Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastrointestinal Cancers

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Saturday, June 4, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty

Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP
John Strickler, MD
Eric Van Cutsem, MD, PhD

Moderator

Neil Love, MD

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Faculty

Tanios Bekaii-Saab, MD
Professor, Mayo Clinic College of Medicine and Science
Program Leader, Gastrointestinal Cancer
Mayo Clinic Cancer Center
Consultant, Mayo Clinic in Arizona
Chair, ACCRU Research Consortium
Phoenix, Arizona

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Associate Professor of Medicine
Division of Hematology/Oncology
Vanderbilt-Ingram Cancer Center
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Section Head, Hepatopancreaticobiliary and
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Attending Physician, Member
Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Cornell Medical College
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Philip A Philip, MD, PhD, FRCP
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Leader, GI and Neuroendocrine Oncology
Henry Ford Cancer Institute
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Detroit, Michigan

John Strickler, MD
Associate Professor
Duke University
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Eric Van Cutsem, MD, PhD
Professor of Medicine
Digestive Oncology
University Hospitals Leuven
Leuven, Belgium

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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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 premeeting survey before the meeting. Survey results will be presented and 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.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

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 premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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

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

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About the Enduring Program

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

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Friday June 3	**Acute Myeloid Leukemia and Myelodysplastic Syndromes** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Lung Cancer 6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)
Saturday June 4	**Prostate Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Gastrointestinal Cancers 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Sunday June 5	**Ovarian Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Monday June 6	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Breast Cancer 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Tuesday June 7	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

Gastrointestinal Cancers

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7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

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Kristen K Ciombor, MD, MSCI
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP
John Strickler, MD
Eric Van Cutsem, MD, PhD

Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

Sunday, June 5, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Ian W Flinn, MD, PhD
Brian T Hill, MD, PhD
John P Leonard, MD
Matthew Lunning, DO
Laurie H Sehn, MD, MPH
Mitchell R Smith, MD, PhD

Ovarian Cancer

Sunday, June 5, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Antonio González-Martín, MD, PhD
Joyce F Liu, MD, MPH
Kathleen N Moore, MD, MS

Urothelial Bladder Cancer

Monday, June 6, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Yohann Loriot, MD, PhD
Elizabeth R Plimack, MD, MS
Jonathan E Rosenberg, MD

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

Breast Cancer

Monday, June 6, 2022

7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty

Javier Cortés, MD, PhD
Matthew P Goetz, MD
Erika Hamilton, MD
Ian E Krop, MD, PhD
Hope S Rugo, MD
Sara M Tolaney, MD, MPH

Multiple Myeloma

Tuesday, June 7, 2022

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

Faculty

Ajai Chari, MD
Elizabeth O'Donnell, MD
Robert Z Orlowski, MD, PhD

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

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

Philip L Brooks, MD
Northern Light Eastern Maine Medical Center and Lafayette Family Cancer Institute
Brewer, Maine

Zanetta S Lamar, MD
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Shams Bufalino, MD
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Park Ridge, Illinois

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Summit, New Jersey

Lionel A Kankeu Fonkoua, MD
Mayo Clinic
Rochester, Minnesota

Vignesh Narayanan, MD
Colorado Permanente Medical Group (CPMG)
Lone Tree, Colorado

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Namrata I Peswani, MD
Harold C Simmons
Comprehensive Cancer Center
Richardson, Texas

Matthew R Strickland, MD
Massachusetts General Hospital
Cancer Center
Boston, Massachusetts

Erik Rupard, MD
The Reading Hospital
West Reading, Pennsylvania

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Inventions/Patents	WO/2018/183488 licensed to Imugene, WO/2019/055687 licensed to Recursion
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Dr Ciombor — Disclosures

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Dr O'Reilly — Disclosures

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Dr Philip — Disclosures

No relevant conflicts of interest to disclose.

Dr Strickler — Disclosures

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Prof Van Cutsem — Disclosures

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Moderator

Neil Love, MD

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Agenda

Module 1 – Integration of Targeted Therapy and Immunotherapy into the Management of Metastatic Colorectal Cancer (mCRC) — Dr Ciombor

Module 2 – Other Considerations in the Management of Localized and Advanced CRC — Dr Strickler

Module 3 – Current and Future Treatment Paradigm for Gastroesophageal Cancers — Prof Van Cutsem

Module 4 – Selection and Sequencing of Therapy for Advanced Hepatocellular Carcinoma (HCC) — Dr Philip

Module 5 – Novel Treatment Strategies for Advanced Biliary Tract Cancers — Dr Bekaii-Saab

Module 6 – Contemporary Management of Pancreatic Cancer — Dr O'Reilly

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MODULE 1: Integration of Targeted Therapy and Immunotherapy for Patients with Metastatic Colorectal Cancer (mCRC) — Dr Ciombor

Dr Shaachi Gupta
Lake Worth, Florida

64-year-old man with T3N0 colon adenocarcinoma with several poor-risk features – MSI-H

Dr Spencer Bachow
Boca Raton, Florida

62-year-old woman with metastatic MSI-H, BRAF V600E-mutant adenocarcinoma of the colon

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Dr Zanetta Lamar
Naples, Florida

62-year-old woman with T3N1a colon adenocarcinoma who experienced 5-FU-induced coronary vasospasm

60-year-old man with colon adenocarcinoma and a solitary liver metastasis

SPECIAL SERIES: PRECISION MEDICINE AND IMMUNOTHERAPY IN GI MALIGNANCIES

review articles

BRAF-Mutated Advanced Colorectal Cancer: A Rapidly Changing Therapeutic Landscape

Kristen K. Ciombor, MD, MSCI[1]; John H. Strickler, MD[2]; Tanios S. Bekaii-Saab, MD[3]; Rona Yaeger, MD[4]

Journal Clin Oncol, 2022; JCO2102541.

Integration of Targeted Therapy and Immunotherapy for Patients with Metastatic Colorectal Cancer (mCRC)

Kristen K. Ciombor, MD, MSCI
Associate Professor of Medicine
Vanderbilt-Ingram Cancer Center

June 4, 2022

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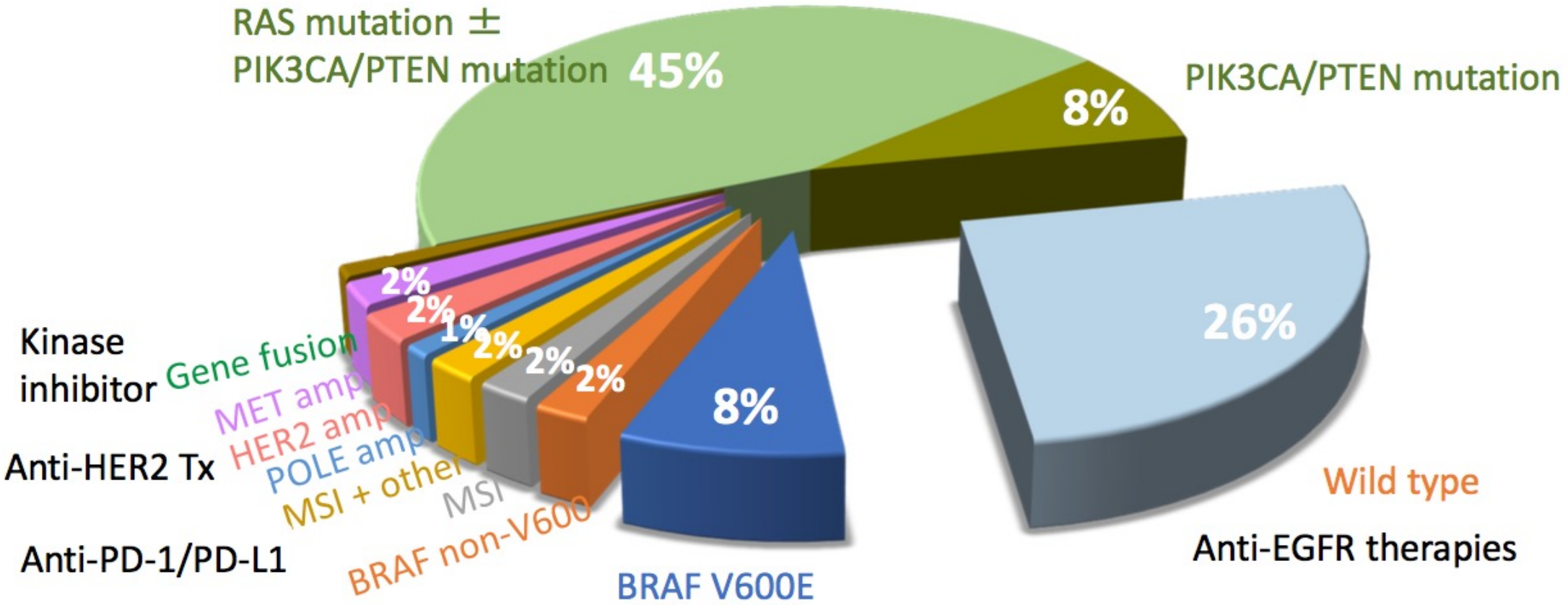
Genomic Markers in CRC

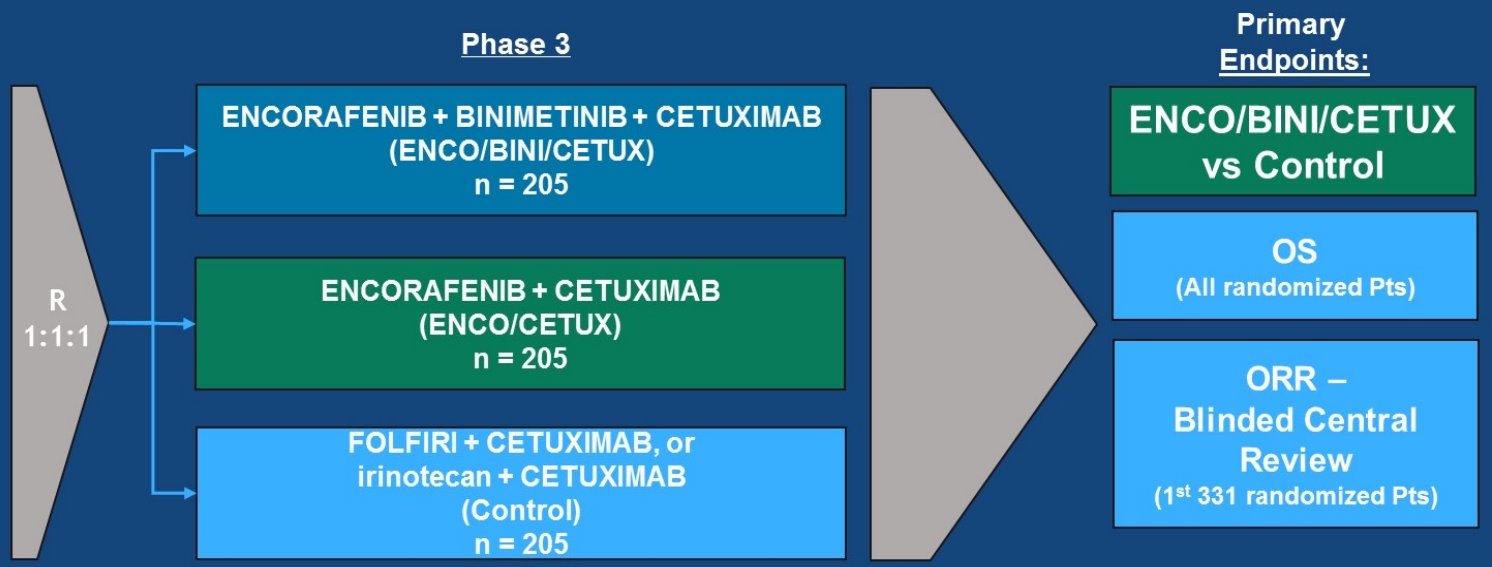


Dienstmann. ASCO Ed Book. 2018.

BEACON CRC

Study Design

Patients with *BRAF* V600E-mutant mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor



Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

Secondary Endpoints: ENCO/CETUX vs Control and ENCO/BINI/CETUX vs ENCO/CETUX - OS & ORR, PFS, Safety, QOL

Post hoc Updated Analysis: includes 6 months of additional follow-up since cut off for primary analysis

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Scott Kopetz, MD, PhD

BEACON CRC

Updated Objective Response Rates

Confirmed Response by BICR	ENCO/BINI/CETUX N=224	ENCO/CETUX N=220	Control N=221
Objective Response Rate[a]	**27%**	**20%**	**2%**
95% (CI)	(21, 33)	(15, 25)	(<1, 5)
Best Overall Response[b]			
Complete Response (CR)	4%	3%	0%
Partial Response (PR)	23%	16%	2%
Stable Disease[c]	48%	56%	29%
Progressive Disease	11%	10%	34%
Non Evaluable by RECIST[d]	14%	15%	32%

BICR=blinded independent central review.

a. Confirmed responses per RECIST 1.1; Objective Response Rate equals the percentage of patients with a complete response or a partial response.

b. Best overall response percentage may not add up to 100% due to rounding.

c. Stable disease includes measurable disease patients who were either stable disease or non-measurable disease patients who were non-complete response/non-progressive disease per RECIST 1. Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions.

d. This category refers to patients who discontinued the trial regimen because of adverse events or whose disease could not be assessed centrally but who had clinical or radiologic disease progression according to local assessment.

BEACON CRC

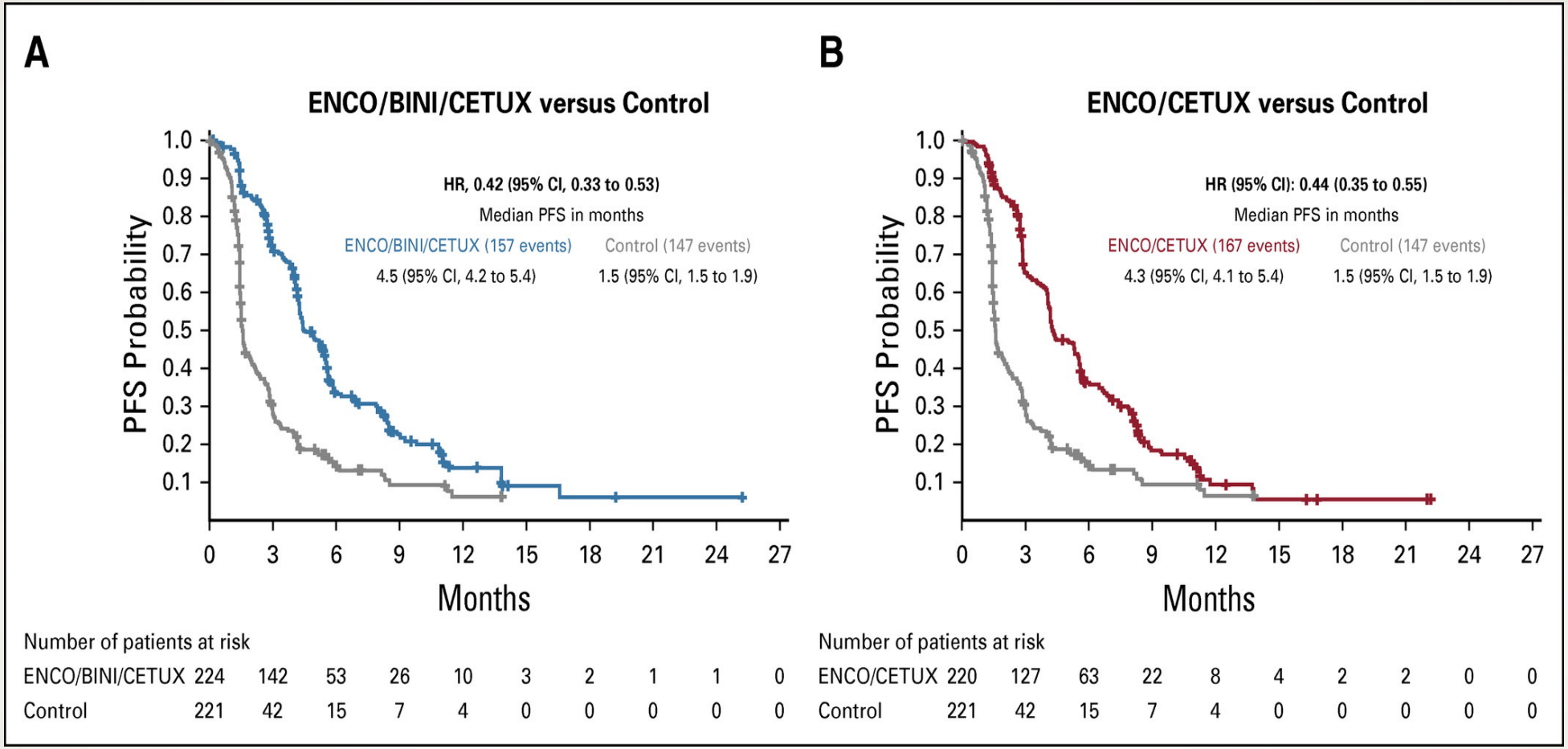


FIG 3. Progression-free survival by blinded independent central review. (A) ENCO/BINI/CETUX versus control. (B) ENCO/CETUX versus control. ENCO/BINI/CETUX, encorafenib, binimetinib plus cetuximab; ENCO/CETUX, encorafenib plus cetuximab; HR, hazard ratio; PFS, progression-free survival.

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Tabernero et al., *JCO* 2021

BEACON CRC

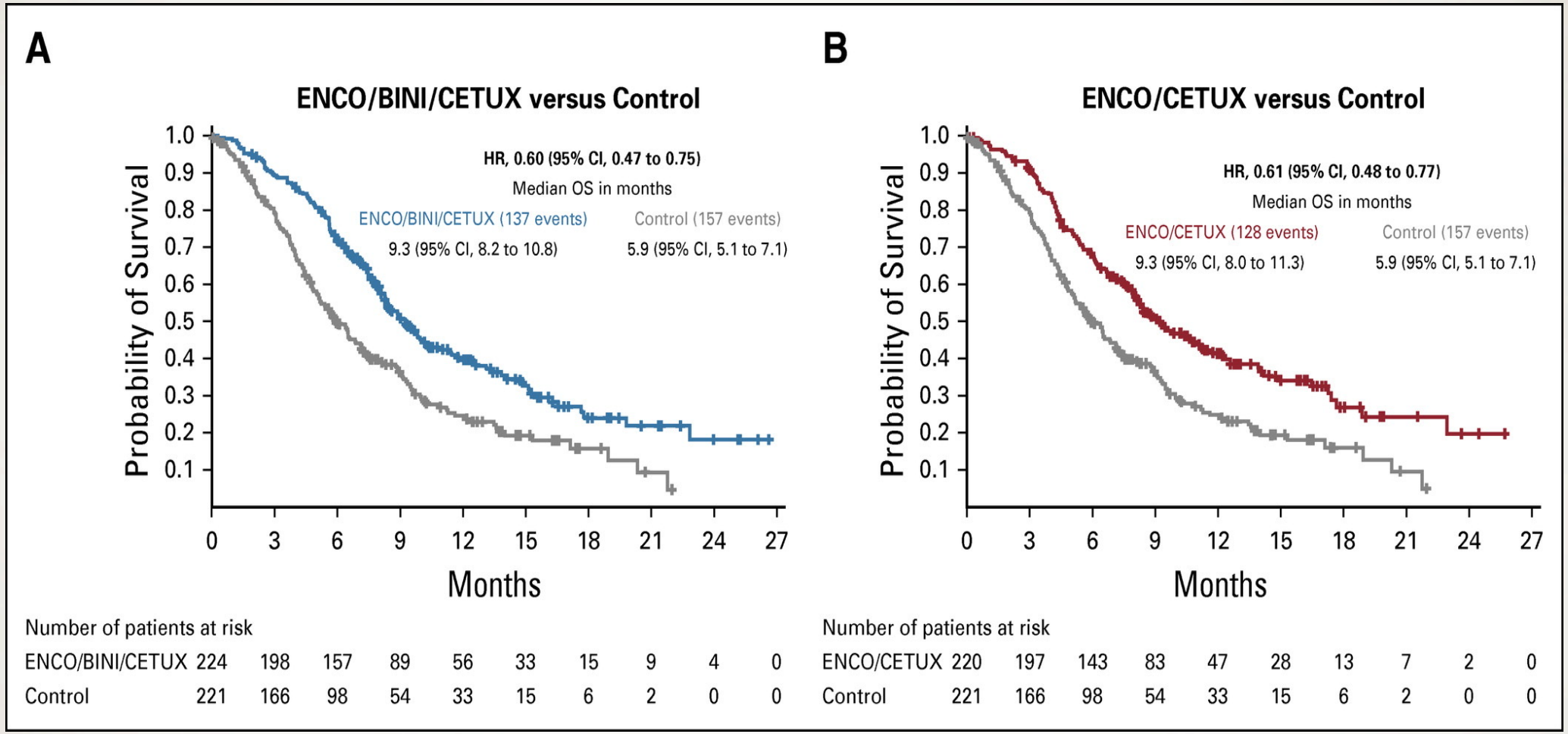

FIG 1. Overall survival results. (A) ENCO/BINI/CETUX versus control. (B) ENCO/CETUX versus control. ENCO/BINI/CETUX, encorafenib, binimetinib plus cetuximab; ENCO/CETUX, encorafenib plus cetuximab; HR, hazard ratio; OS, overall survival.

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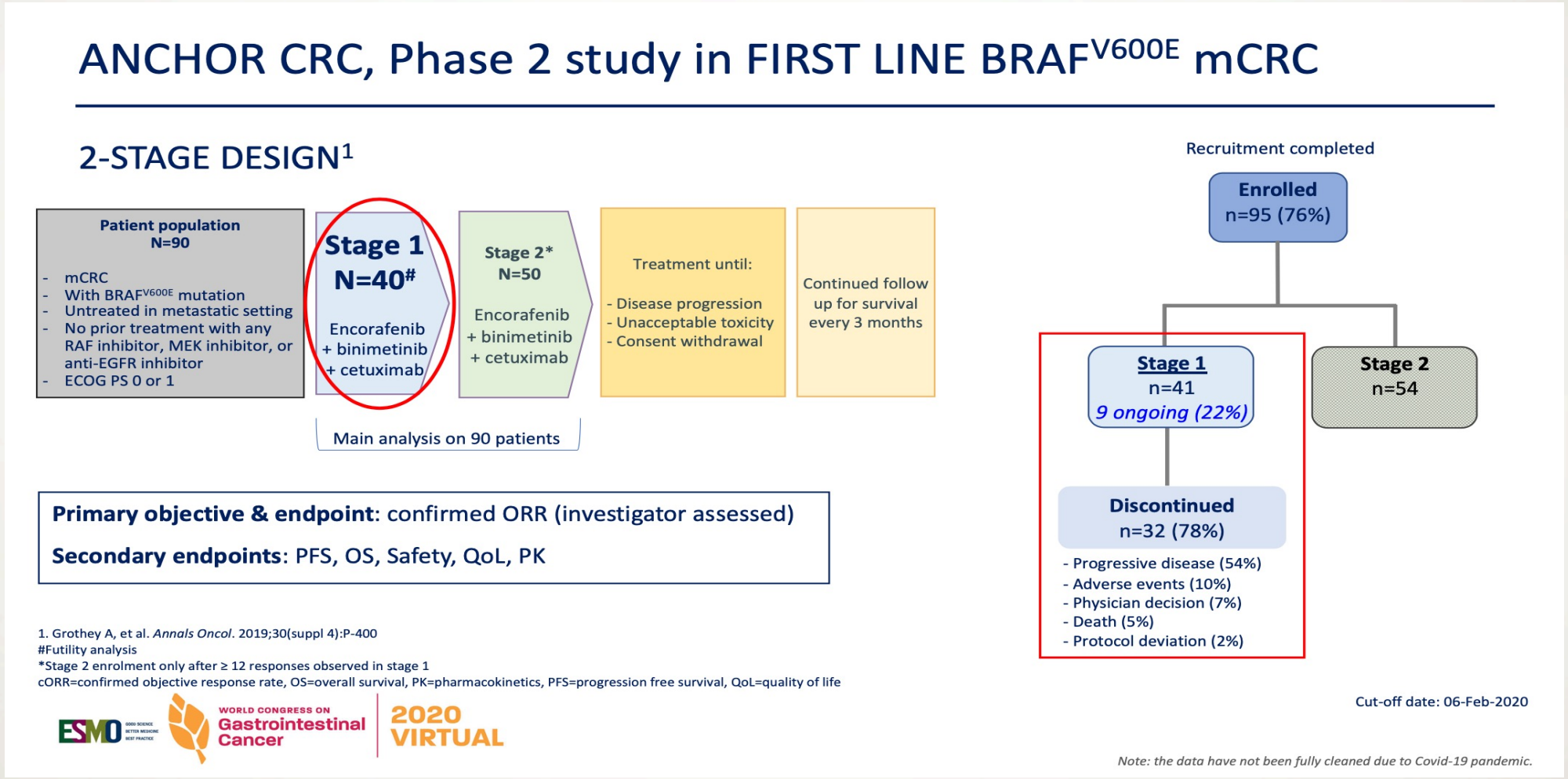
Tabernero et al., *JCO* 2021

- ANCHOR – Ph II encorafenib, binimetinib, cetuximab in 1L BRAF^{V600E}-mutant mCRC
- BREAKWATER



ANCHOR CRC

Confirmed Objective Response Rate (primary endpoint) for Stage 1

Investigator's assessment, median time on treatment: 4.9 months

	Patients (N=40#), n (%)	
Confirmed Objective Response Rate	**20 (50%)**	
95% CI	[34 ; 66]	
Best Overall Confirmed Response		
Complete response	0	
Partial response	20 (50%)	**DCR = 85%**
Stable disease	14 (35%)	
Progressive disease	4 (10%)	
Not evaluable*	2 (5%)	

# 1 patient has been excluded from the efficacy analysis as the BRAF mutation was not confirmed by central lab
DCR=Disease Control Rate
* 1 patient with no adequate post-baseline assessment
1 patient with 1st CT-scan performed < 6 weeks (32 days after study drug start, stable disease) and discontinued due to AE (myocardial infraction)

ESMO WORLD CONGRESS ON Gastrointestinal Cancer 2020 VIRTUAL

Note: the data have not been fully cleaned due to Covid-19 pandemic.

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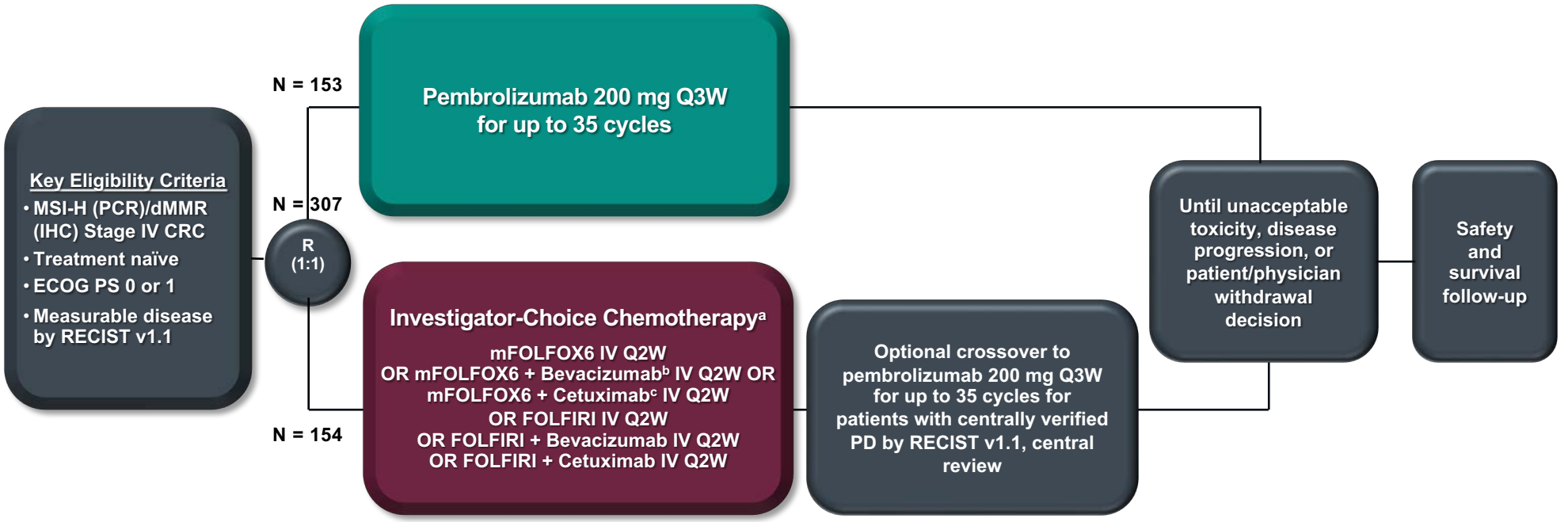
KEYNOTE-177 Study Design
(NCT02563002)

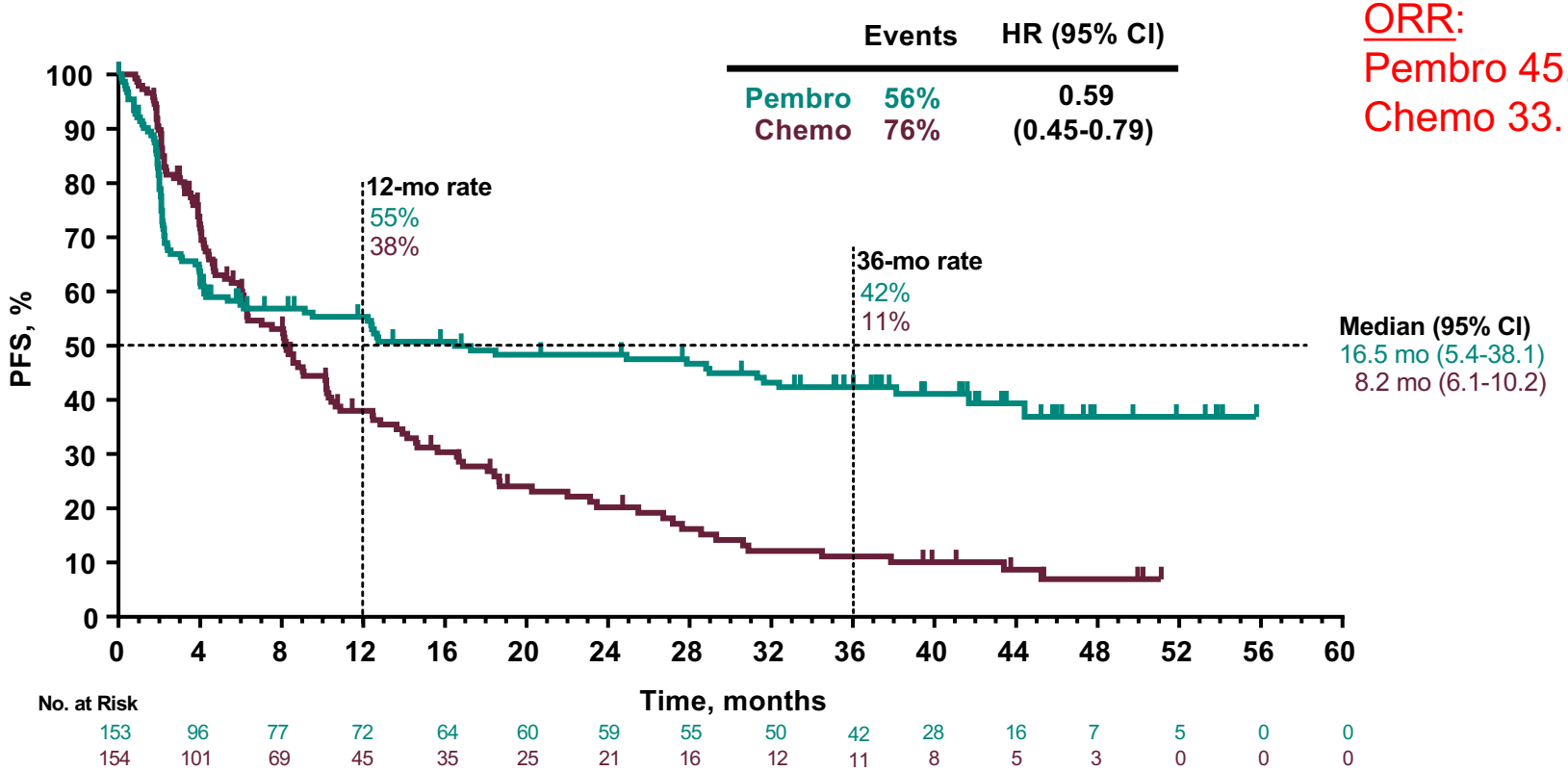


- Dual-Primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
BICR, blinded independent central review; IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Andre T, ASCO 2021

KEYNOTE-177 Progression-Free Survival



ORR:
Pembro 45.1%
Chemo 33.1%

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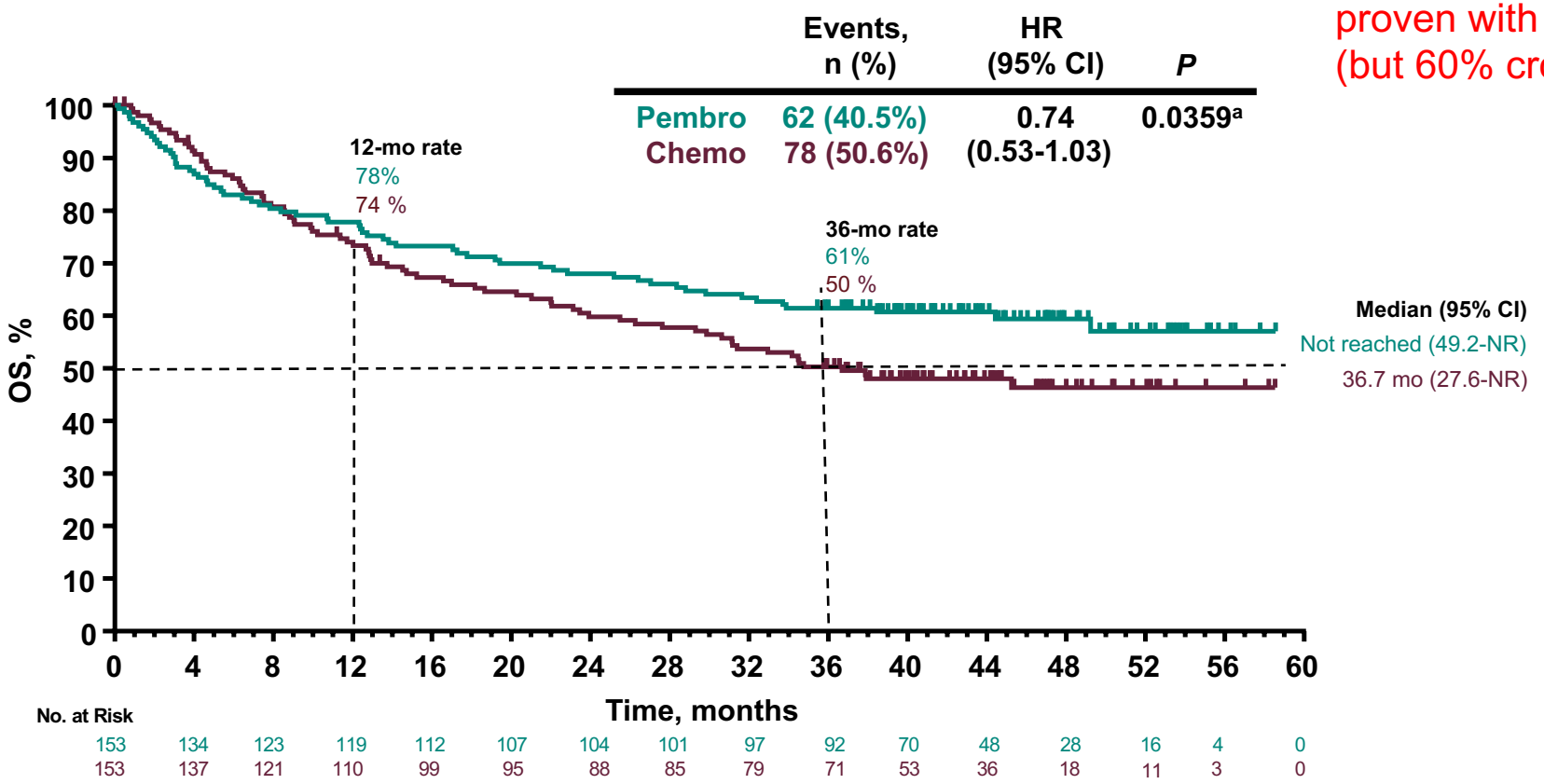
Data cut-off: 19Feb2021.

KEYNOTE-177 Overall Survival

OS benefit not proven with pembro (but 60% crossover)

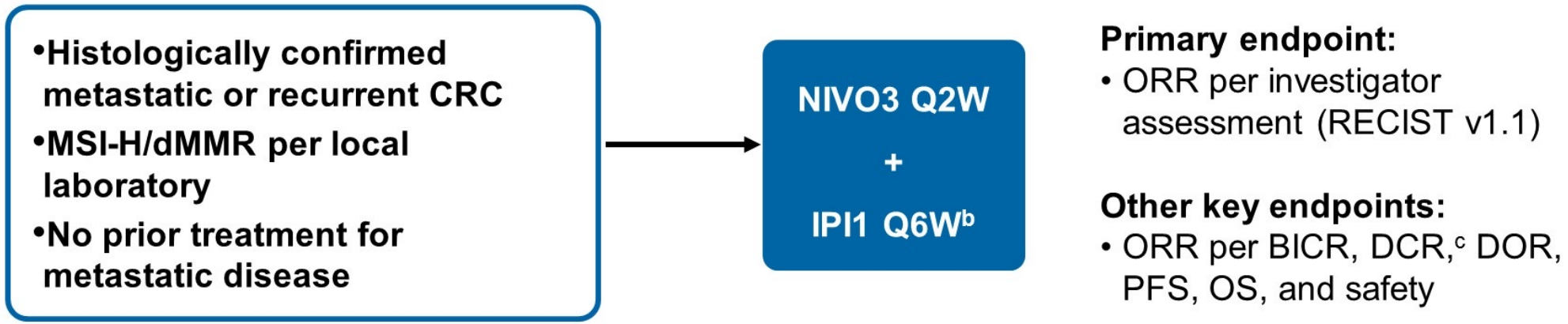


[a]**Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38).** Data cut-off: 19Feb2021.

Andre T, ASCO 2021

CheckMate 142 NIVO3 + IPI1 1L Cohort Study Design

- CheckMate 142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC[a]



- Median duration of follow-up (defined as time from first dose to data cutoff) was 19.9 months (range, 15.1–24.6)

[a]ClinicalTrials.gov number, NCT02060188; [b]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; [c]Patients with a CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients.
BICR, blinded independent central review; CRC, colorectal cancer; DCR, disease control rate; IPI1, ipilimumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

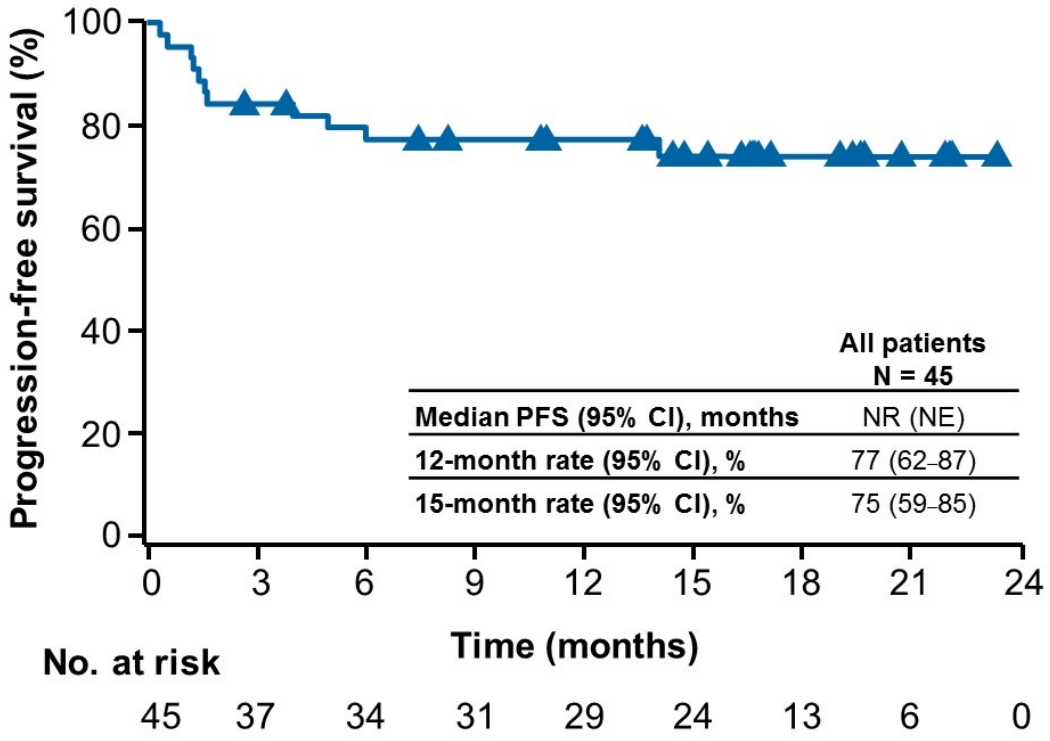
Response, Disease Control, and Durability

	NIVO3 (Q2W) + IPI1 (Q6W) N = 45[a]	
	BICR-assessed	Investigator-assessed
ORR,[b] n (%) [95% CI]	26 (58) [42–72]	29 (64) [49–78]
Best overall response, n (%)		
CR	8 (18)	4[c] (9)
PR	18 (40)	25 (56)
SD	10 (22)	9 (20)
PD	7 (16)	6 (13)
Not determined	2 (4)	1 (2)
DCR,[d] n (%) [95% CI]	35 (78) [63–89]	38 (84) [71–94]
Median TTR (range), months	1.6 (1.2–16.3)	2.6 (1.2–13.8)
Median DOR (range), months	NR (3.3+ to 20.8+)	NR (1.4+ to 20.8+)

[a]Median follow-up of 19.9 months; [b]Patients with CR or PR divided by the number of treated patients; [c]One patient was incorrectly reported as CR instead of PR. CR was based on surgical pathology and not RECIST v1.1; [d]Patients with a CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients.
CI, confidence interval; NR, not reached; PD, progressive disease; TTR, time to response.

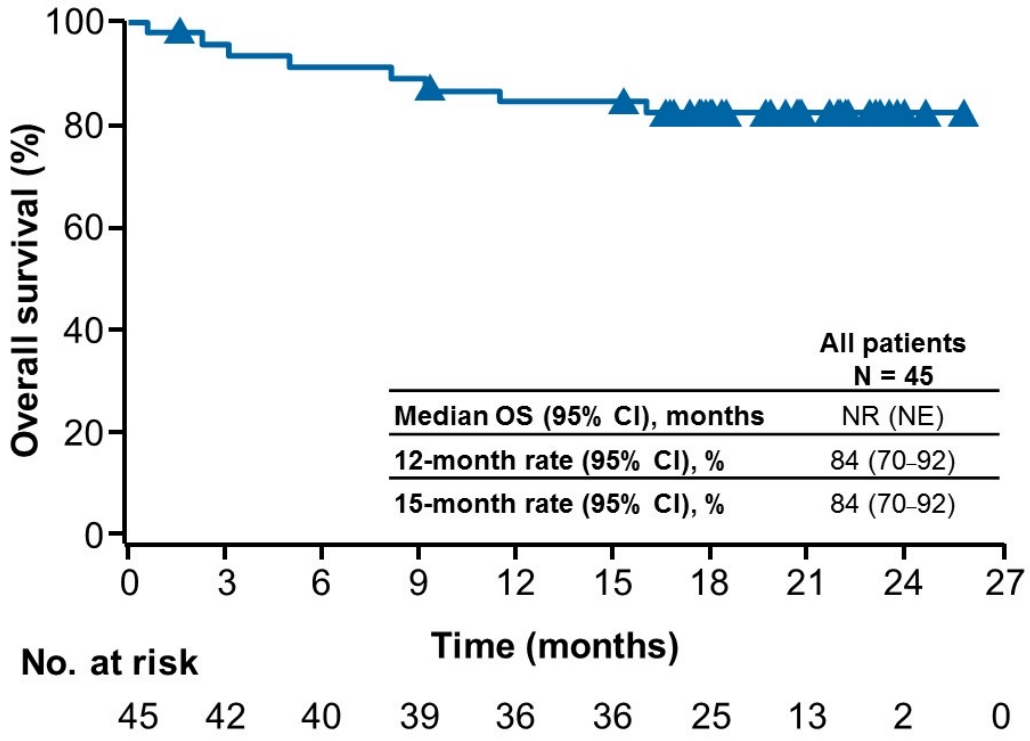
Progression-Free and Overall Survival

Progression-free survival[a]



	All patients N = 45
Median PFS (95% CI), months	NR (NE)
12-month rate (95% CI), %	77 (62–87)
15-month rate (95% CI), %	75 (59–85)

Overall survival



	All patients N = 45
Median OS (95% CI), months	NR (NE)
12-month rate (95% CI), %	84 (70–92)
15-month rate (95% CI), %	84 (70–92)

[a]Per investigator assessment.
NE, not estimable.

CheckMate 142

ORR:
Nivo/ipi: 55%
Nivo: 31%

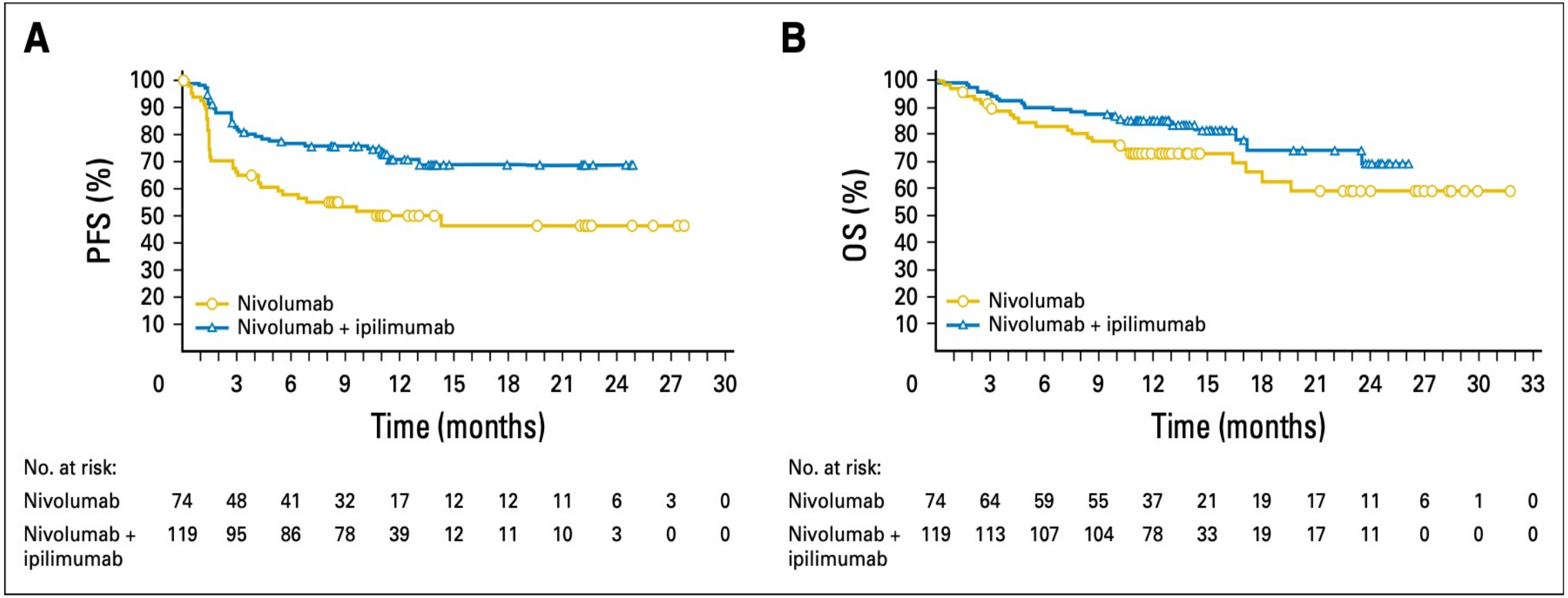
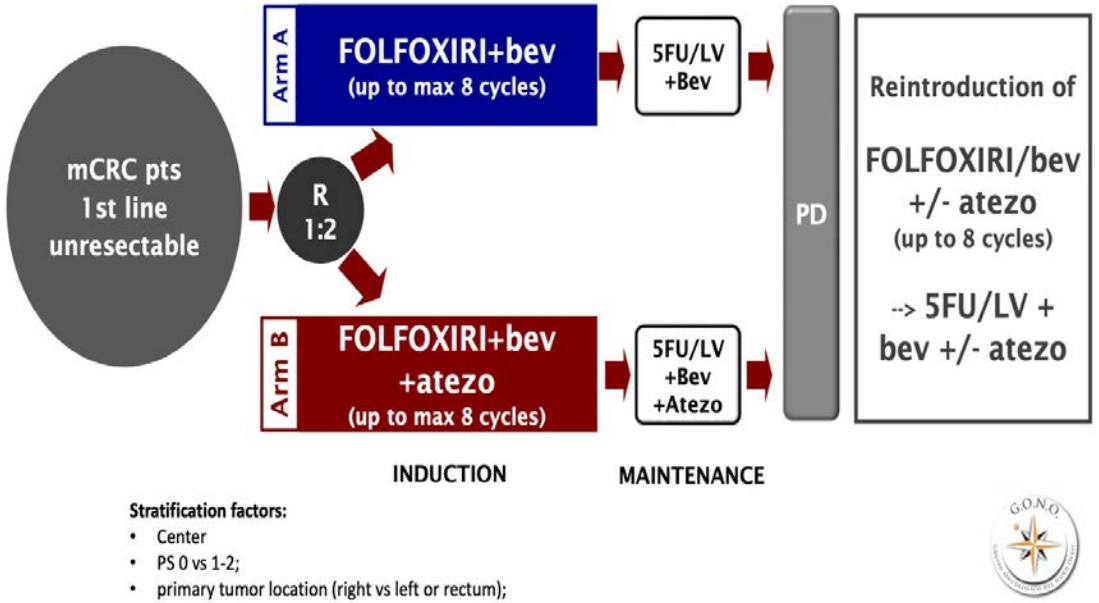


Fig 3. Kaplan-Meier plots of (A) progression-free survival (PFS) per investigator assessment and (B) overall survival (OS) in patients treated with nivolumab plus ipilimumab in the analyses presented herein or nivolumab in the monotherapy cohort of CheckMate-142 from an analysis that had a similar median follow-up (potential time on study from first dose to data cutoff: 13.4 months).[11]

Overman MJ, *JCO* 2018

Anti-PD-L1 + Chemotherapy in MSS mCRC

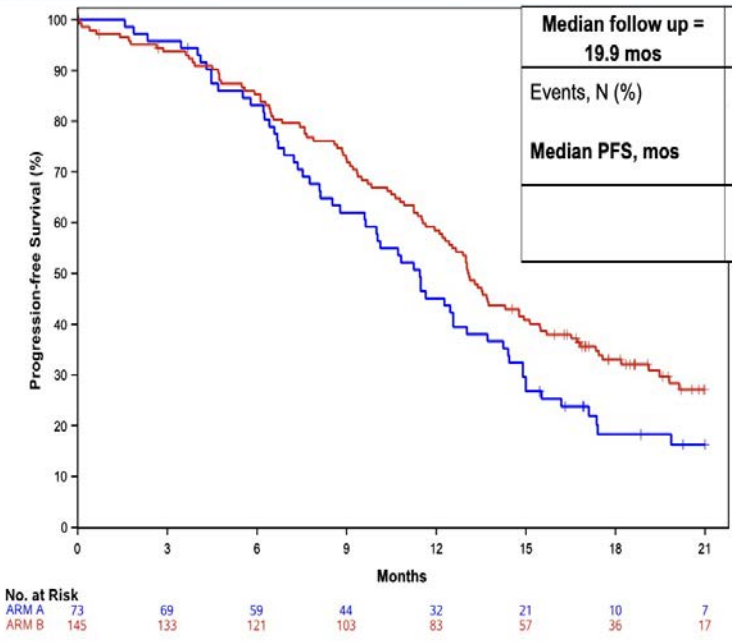
AtezoTRIBE trial



Stratification factors:

- Center
- PS 0 vs 1-2;
- primary tumor location (right vs left or rectum);
- Previous adjuvant CT

Primary endpoint: Progression Free Survival



Median follow up = 19.9 mos	FOLFOXIRI/Bev N = 73	FOLFOXIRI/Bev/Atezo N = 145
Events, N (%)	60 (82%)	99 (68%)
Median PFS, mos	11.5	13.1
	HR = 0.69 [80% CI: 0.56-0.85] p=0.012	

ORR = 64% vs 59%
HR 0.78 [0.54-1.15], p = 0.412

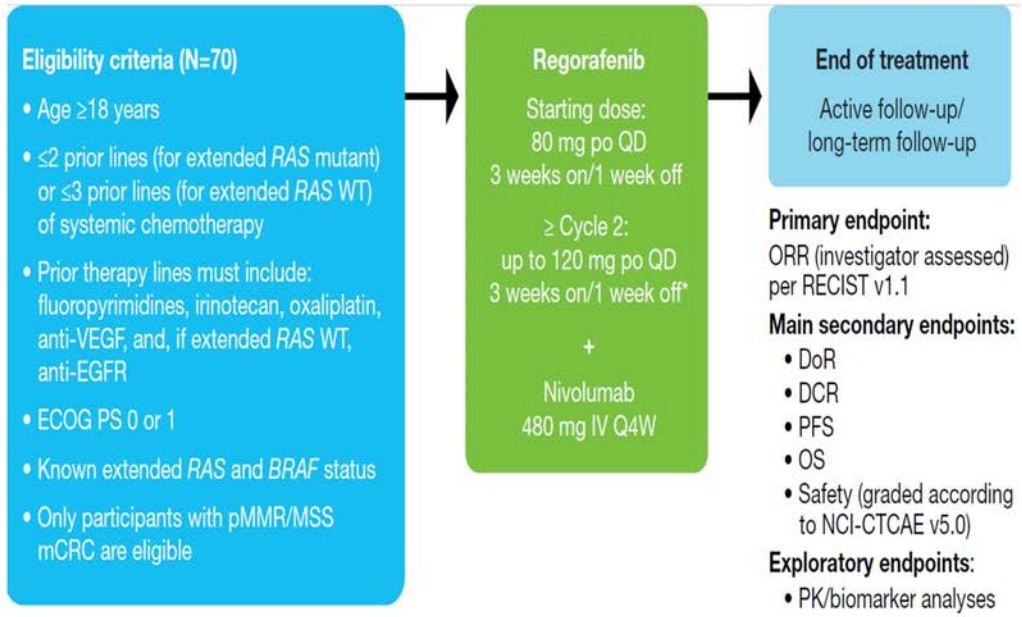
For pMMR subgroup: mPFS 11.4 vs 12.9 mos, HR 0.78, p = 0.071

Cremolini C, ESMO 2021

Anti-PD-1 + Antiangiogenic Agents in MSS mCRC

Regorafenib/nivolumab

Study Design (NCT04126733)



Response, n (%)	Without liver metastases (n=23)	With liver metastases (n=47)	All patients (N=70)
Complete response	0	0	0
Partial response	5 (22)	0	5 (7)
Stable disease	8 (35)	14 (30)	22 (31)
Progressive disease	9 (39)	27 (57)	36 (51)
Not evaluable	1 (4)	6 (13)	7 (10)
Objective response rate	5 (22)	0	5 (7)
Disease control rate ≥8 weeks	13 (57)	14 (30)	27 (39)
Median duration of stable disease, weeks	30	21	30

Fakih M, ASCO 2021

PRESENTED BY: Kristen K. Ciombor, MD, MSCI

Anti-PD-(L)1 + Targeted Therapies in MSS mCRC

- MEK: IMblaze370 (cobimetinib/atezolizumab)
- EGFR: nivo/ipi/pmab; CAVE: cetuximab/avelumab; AVETUX: FOLFOX/cetuximab/avelumab; AVETRIC: FOLFOXIRI/cetuximab/avelumab
- BRAF: encorafenib/cetuximab/nivolumab, dabrafenib/trametinib/spartalizumab; spartalizumab/dabrafenib/LTT462 (ERKi)
- KRAS G12C: CodeBreaK 100: AMG 510 +/- anti-PD-(L)1; TNO155 (SHP2 inhibitor)/spartalizumab/JDQ443
- PI3K: nivolumab/copanlisib
- MGMT silencing: MAYA: TMZ + nivolumab + ipilimumab (TMZ-induced hypermutation); ARETHUSA: TMZ/pembro

Anti-HER2 Therapy in mCRC

		N	ORR	Median PFS	Median OS
HERACLES-A	Trastuzumab + Lapatinib ^	27	30% (14-50)	4.8 mo (3.7-7.4)	10.6 mo (7.6-15.6)
MyPathway (*KRAS* WT subgroup)	Trastuzumab + Pertuzumab ^	43	40% (25-56)	5.3 mo (2.7-6.1)	14.0 mo (8.0-NE)
TRIUMPH	Trastuzumab + Pertuzumab ^	17 (Tissue)	35% (14-62)	4.0 mo (1.4-5.6)	
TAPUR (no RAS data)	Trastuzumab + Pertuzumab ^	28	25% (11-45)	4.0 mo (2.6-6.3)	25.0 mo (6.0-NE)
MOUNTAINEER	Trastuzumab + Tucatinib	23	52% (31-73)	8.1 mo (3.8-NE)	18.7 mo (12.3-NE)
DESTINY-CRC01 *	**T-DXd**	**54**	**45% (32-60)**	**6.9 mo (4.1-NE)**	**NE (0.74-NE)**
HERACLES-B #	T-DM1 + Pertuzumab	30	10% (0-28)	4.8 mo (3.6-5.8)	

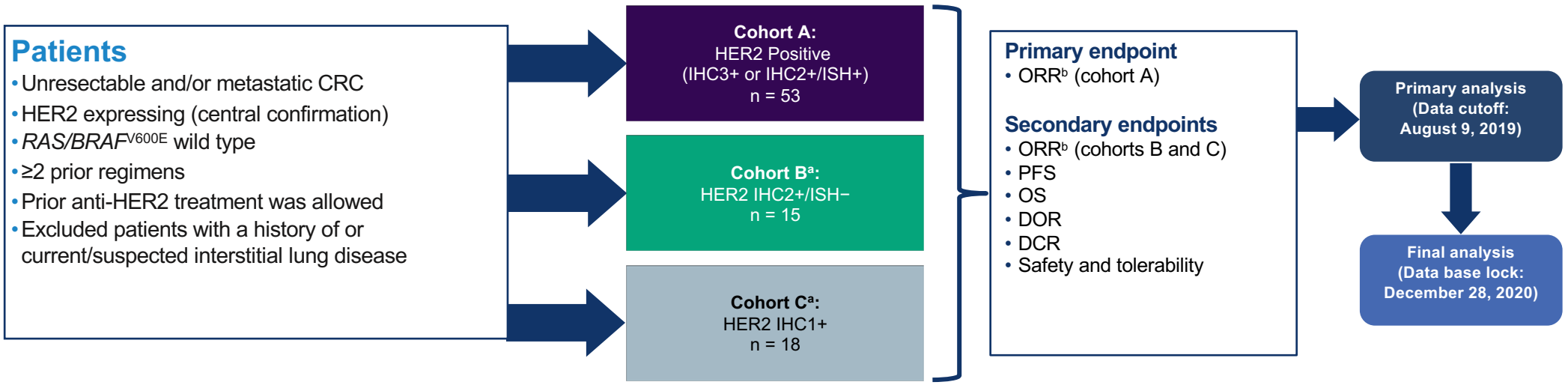
* ORR in subgroup **with prior HER2 rx 43.8% (19.8-70.1)**; without prior HER2 rx 45.9% (29.5-63.1)
# Did not meet primary endpoint. T-DM1 had 0% response rate in MATCH Arm Q and MSKCC basket trial
^ In NCCN guidelines

Sartore-Bianchi A, Lancet Oncol 2016; Meric-Bernstam F, Lancet Oncol 2019; Nakamura Y, ESMO 2019; Gupta R, GI ASCO 2020; Strickler J, ESMO 2019; Sartore-Bianchi A, ESMO 2019; Siena S, ASCO 2020; Jhaveri KL, Ann Oncol 2019; Li BT, ASCO 2018

Presented By Michael Lee at ASCO 2020

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)



Primary analysis of cohort A[1]

- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

Patient disposition at final analysis[c]

- No patients remain on treatment
- At the end of the study, median follow-up was 62.4 weeks for cohort A, 27.0 weeks for cohort B and 16.9 weeks for cohort C

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan.

