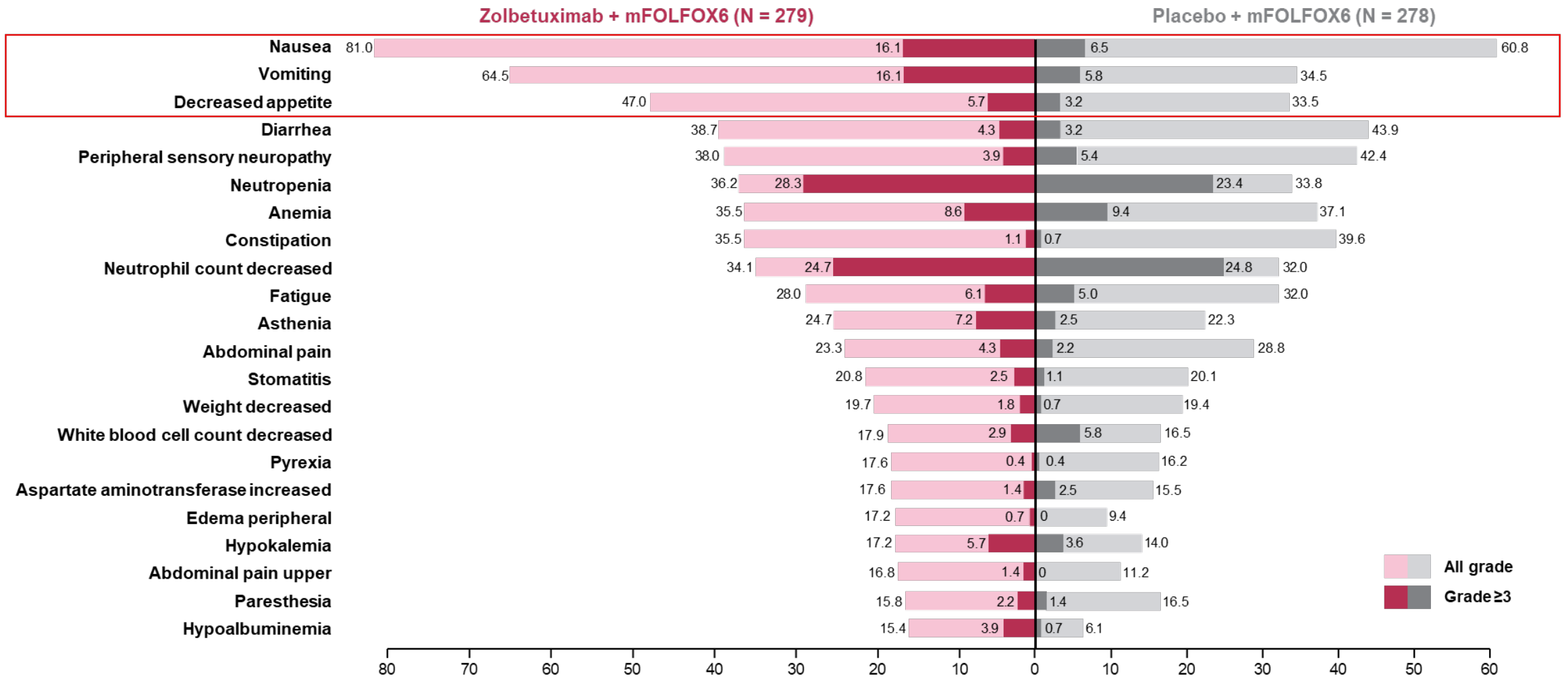
- Response rates were similar between treatment arms
- Formal analysis of PROs is pending
  - Initial descriptive analysis did not indicate differences between treatment arms

[a]Patients with measurable disease. [b]Per RECIST version 1.1 by independent review committee; [c]Patients with non-CR/non-PD, no disease, missing data, or who could not be evaluated are not shown; [d]Patients with missing data had no post-baseline imaging assessment.

Courtesy of Florian Lordick, MD, PhD

Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

SPOTLIGHT – TEAES IN ≥15% OF ALL TREATED PATIENTS



- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

[a]Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0.

Courtesy of Florian Lordick, MD, PhD

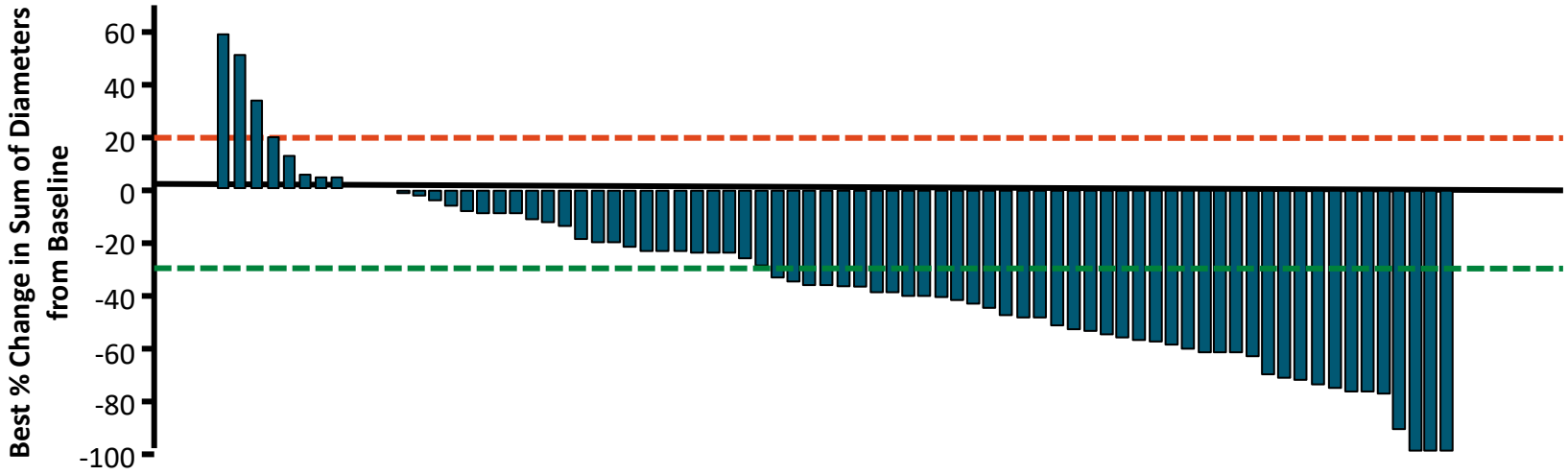
Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

Tumor Size Change with T-DXd in HER2+ Adv Gastric/GEJ Cancer After Trastuzumab (DESTINY-Gastric01 and 02)

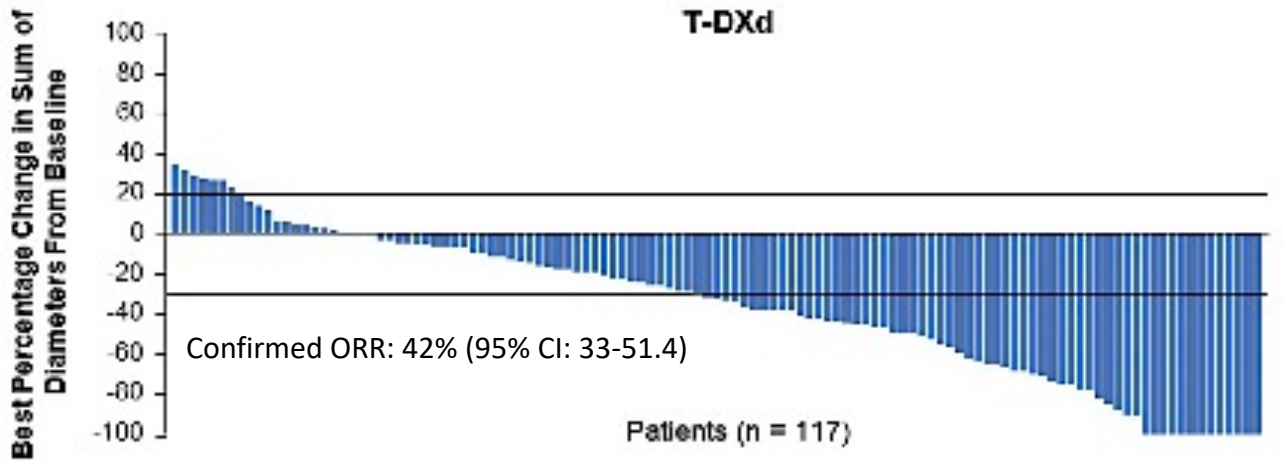
Efficacy[2]	T-DXd (N = 79)
ORR, % (95% CI)	41.8 (30.8-53.4)
Median DOR, mo	8.1
Median PFS, mo (95% CI)	5.6 (4.2-8.3)
Median OS, mo (95% CI)	12.1 (9.4-15.4)

Survival, mo (95% CI)[3,4]	T-DXd (n = 125)	Chemo (n = 62)
Median OS	12.5 (10.3 – 15.2)	8.9 (6.4-10.4)
HR for death: 0.60		
Median PFS	5.6 (4.3-6.9)	3.5 (2.0-4.3)
HR for PD or death: 0.47		

DESTINY-Gastric02 (US/Europe; progression on 1L trastuzumab)[1]



DESTINY-Gastric01 (Japan; progression on ≥2 prior regimens)[4]



1. Van Cutsem. ESMO 2021. Abstr LBA55. 2. Ku ESMO 2022. Abstr 1205MO. 3. Shitara. NEJM. 2020;382:2419. 4. Yamaguchi. ASCO GI 2022. Abstr 242.

