Overview

Sunday, March 24th

Module 10: 7:30 AM – 8:20 AM — Multiple Myeloma

Module 11: 8:20 AM – 9:10 AM — Gastroesophageal Cancers

Module 12: 9:30 AM – 10:20 AM — Hepatobiliary Cancers

Module 13: 10:20 AM – 11:10 AM — Colorectal Cancer

Module 14: 11:10 AM – 12:00 PM — Pancreatic Cancer

Agenda

Module 1: Hepatocellular Carcinoma (HCC) — Dr Abou-Alfa

Module 2: Biliary Tract Cancers (BTCs) — Dr Finn

Agenda

Module 1: Hepatocellular Carcinoma (HCC) — Dr Abou-Alfa

Module 2: Biliary Tract Cancers (BTCs) — Dr Finn

Hepatocellular Carcinoma (HCC)

Ghassan Abou-Alfa

March 24, 2024

Memorial Sloan Kettering Cancer Center

Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Autem Therapeutics, Berry Genomics, BioNTech SE, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Merck, Merus BV, Neogene Therapeutics, Novartis, Servier Pharmaceuticals LLC, Tempus, Vector Pharma, Yiviva
Contracted Research	Agenus Inc, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, BioNTech SE, Bristol Myers Squibb, Digestive Care Inc, Elicio Therapeutics, Genentech, a member of the Roche Group, Helsinn Healthcare SA, Puma Biotechnology Inc, QED Therapeutics, Yiviva
Nonrelevant Financial Relationship	Parker Institute for Cancer Immunotherapy

78 year old woman

- History of hepatitis C secondary to a dental procedure 40 years ago
- Performance ECOG 0
- 6 cm liver segment, 7/8 lesion concerning for HCC. No other sites of disease
- Child-Pugh score A5

78 year old woman with resected HCC

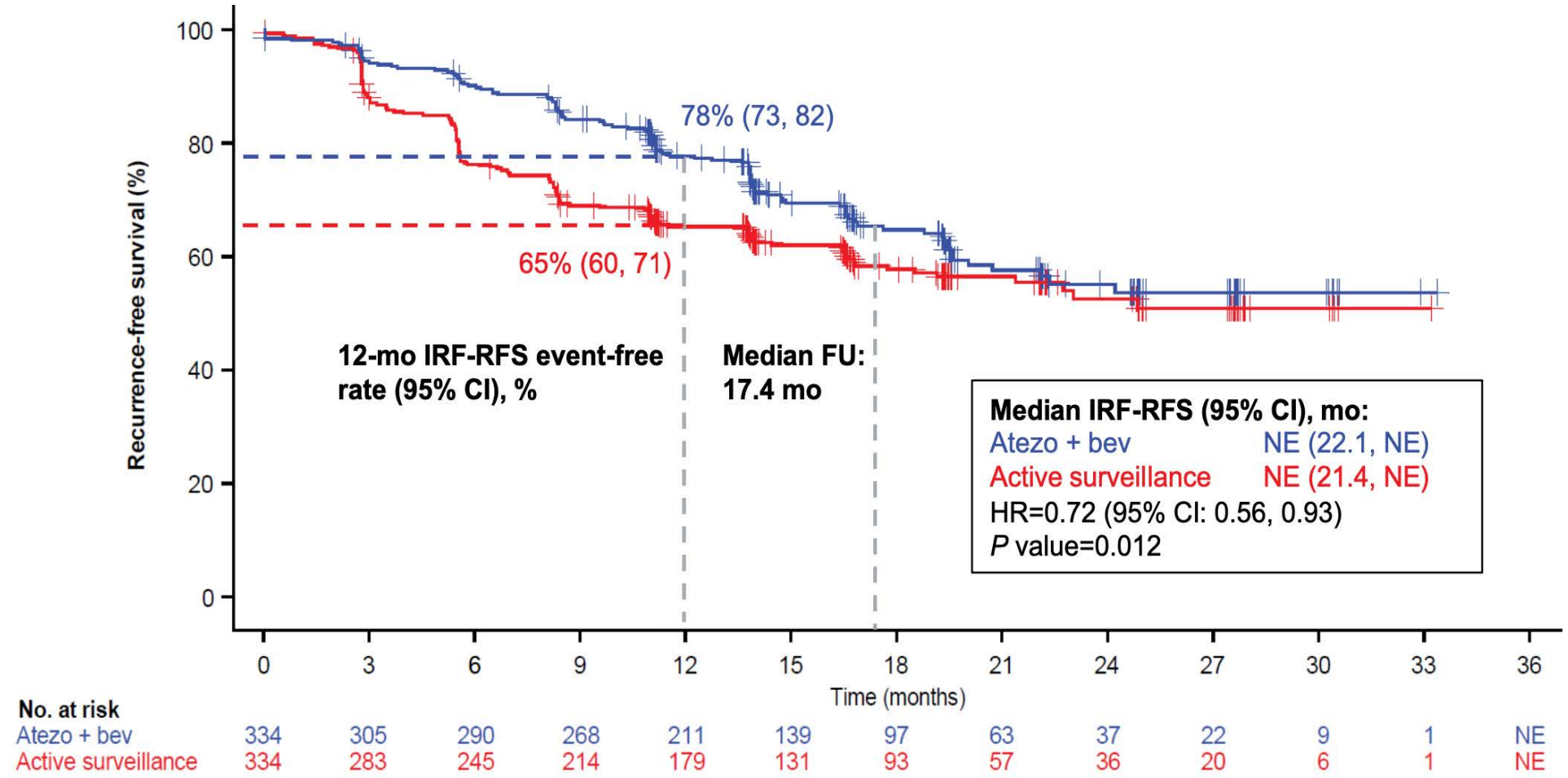
- Tumor resected
- Pathology positive for HCC intermediate grade. Normal liver shows signs of cirrhosis
- Patient recovered well
- She comes to our clinic one month later and says: “I am eager to start chemotherapy. I want to live forever.”

78 year old woman with HCC recurrence

- Adjuvant therapy was not prescribed

- Recurrent liver disease in segment 4/5 with close to vascular involvement. New lesion 8 cm.

IMbrave050 Adjuvant Study



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

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

Chow, P et al. AACR April 2023, New Orleans, LA, USA
Qin S et al. Lancet 2023;402:1835-47.

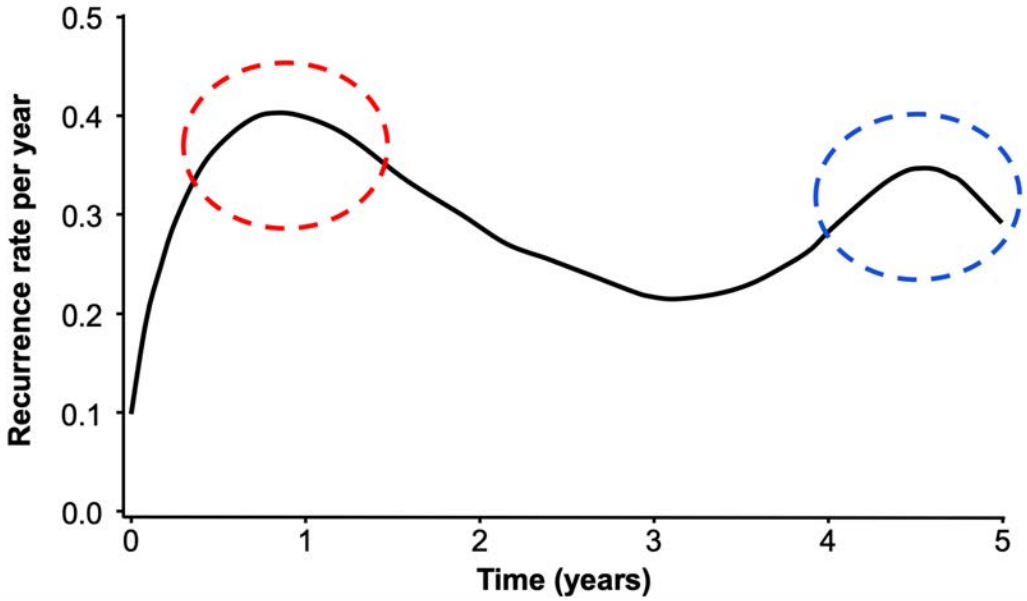
Early- and Late-Stage HCC Recurrence

Factors contributing to early phase (<2 years) recurrence

	Parameter estimate	Standard error	Wald chi-square	*P* value	Hazard ratio	95% CI
Microscopic vascular invasion	0.86	0.194	19.75	<0.0001	2.36	1.62–3.45
Serum AFP value ≥32 ng/ml	0.61	0.195	9.66	0.0019	1.831	1.25–2.68
Non-anatomical resection[a]	0.5	0.192	6.79	0.0091	1.65	1.13–2.40

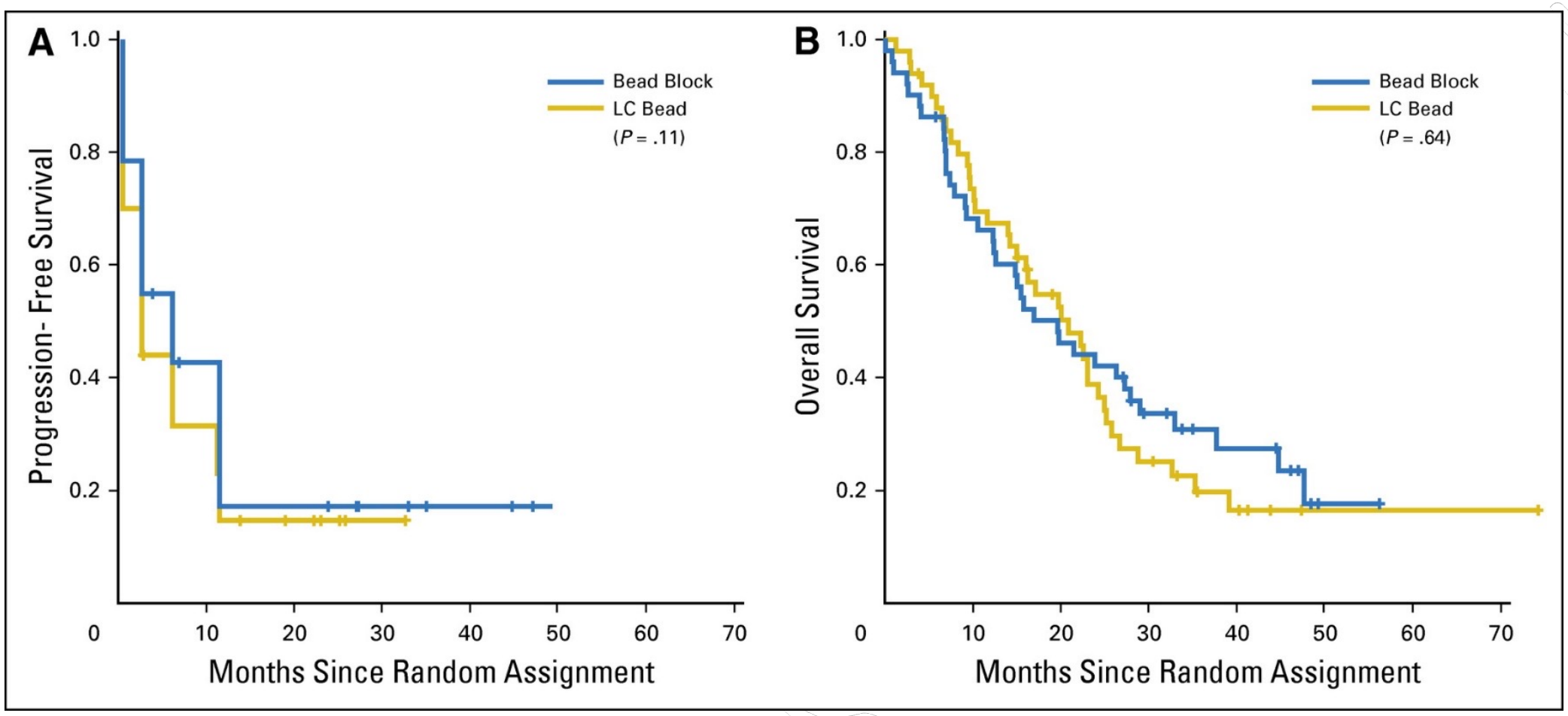
Factors contributing to late phase (≥2 years) recurrence

	Parameter estimate	Standard error	Wald chi-square	*P* value	Hazard ratio	95% CI
Grade of hepatitis activity[a]	0.33	0.21	2.54	0.11	1.39	0.93–2.07
Tumor nodule multiplicity	0.22	0.11	3.86	0.05	1.24	1.00–1.54
Gross tumor classifocation	0.35	0.17	4.43	0.036	1.42	1.02–1.98



Imamura H, et al. J Hepatol. 2003 Feb;38(2):200-7 and Chow, P et al. AACR April 2023, New Orleans, LA, USA

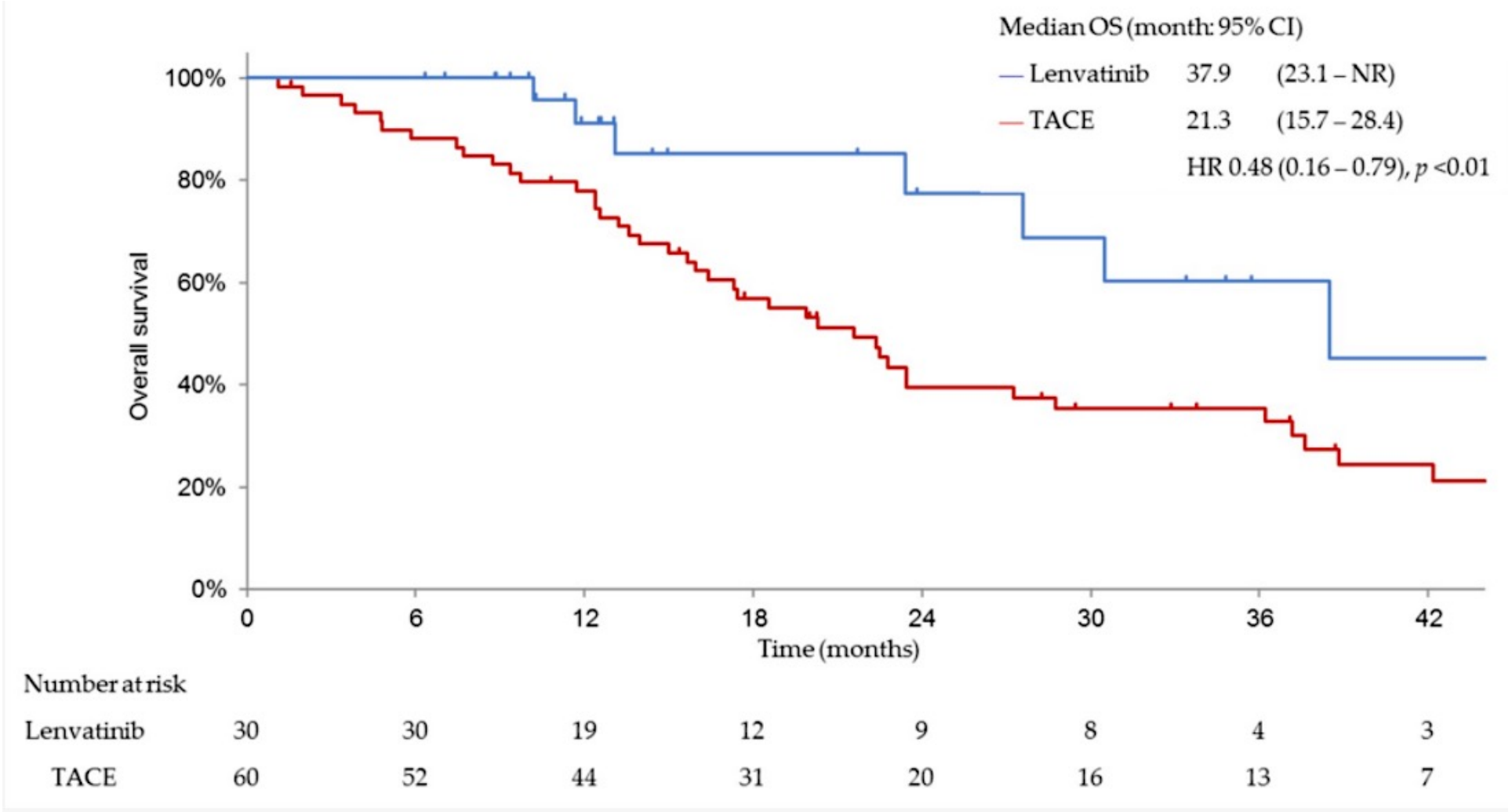
TACE Today's Outcomes



(A) Progression-free survival 6.2 versus 2.8 months (hazard ratio, 1.36; 95% CI, 0.91 to 2.05; P = .11)
(B) Overall survival, 19.6 versus 20.8 months (hazard ratio, 1.11; 95% CI, 0.71 to 1.76; *P* = .64)

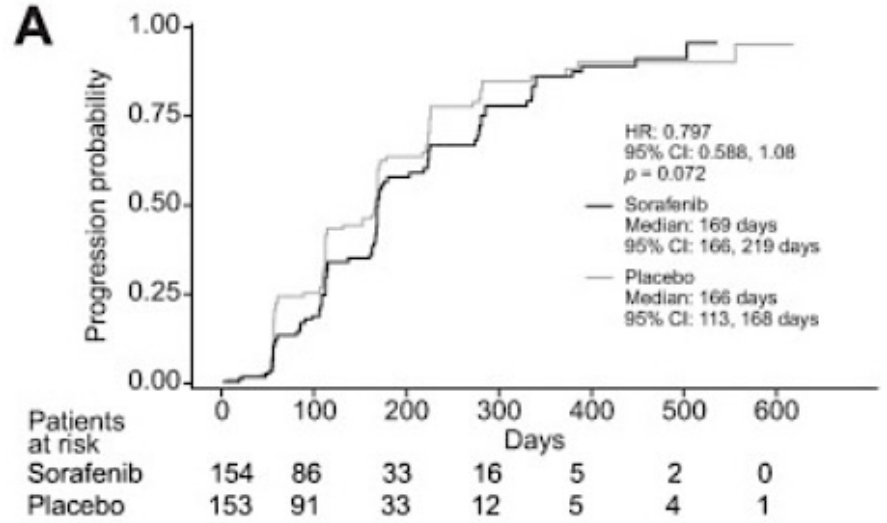
Brown KT, Abou-Alfa, GK, et al. J Clin Oncol. 2016 Jun 10;34(17):2046-53

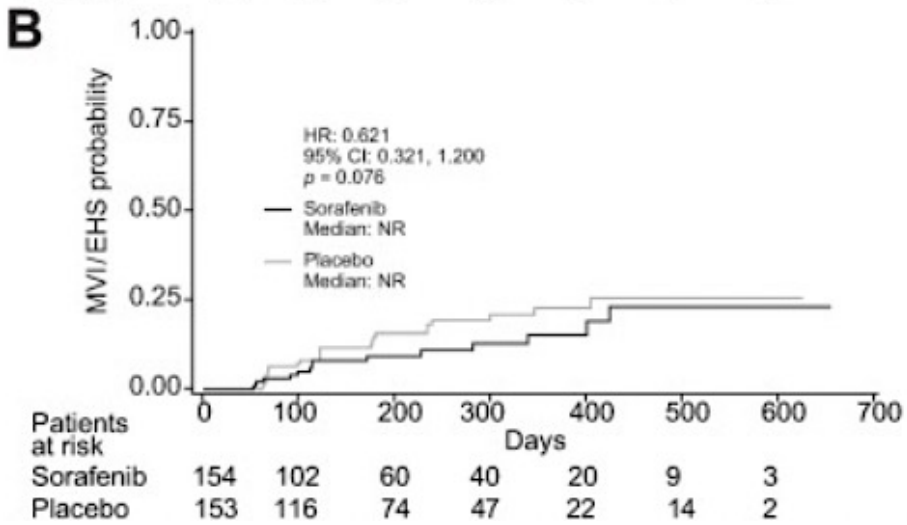
Lenvatinib as Initial Treatment for Intermediate-Stage HCC Beyond Up-To-Seven Criteria and Child–Pugh A

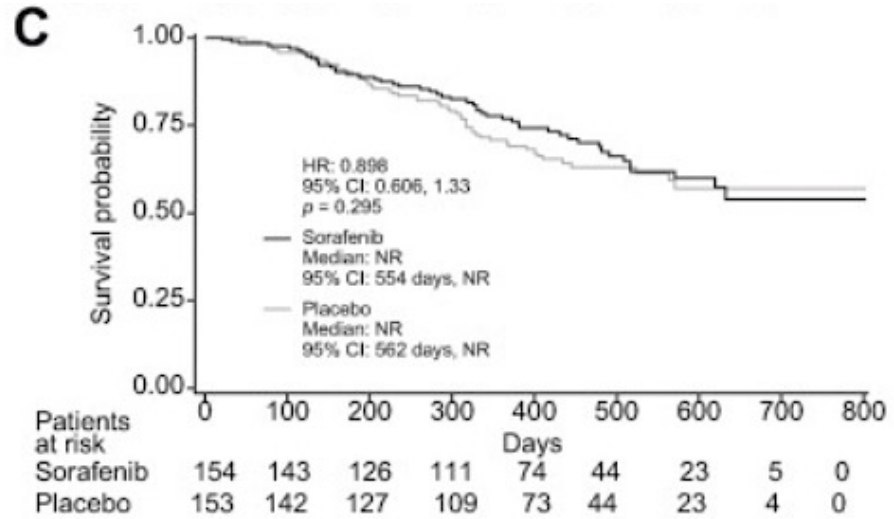


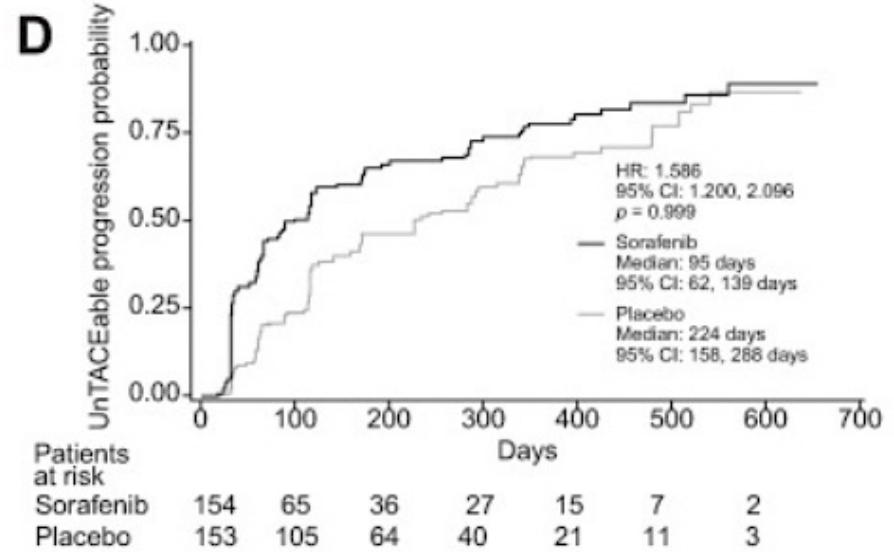
Kudo M, et al. Cancers (Basel). 2019 Jul 31;11(8):1084.