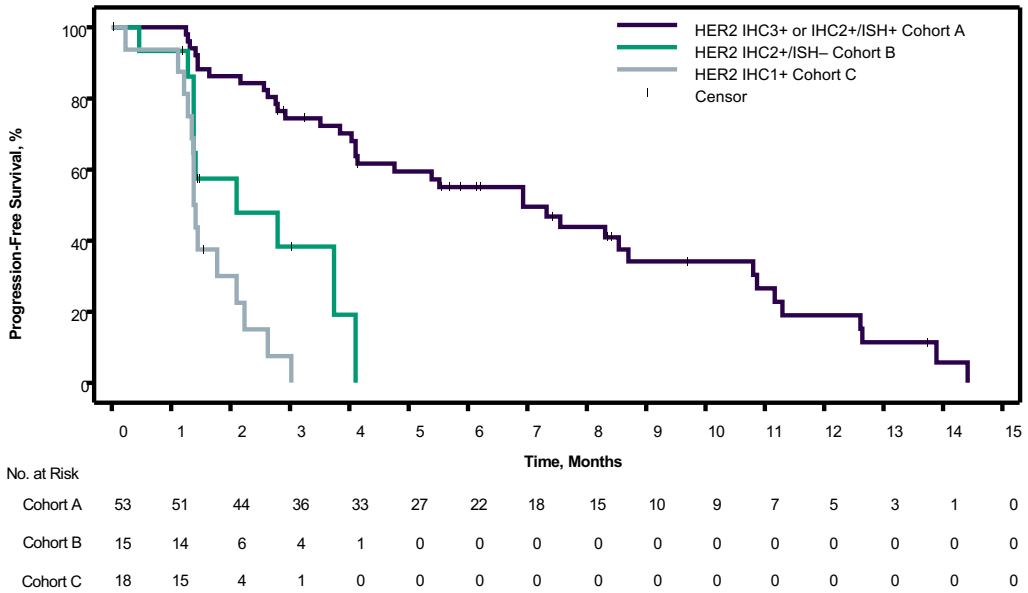
[a]A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C. [b]ORR was based on RECIST version 1.1 in all cohorts. [c]Data presented are from the full analysis set.

1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

Yoshino, ASCO 2021

DESTINY-CRC01
Progression-Free and Overall Survival

Progression-Free Survival

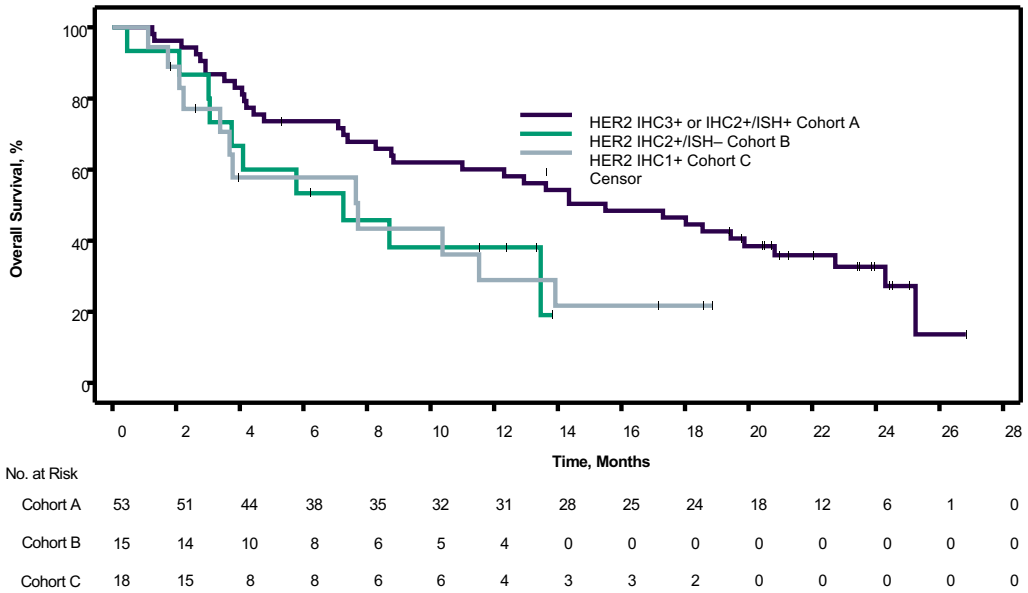


No. at Risk

Cohort A	53	51	44	36	33	27	22	18	15	10	9	7	5	3	1	0
Cohort B	15	14	6	4	1	0	0	0	0	0	0	0	0	0	0	0
Cohort C	18	15	4	1	0	0	0	0	0	0	0	0	0	0	0	0

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mPFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)

Overall Survival



No. at Risk

Cohort A	53	51	44	38	35	32	31	28	25	24	18	12	6	1	0	
Cohort B	15	14	10	8	6	5	4	0	0	0	0	0	0	0	0	
Cohort C	18	15	8	8	6	6	4	3	3	2	0	0	0	0	0	

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mOS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable.

Yoshino, ASCO 2021

DESTINY-CRC01
AEs of Special Interest: Interstitial Lung Disease

All Patients (N=86)	n (%)
Grade 1	0
Grade 2	4 (4.7)
Grade 3	1 (1.2)
Grade 4	0
Grade 5	3 (3.5)[a]
Any Grade/Total	8 (9.3)[b,c]

Adjudicated drug-related ILDs:

- Median time to adjudicated onset was 61.0 days (range, 9-165 days)
- 8 of 8 patients received corticosteroids
- 4 patients with grade 2 recovered and 1 patient with grade 3 did not recover (later died due to disease progression)
- Median time from adjudicated onset date to initiation of steroid treatment in the 8 ILD cases was 3.5 days, (range 0-50)

Grade 5 ILDs:

- In the 3 fatal cases adjudicated as drug-related ILD, onset was from 9 days to 120 days (median: 22 days); and death occurred 6-19 days after diagnosis (median: 6 days)

Updated ILD/pneumonitis guidelines recommend to monitor for symptoms, interrupt or discontinue T-DXd, conduct imaging (as clinically indicated), and start steroids as soon as ILD is suspected.

AE, adverse events; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.
[a]2 patients were from cohort A, 1 from cohort B. [b]4 patients were from cohort A, 3 from cohort B and 1 from cohort C. [c]ILD grades are the highest/most severe grade recorded in a patient.

Yoshino, ASCO 2021

Positive Topline Results Announced for the MOUNTAINEER Phase 2 Clinical Trial of Tucatinib in Combination With Trastuzumab in Previously Treated HER2-Positive Metastatic Colorectal Cancer

Press Release: May 23, 2022

"Data from this trial will form the basis of a planned supplemental New Drug Application to the U.S. Food and Drug Administration (FDA) under the FDA's Accelerated Approval Program.

Results showed a 38.1% confirmed objective response rate (cORR) [95% Confidence Interval (CI): 27.7, 49.3] per blinded independent central review (BICR). The median duration of response (DoR) per BICR was 12.4 months [95% CI: 8.5, 20.5]. The combination of tucatinib and trastuzumab was generally well-tolerated, and the most common (greater than or equal to 20%) treatment-emergent adverse events were diarrhea, fatigue, nausea and infusion-related reaction, which were primarily low-grade.

Full data from the MOUNTAINEER trial will be presented by John H. Strickler, M.D., Duke University Medical Center, at the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer in Barcelona, Spain from June 29 through July 2, 2022."

https://finance.yahoo.com/news/seagen-announces-positive-topline-results-120000073.html

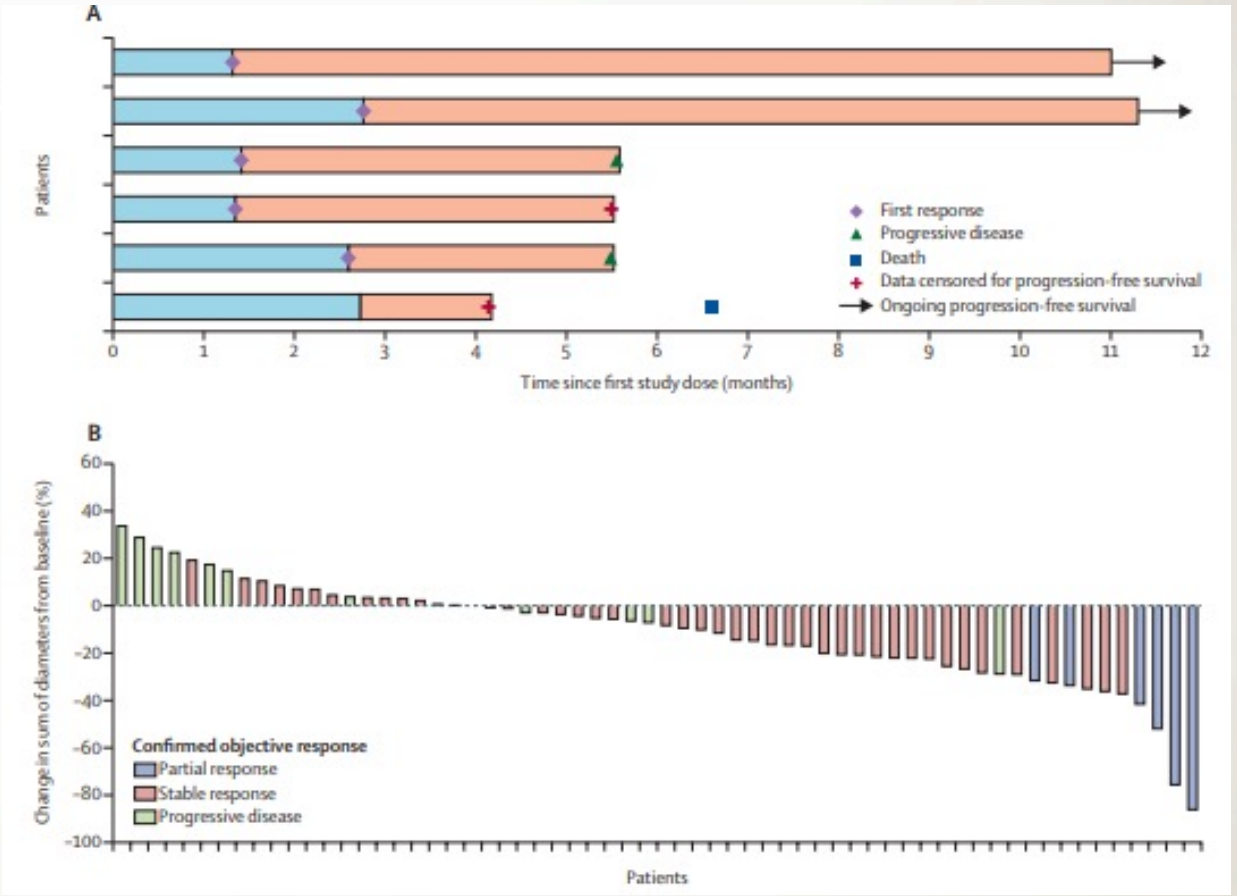
RTP RESEARCH TO PRACTICE

CodeBreaK 100: Phase 2 mCRC Results of Sotorasib

	Patients (n=62)
Objective response, n (%; 95% CI)*	6 (9·7%; 3·6–19·9)
Disease control, n (%; 95% CI)†	51 (82·3%; 70·5–90·8)
Best response, n (%)	
Complete response	0
Partial response	6 (10%)
Stable disease	45 (73%)
Progressive disease	11 (18%)
Median time to response, months (IQR)‡	2·0 (1·4–2·8)
Median duration of response, months (IQR)‡	4·2 (2·9–8·5)

*Objective response was defined as a complete or partial response. †Disease control was defined as a complete response, partial response, or stable disease. ‡Time to response and duration of response were calculated among the six confirmed responders. Kaplan-Meier estimates of the median (95% CI) for duration of response were not calculated given that the analysis had fewer than ten patients. Crude median duration of response is reported.

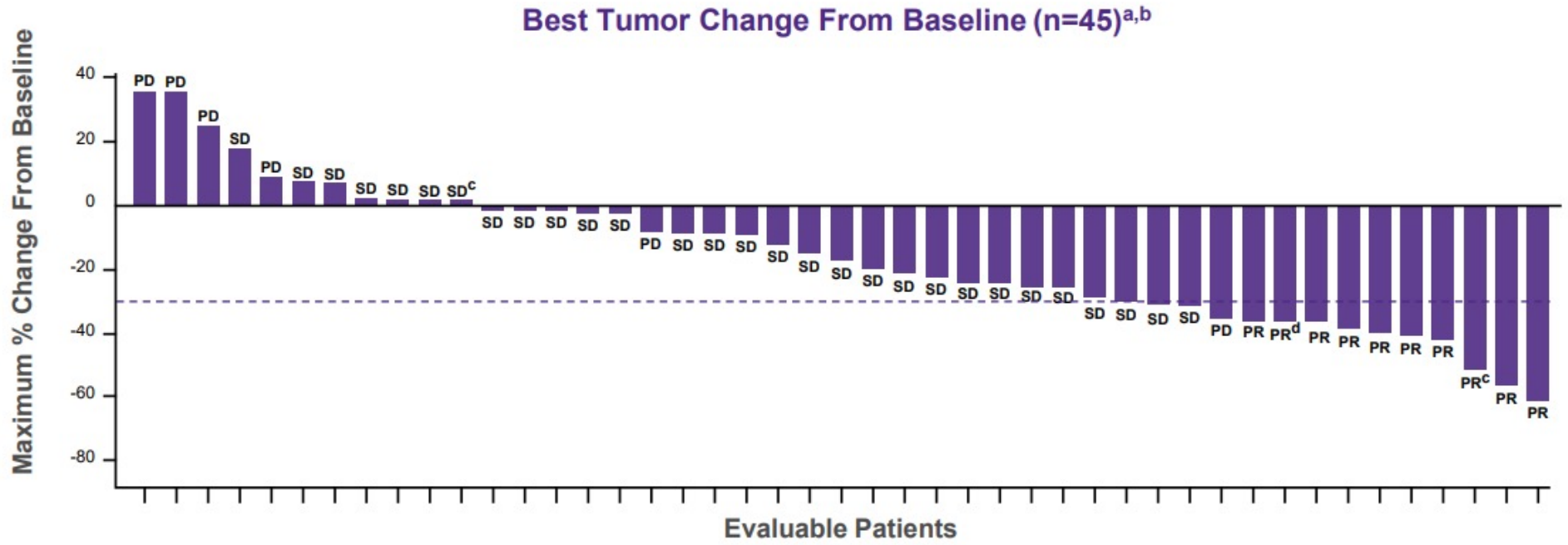
Table 2: Tumour response to sotorasib therapy according to independent central review



VANDERBILT UNIVERSITY MEDICAL CENTER

Fakih M et al, *Lancet Oncol* 2022;23:115-124

Adagrasib in Patients With Advanced CRC: Best Overall Response



- Response rate was 22% (10/45), including 1 unconfirmed PR
- SD was observed in 64% (29/45) of patients
- Clinical benefit (DCR) was observed in 87% (39/45) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

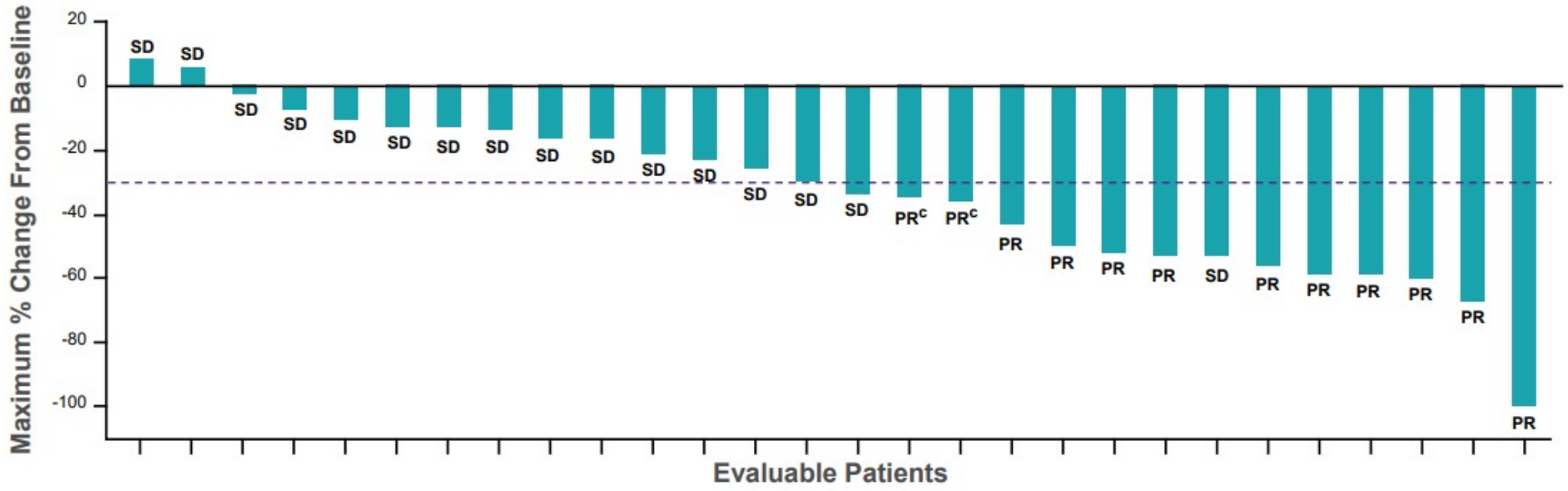
[a]All results are based on investigator assessments. [b]Evaluable population (n=45) excludes 1 patient who withdrew consent prior to the first scan. [c]Phase 1/1b. [d]At the time of the 25 May 2021 data cutoff, the patient had uPR.
[e]Molecular status (BRAF V600E mutation, MSI-H or dMMR, EGFR amplification, TP53 mutation, PIK3CA mutation) includes patients with conclusively evaluable test results.

Data as of 25 May 2021 for monotherapy (median follow-up: 8.9 months).

Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021

Adagrasib + Cetuximab in Patients With Advanced CRC: Best Overall Response

Best Tumor Change From Baseline (n=28)[a,b]



- Response rate was 43% (12/28) including 2 unconfirmed PRs
- SD was observed in 57% (16/28) of patients
- Clinical benefit (DCR) was observed in 100% (28/28) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

[a]All results are based on investigator assessments. [b]Evaluable population (n=28) excludes 4 patients who withdrew consent prior to the first scan. [c]At the time of the 9 July 2021 data cutoff, 2 patients had uPRs.
[e]Molecular status (BRAF V600E mutation, MSI-H or dMMR, EGFR amplification, TP53 mutation, PIK3CA mutation) includes patients with conclusively evaluable test results.

Data as of 9 July 2021 (median follow-up: 7 months).

Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021

MODULE 2: Other Considerations in the Management of Early and Advanced CRC — Dr Strickler

RTP
RESEARCH
TO PRACTICE

Dr Shaachi Gupta
Lake Worth, Florida

52-year-old man with metastatic CRC and an MI

FOLFOXai™ molecular signature

67-year-old man with metastatic CRC who received TAS-102 as third line therapy

RTP
RESEARCH
TO PRACTICE

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
KRAS	**Seq**	**DNA-Tumor**	**Mutation Not Detected**	**BENEFIT**	**cetuximab, panitumumab**	**Level 2**
NRAS	**Seq**	**DNA-Tumor**	**Mutation Not Detected**			
BRAF	Seq	DNA-Tumor	Mutation Not Detected			
ERBB2 (Her2/Neu)	IHC	Protein	Negative | 0	LACK OF BENEFIT	lapatinib, pertuzumab, trastuzumab	Level 2

* Biomarker reporting classification: Level 1 – Companion diagnostic (CDx); Level 2 – Strong evidence of clinical significance or is endorsed by standard clinical guidelines; Level 3 – Potential clinical significance. Bolded benefit therapies, if present, highlight the most clinically significant findings.

MI FOLFOXai **Result:** **DECREASED BENEFIT to FOLFOX + bevacizumab in first-line metastatic CRC**

See Page 2 for important details about clinical data regarding MI FOLFOXai

Cancer-Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
MSI	Seq	DNA-Tumor	Stable
Mismatch Repair Status	IHC	Protein	Proficient
NTRK1/2/3	Seq	DNA-Tumor	Fusion Not Detected

Biomarker	Method	Analyte	Result
PTEN	IHC	Protein	Positive | 1+, 100%
OTHER FINDINGS (see below for additional results)			
PD-L1 (SP142)	IHC	Protein	Negative | 0%

45-year-old man with metastatic CRC and a renal allograft – dMMR

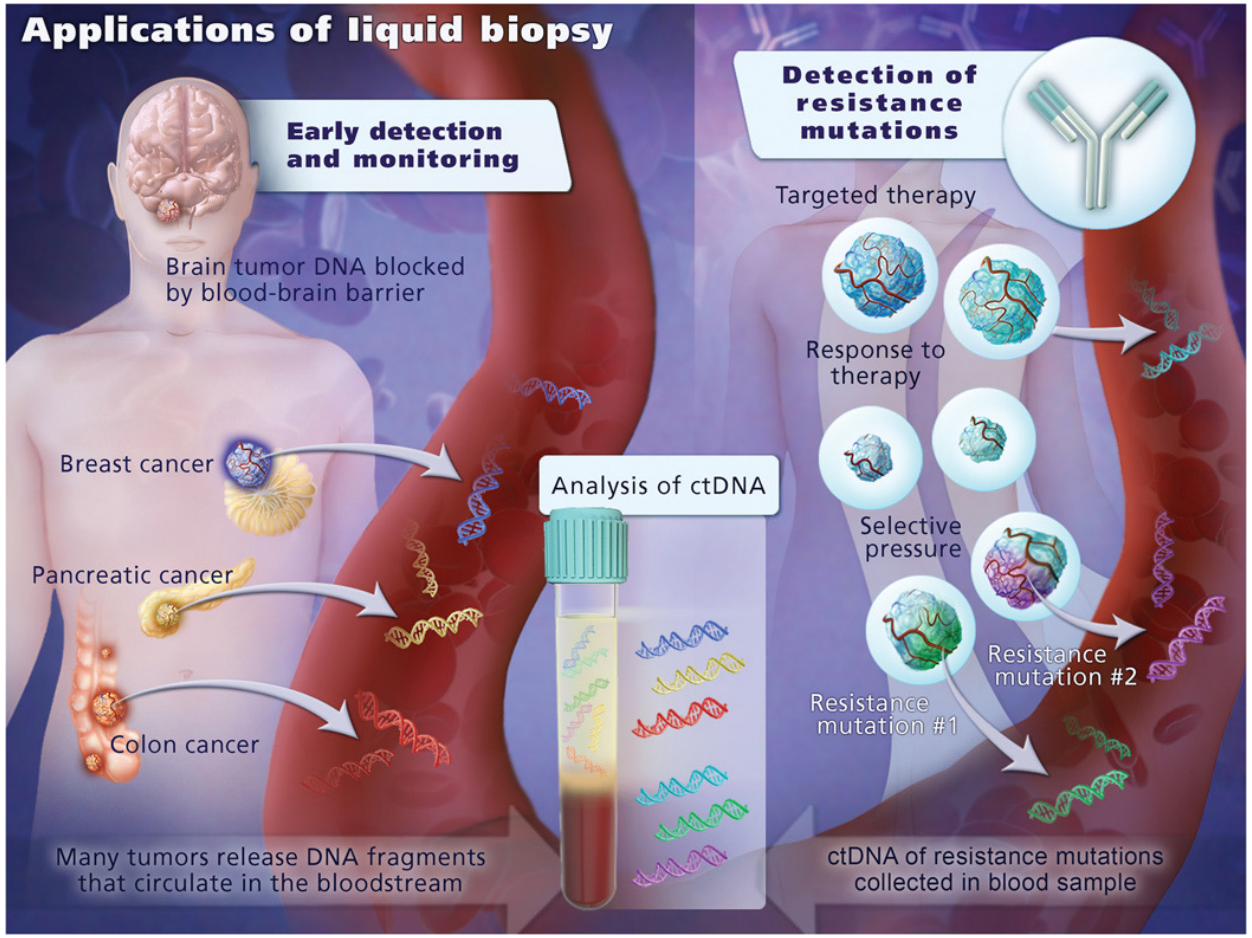
Dr Erik Rupard (West Reading, Pennsylvania)

RTP
RESEARCH
TO PRACTICE

Other Considerations in the Management of Early and Advanced CRC

John Strickler, MD

“Liquid biopsy” in the clinic



Potential clinical applications

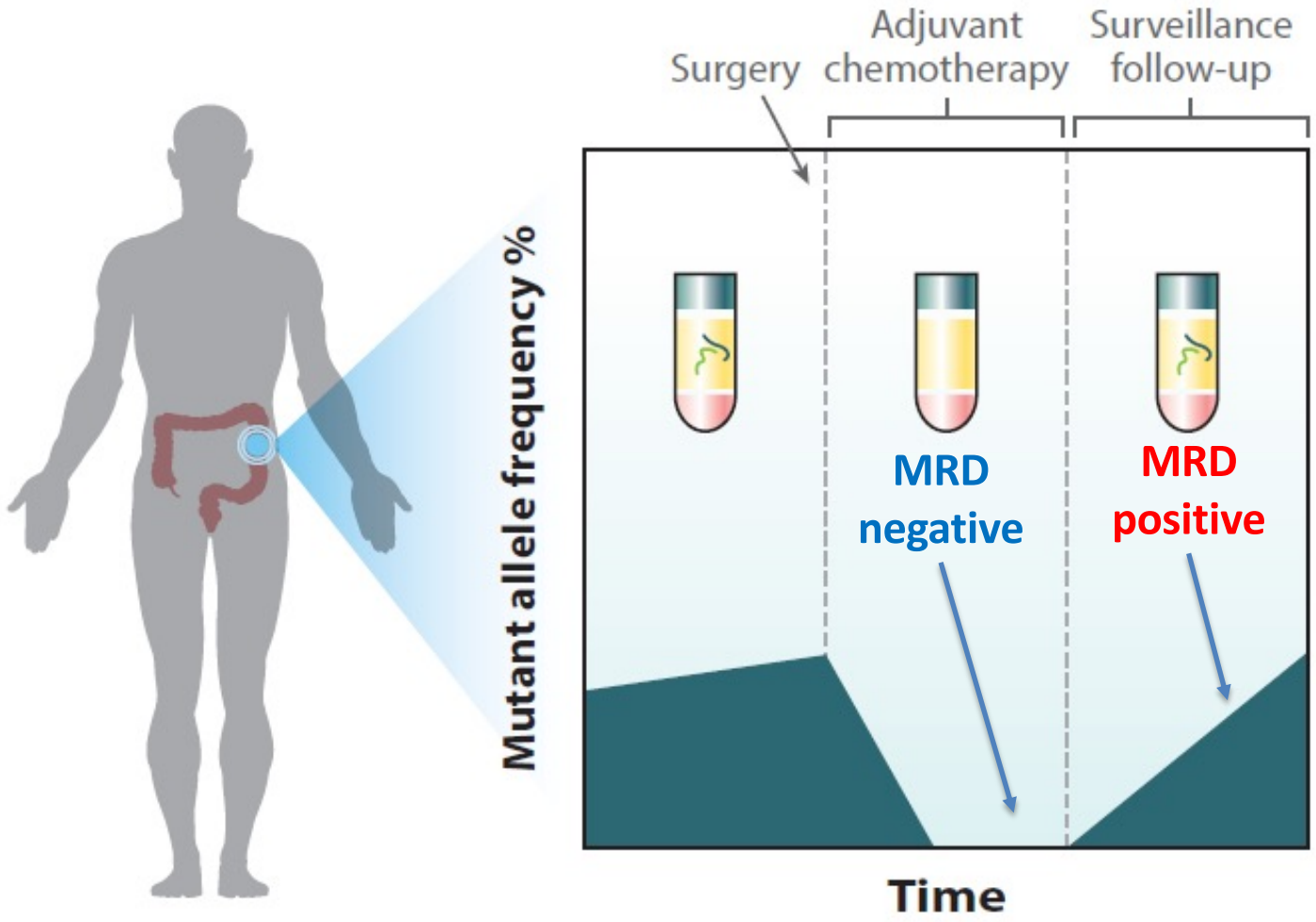
- Screen asymptomatic population
- Detect residual disease following resection
- Identify actionable biomarkers (HER2, etc.)
- Predict treatment response
- Monitor overall tumor burden
- Identify drivers of treatment resistance

C. Bettegowda *et al., Sci Transl Med* 2014;6:224ra24

ctDNA for surveillance: The needle in the haystack

- Average cell free DNA fragment length ~ 150-200bp
- ctDNA detection requires “ultrasensitive” assay
- Specificity must be very high to avoid false positives
  - Germline variants
  - “CHIP”
- When specific target mutations are known in advance, error rate and sensitivity optimized

Defining Minimal Residual Disease (MRD)



ctDNA detection techniques

- Tumor informed
- Plasma only

Morris and Strickler, Annu Rev Med. 2021. 72:399–413.

Stage I-III colon ca: Recurrence risk impacted by ctDNA status (tumor informed assay)

Relapse free survival

218 pts with stage I-III colon ca, monitored with Signatera assay

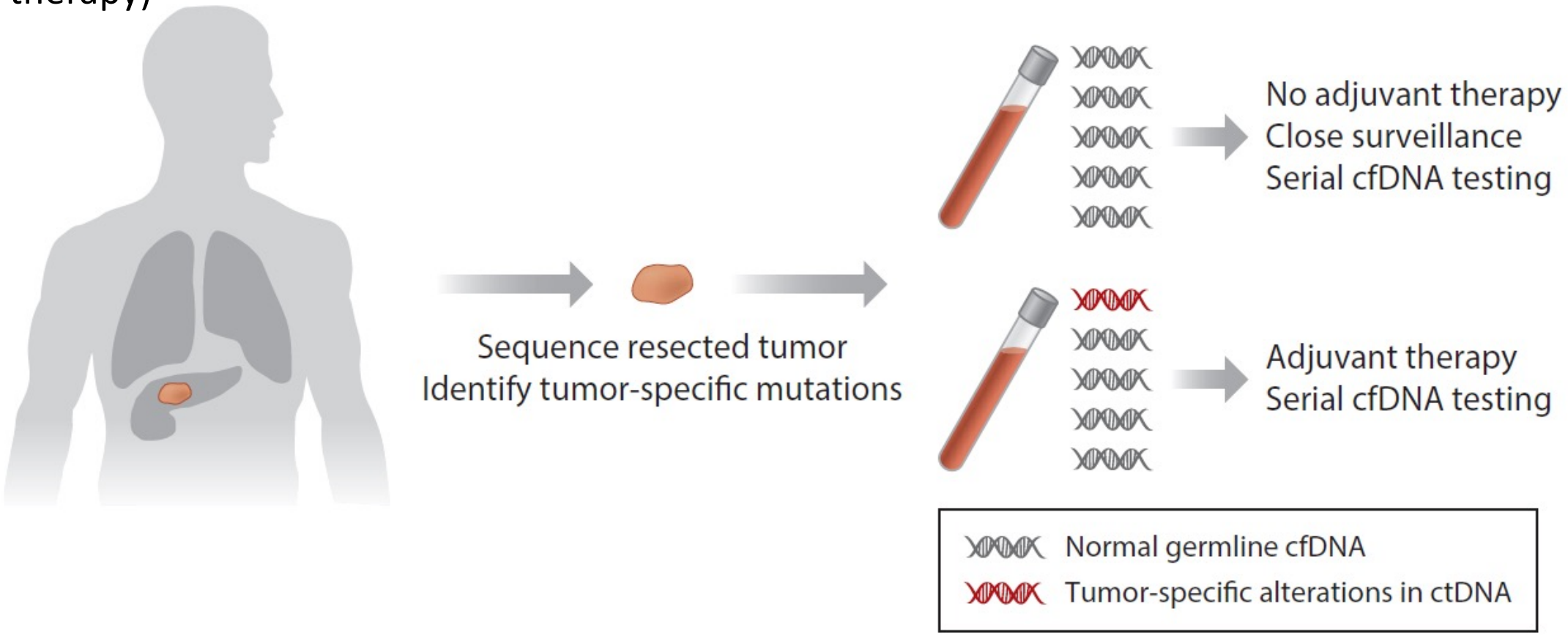
	Post-op ctDNA status	After end of adjuvant chemotherapy	Longitudinal monitoring (Q3 months for 3 yrs)
ctDNA positive	20%	17%	11%
ctDNA negative	87%	88%	97%

Henriksen et al., J Clin Oncol 39, 2021 (suppl 3; abstr 11)

Can we integrate MRD into clinical care?

Potential applications:

- Selecting high risk patients for aggressive therapy when post-operative observation is SOC
- Spare patients chemotherapy/treatment if no residual disease (when SOC calls for additional therapy)



Morris and Strickler, Annu Rev Med. 2021. 72:399–413.

GALAXY : Observational cohort from the CIRCULATE-Japan study

- CIRCULATE-Japan enrolled patients with resectable CRC (all stages) to evaluate the clinical utility of ctDNA MRD analysis
- CIRCULATE-Japan consists of 3 studies:
  - Observational cohort: GALAXY study
  - 2 randomized phase III trials (VEGA and ALTAIR trials)
- Blood samples are collected before surgery and 4, 12, 24, 36, 48, 72, and 96 weeks after surgery
- 1,564 patients enrolled in CIRCULATE-Japan
- 1,040 patients included in the GALAXY study
  - Median follow up time: 11.4 months
  - Data cutoff: 11/9/2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

ctDNA detection at a single post-operative timepoint (4 weeks post op) is associated with poor prognosis

Disease free survival: Post-op-4w ctDNA status

712 pts with stage II-III colon ca, monitored with Signatera assay

ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
Negative	22/597	97.8% (95.3-98.7)	95.2% (92.6–96.9)
Positive	46/115	73.0% (63.9-80.2)	55.5% (44.8–65.0)

HR = 13.3
95% CI, 8.0 to 22.2, P<0.001

Sensitivity for recurrence= 68%

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

Adjuvant chemotherapy is not associated with improved DFS for patients with negative post-op ctDNA

Disease free survival: Negative post-op-4w ctDNA status

531 pts with high risk stage II/ stage III colon ca receiving adjuvant chemotherapy, monitored with Signatera assay

ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	7/214	98.6% (95.7-99.5)	96.2% (92.1–98.2)
W/O ACT	12/317	97.5% (95.0-98.7)	94.7% (90.5–97.1)

Adjusted HR = 1.3
95% CI, 0.5 to 3.6, P=0.63

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

Adjuvant chemotherapy is associated with improved DFS for patients with positive post-op ctDNA

Disease free survival: Positive post-op-4w ctDNA status

High-risk pStage II (n= 23)

	Events/ N	6M-DFS	12M-DFS
W/ ACT	1/9	100%	88.9%
W/O ACT	7/13	53.8%	46.2%

Adjusted HR = 9.4
95% CI, 1.1 to 79.1, P=0.04

pStage III (n= 90)

	Events/ N	6M-DFS	12M-DFS
W/ ACT	17/65	89.2%	68.3%
W/O ACT	19/25	32.0%	24.0%

Adjusted HR = 8.8
95% CI, 3.9 to 19.5, P<0.001

pStage IV (n= 68)

	Events/ N	6M-DFS	12M-DFS
W/ ACT	9/22	72.7%	53.7%
W/O ACT	35/46	28.3%	22.3%

Adjusted HR = 2.4
95% CI, 1.1 to 5.2, P=0.02

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

Clearance of ctDNA is associated with improved DFS (compared to non-clearance)

Disease free survival: According to ctDNA dynamics from post-op-4w to 12w

838 pts with stage I-IV colon ca, monitored with Signatera assay

	Neg > Neg	Neg > Pos	Pos > Neg	Pos > Pos
Events/N	31/660	13/32	4/62	50/84
6M-DFS	**98.0%**	**62.5%**	**100%**	**58.3%**
HR (vs. Pos > Neg)	0.8	9.2	Reference	15.8
P	0.60	**<0.001**	-	**<0.001**

HR = 15.8 (Pos > Pos vs. Pos > Neg)
95% CI, 5.7 to 44.2, P<0.001

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

Clearance of ctDNA is associated with use of adjuvant chemotherapy

Cumulative incidence of ctDNA clearance pStage I-IV

183 pts with ctDNA+ stage I-IV colon ca, monitored with Signatera assay

Clearance rate	Post-op-12w	Post-op-24w
Patients W/ ACT	54% (54/96)	11% (11/96)
Patients W/O ACT	8% (8/87)	1% (1/87)

65%

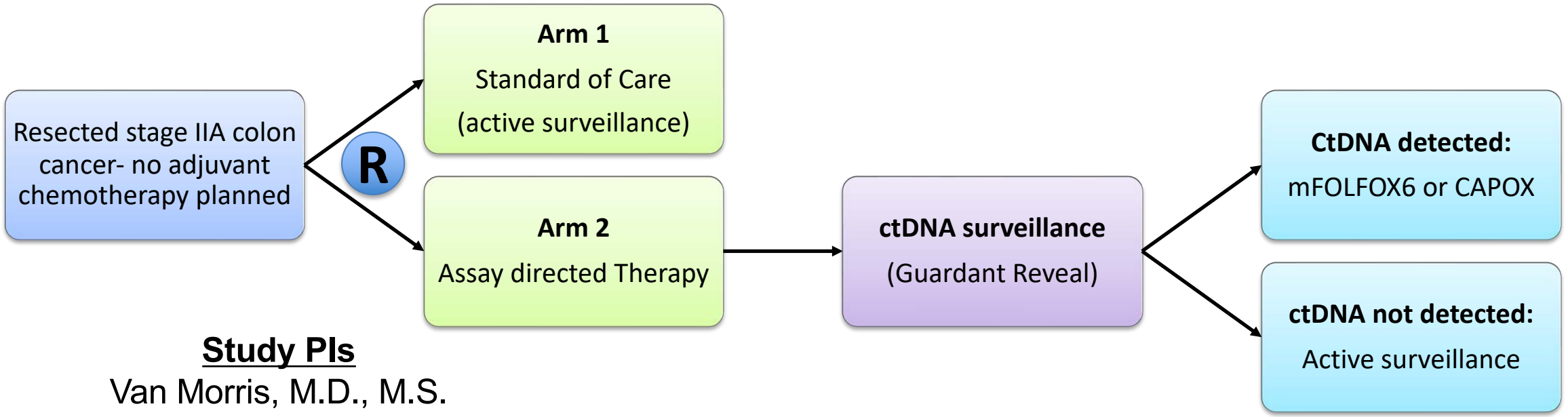
9%

HR = 9.3
95% CI, 4.6 to 18.9, P<0.001

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

NRG-GI005: Phase II/III study of ctDNA as a predictive marker for response to adjuvant chemotherapy in patients with stage IIA colon ca



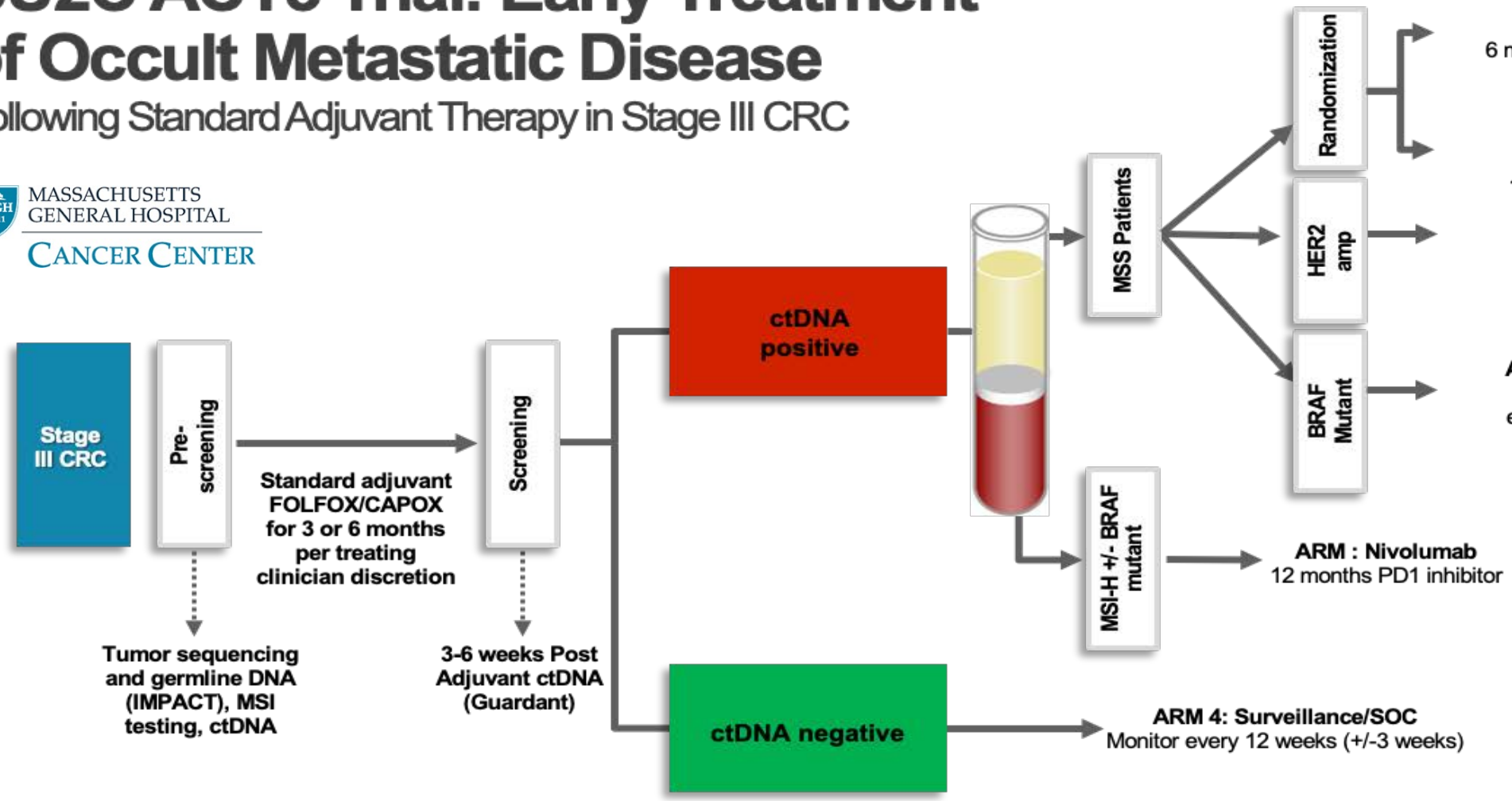
Study PIs

Van Morris, M.D., M.S.
Greg Yothers, Ph.D.,
Scott Kopetz, M.D., Ph.D,
Thom George, M.D.

SU2C ACT3 Trial: Early Treatment of Occult Metastatic Disease

Following Standard Adjuvant Therapy in Stage III CRC

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER



Treatment to begin within 3 months completion of adjuvant therapy

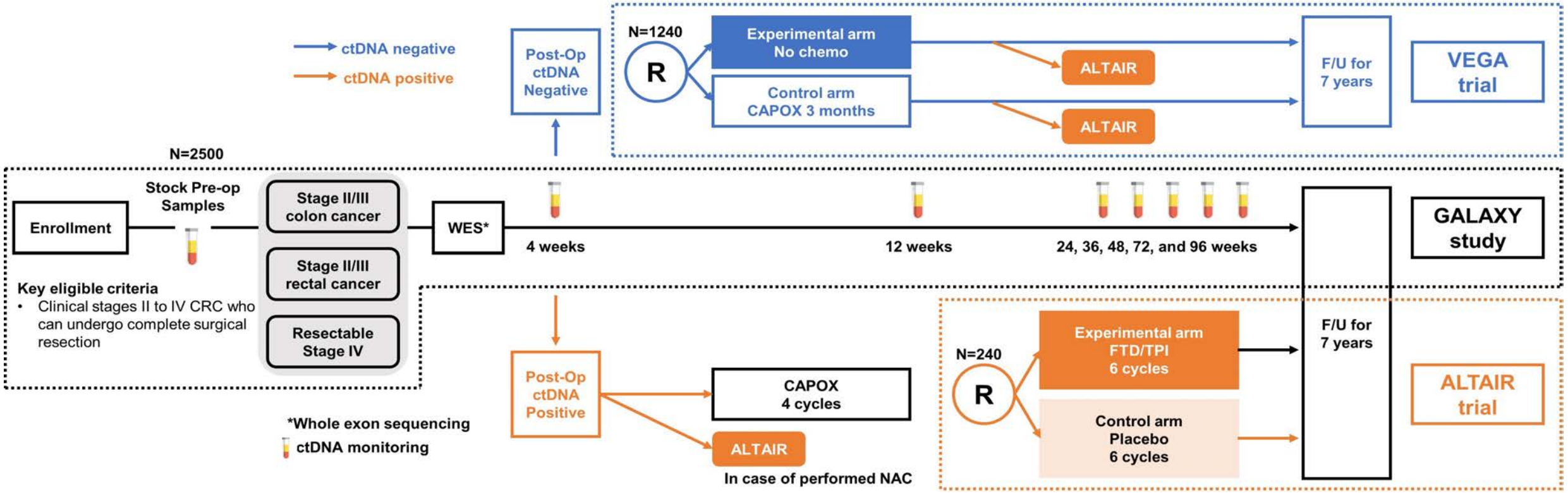
Aparna Parikh, M.D.

SU2C STAND UP TO CANCER

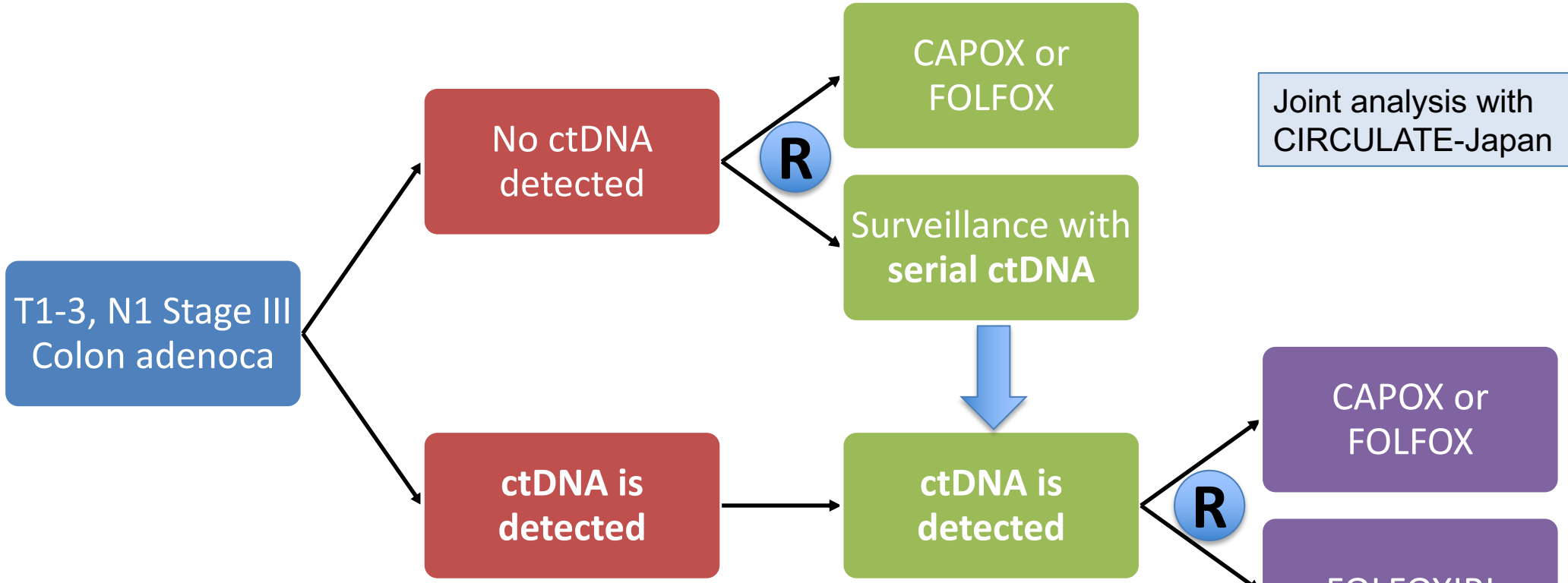
Duke UNIVERSITY

CIRCULATE-Japan: Evaluating the clinical utility of MRD for stage II-IV CRC

Schema of CIRCULATE-Japan project



CIRCULATE-US (NRG-GI008)

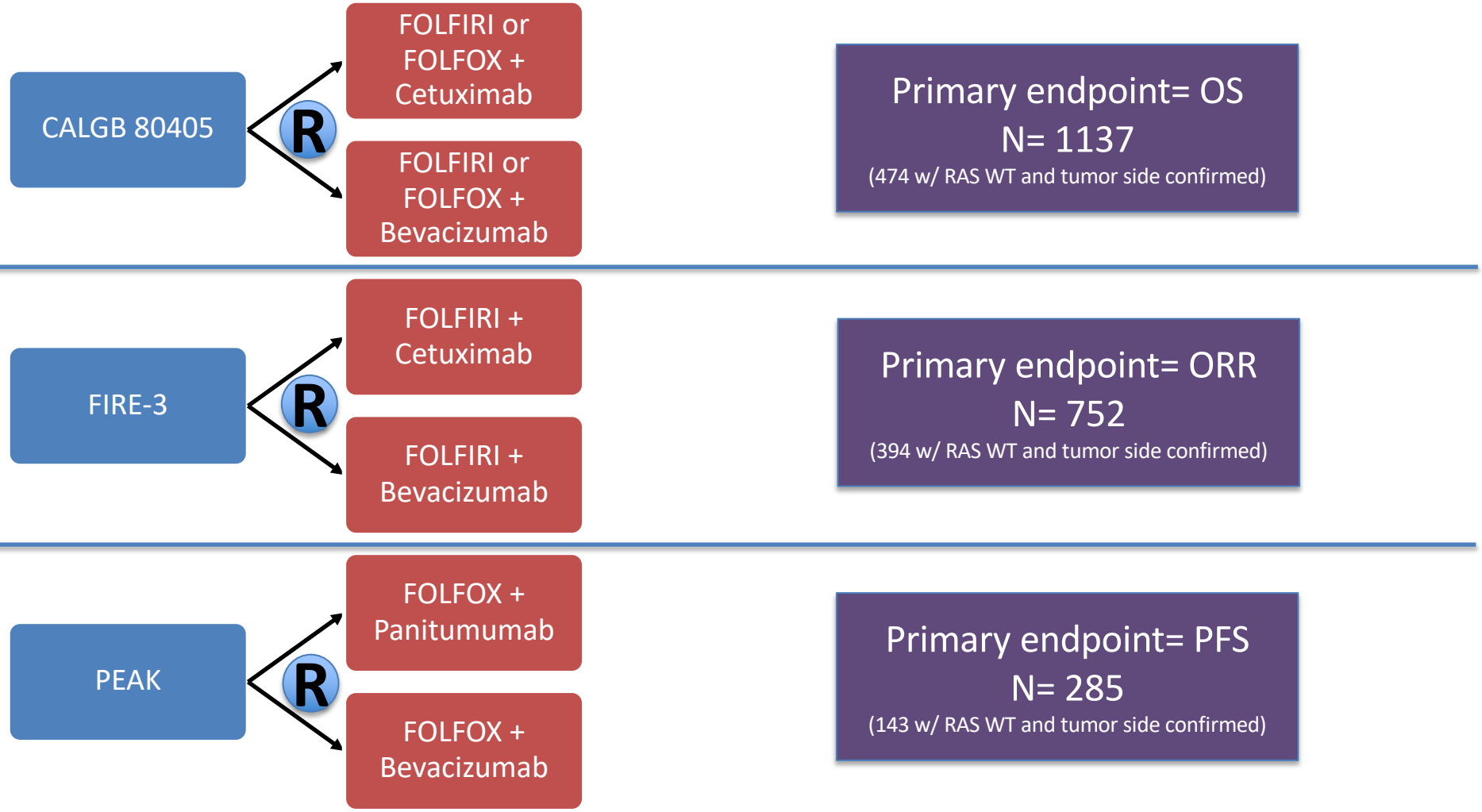


Study PIs

Arvind Dasari (MDACC-NRG)

Christopher Lieu (UCCC-SWOG)

1st line anti-EGFR vs anti-VEGF: 3 key studies



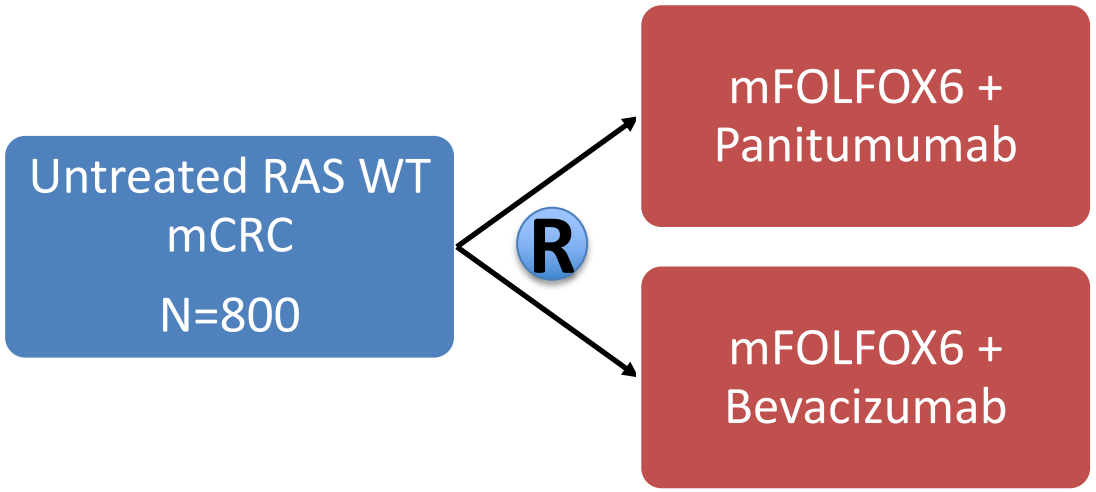
Left sided primary: Anti-EGFR> Anti-VEGF
Right sided primary: Anti-VEGF> Anti-EGFR

Comparison of overall survival

	Right			Left		
	Anti-EGFR	Bevacizumab	HR (95% CI) P-value	Anti-EGFR	Bevacizumab	HR (95% CI) P-value
CALGB 80405	13.7m	29.2m	1.36 (0.93-1.99) 0.11	39.3m	32.6m	**0.77 (0.59-0.99) 0.05**
FIRE-3	18.3m	23.0m	1.31 (0.81-2.11) 0.27	38.3m	28.0m	**0.63 (0.48-0.85) 0.002**
PEAK	17.4m	21.0m	0.67 (0.30-1.50) 0.32	43.4m	32.0m	0.77 (0.46-1.28) 0.31

Arnold et al., *Annals of Oncology* 28: 1713–1729, 2017

PARADIGM Study: Design



- Phase III, RCT
- Multi-site trial (Japan)
- Primary endpoint: Overall Survival
- Secondary endpoints: PFS, ORR, DOR, R0 resection, safety
- stratified according to institution, age (20-64 vs. 65-79 years), and liver metastases (present vs. absent)
- Prespecified subgroup analysis of patients with left-sided primary tumors

PARADIGM Study: Design

HOME > 国内向けニュースリリース > Efficacy and safety evaluation of Panitumumab plus standard chemotherapy as first-line treatment in patients with RAS wild-type metastatic colorectal cancer: Topline results from the phase 3 PARADIGM clinical trial

Share:

Efficacy and safety evaluation of Panitumumab plus standard chemotherapy as first-line treatment in patients with RAS wild-type metastatic colorectal cancer: Topline results from the phase 3 PARADIGM clinical trial

- PARADIGM Trial Achieved Primary Endpoint of Overall Survival (OS) in both left-sided primary tumor population and intent-to-treat population
- First prospective study to evaluate optimal treatment for patients with left-sided *RAS* wild-type metastatic colorectal cancer (mCRC)

Yoshino et al., Clinical Colorectal Cancer, 2017-06-01, 16 (2), 158-163.