Courtesy of Yelena Y Janjigian, MD

DESTINY-Gastric01 and 02: AEs with T-DXd in HER2+ Adv Gastric/GEJ Cancer After Trastuzumab

DESTINY-Gastric02 (US/Europe; progression on 1L trastuzumab)[1]

TEAEs in ≥15% of Patients, n (%)	T-DXd (N = 79)	
	Any Grade	Grade ≥3
Patients with ≥1 TRAEs	74 (93.7)	21 (26.6)
Nausea	46 (58.2)	3 (3.8)
Fatigue	29 (36.7)	3 (3.8)
Vomiting	26 (32.9)	1 (1.3)
Diarrhea	22 (27.8)	1 (1.3)
Decreased appetite	18 (22.8)	1 (1.3)
Alopecia	17 (21.5)	0
Anemia	15 (19.0)	6 (7.6)
Decreased platelet count	13 (16.5)	1 (1.3)
Decreased neutrophil count	12 (15.2)	6 (7.6)

DESTINY-Gastric01 (Japan; progression on ≥2 prior regimens)[2]

TEAEs in ≥20% of Patients Treated with T-DXd[a]

	T-DXd n = 125			PC Overall n = 62		
		Grade			Grade	
Preferred Term, %	Any	3	4	Any	3	4
Neutrophil count decreased[b]	64.8	38.4	12.8	35.5	16.1	8.1
Nausea	63.2	5.6	0	46.8	1.6	0
Decreased appetite	60.8	16.8	0	45.2	12.9	0
Anemia[c]	57.6	38.4	0	30.6	21.0	1.6
Platelet count decreased[d]	40.0	9.6	1.6	6.5	1.6	1.6
White blood cell count decreased[e]	38.4	20.8	0	35.5	8.1	3.2
Malaise	34.4	0.8	0	16.1	0	0
Diarrhea	32.8	2.4	0	32.3	1.6	0
Vomiting	26.4	0	0	8.1	0	0
Pyrexia	24.8	0	0	16.1	0	0
Constipation	24.8	0	0	24.2	0	0
Lymphocyte count decreased[f]	23.2	7.2	4.8	3.2	0	1.6
Alopecia	22.4	0	0	14.5	0	0
Fatigue	21.6	7.2	0	24.2	3.2	0

1. Van Cutsem. ESMO 2021. Abstr LBA55. 2. Yamaguchi. ASCO GI 2022. Abstr 242

Courtesy of Yelena Y Janjigian, MD

DESTINY-Gastric01 Biomarker Analysis: T-DXd in HER2+ Adv Gastric/GEJ Cancer After ≥2 Prior Regimens

- Only 30% of new tumor samples obtained after/during trastuzumab therapy
- ORR slightly higher in patients w/HER2+ tumor after/during first trastuzumab
  - ORR: 57% vs 48%
  - OS confounded by small sample size (same)
- High level of ERBB2 (mRNA or plasma) predicts high ORR
- Tissue mRNA >9.7: ORR 81% vs 23% (small sample size)
- Plasma ERBB2 detected in 64% of patients (Guardant 360)
  - ORR with *ERBB2+* ctDNA*:* 76% vs 40%
  - OS nearly doubled if ctDNA *ERBB2* >6 copy: 21 vs 12 mo median OS
- Co-occurring *EGFR/MET* amplifications associated with worse outcome

- FDA urges biopsy of all patients after trastuzumab progression
  - ~20% of patients with esophagogastric cancer have loss of HER2
- This analysis indicates that ctDNA can be used if biopsy not feasible

Shitara. ESMO World GI 2021. Abstract O14.

Courtesy of Yelena Y Janjigian, MD

DESTINY-Gastric02: Additional T-DXd Results in HER2+ Adv Gastric/GEJ Cancer After First-Line Trastuzumab

- GEJ primary: 66%[1]
  - vs 86% in DESTINY-Gastric01[2]
- Rebiopsy for HER2 mandated for all patients and centrally reviewed[1]
  - vs 30% in DESTINY-Gastric01[2]
- ORR (primary endpoint): 38% w/median PFS 5.5 mo
  - vs 27% ORR, median PFS 4.2 mo with ramucirumab/paclitaxel[3]
- No new safety signals[1]: 7.6% ILD
  - 0 Grade 3/4 events, 1 Grade 5
- Grade ≥3 TEAEs: 27%[1]
  - Compares favorably to ramucirumab/paclitaxel[3]

1. Van Cutsem. ESMO 2021. Abstr LBA55. 2. Shitara. NEJM. 2020;382:2419. 3. Wilke. Lancet. 2014;15:1224.

Courtesy of Yelena Y Janjigian, MD

Finn et al. *New Engl J Med.* 2020

IMbrave150 Study Design

Key eligibility

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy
- ECOG PS 0-1
- Child-Pugh class A liver function

Stratification

- **Region** (Asia excluding Japan[a]/Rest of world)
- **ECOG** (0/1)
- **Macrovascular invasion** and/or **extrahepatic spread** (Presence/Absence)
- **Baseline AFP** (<400/≥400 ng/mL)

R 2:1

Atezolizumab 1200 mg IV q3w + Bevacizumab 15 mg/kg q3w

N = 501

Sorafenib 400 mg bid

(open-label)

Until loss of clinical benefit or un-acceptable toxicity[b]

Survival follow-up

Co-primary endpoints

- OS
- IRF-assessed PFS per RECIST 1.1

No exclusion for main PVT

Secondary endpoints included:

- IRF-assessed ORR, DOR per RECIST 1.1 and HCC mRECIST[b]
- PROs: TTD[c] of QOL, physical and role functioning (EORTC QLQ-C30)
- Safety and tolerability assessed based on the nature, frequency and severity of AEs per NCI CTCAE version 4.0

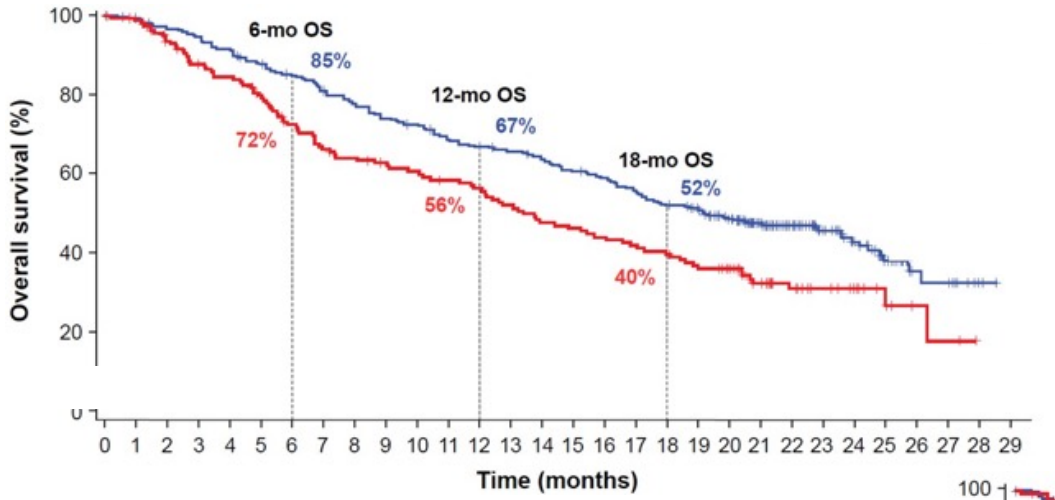
[a] Japan is included in rest of world. [b] Tumor assessment by computed tomography or magnetic resonance imaging was done at baseline and every 6 weeks until 54 weeks, then every 9 weeks thereafter.
[c] Time from randomization to first decrease from baseline of ≥ 10 points maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
AFP, α-fetoprotein; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer; IRF, independent review facility; mRECIST, modified RECIST; NCI, National Cancer Institute; PRO, patient-reported outcomes; QOL, quality of life; TTD, time to deterioration.

Courtesy of Richard S Finn, MD

IMbrave150 Trial

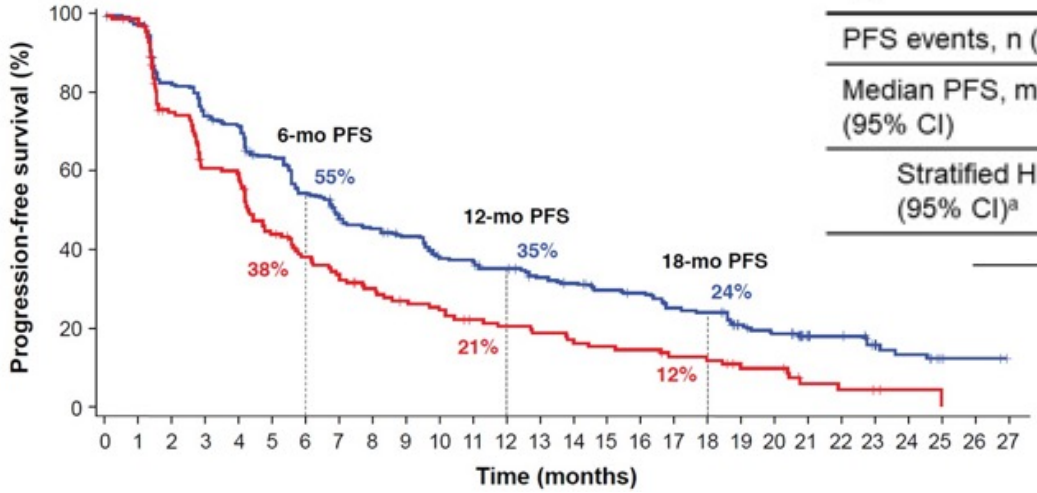
Key Efficacy Data: Updated OS and PFS

– Primary analysis OS/PFS HR: 0.58/0.59 (median follow-up: 8.6 mo)



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

– Median follow-up: 15.6 mo



Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) *P* = 0.0001[b]	

- Finn RS et al NEJM 2020, Finn RS et al ASCO GI 2021, Cheng AL J Hep 2022

Courtesy of Richard S Finn, MD

Updated response and duration of response

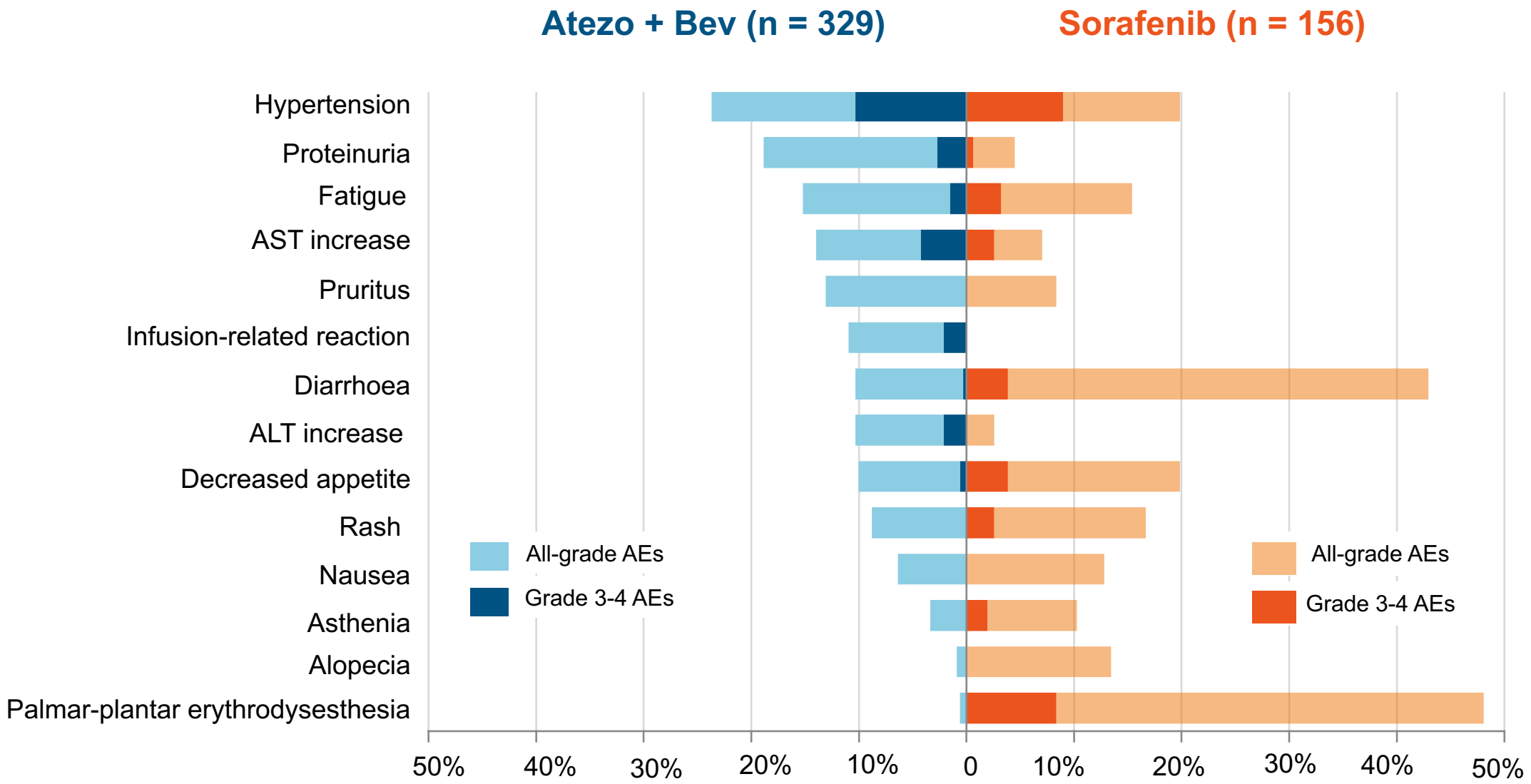
	Updated analysis[a]			
	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. DCR, disease control rate.
[a] Only patients with measurable disease at baseline were included in the analysis of ORR.
[b] Only confirmed responders were included in the analysis of ORR and DOR.