Sorafenib + TACE: SPACE
TTP (A), MVI/EHS (B), OS (C), and TTUP (D)



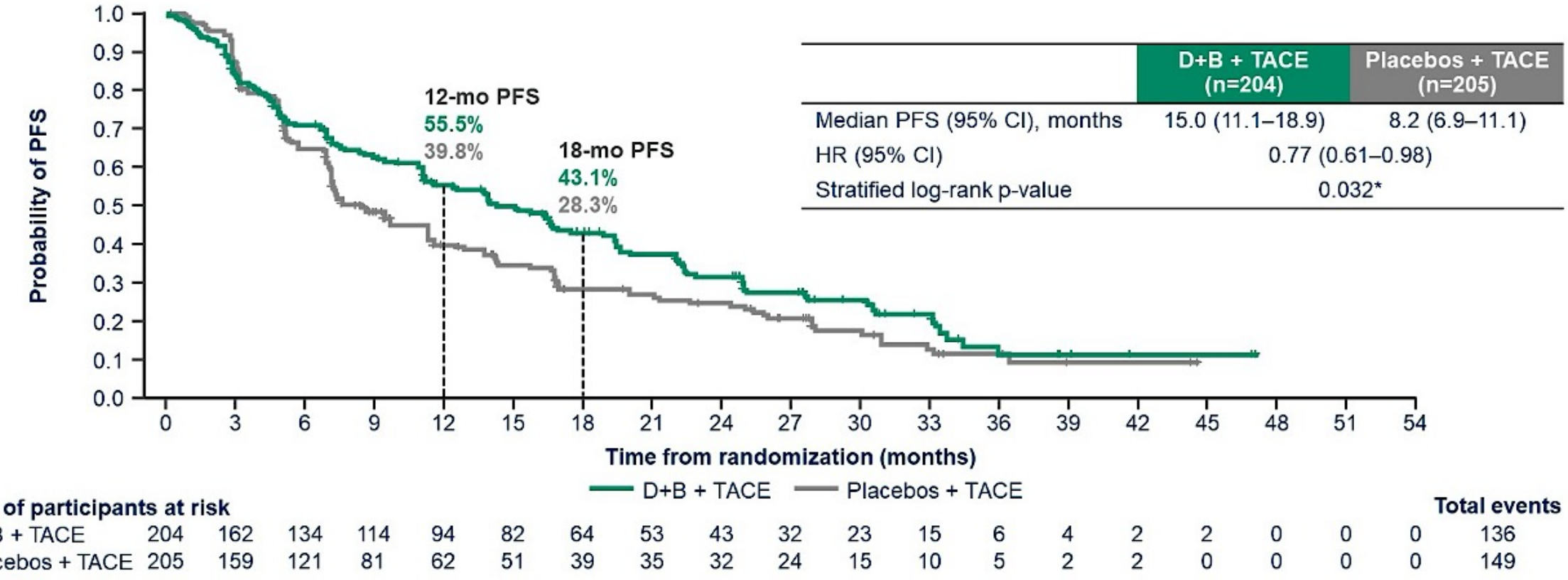






Lencioni R, et al. J Hepatol. 2016 May;64(5):1090-1098.

EMERALD-1



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

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

Median (range) duration of follow-up in censored participants, D+B + TACE 16.7 (0.03–47.1) months, Placebos + TACE 10.3 (0.03–44.3) months. **Median (95% CI) duration of follow-up** in all participants using the reverse Kaplan-Meier method, D+B + TACE 22.2 (16.7–27.3) months, Placebos + TACE 26.3 (16.7–30.4) months. PFS was assessed by BICR (RECIST v1.1)

*The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mo, months, PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

Lencioni R, et al. et al. GI ASCO January 19, 2024

EMERALD-3

POPULATION

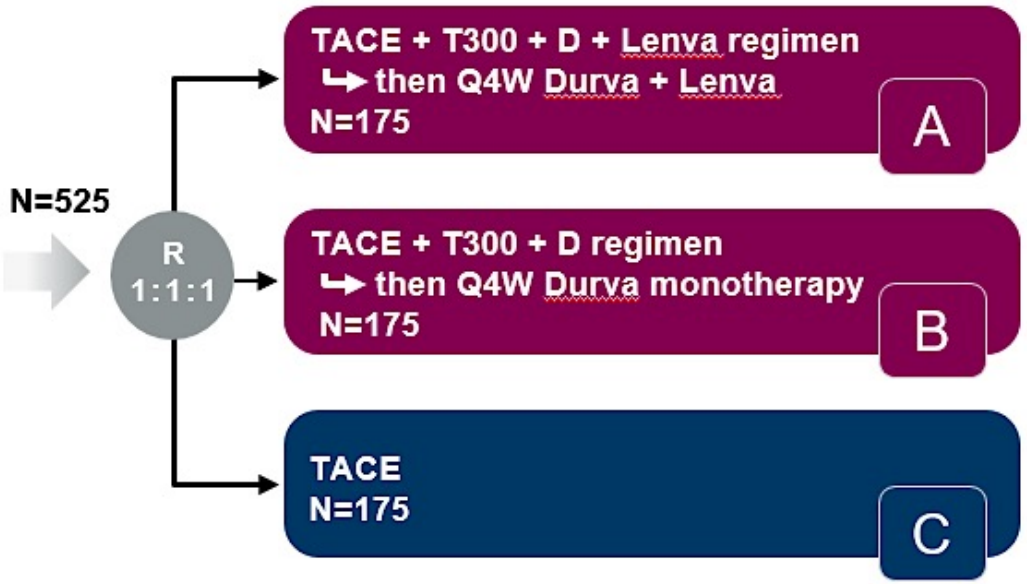
- Pathologically or radiologically confirmed HCC
- Unsuitable for curative treatment e.g. surgical resection, transplantation, ablation
- No prior systemic therapy
- No extrahepatic disease
- Child-Pugh class A
- ECOG: 0 or 1
- Exclude Vp3 and Vp4

Stratification factors

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

TREATMENT

Open label, Phase-3, multi-center study



ENDPOINTS

Primary Endpoint:

PFS (RECIST 1.1 by BICR)

Secondary Endpoint:

OS, ORR, Landmark OS, PROs, Safety

Dosing:

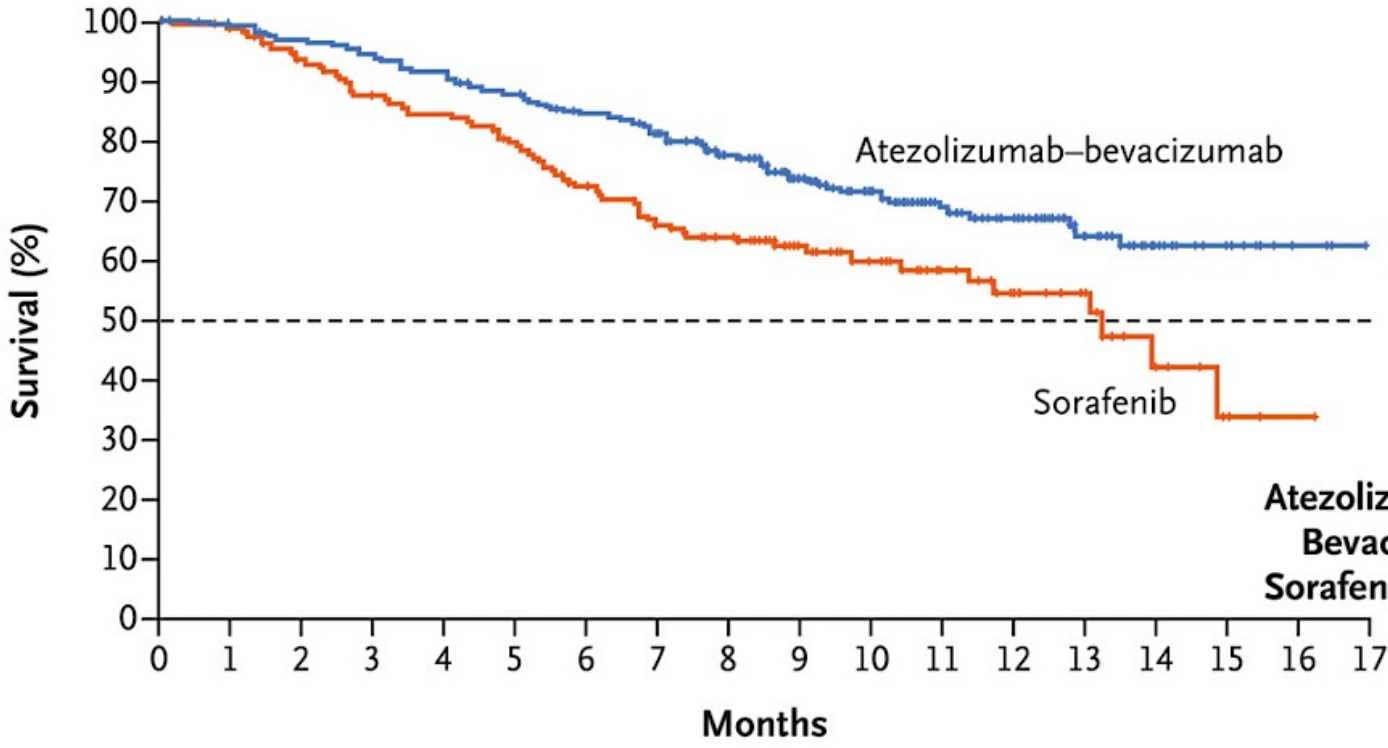
- Treme 300mg + Durva 1500mg IV on Cycle 1 Day 1(C1D1) for one dose
- Followed by Durva Q4W until progression
- Lenvatinib will start Day 1 (D1=first day of systemic therapy) and continue daily

TACE modalities :

- cTACE, DEB-TACE

Abou-Alfa GK et al. Annals of Oncology . VOLUME 33, SUPPLEMENT 7, S874, SEPTEMBER 2022

IMbrave150



	No. of Events/ No. of Patients (%)	Median Overall Survival (95% CI)	Overall Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

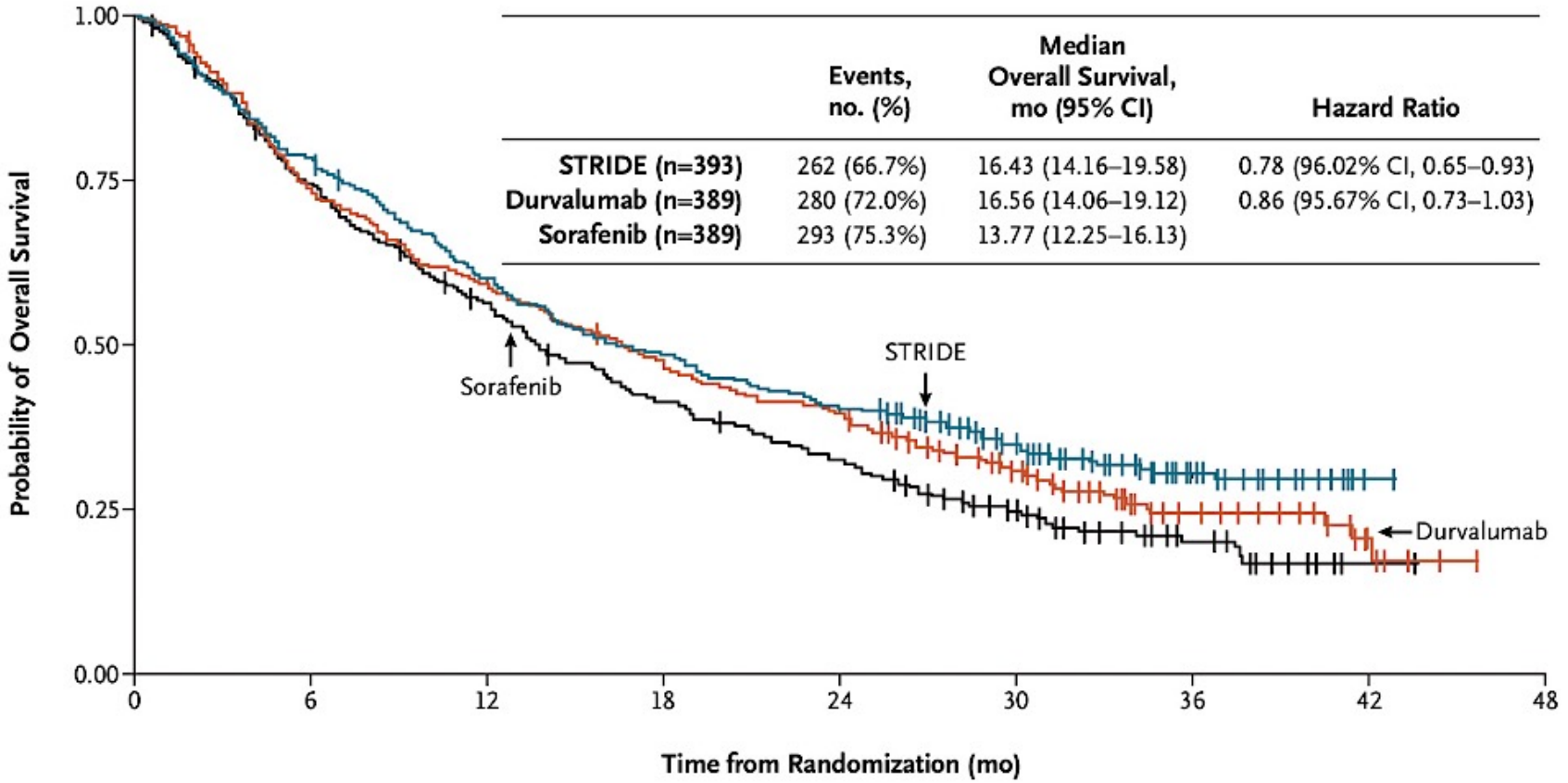
Stratified hazard ratio for death, 0.58 (95% CI, 0.42–0.79)
P<0.001

No. at Risk

Atezolizumab–bevacizumab	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

Finn R. et al. N Engl J Med. 2020 May 14;382(20):1894-1905.

HIMALAYA

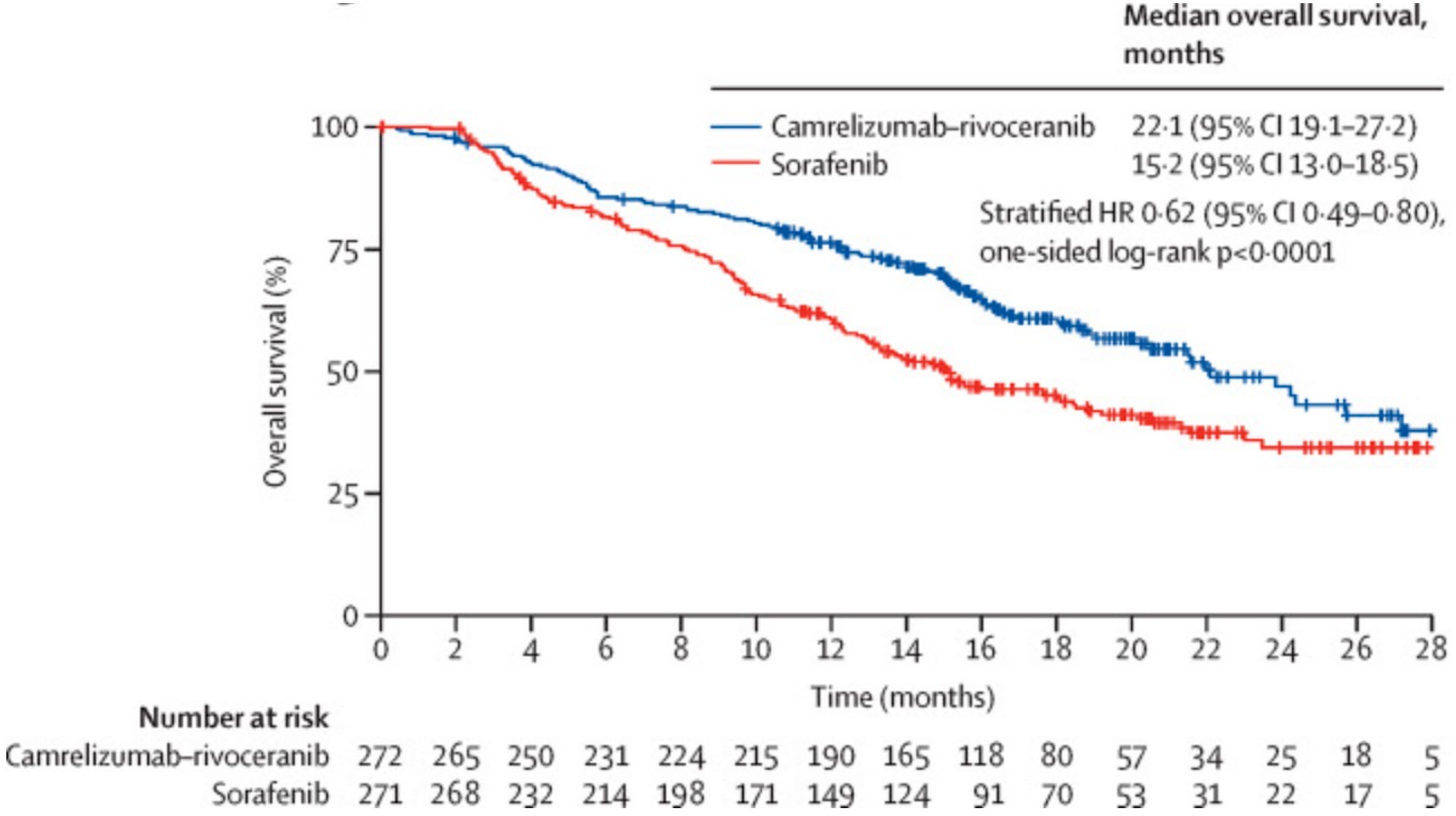


	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

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

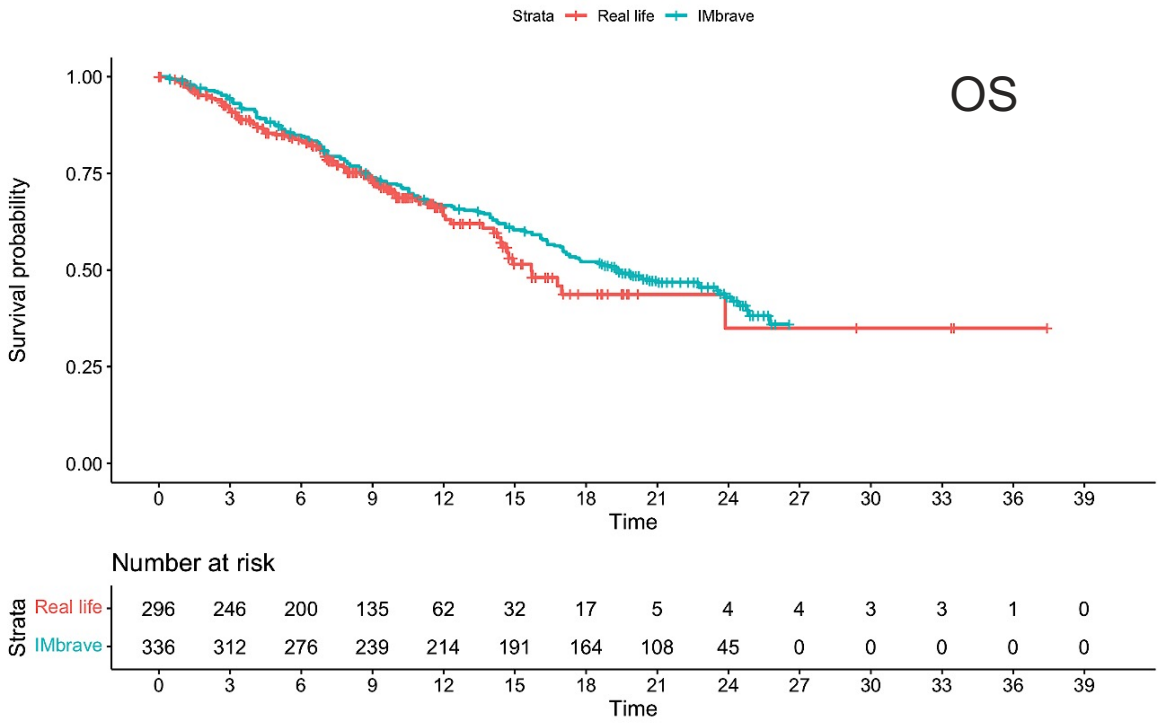
Abou-Alfa GK et al. NEJM Evidence. Published June 6, 2022.
DOI:https://doi.org/10.1056/EVIDoa2100070

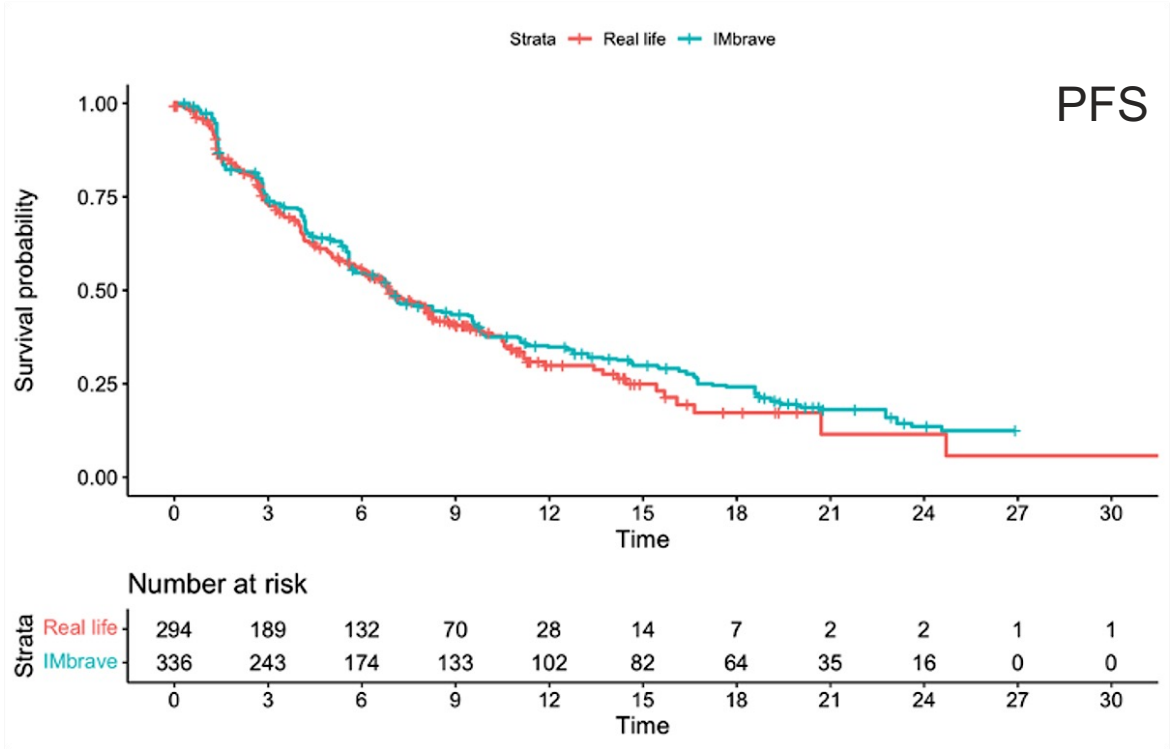
CARES-310



Qin S, et al., Lancet. 2023 Sep 30;402(10408):1133-1146.