Treatment refractory colorectal cancer: ≥3rd line treatment options

	N	ORR (%)	Median PFS (months) (95% CI)	Median OS (months) (95% CI)
RAS* WT only** **Panitumumab vs** **Cetuximab	 499 500	 22.0% 19.8%	 4.1 (3.2-4.8) 4.4 (3.2-4.8)	 10.4 (9.4-11.6) 10.0 (9.3-11.0)
Regorafenib vs Placebo	505 255	1.0% 0.4%	1.9 (n/a) 1.7 (n/a)	6.4 (n/a) 5.0 (n/a)
TAS-102 vs Placebo	534 266	1.6% 0.4%	2.0 (1.9-2.1) 1.7 (1.7-1.8)	7.1 (6.5-7.8) 5.3 (4.6-6.0)

* RAS WT only, EGFR treatment naïve

Grothey et al., Lancet. 2013 Jan; 381(9863): 303-12.
Mayer et al., NEJM. 2015 May 14;372(20):1909- 19.
Price, et al., Lancet Oncol. 2014;15:569-79.

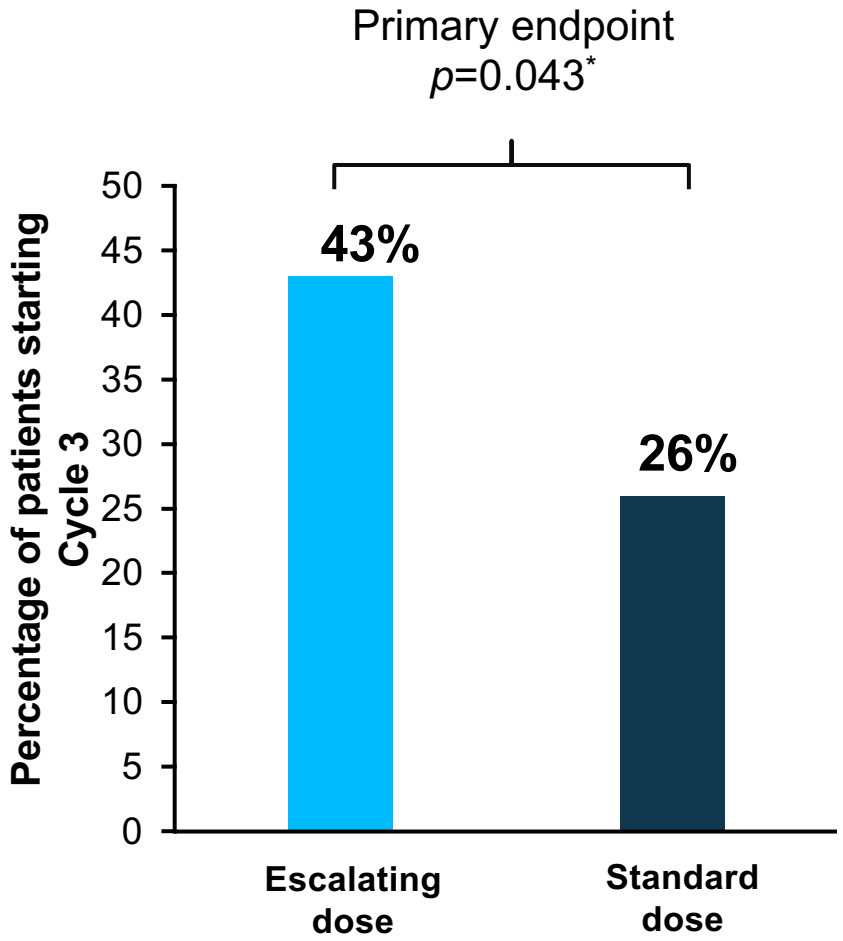
Regorafenib Dose Escalation Study (ReDOS)

Refractory CRC, appropriate for regorafenib

R

Escalating dose	
Week	**Dose**
1	80mg
2	120mg
3	160mg
4	none

Standard dose	
Week	**Dose**
1	160mg
2	160mg
3	160mg
4	none

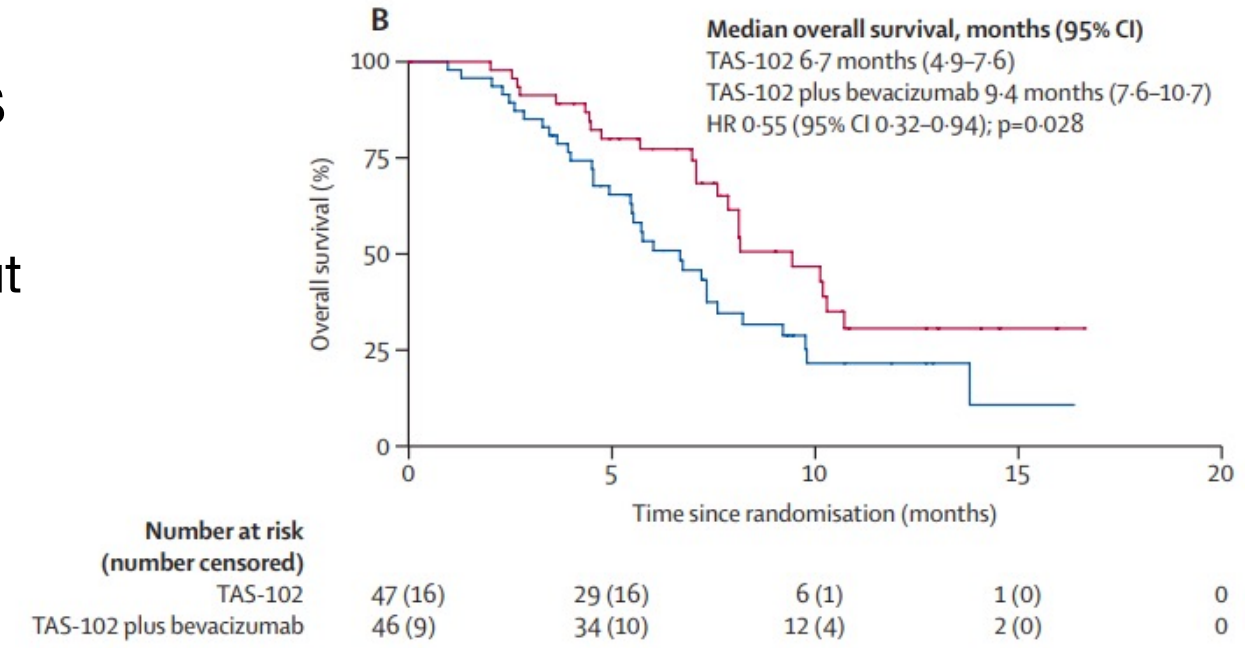


- Median OS numerically superior in Escalating Dose arm compared to Standard Dose arm (9.8 months vs 6.0 months; HR= 0.72; p=0.12)

Bekaii-Saab et al., Lancet Oncology. 2019;20:1070-82.

TAS-102 +/- bevacizumab

- Phase 2 study conducted in Denmark
- Included patients with metastatic CRC refractory or intolerant to a fluoropyrimidine, irinotecan, oxaliplatin, and anti-EGFR (if RAS WT)
- Previous bevacizumab, aflibercept, ramucirumab, or regorafenib was allowed but not mandatory
- Patients randomized 1:1 to TAS-102+bev (n = 46) or TAS-102 (n = 47)
  - Median OS 9.4 months vs 6.7 months; HR 0.55 (95%CI, 0.32-0.94)
  - Median PFS 4.6 months vs 2.6 months; HR 0.45 (95% CI, 0.29 to 0.72)
- SUNLIGHT trial ongoing (ph3, TAS-102 + bev vs TAS-102)



Pfeiffer et al., Lancet Oncology. 2020 Mar, 21(3), 412-420

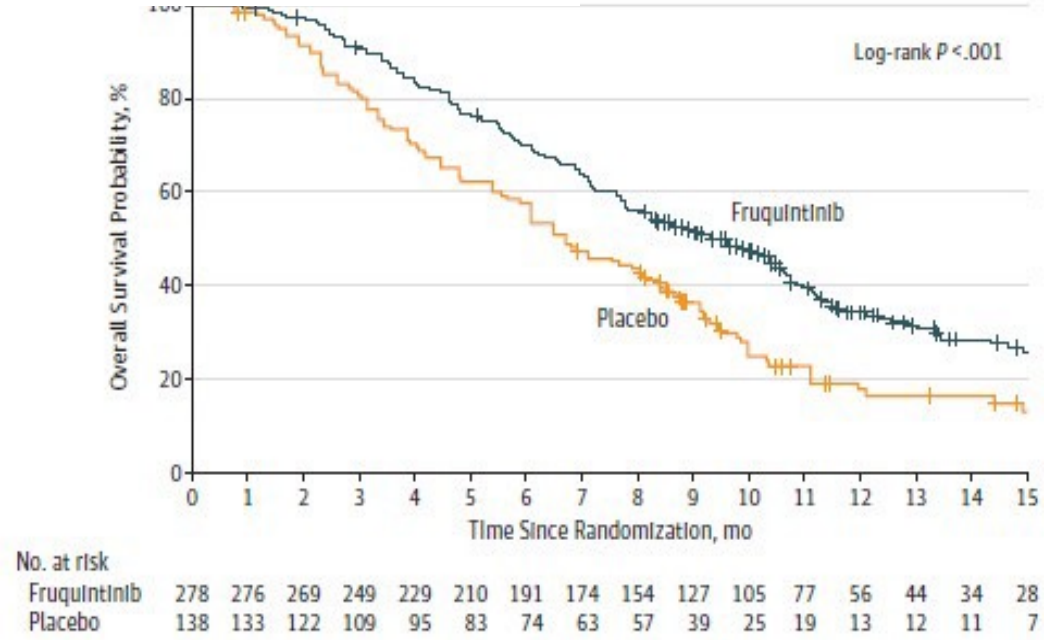
1st/2nd Line TAS-102 combination studies

- Phase 3 SOLSTICE trial
  - 1st line, unresectable/ metastatic CRC; not candidates for intensive chemotherapy
  - TAS-102 + bevacizumab did not show statistically significant improvement in PFS compared to capecitabine + bevacizumab (André et al., presented at ESMO Virtual Plenary, 12/2021)
- Phase 2/3 TRUSTY trial
  - 2nd line metastatic CRC
  - TAS-102 + bevacizumab did not show non-inferiority to FOLFIRI + bevacizumab (Kuboki et al., presented at ASCO 2021)

Novel agents: Fruquintinib

- Oral small molecule inhibitor of VEGFRs
- FRESCO trial
  - Phase III
  - Conducted in China
- Patients randomized 2:1 to fruquintinib (n = 278) or placebo (n = 138)
- Median OS 9.3 months vs 6.6 months HR 0.65 (95%CI, 0.51-0.83)
- Median PFS 3.7 months vs 1.8 months; HR 0.26 (95% CI, 0.21 to 0.34).
- Adverse events
  - Gr 3+ in 61.2% vs 19.7%
  - SAEs 15.5% vs 5.8%
- FRESCO-2 trial ongoing (ph3, fruquintinib vs BSC, includes US sites)

Overall Survival



Li et al. JAMA 2018;319(24):2486-2496.

MODULE 3: Current and Future Treatment Paradigm for Gastroesophageal Cancers — Prof Van Cutsem

RTP
RESEARCH
TO PRACTICE

Dr Neil Morganstein
Summit, New Jersey

78-year-old man with Stage II GEJ adenocarcinoma – PD-L1 CPS <1, HER2 IHC intermediate

Dr Philip Brooks
Brewer, Maine

67-year-old man with HER2-negative gastric adenocarcinoma – PD-L1 CPS 10

Dr Lionel Fonkoua
Rochester, Minnesota

Optimal front-line therapy for disease progression after adjuvant immune checkpoint inhibitor therapy?

RTP
RESEARCH
TO PRACTICE

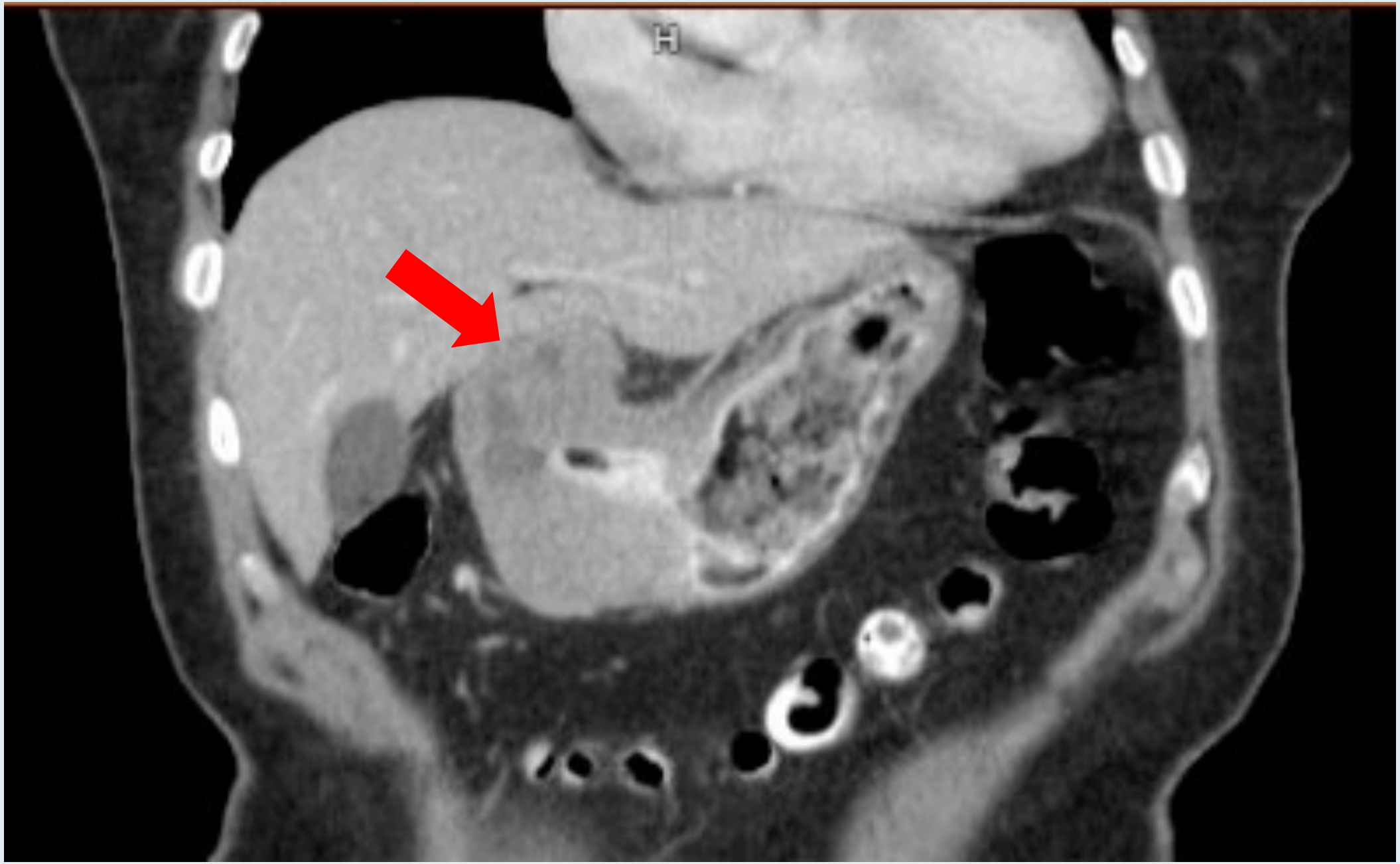
Dr Zanetta Lamar
Naples, Florida

54-year-old man with metastatic HER2-positive GEJ adenocarcinoma with a history of Barrett's esophagus

Dr Matthew Strickland
Boston, Massachusetts

55-year-old woman with HER2-negative gastric adenocarcinoma – PD-L1 CPS 100, dMMR, TMB 94 mut/Mb

RTP
RESEARCH
TO PRACTICE



UZ LEUVEN

Current and Future Treatment Paradigms for Gastroesophageal Cancers

Prof Eric Van Cutsem, MD, PhD
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CheckMate 577 study design in resectable Oesophageal and GEJ cancer

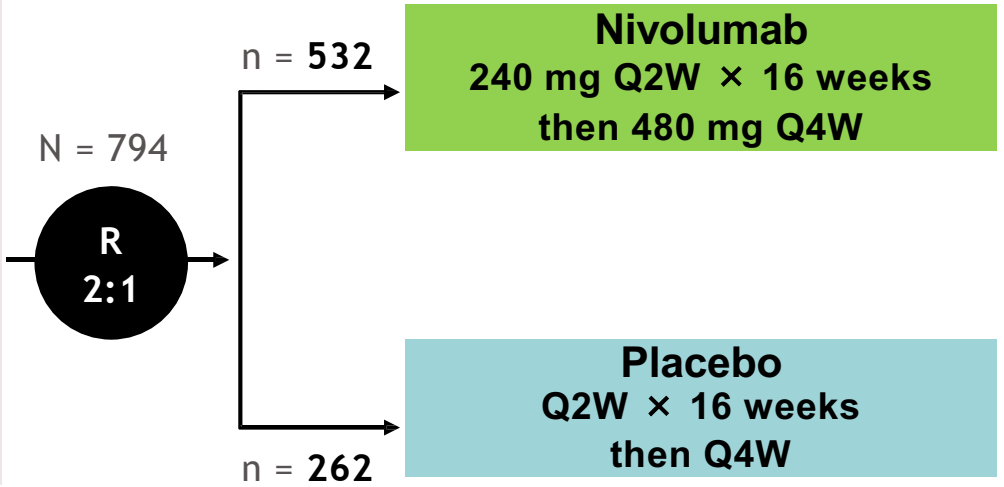
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria

- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0–1

Stratification factors

- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:

- DFS[e]

Secondary endpoints:

- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2–44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

Kelly R, …Van Cutsem E, et al, NEJM 2021, 381, 1191-2003

Adjuvant Nivolumab after CRT + Surgery for Esophageal & GEJ cancer: update of CheckMate 577

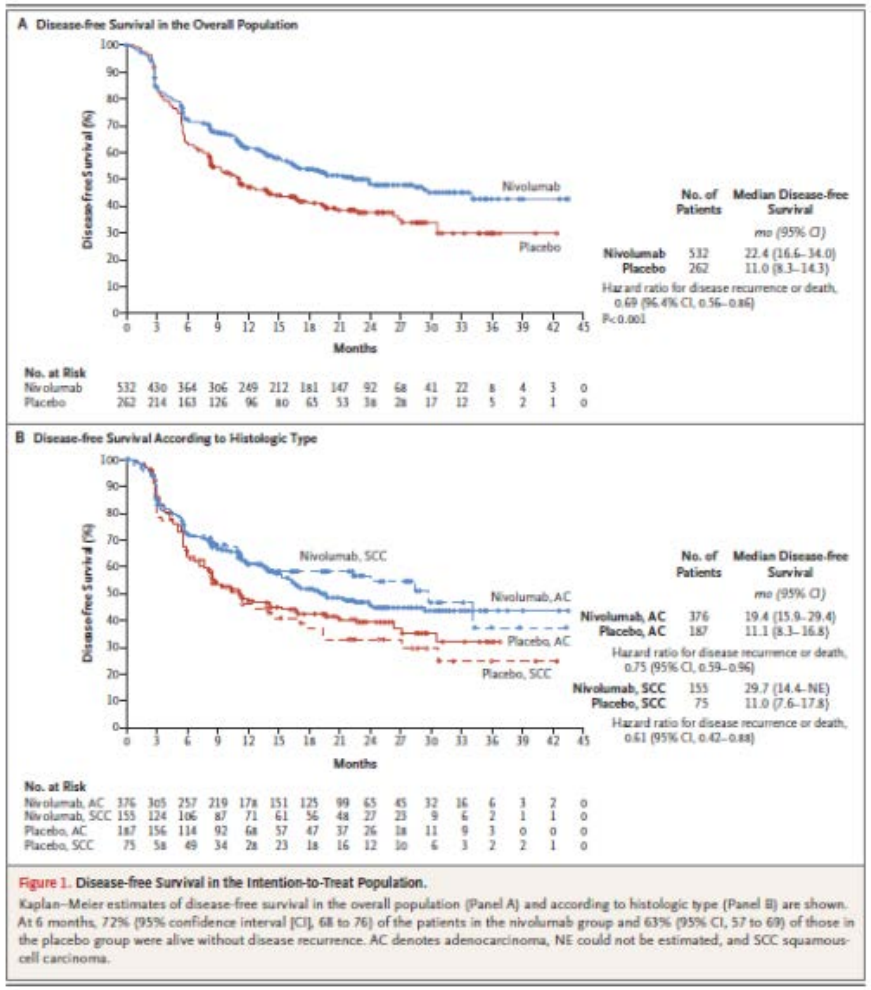
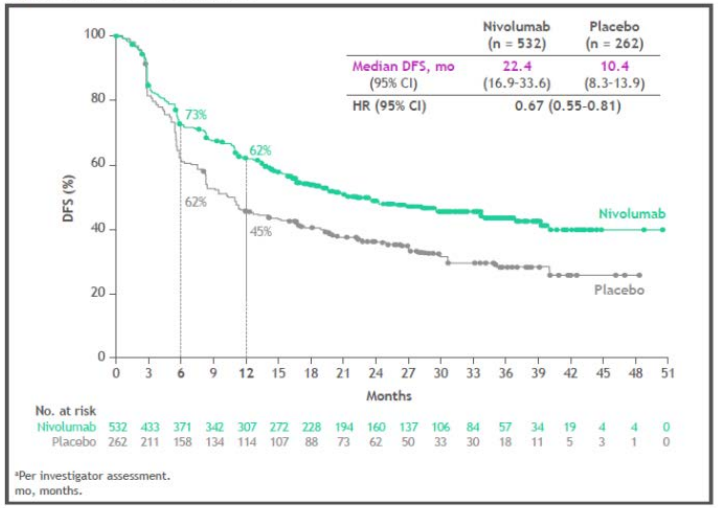


Figure 1. Disease-free Survival in the Intention-to-Treat Population.

Kaplan–Meier estimates of disease-free survival in the overall population (Panel A) and according to histologic type (Panel B) are shown. At 6 months, 72% (95% confidence interval [CI], 68 to 76) of the patients in the nivolumab group and 63% (95% CI, 57 to 69) of those in the placebo group were alive without disease recurrence. AC denotes adenocarcinoma, NE could not be estimated, and SCC squamous-cell carcinoma.

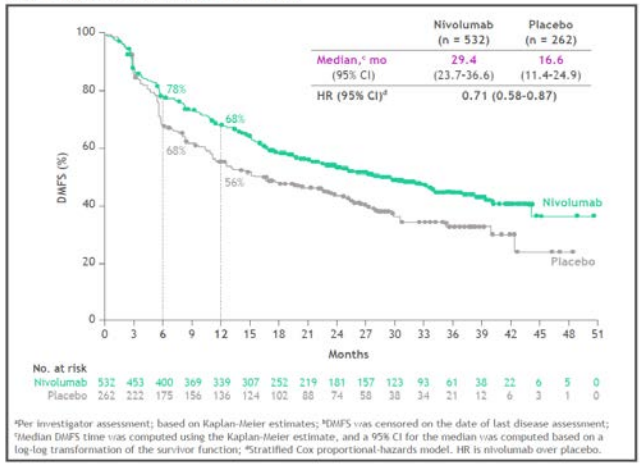
Figure 2. Disease-free survival[a]



[a]Per investigator assessment.
mo, months.

- DFS benefit was observed with nivolumab versus placebo across multiple subgroups (**Figure 3**)
  - Compared with earlier results,[6] there was a numerical reduction in HR for multiple subgroups, including GEJC (HR, 0.80 [95% CI, 0.59-1.08] from 0.87 [95% CI, 0.63-1.21]) and adenocarcinoma (HR, 0.73 [95% CI, 0.58-0.91] from 0.75 [95% CI, 0.59-0.96])

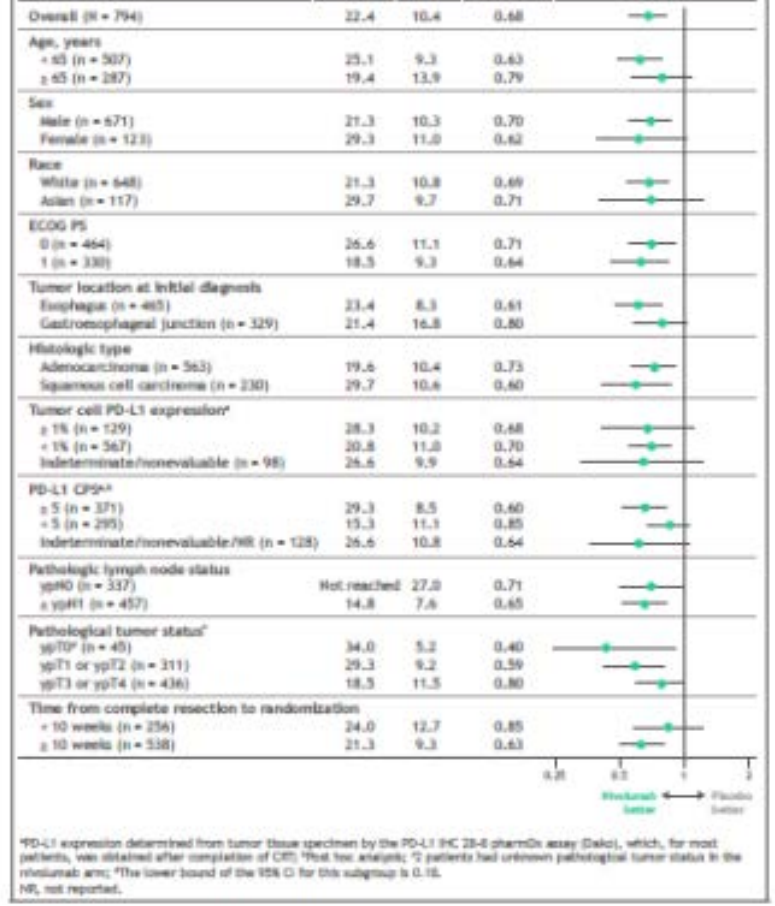
Figure 4. Distant metastasis-free survival[a,b]



[a]Per investigator assessment; based on Kaplan-Meier estimates; [b]DMFS was censored on the date of last disease assessment; [c]Median DMFS time was computed using the Kaplan-Meier estimate, and a 95% CI for the median was computed based on a log-log transformation of the survivor function; [d]Stratified Cox proportional-hazards model. HR is nivolumab over placebo.

Figure 3. Disease-free survival subgroup analysis

Subgroup	Median DFS, mo		Unstratified HR	Unstratified HR (95% CI)
	Nivolumab	Placebo		
Overall (N = 794)	22.4	10.4	0.68	
Age, years				
< 65 (n = 507)	25.1	9.3	0.63	
≥ 65 (n = 287)	19.4	13.9	0.79	
Sex				
Male (n = 671)	21.3	10.3	0.70	
Female (n = 123)	29.3	11.0	0.62	
Race				
White (n = 648)	21.3	10.8	0.69	
Asian (n = 117)	29.7	9.7	0.71	
ECOG PS				
0 (n = 464)	26.6	11.1	0.71	
1 (n = 330)	18.5	9.3	0.64	
Tumor location at initial diagnosis				
Esophagus (n = 465)	23.4	8.3	0.61	
Gastroesophageal junction (n = 329)	21.4	16.8	0.80	
Histologic type				
Adenocarcinoma (n = 563)	19.6	10.4	0.73	
Squamous cell carcinoma (n = 230)	29.7	10.6	0.60	
Tumor cell PD-L1 expression[a]				
≥ 1% (n = 129)	28.3	10.2	0.68	
< 1% (n = 567)	20.8	11.0	0.70	
Indeterminate/nonevaluable (n = 98)	26.6	9.9	0.64	
PD-L1 CPS[a,b]				
≥ 5 (n = 371)	29.3	8.5	0.60	
< 5 (n = 295)	15.3	11.1	0.85	
Indeterminate/nonevaluable/NR (n = 128)	26.6	10.8	0.64	
Pathologic lymph node status				
ypN0 (n = 337)	Not reached	27.0	0.71	
≥ ypN1 (n = 457)	14.8	7.6	0.65	
Pathological tumor status[c]				
ypT0[d] (n = 45)	34.0	5.2	0.40	
ypT1 or ypT2 (n = 311)	29.3	9.2	0.59	
ypT3 or ypT4 (n = 436)	18.5	11.5	0.80	
Time from complete resection to randomization				
< 10 weeks (n = 256)	24.0	12.7	0.85	
≥ 10 weeks (n = 538)	21.3	9.3	0.63	

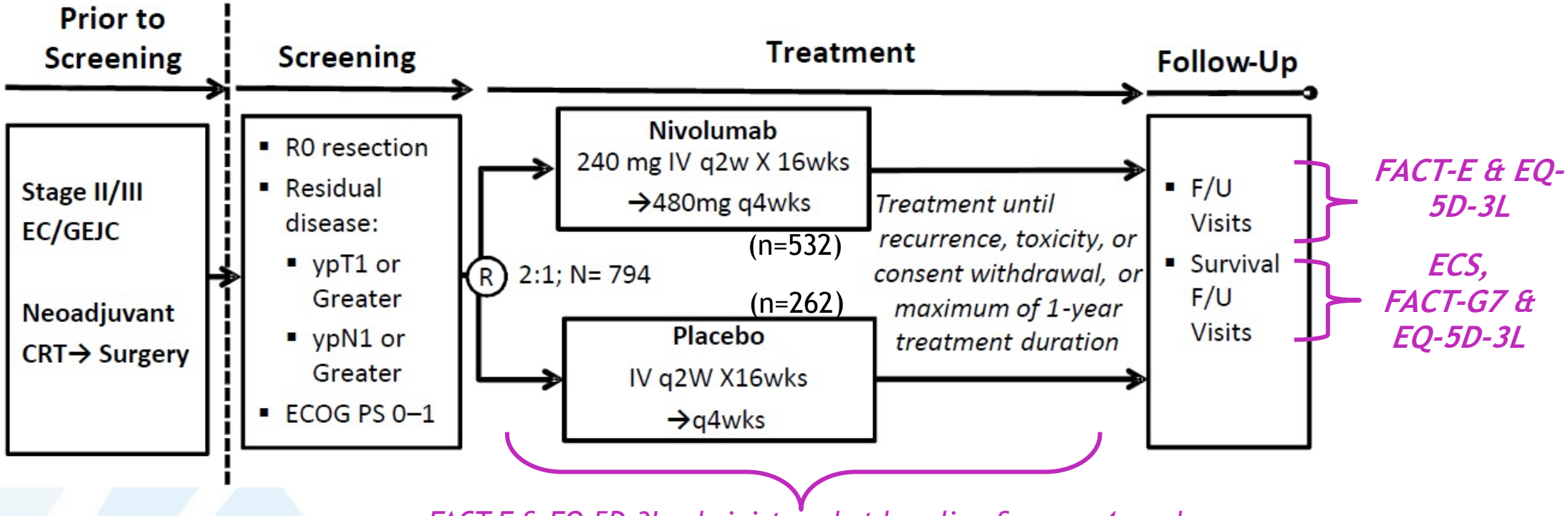


[a]PD-L1 expression determined from tumor tissue specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako), which, for most patients, was obtained after completion of CRT; [b]Post hoc analysis; [c]2 patients had unknown pathological tumor status in the nivolumab arm; [d]The lower bound of the 95% CI for this subgroup is 0.18.
NR, not reported.

Kelly R, …Van Cutsem E, et al, NEJM 2021, 381, 1191-2003

Moehler M, … Van Cutsem E et al, Ann Oncol, ESMO 2021 poster presentation

Patient-Reported Outcome (PRO) in CheckMate 577



- **PRO exploratory endpoints:** Functional Assessment of Cancer Therapy – Esophageal (FACT-E) questionnaire, EQ-5D-3L, Esophageal Cancer Subscale (ECS), and Functional Assessment of Cancer Therapy – General – 7-Item Version (FACT-G7)
- Patients who were treated with NIVO and PBO showed trends for improvement and maintenance of HRQoL from baseline
- There was no significant difference in time to first deterioration of HRQoL between NIVO and PBO
- Patients treated with NIVO did not experience a reduction in HRQoL, further supporting clinical data to demonstrate treatment benefit and tolerability for adjuvant NIVO in patients with resected EC/GEJC

Van Cutsem E et al, ASCO GI, oral presentation 2021

Chemotherapy ± pembrolizumab as 1°line in advanced oesophageal/GEJ cancer: KEYNOTE-590

Study objective

- To evaluate the safety and efficacy of pembrolizumab + chemotherapy in patients with advanced oesophageal cancer

Key patient inclusion criteria
- Locally advanced unresectable or metastatic EAC or ESCC or EGJ Siewert type 1 adenocarcinoma
- Treatment-naïve
- ECOG PS 0–1

(n=749)

R 1:1

Pembrolizumab 200 mg iv q3w (≤35 cycles) + chemotherapy* (n=373) → **PD/ toxicity/ withdrawal**

Stratification
- Region, histology, ECOG PS

Placebo + chemotherapy* (n=376) → **PD/ toxicity/ withdrawal**

CO-PRIMARY ENDPOINTS
- OS and PFS (investigator-assessed, RECIST v1.1)

SECONDARY ENDPOINTS
- ORR, safety

*5FU 800 mg/m^2 iv D1–5 q3w (**≤35 cycles**) + **cisplatin 80** mg/m^2 (**≤6 cycles**). **Data cut-off 02 July 2020.**

Kato K, et al. Ann Oncol 2020;31(suppl):abstr LBA8
Sun JM et al, Lancet 2021

Chemotherapy ± pembrolizumab as 1°line in advanced oesophageal/GEJ cancer: KEYNOTE-590

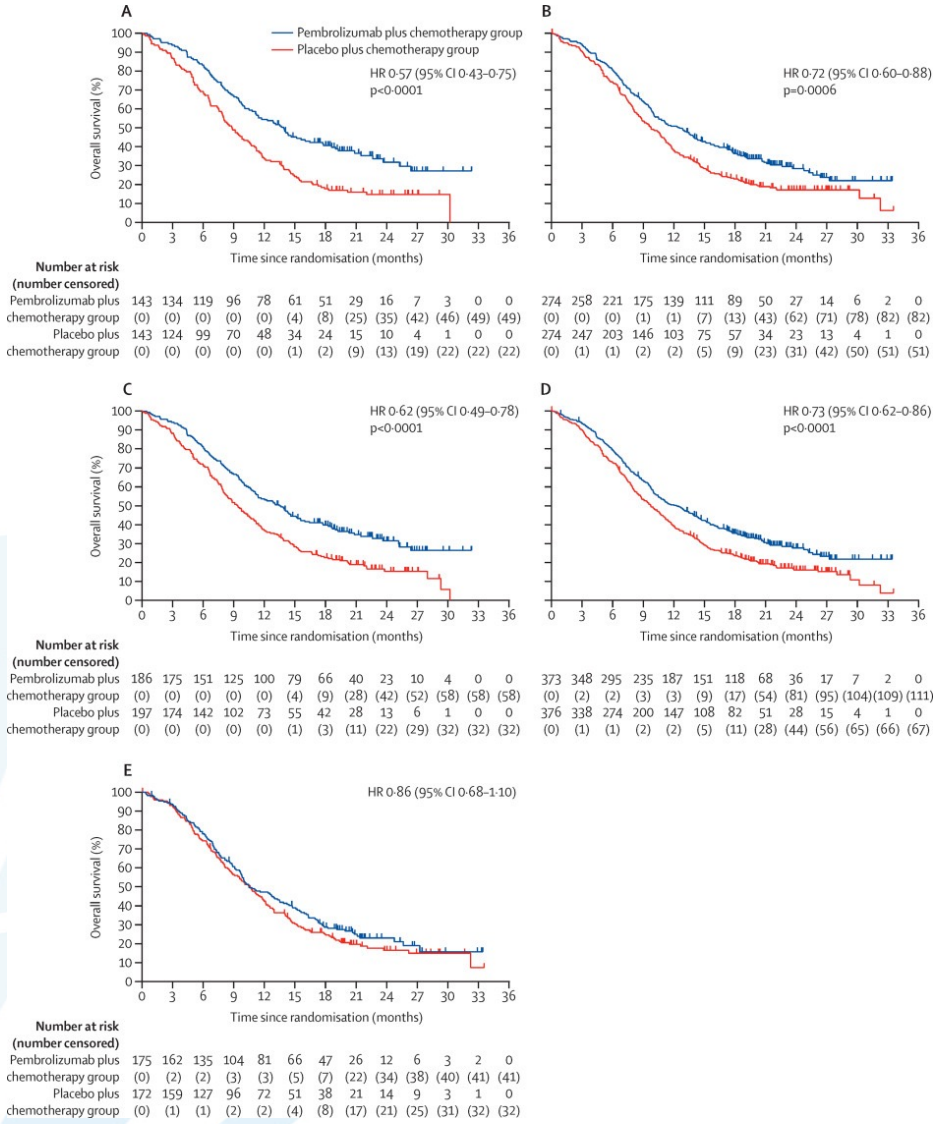


Figure 2: Kaplan-Meier estimates of overall survival
(A) Patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more. (B) Patients with oesophageal squamous cell carcinoma. (C) Patients with PD-L1 CPS of 10 or more. (D) All randomised patients. (E) Patients with PD-L1 CPS of less than 10 (post-hoc analysis). Tick marks represent data censored at the time of last imaging assessment. CPS=combined positive score. HR=hazard ratio.

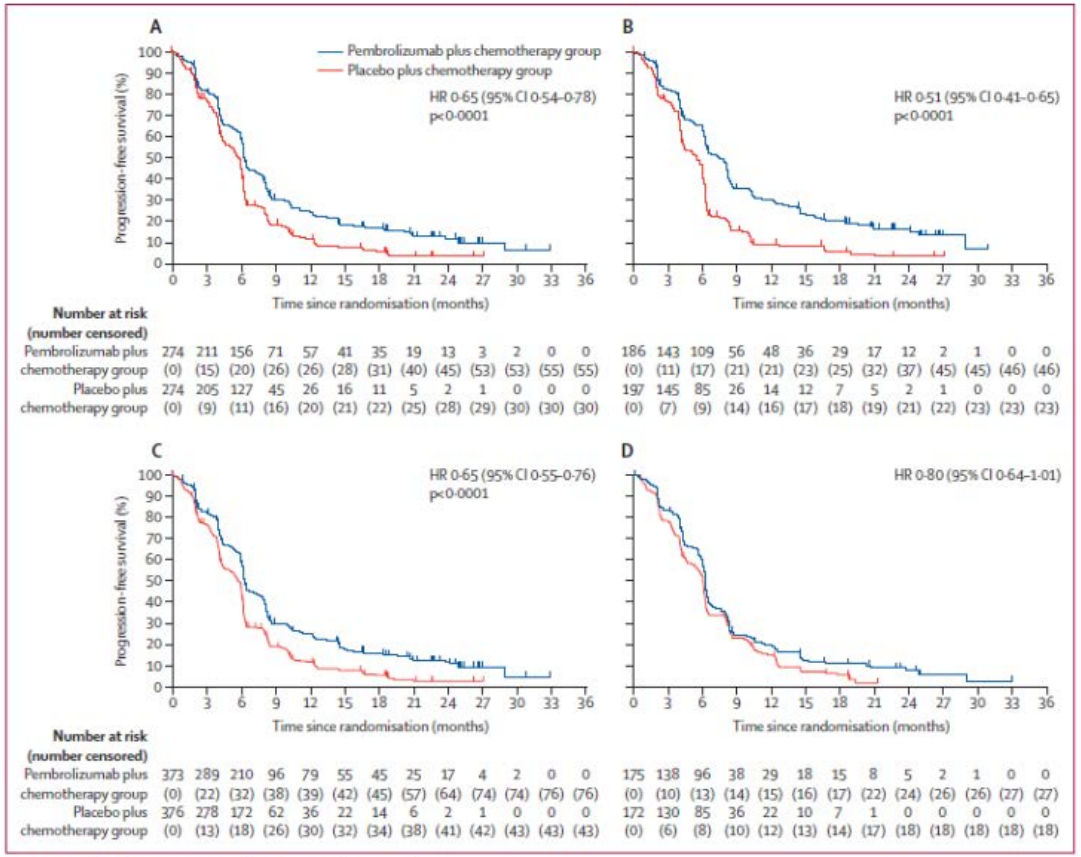


Figure 4: **Kaplan-Meier estimates of progression-free survival**
(A) Patients with oesophageal squamous cell carcinoma. (B) Patients with PD-L1 CPS of 10 or more. (C) All randomised patients. (D) Patients with PD-L1 CPS of less than 10 (post-hoc analysis). Tick marks represent data censored at the time of last imaging assessment. Progression-free survival was assessed per the Response Evaluation Criteria in Solid Tumors version 1.1 by investigators. CPS=combined positive score. HR=hazard ratio.

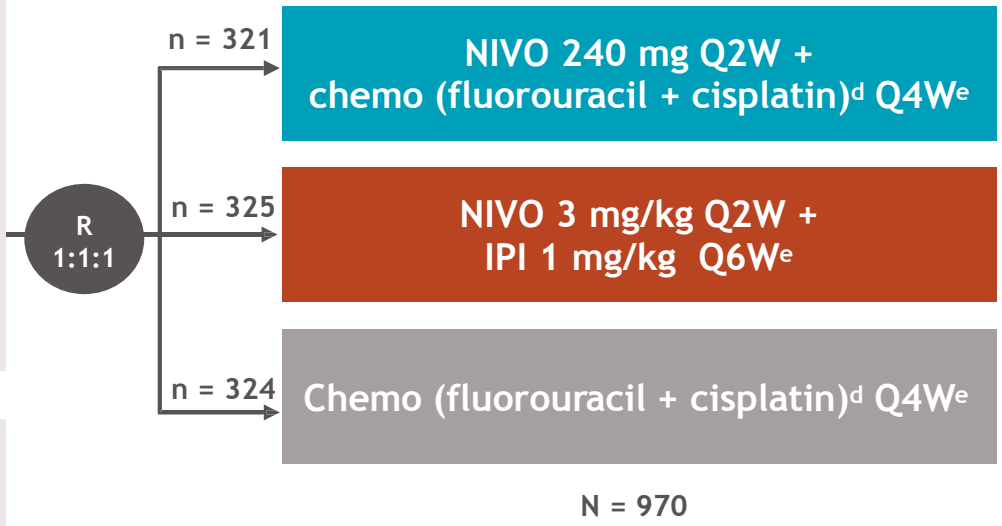
Sun JM et al, Lancet 2021

Chemotherapy ± nivolumab vs NIVO/IPI as 1°line in advanced oesophageal cancer: Checkmate-648

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

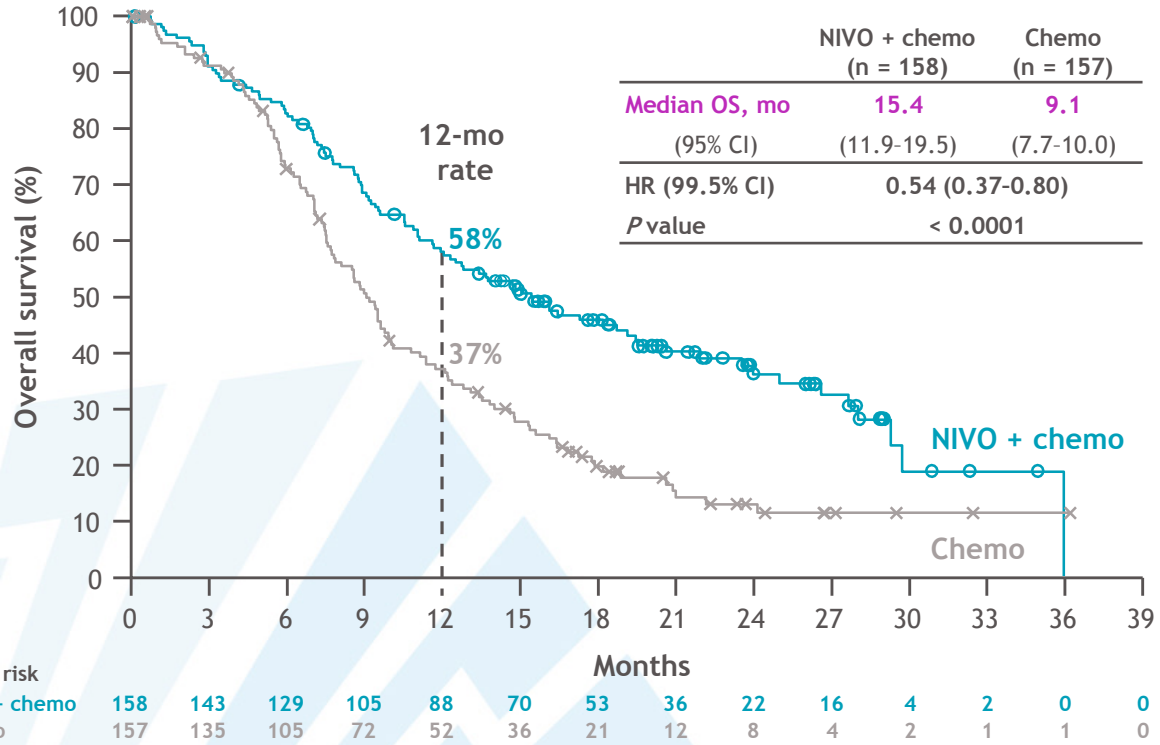
- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m² IV daily (days 1-5) and cisplatin 80 mg/m² IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

Chau I et al, J Clin Onc, 2021, Proc ASCO,*LBA4001*

Checkmate 648: Overall survival: NIVO + chemo vs chemo

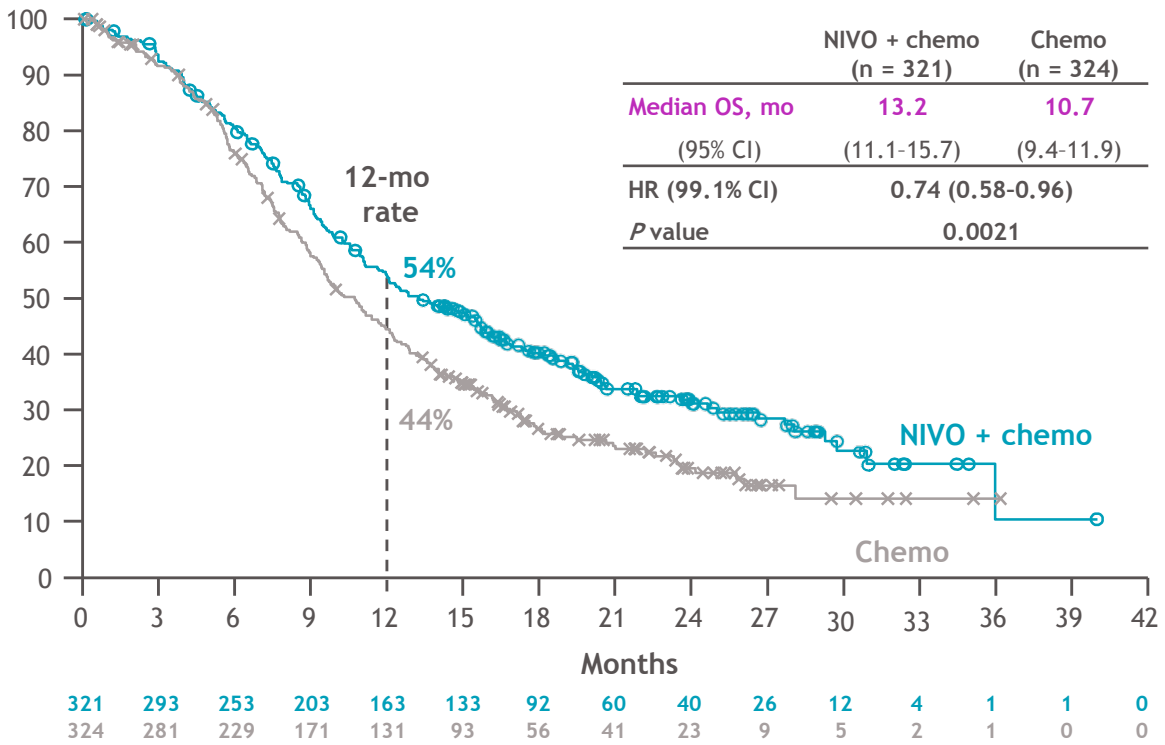
Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)	
P value	0.0021	

NIVO + chemo	321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

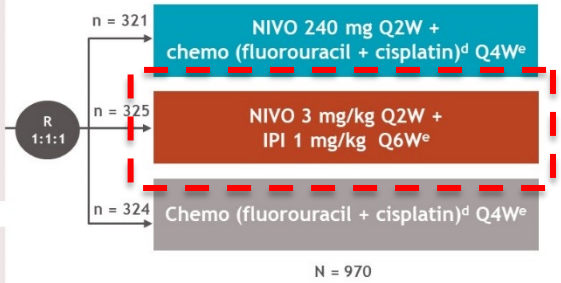
[a]Minimum follow-up 12.9 months.

Chau I et al, J Clin Onc, 2021, Proc ASCO,*LBA4001*

CM-648 (TPS≥1)

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

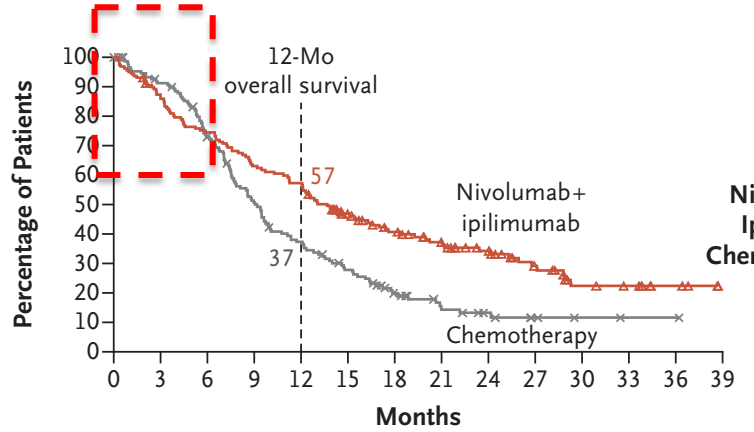
Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

	NIVO + chemo (n = 84)[b]	NIVO + IPI (n = 56)[b]	Chemo (n = 31)[b]
ORR[c], %	53	35	20
(95% CI)	(45-61)	(28-43)	(14-27)
Median DOR, mo	8.4	11.8	5.7
(95% CI)	(6.9-12.4)	(7.1-27.4)	(4.4-8.7)

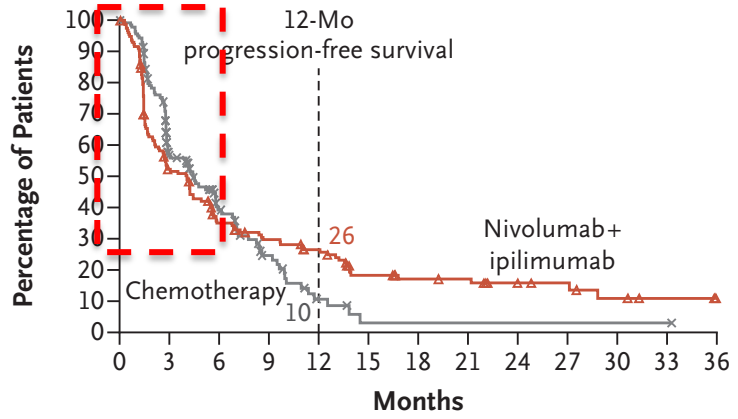


	No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+ Ipilimumab	158	13.7 (11.2–17.0)
Chemotherapy	157	9.1 (7.7–10.0)

Hazard ratio for death, 0.64 (98.6% CI, 0.46–0.90)
P=0.001

No. at Risk

Nivolumab+ipilimumab	158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemotherapy	157	135	105	72	52	36	21	12	8	4	2	1	1	0



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+ Ipilimumab	158	4.0 (2.4–4.9)
Chemotherapy	157	4.4 (2.9–5.8)

Hazard ratio for disease progression or death, 1.02 (98.5% CI, 0.73–1.43)
P=0.90

No. at Risk

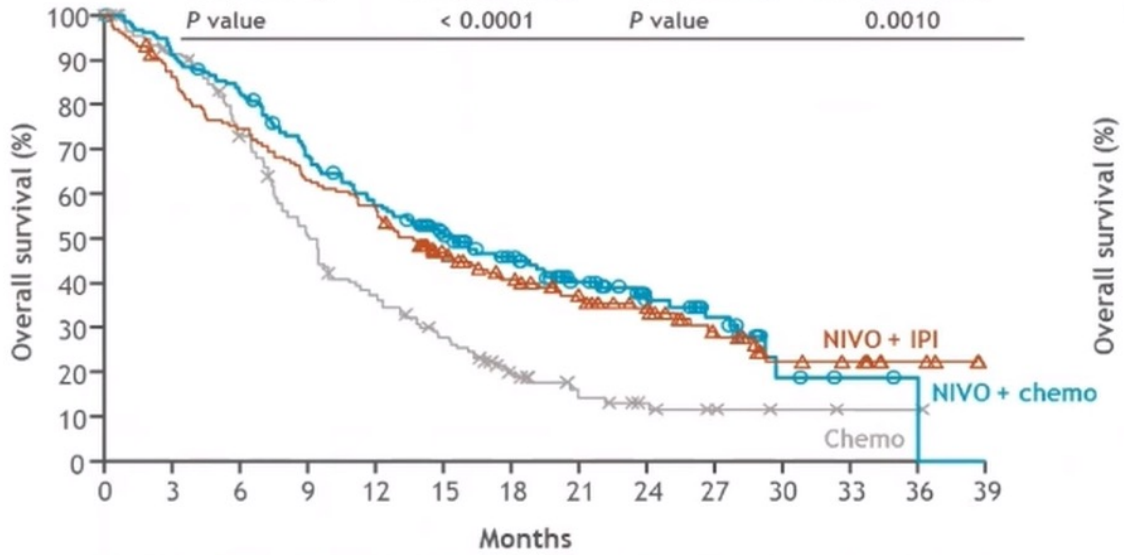
Nivolumab+ipilimumab	158	78	48	38	31	18	14	13	8	7	4	2	0	
Chemotherapy	157	67	35	17	5	1	1	1	1	1	1	1	0	

Doki Y et al, NEJM 2022

CheckMate 648: Overall survival of nivo + chemo and nivo+ ipi vs. chemo

Tumor cell PD-L1 ≥ 1%

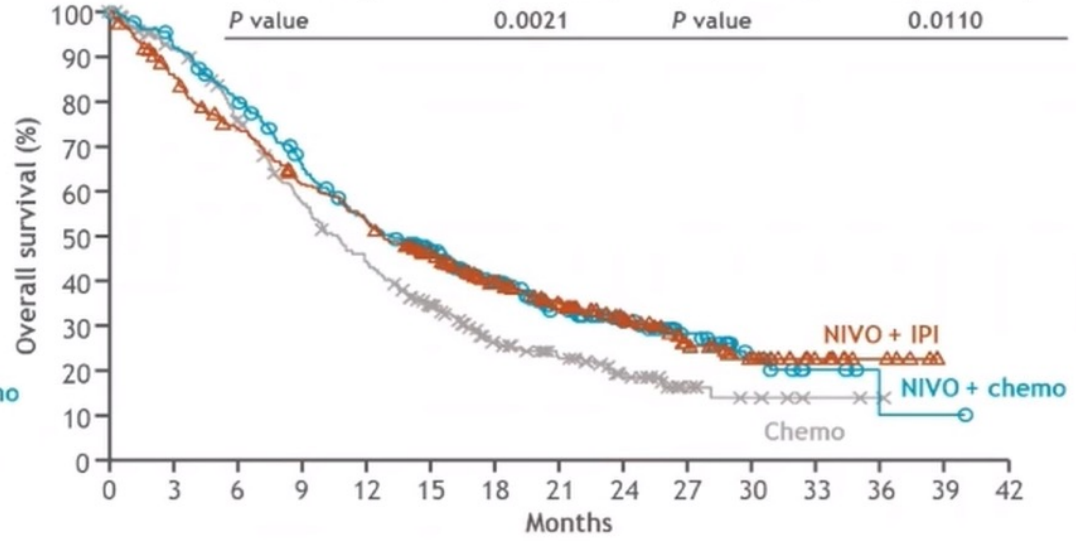
	NIVO + chemo (n = 158)	Chemo (n = 157)		NIVO + IPI (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1		13.7	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)		(11.2-17.0)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)		HR (98.6% CI)	0.64 (0.46-0.90)	
P value	< 0.0001		*P* value	0.0010	



No. at risk														
NIVO + chemo	158	143	129	105	88	70	53	36	22	16	4	2	0	0
NIVO + IPI	158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized

	NIVO + chemo (n = 321)	Chemo (n = 324)		NIVO + IPI (n = 325)	Chemo (n = 324)
Median OS, mo	13.2	10.7		12.8	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)		(11.3-15.5)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)		HR (98.2% CI)	0.78 (0.62-0.98)	
P value	0.0021		*P* value	0.0110	



321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
325	274	232	191	166	129	97	77	55	33	22	12	6	0	0
324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

Chau et al. Presented at ASCO 2021

FDA approves nivolumab in combination with chemotherapy and nivolumab in combination with ipilimumab for first-line esophageal squamous cell carcinoma indications

Press Release – May 27, 2022

"On May 27, 2022, the Food and Drug Administration approved the following for the first-line treatment of patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC):

- Nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy
- Nivolumab in combination with ipilimumab

Efficacy was evaluated in CHECKMATE-648 (NCT03143153), a randomized, active-controlled, open-label trial in 970 patients with previously untreated unresectable advanced, recurrent or metastatic ESCC. The major efficacy outcome measures were overall survival (OS) and blinded independent central review (BICR)-assessed progression-free survival (PFS). CHECKMATE-648 demonstrated statistically significant improvements in OS in all randomized patients and in the subpopulation with tumor cell (TC) PD-L1 ≥1% for both nivolumab-containing regimens when individually compared to chemotherapy."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-opdivo-combination-chemotherapy-and-opdivo-combination-yervoy-first-line-esophageal

RTP RESEARCH TO PRACTICE

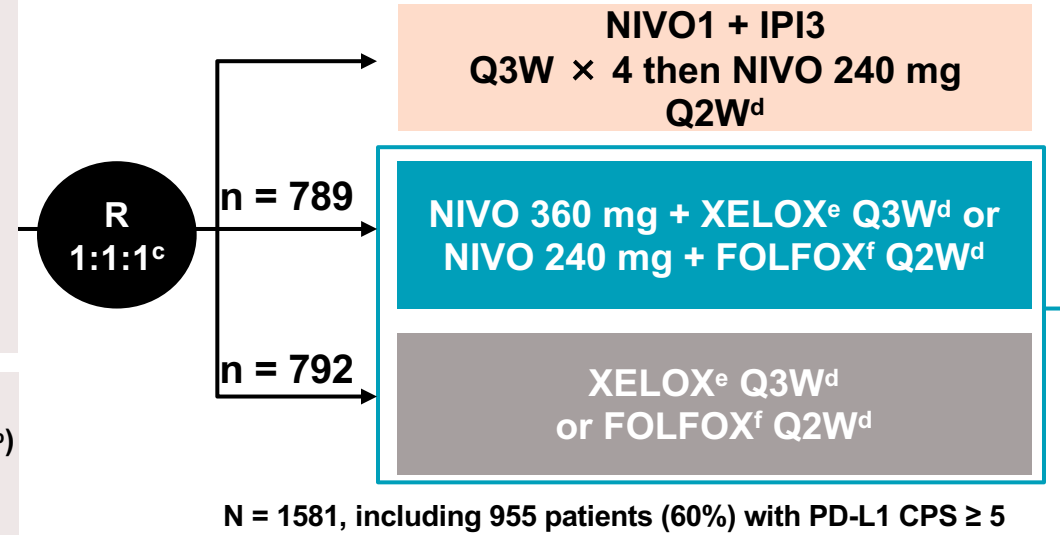
CheckMate 649: randomized, open-label, phase 3 study in 1st line gastric adenocarcinoma

Key eligibility criteria

- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1

Stratification factors

- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

Dual primary endpoints:

- OS and PFS[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:

- OS (PD-L1 CPS ≥ 1 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- ORR[g]

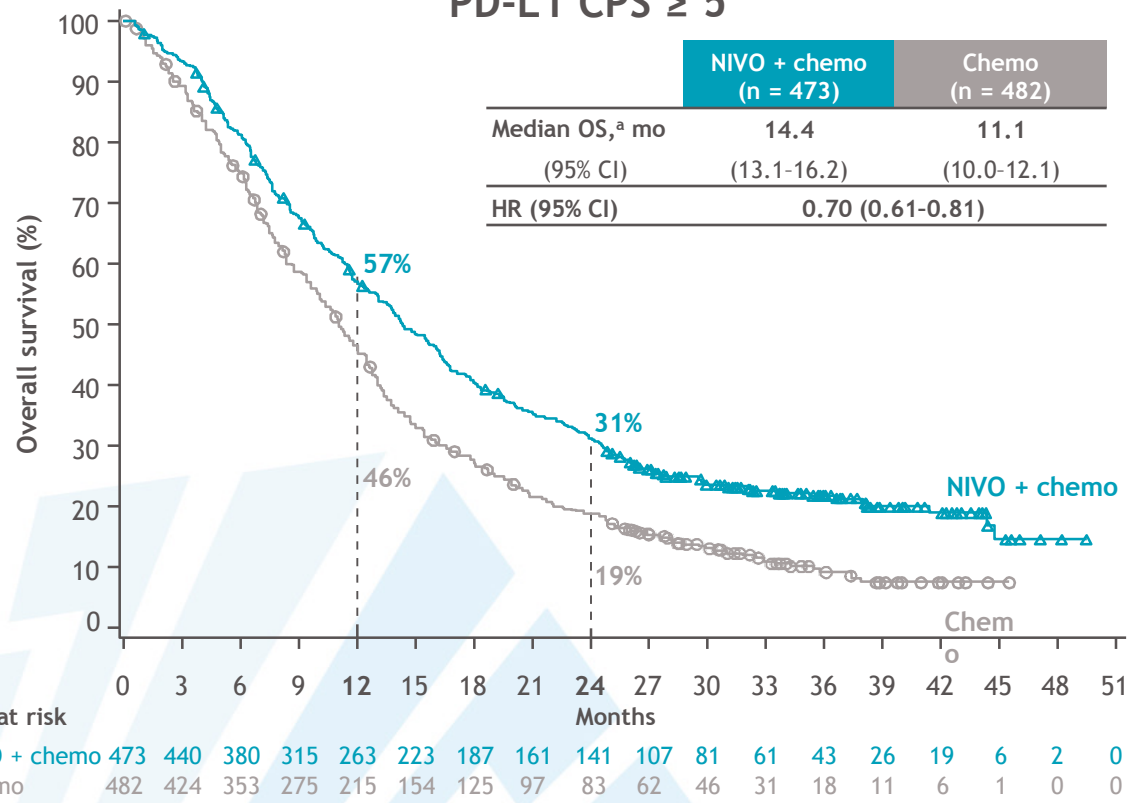
- **At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]**

[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

Moehler M, et al. Ann Oncol 2020;31(suppl):abstr LBA6
Janjigian Y et al, Lancet. 2021 July 03; 398(10294): 27–40.