Cheng AL J Hep 2022

Courtesy of Richard S Finn, MD

TRAEs: ≥ 10% any grade in either arm



Finn et al , *N Engl J Med* 2020.

Courtesy of Richard S Finn, MD

HIMALAYA study design

HIMALAYA was an open-label, multicenter, global, Phase 3 trial

Study population
- Patients with confirmed uHCC
- BCLC B (not eligible for locoregional therapy) and C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

Stratification factors
- Macrovascular invasion: Y / N
- Etiology of liver disease: HBV / HCV / others
- Performance status: ECOG 0 / 1

R
N=1324

T300+D (n=393):
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

Durvalumab (n=389):
Durvalumab monotherapy 1500 mg Q4W*

Sorafenib (n=389):
Sorafenib 400 mg BID*

T75+D (n=153): *arm closed*†
Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

Primary objective
- OS for T300+D vs sorafenib

Key secondary objective
- OS for durvalumab vs sorafenib

Additional secondary objectives
- PFS, ORR, and DoR as assessed by investigator per RECIST v1.1
- Safety

Multiple testing procedure

OS *superiority* for T300+D vs sorafenib

↓

OS *noninferiority* for durvalumab vs sorafenib
Noninferiority margin: 1.08

↓

OS *superiority* for durvalumab vs sorafenib

*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.

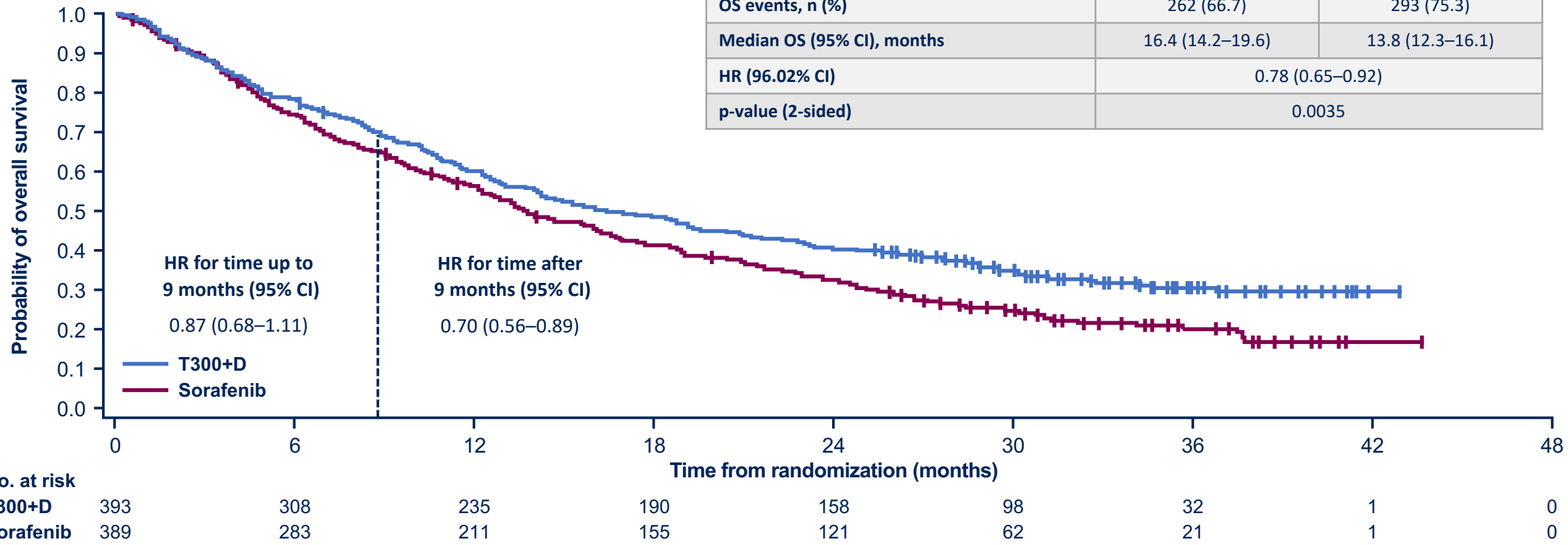
BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.

Ghassan K Abou-Alfa, MD, MBA NEJM Evidence 2022

Courtesy of Richard S Finn, MD

Primary objective: overall survival for T300+D vs sorafenib

	T300+D (n=393)	Sorafenib (n=389)
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65–0.92)	
p-value (2-sided)	0.0035	



No. at risk								
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

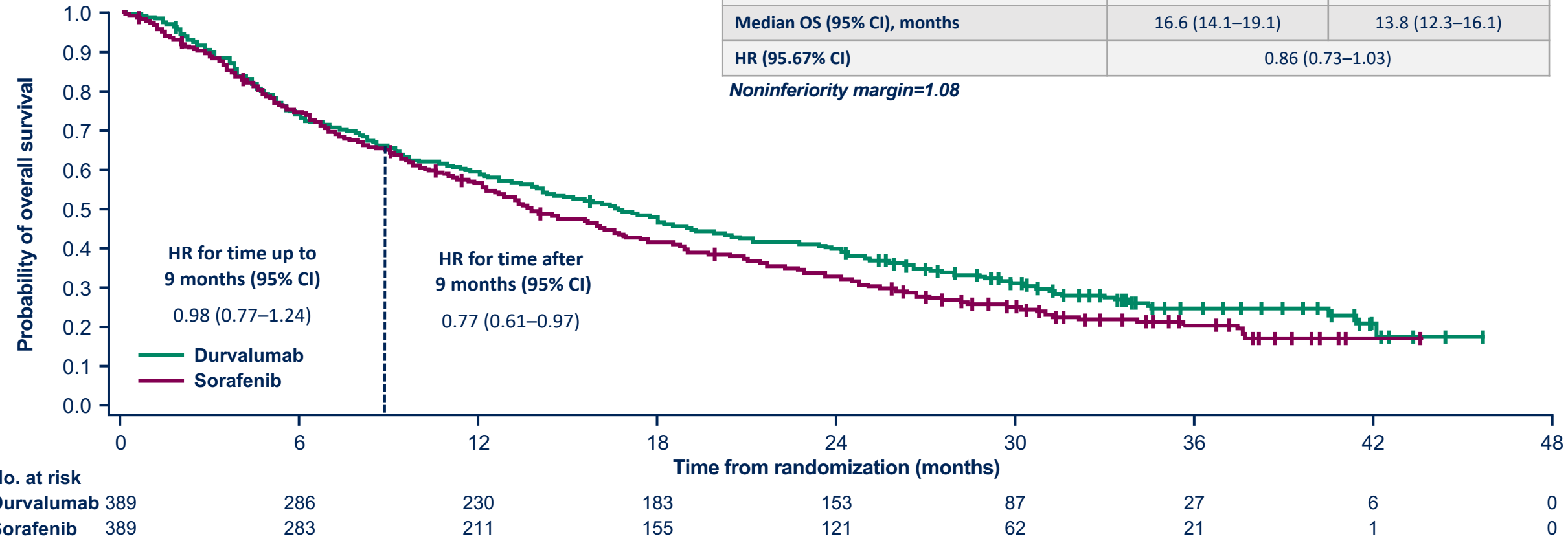
Ghassan K Abou-Alfa, MD, MBA NEJM Evidence 2022

Courtesy of Richard S Finn, MD

Secondary objective: overall survival for durvalumab vs sorafenib

	Durvalumab (n=389)	Sorafenib (n=389)
OS events, n (%)	280 (72.0)	293 (75.3)
Median OS (95% CI), months	16.6 (14.1–19.1)	13.8 (12.3–16.1)
HR (95.67% CI)	0.86 (0.73–1.03)	