AB-real



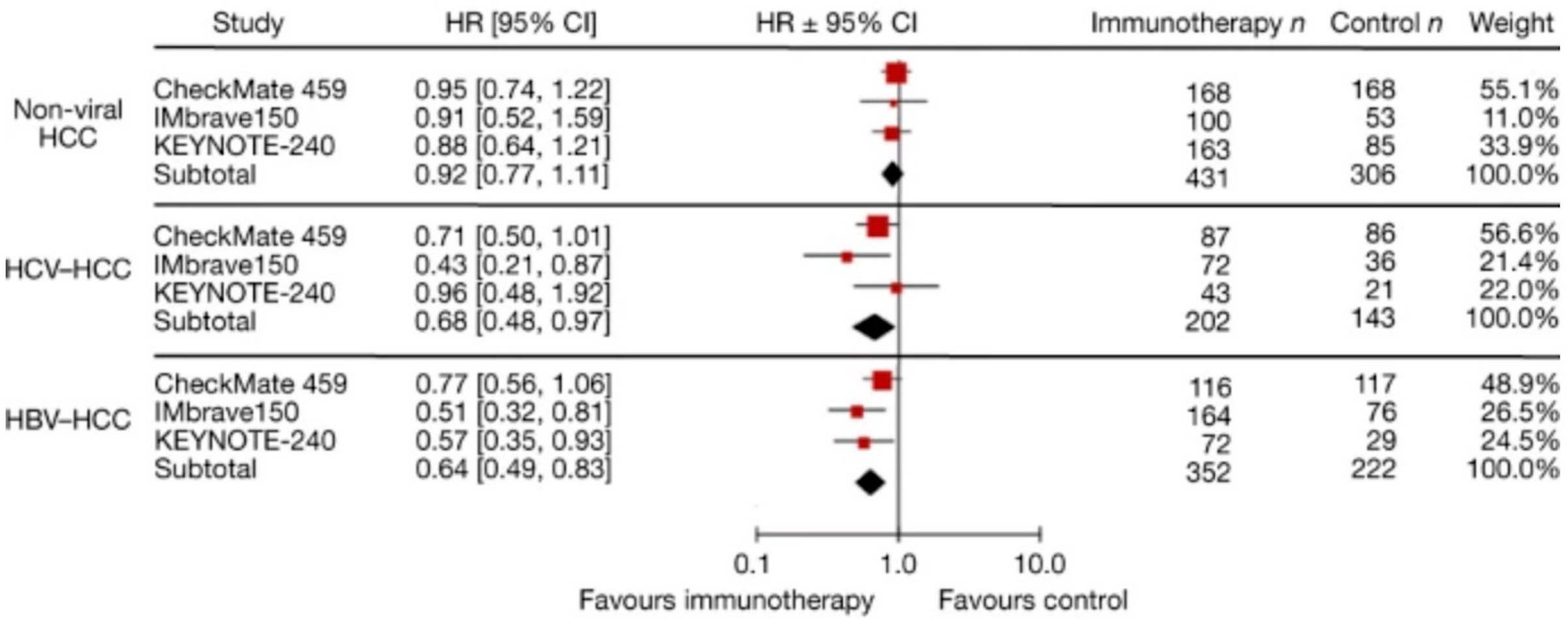


AB-real	IMbrave150
mOS: 15.74 months (95%CI: 14.4-NA)	mOS: 19.20 months (95%CI: 17.0-23.7)
HR: 0.87 (95%CI: 0.67-1.13; p=0.3)	

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

Fulgenzi C, et al. Eur J Cancer. 2022 Nov;175:204-213

Etiology and Response to Checkpoint Inhibitors



Pfister D, et al. Nature. 2021 Apr;592(7854):450-456.

IMbrave150 Patient Demographics

Table 1. Patient Characteristics at Baseline.*

Variable	Atezolizumab–Bevacizumab (N = 336)	Sorafenib (N = 165)
Median age (IQR) — yr	64 (56–71)	66 (59–71)
Male sex — no. (%)	277 (82)	137 (83)
Geographic region — no. (%)		
Asia, excluding Japan	133 (40)	68 (41)
Rest of the world†	203 (60)	97 (59)
ECOG performance status score — no. (%)‡		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child–Pugh classification — no./total no. (%)§		
A5	239/333 (72)	121/165 (73)
A6	94/333 (28)	44/165 (27)
Barcelona Clinic liver cancer stage — no. (%)¶		
A	8 (2)	6 (4)
B	52 (15)	26 (16)
C	276 (82)	133 (81)
Alpha-fetoprotein ≥400 ng per milliliter — no. (%)	126 (38)	61 (37)
Presence of macrovascular invasion, extrahepatic spread, or both — no. (%)	258 (77)	120 (73)
Macrovascular invasion	129 (38)	71 (43)
Extrahepatic spread	212 (63)	93 (56)
Varices — no. (%)		
Present at baseline	88 (26)	43 (26)
Treated at baseline	36 (11)	23 (14)
Cause of hepatocellular carcinoma — no. (%)		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Nonviral‖	100 (30)	53 (32)
Prior local therapy for hepatocellular carcinoma — no. (%)	161 (48)	85 (52)

Finn R. et al. N Engl J Med. 2020 May 14;382(20):1894-1905.

HIMALAYA Patient Demographics

Parameter	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Median age (range) — yr	65.0 (22–86)	64.0 (20–86)	64.0 (18–88)
Male sex	327 (83.2)	323 (83.0)	337 (86.6)
Region			
Asia (excluding Japan)	156 (39.7)	167 (42.9)	156 (40.1)
Rest of world (including Japan)†	237 (60.3)	222 (57.1)	233 (59.9)
ECOG performance status score‡			
0	244 (62.1)	237 (60.9)	241 (62.0)
1	148 (37.7)	150 (38.6)	147 (37.8)
2	1 (0.3)	2 (0.5)	1 (0.3)
Child-Pugh class/score§			
A/5	295 (75.1)	284 (73.0)	277 (71.2)
A/6	92 (23.4)	96 (24.7)	102 (26.2)
B/7	4 (1.0)	8 (2.1)	10 (2.6)
Other¶	2 (0.5)	1 (0.3)	0
BCLC stage‖			
B	77 (19.6)	80 (20.6)	66 (17.0)
C	316 (80.4)	309 (79.4)	323 (83.0)
Etiology			
HBV	122 (31.0)	119 (30.6)	119 (30.6)
HCV	110 (28.0)	107 (27.5)	104 (26.7)
Nonviral**	161 (41.0)	163 (41.9)	166 (42.7)
Macrovascular invasion	103 (26.2)	94 (24.2)	100 (25.7)
Extrahepatic spread	209 (53.2)	212 (54.5)	203 (52.2)
AFP ≥400 ng/ml	145 (36.9)	137 (35.2)	124 (31.9)
PD-L1 status††			
Positive	148 (37.7)	154 (39.6)	148 (38.0)
Negative	189 (48.1)	190 (48.8)	181 (46.5)
Missing	52 (13.2)	42 (10.8)	45 (11.6)
Prior disease-related radiotherapy	48 (12.2)	32 (8.2)	37 (9.5)

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

CARES-310

	Camrelizumab–rivoceranib (n=272)	Sorafenib (n=271)
Age, years	58 (48–66)	56 (47–64)
<65	191 (70%)	210 (77%)
≥65	81 (30%)	61 (23%)
Sex		
Male	227 (83%)	230 (85%)
Female	45 (17%)	41 (15%)
Geographical region		
Asia*	225 (83%)	224 (83%)
Non-Asia†	47 (17%)	47 (17%)
Race		
Asian	226 (83%)	224 (83%)
White	44 (16%)	46 (17%)
Black or African American	1 (<1%)	0
Other	1 (<1%)	1 (<1%)
Ethnicity		
Hispanic or Latinx	4 (1%)	2 (<1%)
Macrovascular invasion, extrahepatic metastasis, or both	200 (74%)	200 (74%)
Macrovascular invasion‡	40 (15%)	52 (19%)
Extrahepatic metastasis	175 (64%)	180 (66%)
Aetiology§		
Hepatitis B virus	208 (76%)	197 (73%)
Hepatitis C virus	22 (8%)	29 (11%)
Non-viral¶	42 (15%)	45 (17%)
Previous local therapy for hepatocellular carcinoma	161 (59%)	150 (55%)
PD-L1 expression		
TPS <1%	220 (81%)	212 (78%)
TPS ≥1%	32 (12%)	39 (14%)
CPS <1	190 (70%)	180 (66%)
CPS ≥1	62 (23%)	71 (26%)
Unknown	20 (7%)	20 (7%)

Data are median (IQR) or n (%). CPS=combined positive score. TPS=tumour proportion score.

Aetiology§

Hepatitis B virus 208 (76%) 197 (73%)

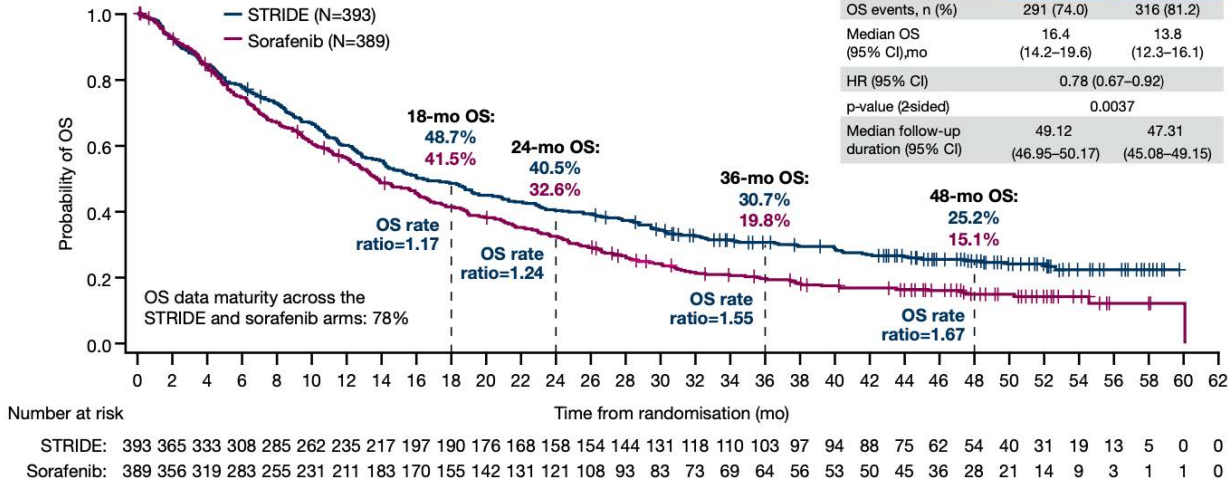
Hepatitis C virus 22 (8%) 29 (11%)

Non-viral¶ 42 (15%) 45 (17%)

Qin S, et al., Lancet. 2023 Sep 30;402(10408):1133-1146.

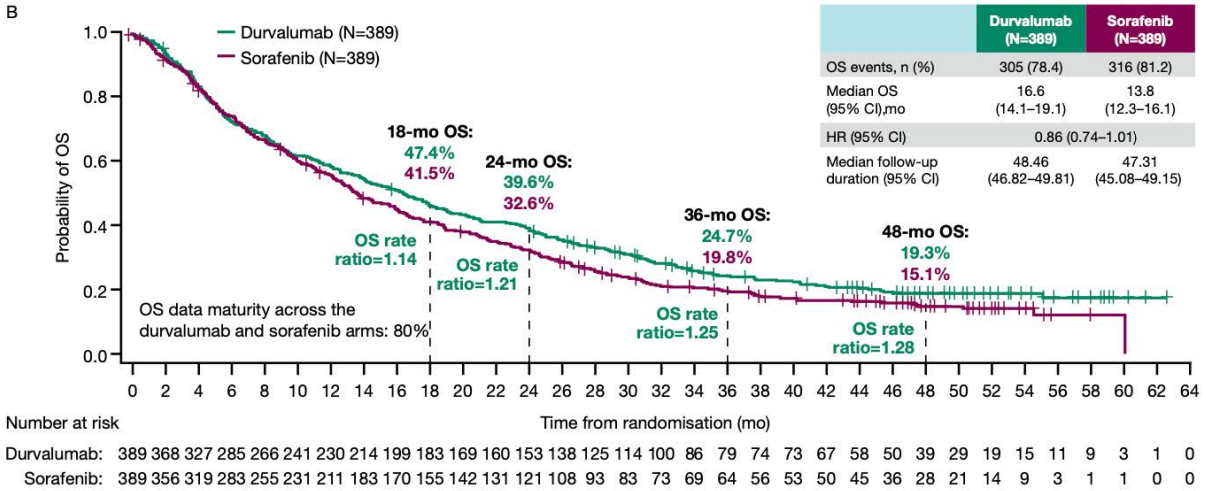
HIMALAYA 4 Years Overall Survival

A



	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS (95% CI),mo	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (95% CI)	0.78 (0.67–0.92)	
p-value (2sided)	0.0037	
Median follow-up duration (95% CI)	49.12 (46.95–50.17)	47.31 (45.08–49.15)

B



	Durvalumab (N=389)	Sorafenib (N=389)
OS events, n (%)	305 (78.4)	316 (81.2)
Median OS (95% CI),mo	16.6 (14.1–19.1)	13.8 (12.3–16.1)
HR (95% CI)	0.86 (0.74–1.01)	
Median follow-up duration (95% CI)	48.46 (46.82–49.81)	47.31 (45.08–49.15)

OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. The OS rate for STRIDE versus sorafenib at 36 months had a nominal 2-sided p-value of 0.0006. The noninferiority margin for durvalumab versus sorafenib was 1.08. Updated analysis data cut-off: 23 January 2023.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, month; MVI, macrovascular invasion; OS, overall survival; PS, performance status.

Sangro B, et al. APPLE 2023 Seoul South Korea

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

Press Release: March 20, 2024

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

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

The company will complete a full evaluation of the data and work with investigators to share the results with the scientific community at an upcoming medical conference, as well as discuss with health authorities."

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

RTP RESEARCH TO PRACTICE

Should be Available Options

First Line	Atezolizumab + Bevacizumab	Durvalumab + Tremelimumab	Sorafenib	Lenvatinib		
Second Line	Regorafenib	Cabozantinib	Ramucirumab	Pembrolizumab	Nivolumab	Ipilimumab + Nivolumab
Third Line	Cabozantinib					

Ghassan K. Abou-Alfa personal teaching perspective

HCC Summary

- Continued increasing incidence of HCC worldwide mainly due to MASH
- Adjuvant therapy for HCC not there yet
- Local plus systemic is holding the future from both ends
- Checkpoint inhibitors and combination of are the mainstay therapy for advanced HCC
- Response to checkpoint inhibitors is dependent on the tumor immune microenvironment
- Access to checkpoint inhibitors remains a challenge worldwide

Agenda

Module 1: Hepatocellular Carcinoma (HCC) — Dr Abou-Alfa

Module 2: Biliary Tract Cancers (BTCs) — Dr Finn

Systemic Therapy for BTC

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Disclosures

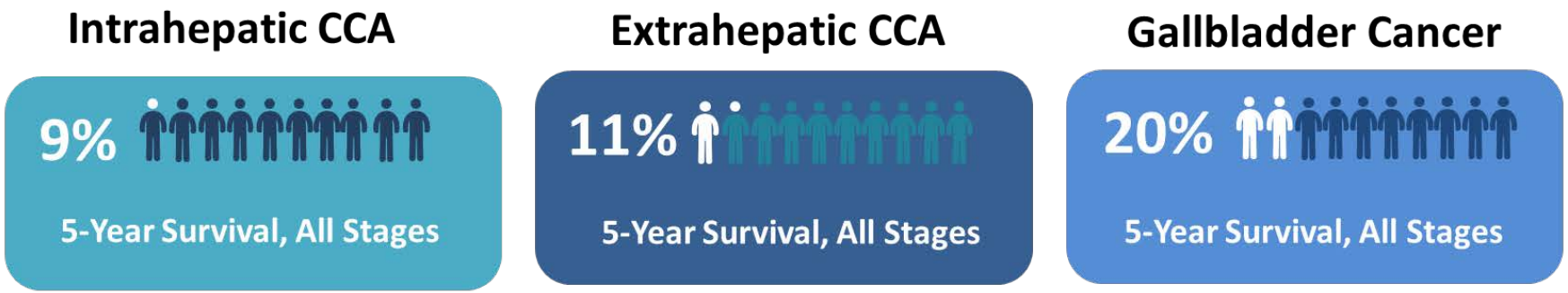
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, CStone Pharmaceuticals, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Hengrui Therapeutics Inc, Lilly, Merck, Pfizer Inc
Contracted Research	Bristol Myers Squibb, Eisai Inc, Genentech, a member of the Roche Group, Merck, Pfizer Inc
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP
Speakers Bureau	Genentech, a member of the Roche Group

Case: Front Line- IO

- 47 y/o female, presents to PMD with increasing RUQ pain
- PMH: HTN, Borderline DM
- Exam- unremarkable except for palpable liver
- Labs: Essentially normal except AST 98, ALT 86, Alk phos 360, T bili 1.8
- AFP 45, CA 19-9 390
- Imaging: 8 cm mass in rt lobe, extending to the left
- Small nodules in the lungs
- Biopsy: well diff cholangio ca,
  - Foundation Medicine: FGFR2 translocation

Biliary Tract Cancer Survival Statistics

NIH SEER, 5-year Relative Survival



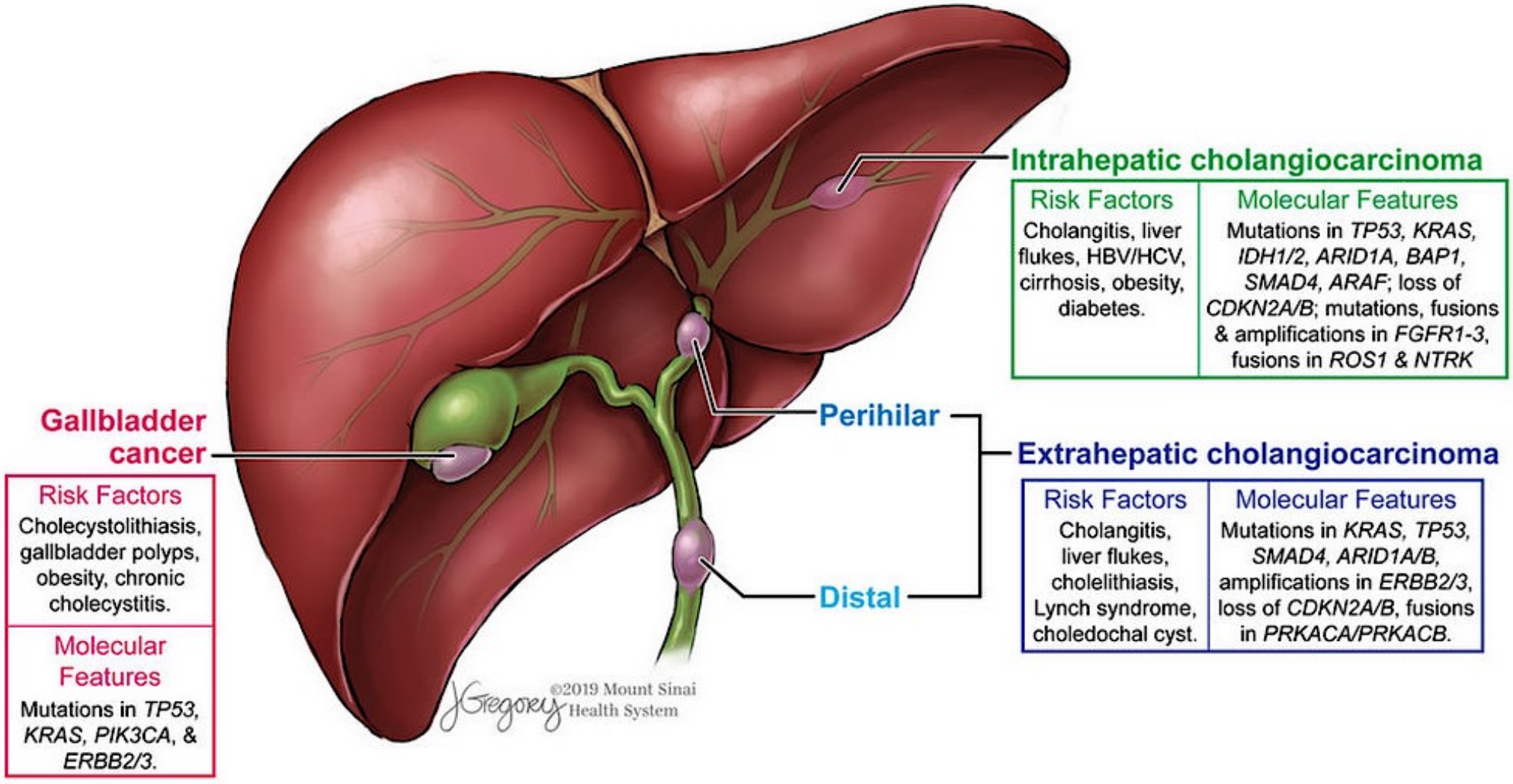
9%

5-year relative survival rate by stage			
SEER stage	**Intrahepatic**	**Extrahepatic**	**Gallbladder**
Localized	23%	18%	69%
Regional	9%	18%	28%
Distant	3%	2%	3%

SEER = Surveillance, Epidemiology, and End Results Program; CCA= Cholangiocarcinoma

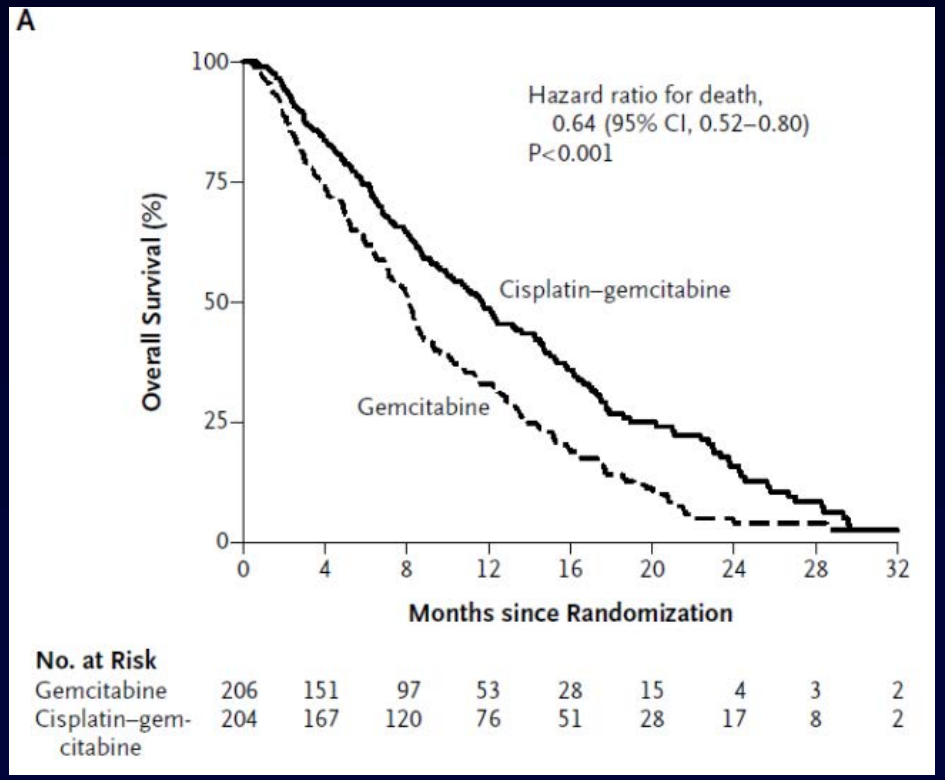
American cancer society. Gall Bladder Cancer. www.cancer.org. Accessed 12/02/23; NIH SEER Program. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer; Gallbladder Cancer https://seer.cancer.gov/statfacts. Accessed 11/18/23.

Heterogeneity Among Biliary Tract Cancers

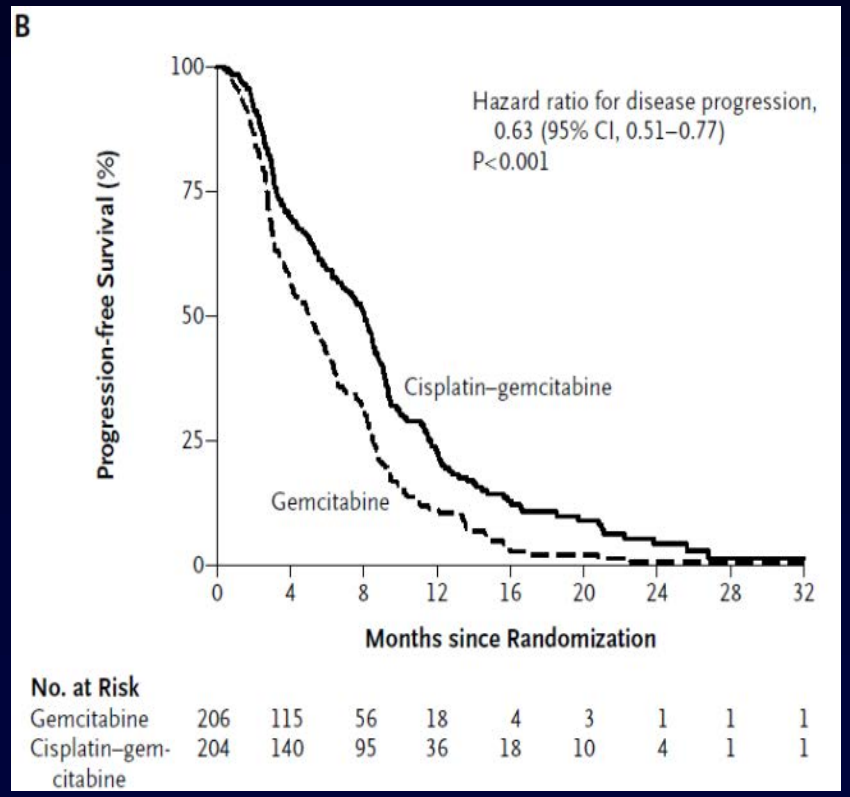


Haber PK. *Discov Med*. 2019;28(155):255-265.