CheckMate 649: randomized, open-label, phase 3 study in 1st line gastric cancer: survival

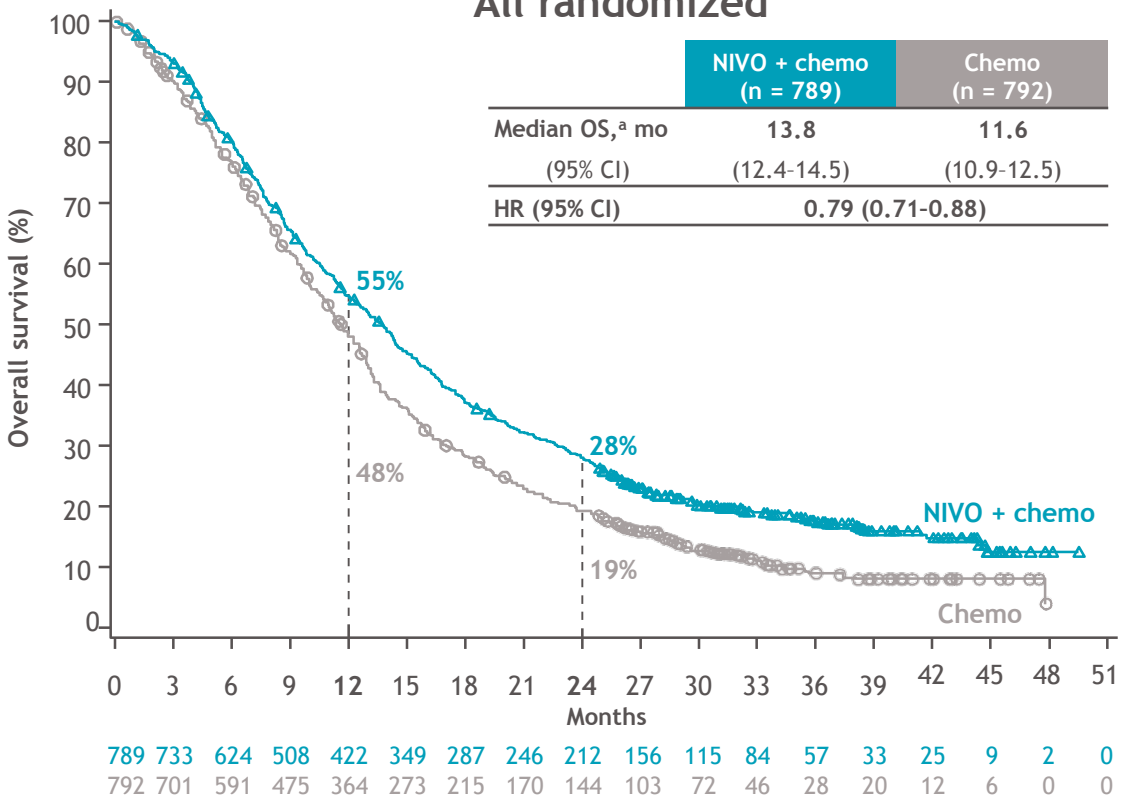
PD-L1 CPS ≥ 5



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS,[a] mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (95% CI)	0.70 (0.61-0.81)	

No. at risk																		
NIVO + chemo	473	440	380	315	263	223	187	161	141	107	81	61	43	26	19	6	2	0
Chemo	482	424	353	275	215	154	125	97	83	62	46	31	18	11	6	1	0	0

All randomized



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS,[a] mo	13.8	11.6
(95% CI)	(12.4-14.5)	(10.9-12.5)
HR (95% CI)	0.79 (0.71-0.88)	

NIVO + chemo	789	733	624	508	422	349	287	246	212	156	115	84	57	33	25	9	2	0
Chemo	792	701	591	475	364	273	215	170	144	103	72	46	28	20	12	6	0	0

- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up
  - PD-L1 CPS ≥ 5: 30% reduction in the risk of death and 12% improvement in 24-month OS rate
  - All randomized: 21% reduction in the risk of death and 9% improvement in 24-month OS rate
  - Directionally improved HRs relative to the 12-month follow-up (PD-L1 CPS ≥ 5, 0.71 [98.4% CI, 0.59-0.86]; all randomized, 0.80 [99.3% CI, 0.68-0.94])[1]

[a]Minimum follow-up, 24.0 months.

Janjigian Y et al, Lancet. 2021 July 03; 398(10294): 27-40.
Janjiigian Y et al, Ann Oncology, ESMO presentation 2021
Shitara K et al. ASCO GI 2022;Abstract 240

Phase 3 studies with anti-PD1 and chemotherapy in first line advanced gastro-oesophageal cancer*

	KEYNOTE-590	CheckMate-648	CheckMate-649
Design	5FU/Cisplat +/- PEMBROLIZUMAB	5FU/Cisplat +/- NIVOLUMAB	FOLFOX/XELOX +/- NIVOLUMAB
Location	Esophagus and GEJ (Siew. I)	Esophagus	Stomach and GEJ
Histology	SCC / adenocarcinoma	SCC	adenocarcinoma
Patients	53% Asian	70% Asian	23% Asian
Objective	OS / PFS (CPS≥10, all)	OS / PFS (TPS≥1%)	OS / PFS (CPS≥5)
PD-L1 testing	CPS≥10: 51%	TPS≥1: 49%	CPS≥5: 60%
OS (HR)	CPS≥10: 0.57 All: 0.72	TPS≥1: 0.54 All: 0.74	CPS≥5: 0.70 All: 0.79
PFS (HR):	CPS≥10: 0.51 All:0.65	TPS≥1: 0.65 All: 0.81	CPS≥5: 0.69 All: 0.77
ORR (%)	45% vs 29%	53% vs 20%	60% vs 45%
Grade 3-5 SAE (%)	72% vs 67%	47% vs 36%	60% vs 45%
Reference	Sun, Lancet 2021	Doki, NEJM 2022	Janjigian, Lancet 2021

*Therapeutic approaches have not been directly compared in clinical trials and cross-trial comparisons cannot be made

HER2 targeted therapy and testing in first line treatment of gastric cancer

TOGA study: chemo ± trastuzumab

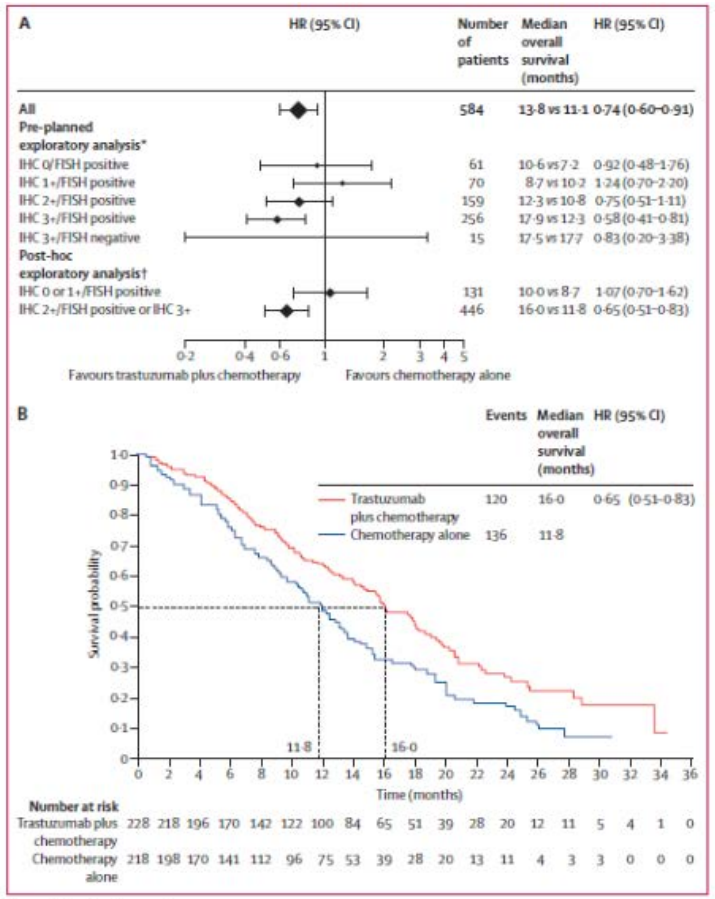


Figure 4: **Exploratory analyses**
HR=hazard ratio. (A) Pre-planned exploratory and post-hoc exploratory analyses of patients stratified by human epidermal growth factor receptor 2 (HER2) status. *n=561; patients with no immunohistochemistry (IHC) data (n=7) or IHC 3+ tumours with no fluorescence in-situ hybridisation (FISH) data (n=16) were excluded from this analysis. †n=577; patients with no IHC data (n=7) were excluded from this analysis. (B) Overall survival according to the post-hoc exploratory analysis (FISH and IHC) in patients with IHC 2+ and FISH-positive tumours or IHC 3+ tumours.

Bang Y, Van Cutsem E et al, Lancet 2010

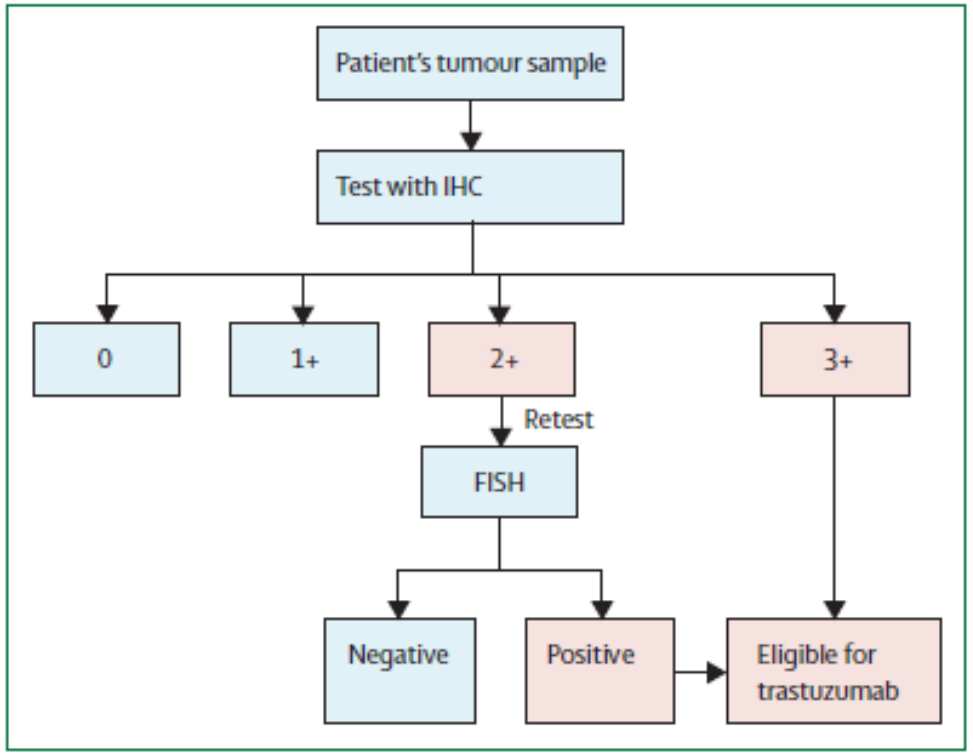
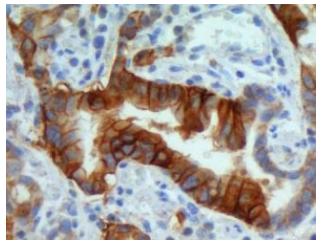
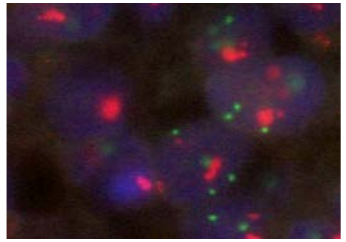


***Figure 2:* Testing algorithm for *HER2* status in gastric and gastro-oesophageal-junction adenocarcinomas**
IHC–immunohistochemistry. FISH–fluorescence in-situ hybridisation.



IHC 3+



FISH +

Van Cutsem E et al, Lancet 2016

KEYNOTE-811 Global Cohort in HER2+ gastric cancer: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

- Unresectable or metastatic gastric or GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2-positive tumor by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

Stratification Factors

- Geographic region (Australia/Europe/ Israel/North America vs Asia vs ROW)
- PD-L1 CPS (≥1 vs <1)
- Chemotherapy choice (FP vs CAPOX)

R 1:1
N ≈ 692

Pembrolizumab 200 mg IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by BICR
- **Key secondary:** ORR and DOR per RECIST v1.1 by BICR and safety

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100). KEYNOTE-811 ClinicalTrials.gov identifier, NCT03615326.

Yanjigian Y… Van Cutsem E et al. ESMO GI/WCIGC Ann Onc 2021,LBA4

KEYNOTE-811 Global Cohort:
Phase 3 Study in HER2 pos. Gastric Adenocarcinoma

Table 1 | Summary of confirmed objective response in the efficacy population

Variable	Pembrolizumab group (*n* = 133)	Placebo group (*n* = 131)
Objective response (% (95% confidence interval))[a]	74.4 (66.2–81.6)	51.9 (43.0–60.7)
Disease control (% (95% confidence interval))[b]	96.2 (91.4–98.8)	89.3 (82.7–94.0)
Best overall response (number (%))		
Complete response	15 (11.3)	4 (3.1)
Partial response	84 (63.2)	64 (48.9)
Stable disease	29 (21.8)	49 (37.4)
Progressive disease	5 (3.8)	7 (5.3)
Not evaluable[c]	0 (0.0)	2 (1.5)
Not assessed[c]	0 (0.0)	5 (3.8)

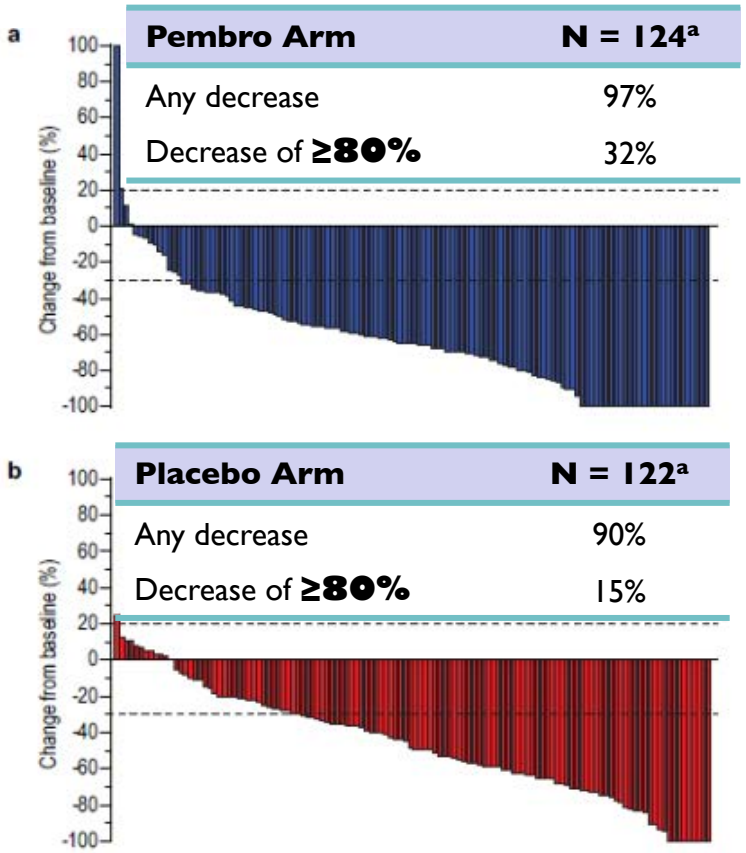
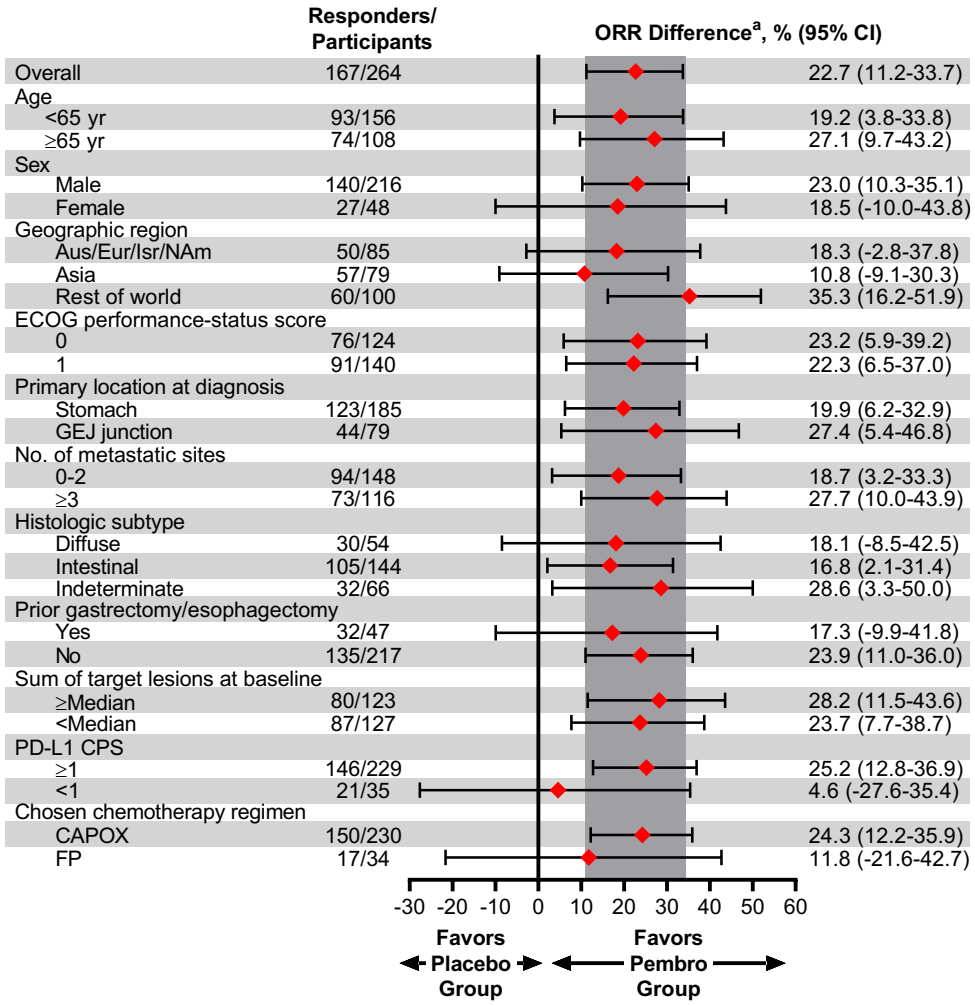


Fig. 1 | Best percentage change from baseline in the size of target lesions among participants in the efficacy population. a, Pembrolizumab group. **b**, Placebo group. Only those participants in the efficacy population who had RECIST-measurable disease at baseline and at least one evaluable post-baseline measurement are evaluable for change from baseline ($n = 124$ in the pembrolizumab group, $n = 122$ in the placebo group). The treatment regimen included trastuzumab and chemotherapy in both groups. Increases from baseline greater than 100% were truncated at 100%.



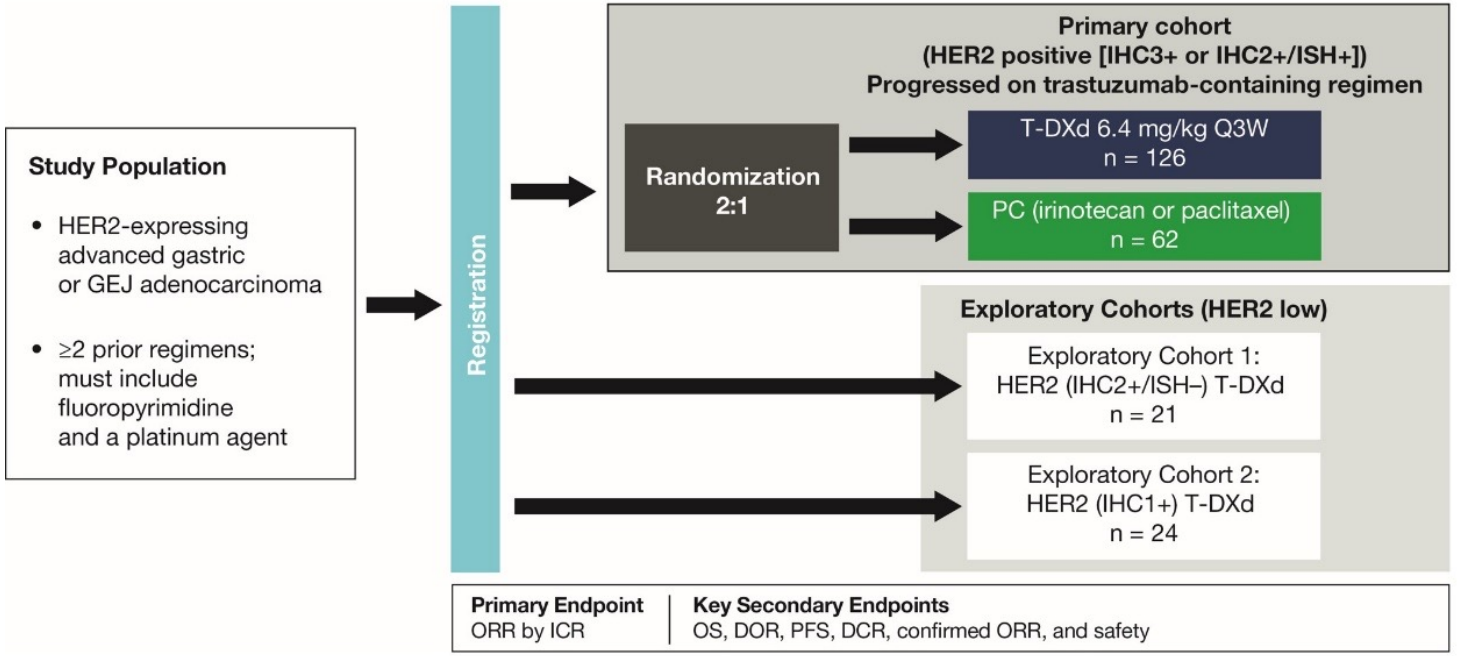
Janjigian Y, …Van Cutsem E et al Nature 2021 & ESMO GI/WCIGC Ann Onc 2021,LBA4

DESTINY-Gastric01

An open-label, multicenter, randomized, phase 2 study in ASIA

- ✓ Patients had a median of 2 prior lines of therapy (range, 2-9); 44.4% of patients had ≥3 previous lines
- ✓ As of June 3, 2020, 10 patients (8%) receiving T-DXd and no patients receiving PC remained on treatment

DESTINY-Gastric01 Study Design



Key secondary endpoint of OS was to be statistically evaluated hierarchically if the primary endpoint was statistically significant

Shitara K, et al. *N Engl J Med*. 2020;382(25):2419-2430

DESTINY-Gastric01: Response Rate IHC3+ or IHC2+/ISH+

Best Percent Change from Baseline in the Sum of Longest Diameters of Measurable Tumors

Confirmed ORR[a]	T-DXd	PC
	42.0%	12.5%

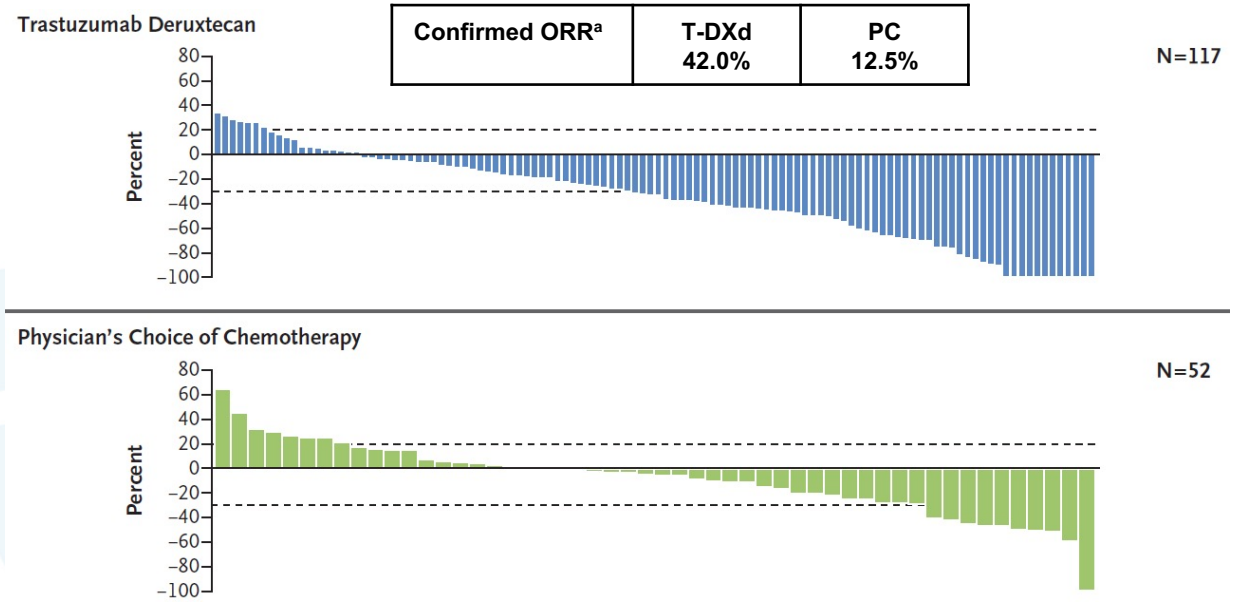
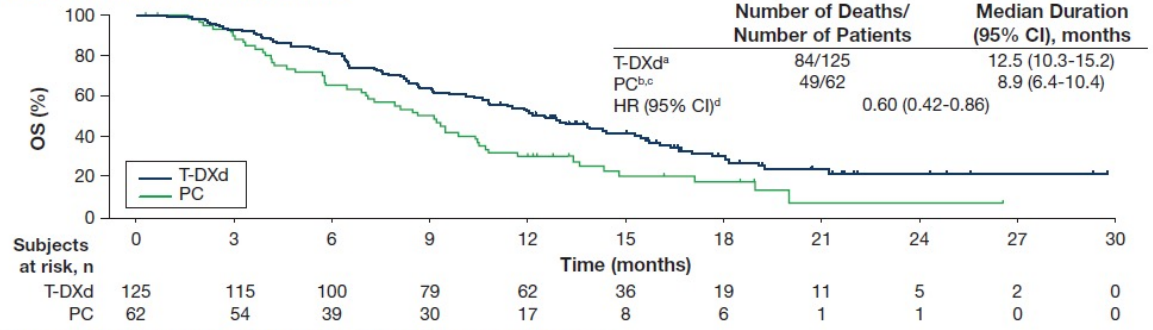


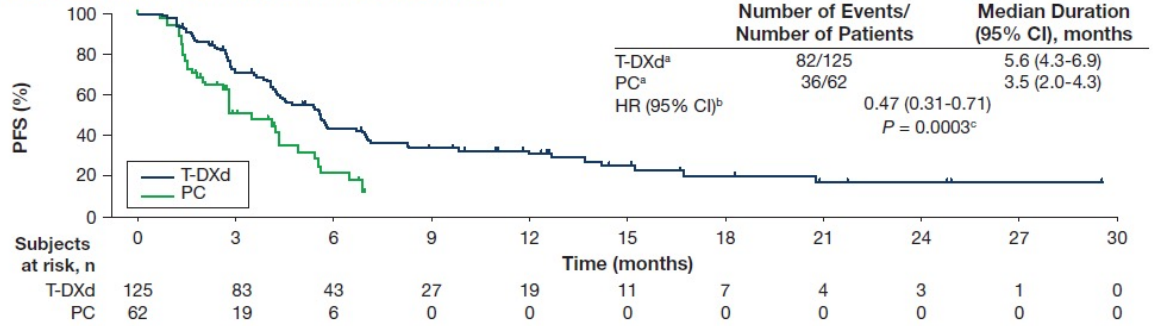
Figure 4. Kaplan-Meier Analysis of OS



HR, hazard ratio; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.

[a]In the T-DXd arm, 41 patients (32.8%) were censored.
[b]In the PC arm, 13 patients (21.0%) were censored.
[c]One patient in the PC arm received crossover treatment of T-DXd.
[d]HR and corresponding 95% CI were estimated using Cox proportional hazards model stratified by region.

Figure 5. Kaplan-Meier Analysis of PFS Based on ICR



HR, hazard ratio; ICR, independent central review; PC, physician's choice; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

[a]In the T-DXd arm, 71 patients (56.8%) had PD and 11 (8.8%) had death as the first event. In the PC arm, 34 patients (54.8%) had PD and two (3.2%) had death as the first event. 43 (34.4%) and 26 (41.9%) patients were censored in the T-DXd and PC arms, respectively, for no baseline (T-DXd [n = 0]; PC [n = 2]) or postbaseline tumor assessment (n = 1; n = 3), receiving new anticancer therapy (n = 14; n = 14), and missing two consecutive tumor assessments (n = 5; n = 1); the remaining patients were censored without an event.
[b]HR and corresponding 95% CI were estimated using Cox proportional hazards model stratified by region.
[c]Comparison between T-DXd and PC overall using a stratified log-rank test with region as a stratification factor.

Shitara K, et al. *N Engl J Med*. 2020;382(25):2419-2430
Yamaguchi K, et al. Presented at ASCO 2021 Virtual Meeting; June 4-8, 2021
Yamaguchi K et al, ASCO GI, JCO.2022.40.4_suppl.242.

DESTINY-Gastric02 in second line HER2+ gastric cancer

An open-label, multicenter phase 2 study in Western patients with HER2+ gastric or GEJ cancer (NCT04014075)

Key eligibility criteria

- Pathologically documented, unresectable or metastatic gastric or GEJ cancer
- Centrally confirmed HER2 positive disease (defined as IHC 3+ or IHC 2+/ISH+) on biopsy after progression on first-line trastuzumab-containing regimen
- ECOG PS 0 or 1

T-DXd
6.4 mg/kg Q3W
N = 79[a]

Primary endpoint

- Confirmed ORR by ICR

Secondary endpoints[b]

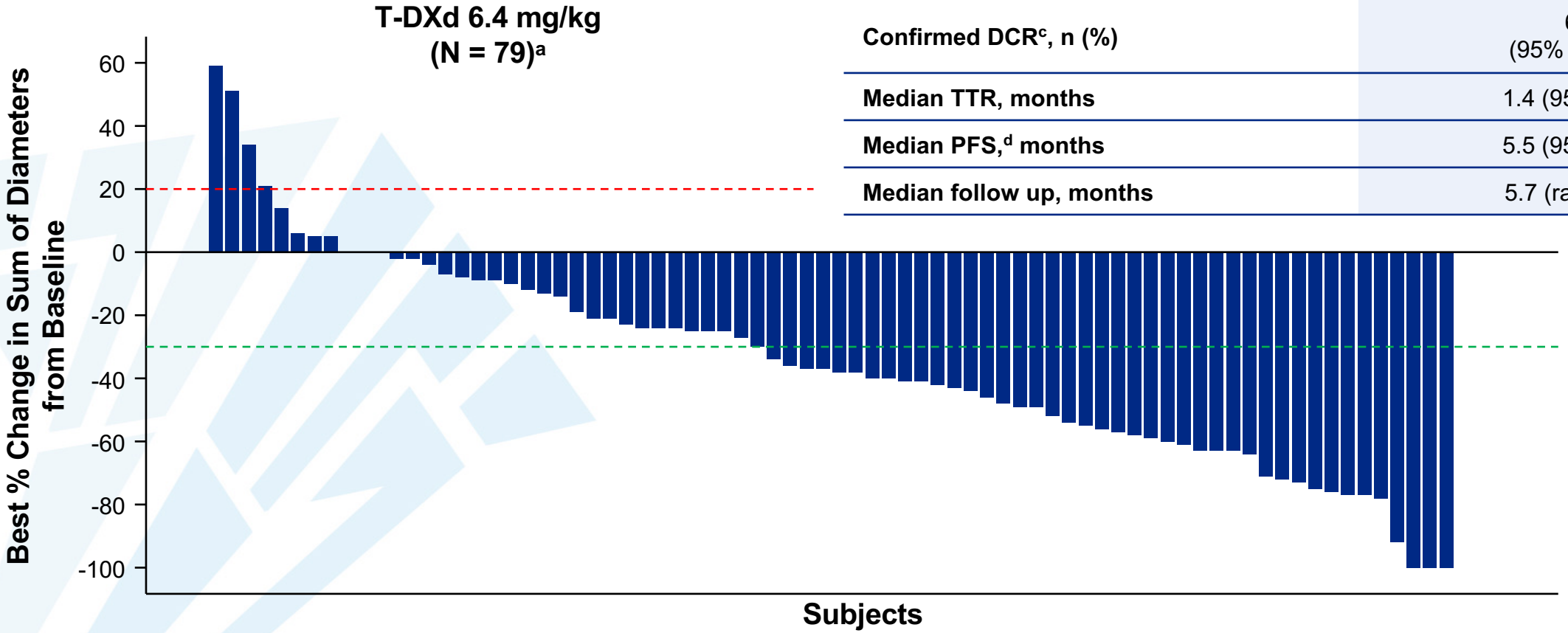
- PFS by ICR
- OS
- DOR by ICR
- Safety and tolerability

- DESTINY-Gastric02 is the first study focused only on second-line T-DXd monotherapy in Western patients with HER2+ gastric/GEJ cancer who have progressed on a trastuzumab-containing regimen
  - It is the follow-on study to DESTINY-Gastric01, which evaluated T-DXd third-line or later in Asian patients[1]
- Patients were enrolled in Europe (Belgium, Great Britain, Italy, Spain) and the United States (data cutoff: April 9, 2021)

Van Cutsem E et al, ESMO LBA - Annals of Oncology (2021) 32 (suppl_5): S1283-S1346

DESTINY-Gastric02 in second line HER2+ gastric cancer

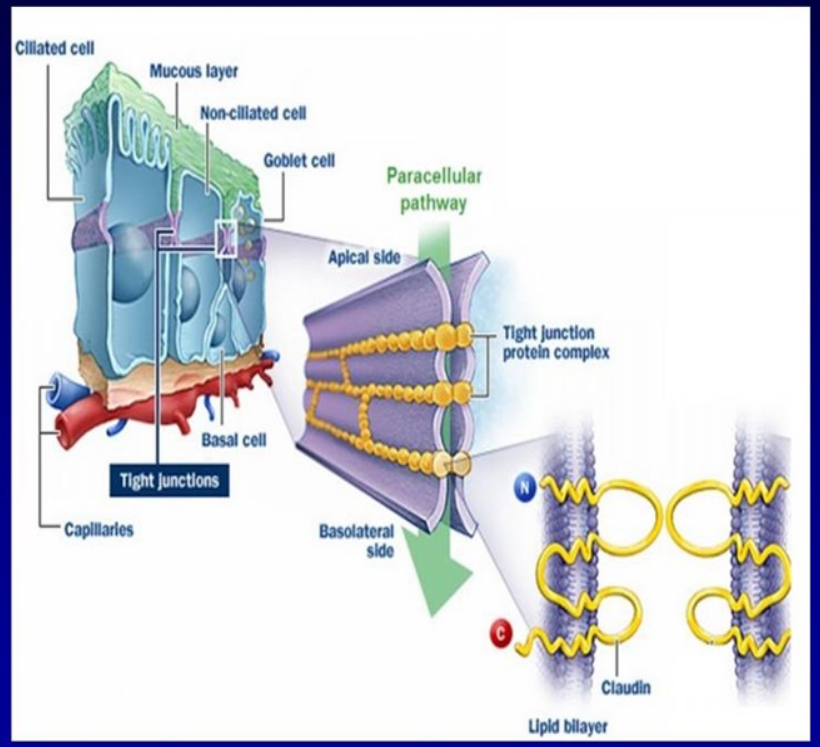
	Patients (N = 79)
Confirmed ORR[a], n (%)	**30 (38)** (95% CI, 27.3-49.6)
Confirmed best overall response, n (%)	
CR	**3 (3.8)**
PR	**27 (34.2)**
SD	**34 (43.0)**
PD	**13 (16.5)**
Not evaluable	**2 (2.5)**
Median DOR,[b] months	8.1 (95% CI, 4.1-NE)
Confirmed DCR[c], n (%)	64 (81.0) (95% CI, 70.6-89.0)
Median TTR, months	1.4 (95% CI, 1.4-2.6)
Median PFS,[d] months	5.5 (95% CI, 4.2-7.3)
Median follow up, months	5.7 (range, 0.7-15.2)



Van Cutsem E et al, ESMO LBA - Annals of Oncology (2021) 32 (suppl_5): S1283-S1346

Zolbetuximab in Claudin 18.2 positive gastric adenocarcinoma

The Target: CLDN18.2

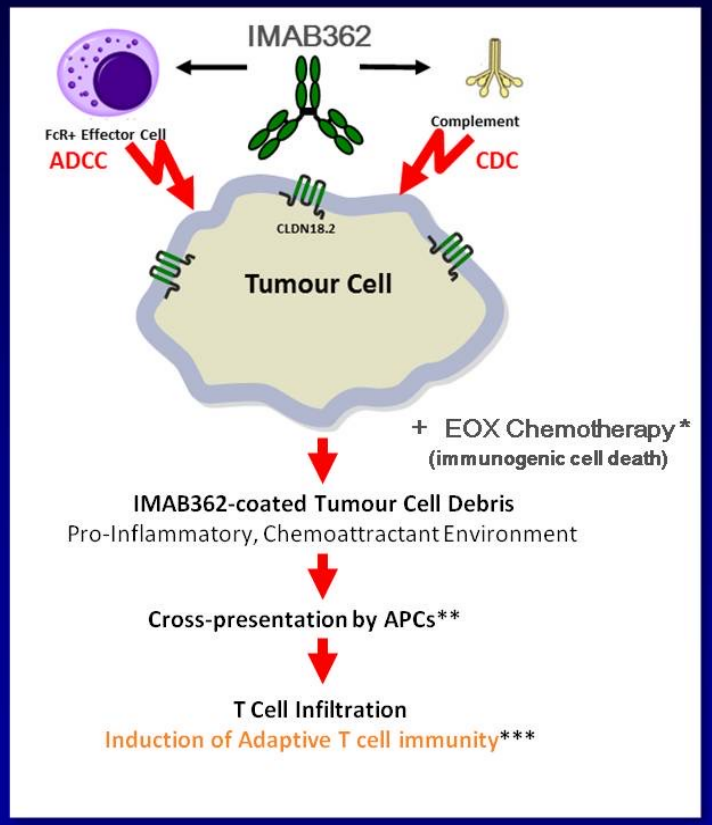


- Member of the claudin family
- Major structural component of tight junctions
  - Seals intercellular space in epithelial sheets
  - Defines cell polarity, regulates para-cellular transport of water, solutes, immune cells
- Broadly expressed in various cancer types
  - ~80-90% biliary duct, gastric, and mucinous ovarian cancer
  - ~10% ovarian cancer, NSCLC and others
- Not expressed on the vast majority of healthy tissues

Al-Batran SE, et al. ASCO 2016 (LBA4001)

Zolbetuximab in Claudin 18.2 positive gastric adenocarcinoma

The IMAB362 Antibody



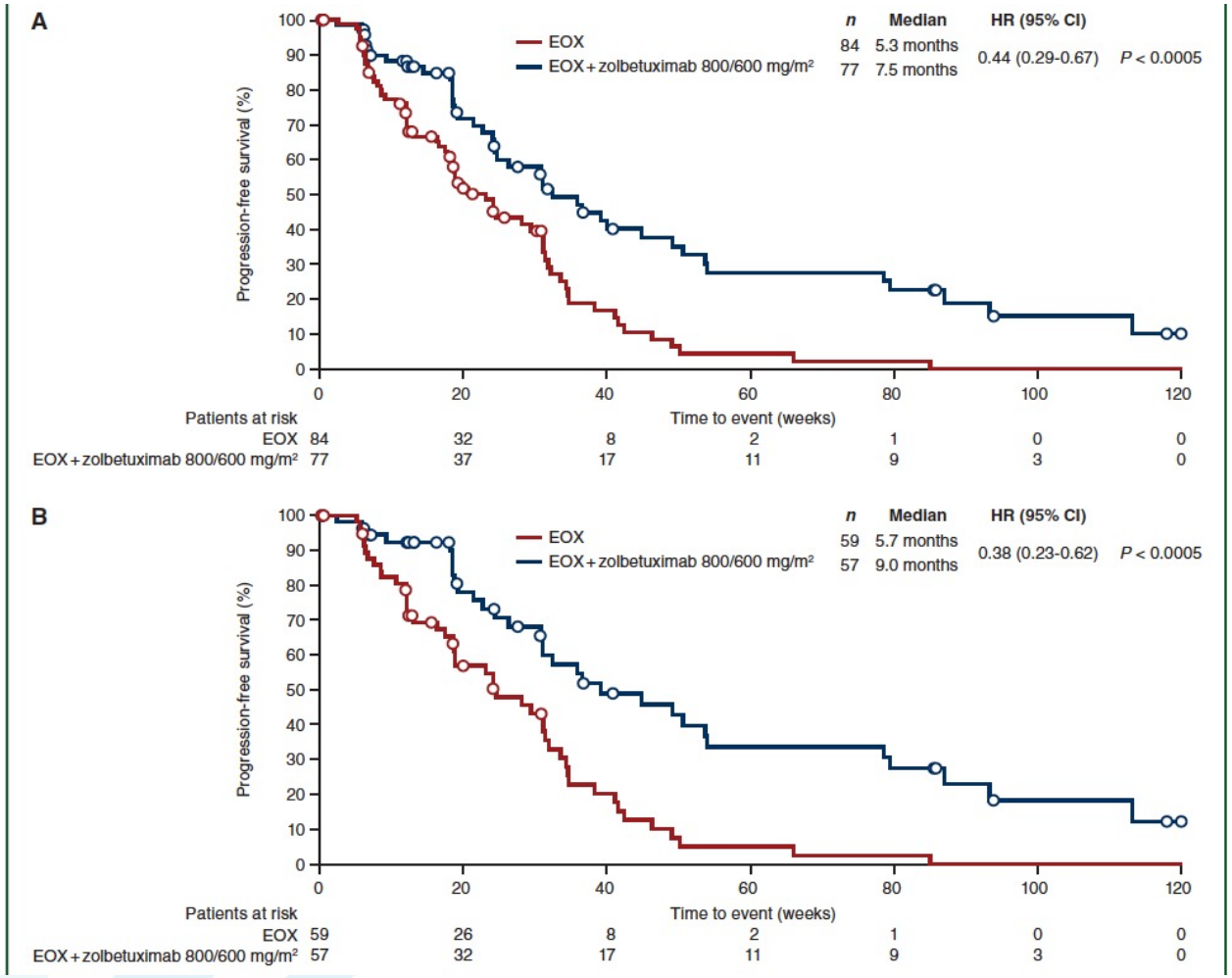
- Chimeric IgG1 backbone antibody
- Highly specific for CLDN18.2
- Modes of action:
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Complement-dependent cytotoxicity (CDC)
  - In Combination with chemotherapy: Immunomodulation of tumor-microenvironment

*Kroemer et al, 2013; **Rogers, Veeramani and Weiner, 2014; ***Biachini and Gianni, 2014
EOX: Epirubicine, Oxaliplatin, Capecitabine

Al-Batran SE, et al. ASCO 2016 (LBA4001)

Zolbetuximab in Claudin 18.2 positive gastric adenocarcinoma

FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma



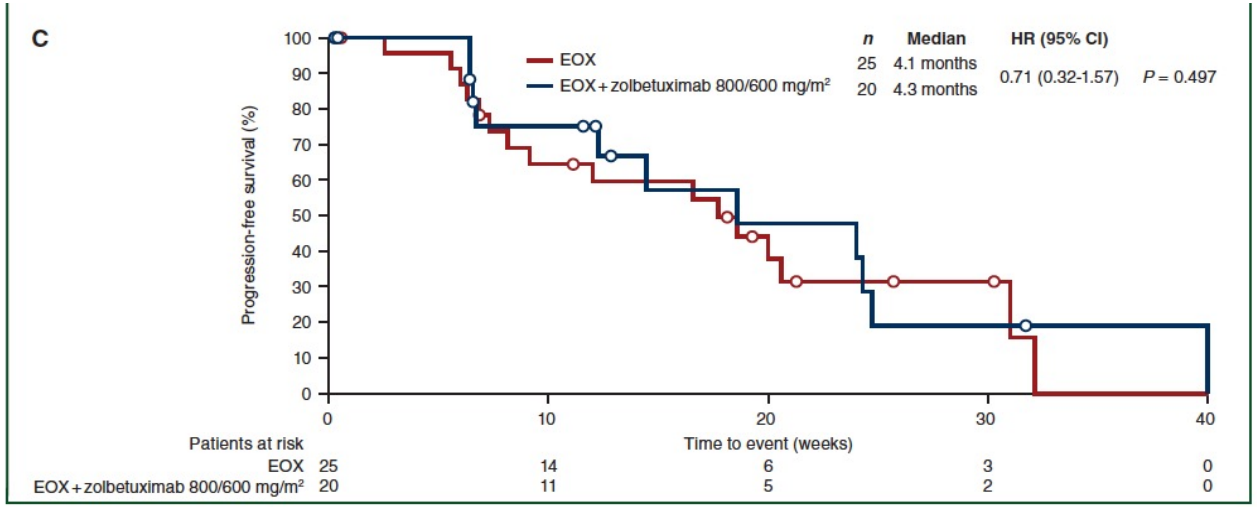


Figure 2. Progression-free survival (A-C) and overall survival (D-F) estimates.
(A) Overall population. (B) Patients with ≥70% of tumour cells positive for CLDN18.2. (C) Patients with 40%-69% of tumour cells positive for CLDN18.2. (D) Overall population. (E) Patients with ≥70% of tumour cells positive for CLDN18.2. (F) Patients with 40%-69% of tumour cells positive for CLDN18.2.
CI, confidence interval; EOX, epirubicin, oxaliplatin, and capecitabine; HR, hazard ratio.

Sahin U et al, Ann Oncol 2021

Bemarituzumab in FGFR positive gastric cancer

FIGHT Phase 2 Study Design

Key Eligibility Criteria

- No prior therapy for unresectable, locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression and/or *FGFR2* gene amplification
- Not HER2-positive

Stratification Factors

- Geographic region
- Single dose of FOLFOX while screening
- Prior perioperative chemotherapy

Randomization 1:1

- Bemarituzumab* + mFOLFOX6 (n = 77)
- vs
- Placebo + mFOLFOX6 (n = 78)

Primary endpoint
- PFS

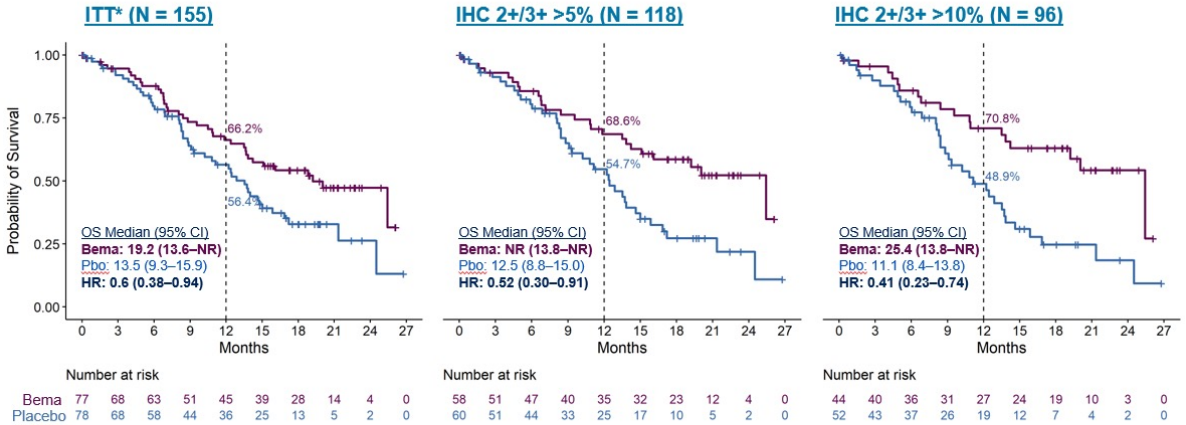
Secondary endpoints
- OS
- Response rate

Treatment may continue until progression, unacceptable toxicity, or the patient meets other withdrawal criteria

*Bemarituzumab dosing: 15 mg/kg Q2W beginning cycle 1 day 1 (plus 1 dose of 7.5 mg/kg on day 8 of cycle 1 only). FOLFOX6 dosing: standard fixed doses Q2W.
FGFR2b, fibroblast growth factor receptor 2b.