Noninferiority margin=1.08



No. at risk								
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

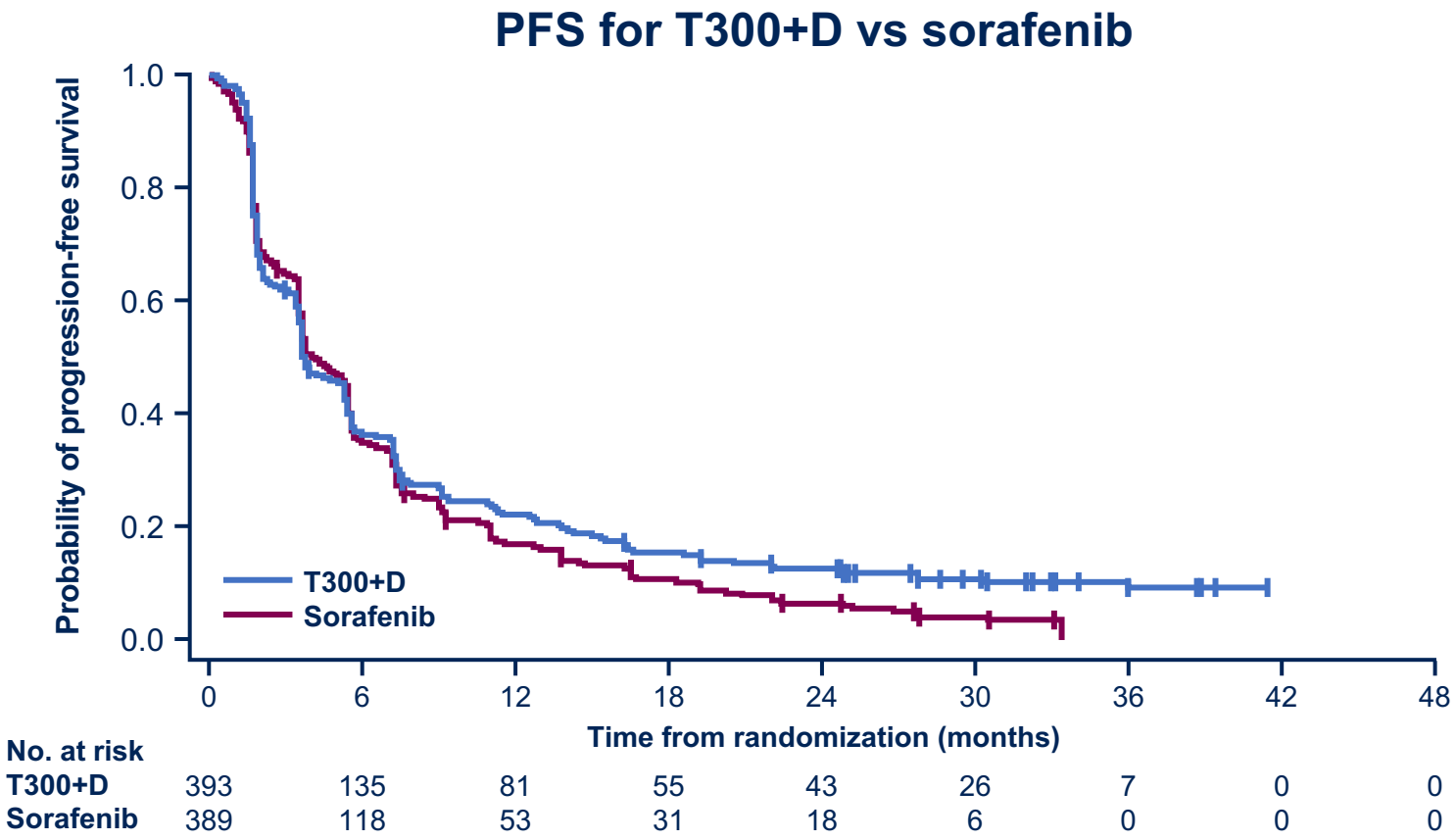
Data cut-off: August 27, 2021. Median duration of follow-up was 32.56 (95% CI, 31.57–33.71) months for durvalumab and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

CI, confidence interval; HR, hazard ratio; NI, noninferiority; OS, overall survival.

Ghassan K Abou-Alfa, MD, MBA NEJM Evidence 2022

Courtesy of Richard S Finn, MD

Progression-free survival



	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
PFS events, n (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68–5.32)	3.65 (3.19–3.75)	4.07 (3.75–5.49)
PFS HR* (95% CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	–
Progression-free at DCO, n (%)	49 (12.5)	32 (8.2)	19 (4.9)
Median TTP (95% CI), months	5.42 (3.81–5.62)	3.75 (3.68–5.42)	5.55 (5.13–5.75)
Treated ≥1 cycle beyond progression, n (%)†	182 (46.9)	188 (48.5)	134 (34.4)

*Versus sorafenib. †Percent calculated from total patients in the safety analysis set: T300+D, N=388; durvalumab, N=388, sorafenib, n=374.

CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTP, time to progression.

Ghassan K Abou-Alfa, MD, MBA NEJM Evidence 2022

Courtesy of Richard S Finn, MD

Tumor response

	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* n (%)	**79 (20.1)**	**66 (17.0)**	**20 (5.1)**
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months 25th percentile 75th percentile	22.34 8.54 NR	16.82 7.43 NR	18.43 6.51 25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ % 6 months 12 months	 82.3 65.8	 81.8 57.8	 78.9 63.2

*By investigator assessment according to RECIST v1.1. Responses are confirmed. †Defined as neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD. ‡Calculated using Kaplan-Meier technique.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTR, time to response.

Courtesy of Richard S Finn, MD

Safety and tolerability

Event, n (%)	T300+D (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE*	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
Any TRAE leading to death	9 (2.3)[†]	0	3 (0.8)[‡]
Any TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy.

*Treatment-related was as assessed by investigator. [†]Nervous system disorder (n=1), acute respiratory distress syndrome (n=1), hepatitis (n=1), myocarditis (n=1), immune-mediated hepatitis (n=2), pneumonitis (n=1), hepatic failure (n=1), myasthenia gravis (n=1). [‡]Hematuria (n=1), cerebral hematoma (n=1), hepatic failure (n=1).

AE, adverse event; SMQ, Standardized MedDRA Query; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TRAE, treatment-related adverse event.

Courtesy of Richard S Finn, MD

Immune-mediated adverse events

Event, n (%)	T300+D (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0

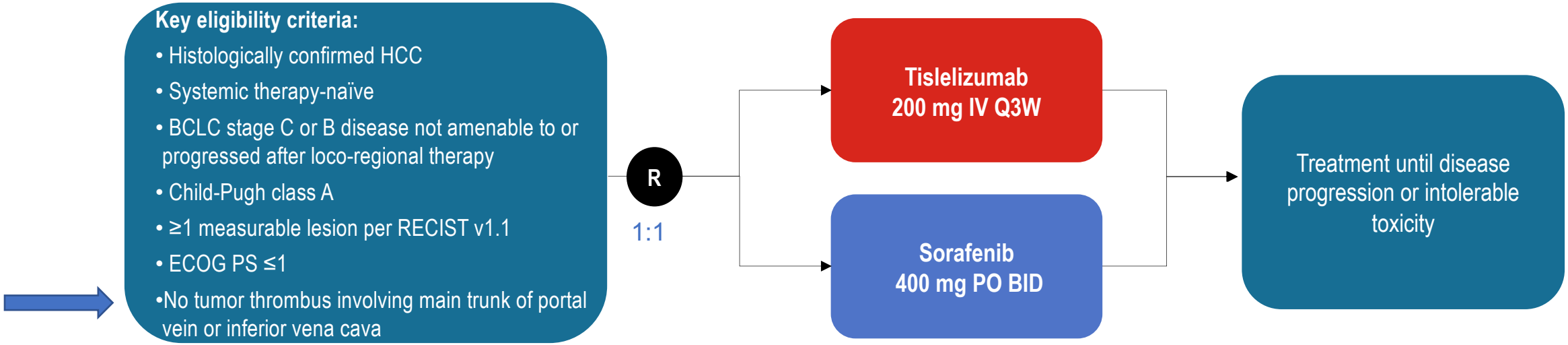
Includes adverse events with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Patients may have had >1 event. Events include those that occurred in ≥1% of patients in either treatment arm.

T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Courtesy of Richard S Finn, MD

RATIONALE-301: Study Design

Randomized, open-label, multicenter, multiregional phase 3 study



Primary endpoint: OS in the ITT population
Key secondary endpoints: ORR, PFS, and DoR by BIRC per RECIST v1.1, and safety
Stratification factors: Macrovascular invasion (present vs absent), extrahepatic spread (present vs absent), ECOG PS (0 vs 1), etiology (HCV vs other[a]), geography (Asia [excluding Japan], vs Japan vs rest of world)

[a]Includes HBV. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; BIRC, blinded independent review committee; DoR, duration of response; ECOG PS, European Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

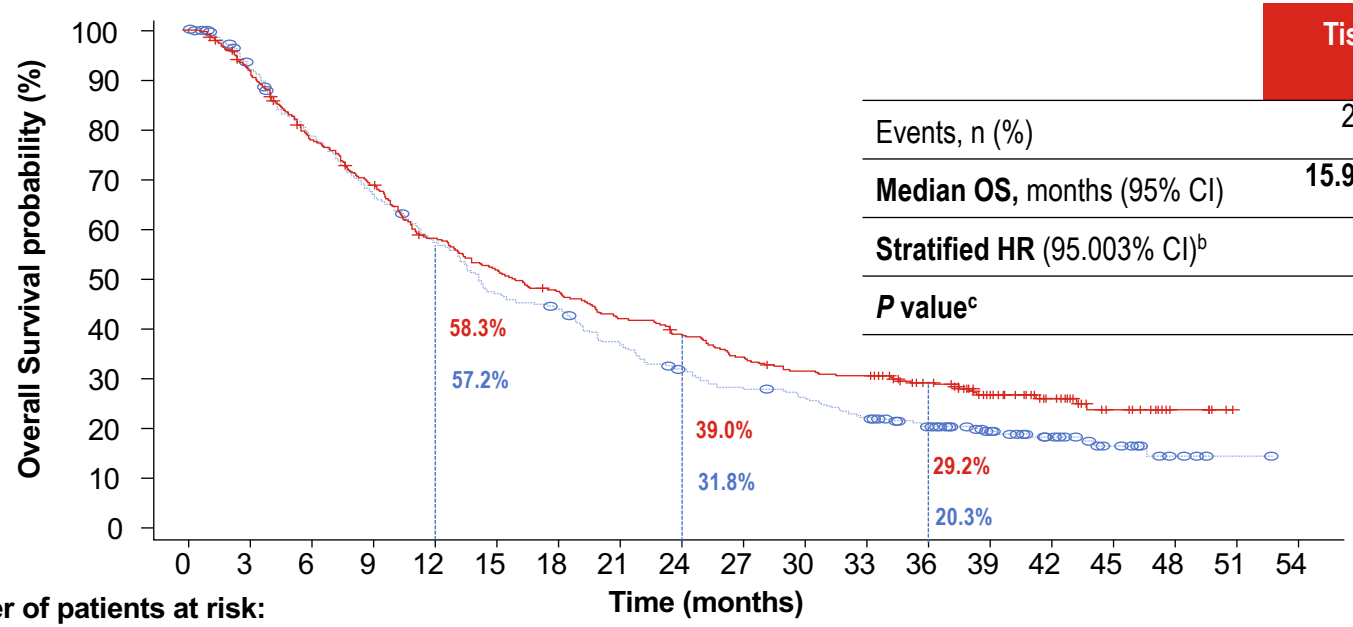
PARIS 2022 ESMO congress Abstract LBA36

Masatoshi Kudo

Courtesy of Richard S Finn, MD

RATIONALE-301: Overall Survival

Tislelizumab demonstrated OS noninferiority[a] vs sorafenib; OS superiority vs sorafenib was not met



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

Number of patients at risk:

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

Data cutoff: July 11, 2022. OS was assessed in the ITT population. [a]Prespecified boundary of NI: upper bound of 95.003% CI of stratified HR <1.08; pre-specified boundary of superiority: one-sided *P* value <0.0223 (approximate HR <0.8352). [b]HR was based on a Cox proportional hazard model including treatment as a covariate, geography (Asia [including Japan] vs rest of world [EU/US]), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other), and ECOG PS (0 vs 1) as stratification factors. [c]One-sided stratified log-rank test. Abbreviations: CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; HCV, hepatitis C virus; HR, hazard ratio; ITT, intent-to-treat; NI, non-inferiority; OS, overall survival.