Gemcitabine and cisplatin: the SOC for >10 years



OS: 11.7 v 8.1 mos



PFS: 8.0 v 5.0 mos

ORR: 26.1% v 15.5%

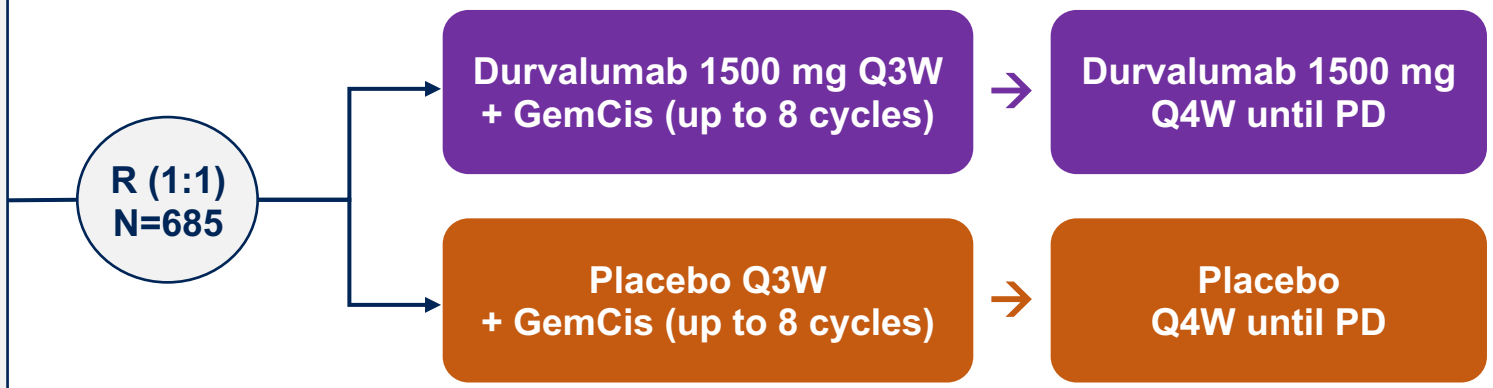
Valle NEJM 2010

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)



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.

Patient demographics and baseline characteristics

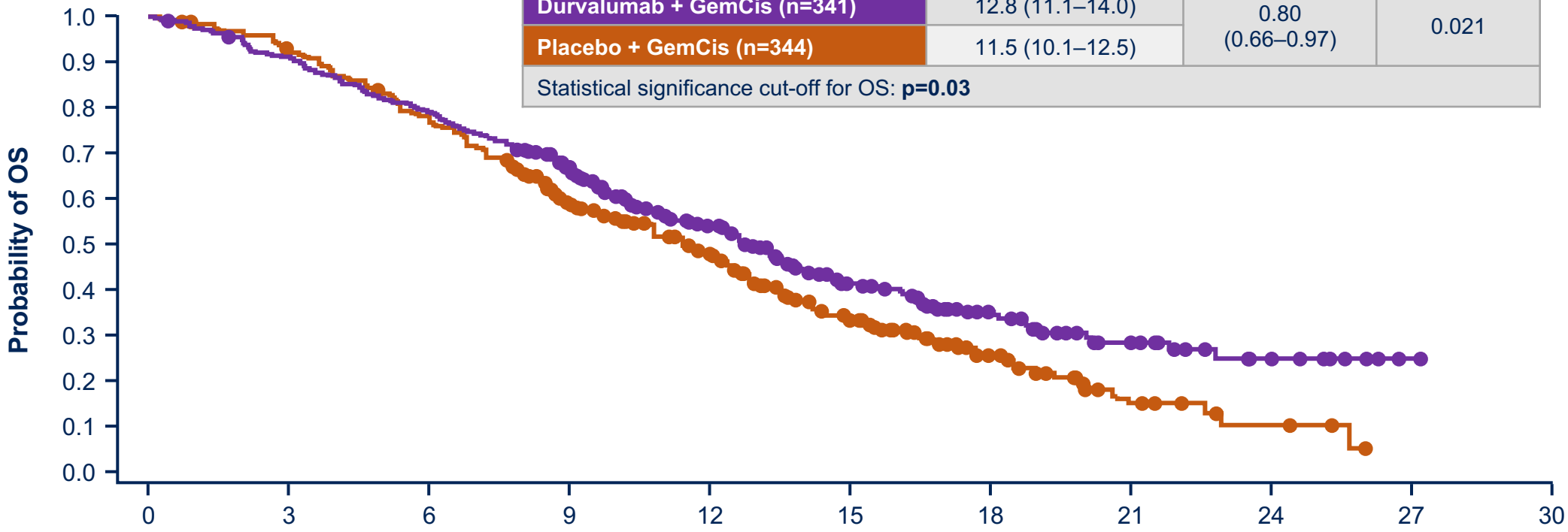
	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Median age (range), years	64 (20–84)	64 (31–85)
Sex, female, n (%)	172 (50.4)	168 (48.8)
Race, n (%)		
Asian	185 (54.3)	201 (58.4)
White	131 (38.4)	124 (36.0)
Black or African American	8 (2.3)	6 (1.7)
American Indian or Alaska Native	0	1 (0.3)
Other	17 (5.0)	12 (3.5)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of the world	163 (47.8)	148 (43.0)
ECOG PS 0 at screening, n (%)	173 (50.7)	163 (47.4)
Primary tumor location at diagnosis, n (%)		
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)
Disease status at randomization, n (%)		
Initially unresectable	274 (80.4)	279 (81.1)
Recurrent	67 (19.6)	64 (18.6)
Disease classification at diagnosis,* n (%)		
Metastatic	303 (88.9)	286 (83.1)
Locally advanced	38 (11.1)	57 (16.6)
PD-L1 expression,* n (%)		
TAP ≥1%	197 (57.8)	205 (59.6)
TAP <1%	103 (30.2)	103 (29.9)

*Data missing for remaining patients. Unless otherwise indicated, measurements were taken at baseline.

ECOG, Eastern Cooperative Oncology Group; GemCis, gemcitabine and cisplatin; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

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**			



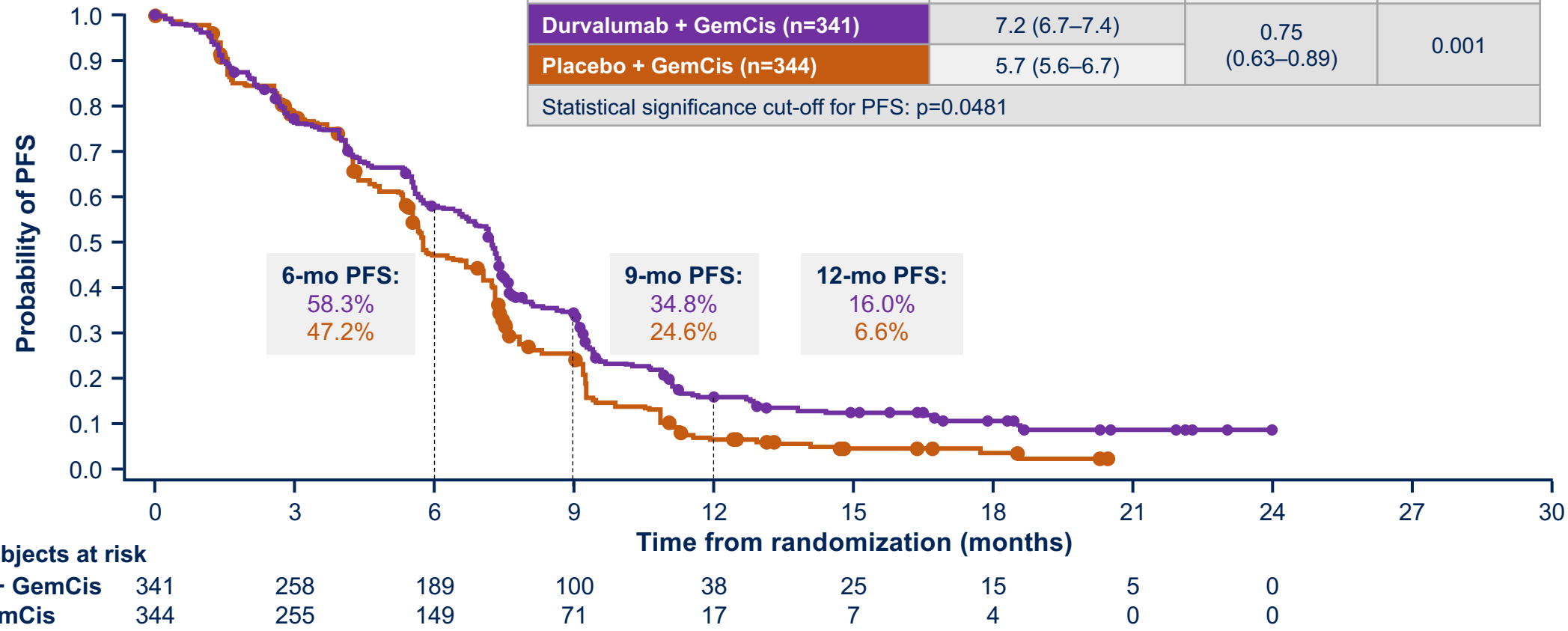
Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

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.

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			

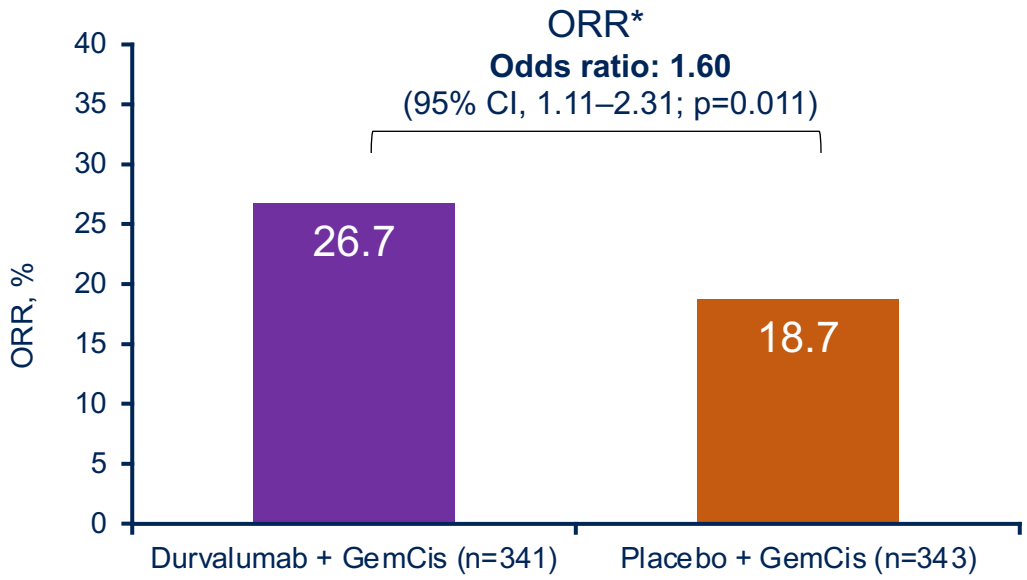


Number of subjects at risk

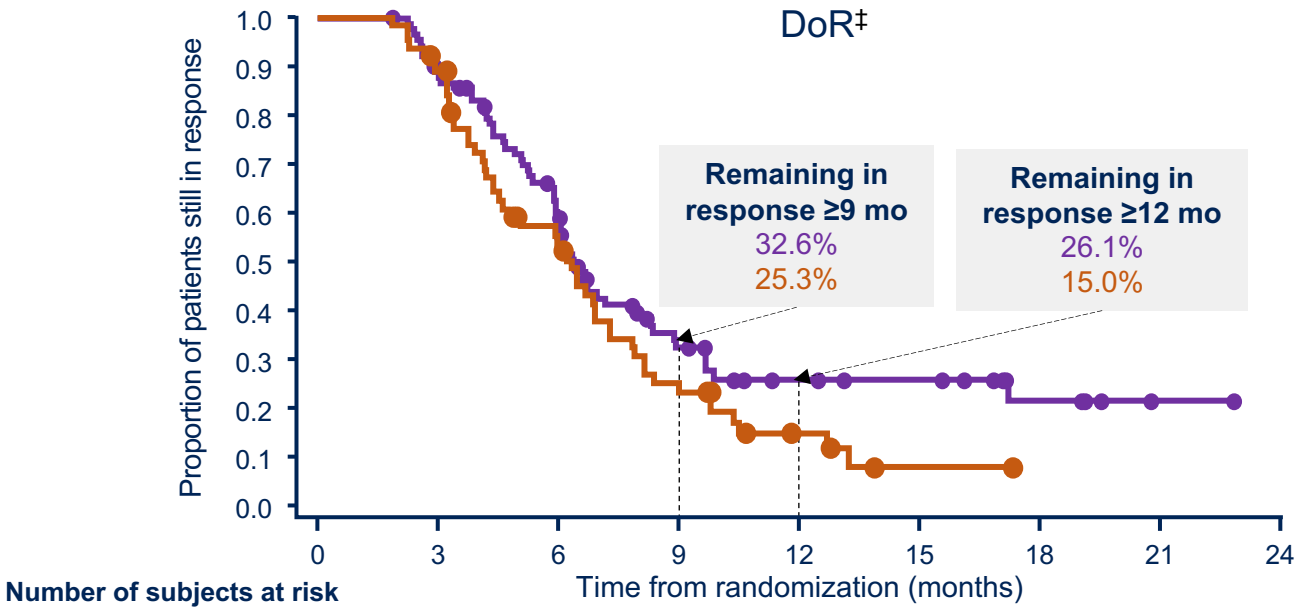
Durvalumab + GemCis	341	258	189	100	38	25	15	5	0
Placebo + GemCis	344	255	149	71	17	7	4	0	0

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.

Secondary endpoint: Tumor response



	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=343)
ORR, n (%)	91 (26.7)	64 (18.7)
CR, n (%)	7 (2.1)	2 (0.6)
PR, n (%)	84 (24.6)	62 (18.1)
DCR, n (%)†	291 (85.3)	284 (82.6)



	Durvalumab + GemCis (n=91)	Placebo + GemCis (n=64)
Median DoR (quartile 1–3), months	6.4 (4.6–17.2)	6.2 (3.8–9.0)
Median time to response (quartile 1–3), months	1.6 (1.3–3.0)	2.7 (1.4–4.1)

*By investigator assessments using RECIST v1.1 based on patients in the final analysis set who had measurable disease at baseline. †Analysis of DCR was based on all patients in the full analysis set. ‡Analysis of DoR was based on patients in the full analysis set who had an objective response and measurable disease at baseline.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; GemCis, gemcitabine and cisplatin; mo, month; ORR, objective response rate; PR, partial response.

KEYNOTE-966 Study Design
Randomized, Double-Blind, Phase 3 Trial

Key Eligibility Criteria

- Histologically confirmed extrahepatic or intrahepatic cholangiocarcinoma or gallbladder cancer
- Unresectable locally advanced or metastatic disease measurable per RECIST v1.1 by investigator review
- No prior systemic therapy[a]
- ECOG PS 0 or 1
- Life expectancy >3 months

R
1:1

Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 yr)
+
Gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W
+
Cisplatin 25 mg/m^2 IV on days 1 and 8 Q3W for 8 cycles

Placebo IV Q3W for ≤35 cycles (~2 yr)
+
Gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W
+
Cisplatin 25 mg/m^2 IV on days 1 and 8 Q3W for 8 cycles

Stratification Factors

- Geographic region (Asia vs not Asia)
- Disease stage (locally advanced vs metastatic)
- Site of origin (extrahepatic vs gallbladder vs intrahepatic)

- **Primary End Point:** OS
- **Secondary End Points:** PFS, ORR, and DOR assessed per RECIST v1.1 by blinded, independent central review (BICR) and safety

Treatment was continued until disease progression, unacceptable toxicity, investigator decision, or, for pembrolizumab and cisplatin, the maximum number of cycles was reached.
[a]Neoadjuvant or adjuvant chemotherapy was permitted if it was completed ≥6 months before the diagnosis of unresectable or metastatic disease.
ClinicalTrials.gov identifier: NCT04003636.

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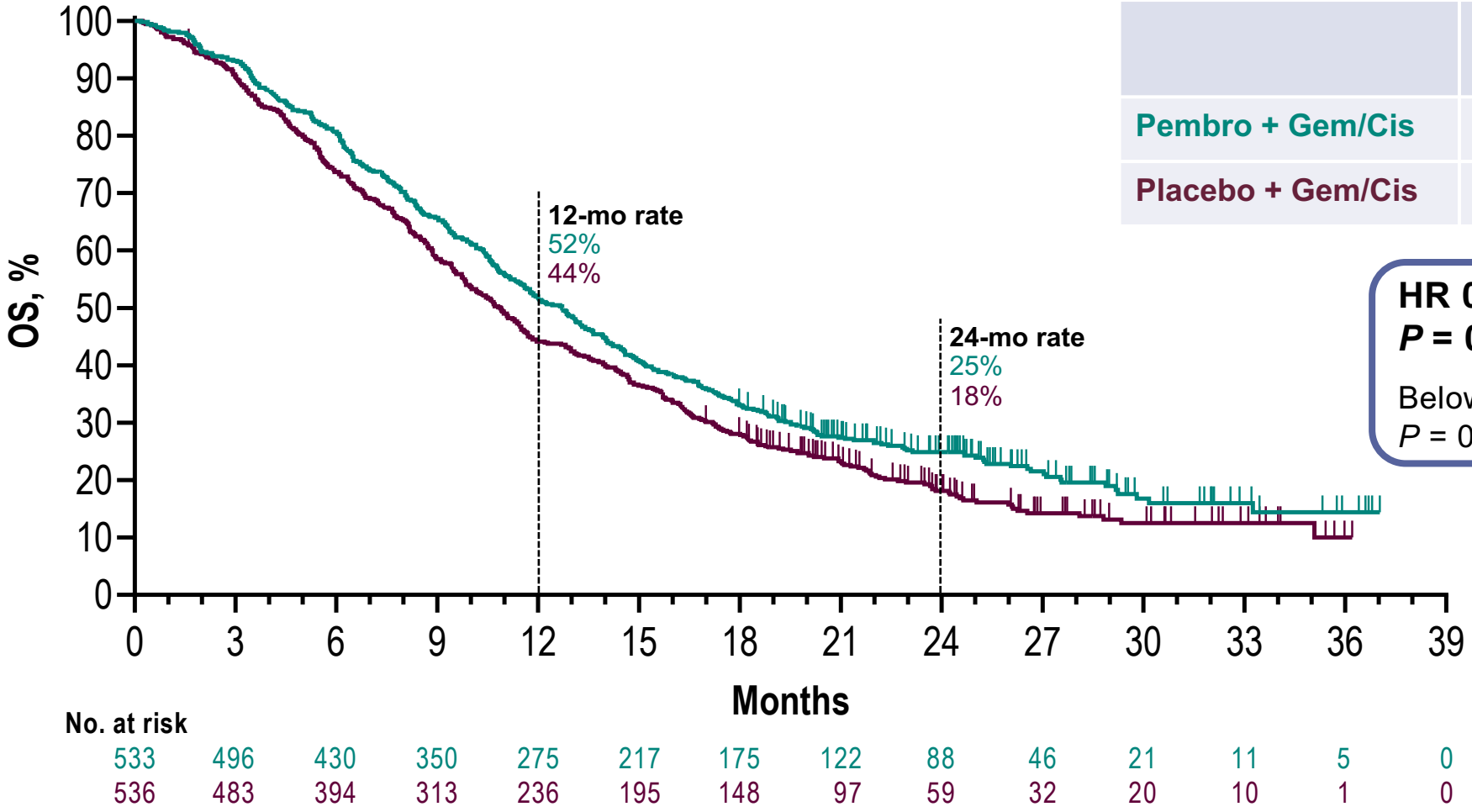
Baseline Characteristics

	Pembro + Gem/Cis (n = 533)	Placebo + Gem/Cis (n = 536)
Median age (IQR), years	64 (57-71)	63 (55-70)
Male	280 (53%)	272 (51%)
Race		
American Indian or Alaska Native	2 (<1%)	1 (<1%)
Asian	245 (46%)	250 (47%)
Black or African American	11 (2%)	3 (1%)
Multiple	5 (1%)	2 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0
White	256 (48%)	268 (50%)
Missing	13 (2%)	12 (2%)
Geographic region		
Asia	242 (45%)	244 (46%)
Not Asia	291 (55%)	292 (54%)
ECOG PS 1	274 (51%)	308 (57%)

	Pembro + Gem/Cis (n = 533)	Placebo + Gem/Cis (n = 536)
Site of origin		
Extrahepatic	98 (18%)	105 (20%)
Gallbladder	115 (22%)	118 (22%)
Intrahepatic	320 (60%)	313 (58%)
Disease status		
Locally advanced	60 (11%)	66 (12%)
Metastatic	473 (89%)	470 (88%)
Biliary stent or drain	33 (6%)	41 (8%)
Prior neoadjuvant or adjuvant chemo	50 (9%)	48 (9%)
Antibiotics within 1 month of study start	291 (55%)	273 (51%)
MSI-H status[a]	6 (1%)	4 (1%)
PD-L1 CPS ≥1[b]	363 (68%)	365 (68%)
HBV infection	164 (31%)	165 (31%)
HCV infection[d]	19 (4%)	14 (3%)

[a]94 (18%) in the pembro group and 110 (21%) in the placebo group had unknown MSI status. [b]57 (11%) in the pembro group and 61 (11%) in the placebo group had unknown PD-L1 combined positive score (CPS). [c]14 (3%) in the pembro group and 16 (3%) in the placebo group had chronic HBV infection (ie, HBsAg positive or HBV DNA ≥20 IU/mL). 150 (28%) and 149 (28%), respectively, had clinically resolved HBV infection (ie, HBsAg negative, anti-HBc positive, and HBV DNA <20 IU/mL). 3 (1%) and 5 (1%), respectively, had missing HBV status. [d]1 (<1%) in the pembro group and 1 (<1%) in the placebo group had active HCV infection (ie, anti-HCV positive with detectable HCV RNA). 18 (3%) and 13 (2%), respectively, had prior HCV infection (ie, anti-HCV positive with undetectable HCV RNA). 0 and 2 (<1%), respectively, had missing HCV status.
Data cutoff date for protocol-specified final analysis: December 15, 2022.

Overall Survival at Final Analysis



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	78%	12.7 (11.5-13.6)
Placebo + Gem/Cis	83%	10.9 (9.9-11.6)

HR 0.83 (95% CI, 0.72-0.95)
***P* = 0.0034**

Below the signficance boundary of *P* = 0.0200

Data cutoff date: December 15, 2022.