Median OS Reached With Longer Follow-up

Addition of Bemarituzumab Showed a +5.7 Month Improvement in Median OS

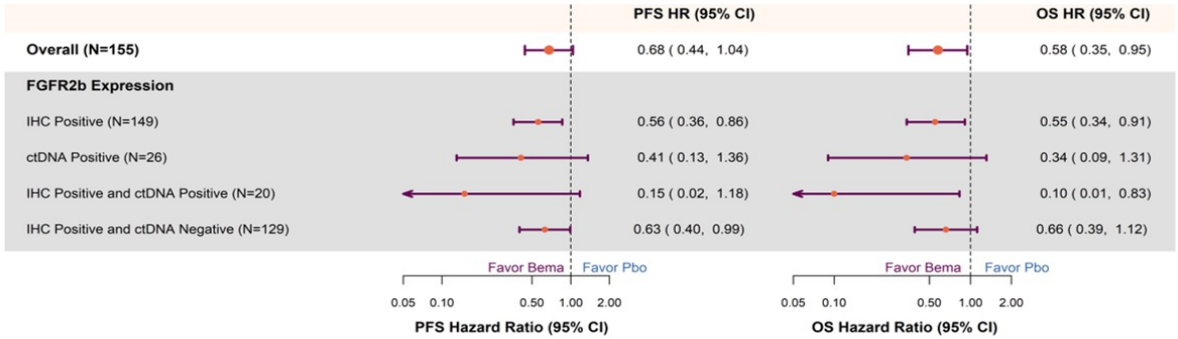


*ITT = includes 149 patients with IHC 2+/3+ and 6 with IHC <2+ or not available who were enrolled based on ctDNA alone.
NR, not reached.
Median Follow-up 12.5 months

*Based on February, 28th 2021 data cut

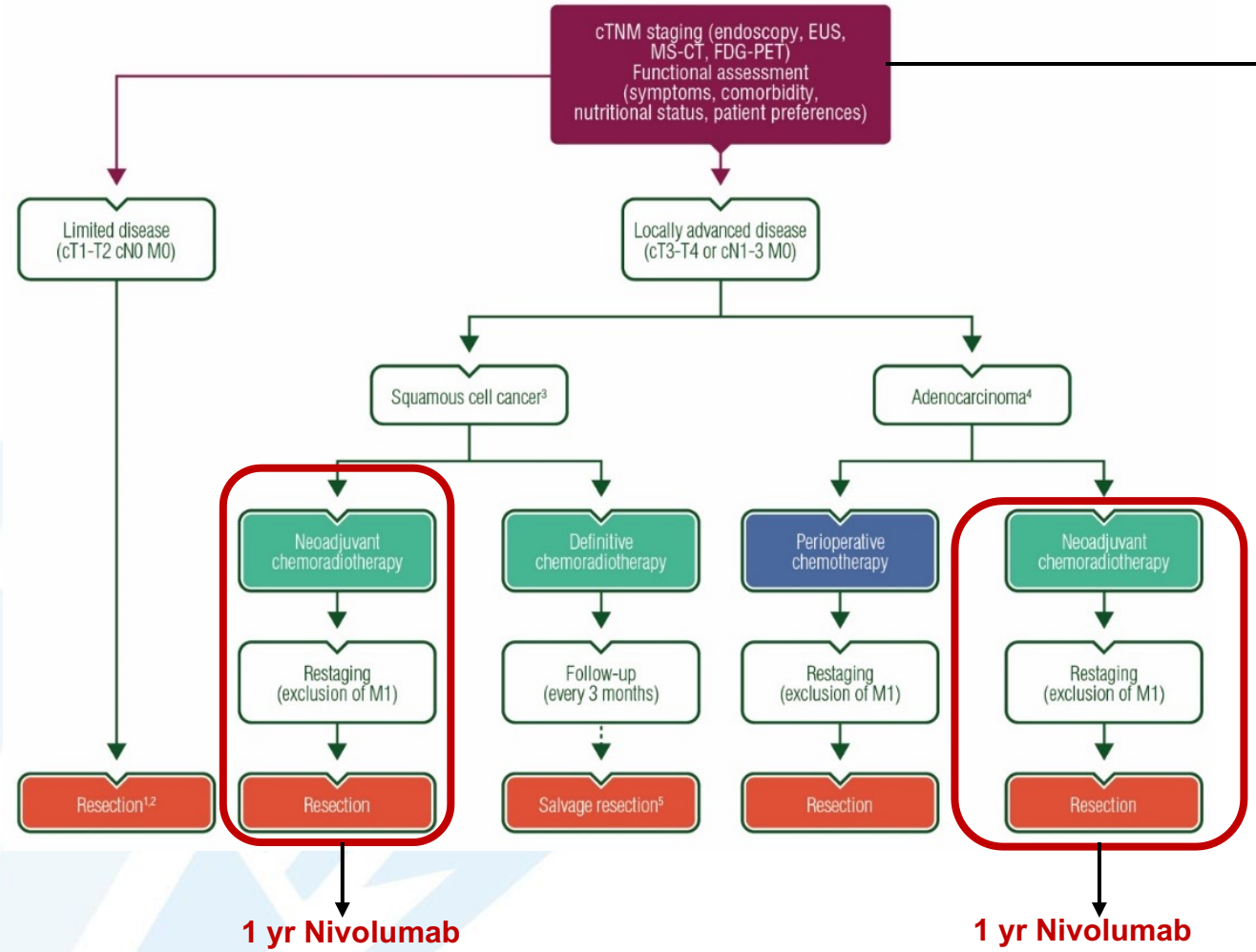
Evaluation of Efficacy by Biomarker Status

Overexpression was Sufficient, ctDNA+ with Most Pronounced Benefit



Catenacci et al. FIGHT: A randomized, double-blind, placebo-controlled, phase 2 study of bemarituzumab (bema) combined with modified FOLFOX6 in 1L FGFR2b+ advanced gastric/gastroesophageal junction adenocarcinoma (GC) (NCT03694522). ASCO abstr 2021

Esophageal Cancer
ESMO guidelines and JSMO/ESMO guidelines
updates in 2022 (personal opinion EVC based on evidence)



Metastatic disease

SCC

1° line:
fluorop. + platinum
+ Pembrolizumab in CPS ≥ 10
Or
+ Nivolumab or Nivolumab + Ipilimumab in tumor cell PD-L1 ≥ 1% (CM 648)

2° line:
Taxane or irinotecan

Nivolumab
Pembrolizumab/Tislelizumab

ADENO

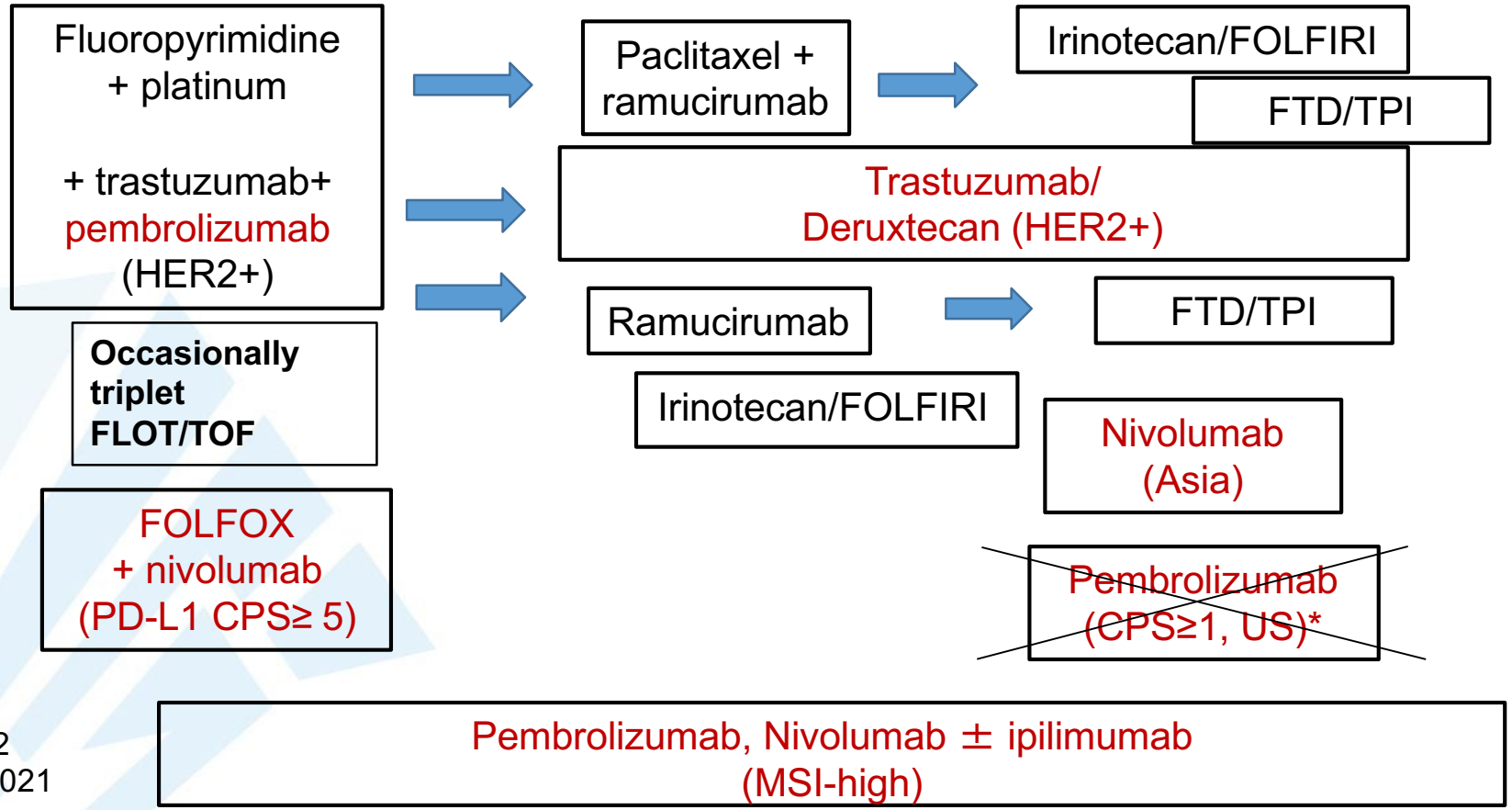
1° line:
fluorop. + platinum
+ Pembrolizumab in CPS ≥ 10
Or
+ Nivolumab in CPS ≥ 5 (CM 649)

2° line:
Paclitaxel + ramucirumab
or irinotecan

1. Lordick F et al. *Ann Oncol* . 16;27(suppl 5):v50-v57.
2. **MODIFIED** by Eric Van Cutsem from Muro K, Van Cutsem E et al. Published in 2018 – *Ann Oncol* 2019;30:19–33.

Updated algorithm for metastatic gastric adenocarcinoma in 2022

(personal opinion EVC based on evidence)



FTD/TPI = TAS-102
* Withdrawn May 2021

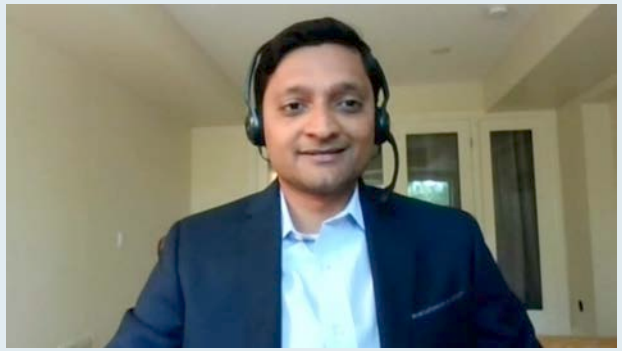
MODIFIED by Eric Van Cutsem from Muro K, Van Cutsem E et al. JSMO-ESMO guidelines. *Ann Onc* 2019;30(1):19-33.

MODULE 4: Selection and Sequencing of Therapy for Advanced Hepatocellular Carcinoma (HCC) — Dr Philip

RTP
RESEARCH
TO PRACTICE

Dr Zanetta Lamar
Naples, Florida

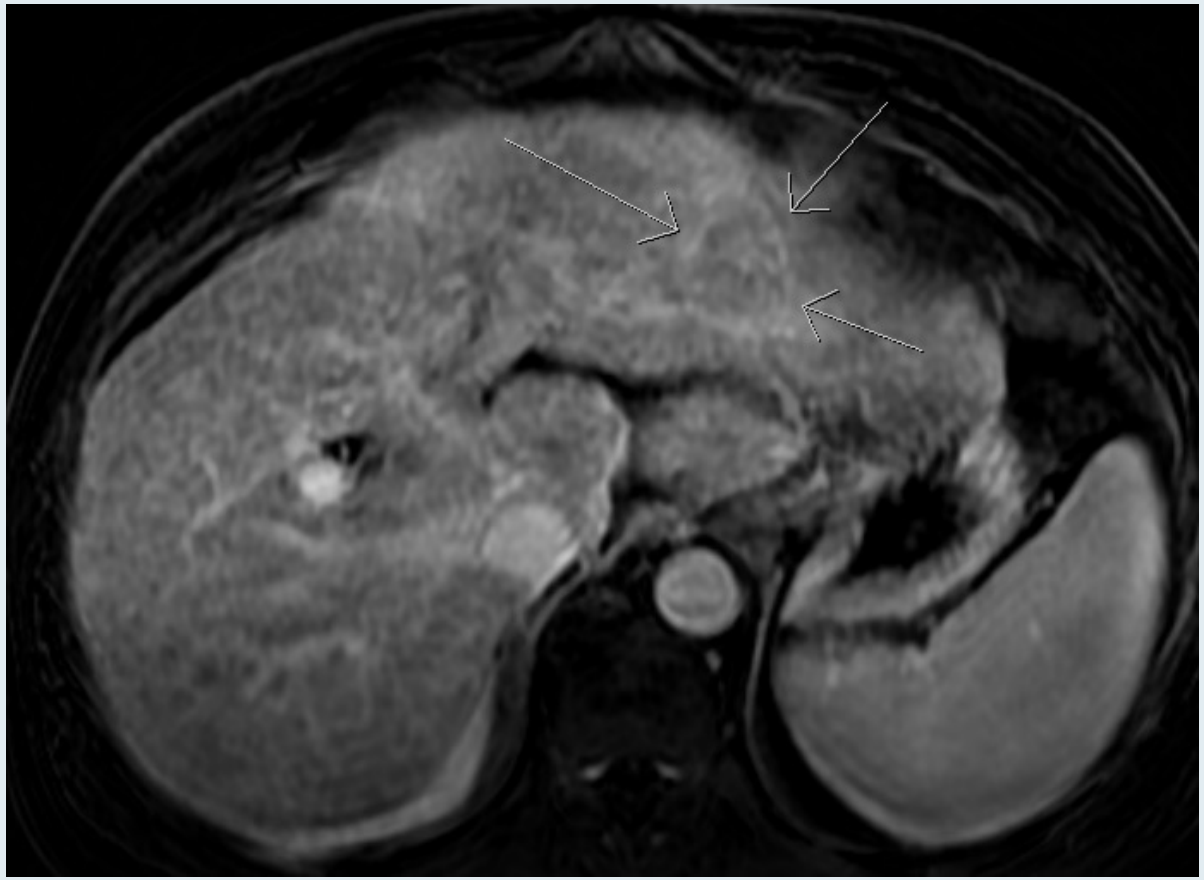
62-year-old woman with a history of autoimmune hepatitis who is diagnosed with Child-Pugh A metastatic HCC and an elevated AFP: 321 ng/mL

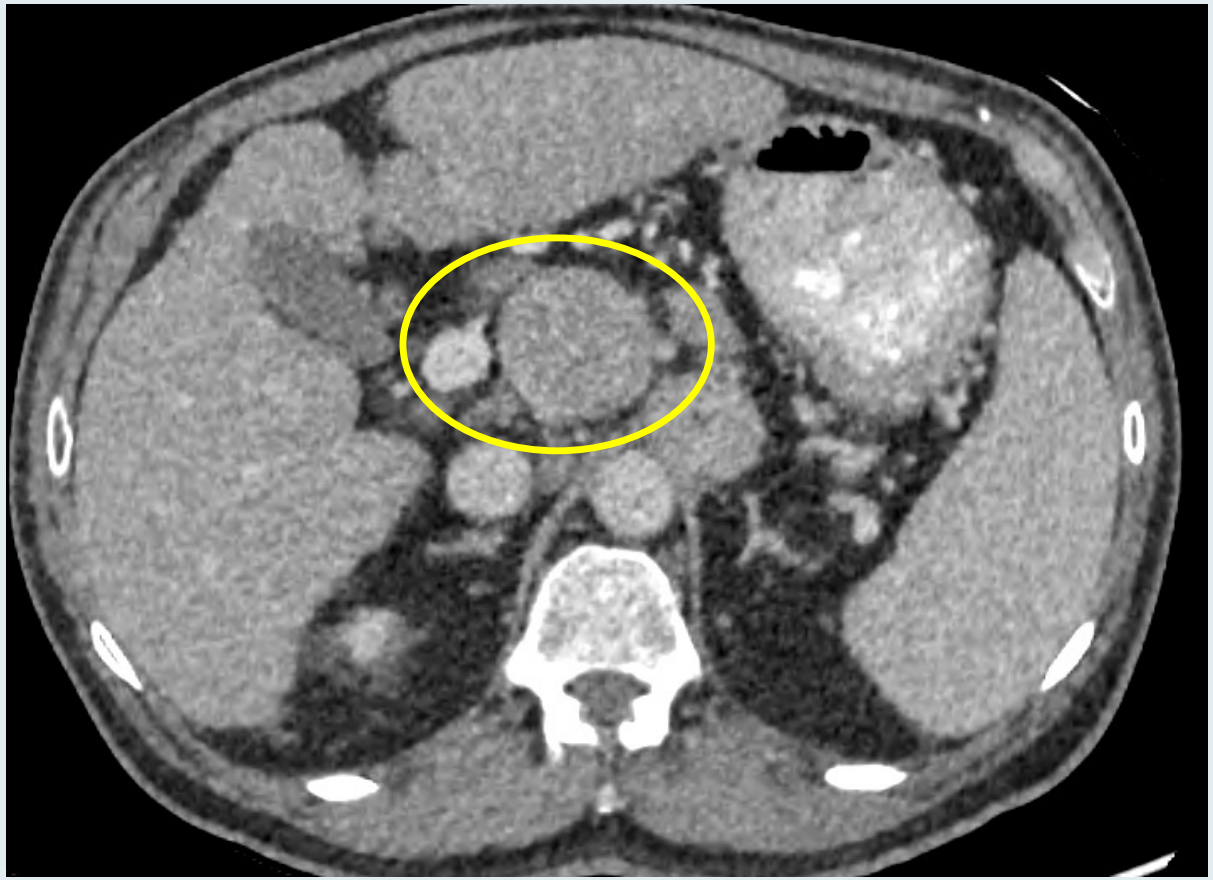


Dr Vignesh Narayanan
Lone Tree, Colorado

60-year-old man with HCC and myasthenia gravis with an elevated AFP: 325 ng/mL

RTP
RESEARCH
TO PRACTICE





78-year-old woman with Child-Pugh A5 HCC and an elevated AFP: 16 ng/mL

Dr Erik Rupard (West Reading, Pennsylvania)

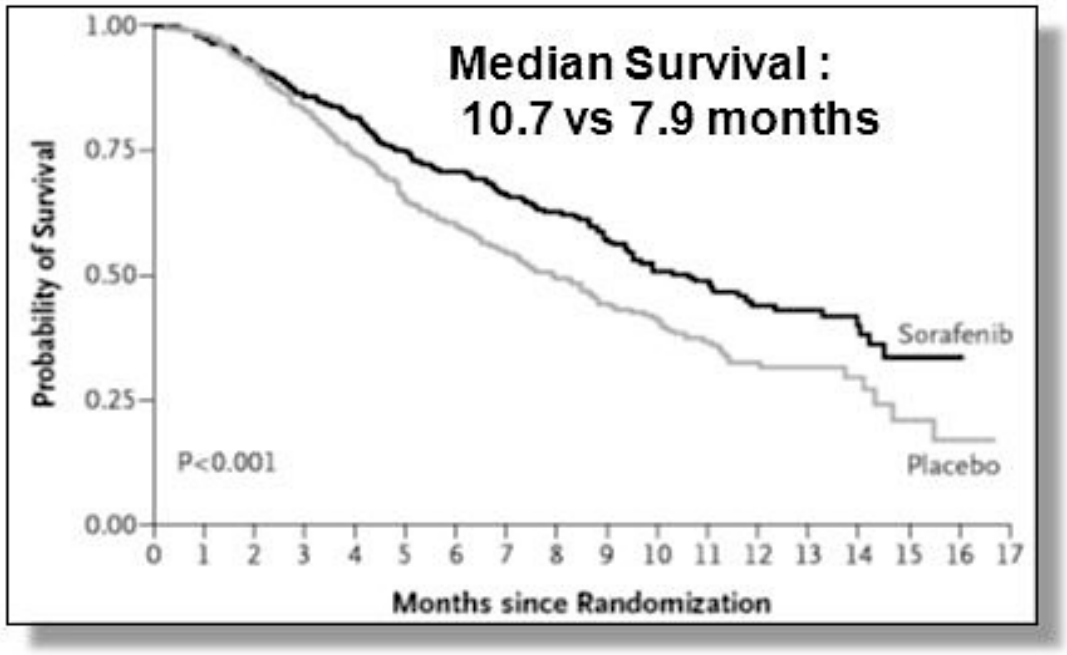
RTP RESEARCH TO PRACTICE

Selection and Sequencing of Therapy for Advanced Hepatocellular Carcinoma (HCC)

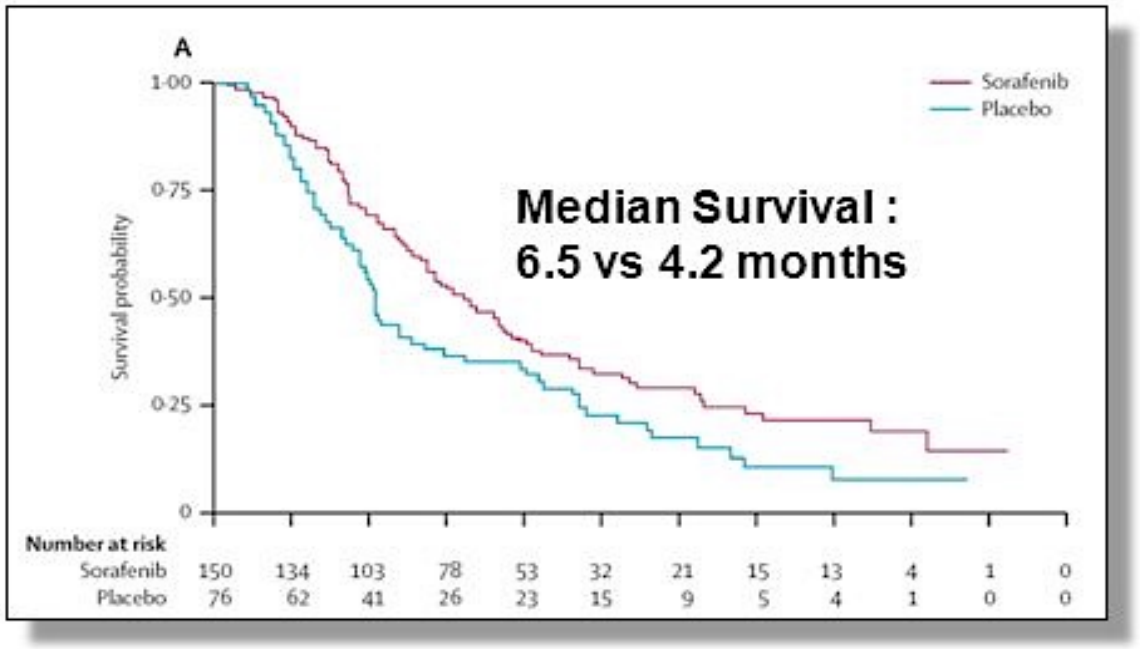
Philip Agop Philip, MD, PhD, FRCP

Sorafenib versus placebo in advanced HCC: Phase 3 trials

SHARP trial

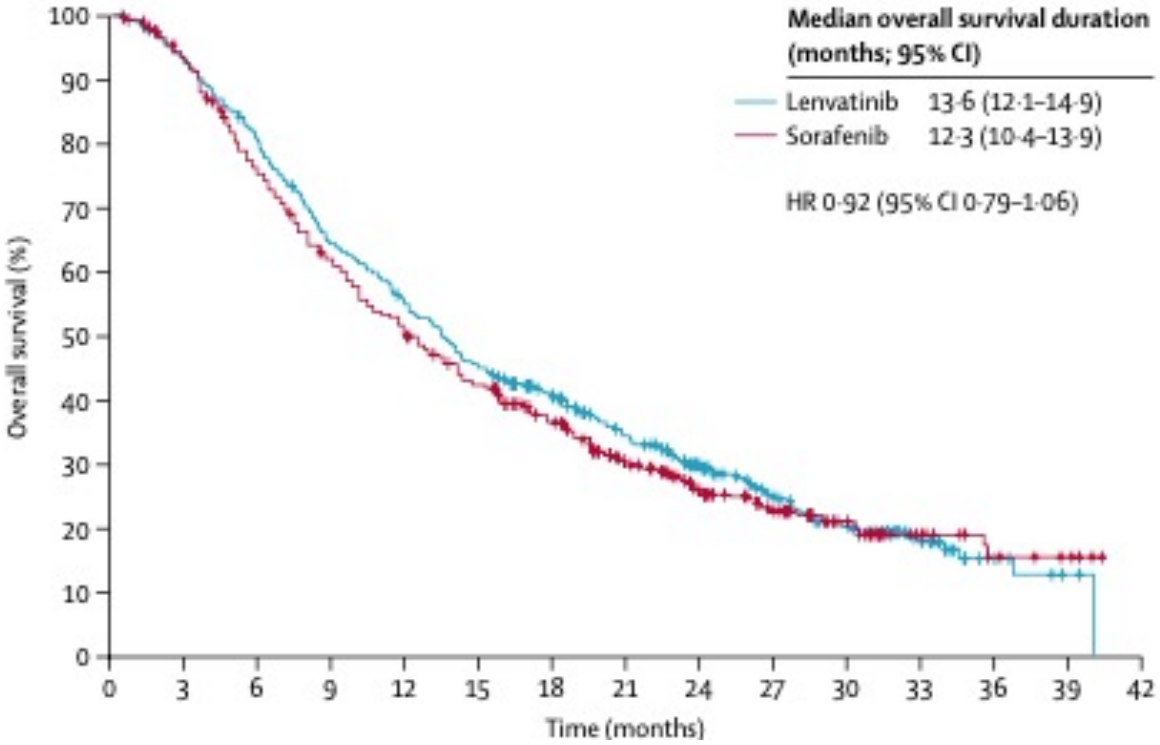


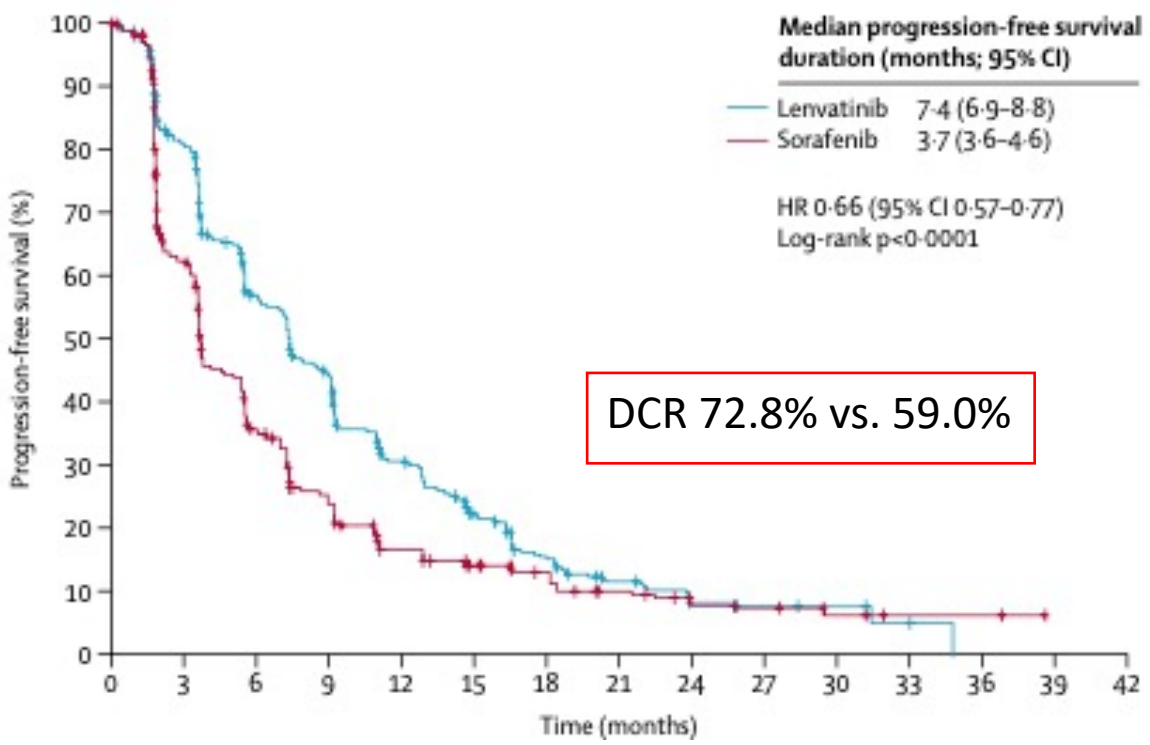
Asia-Pacific trial



Llovet et al. NEJM 2008
Cheng et al. Lancet Oncol 2009

REFLECT: Non-inferiority of lenvatinib vs sorafenib based on OS primary endpoint and improvements in PFS and disease control

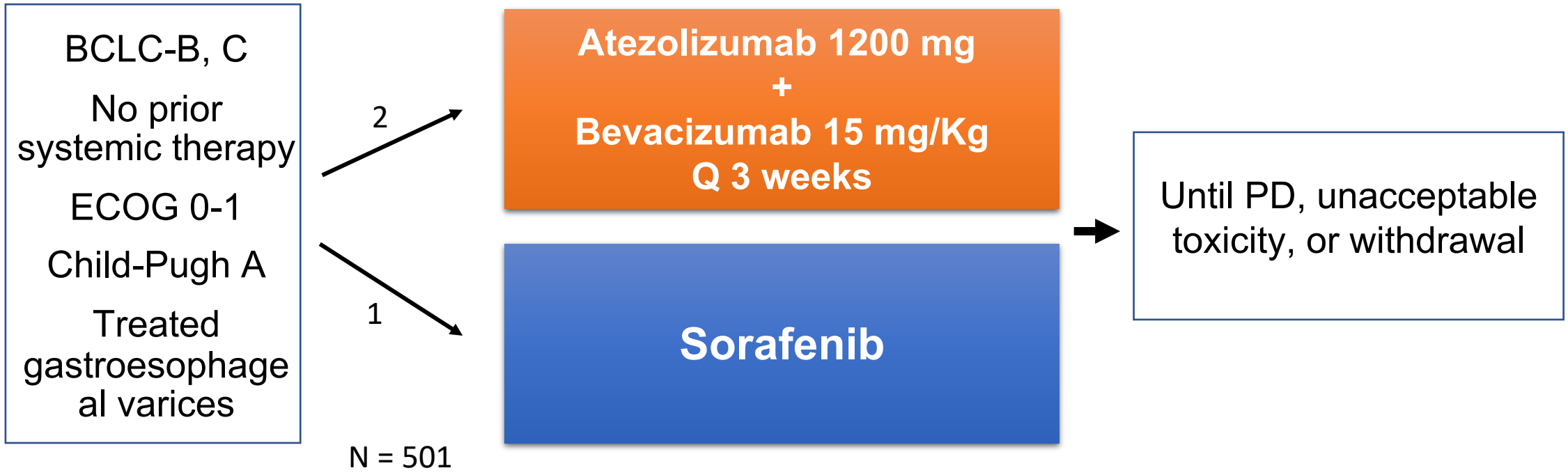




DCR 72.8% vs. 59.0%

Kudo M et al, Lancet, 2018

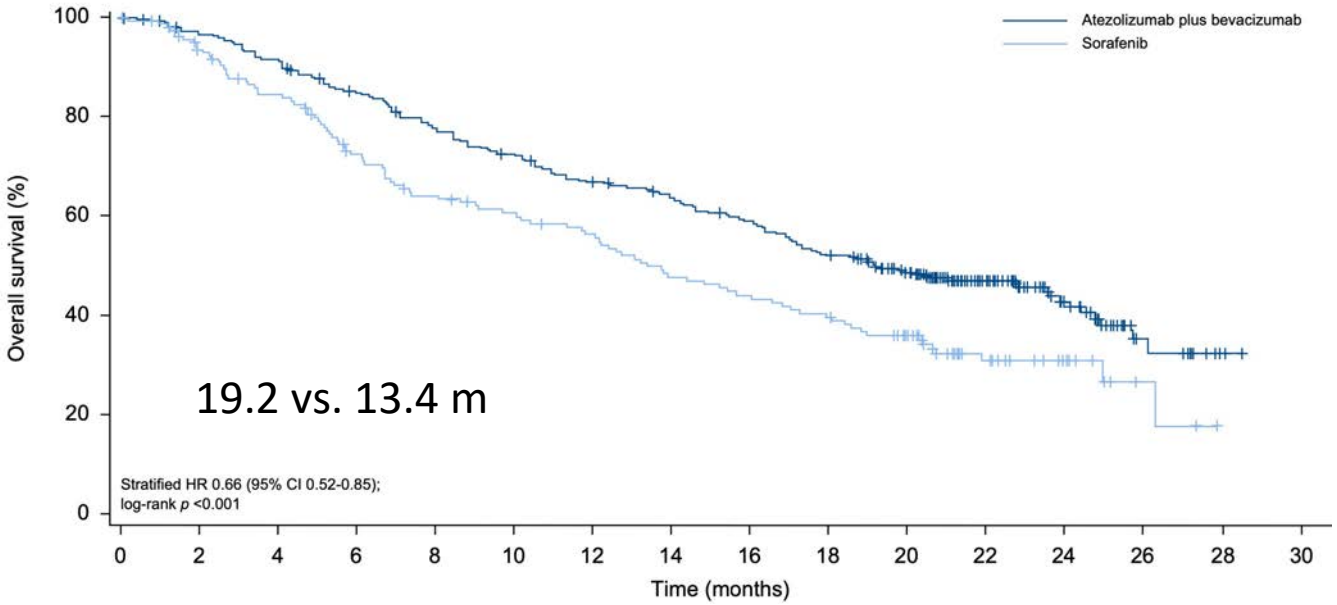
IMbrave150: Phase 3 trial of atezolizumab plus bevacizumab in unresectable HCC Frontline treatment

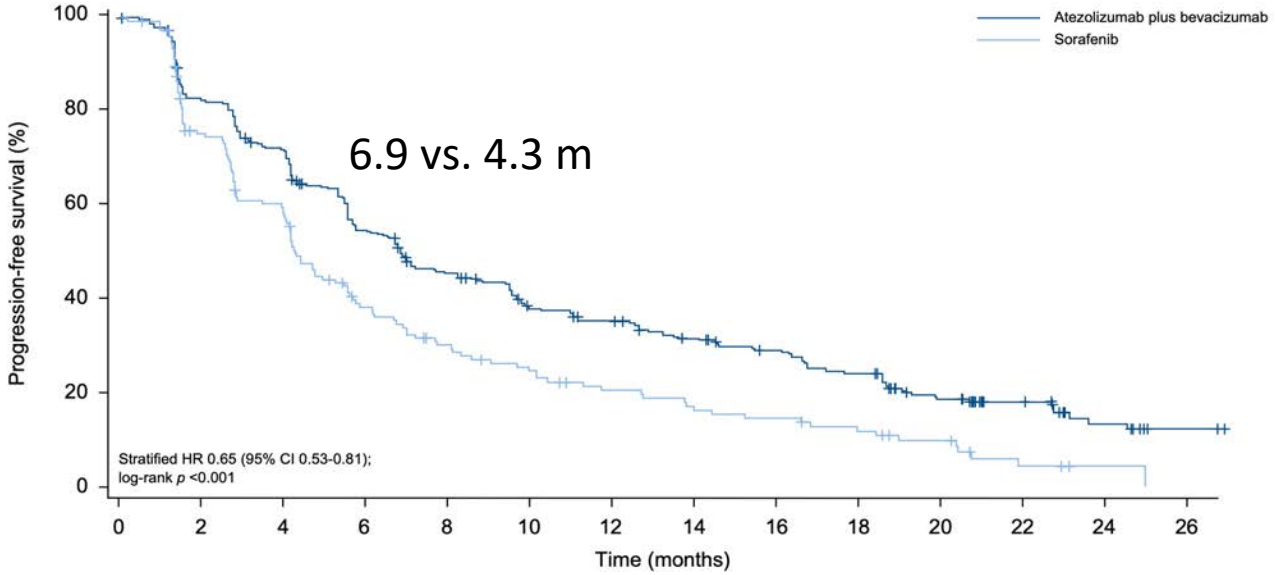


- Co-primary endpoints of PFS and OS
- Stratified by region, MVI/EHS, ECOG PS, AFP (< 400 ng/mL vs ≥ 400 ng/mL), and geography

Finn RS, et al, NEJM, 382:1894-1905, 2020.

IMbrave150: updated efficacy data



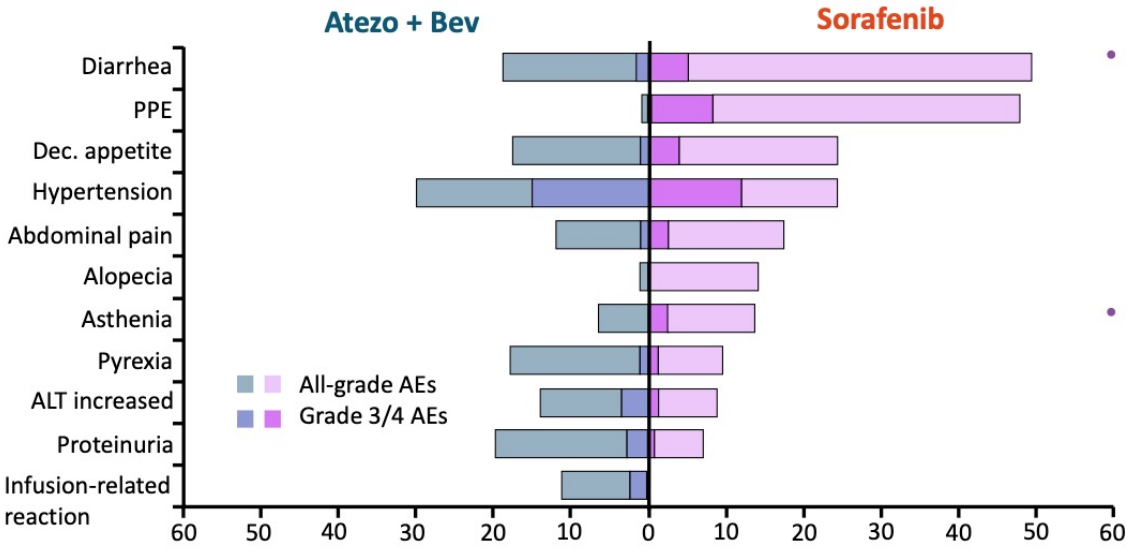


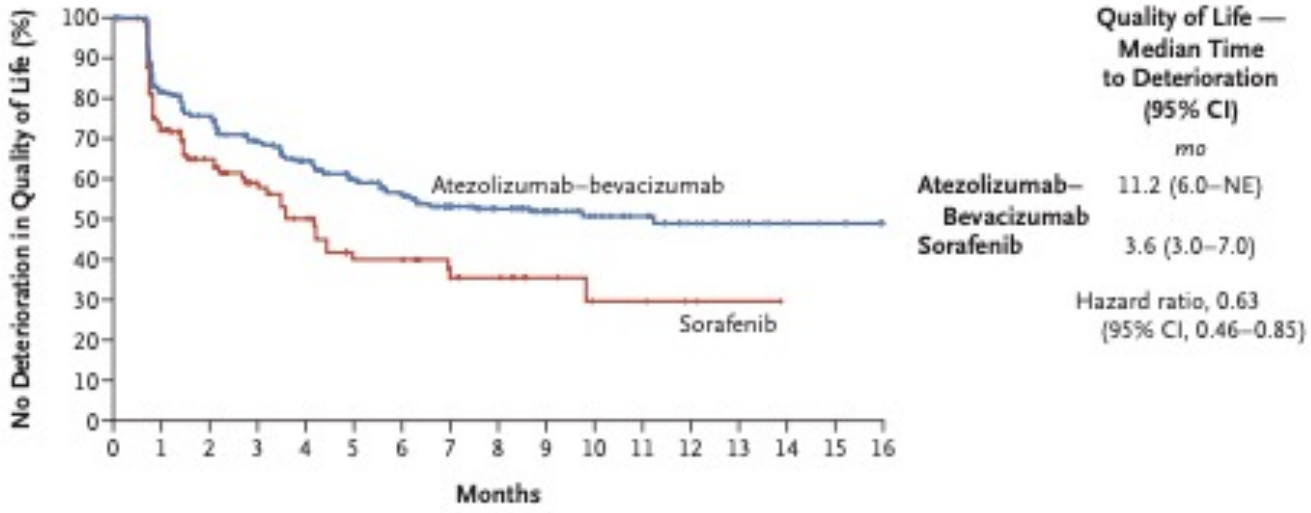
	Atezo/bev	Sorafenib
RECIST Response rate, %	30	11
Complete response, %	8	<1
Partial response, %	22	11
Disease control, %	74	55
Median DOR, months	18.1	14.9
GI hemorrhage Gr ¾, n	2 pt	2 pt
GI hemorrhage grade 5, n	1 pt	0 pt

Finn et al, ASCO GI, 2021;Cheng et al, J Hepatol, 2021

The combination of atezolizumab and bevacizumab was well tolerated and QoL was better preserved

≥10% frequency in either arm and >5% difference between arms





Cheng et al. Annals of Oncology 2019; Finn et al, NEJM, 2020

ASCO Gastrointestinal Cancers Symposium

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

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

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

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

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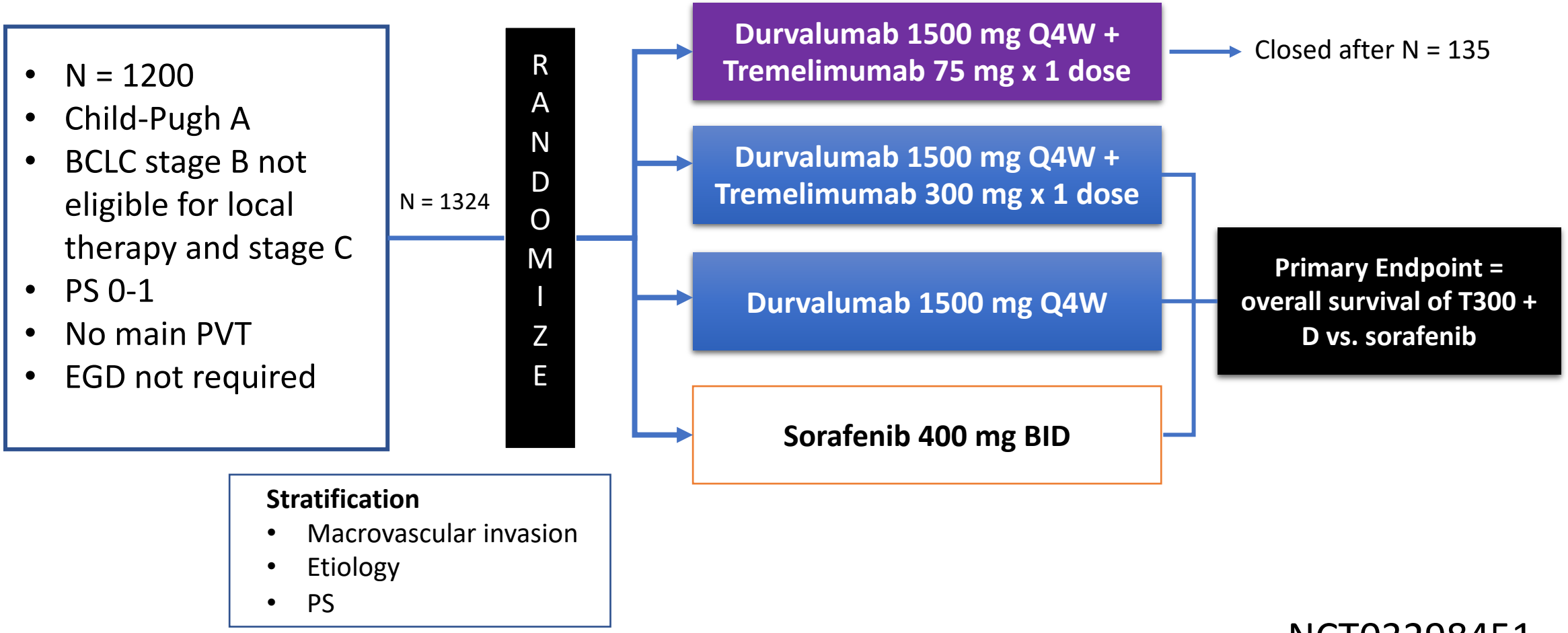
HIMALAYA: Phase III trial of dual IO versus sorafenib in frontline treatment of HCC

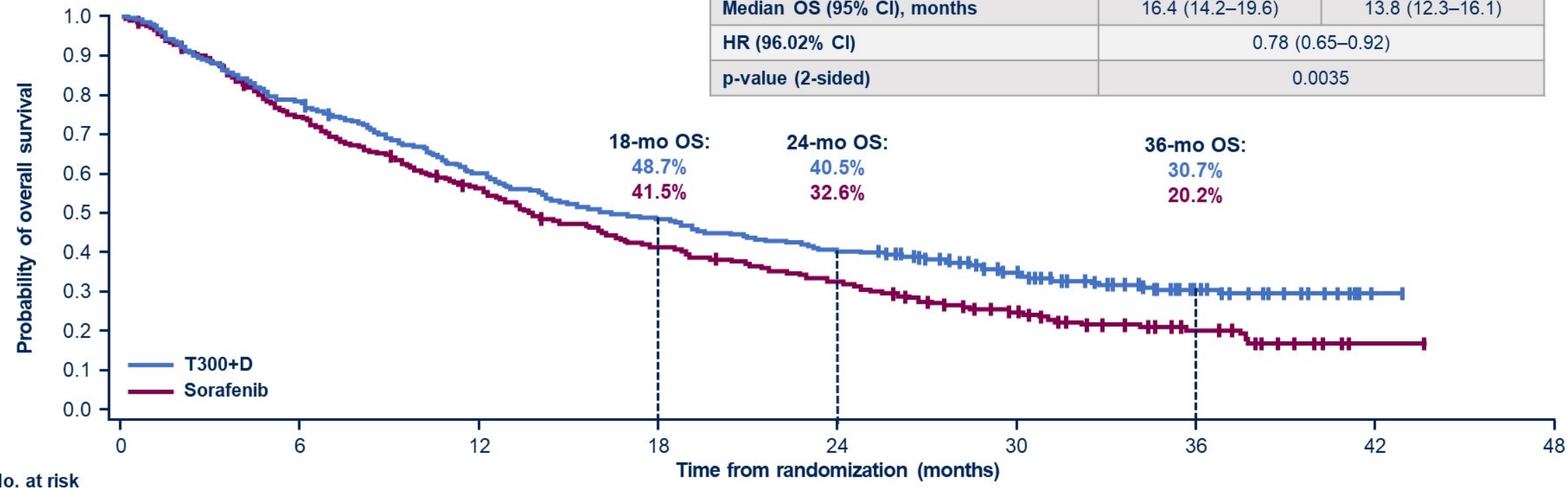


NCT03298451

Abou-Alfa et al, ASCO GI, 2022

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

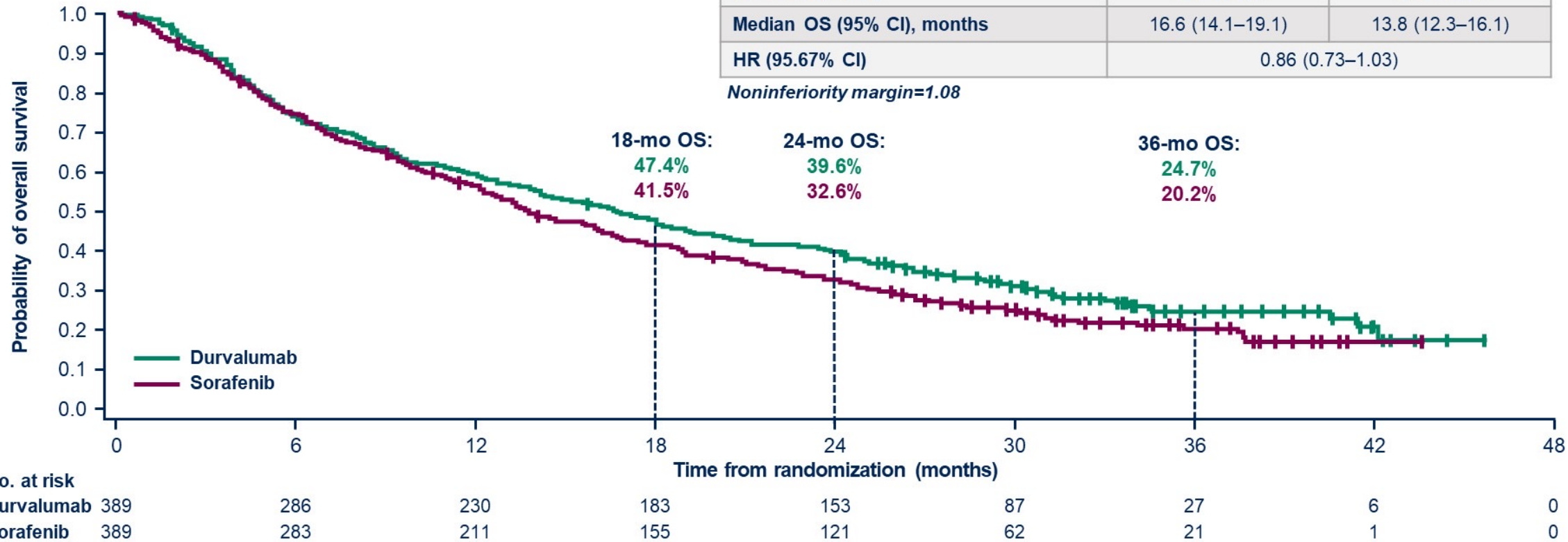
Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.
CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

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

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



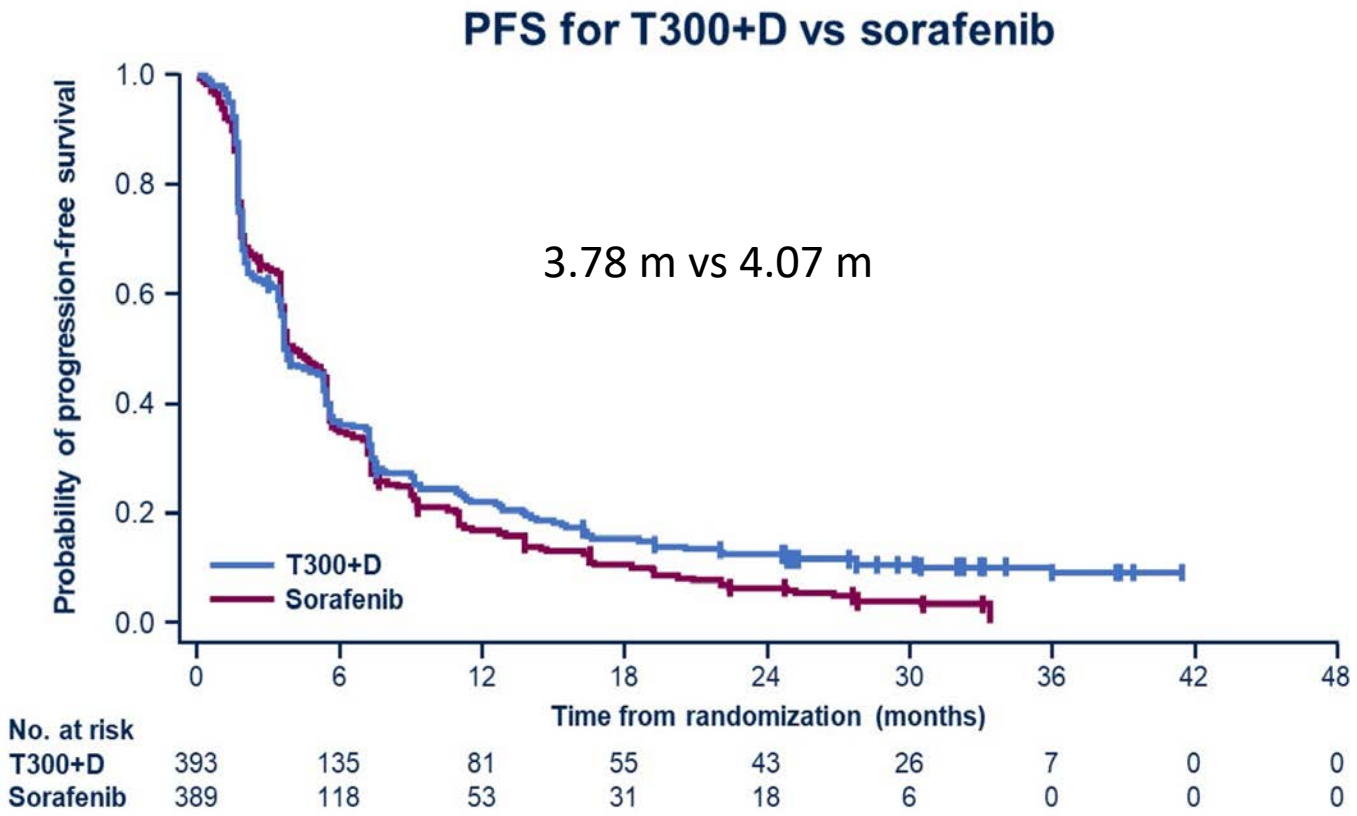
No. at risk									
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

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.

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

HIMALAYA: Select Secondary endpoint outcomes

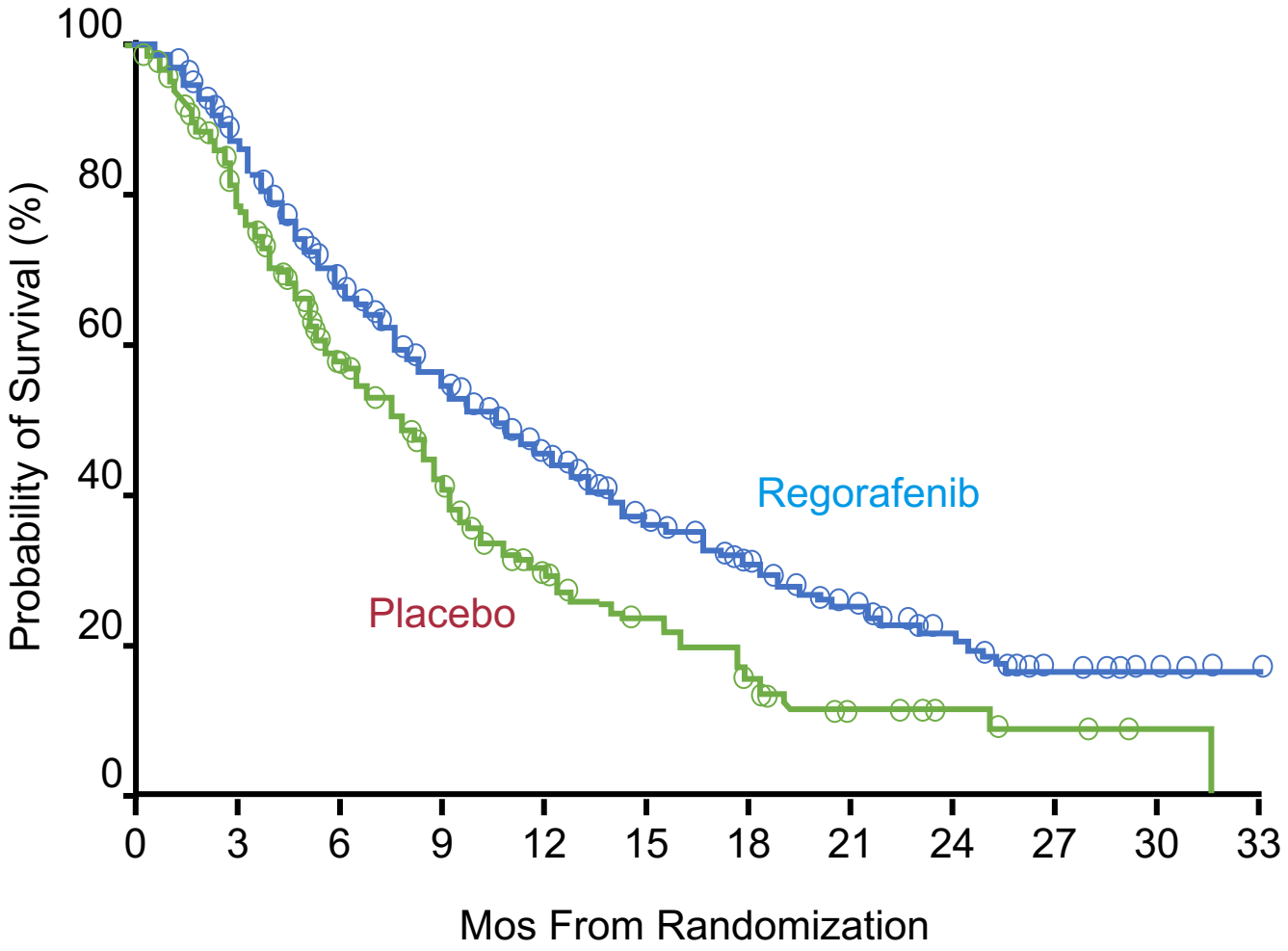


3.78 m vs 4.07 m

	T300 + D	D	Sorafenib
ORR, %	20.1	17.0	5.1
CR, %	3.1	1.5	0.0
PR, %	17	15.4	5.1
DCR, %	60.1	54.8	60.7
mDOR, m	22.34	16.82	18.43
Bleeding	0	0	0
Serious TRAE, %	17.5	8.2	9.4

Abou-Alfa et al, ASCO GI, 2022

RESORCE: regorafenib is active in second line setting after sorafenib



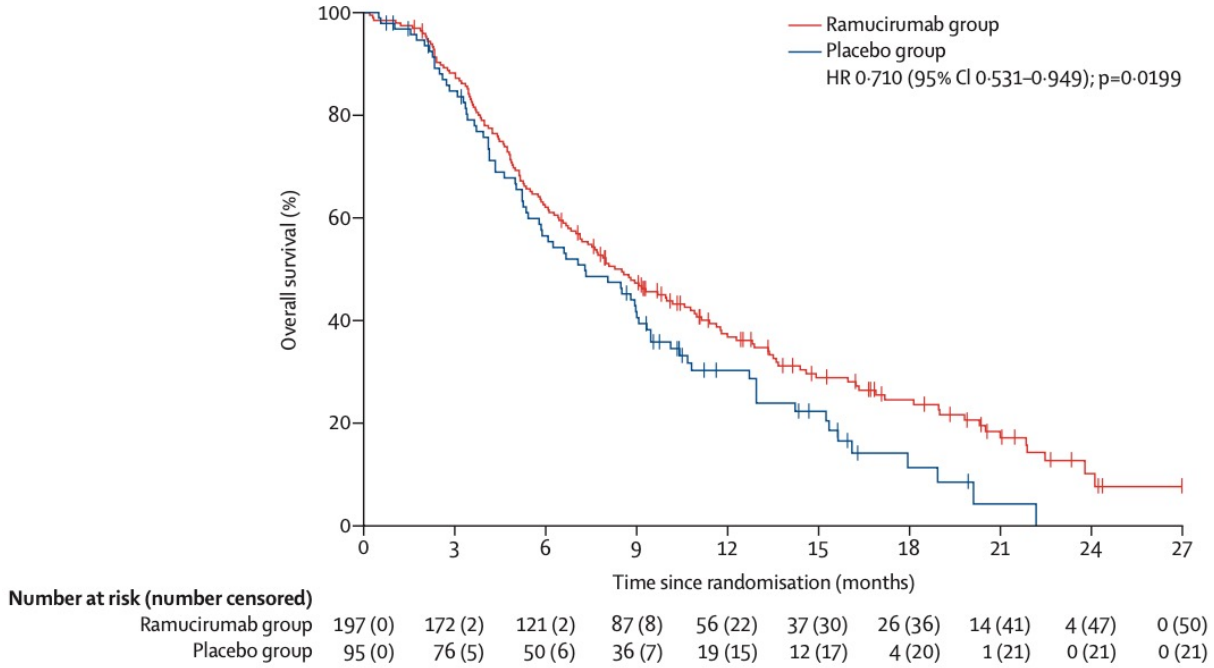
	Regorafenib (n = 379)	Placebo (n = 194)
mOS, mos	10.6	7.8
(HR: 0.63; 95% CI: 0.50-0.79; 1-sided *P* < .0001)		
mPFS, mos	3.1	1.5

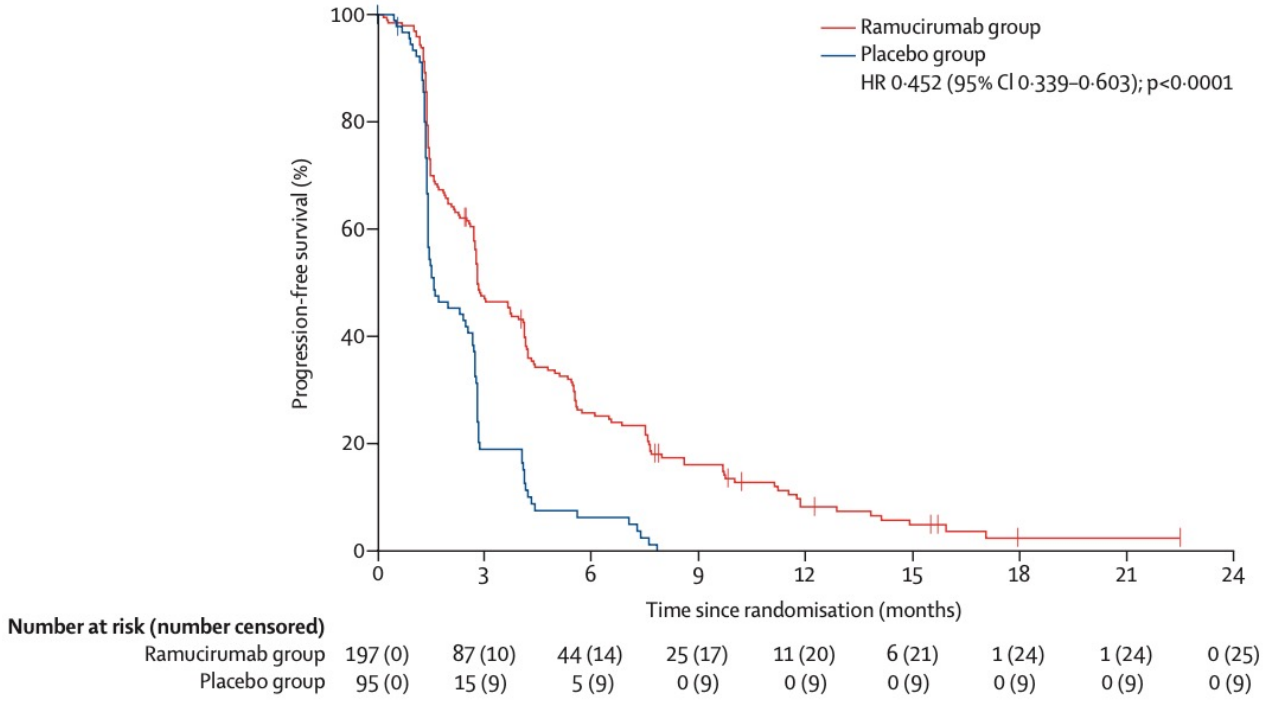
Outcome, %	Modified RECIST	
	Regorafenib (n = 379)	Placebo (n = 194)
ORR	11*	4
DCR	65*	36

*$P < .05$ vs placebo.