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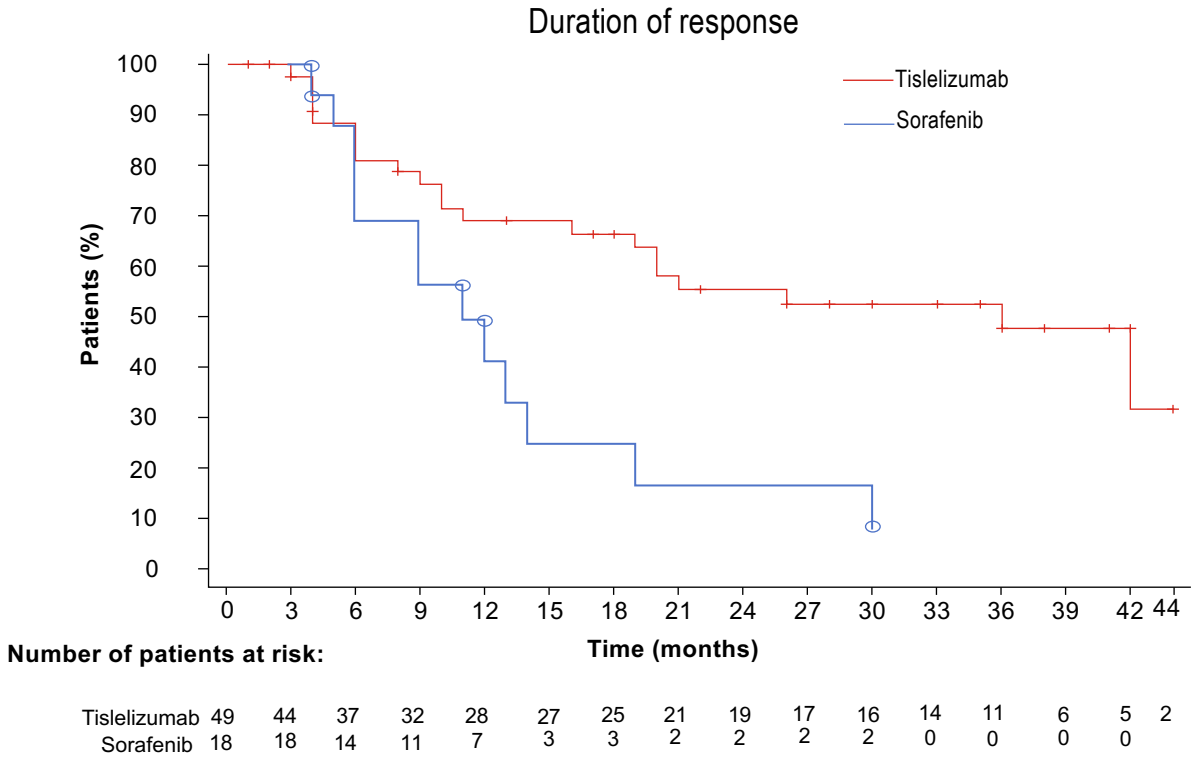
Masatoshi Kudo

Courtesy of Richard S Finn, MD

RATIONALE-301: Overall Response Rate by IRC

Tislelizumab was associated with a higher ORR and more durable responses vs sorafenib

	Tislelizumab (n=342)	Sorafenib (n=332)
ORR, n (%) [95% CI][a]	49 (14.3) [10.8, 18.5]	18 (5.4) [3.2, 8.4]
Best overall response, n (%)[a]		
CR	10 (2.9)	1 (0.3)
PR	39 (11.4)	17 (5.1)
SD	94 (27.5)	137 (41.3)
PD	166 (48.5)	117 (35.2)
Undetermined[b]	26 (7.6)	50 (15.1)
Non-CR/non-PD[c]	7 (2.0)	10 (3.0)
Responders	**Tislelizumab (n=49)**	**Sorafenib (n=18)**
Median DoR, months (95% CI)	36.1 (16.8, NE)	11.0 (6.2, 14.7)
Patients with ongoing response, n (%)[d]	20/28 (71.4)	2/5 (40.0)



Data cutoff: July 11, 2022. ORR was assessed in the ITT population. [a]Confirmed responses; [b]Patients with no postbaseline tumor assessment (not assessable) or a nonevaluable tumor assessment. [c]Patients were assessed as non-CR/non-PD if the IRC was not able to identify the target lesions at screening. Patients with no target lesions were evaluated based on the assessment of nontarget lesions or the presence of new lesions. [d]Patients who had PD or died were excluded from this analysis. Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; IRC, independent review committee; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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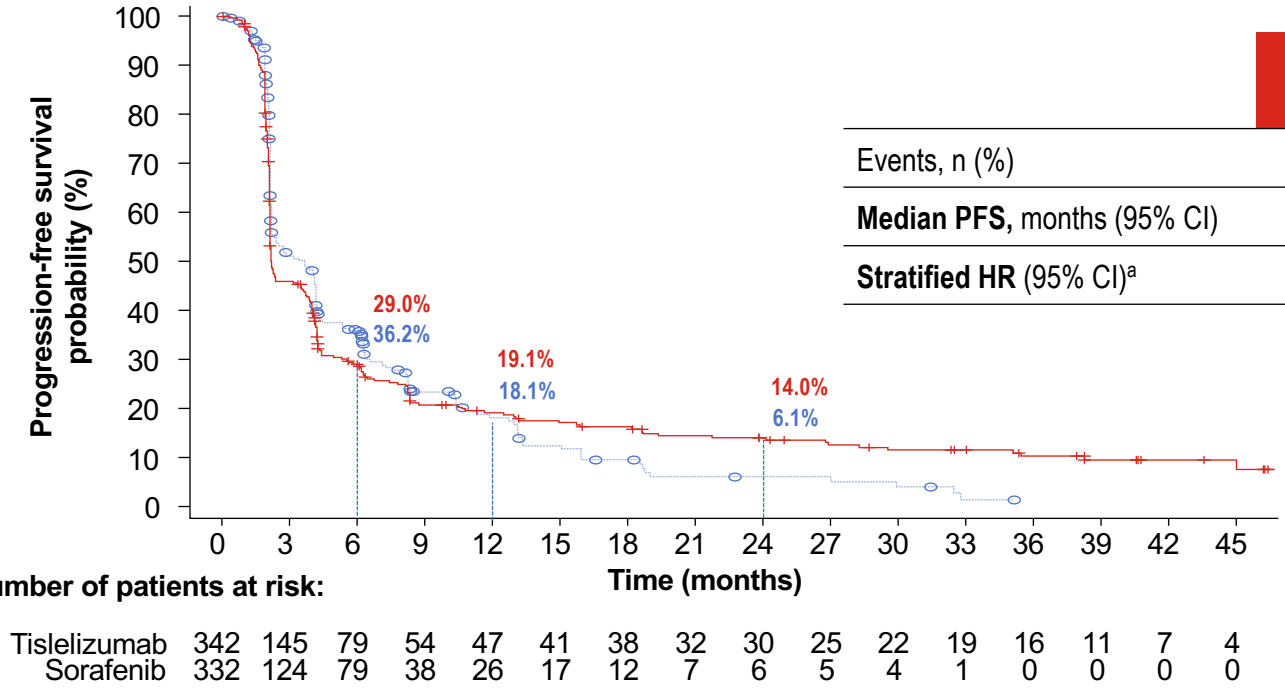
Masatoshi Kudo

Courtesy of Richard S Finn, MD

RATIONALE-301: Progression-Free Survival by IRC

The median PFS was longer with sorafenib versus tislelizumab



	Tislelizumab (n=342)	Sorafenib (n=332)
Events, n (%)	273 (79.8)	220 (66.3)
Median PFS, months (95% CI)	**2.2** (2.1, 3.5)	**3.6** (2.2, 4.1)
Stratified HR (95% CI)[a]	**1.10** (0.92, 1.33)	

Data cutoff: July 11, 2022. PFS was assessed in the ITT population. [a]HR was based on a Cox proportional hazard model including treatment as a covariate, geography (Asia [including Japan] vs rest of world [EU/US]), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other), and ECOG PS (0 vs 1) as stratification factors. Abbreviations: CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; HCV, hepatitis C virus; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival.

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Masatoshi Kudo

Courtesy of Richard S Finn, MD

RATIONALE-301: Safety Summary

TEAEs and treatment-related TEAEs at grade ≥3 were less frequent with tislelizumab and treatment with tislelizumab led to fewer discontinuations/dose modifications vs sorafenib

Patients	Tislelizumab (n=338)	Sorafenib (n=324)
Safety, n (%)		
Any TEAE	325 (96.2)	324 (100.0)
Treatment-related	259 (76.6)	311 (96.0)
TEAE at ≥grade 3	163 (48.2)	212 (65.4)
Treatment-related	75 (22.2)	173 (53.4)
Serious TEAE	101 (29.9)	91 (28.1)
Treatment-related	40 (11.8)	33 (10.2)
TEAE leading to discontinuation	37 (10.9)	60 (18.5)
Treatment-related	21 (6.2)	33 (10.2)
TEAE leading to drug modification[a]	105 (31.1)	210 (64.8)
Treatment-related	68 (20.1)	187 (57.7)
TEAE leading to death	15 (4.4)	17 (5.2)
Treatment-related	3 (0.9)	2 (0.6)
Immune-mediated AEs	58 (17.2)	10 (3.1)
Immune-mediated AEs treated with systemic corticosteroids	43 (12.7)	10 (3.1)
Immune-mediated AEs in ≥5% of patients		
Hepatitis	18 (5.3)	1 (0.3)
Hypothyroidism	18 (5.3)	0 (0)
Treatment		
Median duration of treatment, months	4.1	2.7

Safety was assessed in the safety population. Data cutoff: July 11, 2022. [a]Drug modification included an interrupted/held or reduced dose. Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