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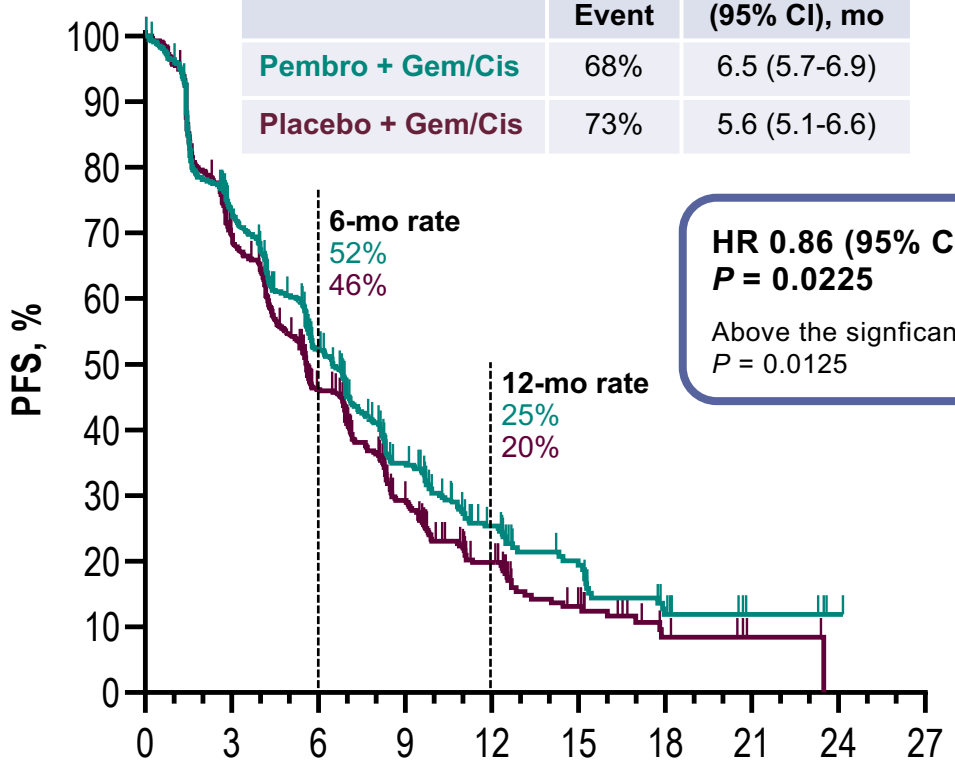
Progression-Free Survival

Interim Analysis 1

	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	68%	6.5 (5.7-6.9)
Placebo + Gem/Cis	73%	5.6 (5.1-6.6)



HR 0.86 (95% CI, 0.75-1.00)
***P* = 0.0225**

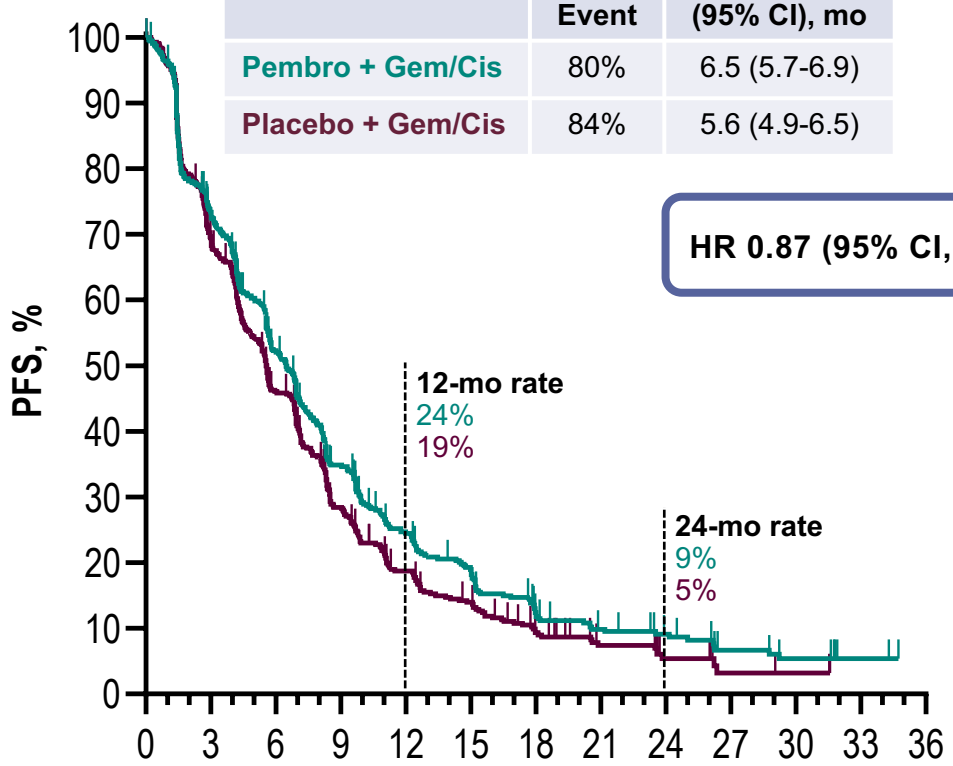
Above the signficance boundary of *P* = 0.0125

No. at risk

533	368	238	121	62	29	14	5	1	0
536	352	211	99	51	21	7	2	0	0

Final Analysis

	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	80%	6.5 (5.7-6.9)
Placebo + Gem/Cis	84%	5.6 (4.9-6.5)



HR 0.87 (95% CI, 0.76-0.99)

No. at risk

533	368	245	156	99	71	41	29	20	11	7	3	0
536	353	222	128	76	54	31	17	8	3	2	0	0

PFS was assessed per RECIST v1.1 by BICR.
[a]Significance boundary of *P* = 0.0125 was not crossed.
Data cutoff date: December 15, 2021 (IA1) and December 15, 2022 (FA). IA1 was the prespecified final analysis of PFS. PFS analysis at FA was exploratory.

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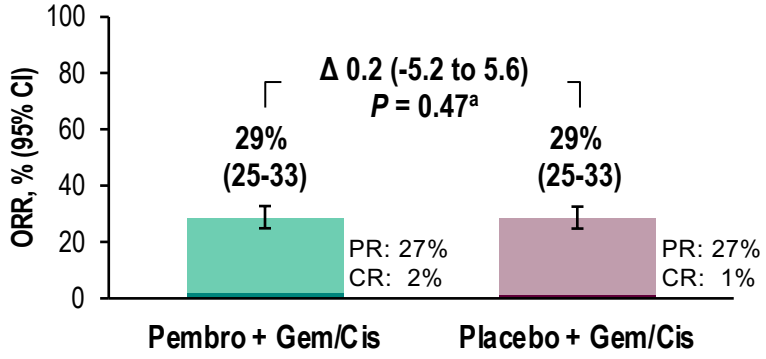
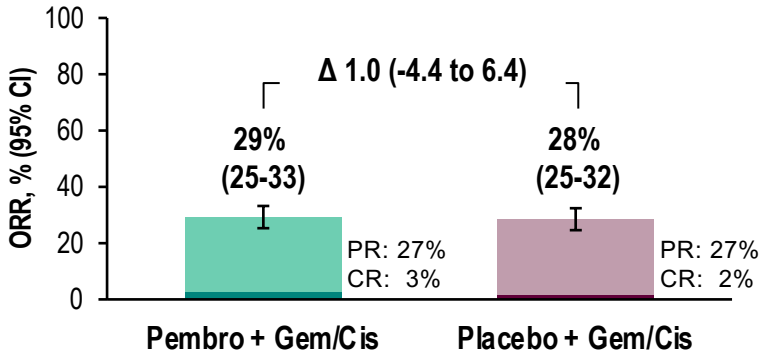
Objective Response Rate and Duration of Response

ORR

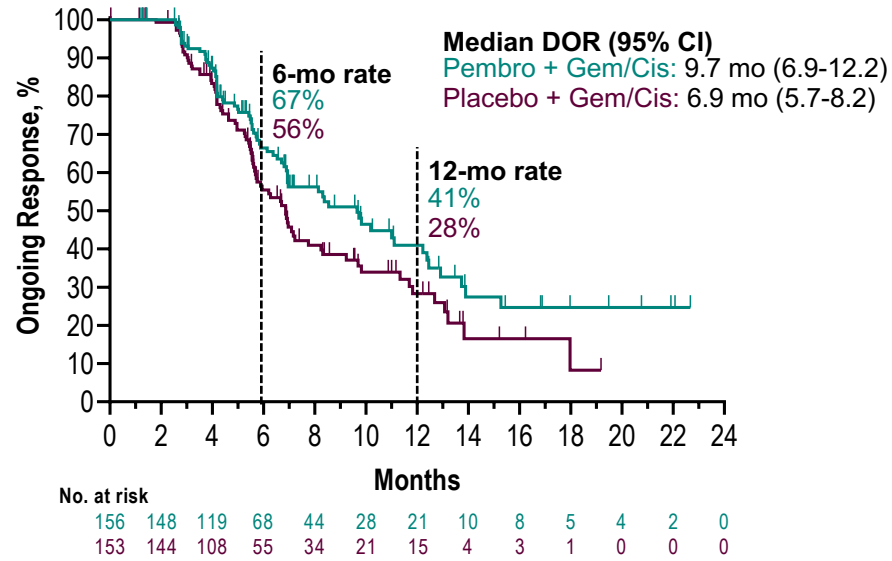
Interim Analysis 1

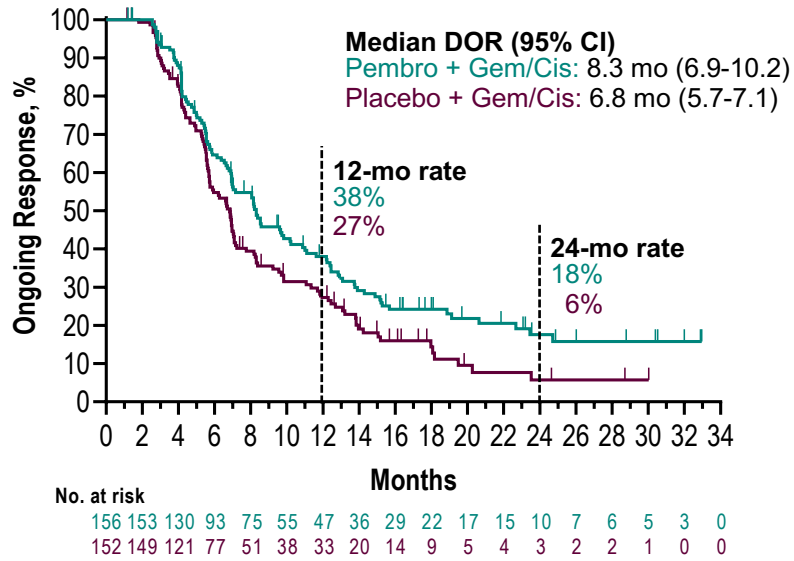


Final Analysis



DOR





ORR was assessed per RECIST v1.1 by BICR. [a]Above the significance boundary of $P = 0.0125$.
Data cutoff date: December 15, 2021 (IA1) and December 15, 2022 (FA). IA1 was the prespecified final analysis of ORR. ORR analysis at FA was exploratory.

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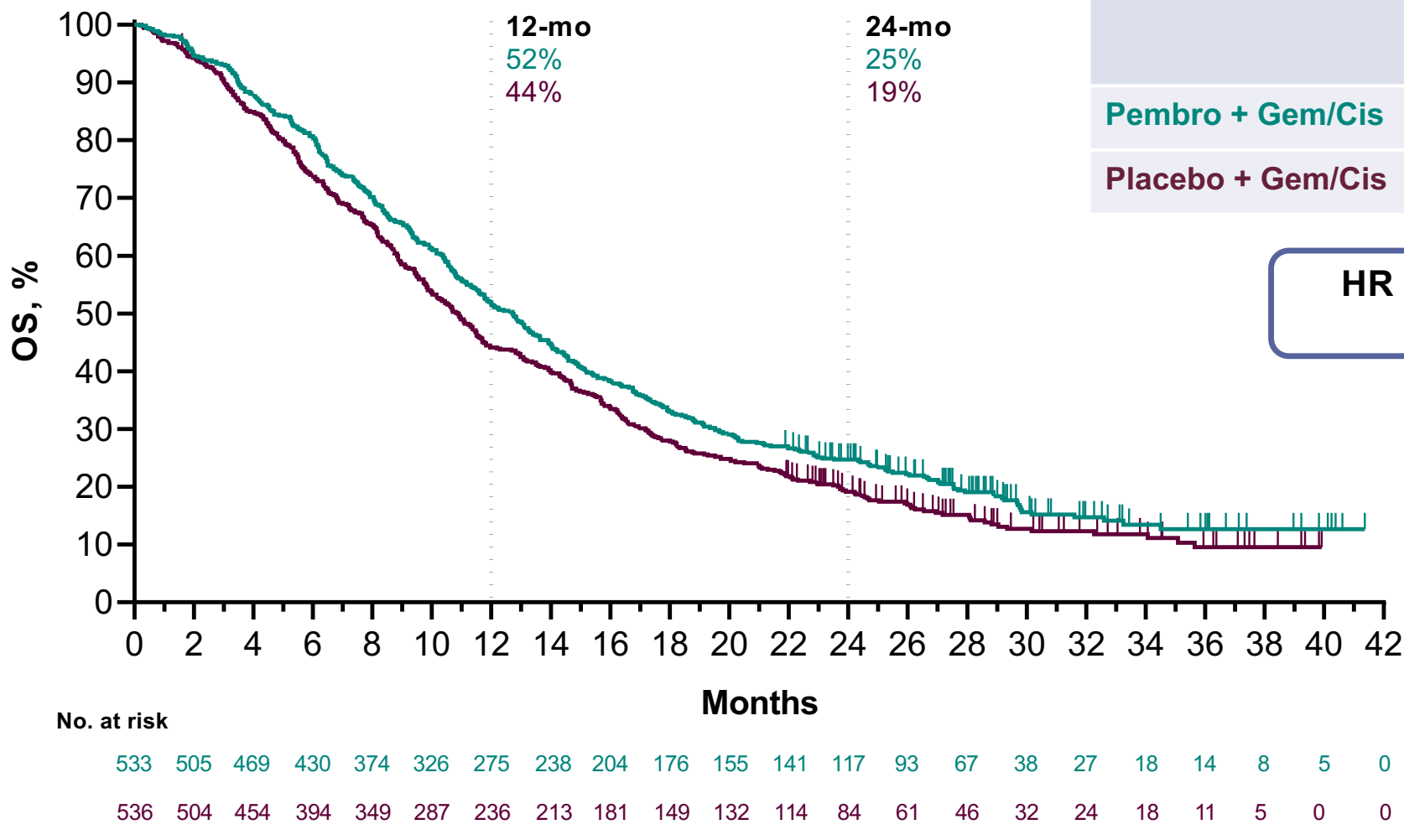
Updated Overall Survival Kaplan-Meier Curve



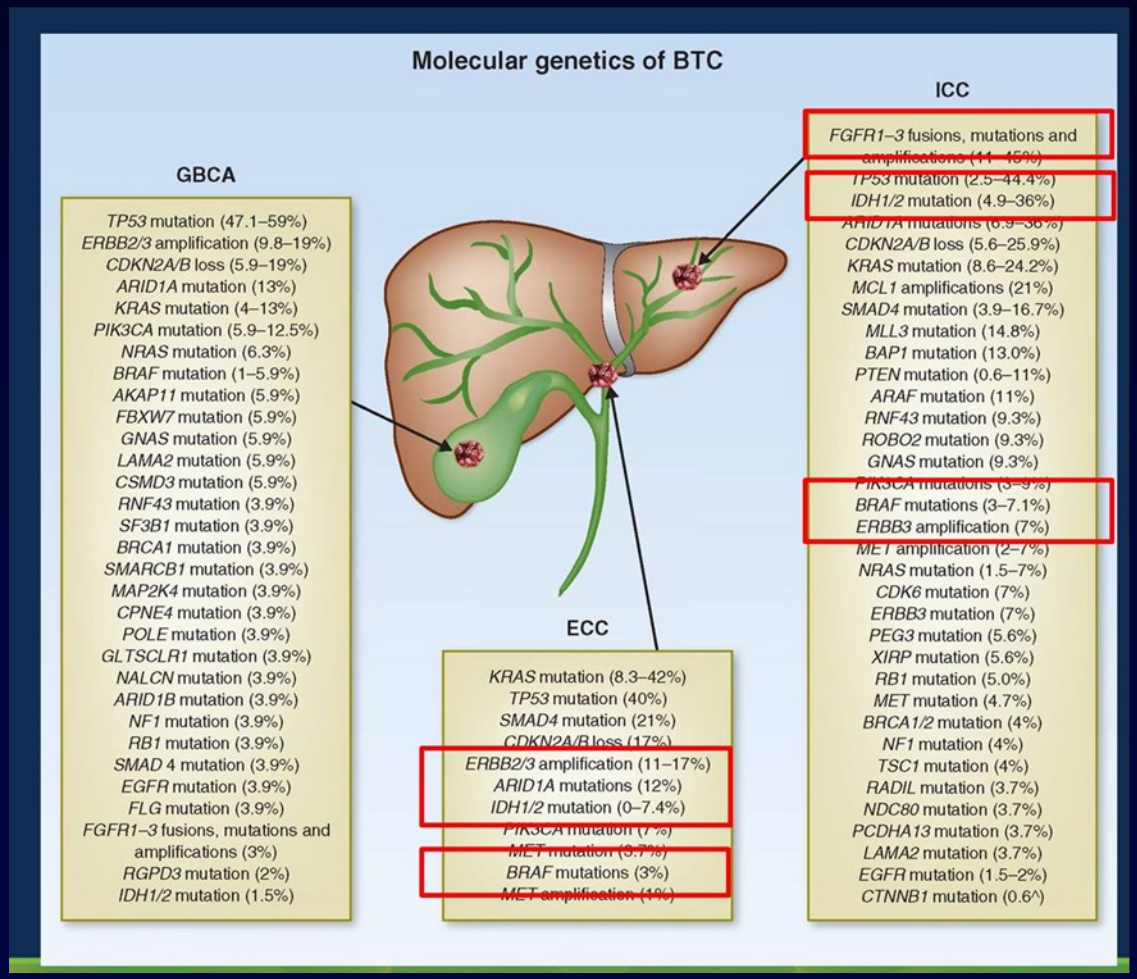
	Pts w/ Event	Median OS (95% CI), mo
Pembro + Gem/Cis	82%	12.7 (11.5-13.6)
Placebo + Gem/Cis	85%	10.9 (9.9-11.6)

HR 0.84 (95% CI, 0.74-0.96)
nominal *P* = 0.0055

29.5 mos f/u

Data cutoff date: April 13, 2023.

BTC: a heterogenous group of tumors



Targeted Therapy for Biliary Tract Cancers

Recommend molecular profiling for advanced disease

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

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

Targeted Therapy for *FGFR2*-rearranged BTC

FOENIX-CCA2 Trial

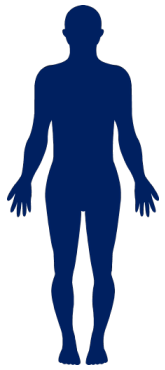
Unresectable or metastatic IHCC with FGFR2 fusion or rearrangement

Futibatinib

N = 103

42%
ORR

9.0 Months
Median PFS



9.7 Months
Median DOR

21.7 Months
Median OS

Futibatinib provided measurable clinical benefit

FIGHT-202 Trial

Previously treated, locally advanced/metastatic BTC +/- FGFR2 fusions or rearrangements

Pemigatinib

***FGFR2* fusions or rearrangements N=107**	**Other *FGF/FGFR* alterations N=20**	**No *FGF/FGFR* alteration N=18**
7.0 Months Median PFS	**2.1 Months** Median PFS	**1.7 Months** Median PFS
17.5 Months Median OS	**6.7 Months** Median OS	**4.0 Months** Median OS
37% ORR		

Only patients with FGFR2 fusions/rearrangements achieved an objective response

ORR = Objective Repose Rate; PFS = Progression-Free Survival; DoR = Duration of Response; OS = Overall Survival; IHCC = Intrahepatic Cholangiocarcinoma.

Goyal L, et al. *N Engl J Med*. 2023;388(3):228-239; Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21(5):671-684; Vogel A et al ESMO 2022; Abstract O-2

Safety Profile for *FGFR2* Targeted Therapies

Comparable Toxicities		
AEs in ≥10% of patients	**Futibatinib FOENIX-CCA2**	**Pemigatinib FIGHT-202**
Hyperphosphatemia	**85%**	**60%**
Alopecia	33%	49%
Diarrhea	28%	44%
Fatigue	25%	38%
Dysgeusia	30%	40%
Discontinuation	2%	1%

Warnings and Precautions

Hyperphosphatemia

- Monitor for hyperphosphatemia throughout treatment
- Initiate a low-phosphate diet and phosphate-lowering therapy when serum phosphate level is ≥5.5 mg/dL
- Initiate or intensify phosphate-lowering therapy when >7 mg/dL
- Reduce dose, withhold, or permanently discontinue based on duration and severity of hyperphosphatemia

Ocular Toxicity

Retinal Pigment Epithelial Detachment

- Perform a comprehensive ophthalmological examination including OCT prior to initiation therapy and every 2 months for the first 6 months and every 3 months
- For onset of visual symptoms, refer for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation. Modify the dose or permanently discontinue.

Goyal L, et al. *N Engl J Med*. 2023;388(3):228-239; Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21(5):671-684; Futibatinib [prescribing information]. 9/22; Pemigatinib [prescribing information]. 8/22.

Targeted Therapy for *IDH1*-mutant BTC

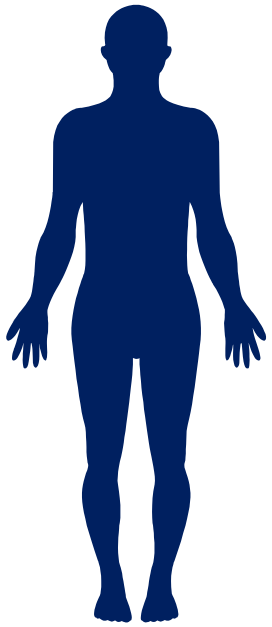
ClarIDHy Trial

IDH1-mutant, advanced chemo-refractory BTC with up to 2 previous treatments

Ivosidenib
N = 126

2.7 Months
Median PFS

10.3 Months
Median OS



Placebo
N = 61

1.4 Months
Median PFS

7.5 months
Median OS

Cross-over from placebo to Ivosidenib allowed upon radiological progression (per investigator assessment)

PFS HR = 0.37 (95% CI, 0.25-0.54; *P* < 0.0001)

AEs in ≥ 10% of patients	Patients
Nausea	33%
Diarrhea	31%
Fatigue	23%
Cough	21%
Dose reduction	3%
Discontinuation	6%

⚠ Warnings and Precautions

QTc Interval Prolongation

- Monitor ECG and electrolytes – frequent monitoring in patients with CCF, electrolyte abnormalities and congenital long QTc
- Interrupt or reduce Ivosidenib if QTc >480-500msec, discontinue if life-threatening arrythmia develops

Guillan-Barre Syndrome : Monitor for motor and/or sensory neuropathy symptoms. Permanently discontinue if GBS diagnosis

BTC = Biliary Tract Cancer; CI = Confidence Interval; HR = Hazard Ratio; OS = Overall Survival; PFS = Progression-Free Survival

Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21(6):796-807;Zhu AZ et al. *JAMA Oncol* Ivosidenib prescribing information. 10/23.

Targeted Therapy for *BRAF^{V600E}*-mutant BTC

ROAR trial

Unresectable, metastatic or locally advanced BRAF^{V600E}-mutant BTC

Dabrafenib + Trametinib

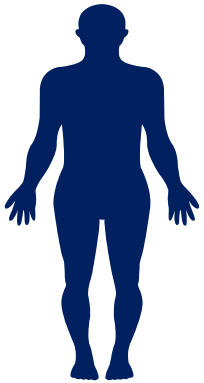
N = 43

53%

ORR

8.9 Months

Median DoR



9.0 Months

Median PFS

13.5 Months

Median OS

AEs in ≥20% of patients	Patients
Pyrexia	**67%**
Fatigue	33%
Nausea	42%
Diarrhea	33%
Rash	28%
Anemia	23%
Discontinuation	2%

Warnings and Precautions

Serious Febrile Reactions

- Withhold for temperature of ≥100.4 ºF. In case of recurrence, interrupt therapy at the first symptom of pyrexia
- Evaluate for infection; monitor serum creatinine and renal function during and following severe pyrexia
- Administer corticosteroids for at least 5 days for second or subsequent pyrexia if pyrexia does not resolve or pyrexia complicated with hypotension, severe rigors or chills, dehydration, or renal failure, and there is no evidence of active infection

BTC = Biliary Tract Cancer; DoR = Duration of Response; ORR = Objective Response Rate; OS = Overall Survival; PFS = Progression-Free Survival.

Shubbiah V, et al. *Nat Med.* 2023, 1103–1112; Dabrafenib + Trametinib [prescribing information]. 8/23.