Bruix J, et al. Lancet. 2017;389:56-66. Bruix J, et al. ESMO GI 2016. Abstract LBA03.

REACH-2: Ramucirumab vs. placebo effective in advanced HCC after sorafenib and AFP ≥ 400

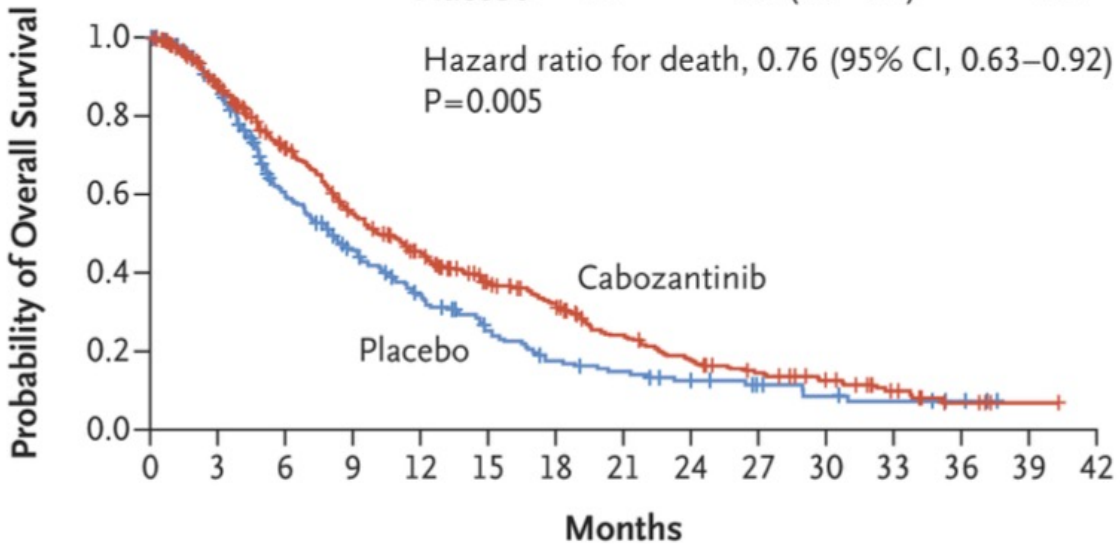




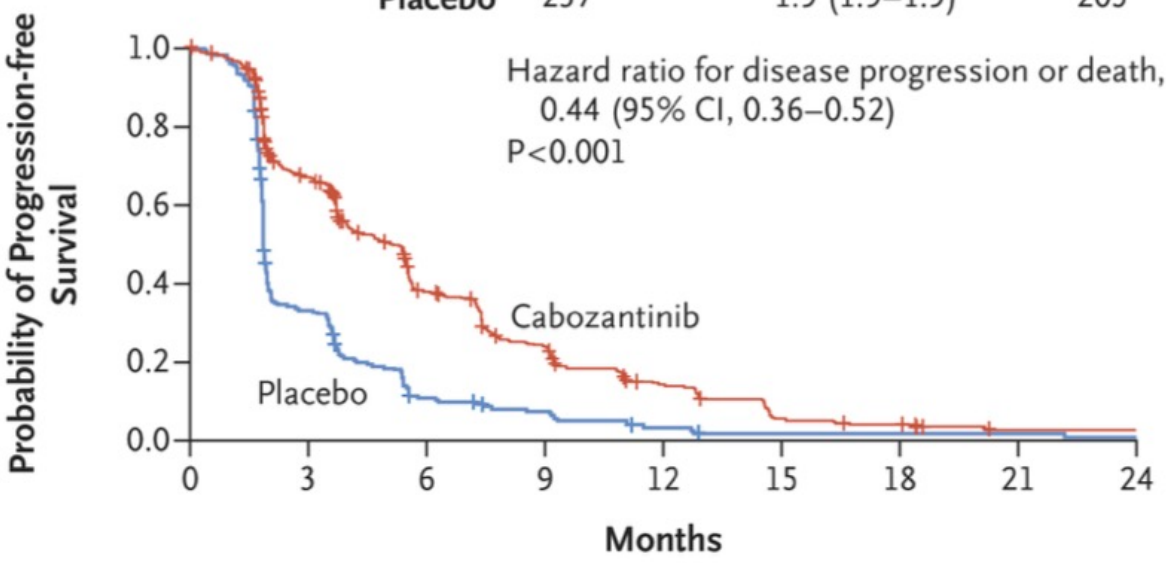
Zhu et al, The Lancet, 2019

CELESTIAL: Cabozantinib improved both overall survival & progression free survival after failure on 1-2 prior treatments

	No. of Patients	Median Overall Survival *mo (95% CI)*	No. of Events
Cabozantinib	470	10.2 (9.1–12.0)	317
Placebo	237	8.0 (6.8–9.4)	167

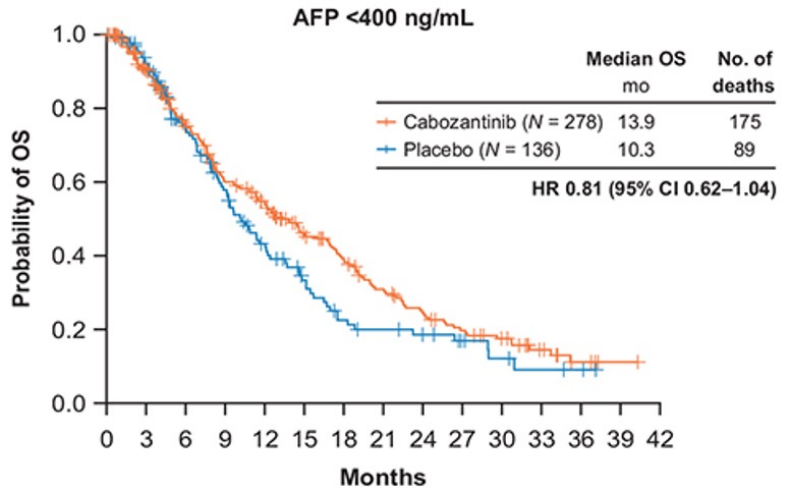


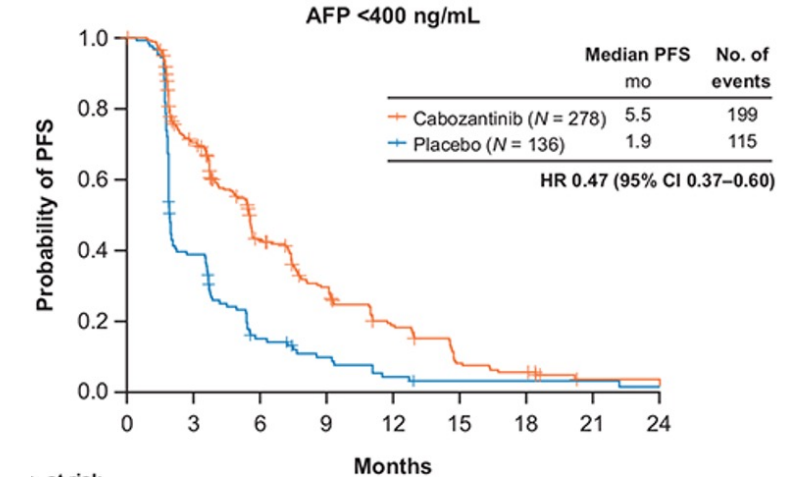
	No. of Patients	Median Progression-free Survival *mo (95% CI)*	No. of Events
Cabozantinib	470	5.2 (4.0–5.5)	349
Placebo	237	1.9 (1.9–1.9)	205

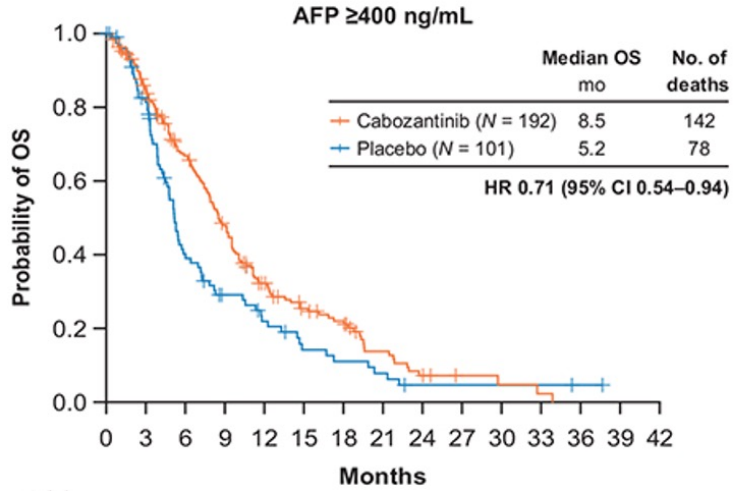


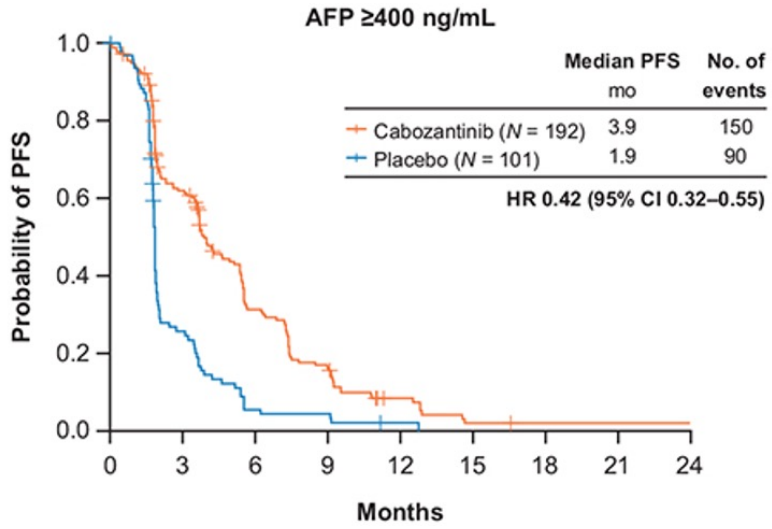
Abou-Alfa GK, et al, NEJM, 379:54-63, 2018

Improved outcomes with cabozantinib in HCC across all serum AFP levels









Kelly et al, Clinical Cancer Research, 2020 Sep 15;26(18):4795-4804.

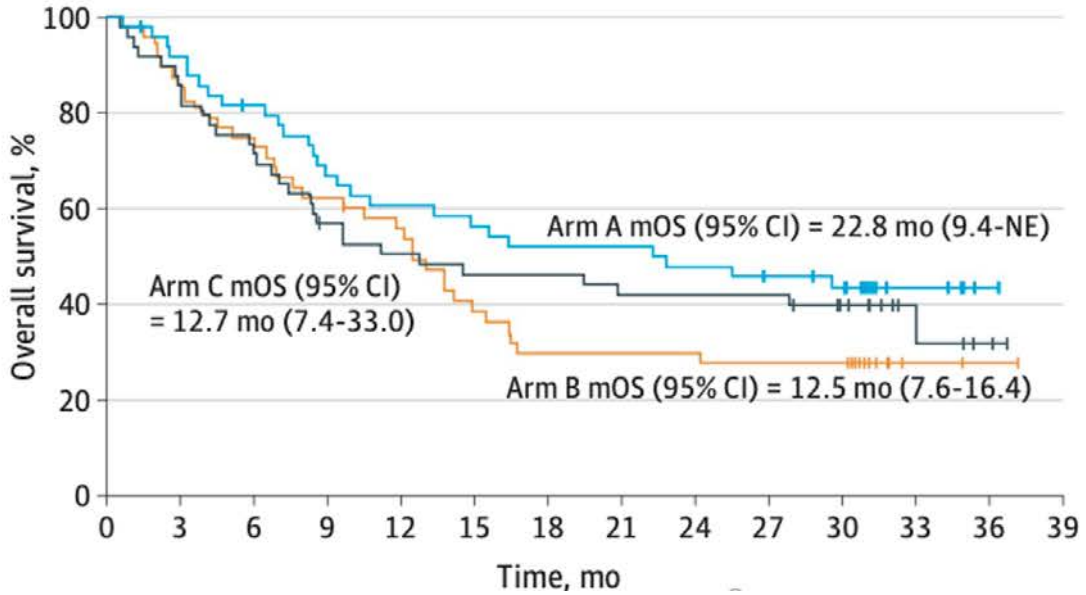
Single immune checkpoint inhibitors: efficacy data in first line or after sorafenib

	Agent	Phase	Line of treatment	ORR of IO agent (%)	Median OS of IO agent (months)
HIMALAYA[1]	Durvalumab	3	First	17	16.6
CheckMate 459[2]	Nivolumab	3	First	15	16.4
CheckMate 040[3]	Nivolumab	I/2	Second	10	7.6
KEYNOTE-224[4]	Pembrolizumab	2	Second	17	12.9
KEYNOTE-240[5]	Pembrolizumab	3	Second	18.3	13.9
KEYNOTE-394[6]	Pembrolizumab	3	Second	12.7	14.6

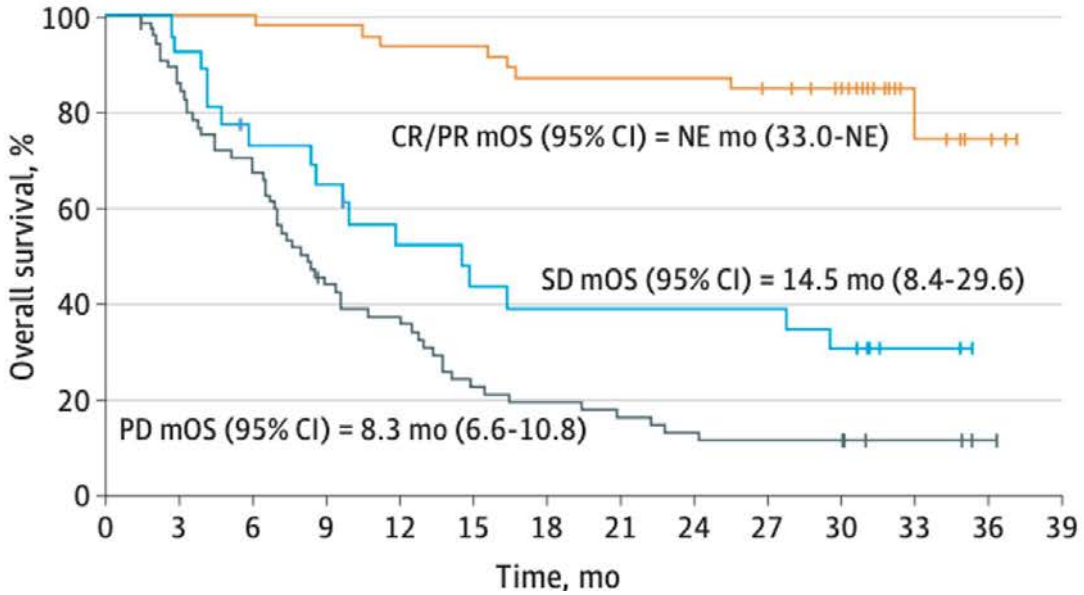
[1]Abu-Alfa et al, ASCO GI, 2022, [2]Yau et al, Lancet Oncology, 2022; [3]El-Khoueiry et al, Lancet 2017; [4]Zhu et al, Lancet Oncol, 2018; [5]Finn et al, JCO, 2019; [6]Qin et al, ASCO GI 2022

CheckMate 040: Nivolumab + Ipilimumab in second-line HCC

All participants



Participants with CR/PR/SD/PD



A - Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks.

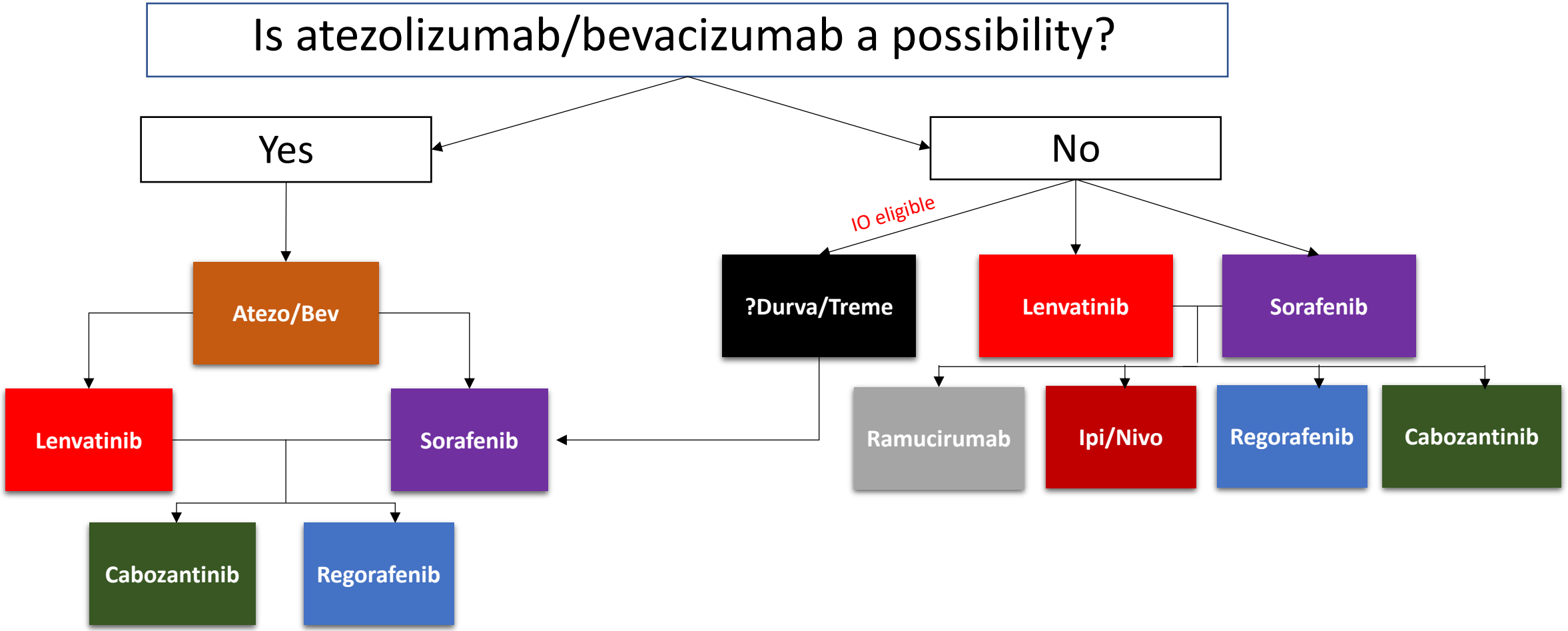
B - Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks.

C - Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks.

CheckMate 9DW: Phase 3 trial of Ipi/Nivo vs. sorafenib or lenvatinib in first line is currently accruing (NCT04039607)

Yau et al. JAMA Oncol 2020

Sequencing systemic therapy in advanced HCC: BCLC-C and liver artery therapy ineligible patients

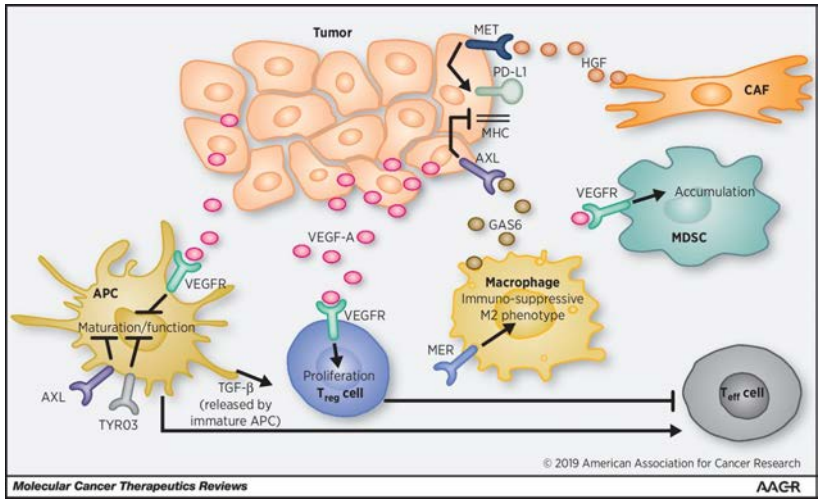


Sequencing and drug selection in HCC based on mechanism: Anti-VEGF/VEGR2 mABs, multitarget TKIs, and immunotherapy

	VEGF/ VEGFR axis	PD-1 PD-L1 CTLA-4	PDGFR/ C-kit	BRAF	RAF	FGFR	RET	MET	AXL FLT3 TRKB	TIE-2
Bevacizumab	✓									
Ramucirumab (AFP driven)	✓									
ICIs		✓								
RTKs: Sorafenib	✓		✓		✓					
RTKs: Regorafenib	✓		✓	✓	✓	✓	✓			✓
RTKs: Cabozantinib	✓						✓	✓	✓	✓
RTKs: Lenvatinib	✓		✓			✓	✓			

Select first-line phase 3 trials of IO + multitargeted TKI: Modifying the microenvironment to enhance IO activity

Immune modification by cabozantinib



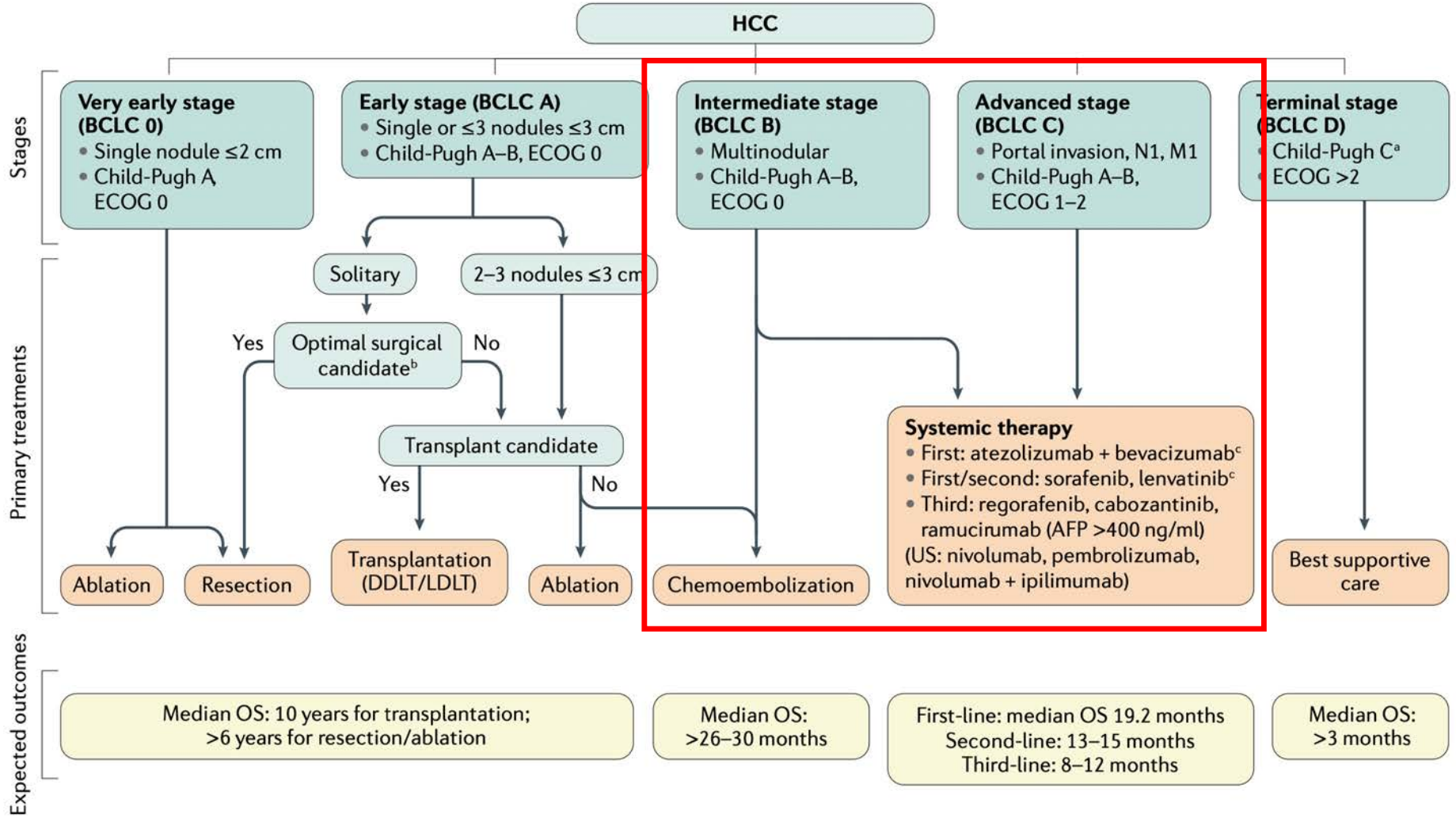
Paulo Bergerot et al. Mol Cancer Ther 2019;18:2185-2193

COSMIC-312 N = 837			
Primary Endpoints	Atezo + cabo	Soraf	HR/p value
PFS, mon	6.8	4.2	0.63/0.0012
OS, mon	15.4	15.5	0.90/0.438

Kelly, et al, ESMO 2021

Study	N	Arms	Primary Endpoint	NCT#
IMbrave251	554	• Atezo + sorafenib or Lenvatinib • Sorafenib or Lenvatinib	OS	04770896
LEAP 002	750	• Lenvatinib + pembro • Lenvatinib + placebo	PFS OS	03713593

Evolving management strategy for HCC



Llovet et al, Nature Reviews, 2021

Phase 3, First-line Trials in intermediate stage HCC (BCLC-B) to determine the roles of systemic and arterial therapy

Trial	N	Arms	Primary Endpoint	NCT
LEAP-012	950	• Lenvatinib/pembro + TACE • TACE	• PFS • OS	04246177
EMERALD-1	710	• Durva +TACE • Durva/bev + TACE • TACE	• PFS	03778957
EMERALD-3	525	• Durva/Treme +TACE • Durva/Treme/Lenvatinib + TACE	• PFS	05301842
CheckMate 74W	765	• Nivo/Ipi +TACE • Nivo + TACE • TACE	• Time to TACE progression • OS	04340193
ABC-HCC	434	• Atezo/bev • TACE	• Time to failure of treatment	04803994
RENOTACE	496	• Rego/nivo • TACE	• PFS	04777851
TACE-3	522	• DEB TACE + nivolumab • TACE	• OS	04268888

Adjuvant phase 3 trials in high-risk HCC following resection or ablation

Study	N	Study Arms	Primary Endpoint	NCT#
EMERALD-2	877	• Durvalumab/bevacizumab • Durvalumab • Placebo	Recurrence-free survival	03847428
CheckMate 9DX	545	• Nivolumab • Placebo	Recurrence-free survival	03383458
Keynote-937	950	• Pembrolizumab • Placebo	• Recurrence-free survival • Overall survival	03867084
IMbrave 050	668	• Atezolizumab/bevacizumab • Active surveillance	Recurrence-free survival	04102098

SUMMARY

- Atezolizumab plus bevacizumab is preferred frontline regimen in eligible HCC patients based on efficacy, safety, and quality of life
- Sequential use of multitarget tyrosine kinase inhibitors after or without frontline atezolizumab and bevacizumab
- IO plus TKI is still experimental
- Ramucirumab is an option beyond first-line in select patients with AFP $\geq$ 400
- Single agent immune checkpoint inhibitor has a limited role
- Role of immunotherapy in earlier stages of HCC (adjuvant and BCLC-B) is being investigated
- *Unmet needs in HCC*: biomarkers, Child Pugh B, adjuvant/neoadjuvant, and treatment optimization in BCLC-B

MODULE 5: Novel Treatment Strategies for Advanced Biliary Tract Cancers — Dr Bekaii-Saab

RTP
RESEARCH
TO PRACTICE

71-year-old man with cholangiocarcinoma and PIK3CA, FGFR1 and ROS1 mutations – TMB 10 mut/Mb, MSS

Dr Zanetta Lamar (Naples, Florida)

RTP RESEARCH TO PRACTICE

Dr Shaachi Gupta
Lake Worth, Florida

52-year-old man with hilar cholangiocarcinoma and an IDH1 mutation

Dr Philip Brooks
Brewer, Maine

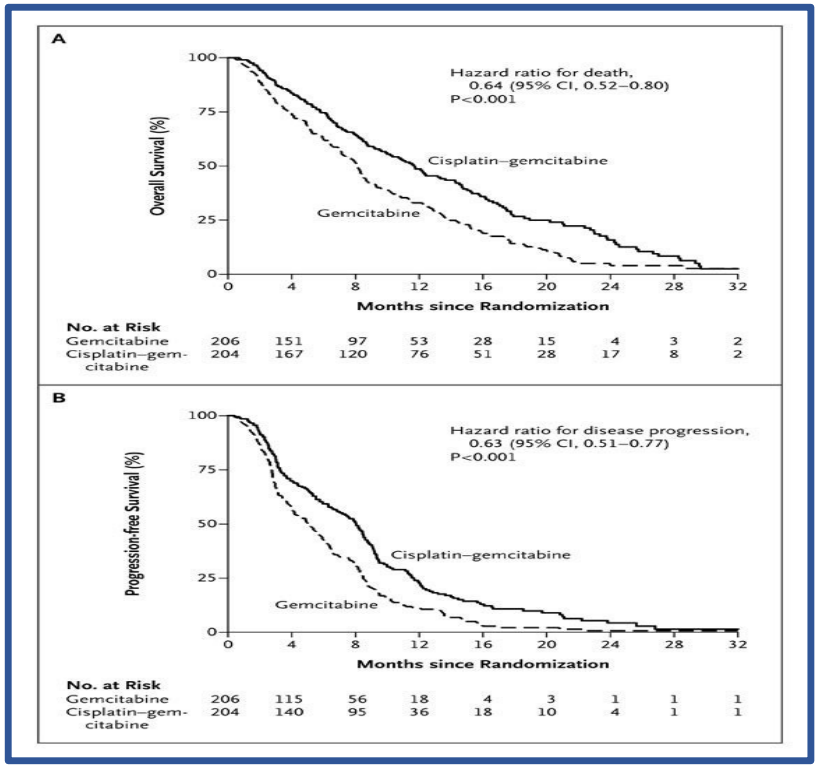
77-year-old man with metastatic cholangiocarcinoma and IDH1 and BRAF mutations – PD-L1 CPS 10

RTP
RESEARCH
TO PRACTICE

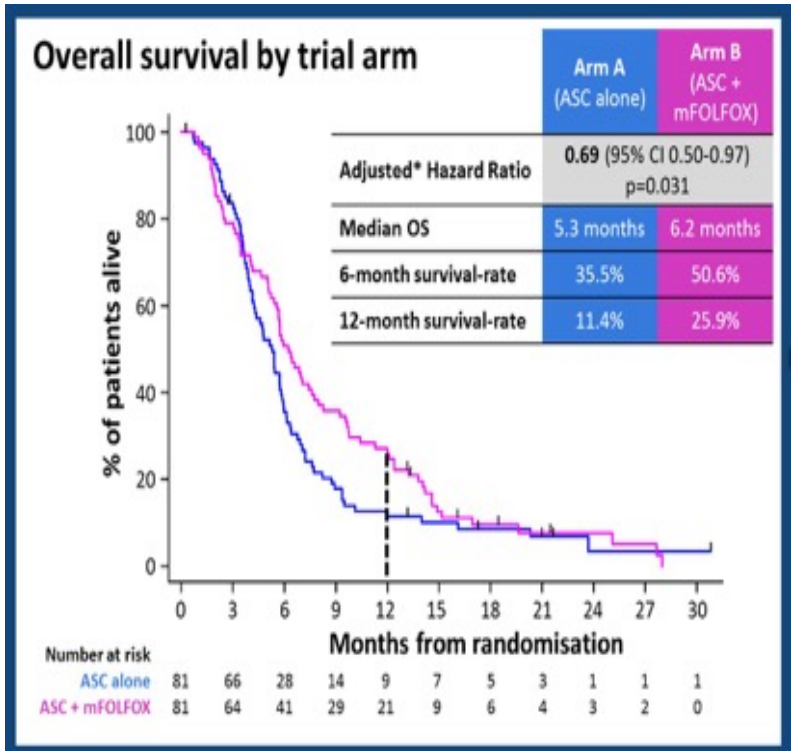
Novel Treatment Strategies for Advanced Biliary Tract Cancers

Tanios Bekaii-Saab, MD ,FACP
Program Leader, GI Cancer, Mayo Clinic Cancer Center
Professor , Mayo Clinic College of Medicine and Science
Consultant, Mayo Clinic AZ
Chair , ACCRU Consortium

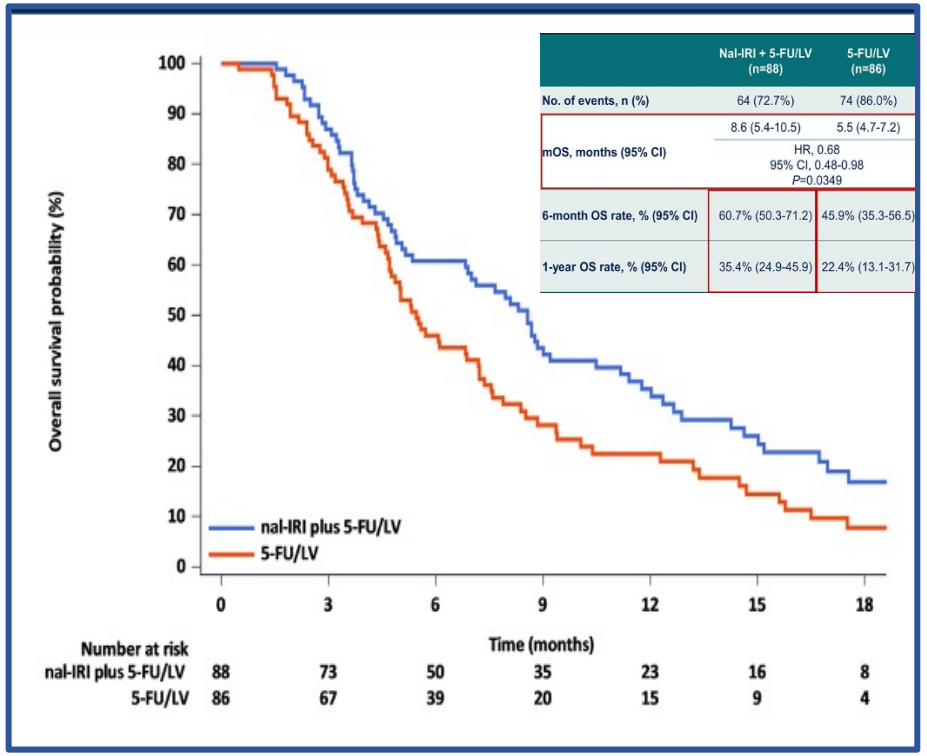
Chemotherapy is Marginally Effective in Unselected CCA



Valle J et al. N Engl J Med 2010;362:1273-1281.

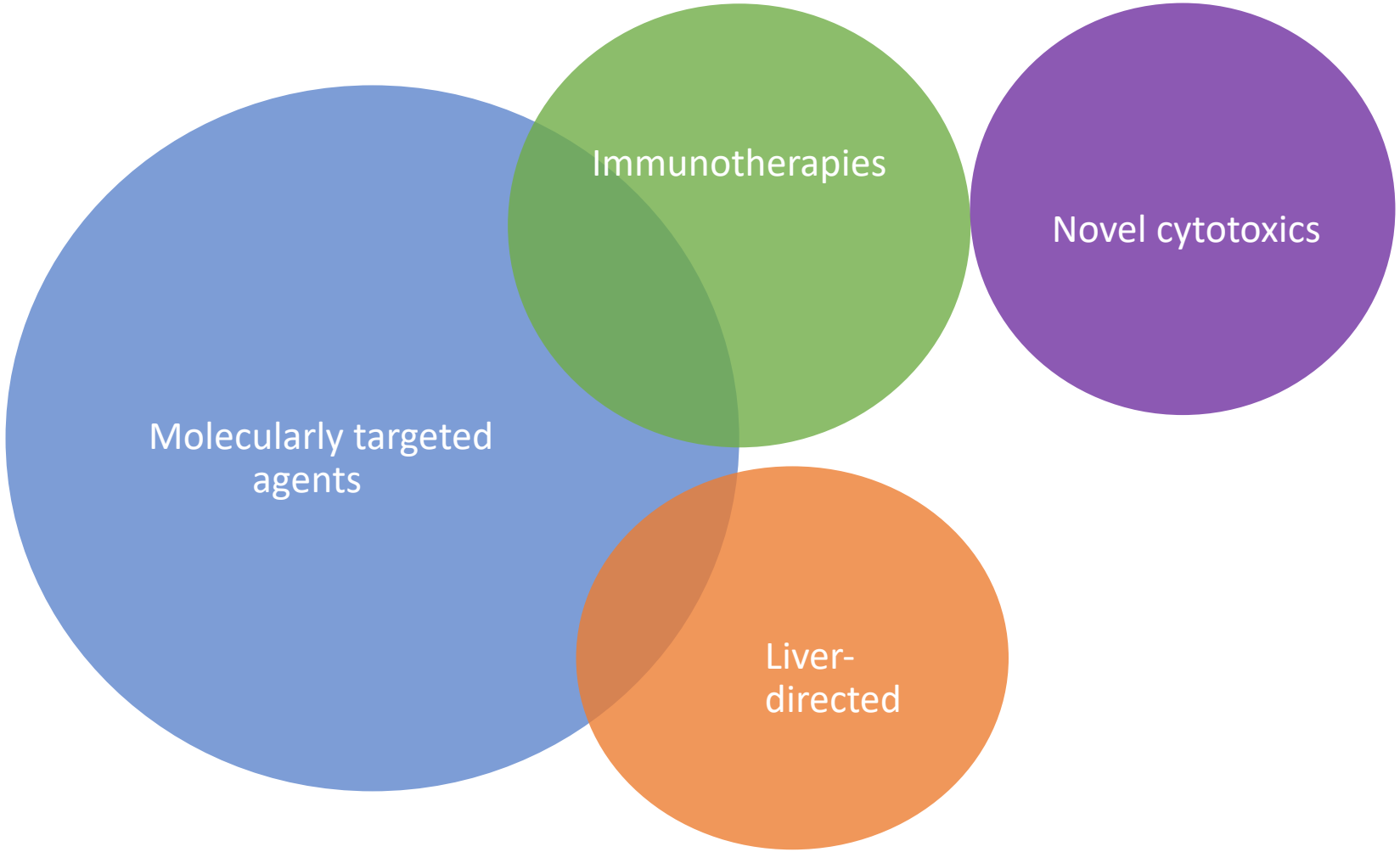


Lamarca A et al . ASCO 2019



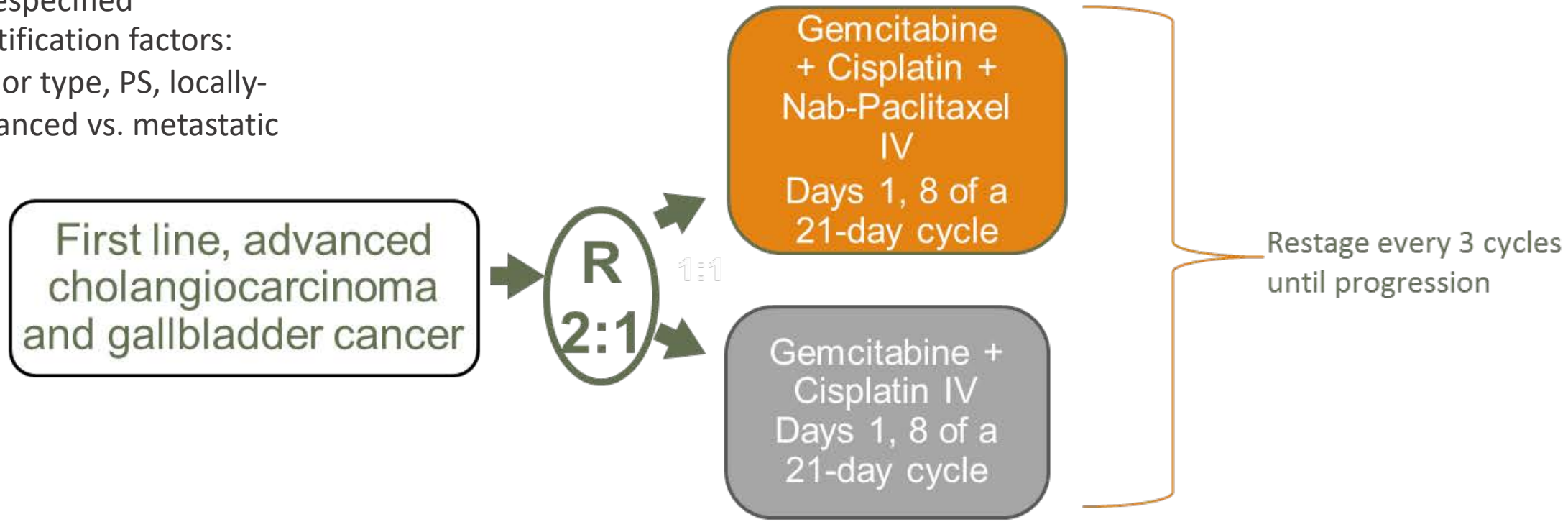
Yoo C et al . ASCO 2021

Classes of novel therapeutics under investigation for BTC



S1815: study design

*Prespecified stratification factors: tumor type, PS, locally-advanced vs. metastatic



Primary EP: OS
Secondary: ORR, PFS, DCR, safety, CA 19-9 changes

Archival blood and tissue specimens to be banked

NIH 2020. NCT03768414. https://clinicaltrials.gov/ct2/show/NCT03768414. Accessed 7 January 2021

Summary of efficacy results from immunotherapy studies in BTC

Study	Agent(s)	Line of therapy	Patients (n)	ORR	DCR	PFS	OS
KEYNOTE-158[1]	**Pembrolizumab**	**≥2L**	**104 (BTC cohort)**	**6% (95% CI, 2.1–12.1)**	**22%**	**2.0 months (95% CI, 1.9–2.1)**	**9.1 months (95% CI, 5.6–10.4)**
Kim R, et al[2]	Nivolumab	≥2L	54 (46 evaluable for response)	IR: 22% ICR: 11%	IR: 59% ICR: 50%	ITT: 3.7 months (95% CI, 2.3–5.7)	ITT: 14.2 months (95% CI, 6.0–NR)
Kelley RK, et al[3]	**Pembrolizumab + GM-CSF**	**≥2L**	**27**	**19% (95% CI, 3–34)**	**33%**	**6-month PFS: 35% (95% CI, 15–54)**	**NR**
Klein O, et al[4]	Nivolumab + ipilimumab	≥1L	39	23%	44%	2.9 months (95% CI, 2.2–4.6)	5.7 months (95% CI, 2.7–11.9)
Ueno M, et al[5]	**Nivolumab**	**≥2L**	**30**	**3% (90% CI, 0.7–13.6)**	**23% (90% CI, 13.2–37.9)**	**1.4 months (90% CI, 1.4–1.4)**	**5.2 months (90% CI, 4.5–8.7)**
	Nivolumab + GemCis	**1L**	**30**	**37% (90% CI, 23.9–51.7)**	**63% (90% CI, 48.3–76.1)**	**4.2 months (90% CI, 2.8–5.6)**	**15.4 months (90% CI, 11.8–NE)**
Ioka T, et al[6]	Durvalumab	≥2L	42	5% (95% CI, 0.6–16.2)	17%	1.5 months (95% CI, 1.4–2.6)	8.1 months (95% CI, 5.6–10.1)
	Tremelimumab + durvalumab		65	11% (95% CI, 4.4–20.9)	32%	1.6 months (95% CI, 1.4–2.8)	10.1 months (95% CI, 6.2–11.4)

1. Ueno M et al. Presented at: ESMO Congress 2018; 19–23 October 2018; Munich, Germany. Abs 4525; 2. Kim R et al. *JAMA Oncol* 2020;6:888–894; 3. Kelley RK, et al. Presented at: ASCO Annual Meeting 2018; 1–5 June 2018; Chicago, IL. Abs 4087; 4. Klein O, et al. Poster presented at: ASCO Annual Meeting 2020; 29–31 May, 2020. Pos 196; 5. Ueno M, et al. *Lancet Gastroenterol Hepatol* 2019;4:611–621; 6. Ioka T, et al. Poster presented at: ASCO GI; 17–19 January 2019; San Francisco, CA. Poster 387

ICR, independent central review; IR, investigator review; ITT, intent-to-treat; NE, not estimable; NR, not reached

TOPAZ-1 study design

TOPAZ-1 is a double-blind, multicenter, global, Phase 3 study

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)

R (1:1) N=685

Durvalumab 1500 mg Q3W + GemCis (up to 8 cycles) → **Durvalumab 1500 mg Q4W until PD**

Placebo Q3W + GemCis (up to 8 cycles) → **Placebo Q4W until PD**

Primary objective
- Overall survival

Secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC; intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

PRESENTED BY: Do-Youn Oh, MD, PhD

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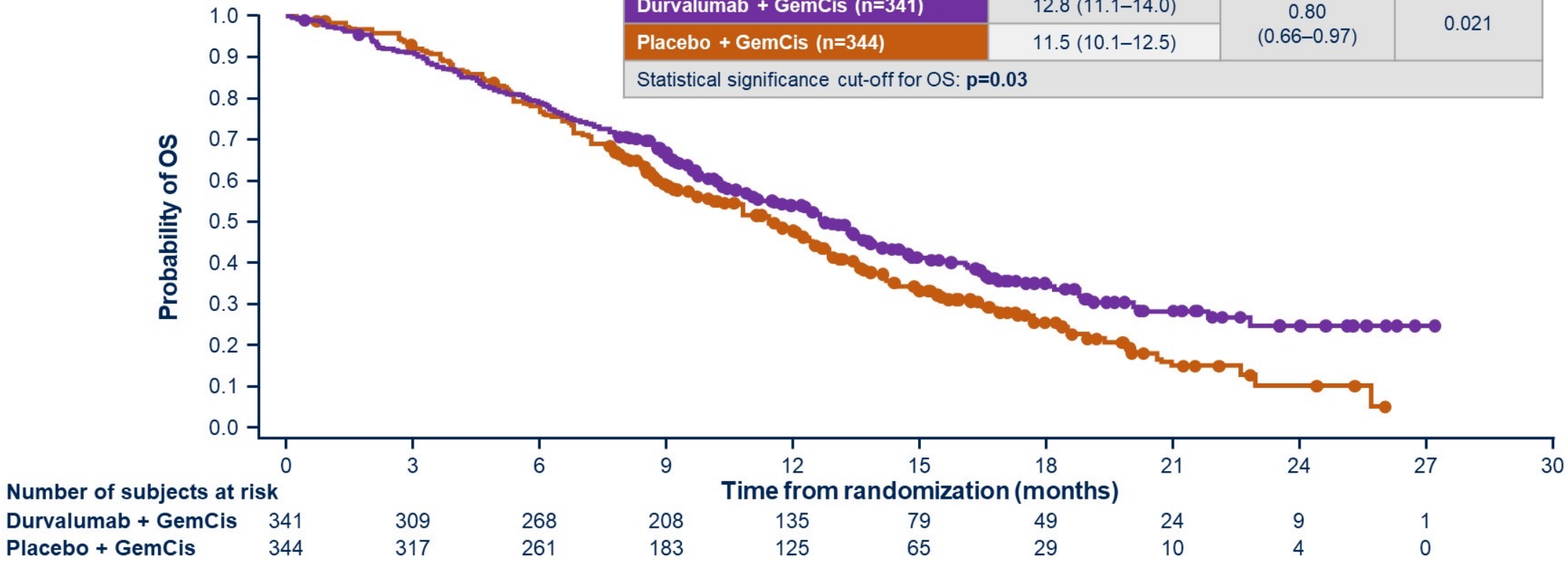
Primary endpoint: OS

	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			



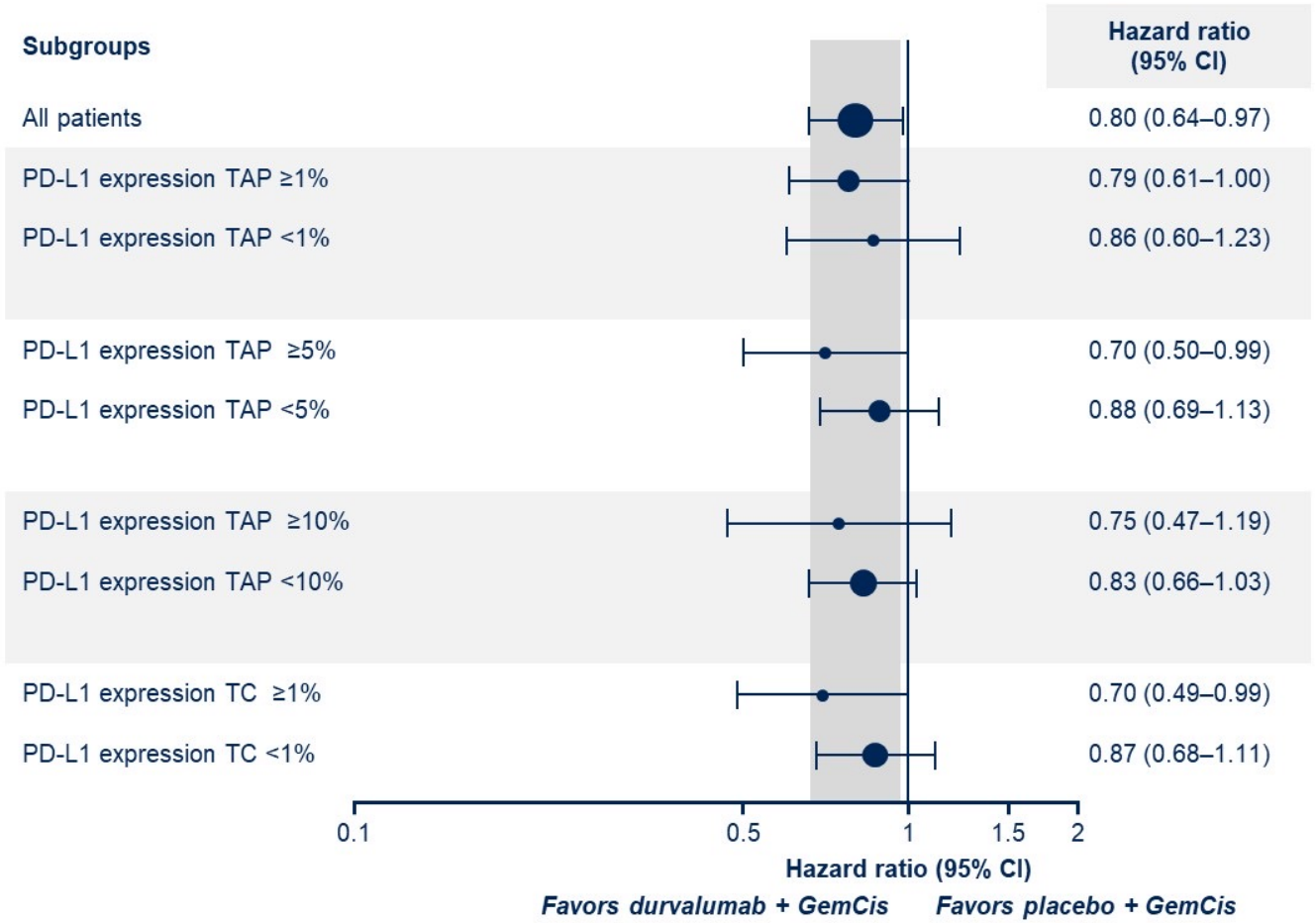
Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.

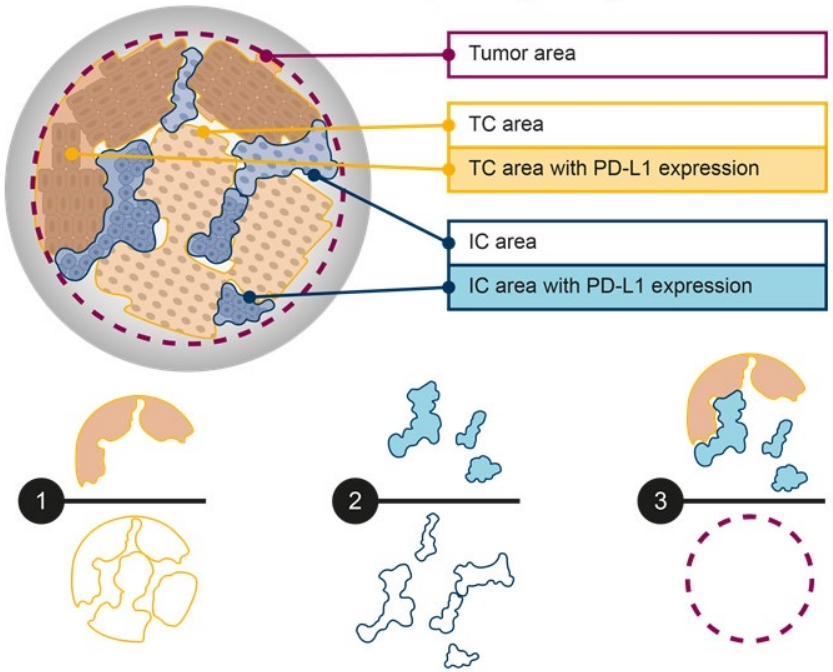
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, month; OS, overall survival.