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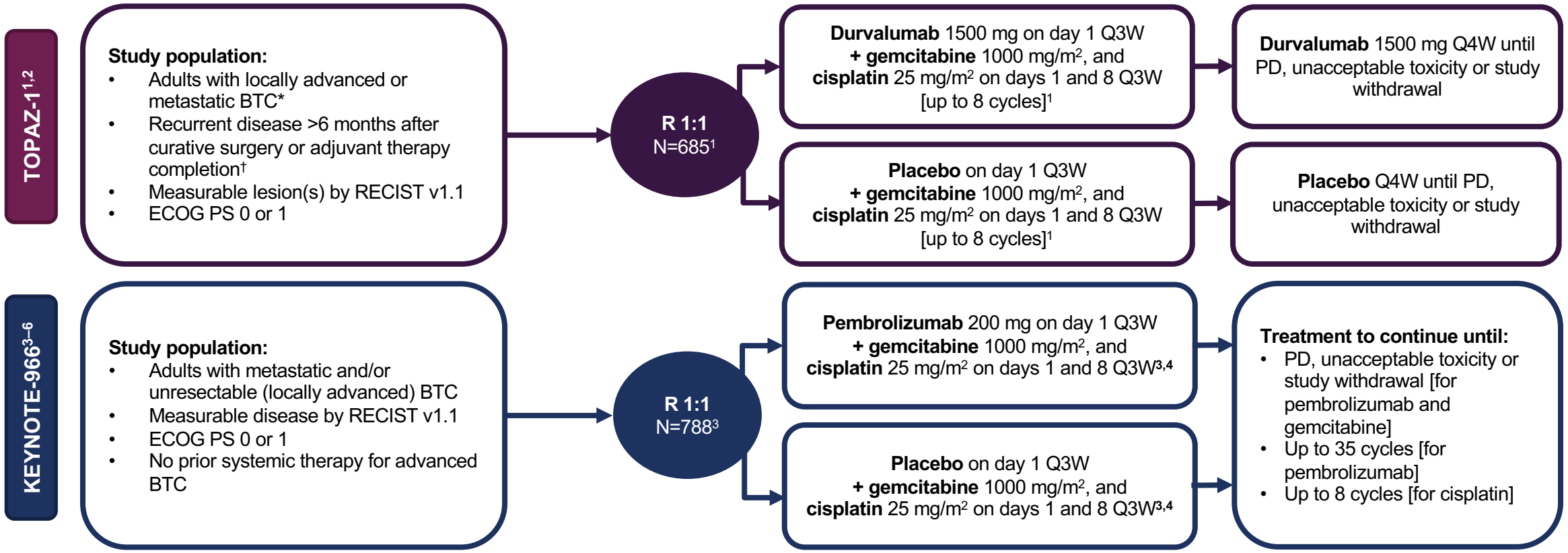
Abstract LBA36

Masatoshi Kudo

Courtesy of Richard S Finn, MD

IO-Phase-III studies in BTC: TOPAZ-1 & KEYNOTE-966



Courtesy of Professor Arndt Vogel, MD

IO-Phase-III studies in BTC: TOPAZ-1 & KEYNOTE-966

TOPAZ-1[1,2]

Study popula
- Adults wi metastati
- Recurren curative s completic
- Measural
- ECOG PS

ab 1500 mg Q4W until eptable toxicity or study withdrawal

ebo Q4W until PD, table toxicity or study withdrawal

KEYNOTE-966[3–6]

Study popula
- Adults wi unresecta
- Measural
- ECOG PS
- No prior s BTC

t to continue until:
acceptable toxicity or withdrawal [for olizumab and abine]
35 cycles [for olizumab]
cycles [for cisplatin]

NEJM Evidence

Published June 1, 2022

DOI: 10.1056/EVIDoa2200015

ORIGINAL ARTICLE

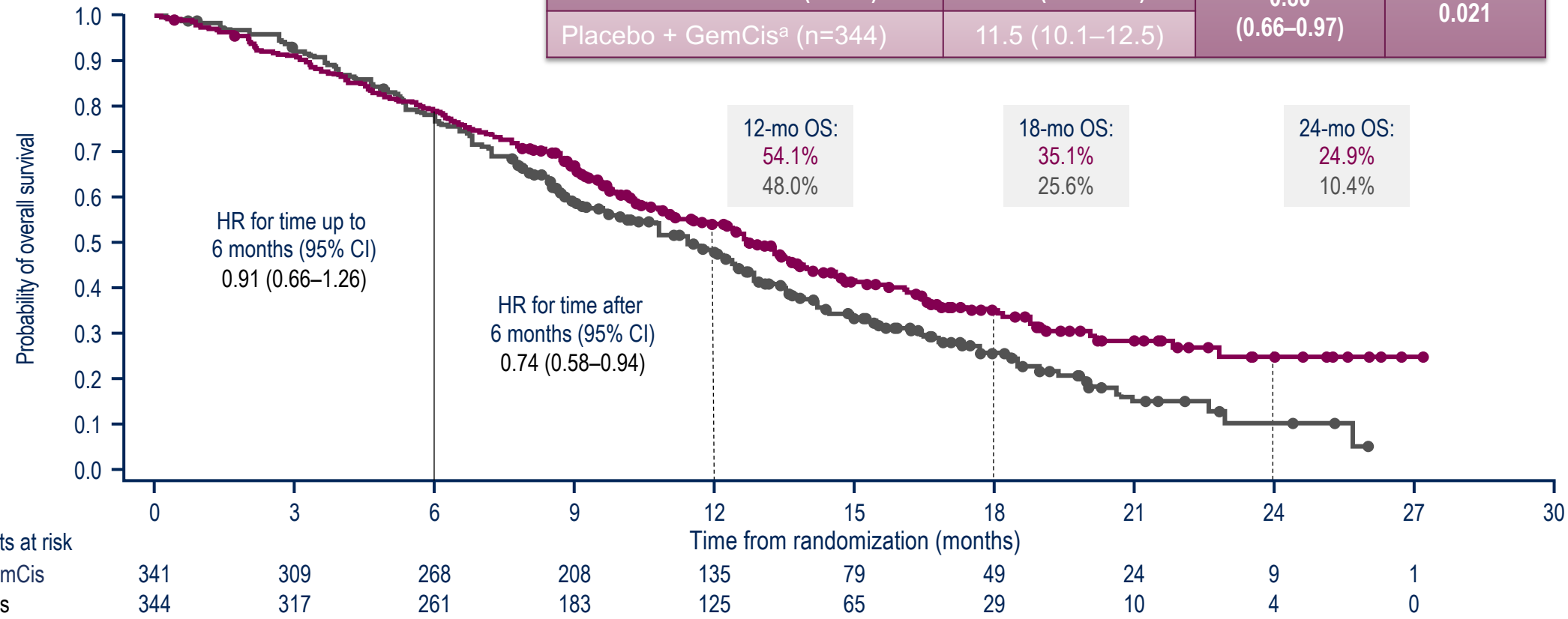
Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

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]

Courtesy of Professor Arndt Vogel, MD

TOPAZ-1: Durvalumab + GemCis Improved OS vs. GemCis

	Median OS, months (95% CI)	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis[a] (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis[a] (n=344)	11.5 (10.1–12.5)		



Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

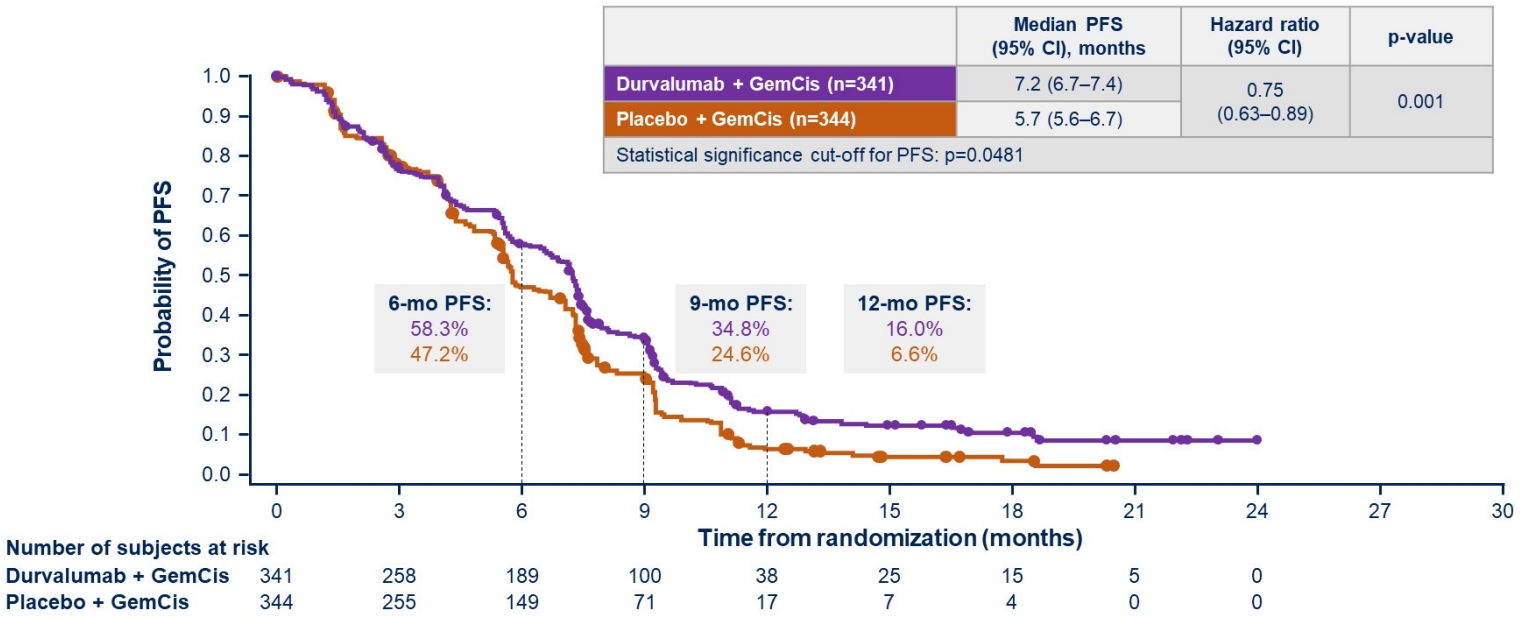
Oh D-Y, et al. @ ASCO GI

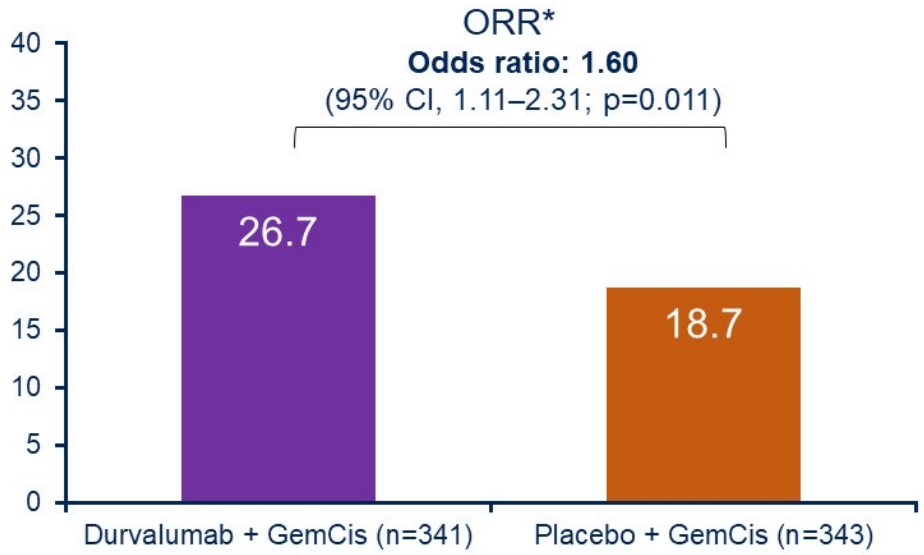
Arndt Vogel

Courtesy of Professor Arndt Vogel, MD

IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

Efficacy data 2ndary objectives: PFS and ORR





Courtesy of Professor Arndt Vogel, MD

Oh D-Y et al. Gastrointestinal Cancers Symposium 2022.

IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

Relevant Subgroups: "RACE"

	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of the world	163 (47.8)	148 (43.0)

Oh D-Y et al. Gastrointestinal Cancers Symposium 2022.

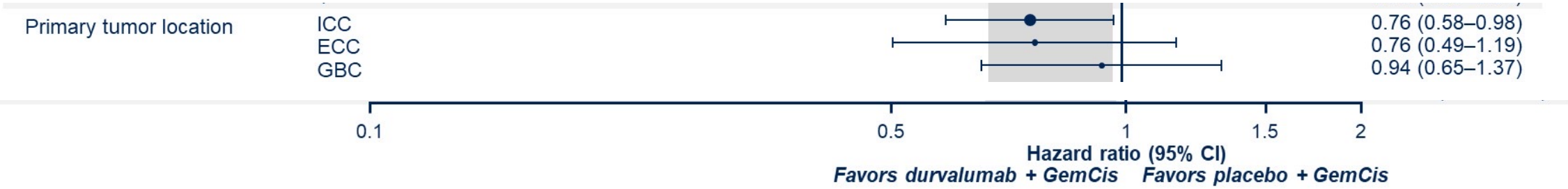
ORR MEDITREME (Chemo + Durva, all Asian): 73%
ORR Topaz: 26%

Courtesy of Professor Arndt Vogel, MD

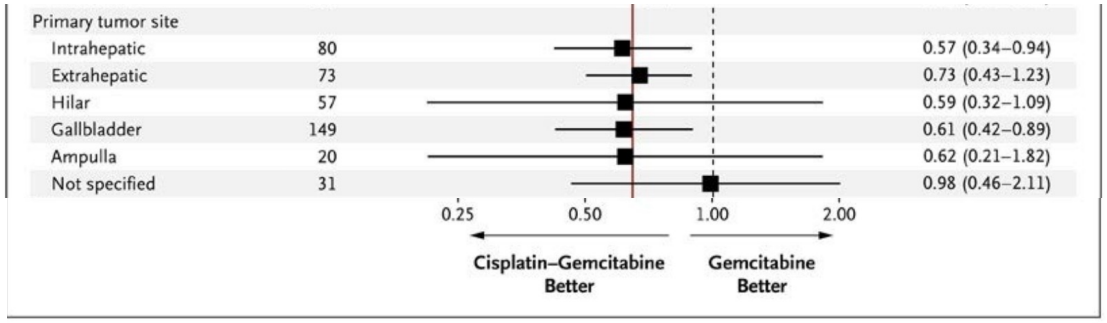
IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

Relevant Subgroups: "anatomic location"

	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Primary tumor location at diagnosis, n (%)		
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)



Oh D-Y et al. Gastrointestinal Cancers Symposium 2022.



Valle et al, NEJM 2010

Courtesy of Professor Arndt Vogel, MD

IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

Adverse events profile

	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Any grade 3/4 AE	256 (75.7)	266 (77.8)
Any grade 3/4 TRAE	212 (62.7)	222 (64.9)

No added Durvalumab-associated toxicity

Immune-mediated AEs

Event, n (%)	Durvalumab + GemCis (n=338)		Placebo + GemCis (n=342)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any immune-mediated AE*	43 (12.7)	8 (2.4)	16 (4.7)	5 (1.5)
Hypothyroid events	20 (5.9)	0	5 (1.5)	0
Dermatitis/rash	12 (3.6)	3 (0.9)	1 (0.3)	0
Pneumonitis	3 (0.9)	1 (0.3)	2 (0.6)	1 (0.3)
Hepatic events	4 (1.2)	2 (0.6)	2 (0.6)	1 (0.3)
Adrenal insufficiency	4 (1.2)	0	1 (0.3)	0
Diarrhea/colitis	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)
Hyperthyroid events	2 (0.6)	0	0	0
Type 1 diabetes mellitus	1 (0.3)	1 (0.3)	0	0
Pancreatic events	1 (0.3)	0	2 (0.6)	1 (0.3)
Hypophysitis	1 (0.3)	0	0	0
Thyroiditis	1 (0.3)	0	0	0
Renal events	0	0	2 (0.6)	0
Myositis	0	0	1 (0.3)	1 (0.3)
Other rare/miscellaneous†	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)

irAE: 12.7%

9.5% Hypothyroid events or Dermatitis

Oh D-Y et al. Gastrointestinal Cancers Symposium 2022.

Courtesy of Professor Arndt Vogel, MD

TOPAZ update @ ESMO 2022

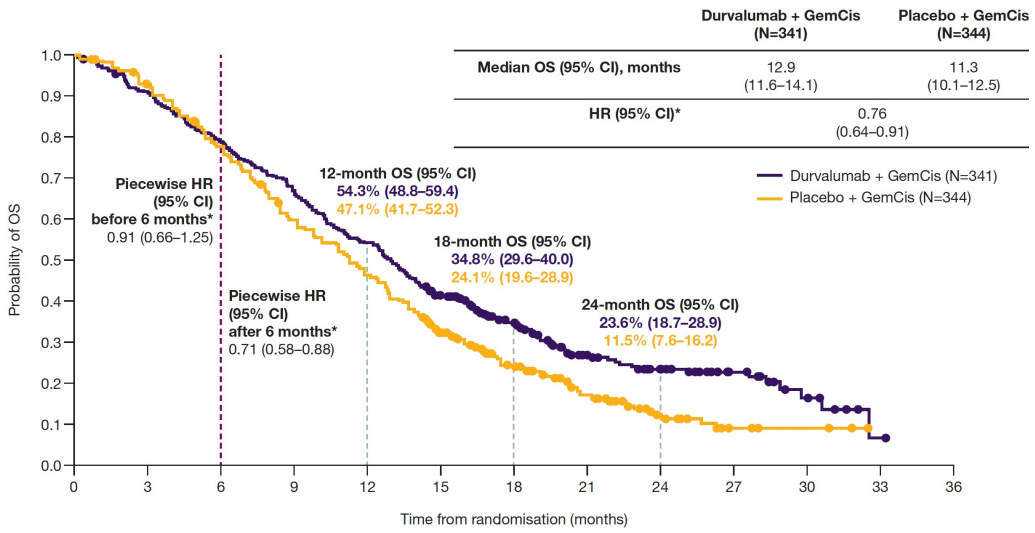


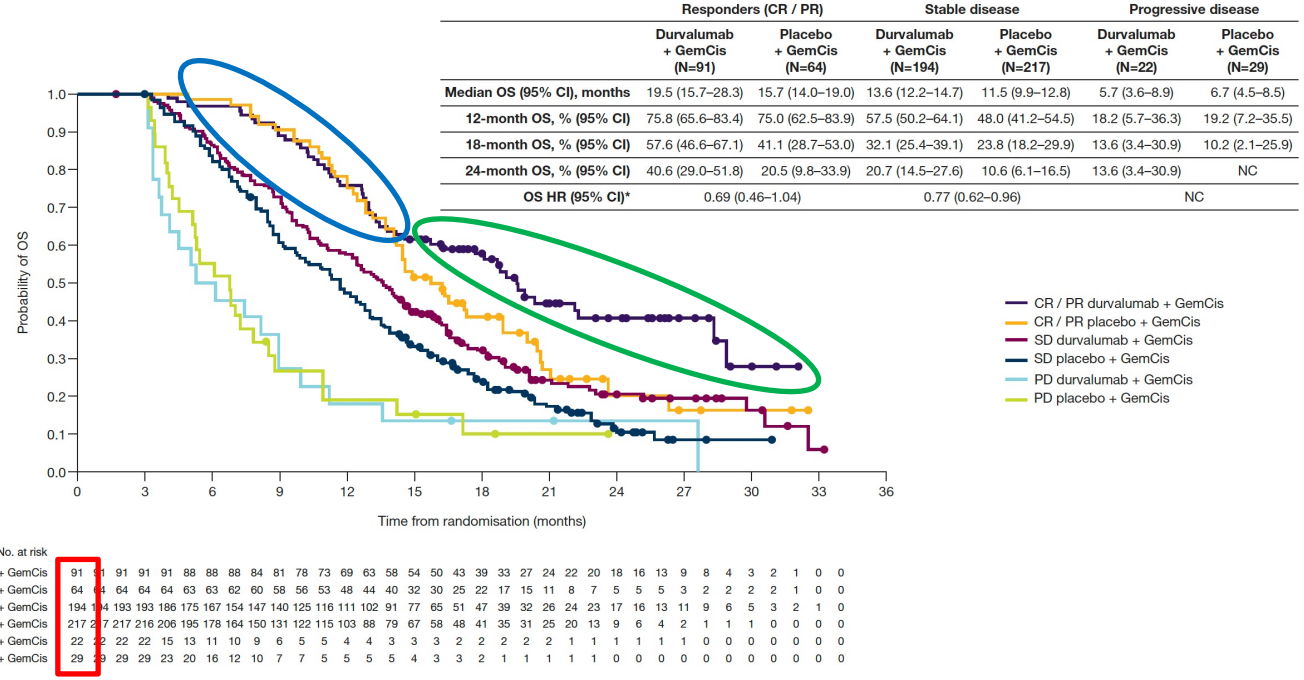
Table 1. Best objective response

	Durvalumab + GemCis (N=341)	Placebo + GemCis (N=343)
Responders,[1,*] n (%)	91 (26.7)	64 (18.7)
Complete response,[†] n (%)	7 (2.1)	2 (0.6)
Partial response,[†] n (%)	84 (24.6)	62 (18.1)
Non-responders, n (%)	250 (73.3)	279 (81.3)
Stable disease, n (%)	200 (58.7)	220 (64.1)
Progressive disease,[†] n (%)	47 (13.8)	51 (14.9)
Not evaluable	3 (0.9)	8 (2.3)

*Confirmed response; †Death recorded within 13 weeks after randomisation is considered progression
GemCis, gemcitabine and cisplatin