Targeted Therapy for HER2+ BTC

Pertuzumab + Trastuzumab
MyPathway Basket study

HER2 amplification and/or overexpression*
N = 263

25.9%
ORR (Overall)

7.1%
ORR (Mutated *KRAS*)

28.1%
ORR (KRAS WT)

HER2 mutations alone
N = 83

6.0%
ORR

Limited activity in tumors with *KRAS* mutations, *HER2* mutations alone, or 0-1+ HER2 expression

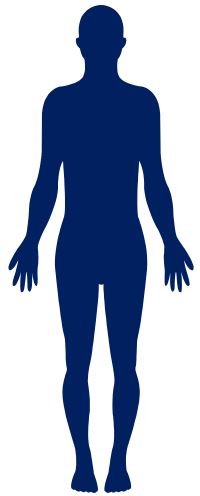
Pertuzumab + Trastuzumab
TAPUR Basket study

Advanced BTC with ERBB2/3 amplication, overexpression or mutation

N =29

11 Weeks
Median PFS

30 Weeks
Median OS



32%
ORR

32 Weeks
Median DoR

Grade 3 drug-related adverse or serious adverse events included anemia, diarrhea, infusion related reaction, and fatigue.

*With or without HER2 mutations.

ORR = Objective Response Rate; WT = Wild-Type; OS = Overall Survival; PFS = Progression-Free Survival; DoR = Duration of Response

Sweeney CJ, et al. *J Clin Oncol.* 2023;JCO2202636; Cannon TL, et al. *J Clin Oncol*. 2023;41(4):546-546.

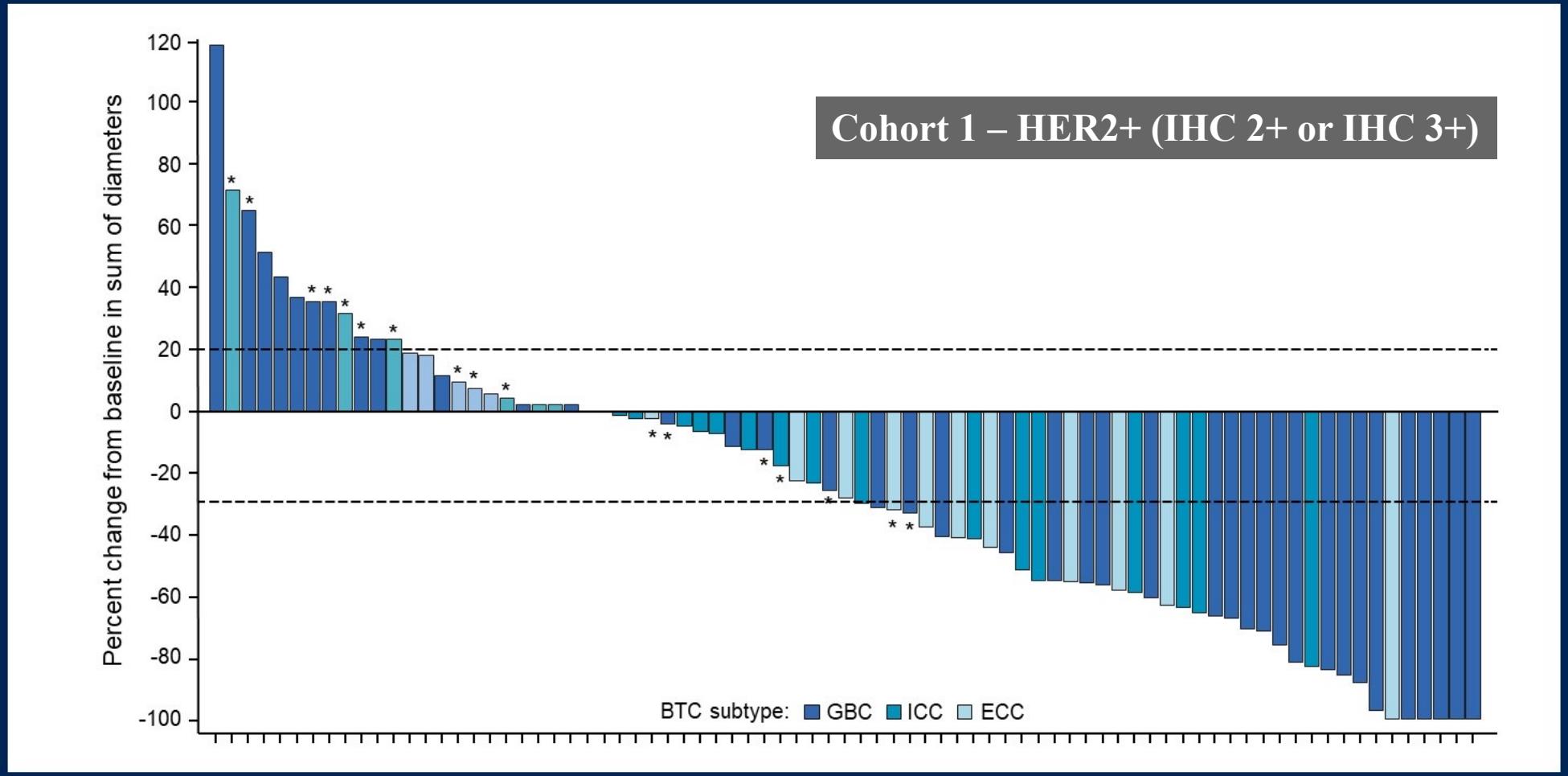
HER2-Directed Therapies in Advanced HER2+ BTC

Study	MyPathway[1]	HERIZON-BTC-01[2]	SGNTUC-019[3]	KCSG-HB19-14[4]	HERB[5]
	Trastuzumab + pertuzumab[7]	Zanidatamab[8,9]	Trastuzumab + tucatinib[10]	Trastuzumab + FOLFOX[11]	Trastuzumab deruxtecan[12]
ORR, %	23.0	41.0	46.7	29.4	36.4
DCR, %	51.0	68.8	76.7	79.4	81.8
mPFS, mo	4.0	5.5	5.5	5.1	4.4
mOS, mo	10.9	NA	15.5	10.7	7.1
HER2+ Status	*Overexpression* defined as: • IHC 3+ *Amplification* defined as: • HER2/CEP17 ratio >2.0 or HER2 copy number >6.0	*Amplified* defined as: • Cohort 1 (IHC 2+ or 3+) • Cohort 2 (IHC 0 or 1+)	*Overexpression* defined as: • IHC 3+ *Amplification* defined as: • HER2/CEP17 signal ratio ≥ 2.0 or gene copy number ≥6.0 or NGS amplification	HER2+ defined as: • IHC 3+ • IHC 2+ AND in-situ hybridization positive OR *ERBB2* gene copy number ≥6·0 by NGS	HER2+ defined as: • IHC 3+ • IHC 2+ AND in-situ hybridization positive (HER2/chromosome 17 copy number ≥ 2.0

1. Meric-Bernstam F, et al. ASCO 2021. Abstract 3004; 2. Pant S, et al. ASCO 2023. Abstract 4008; 3. Nakamura Y, et al. *J Clin Oncol.* 2023;41(36):5569; 4. Lee C, et al. *Lancet Gastroenterol Hepatol.* 2023;8(1):56:65; 5. Ohba A, et al. ASCO 2022. Abstract 4006; 6. Swed B, et al. ASCO Daily News. 2023. https://dailynews.ascopubs.org/do/implementing-her2-directed-therapies-advanced-biliary-tract-cancers-practice-do-we

Majority of evaluable patients (68.4%) had a decrease in target lesions (Cohort 1)

Zanidatamab



*Indicates patients with IHC 2+ status; all other patients had IHC status of 3+.
Dotted lines indicate 20% increase and 30% decrease in sum of diameters of target tumors.

Conclusions:

- Front-line gem-cis +IO is standard of care based on 2 phase 3 studies (durva or pembro)
- Molecular profiling is a must for all patients
  - FDA approved agents for FGR2 alterations, IDH mutations, and BRAF mutations
  - Early signals of activity for new HER2 directed therapies
- For patients without genomic alterations, second-line chemotherapy appropriate
  - FOLFOX or nal-IRI

Overview

Sunday, March 24th

Module 10: 7:30 AM – 8:20 AM — Multiple Myeloma

Module 11: 8:20 AM – 9:10 AM — Gastroesophageal Cancers

Module 12: 9:30 AM – 10:20 AM — Hepatobiliary Cancers

Module 13: 10:20 AM – 11:10 AM — Colorectal Cancer

Module 14: 11:10 AM – 12:00 PM — Pancreatic Cancer

Agenda

Module 1: Select Biomarker-Directed Approaches for CRC — Dr Ciombor

Module 2: HER2-Targeted Approaches for mCRC; Other Available and Emerging Therapeutic Strategies — Dr Strickler

Agenda

Module 1: Select Biomarker-Directed Approaches for CRC — Dr Ciombor

Module 2: HER2-Targeted Approaches for mCRC; Other Available and Emerging Therapeutic Strategies — Dr Strickler

Biomarker Directed Approaches for Colorectal Cancer (CRC)

Kristen K. Ciombor, MD, MSCI
Associate Professor of Medicine
Co-Leader, Translational Research and Interventional Oncology
Vanderbilt-Ingram Cancer Center
March 24, 2024

Disclosures

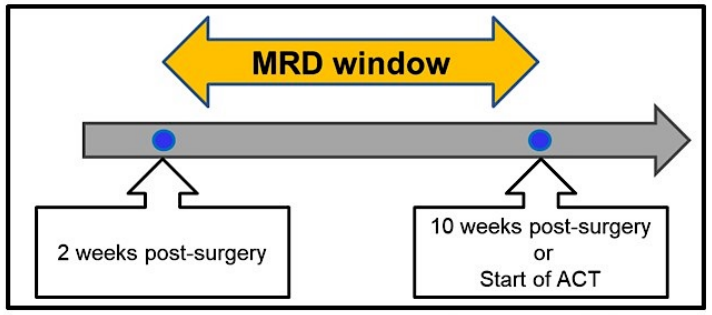
Advisory Committees	Bayer HealthCare Pharmaceuticals, Exelixis Inc, Incyte Corporation, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Personalis, Pfizer Inc, Replimune, Seagen Inc
Consulting Agreements	Merck, Pfizer Inc
Contracted Research	Array BioPharma Inc, a subsidiary of Pfizer Inc, Bristol Myers Squibb, Calithera Biosciences, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Incyte Corporation, Merck, NuCana, Pfizer Inc, Seagen Inc

Patient Case

- 51-year-old female with abdominal pain, change in bowels
- Went to PCP, Hg was 6 (previously normal)
- CT with large colonic mass at the hepatic flexure, no mets
- Colonoscopy confirmed ascending colon mass; biopsy: adenocarcinoma, dMMR; CEA WNL
- R hemicolectomy: 8.4 cm invasive moderately differentiated adenocarcinoma, invading to pericolonic tissue, LVI+/PNI-, 2/31 LN+, negative margins; pT3N1b, dMMR
- Discussed adjuvant therapy, ctDNA testing
- Restaging scans done prior to adjuvant therapy initiation

Updated GALAXY Data (CIRCULATE-JAPAN)

DFS according to status in the MRD window in all stages

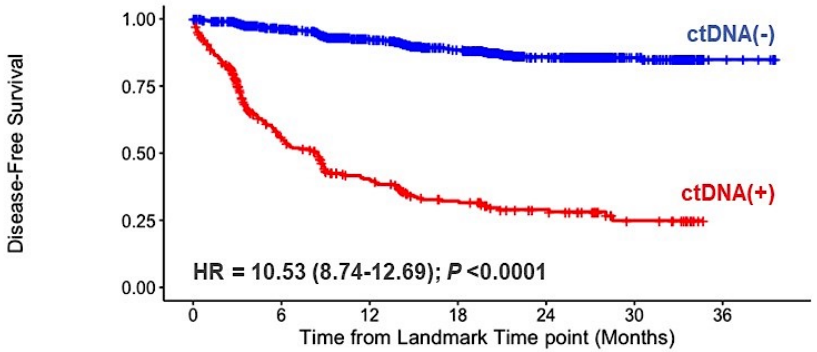


ACT: adjuvant chemotherapy

2,998 stage I-IV patients included in the outcome cohort

Excluded (N=138)
- DFS event prior to the 10 weeks landmark timepoint (n=138)

MRD Window analysis cohort (n=2,860)



Number at risk

ctDNA Negative	2491	2031	1441	1041	495	135	8
ctDNA Positive	369	165	98	59	35	13	0

ctDNA status	Negative	Positive
Events %	9.4 (235/2491)	58.8 (217/369)
24M-DFS % (95% CI)*	85.9 (83.9–87.7)	28.9 (23.4–34.8)

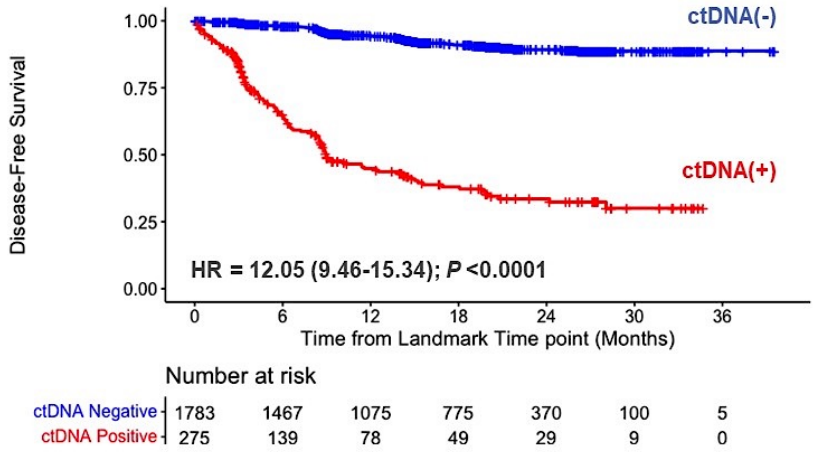
**DFS % from landmark time point*

MRD window: 2-10 weeks post surgery, prior to start of any adjuvant therapy - Landmark 10 weeks post-surgery

ctDNA-positive in the MRD window is predictive of inferior DFS

Updated GALAXY Data (CIRCULATE-JAPAN)

DFS according to status in the MRD window in pStage II/III

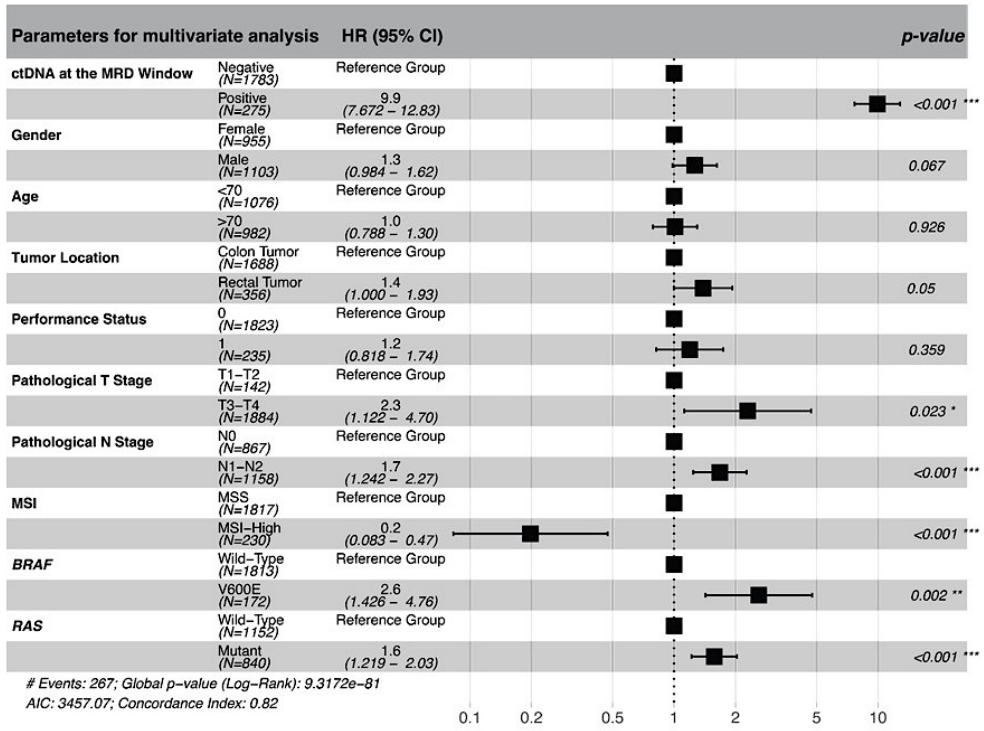


Dynamics	ctDNA Negative	ctDNA Positive
Events %	7.8 (126/1783)	56.5 (143/275)
24M-DFS % (95% CI)*	89.3 (87.2–91.1)	33.5 (26.5–40.7)

**DFS % from landmark time point*

MRD window: 2-10 weeks post surgery, prior to start of any adjuvant therapy - Landmark 10 weeks post-surgery

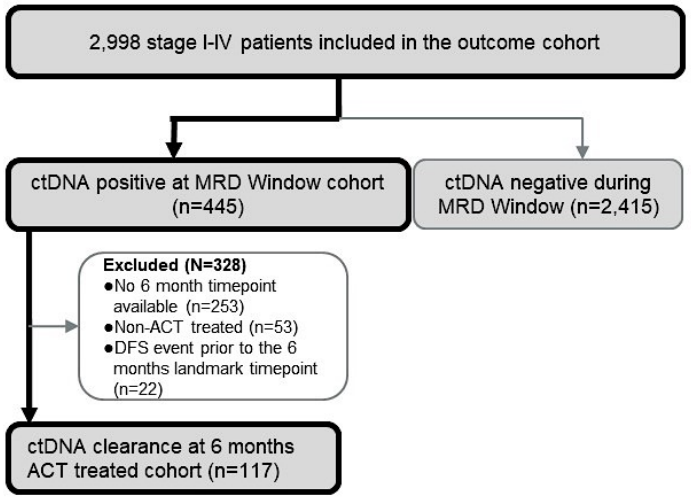
Multivariate Regression Model for DFS



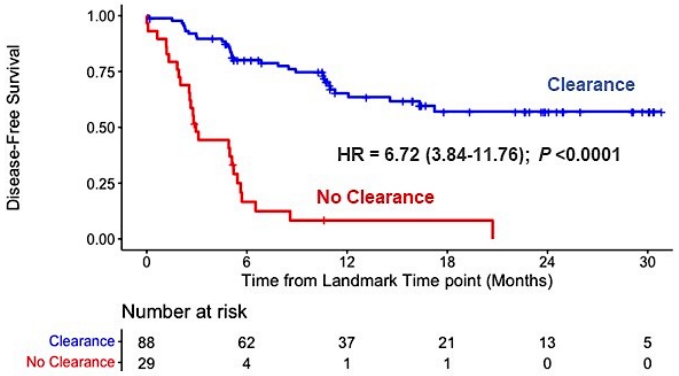
ctDNA-positive in the MRD window is predictive of inferior DFS (pStage II/III)

Updated GALAXY Data (CIRCULATE-JAPAN)

Clearance and reduction in MTM/mL at 6 months in ACT treated patients

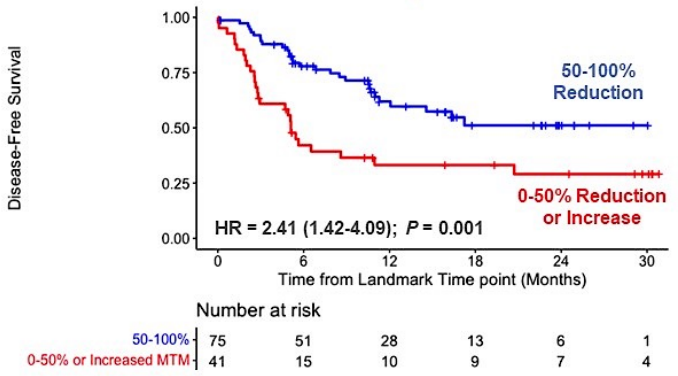


ctDNA clearance at 6 months



ctDNA Clearance	Clearance	No Clearance
Events %	35.2 (31/88)	89.7 (26/29)
24M-DFS % (95% CI)	57.1 (44–68.2)	NR

Positive at the MRD window to 6 months MTM/mL Reduction | ACT-treated



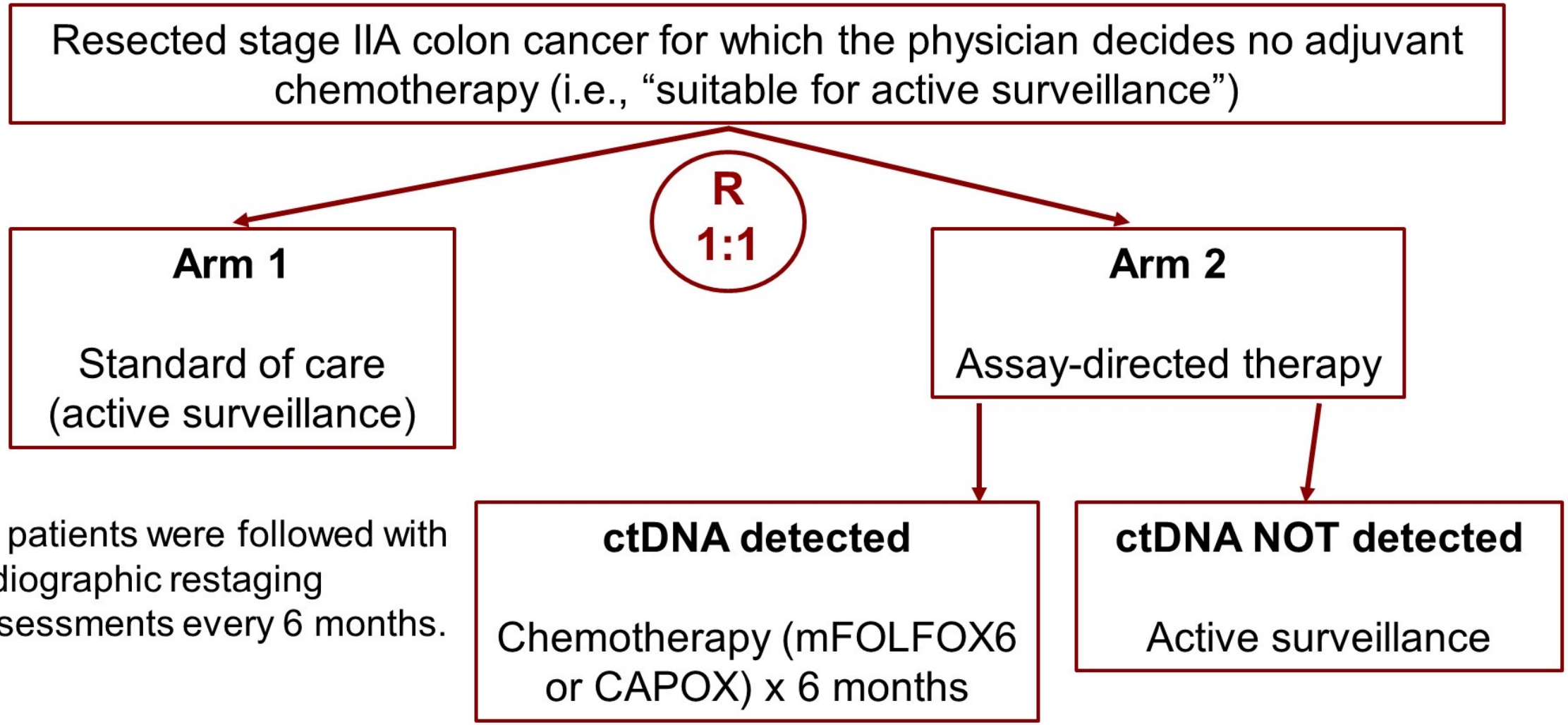
ctDNA Clearance	50-100% Reduction	0-50% Reduction or Increase
Events %	38.7 (29/75)	65.9 (27/41)
24M-DFS % (95% CI)	51.1 (36.4–64.1)	29 (15–44.6)

**DFS % from landmark time point*

Landmark 6 months post-surgery

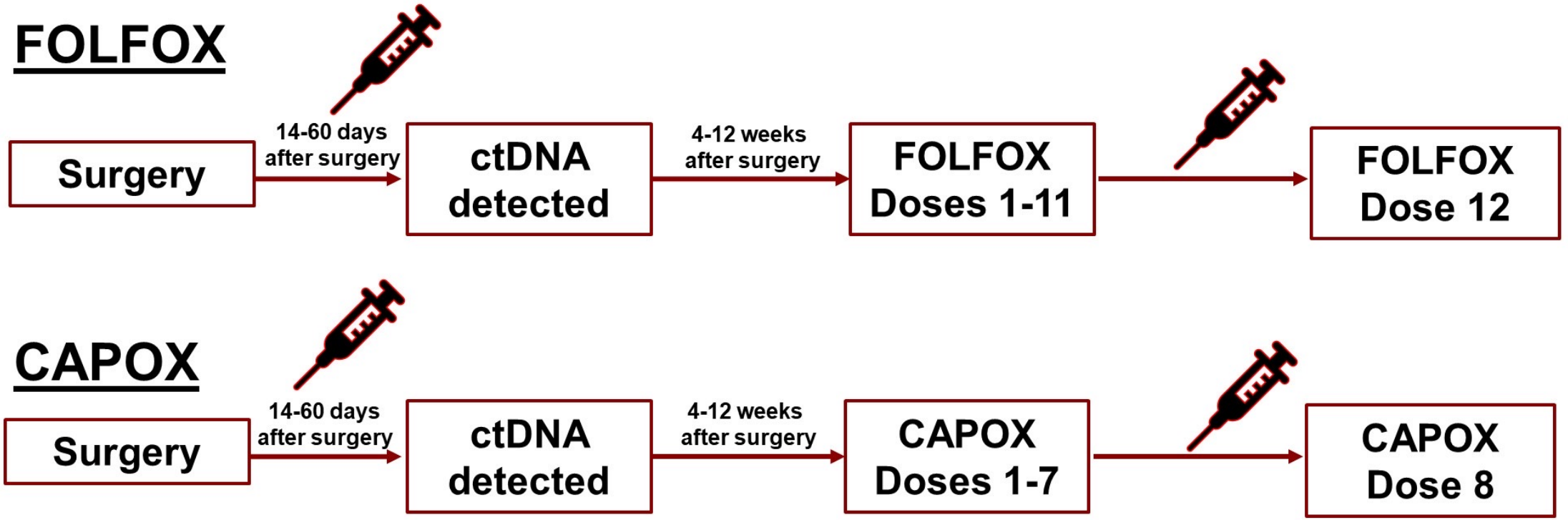
ctDNA clearance and MTM/mL reduction on ACT is an indicator of treatment efficacy and results in better outcomes

NRG-GI005 (COBRA) Study Schema



Morris, ASCO GI 2024

Treatment schema: Arm 2 “ctDNA detected”

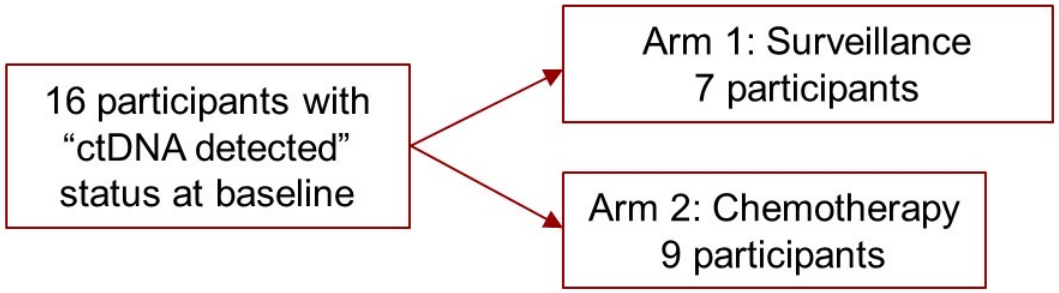


The 6-month timepoint was collected two weeks after prior dose of chemotherapy/ immediately prior to the administration of the last dose of chemotherapy.