PRESENTED BY: Do-Youn Oh, MD, PhD

OS in subgroups by PD-L1 expression



Tumor Area Positivity (TAP) score using the Ventana PD-L1 (SP263) Assay



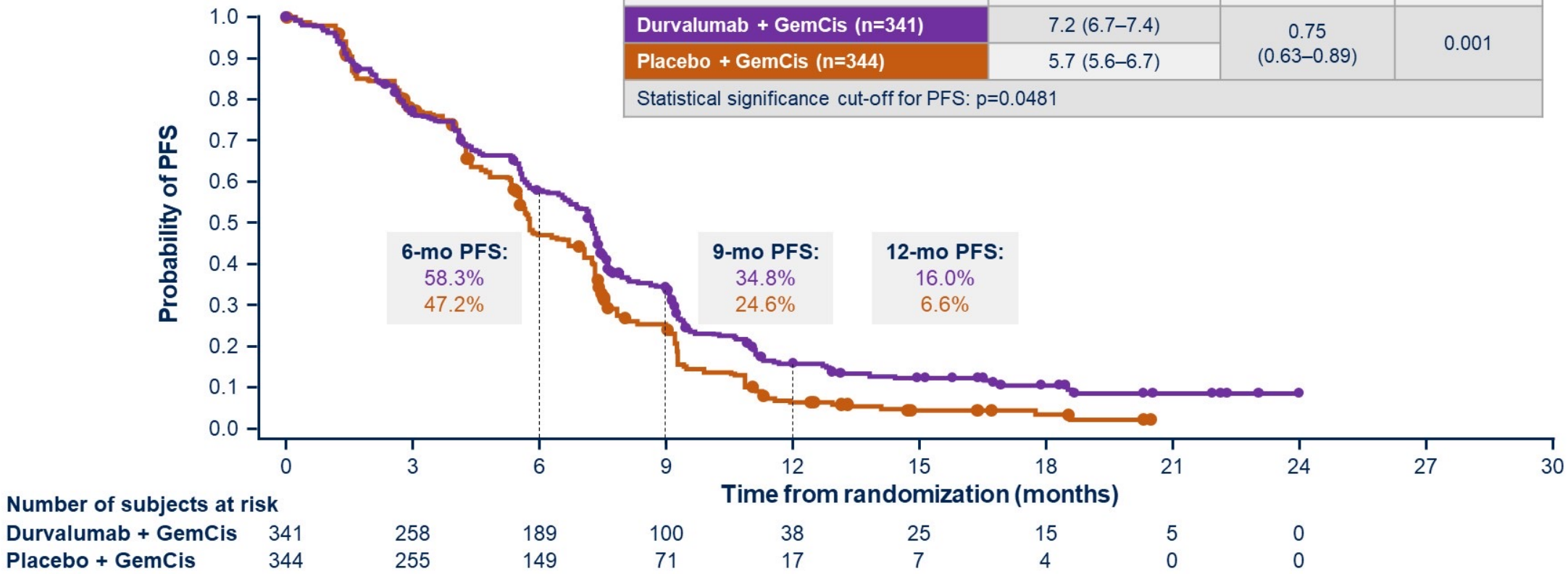
1. TC: proportion of TCs with PD-L1 membrane staining at any intensity
2. IC: proportion of tumor-associated ICs with PD-L1 cytoplasmic/membrane staining at any intensity
3. **Combined TCs and ICs:** Proportion of tumour area occupied by TCs with membrane and ICs with cytoplasmic/membrane PD-L1 staining at any intensity (TAP score)

CI, confidence interval; IC, immune cell; OS, overall survival; PD-L1, programmed cell death ligand-1; TC, tumor cell; TAP, tumor area positivity

PRESENTED BY: Do-Youn Oh, MD, PhD

Secondary endpoint: PFS

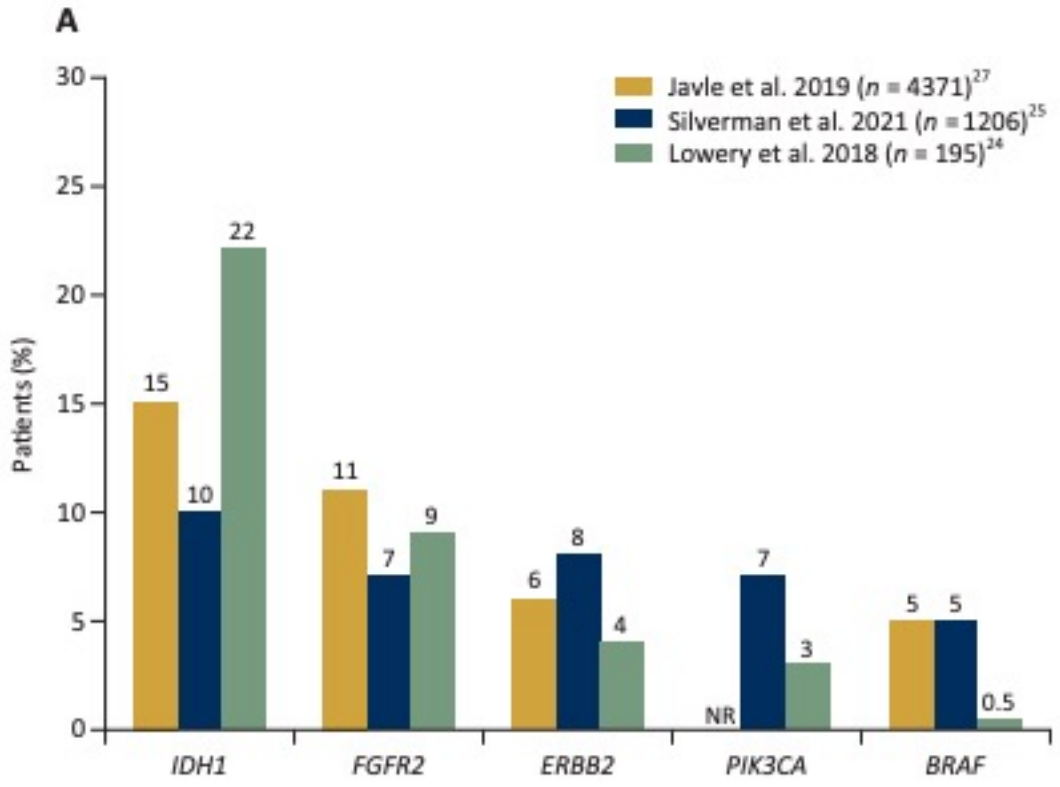
	Median PFS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	7.2 (6.7–7.4)	0.75 (0.63–0.89)	0.001
Placebo + GemCis (n=344)	5.7 (5.6–6.7)		
Statistical significance cut-off for PFS: p=0.0481			



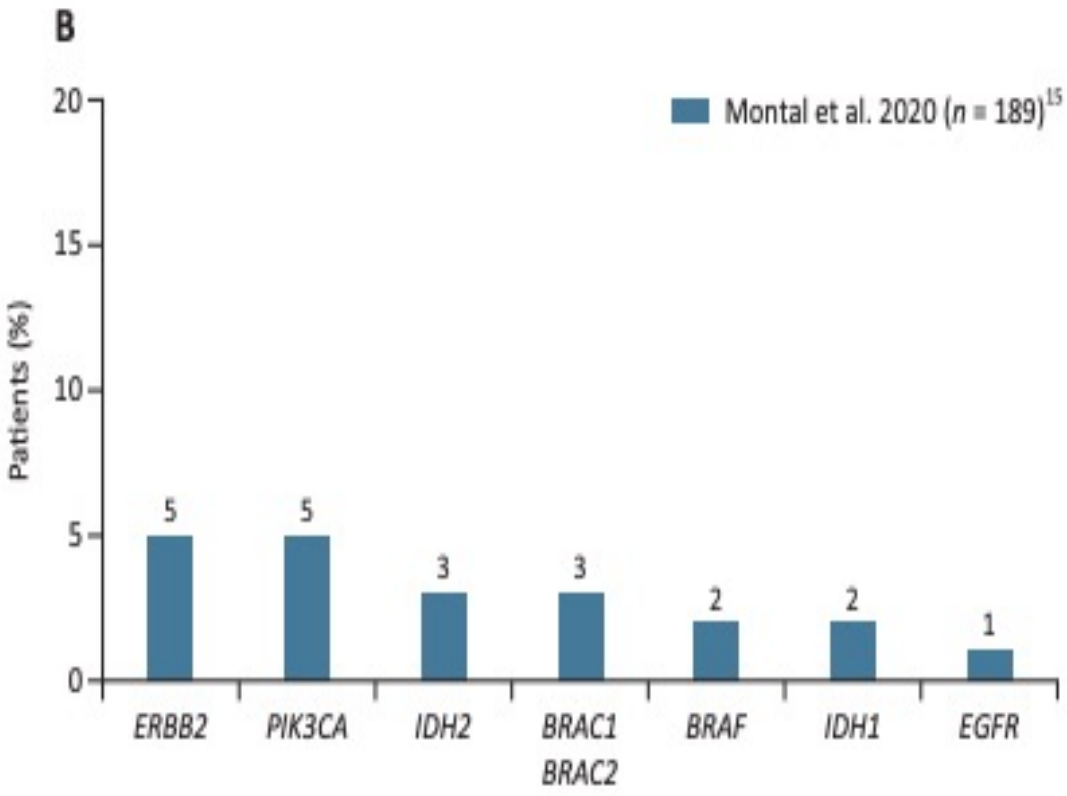
Median duration of follow-up (95% CI) was 9.2 (0.0–24.0) months with durvalumab + GemCis and 6.9 (0.0–20.4) months with placebo + GemCis.
CI, confidence interval; GemCis, gemcitabine and cisplatin; PFS, progression-free survival.

PRESENTED BY: Do-Youn Oh, MD, PhD

Commonly altered genes with actionable alterations in cholangiocarcinoma (CCA)



Intrahepatic CCA (iCCA)



Extrahepatic CCA (eCCA)

Bekaii-Saab T , et al. *Annals of Oncology* ; 2021

Molecular heterogeneity: Western vs Asian CCA patients

Modulator genes of dysregulation pathways or gene subgroups with statistically significant levels between the two patient cohorts

Cao J, et al. *JCO Precis Oncol* 2020;4:557–569

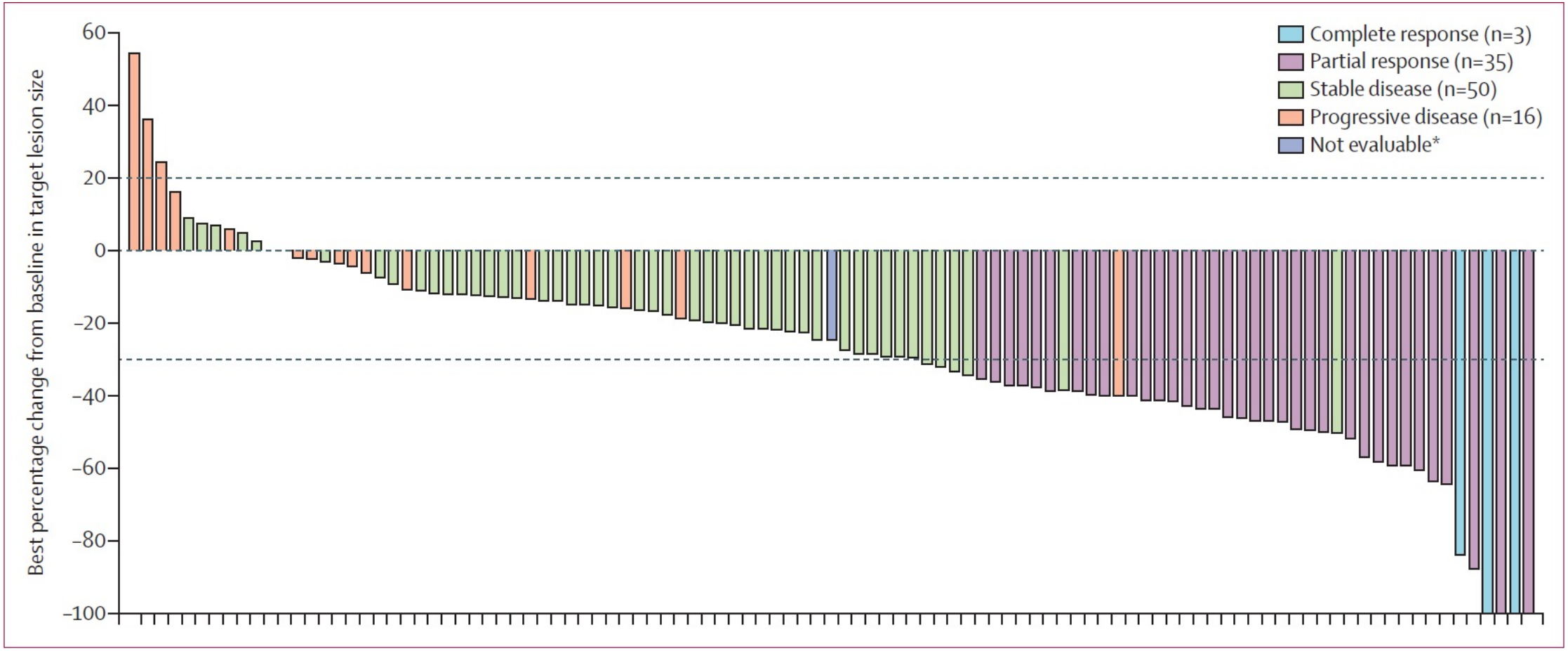
FGFR Inhibitor Efficacy in *FGFR2* Fusion CCA

	Pemigatinib* (N=107)	Infigratinib* (N=108)	Futibatinib (N=67)	Derazantinib (N=29)
ORR	35.5%	23.1%	37.3%	20.7%
DCR	82.2%	84.3%	82.1%	82.8%
mPFS	6.9 mos	7.3 mos	7.2 mos	5.7 mos
mOS	21.1 mos	12.2 mos	NR	NR
Toxicities	Hyperphosphatemia, Alopecia, Diarrhea	Hyperphosphatemia, Stomatitis, Fatigue	Hyperphosphatemia, Diarrhea, Dry mouth	Hyperphosphatemia, Fatigue, Ocular

*FDA Approved

1. Abou-Alfa GK et al. *Lancet Oncol*. 2020;21(5):671-684; 2. Javle M et al. ASCO GI 2021; 3. Goyal L et al. ASCO 2020; 4. Mazzaferro V et al. *Br J Cancer*. 2019;120(2):165-171.

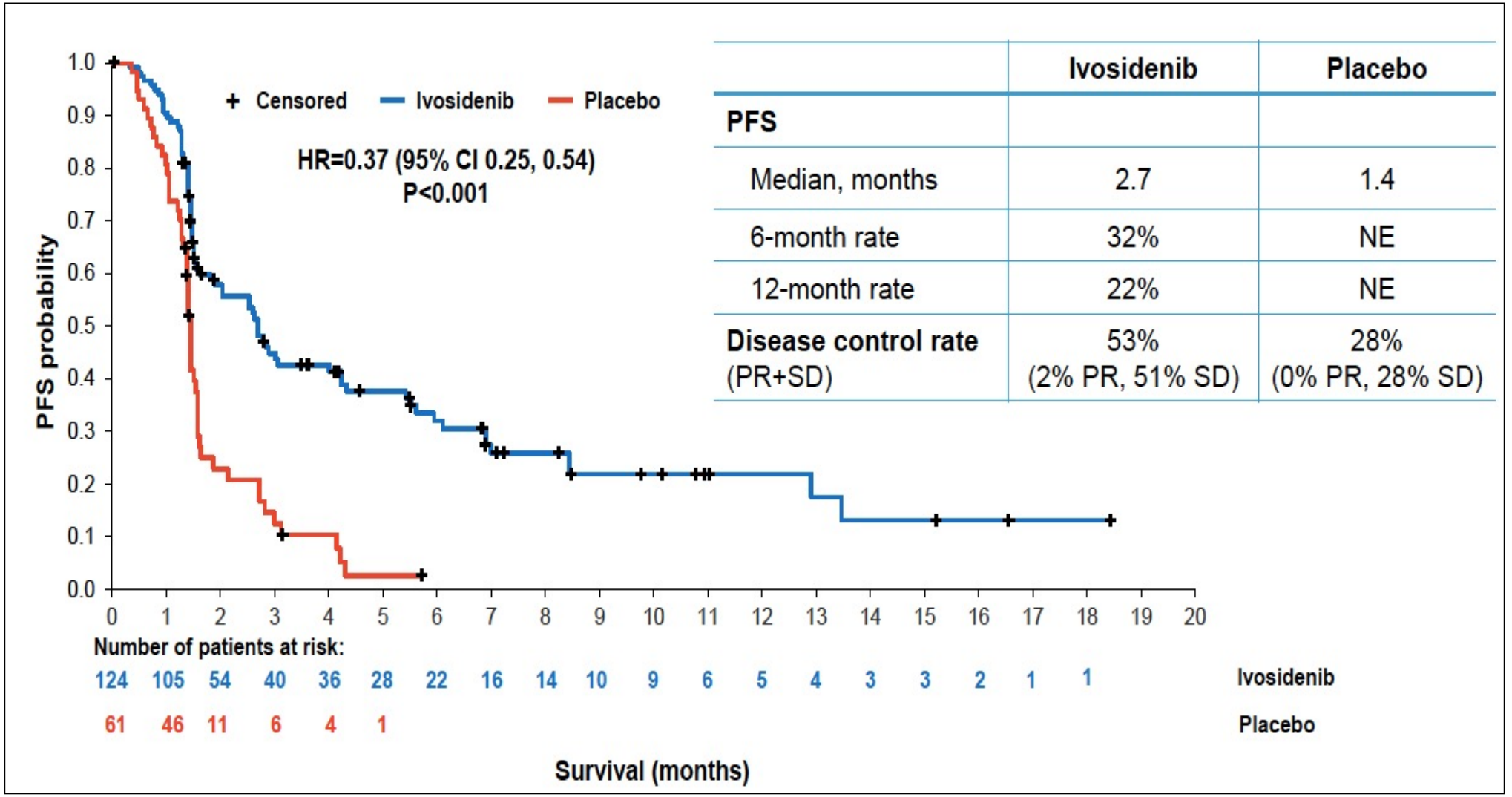
FIGHT 202: Pemigatinib in Patients With iCCA Harboring *FGFR2* Fusions or Rearrangements



Colored 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.

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

ClarIDHy: Targeting IDH-1 in BTC: Ivosidenib vs. Placebo



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

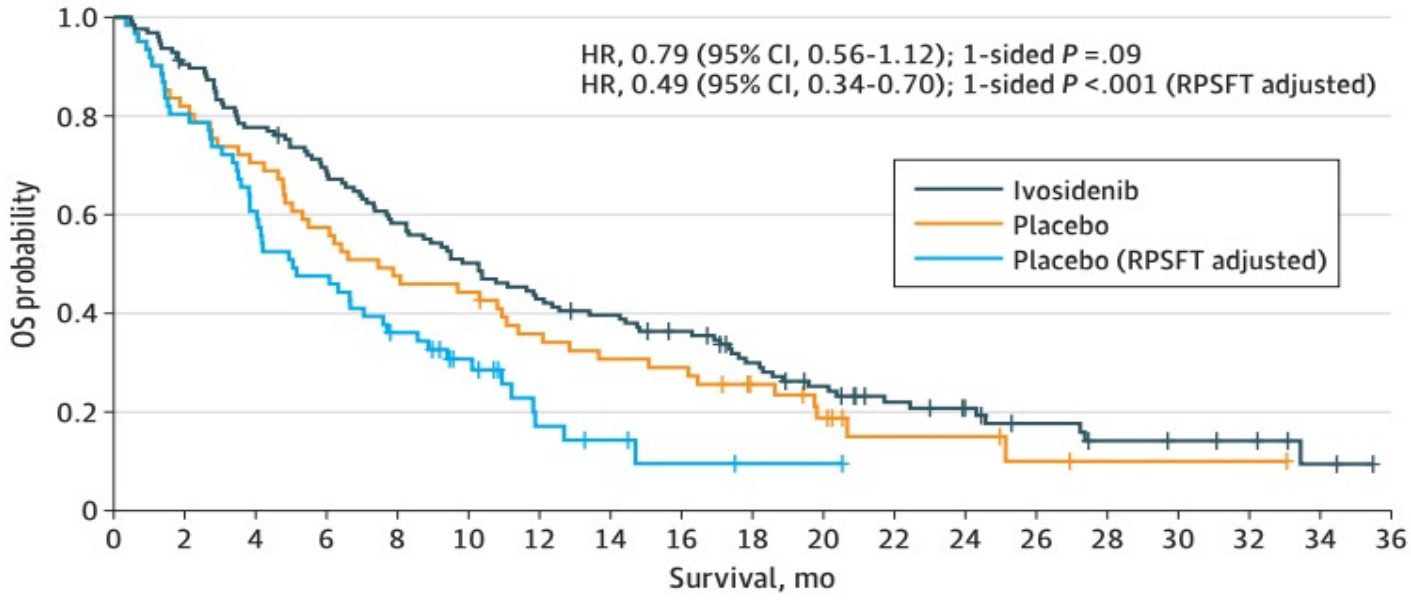
Abou-Alfa G et al. ESMO 2019;Abstract LBA10_PR.

JAMA Network™

From: **Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial**

JAMA Oncol. 2021;7(11):1669-1677. doi:10.1001/jamaoncol.2021.3836

A Overall survival

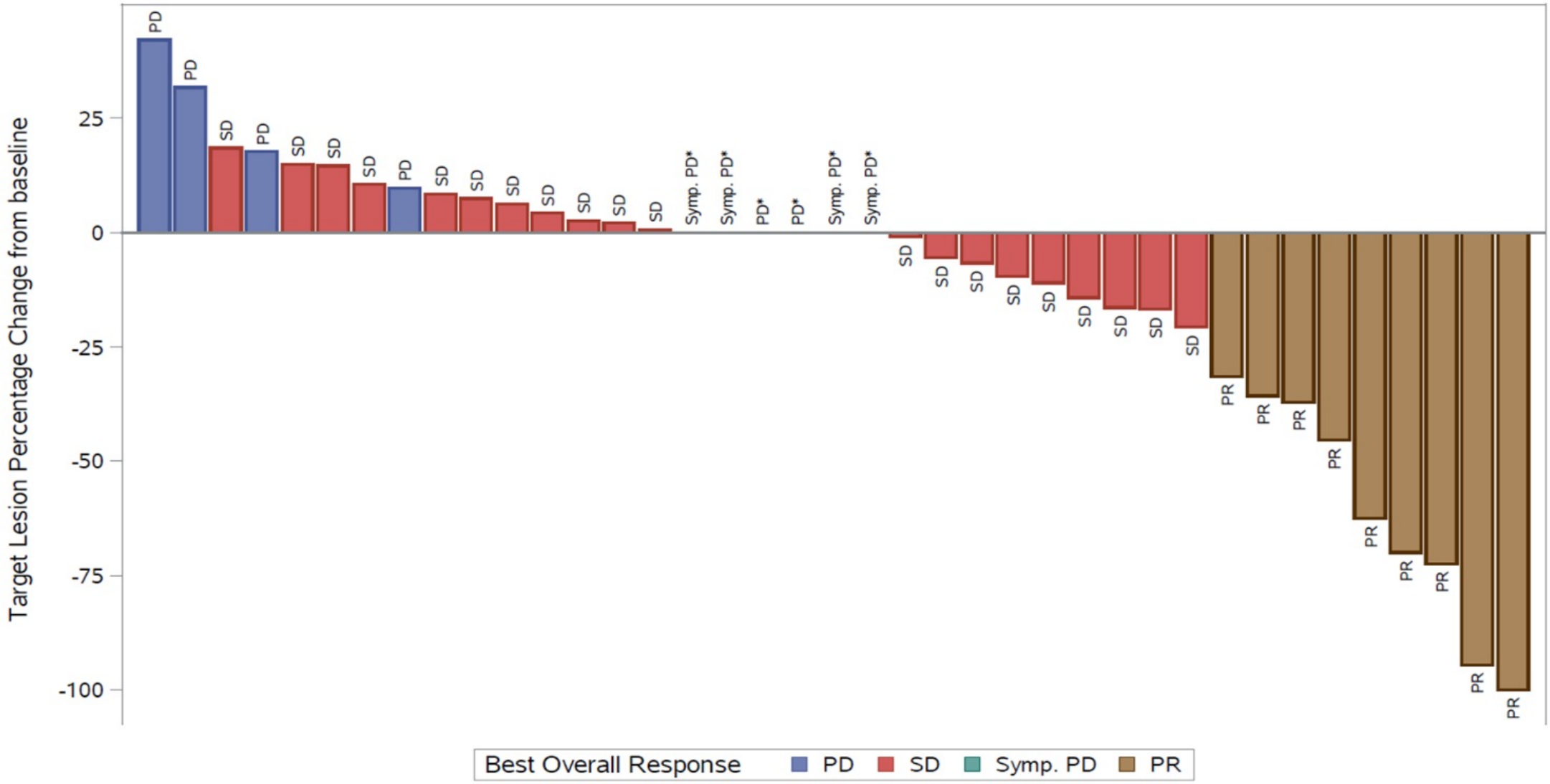


No. at risk

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

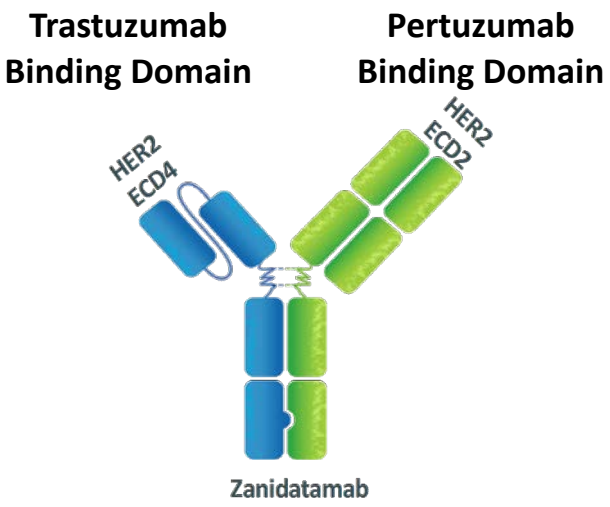
Treatment group	Events/patients, No.	OS, median (95% CI), mo
Ivosidenib	100/126	10.3 (7.8-12.4)
Placebo	50/61	7.5 (4.8-11.1)
Placebo adjusted by RPSFT	49/61	5.1 (3.8-7.6)

Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway)



Javle M, et al. *Lancet Oncol* 2021

Zanidatamab, a Bispecific HER2-Targeted Antibody for HER2-expressing BTC



Phase I Study: BTC Patients

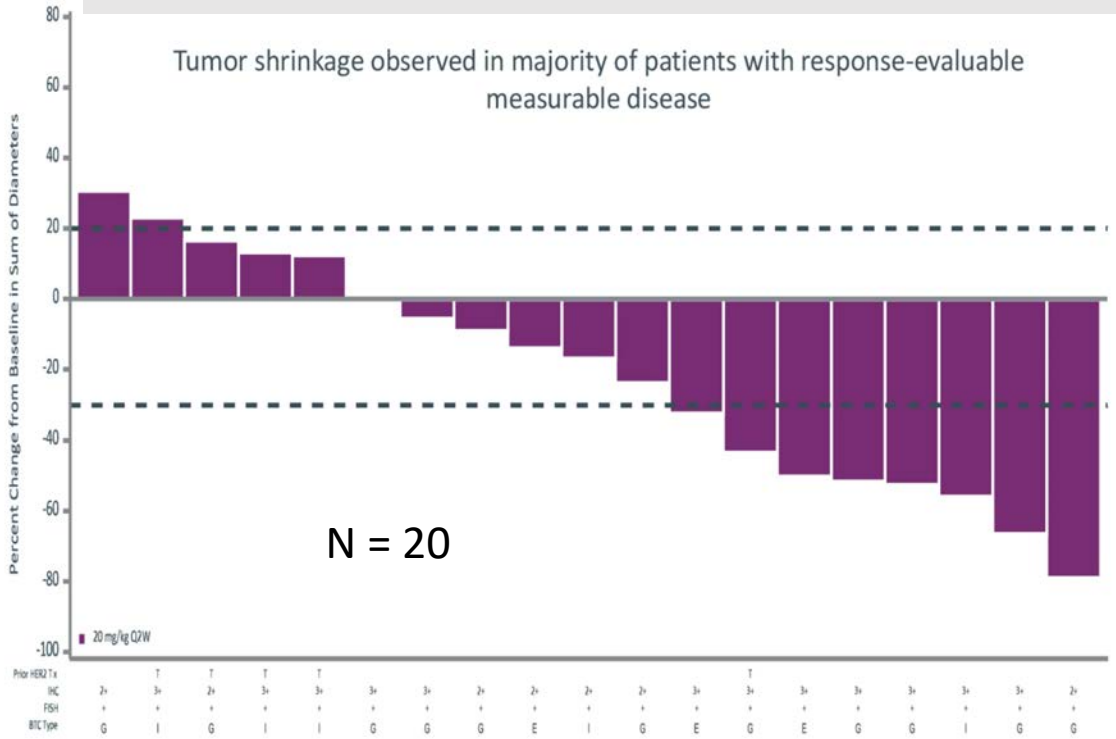


Table 3: Disease Response Endpoints[a] and DOR

	(N = 20)
Confirmed objective response, n (%) (95% CI)	8 (40) (19.1, 63.9)
Partial response	8 (40)
Stable disease	5 (25)
Progressive disease	7 (35)
Disease control rate, n (%)	13 (65)

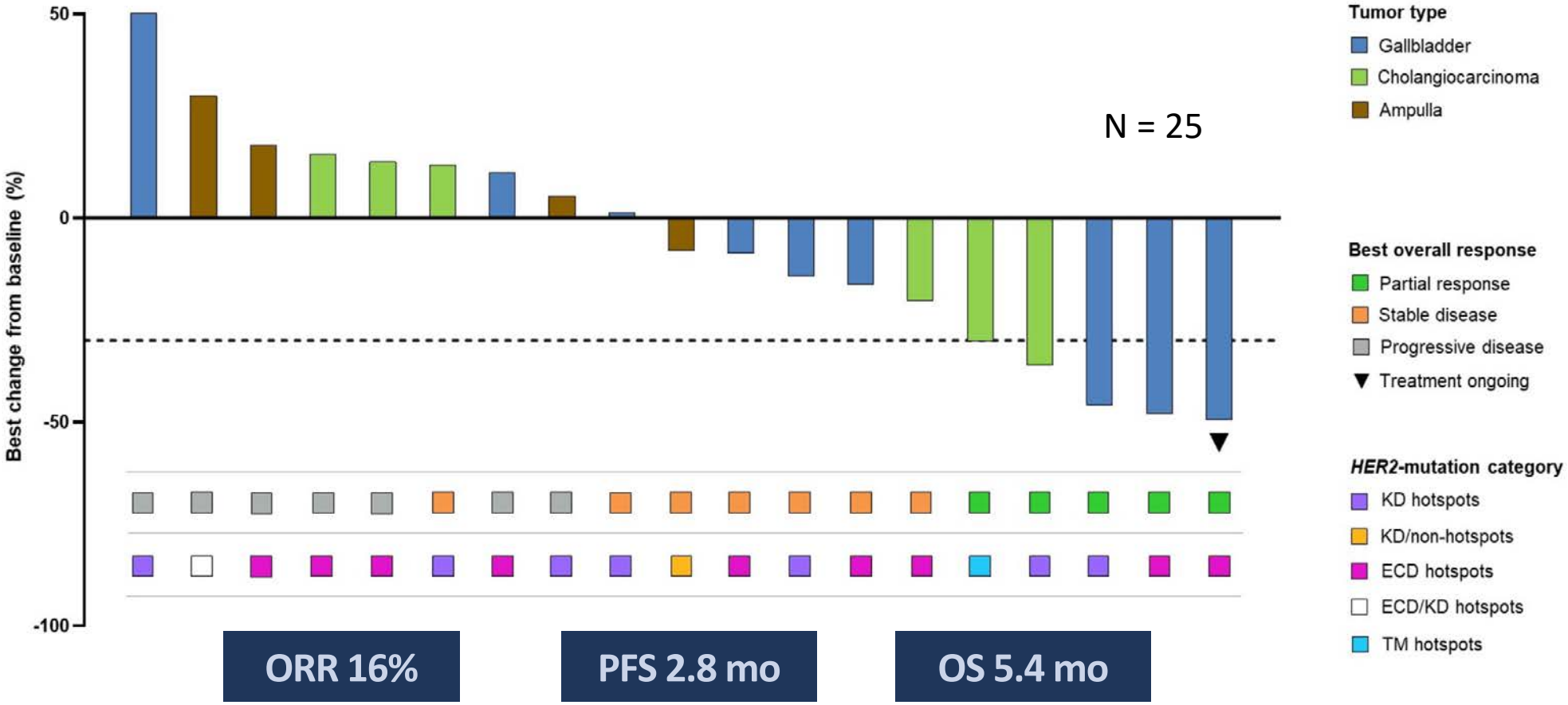
Duration of response,[b] months	(N=8)
Median (95% CI)	7.4 (3.2, NE)

DOR=duration of response; NE= not estimable.
a, per Investigator Assessment using RECIST 1.1 in response-evaluable patients; b, in response-evaluable patients who had a complete or partial response followed by at least one more response assessment.

Meric-Bernstam et al, *J Clin Oncol* 2021

Neratinib, a TKI for Activating HER2 Mutations

Phase II SUMMIT Study: BTC Patients



Harding, *ASCO GI 2021*

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)

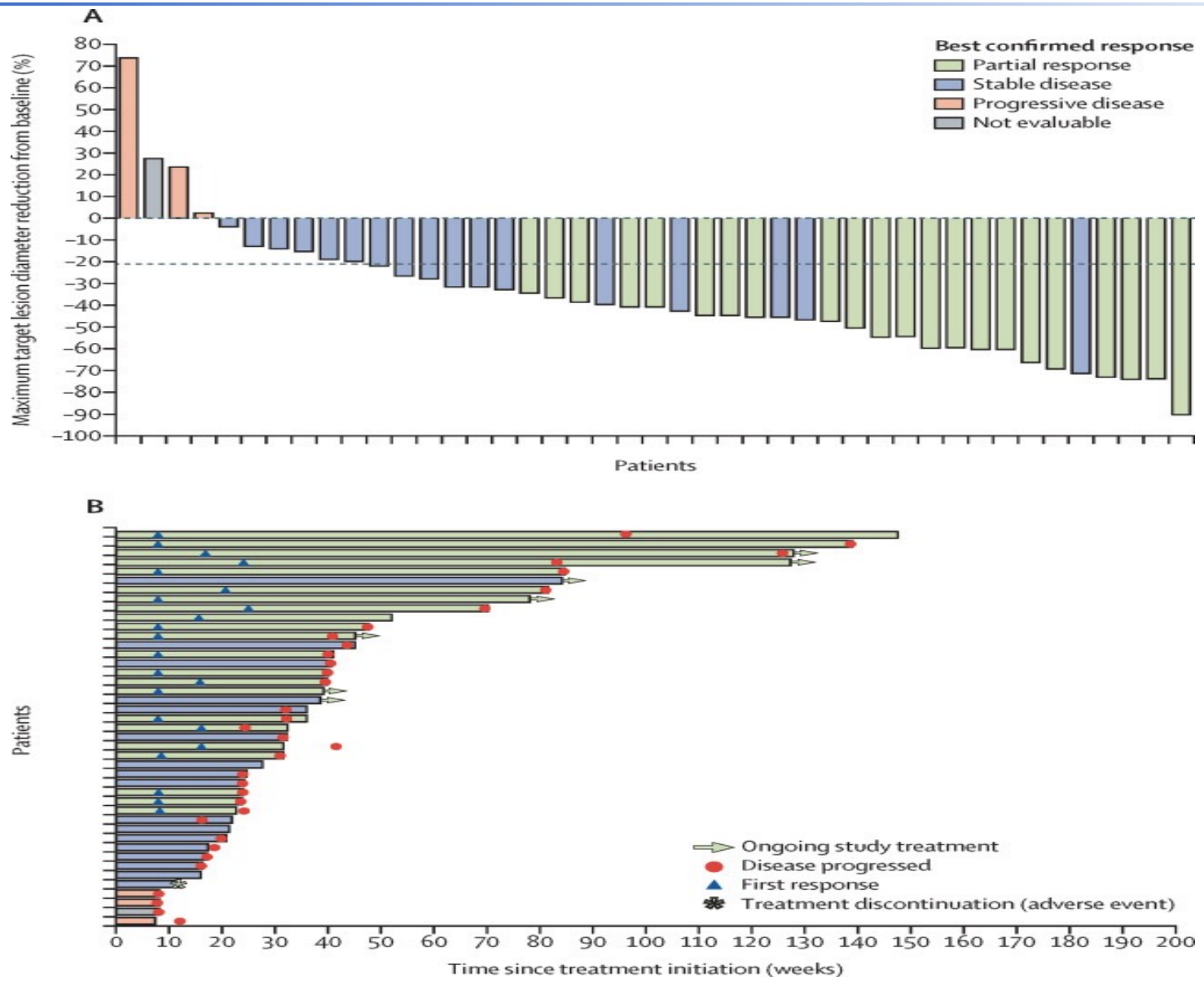
Ohba A et al.

ASCO 2022;Abstract 4006.

Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary
June 5, 2022
9:00 AM– 12:00 PM EDT

BRAF V600E mutated cholangiocarcinoma: The ROAR Basket Trial

Efficacy of
Dabrafenib + Trametinib



Subbiah V, et al. *Lancet Oncol* 2020;21:1234–1243

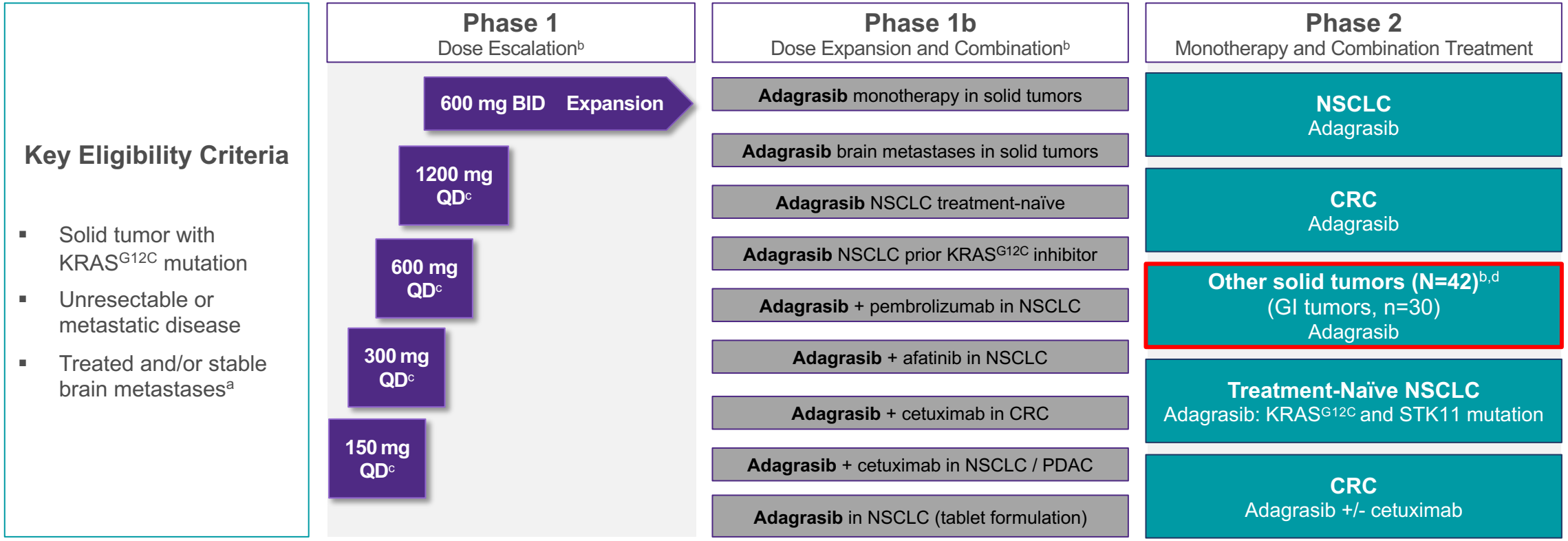
ASCO Gastrointestinal Cancers Symposium

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

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

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

KRYSTAL-1 (849-001) Study Design



Phase 2 Endpoints **Primary:** ORR (RECIST 1.1) **Secondary:** DOR, PFS, OS, safety

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

CRC, colorectal cancer; ctDNA, circulating tumor deoxyribonucleic acid; GI, gastrointestinal; NSCLC, non–small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

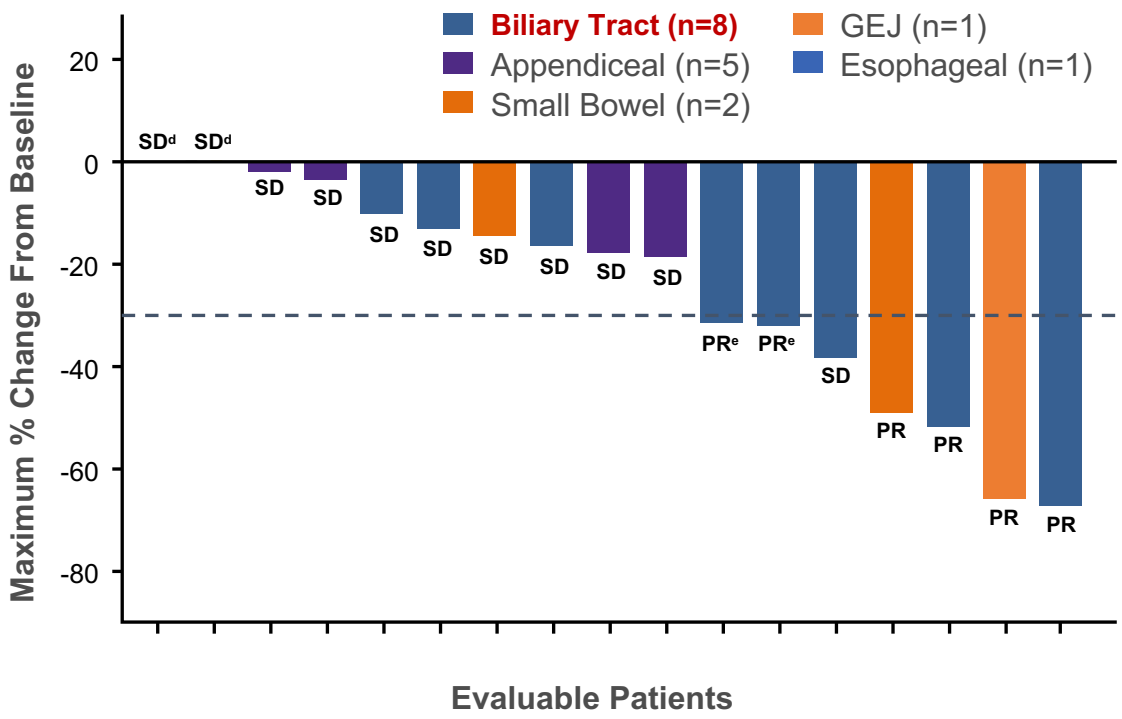
1. Jänne PA et al. Presented at: 2020 EORTC-NCI-AACR Symposium; Oct 25, 2020. 2. Weiss J et al. Presented at: 2021 ESMO Congress; Sept 19, 2021. 3. Johnson ML et al. Presented at: 2020 EORTC-NCI-AACR Symposium; Oct 25, 2020.

[a]Most cohorts allow patients with brain metastases if adequately treated and stable; additional phase 1/1b cohort allows limited brain metastases; [b]KRAS^{G12C} mutation detected in tumor tissue and/or ctDNA; [c]Patients subsequently dose escalated up to 600 mg BID; [d]Solid tumors included GI tumors (n=30) and non-GI tumors (n=12).

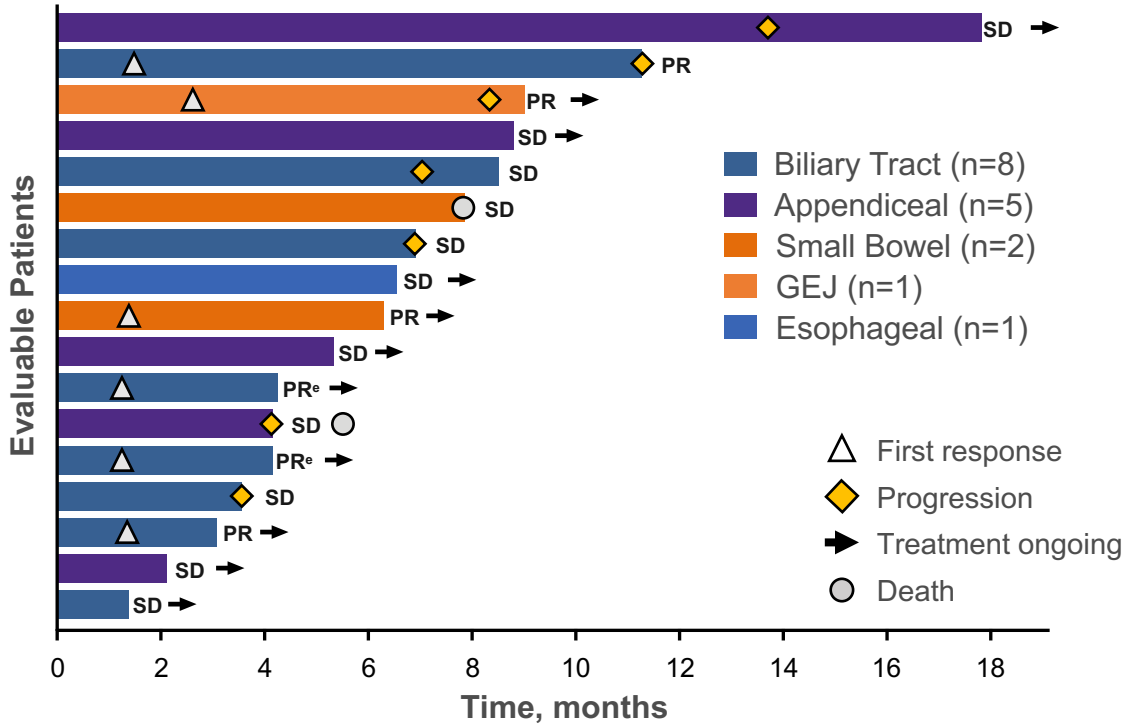
Data as of 10 September 2021. ClinicalTrials.gov. NCT03785249.

Adagrasib in Patients With Other GI Tumors:[a] Best Tumor Change From Baseline and Duration of Treatment

Best Tumor Change From Baseline (n=17)[b,c]



Duration of Treatment (n=17)[b,c]



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

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

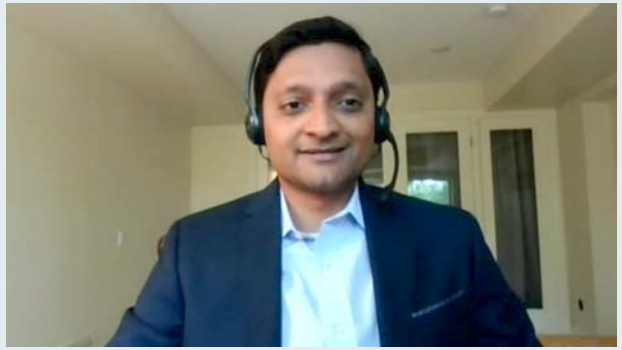
DCR, disease control rate; DOR, duration of response; GEJ, gastro-esophageal junction; PR, partial response; SD, stable disease; TTR, time to response.
[a]Excluding CRC and PDAC; [b]Evaluable population (n=17) excludes 1 patient who withdrew consent prior to the first scan; [c]All results are based on investigator assessments; [d]1 patient with appendiceal cancer and 1 patient with esophageal cancer had maximum % change from baseline of 0; [e]At data cut-off, 2 patients had unconfirmed PR.
Data as of 10 Sept 2021 (median follow-up: 6.3 months).

Conclusions/Take-Away

- Immunotherapy moving to 1L in cholangiocarcinoma although questions remain.
  - TOPAZ-1 with Gem/Cis +/- Durvalumab marginally positive
  - KEYNOTE 966 (G/C +/- P) ongoing
- NGS testing is central to future applications of novel therapies in Biliary Cancer
  - Applying genomic technology and molecular classification critically and timely in cholangiocarcinoma is changing the therapeutic landscape.
- Molecularly targeted agents such as those targeting FGFR and IDH1 are providing patients with advanced cholangiocarcinoma new treatment options
  - Ongoing efforts to expand the role of targeted therapies to IDH2, BRAF V600E, Her2 amplifications and others.
- Ongoing trials with first line strategies in iCCA and FGFR2 fusions vs. standard gemcitabine/cisplatin

MODULE 6: Contemporary Management of Pancreatic Cancer — Dr O'Reilly

RTP
RESEARCH
TO PRACTICE



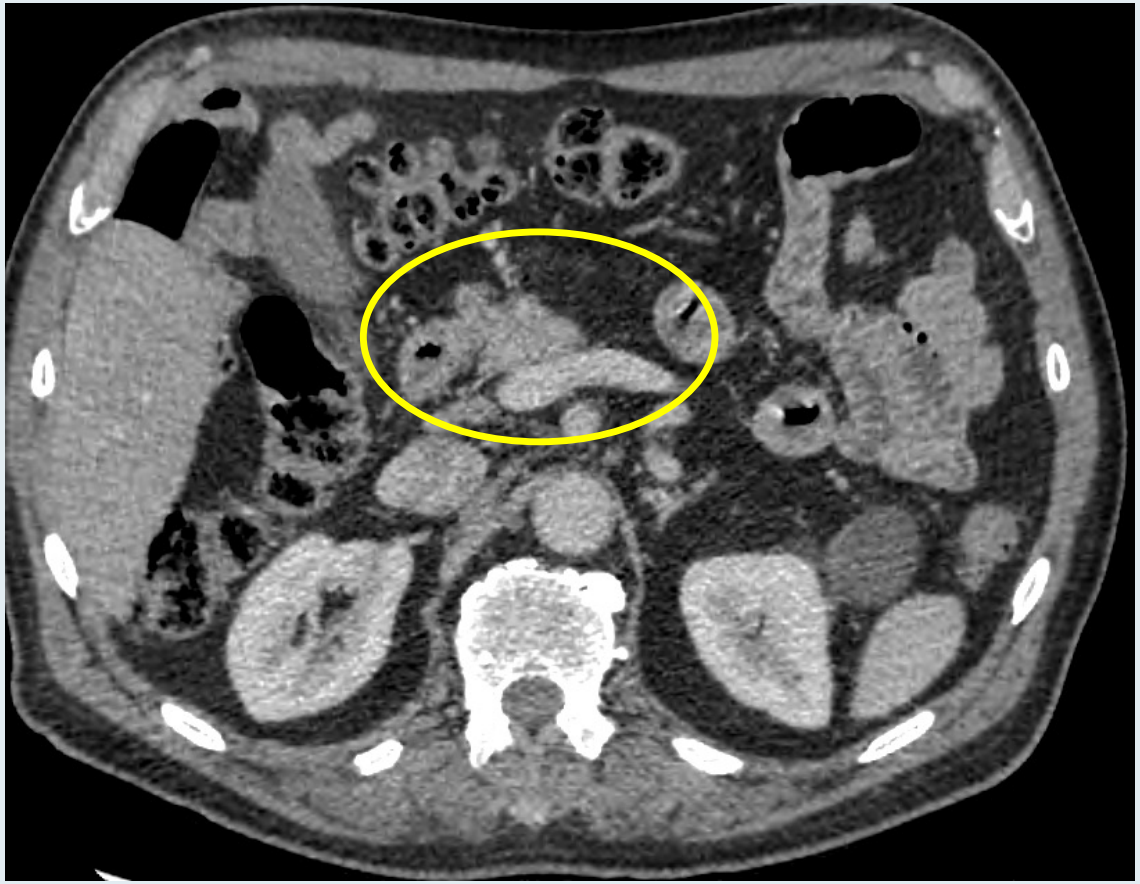
Dr Vignesh Narayanan
Lone Tree, Colorado

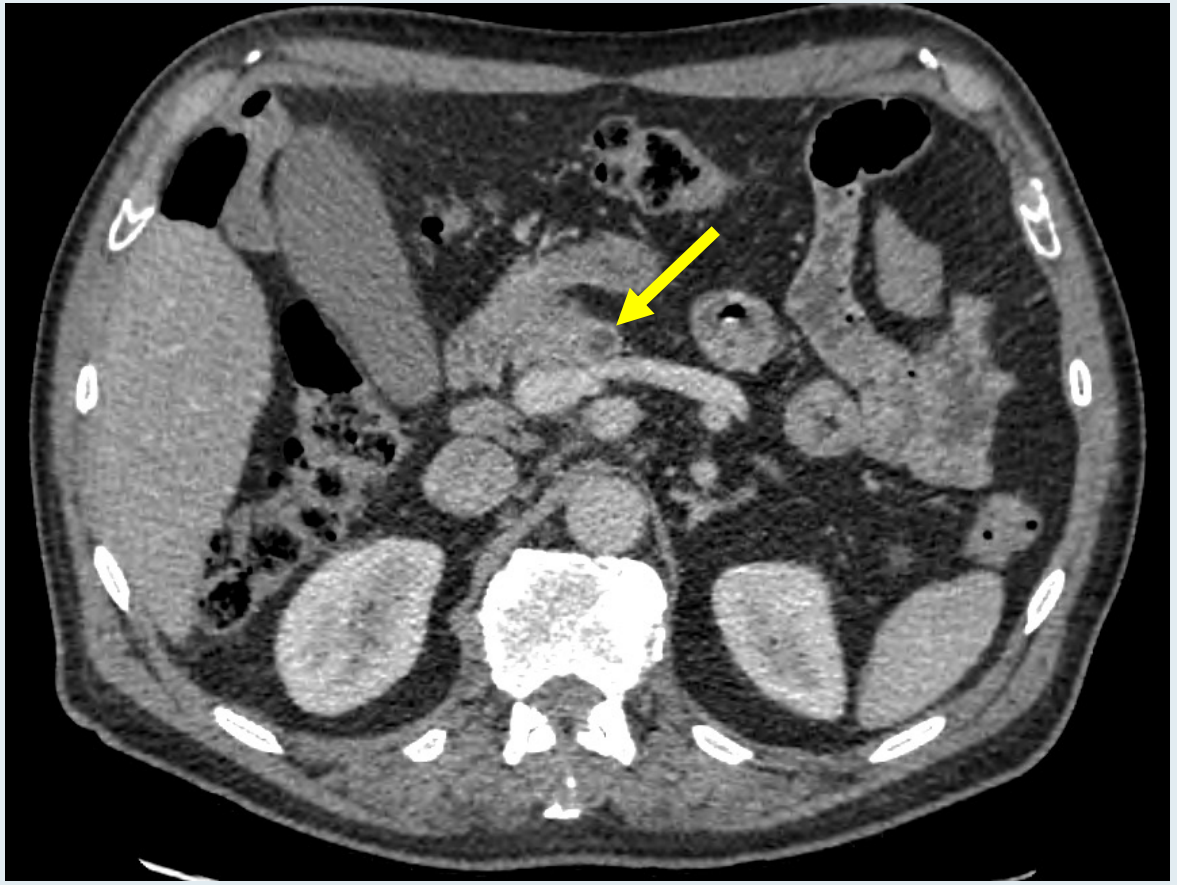
73-year-old man with pancreatic adenocarcinoma abutting the portal vein

Dr Erik Rupard
West Reading, Pennsylvania

76-year-old woman with metastatic pancreatic adenocarcinoma who cares for her elderly mother

RTP
RESEARCH
TO PRACTICE





Dr Lionel Fonkoua
Rochester, Minnesota

58-year-old woman with metastatic pancreatic adenocarcinoma and a germline BRCA2 mutation — pMMR

Dr Namrata Peswani
Richardson, Texas

48-year-old man with metastatic pancreatic adenocarcinoma and KRAS, TP53 and BLM mutations — MSS

RTP
RESEARCH
TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

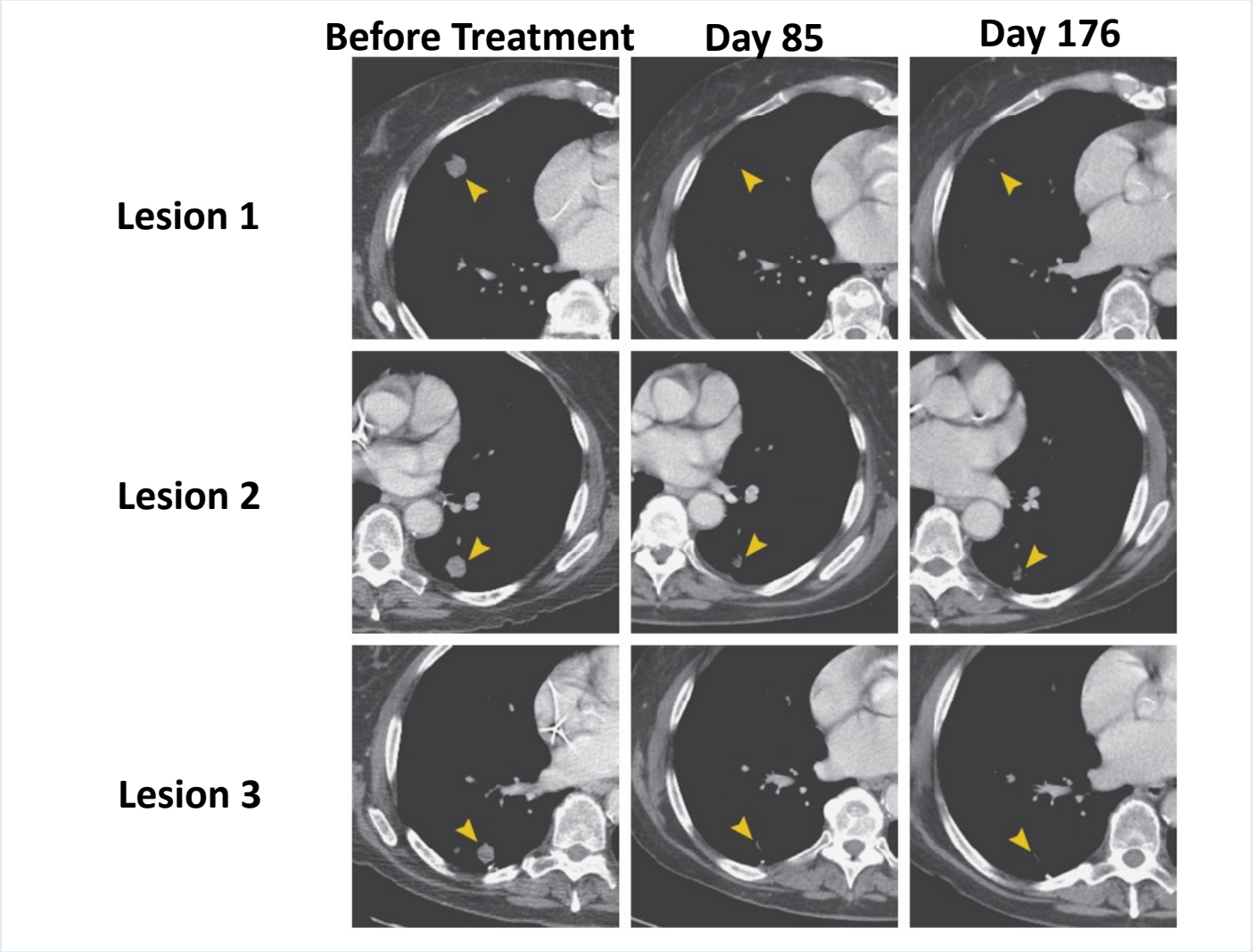
BRIEF REPORT

Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

Rom Leidner, M.D., Nelson Sanjuan Silva, B.S., Huayu Huang, M.S., David Sprott, B.S., Chunhong Zheng, Ph.D., Yi-Ping Shih, Ph.D., Amy Leung, B.S., Roxanne Payne, M.N., Kim Sutcliffe, B.S.N., Julie Cramer, M.A., Steven A. Rosenberg, M.D., Ph.D., Bernard A. Fox, Ph.D., Walter J. Urba, M.D., Ph.D., and Eric Tran, Ph.D.

N Engl J Med 2022;386(22):2112-9.

CT Scans Showing Regression of Pancreatic Lesions in Patient who Received Immunotherapy with T-Cell Receptor (TCR)–Engineered T Cells Targeting KRAS G12D Mutation Expressed in Tumors



Leidner R et al. *N Engl J Med* 2022;386(22):2112-9.