Do-Youn Oh et al, ESMO 2022 poster 56P

Figure 4. Kaplan-Meier curve of overall survival by best objective response



Responders: late separation, but strong long-term effect

SD: early & continuous separation

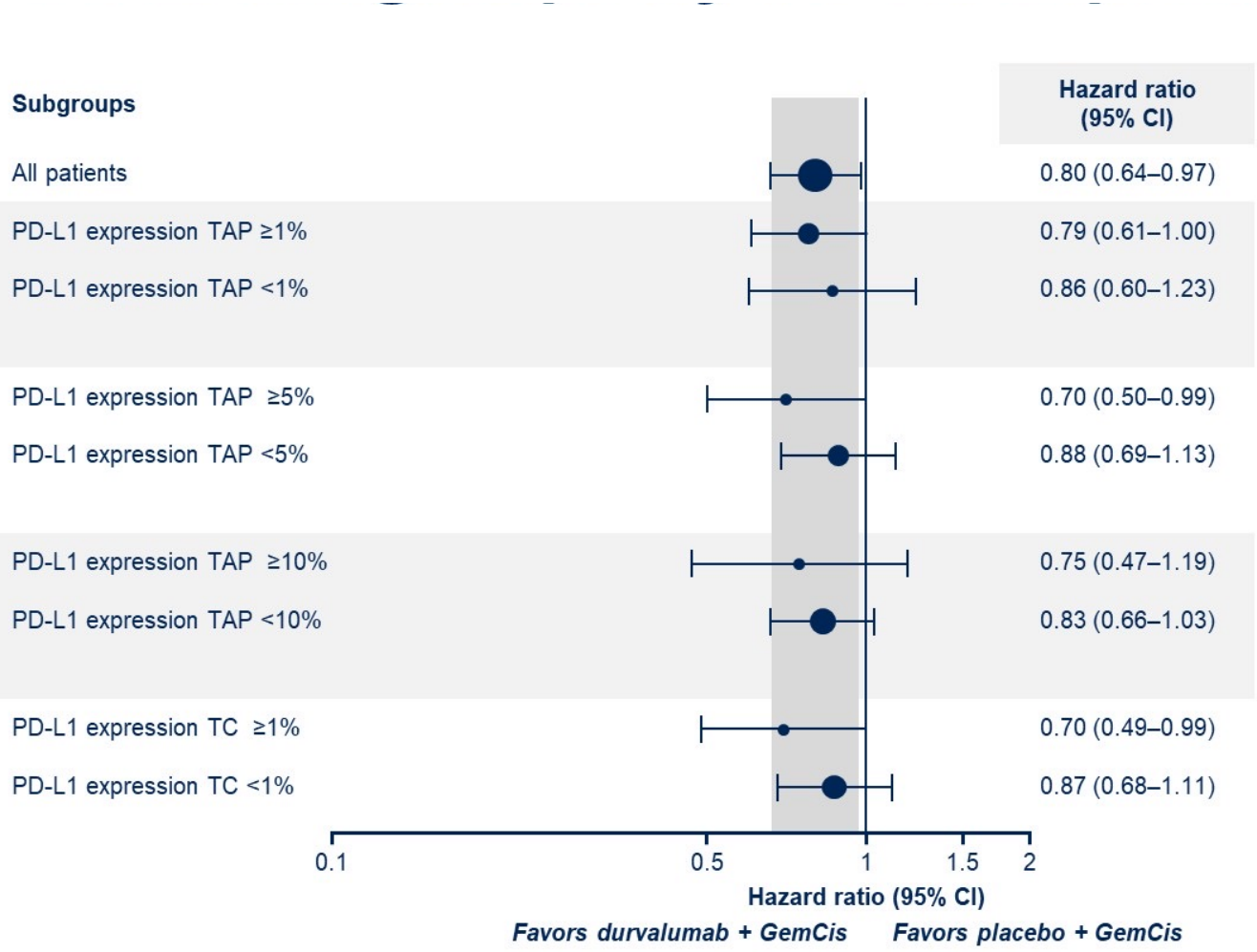
PD: no separation

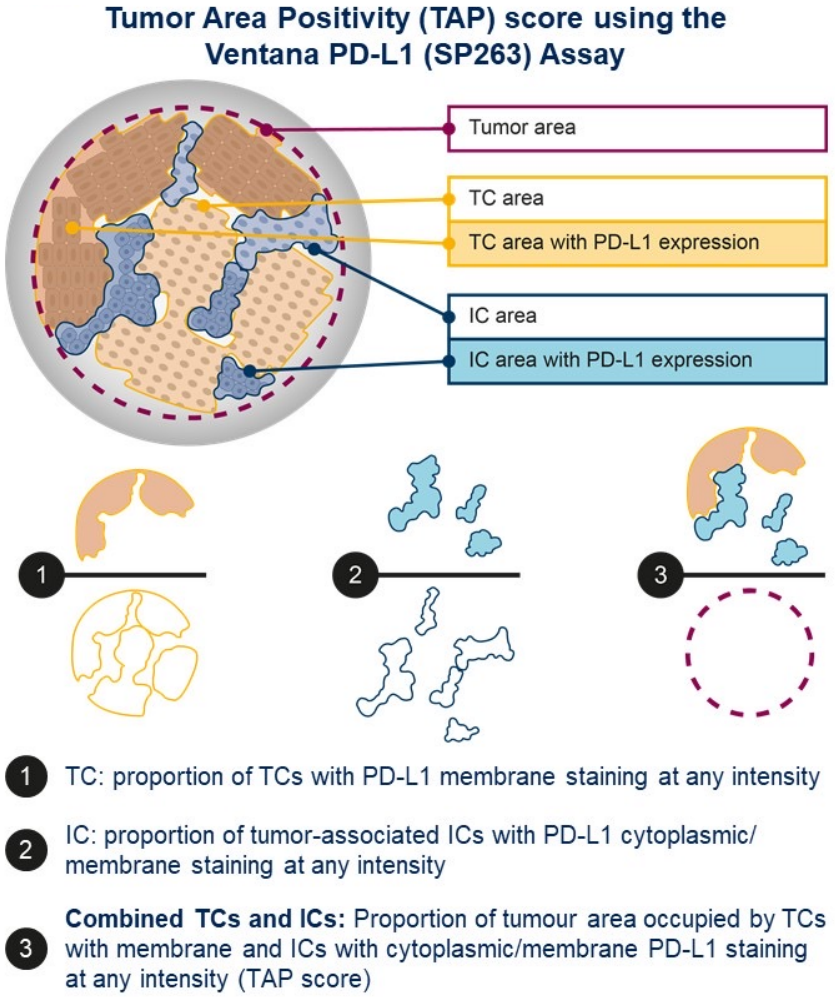
Speculation: „initial 6 mo“ of responses influenced by „lifting“ of selected SD pts

Courtesy of Professor Arndt Vogel, MD

IO + Chemo in BTC 1st line: TOPAZ-1 Phase 3

OS in subgroups by PD-L1 expression





Courtesy of Professor Arndt Vogel, MD

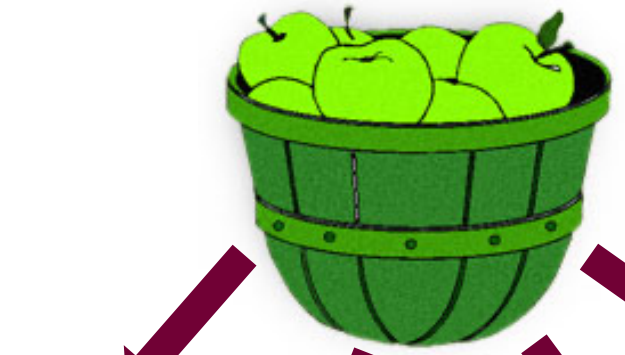
Evaluating Targeted Therapy in an Uncommon Cancer: Approaches

Target-Specific Cholangiocarcinoma Trial

FGFR2 fusions 10%–15%

IDH1 mutations 15%–20%

Target-Specific All Comer Basket Trial



BRAF V600E mutations 4%–5%

HER2 amplification 5-15%

MSI-high 1%–2%

NTRK-fusion <1%

RET-fusion <1%

Biliary Umbrella Trial With Target-Specific Arms

ABC10

ABC10, ABC transporter 10; BRAF, v-raf murine sarcoma viral oncogene homolog B; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor 2; IDH, isocitrate dehydrogenase; MSI, microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection.

Valle JW, et al. Cancer Discov 2017;7(9):943–962.

Courtesy of Lipika Goyal, MD, Mphil

Selective FGFR Inhibitors for FGFR2 Fusions or Rearrangement Positive Cholangiocarcinoma[1–4]

Pemigatinib
ATP-competitive FGFR1–3 inhibitor

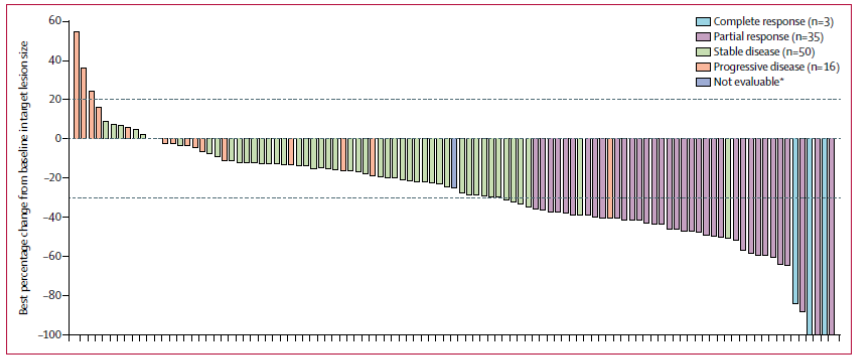
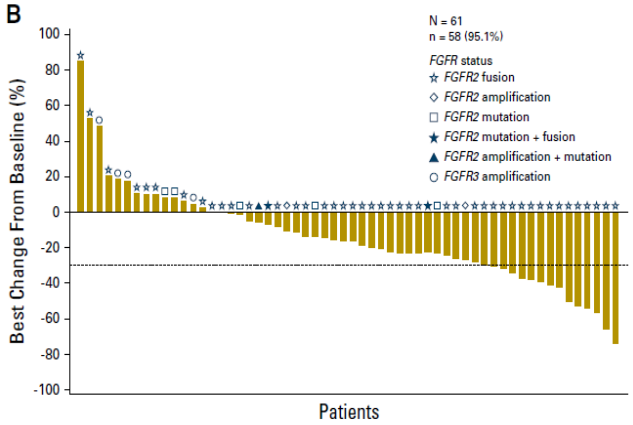


Figure 2: **Best percentage change from baseline in target lesion size for individual patients with *FGFR2* fusions or rearrangements**
Coloured bars indicate confirmed responses assessed by RECIST 1·1. FGFR=fibroblast growth factor receptor. RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1. *Patient had a decrease in target lesion size but was not evaluable for response using RECIST.

ORR: 35.5% (updated: 37.0%)
DCR: 82.2% (updated 82.4%)
PFS (updated): 7.0 months

Infigratinib
ATP-competitive FGFR1–3 inhibitor



ORR: 18.8% (updated: 23.1%)
DCR: 83.3% (updated: 84.3%)
PFS (updated): 7.3 months

ATP, adenosine triphosphate; DCR, disease control rate; FGFR, fibroblast growth factor receptor; ORR, overall response rate; PFS, progression-free survival.

1. Javle M, et al. J Clin Oncol 2018;36(3):276–282; 2. Javle M, et al. ASCO Gastrointestinal (GI) Cancers Symposium, 2021;
3. Abou-Alfa GK, et al. Lancet Oncol 2020;21(5):671–684; 4. Abou-Alfa GK et al. ASCO 2021;Abstract 4086.

Courtesy of Lipika Goyal, MD, Mphil