Morris, ASCO GI 2024

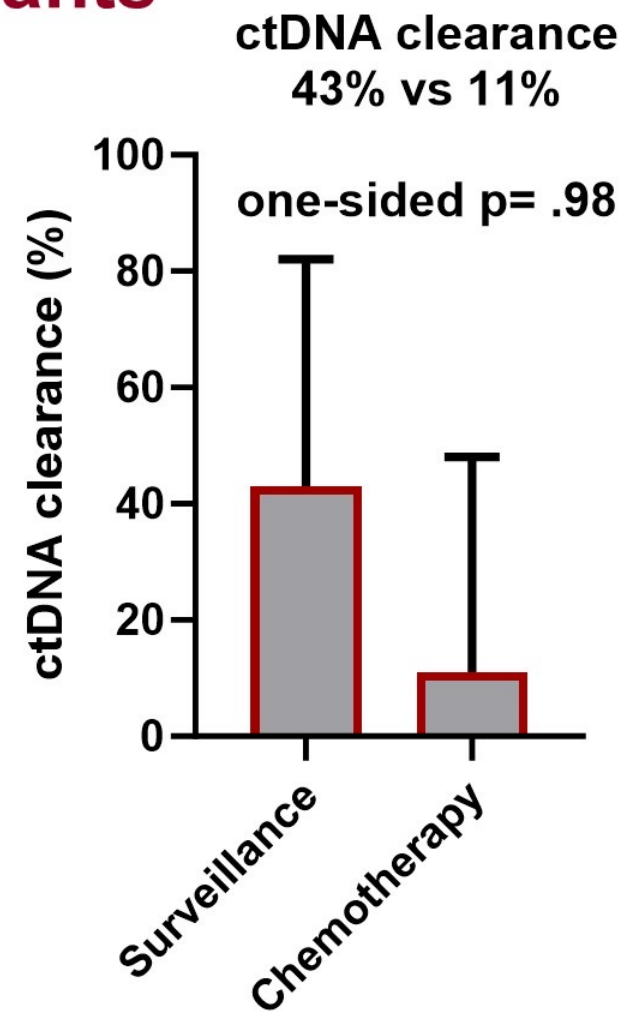
Phase II Endpoint Analysis: ctDNA(+) baseline participants

- Among 596 participants with baseline ctDNA status available, ctDNA(+) detection was observed in 33 (5.54%).



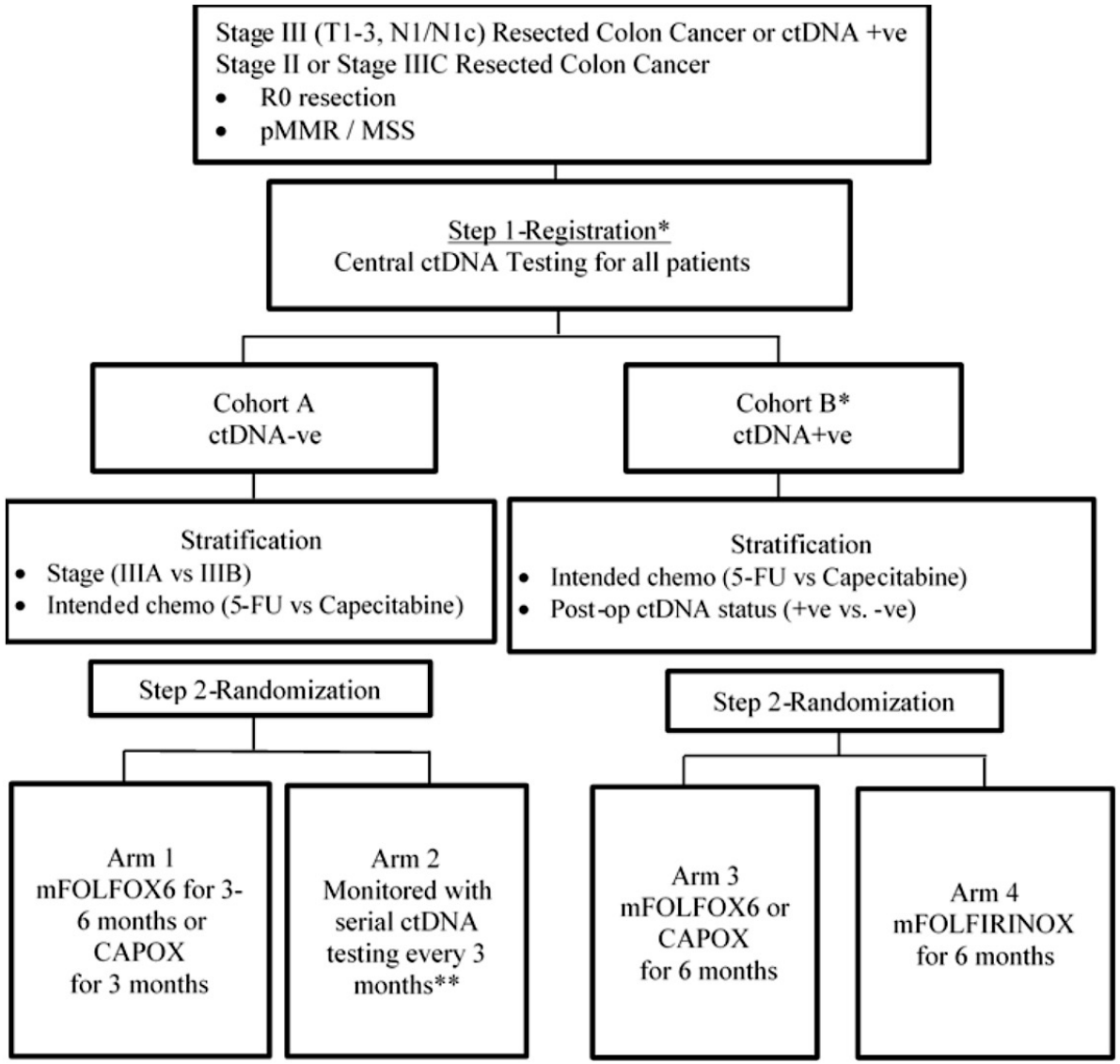
- Clearance of ctDNA at 6 months among ctDNA(+) participants at baseline was observed in:
  - **Arm 1 (surveillance):** 3 of 7 (43%, 95% CI 10 - 82%) participants
  - **Arm 2 (chemotherapy):** 1 of 9 patients (11%, 95% CI 0.3 - 48%) participants

- **Because the 1-sided Fisher's Exact Test yields p = 0.98 exceeding 0.35, H_o was not rejected, and the decision rule calls for early stopping due to futility.**



Morris, ASCO GI 2024

CIRCULATE-US (NRG-GI008)



High-risk stage II/stage III

Assay: Signatera (tumor-informed)

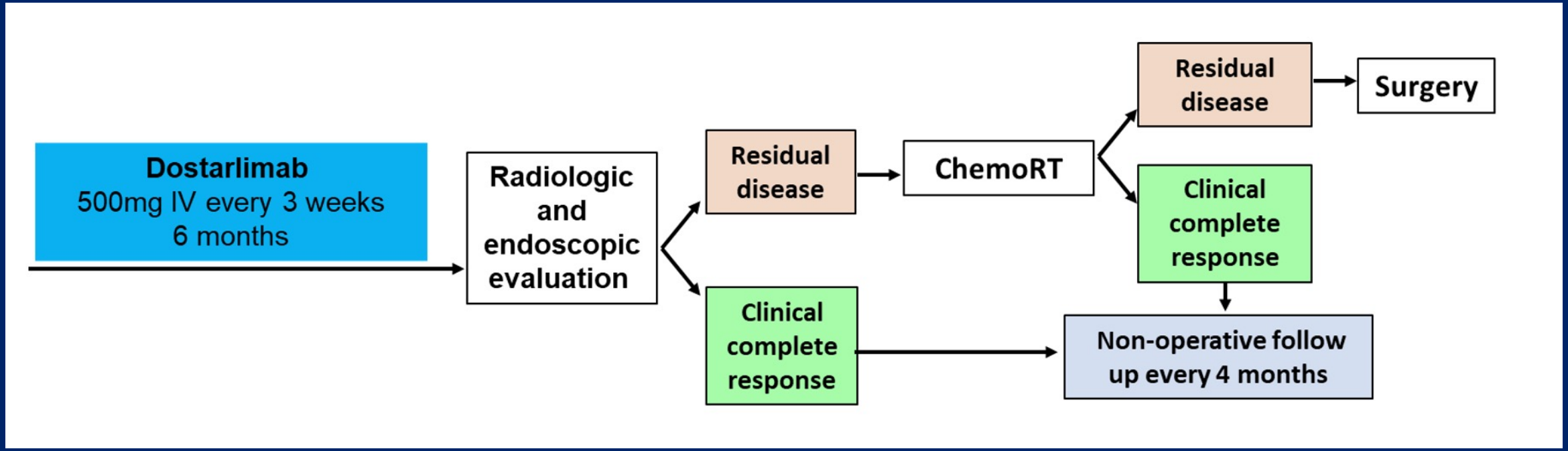
Primary Outcomes: TTPos (time from randomization until ctDNA+), DFS

Secondary Outcomes: baseline post-sx ctDNA+ rate, OS, time to recurrence, compliance with adjuvant chemo

Principal Investigators:
Dr. Arvind Dasari (MD Anderson)
Dr. Christopher Lieu (Colorado)

NCT04089631

NRG ONCOLOGY™



Patient population: Stage II and III mismatch repair deficient rectal cancer

Target Enrollment: 30 subjects

Study Design: Simon's two stage minimax design

NCT04165772

Cercek, ASCO 2022

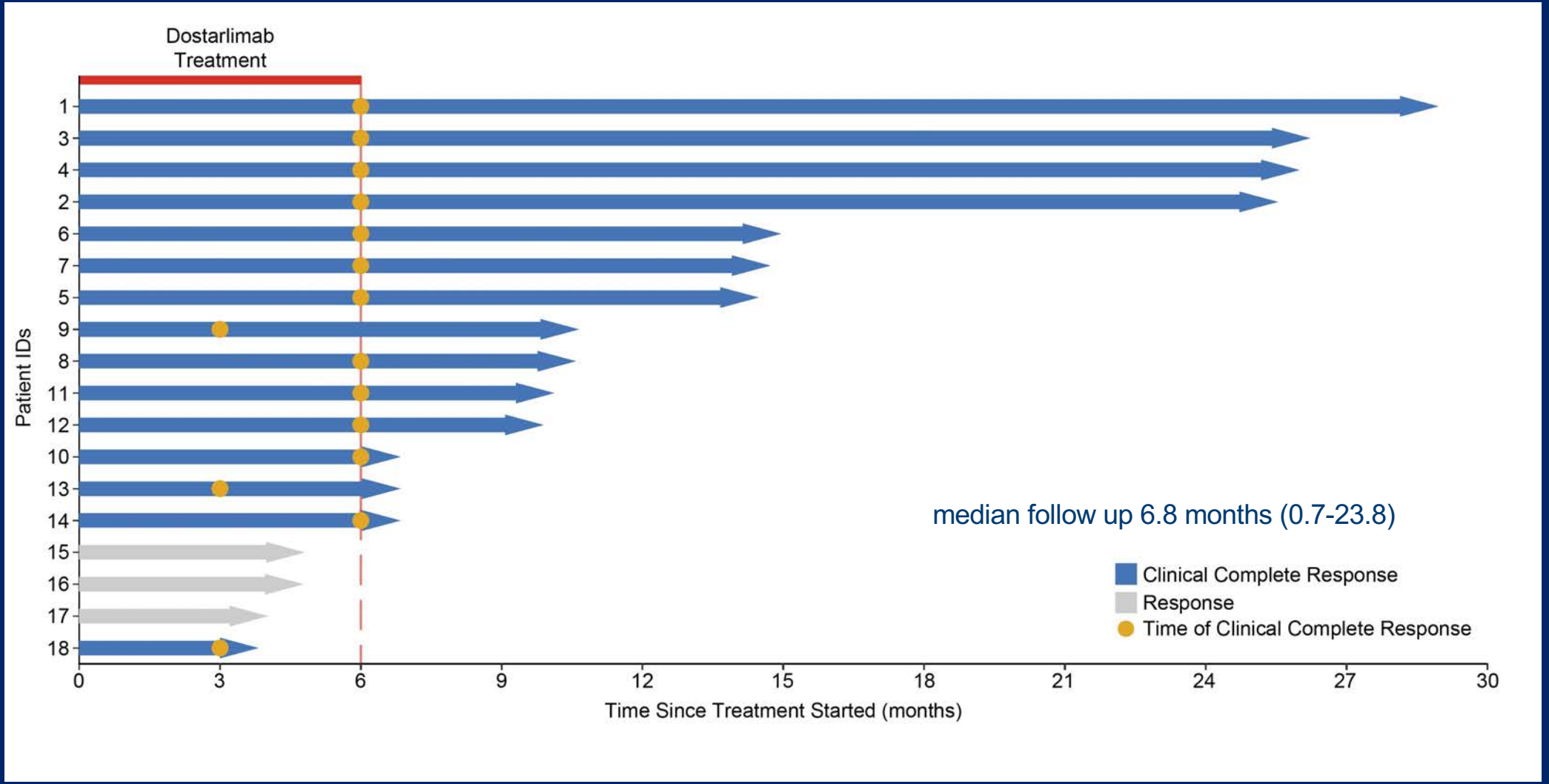
Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Cercek, ASCO 2022

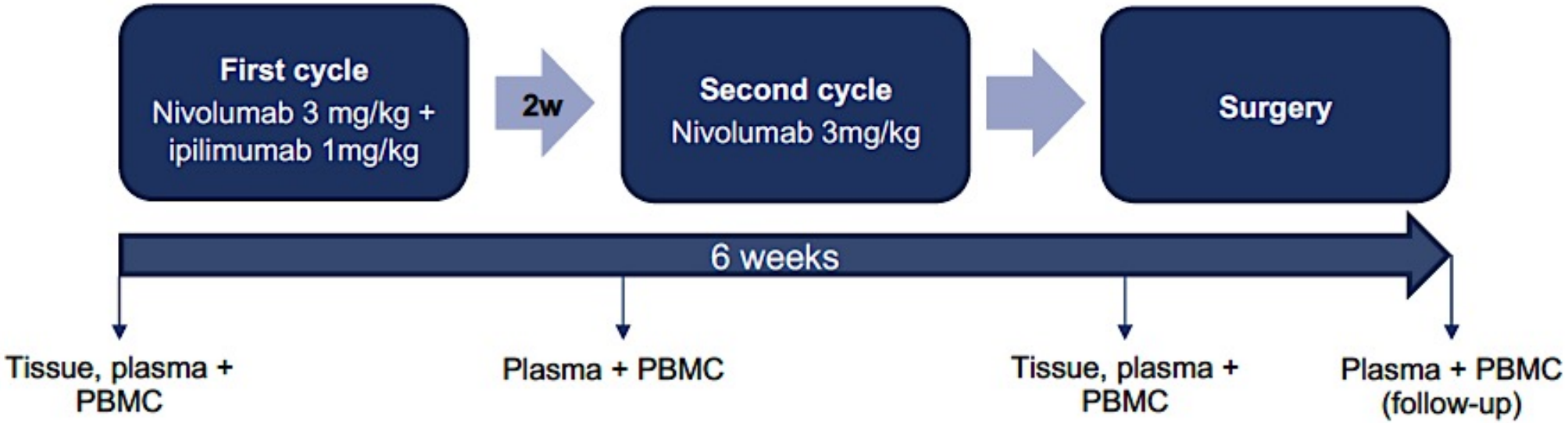
Duration of response



Cercek, ASCO 2022

NICHE-2 study design

- Investigator-initiated, non-randomized multicenter* study



*6 participating hospitals in the Netherlands
PBMC = peripheral blood mononuclear cells

PARIS 2022 ESMO congress

Myriam Chalabi, MD PhD

VANDERBILT UNIVERSITY MEDICAL CENTER

Chalabi, ESMO 2022

Major pathologic response in 95% of patients; 67% pCR

Pathologic response (RVT)		Patients *n*= 107
Yes	(≤ 50%)	106 (99%)
Major	(≤10%)	**102 (95%)**
Complete	(0%)	**72 (67%)**
Partial	(10% - 50%)	4 (4%)
No	(≥50%)	1 (1%)

RVT = residual viable tumor

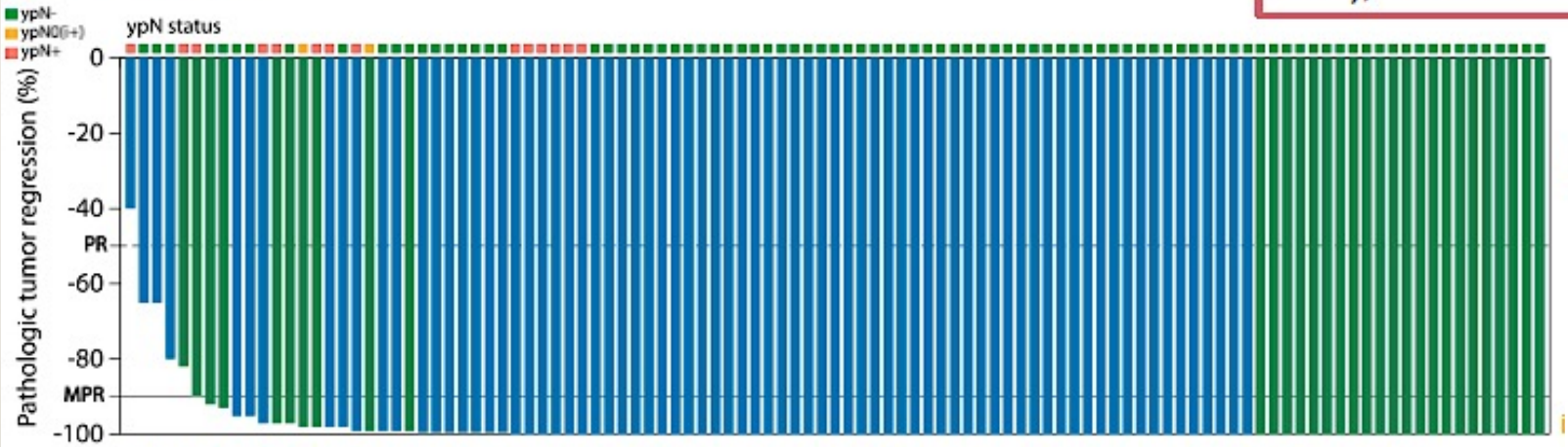
Adjuvant chemotherapy (CTx)

14 patients with ypN+ disease
- 3 patients received adjuvant CTx*
- 5 patients >70 years
- 6 patients refused

* 1 non-responder, 1 partial responder and 1 MPR

Disease recurrence

With a median follow-up of 13.1 months (1.4 - 57.4), there have been no disease recurrences



Green bars = NICHE-1 cohort
Blue bars = NICHE-2 cohort

ypN- = tumor-free lymph nodes; ypN+ = lymph nodes with tumor, including micrometastases; ypN(i+) = lymph nodes with isolated tumor cells

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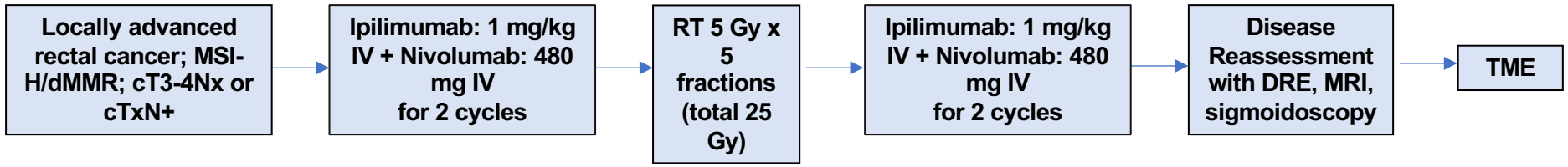
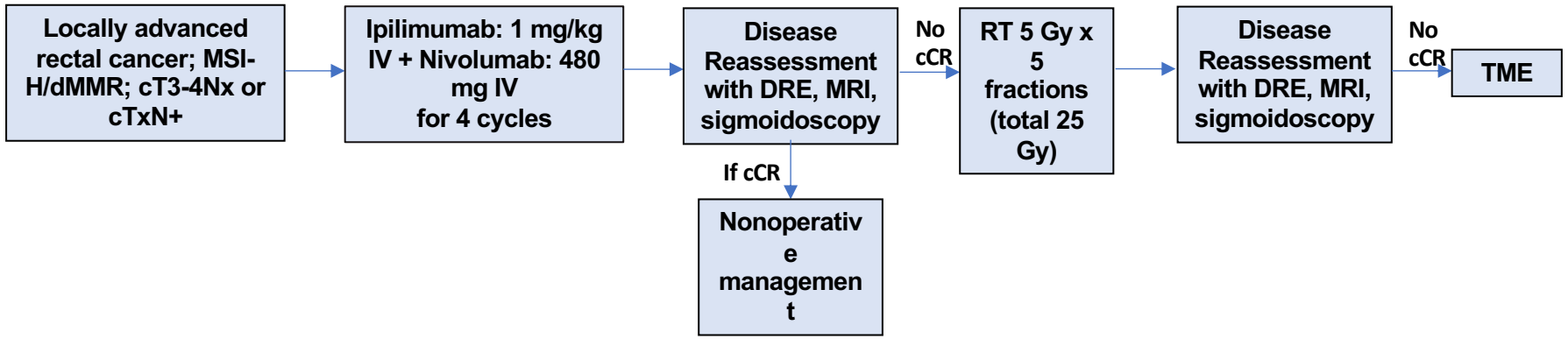
Chalabi, ESMO 2022