Contemporary Management of Pancreatic Cancer

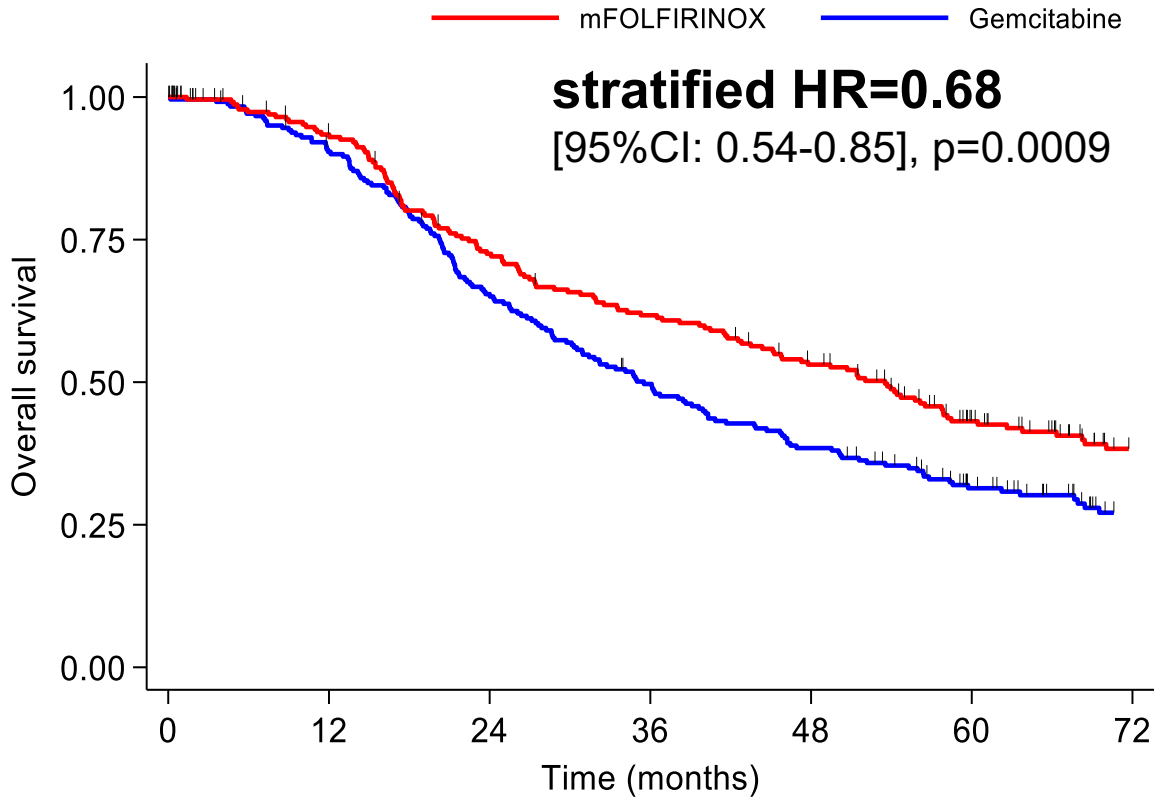
Research To Practice 06-04-2022

Eileen M. O'Reilly, MD
Winthrop Rockefeller Endowed Chair in Medical Oncology
Co-Director Medical, David M. Rubenstein Pancreas Center
Section Head, HPB & Neuroendocrine Cancers
Attending Physician, Member, Memorial Sloan Kettering
Professor of Medicine, Weill Cornell Medicine

Memorial Sloan Kettering
Cancer Center

PRODIGE 24: Adjuvant mFOLFIRINOX vs Gem

Primary Endpoint: Overall Survival



5-Year OS

- **mFOLFIRINOX 43.2%**
  [95%CI: 36.5-49.7]
- **Gemcitabine 31.4%**
  [95%CI: 25.5-37.5]

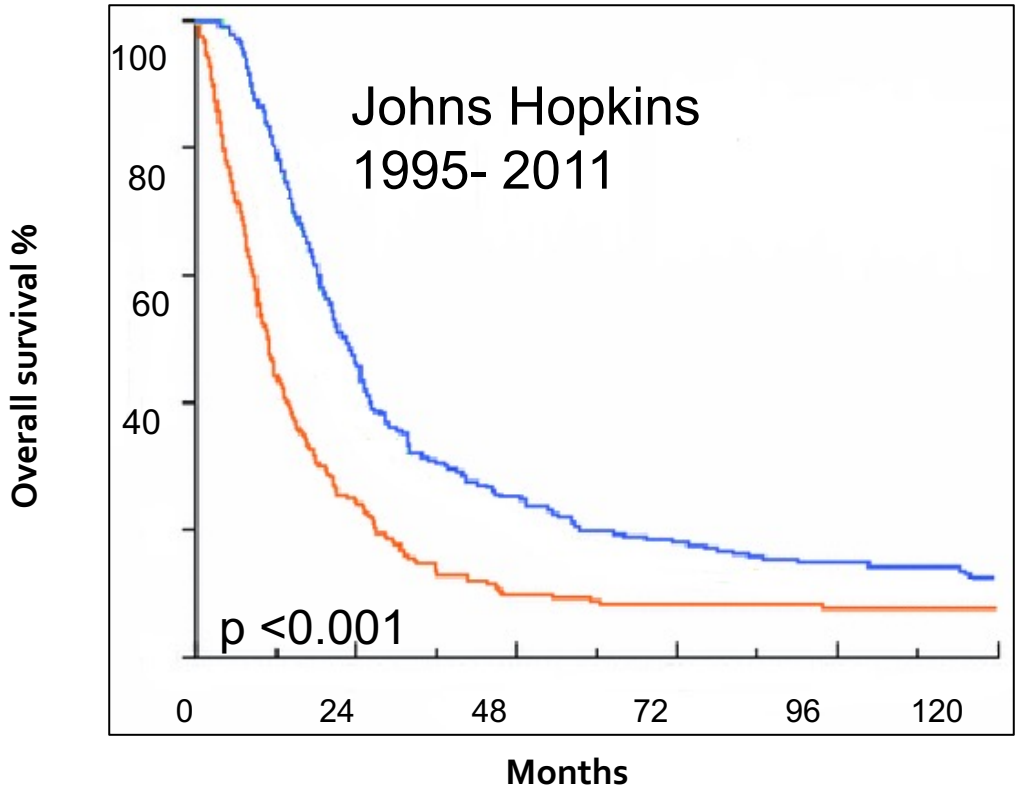
Median OS

- **mFOLFIRINOX 53.5 months**
  [95%CI: 43.5-58.4]
- **Gemcitabine 35.5 months**
  [95%CI: 30.1-40.3]

Conroy, T. New Engl J Med, 2018. Conroy, T. ESMO, 2021

Issues with Surgery First (N= 1,144)

Postoperative complications delay/preclude adjuvant therapy



No Complications and Adjuvant Therapy

N= 320

Median OS: 22.5 months

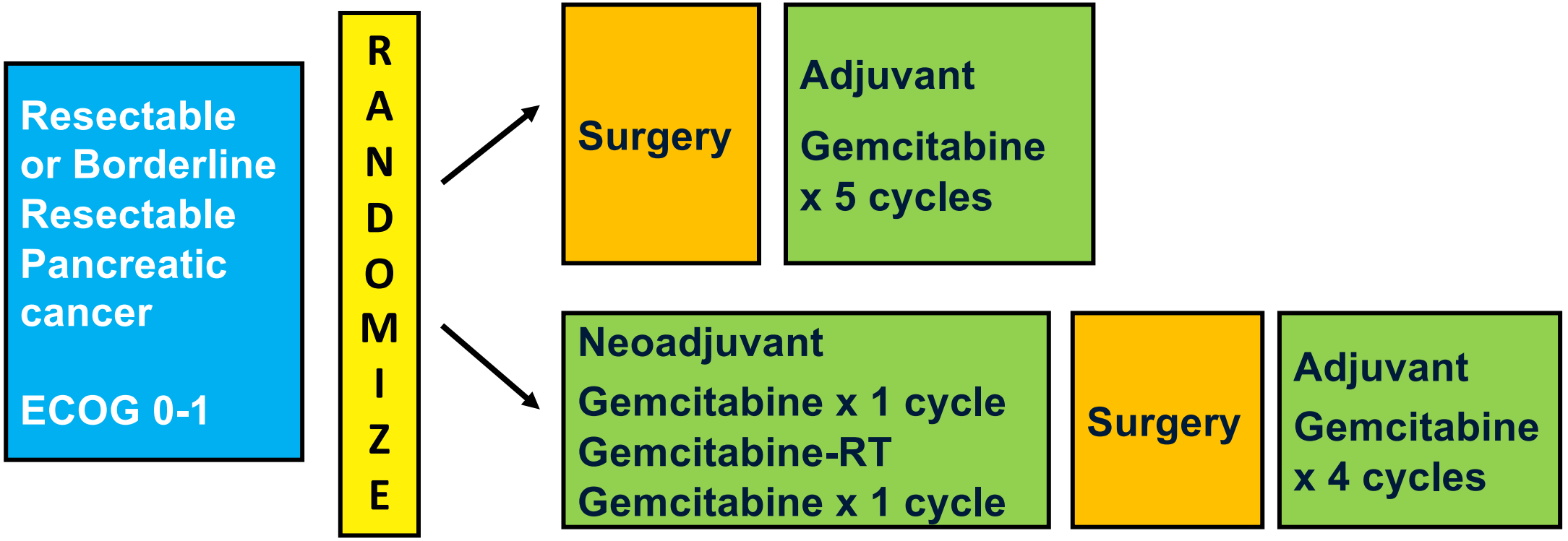
Complications and No Adjuvant Therapy

N= 260

Median OS: 10.7 months

Wu, L. Ann Surg Oncol 2014

Randomized Data Neoadjuvant Therapy
PREOPANC: Resectable, Borderline



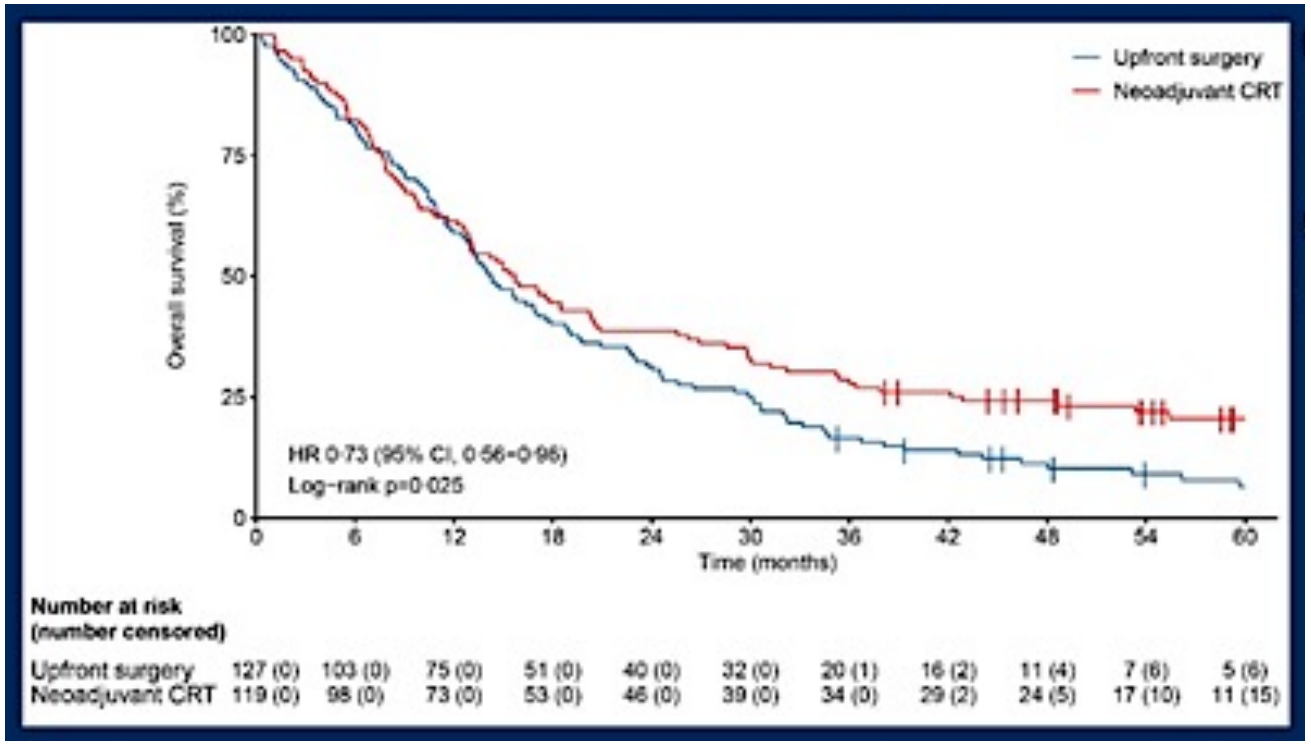
Primary endpoint: Overall survival

Stratify: Resectability, Institution

Hypothesis: Improvement median OS from 11-17 months

van Tienhoven, G. J Clin Oncol. 2020. Editorial: O'Reilly, EM J Clin Oncol, 2020

Long-term PREOPANC: Updated ASCO 2021



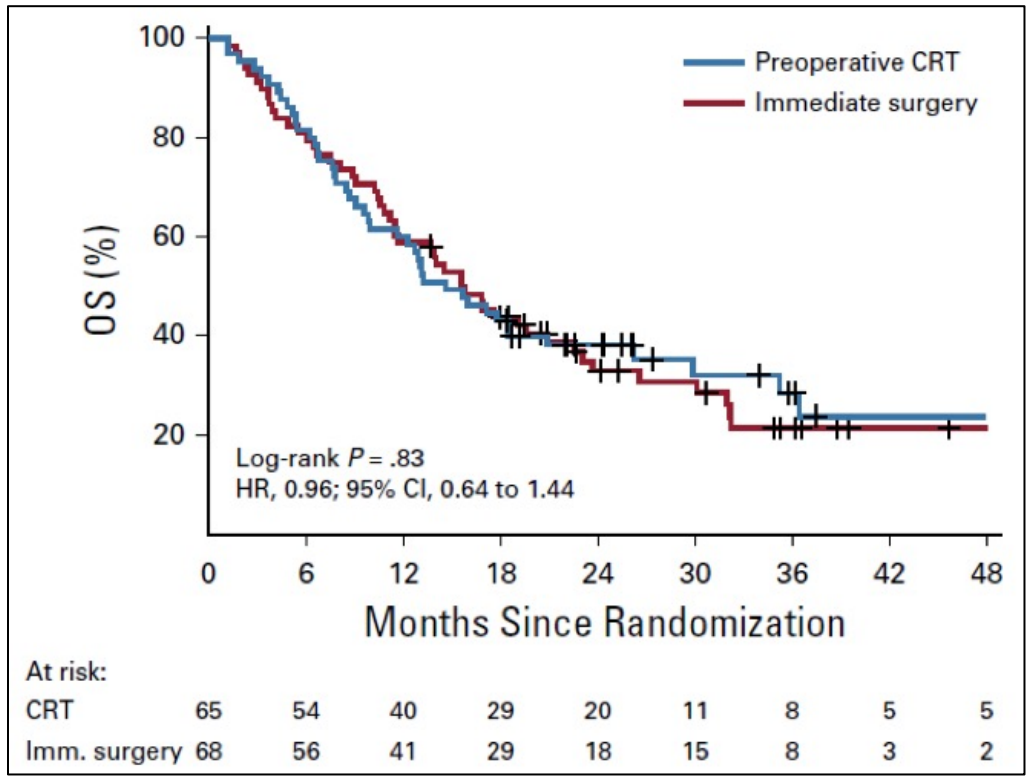
HR 0.73 (0.56-0.96) Log-rank p= 0.025

	Median OS	5-Year OS
Neoadjuvant CRT	15.7 mo	20.5%
Upfront Surgery	14.3 mo	6.5%

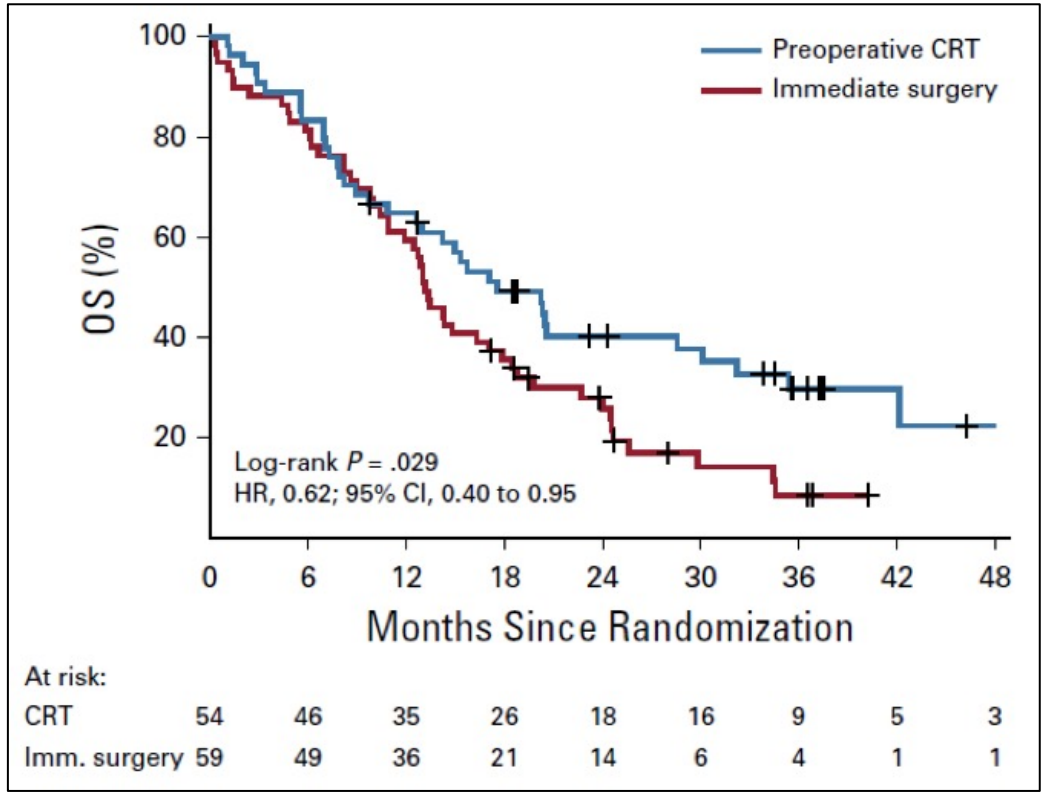
van Eijck, C, et al. Proc ASCO, 2021 [Abstr 4016] Versteijne, E. J Clin Oncology, 2022

PREOPANC: Overall Survival – Benefit in Borderline

OS Resectable PDAC

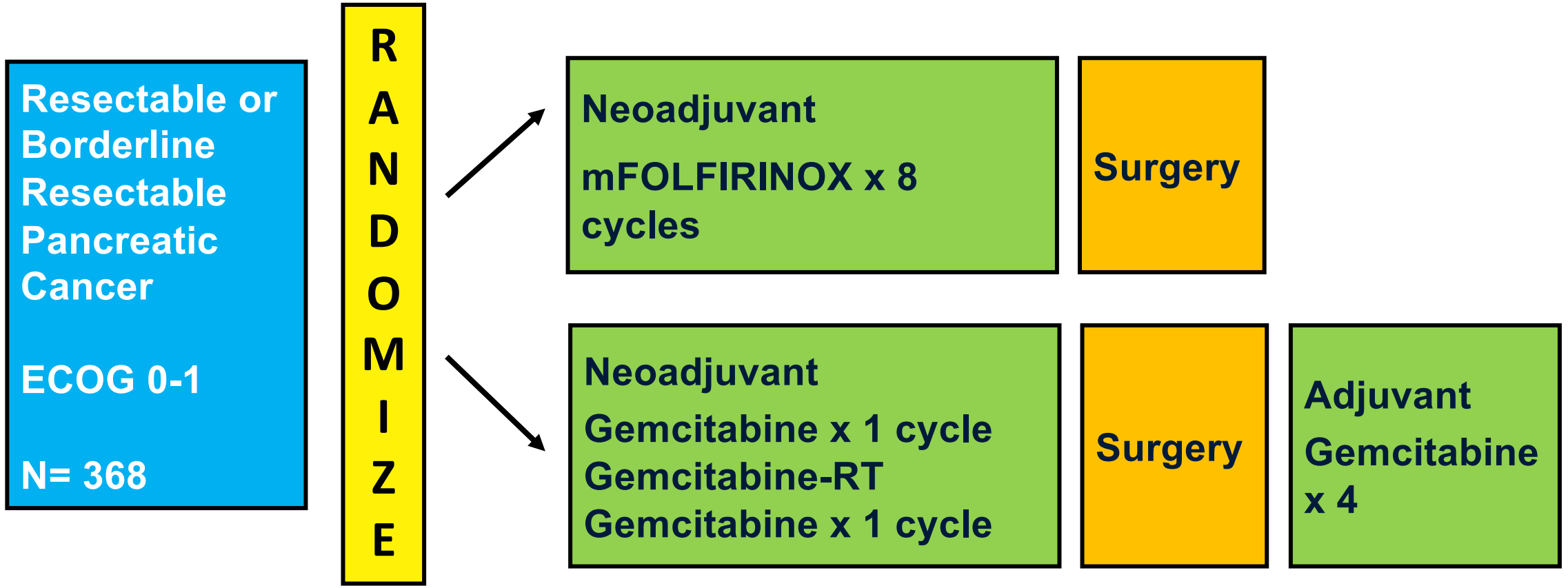


OS Borderline Resectable PDAC



PREOPANC-2: Resectable/Borderline

Completed Recruitment 2021 and Results Pending



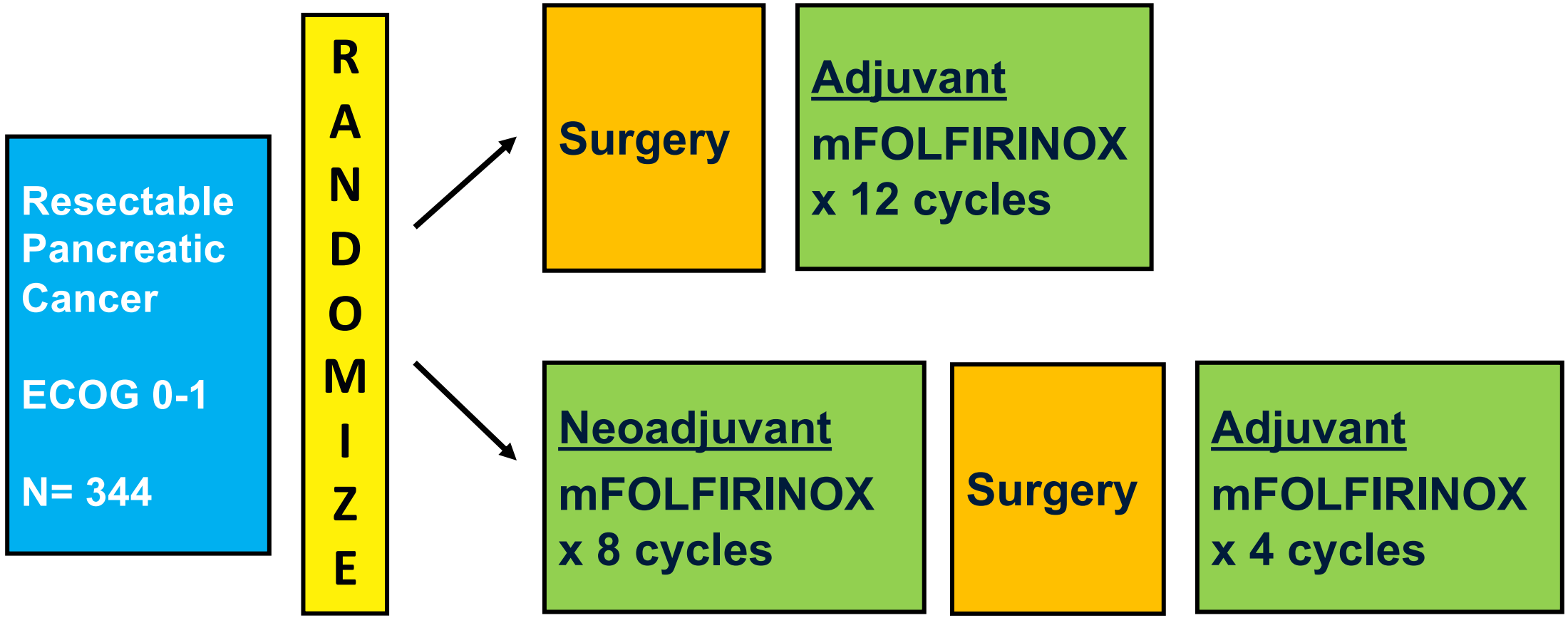
Primary endpoint: Overall survival

Stratify: Resectability, Institution

S1505: Perioperative Trial Results (Resectable PDAC)

	mFOLFIRINOX N= 55	Gem/Nab-Paclitaxel N= 47	P-Value
Surgical Resection	40 (73%)	33 (70%)	
CR/Major Path response	10 (25%)	14 (42%)	
Completed All Therapy	27 (49%)	19 (40%)	
Two Year OS	41.6%	48.8%	NS
Median OS	22.4 m	23.6 m	
Median DFS after Surgery	10.9 m	14.2 m	p= 0.87

A021806: Alliance Resectable PDAC (ongoing)



Primary endpoint: Overall survival

FOLFIRINOX Localized PDAC (N= 1,835)

Trans-Atlantic Pancreatic Cancer Surgery (TAPS) Consortium

- MSK, UPMC, MD Anderson, Erasmus MC, Amsterdam UMC

Median # cycles 6 (IQ range 4-8)

Stage	N	Resection Rate	Median OS (mths; 95% CI)
Locally Advanced	958 (52%)	17.6%	18.7 (17.7- 19.9)
Borderline Resectable	531 (29%)	53.1%	23.2 (21.0- 25.7)
Potentially Resectable	346 (19%)	70.5%	31.2 (26.2- 36.6)

- For N= 695 whom underwent surgery:
  - Median OS 38.3 months (36.1- 42)

Conclusions for Resectable, Borderline PDAC

Level 1 evidence supports surgery followed by adjuvant mFOLFIRINOX for resectable PDAC

Neoadjuvant therapy: tumor shrinkage, N0, R0, less fistula, OS benefit; More randomized trials awaited

- Established for borderline resectable (expert consensus, NCCN, etc)
- Debated for resectable PDAC

Optimal neoadjuvant regimen, chemotherapy, chemoRT, both, remains to be defined

A021806, PREOPANC-3 will answer for resectable PDAC

Multidisciplinary evaluation

Factors For Therapy Selection: 1L Therapy

Performance status, co-morbidities, age, organ function

Patient preferences

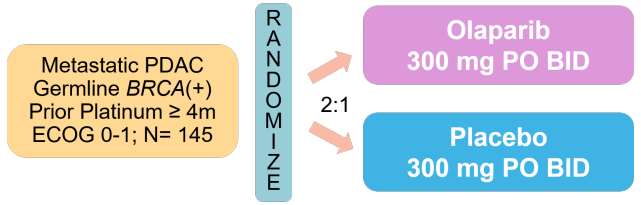
Comparative efficacy, toxicity, cost

Logistics

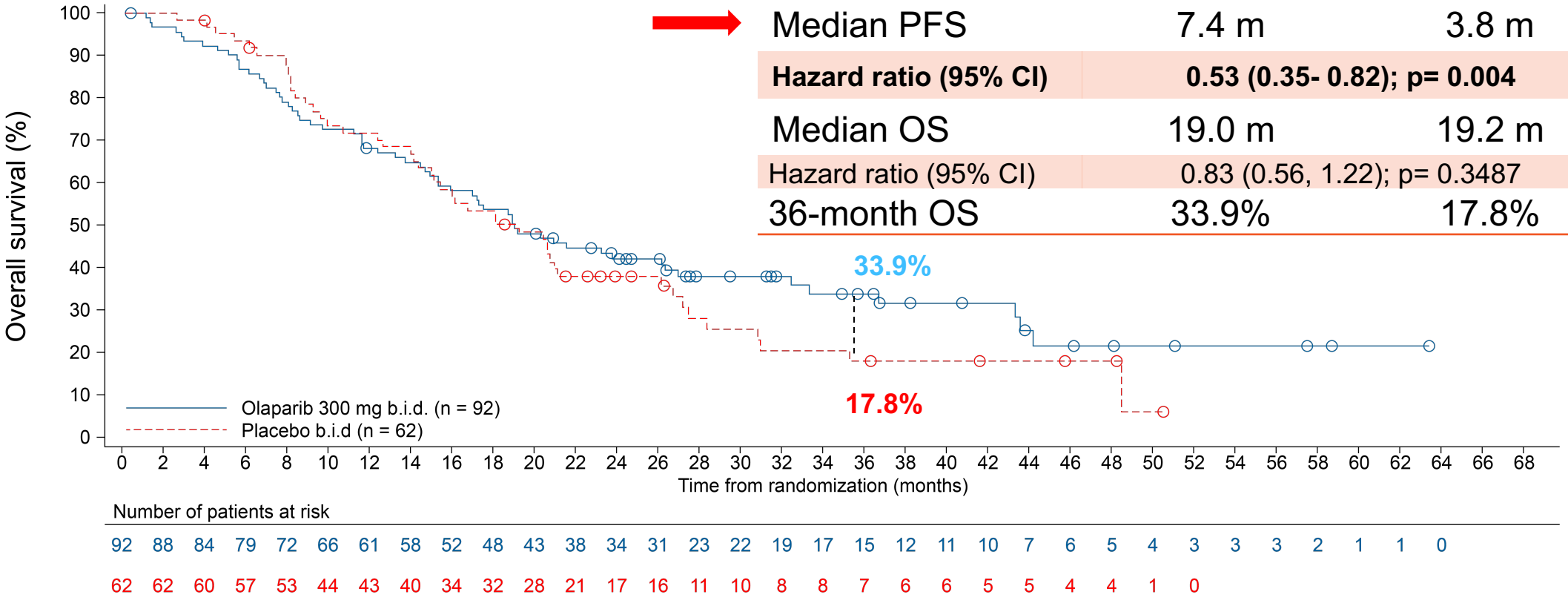
Treatment sequencing

Genomic context

POLO g*BRCA*1/2: Maintenance Olaparib vs Placebo

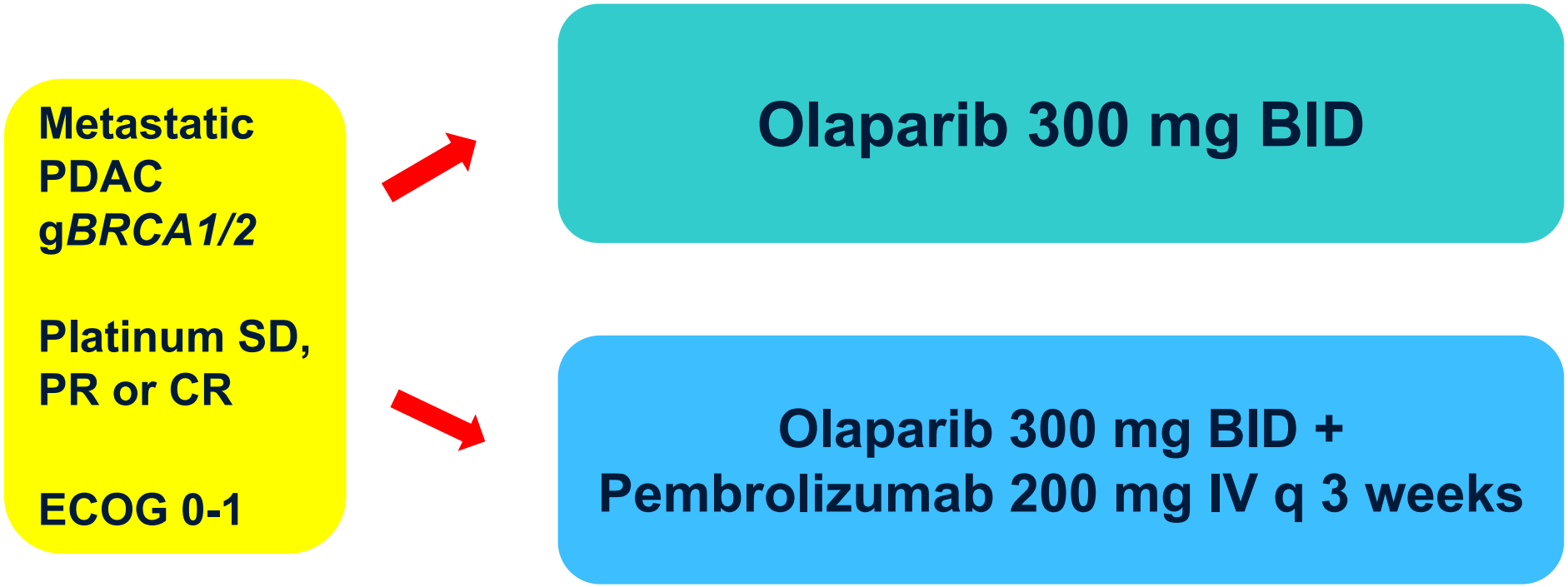


	Olaparib N=92	Placebo N=62
Events, n	61 (66.3%)	47 (75.8%)
Median PFS	7.4 m	3.8 m
Hazard ratio (95% CI)	**0.53 (0.35- 0.82); p= 0.004**	
Median OS	19.0 m	19.2 m
Hazard ratio (95% CI)	0.83 (0.56, 1.22); p= 0.3487	
36-month OS	33.9%	17.8%



SWOG S2001: Olaparib +/- Pembrolizumab (g*BRCA1/2*)

Maintenance Trial (ongoing)



Primary endpoint: PFS (HR 0.6; 7→ 11.7 m)

PARPVAX Trial (Maintenance; Unselected PDAC)
ASCO 2022

Phase Ib/II niraparib + ipilimumab or niraparib + nivolumab in PDAC
Primary Endpoint: PFS @ 6 months for both combinations (H0= PF6 44%)

Eligibility

- LA or M1 PDAC ≥ 16 weeks of platinum/non-progression, ECOG 0/1

	Niraparib + Ipilimumab N= 40	**Niraparib + Nivolumab N= 44**
PFS @ 6 months	**59.6%** (44.3- 74.9)	20.6% (8.3- 32.9)
Median PFS	8.1 m (5.5- 10.6)	1.9 m (1.4- 2.3)
Overall RR	15.4%	7.1%
Overall Survival	17.3 m (12.8- 21.9)	14 m (7.4- 20.6)
Non-DDR (med PFS)	1.9 m	7.6 ms

APOLLO EA2192: Adjuvant Olaparib vs Placebo PDAC

Ongoing

Resected PDAC
g/s*BRCA1/2, PALB2*

≤ 12 weeks from adjuvant therapy

ECOG 0-2

2: 1

Olaparib 300 mg BID x 1 year
N= 102

Placebo 300 mg BID x 1 year
N= 50

Primary endpoint: Relapse free survival 22 → 44 months (90% power, 1 sided alpha; HR 0.5)
Stratify: R0 vs R1; Platinum vs Non-platinum; Neoadjuvant vs No

KRAS and *KRAS* Mutations in PDAC

KRAS gene encodes KRAS protein

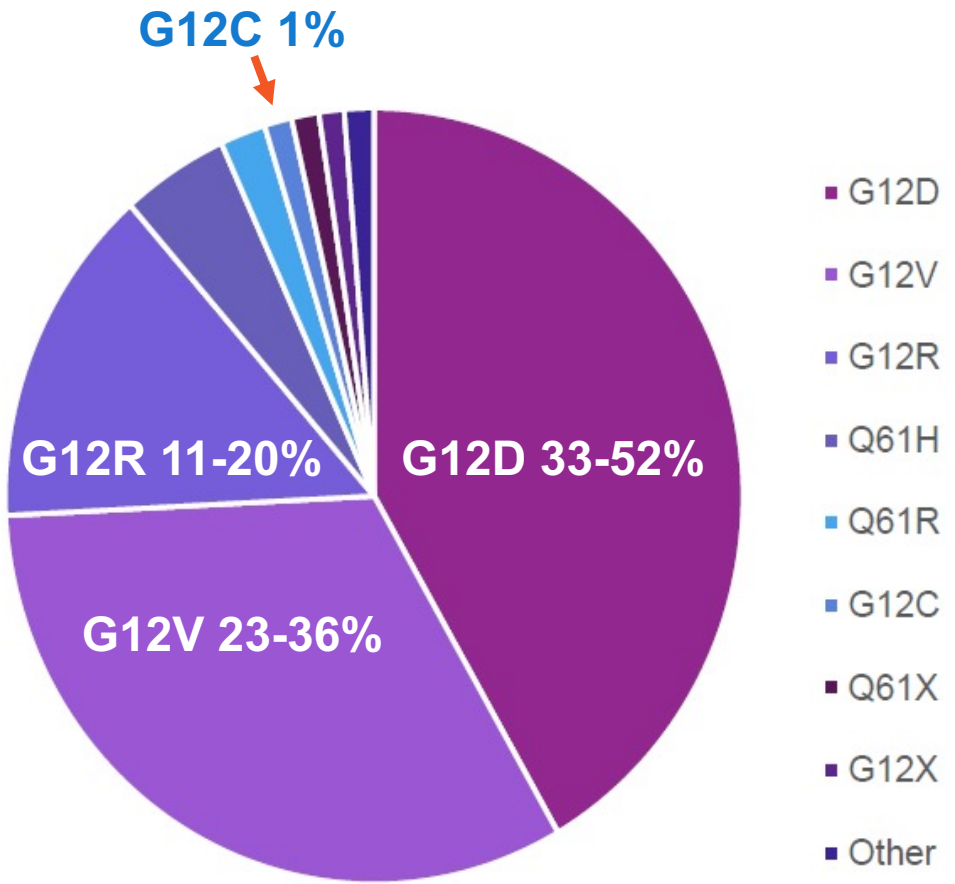
21 kDA guanosine triphosphatase (GTPase)

Cancer associated *RAS* genes: 3 mutational hotspot missense mutations

- Glycine-12 (G12)
- Glycine-13 (G13)
- Glutamine-61 (Q61)

Mutated *KRAS*: persistent GTP-bound (active) and activated effector signaling pathways

G12D (glycine→ aspartic acid) – commonest GI



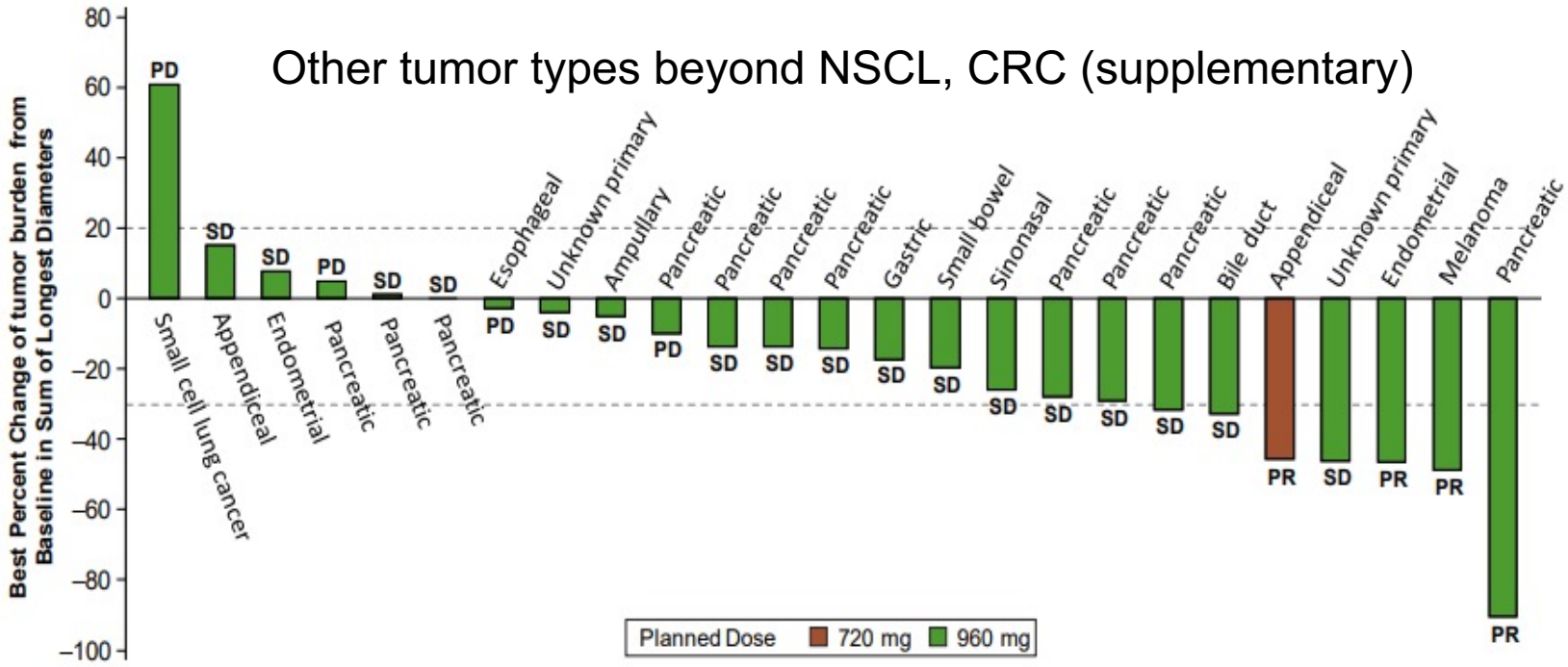
Biankin, A. Nature, 2012, Guo, S, BJC, 2020. Singhi, AD. Gastroenterology, 2019. Cancr Genome Network Atlas. Cancer Cell, 2017. cbioportal.mskcc.org (courtesy A. Varghese). Johnson, C. Can Disc, 2022. Hofmann, MH. Can Disc, 2022

Allele Covalent Specific Targeting of *KRAS* G12C Sotorasib in PDAC: CodeBreaK 100 Trial

KRAS-mutant G12C 1-2% PDAC

Sotorasib (AMG510)

N= 11 PDAC: 1 PR, 8 SD, 2 PD



ASCO Plenary 2022

N= 38 PDAC

RR 21%

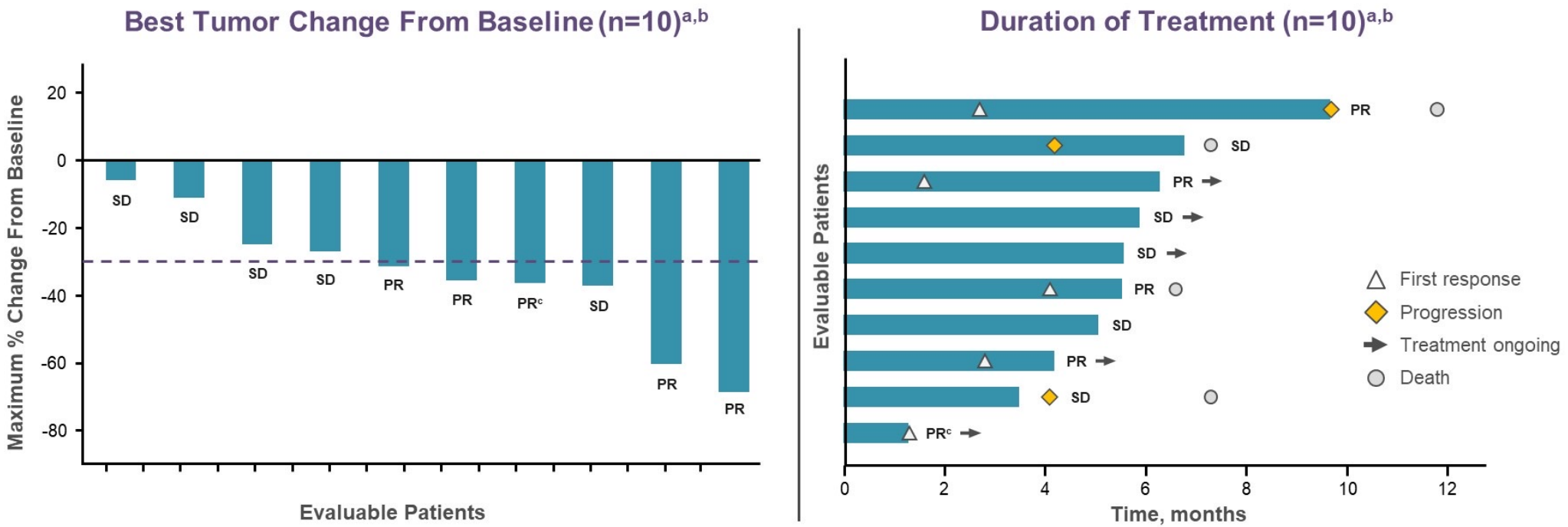
mDOR 5.7 m (1.9- NR)

mPFS 4.0 m

mOS 6.9 m

Hong, DS….Li, B. NEJM, 2020. NCT03600883, NCT03785249, NCT04006301
Strickler, JH. ASCO Plenary, 2022

KRYSTAL-1: Adagrasib *KRAS* G12C in PDAC (N= 12)

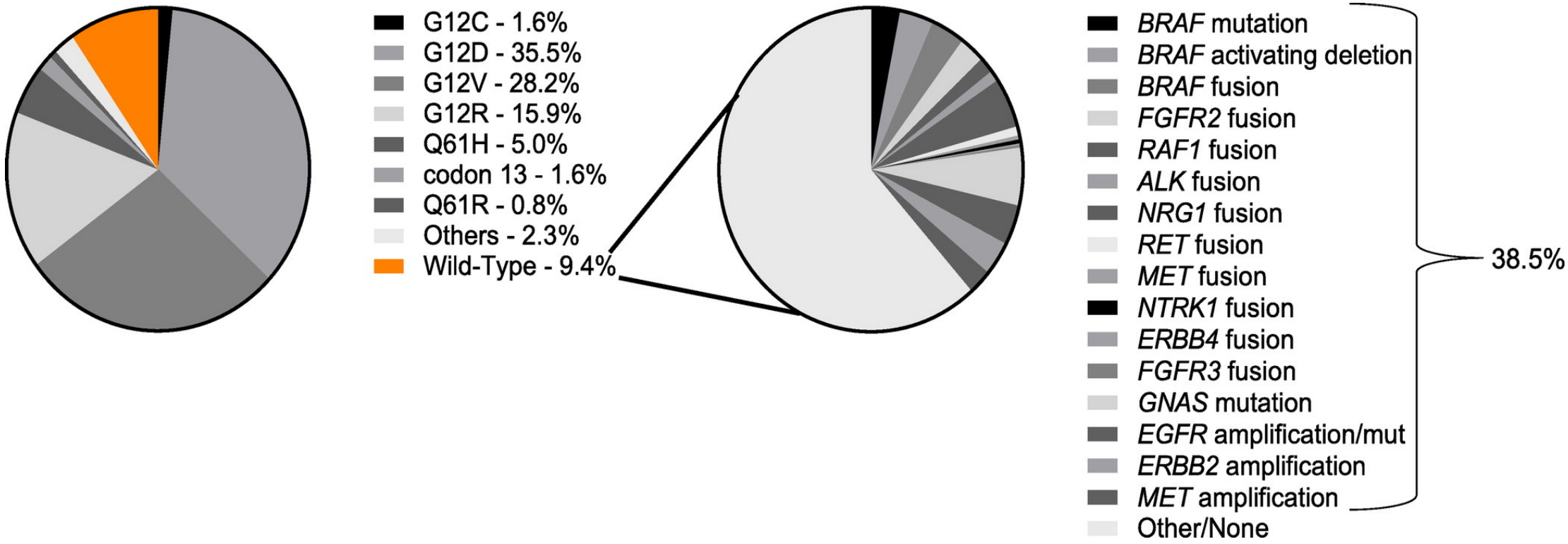


Median lines therapy: 2.5
Median RR 50% (10 evaluable); Median duration of response 6.9 m
Median PFS 6.6 m; Median OS: Not reached

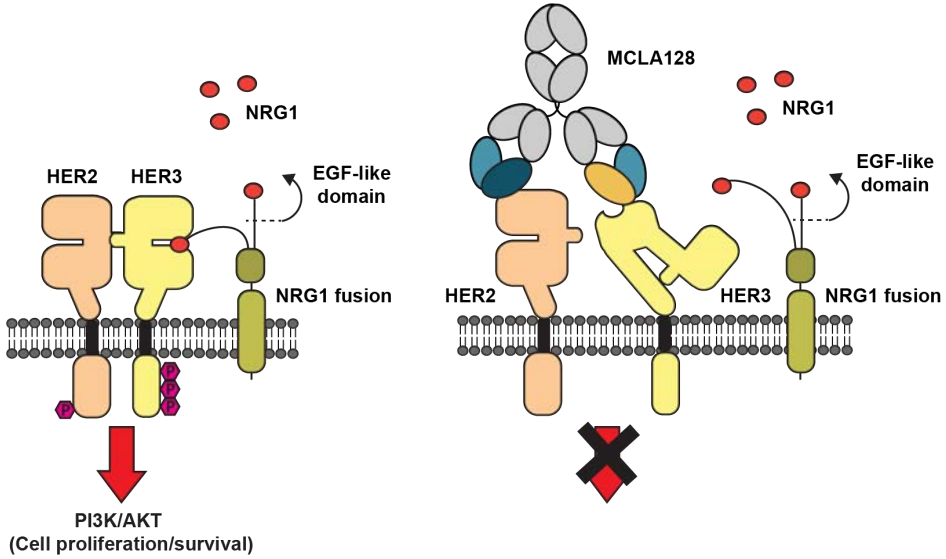
KRAS Wild-Type PDAC (~8% PDAC)

Rare finding in PDAC

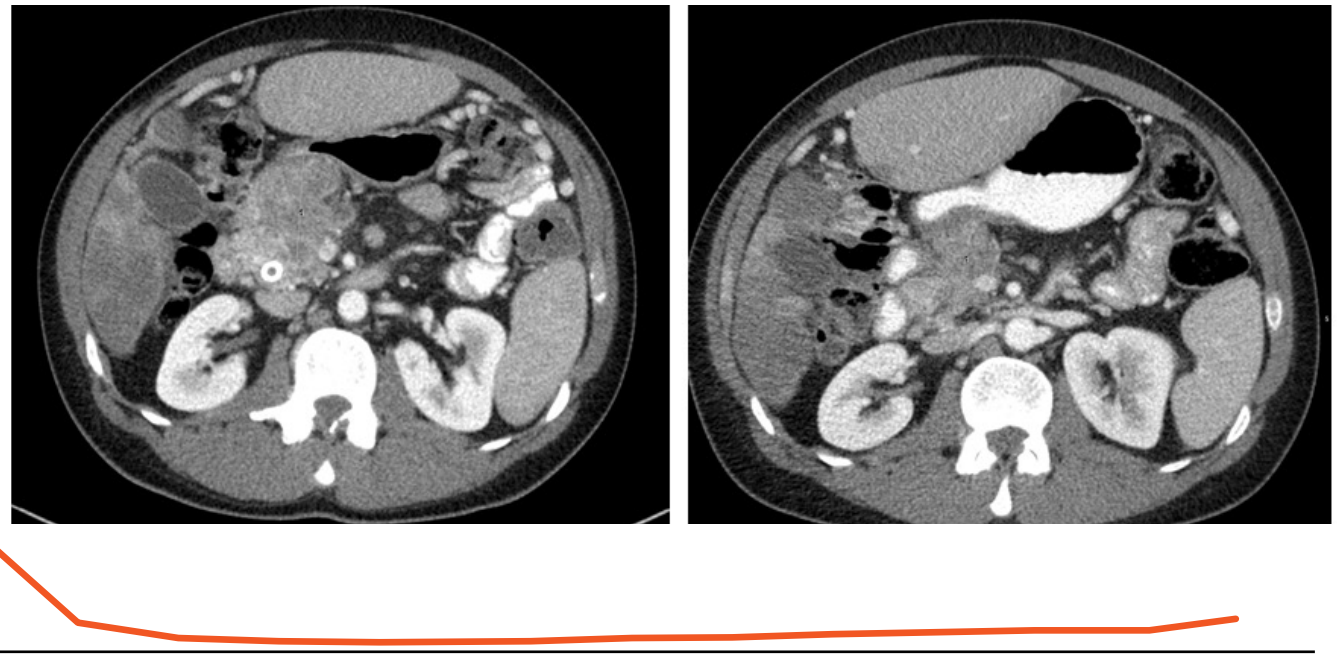
- Actionable alterations
- Fusions: *NTRK, NRG-1, ROS, ALK, FGFR, RET, MEK*



MCLA-128 (Zenocutuzumab) *NRG-1* Fusion *KRAS*-WT PDAC



Bispecific, IgG1 mAb ADCC inhibits HER3

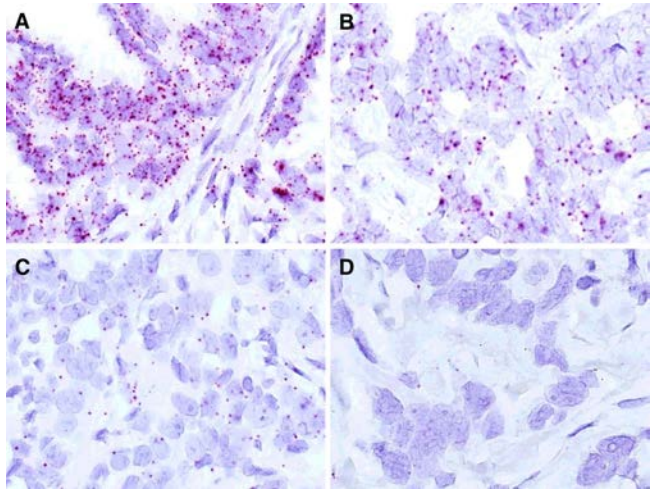


PDAC Cohort (N= 12)
Median age 47.5 years
Response rate 42%
100% decline Ca 19-9

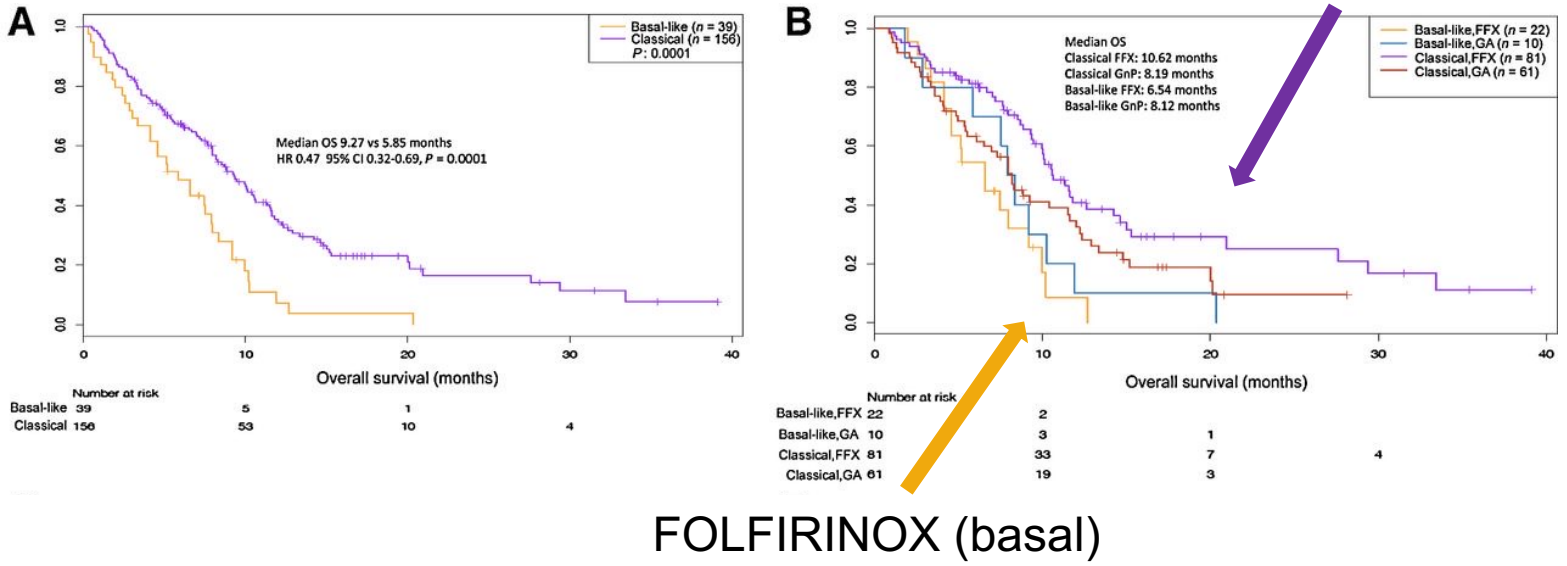
Schram, A… AACR-EORTC, 2019. Schram, A. O'Reilly, E.M…..ASCO, 2021
Schram, A. Cancer Discovery, 2022

COMPASS Trial: Non-Randomized, Metastatic 1st-Line PDAC (N= 195)

Panels A, B: Classical Moffit



Overall Survival **Classical** vs **Basal**



FOLFIRINOX (classical)

FOLFIRINOX (basal)

Panels C, D: Basal-type

Med OS 9.3m **Classical** vs 5.9m **Basal**, HR 0.47, p= 0.0001

GATA6 expression RNA ISH: Biomarker for classical vs basal and outcomes

Aung, K…Gaillinger, S. Clin Can Res, 2018. O'Kane, G…Knox, J. Clin Can Res, 2020

PASS-01 Trial: Advanced PDAC

Pancreatic **A**denocarcinoma **S**ignature **S**tratification for treatment

Ongoing

Untreated Metastatic PDAC

ECOG 0-1

No g*BRCA12, PALB2*

→ **mFOLFIRINOX** N= 75

→ **Gemcitabine/nab-P** N= 75

Correlative Science

WGS/WES (PMH/OICR)
RNAseq (PMH/OICR)
Organoid (Cold Spring H)
ctDNA (Dana Farber)
Circulating tumor cells (MSK)
Immune (JHU)

Randomization 1: 1
Primary: PFS superiority of mFFX over Gem/nabP (mFFX 7m, Gem/nab-P 5m; HR 0.7; 80% power)
Secondary: OS, RR, GATA6 (ISH, IHC)

NeoPancONE (resectable PDAC): Canadian Phase II periop mFOLFIRINOX: DFS by GAT6 expression

Conclusions: PDAC Opportunities 2022 & Beyond…

- Survival improvements for SOC therapies
- Small, although increasing subsets of patients have targeted opportunities
    - *g/sBRCA1/2, PALB2*, MSI-H, *KRAS* G12C, *KRAS* wild-type
- For all: germline testing, somatic profiling (tissue preferred; emerging cfDNA)
- In development: IO, stromal/TME targeting, DNA biology, cell signaling, metabolism; Direct *KRAS* G12D & pan *RAS* inhibitors; multiple other *RAS* directed approaches
- Novel clinical trial designs

Breakfast with the Investigators: Ovarian Cancer

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Sunday, June 5, 2022

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

Faculty

Antonio González-Martín, MD, PhD

Joyce F Liu, MD, MPH

Kathleen N Moore, MD, MS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME links will be posted in the chat (Zoom participants only) and emailed to all participants within 24 hours of the program.

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