EA2201: Current and Proposed Schemas



Current primary endpoint: Pathologic complete response rate (pCR)



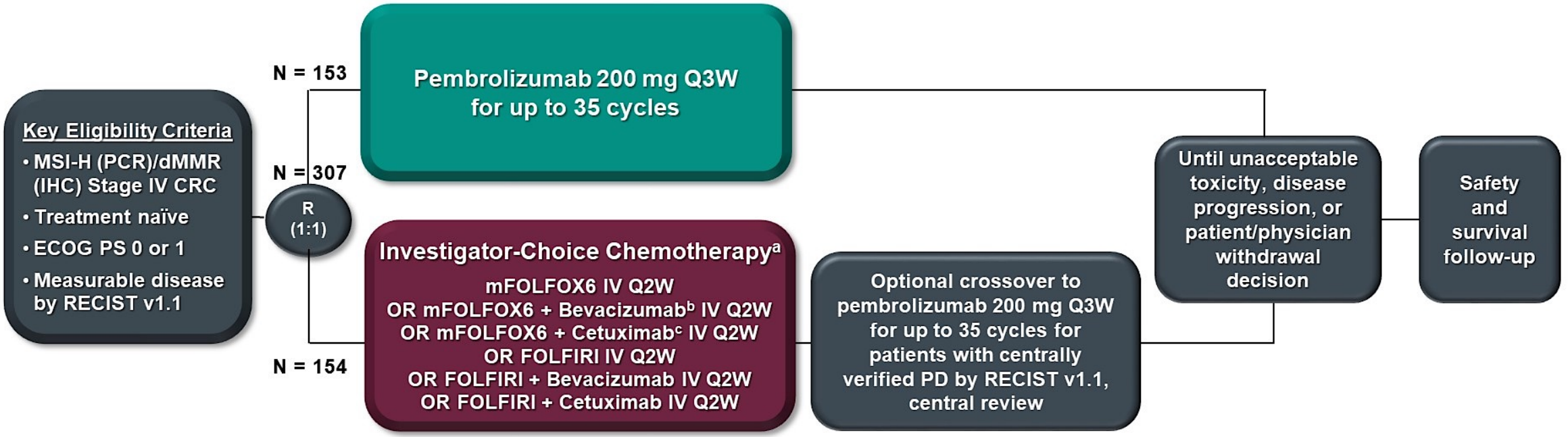
Proposed primary endpoint: Clinical complete response rate (cCR)

PI: Kristen Ciombor

Statistical design:

- Two-stage single-arm phase II study (n=31)

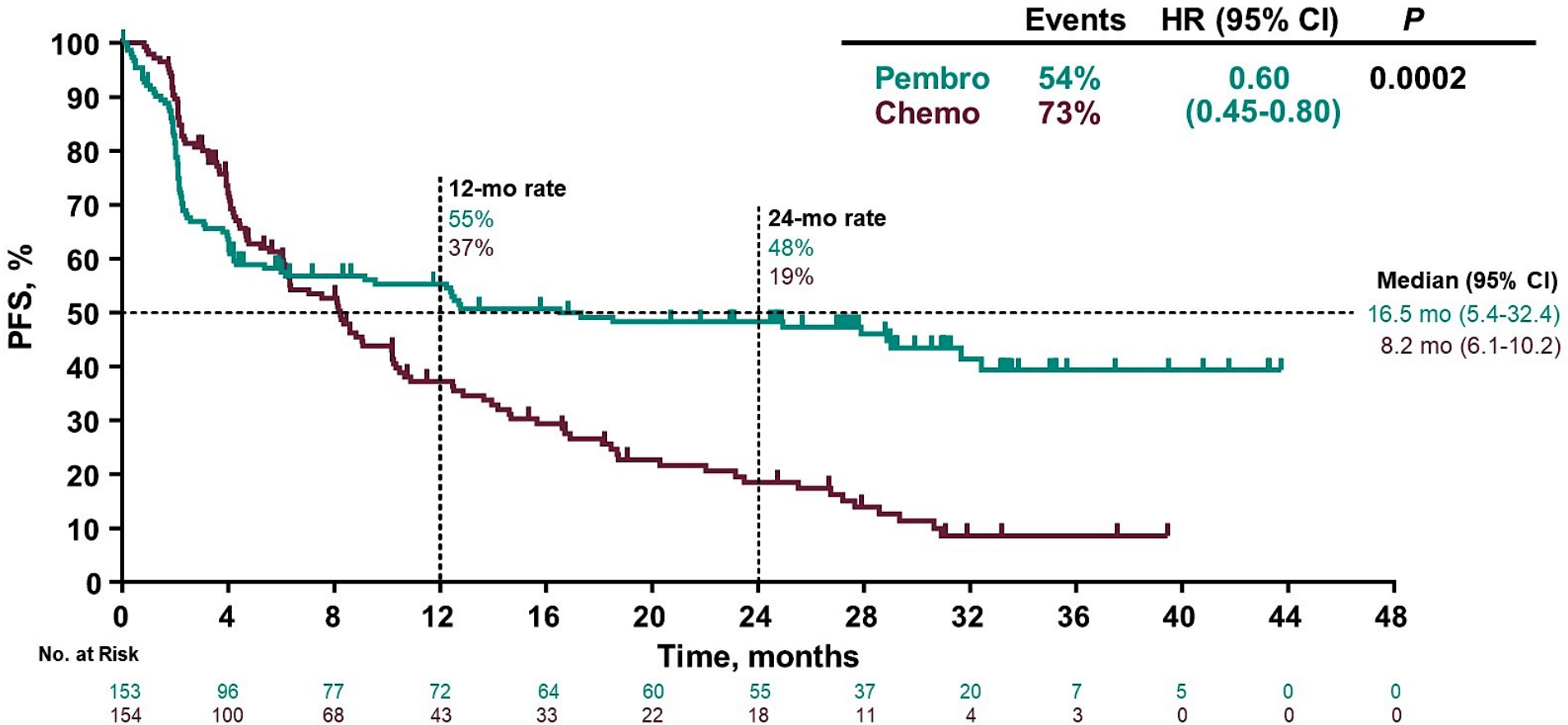
KEYNOTE-177 Study Design (NCT02563002)



- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Exploratory endpoints: DOR per RECIST v1.1 by BICR, PFS2, HRQoL
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

Shiu, ASCO GI 2021

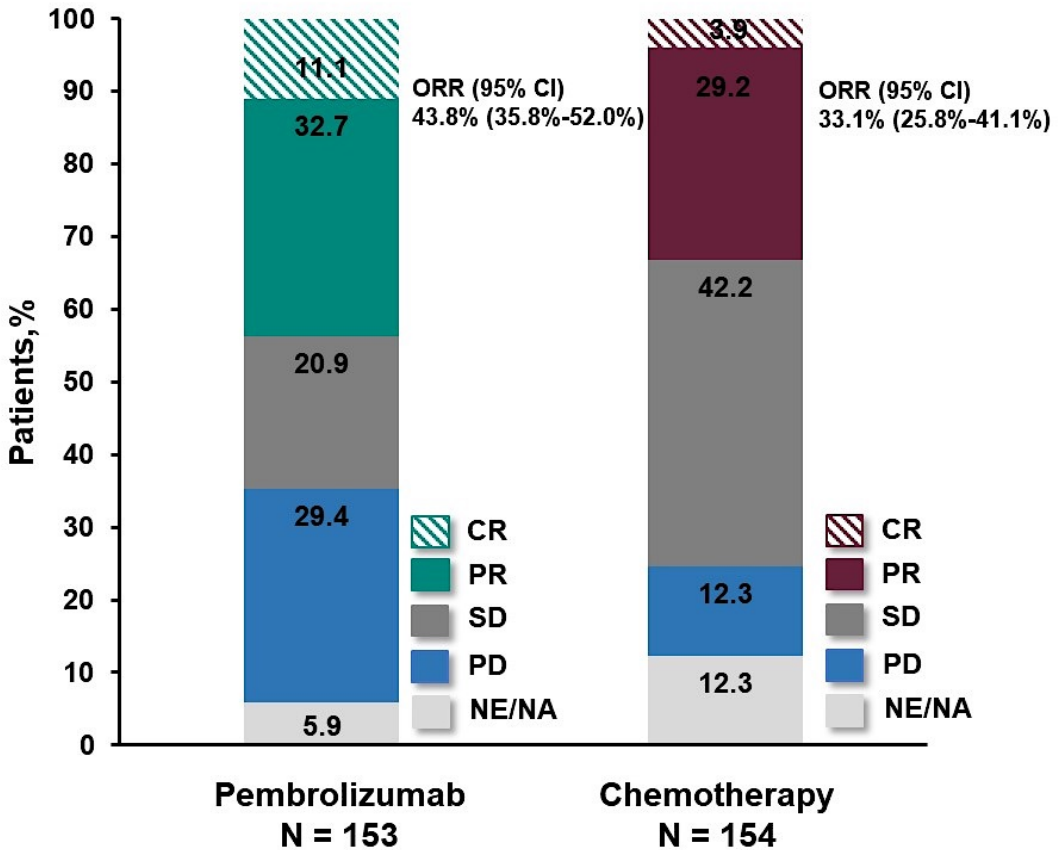
Progression-Free Survival

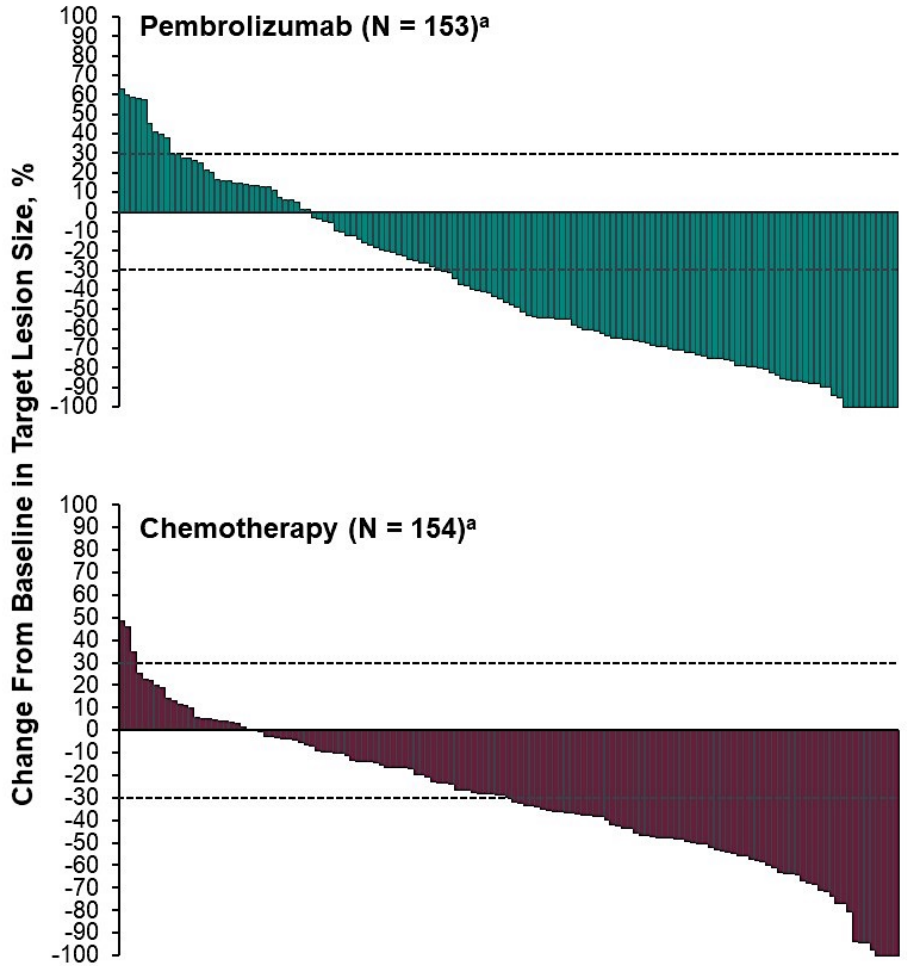


Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

Diaz LA Jr, Shiu KK, Kim TW, et al. *Lancet Oncol*. 2022;23(5):659-670. Shiu, ASCO GI 2021

Summary of Best Anti-Tumor Response



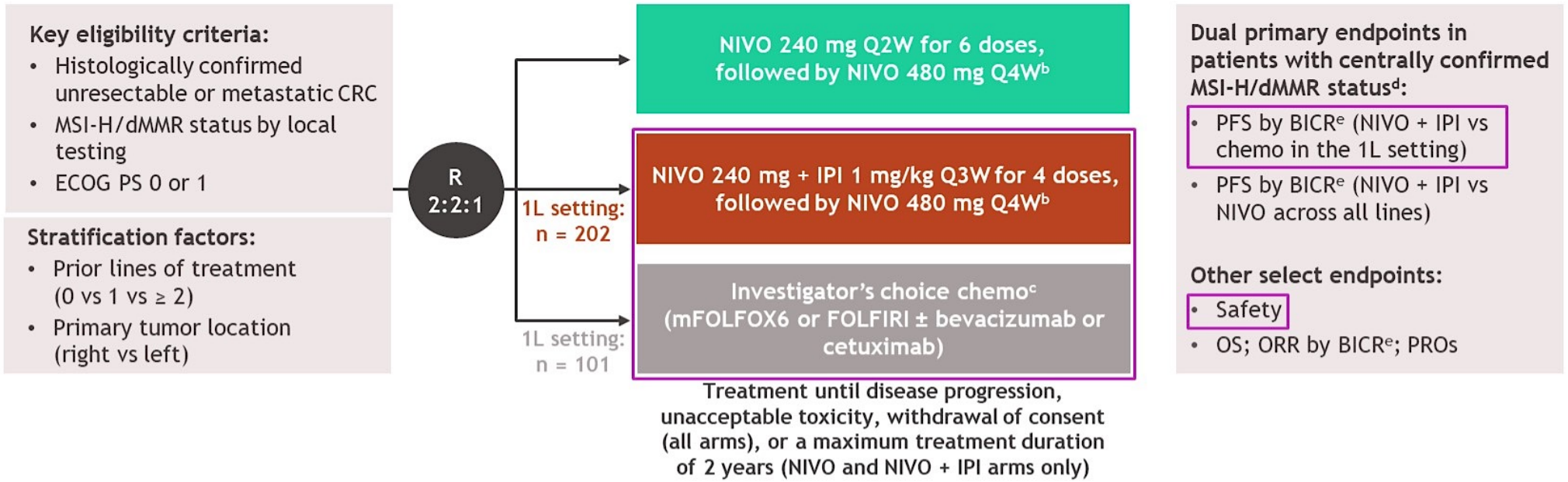


9 (6%) patients in the pembrolizumab arm and 19 (12%) in the chemotherapy arm were not evaluable (NE) or had no assessment (NA); [a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion size. Evaluable patients include those with ≥1 post-baseline target lesion imaging assessment in the intention-to-treat population; Data cut-off: 19Feb2020.

Diaz LA Jr, Shiu KK, Kim TW, et al. *Lancet Oncol*. 2022;23(5):659-670. Shiu, ASCO GI 2021

CheckMate 8HW study design

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

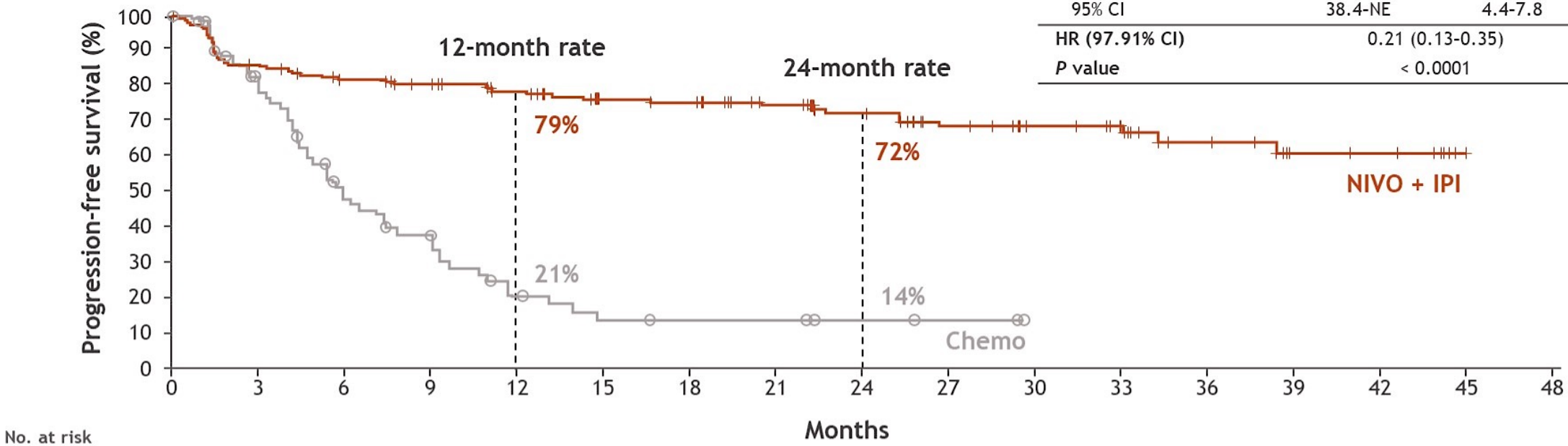


- At data cutoff (October 12, 2023), the median follow-up[f] was 24.3 months

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and last known date alive or death.

Progression-free survival

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	



No. at risk

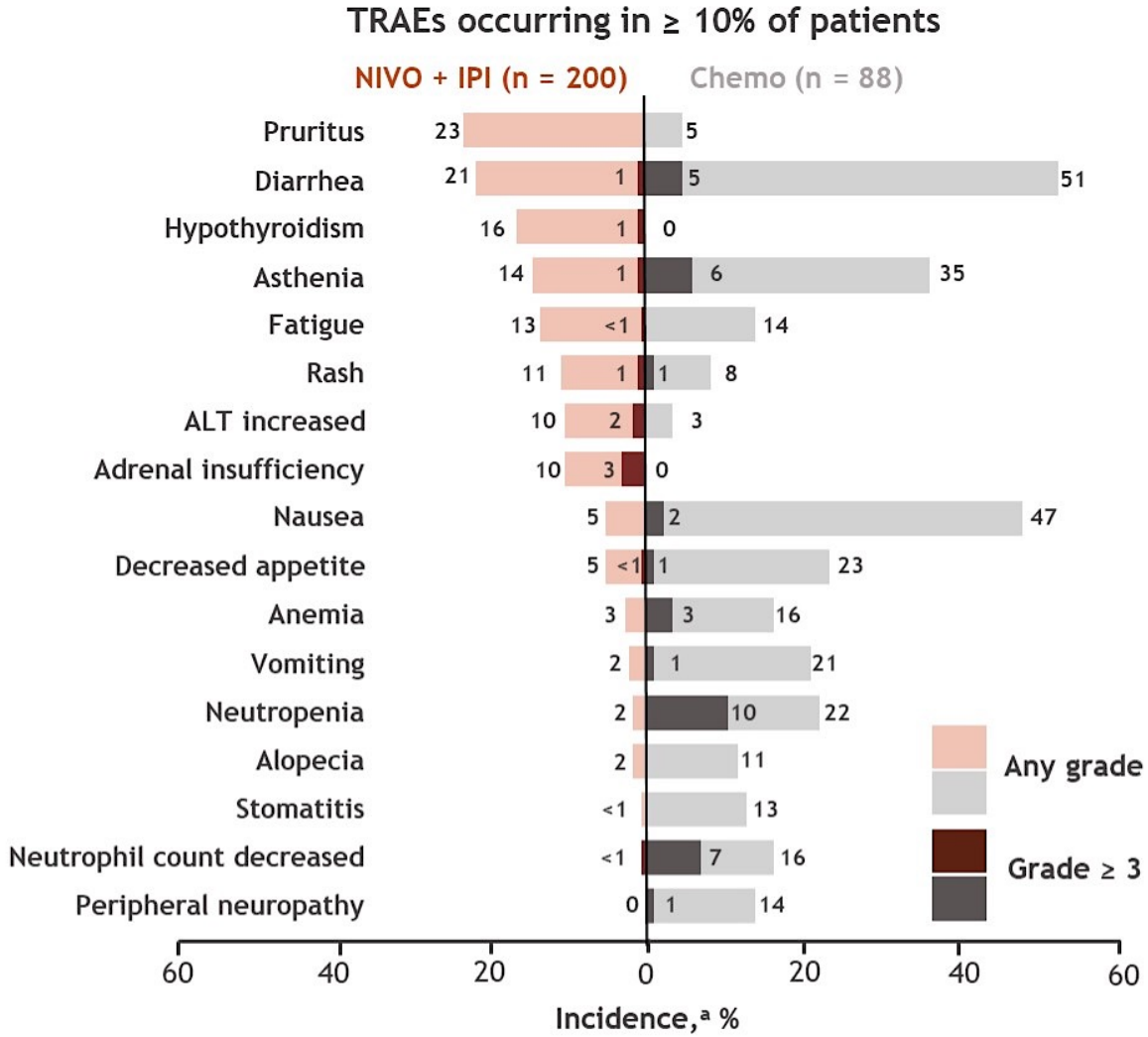
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

[a]Per BICR. [b]Median follow-up, 24.3 months.

Andre, ASCO GI 2024

Treatment-related adverse events

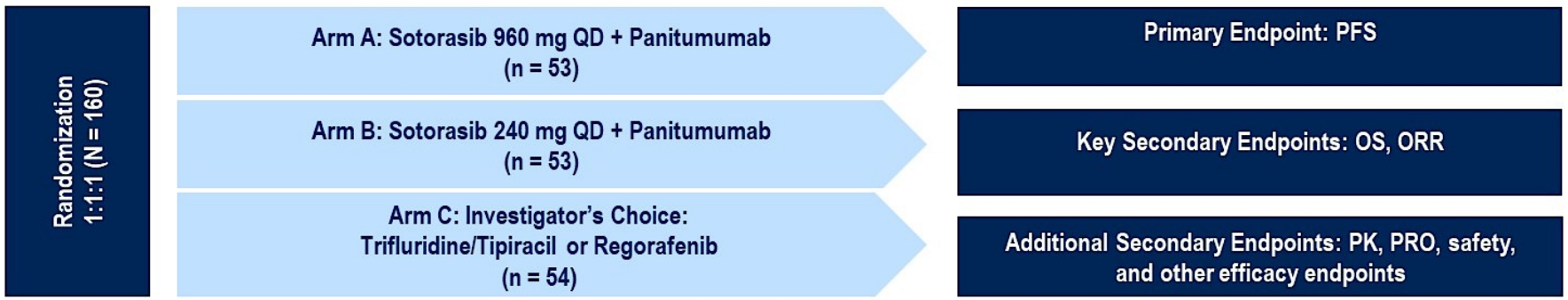


1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	
IMAEs,[d] n (%)				
Non-endocrine events				
Diarrhea/colitis	13 (7)	9 (5)	1 (1)	0
Hepatitis	11 (6)	6 (3)	0	0
Rash	11 (6)	3 (2)	0	0
Pneumonitis	4 (2)	3 (2)	0	0
Endocrine events				
Hypothyroidism/thyroiditis	34 (17)	3 (2)	1 (1)	0
Adrenal insufficiency	21 (11)	7 (4)	0	0
Hyperthyroidism	18 (9)	0	1 (1)	0
Hypophysitis	10 (5)	5 (3)	0	0

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Includes 1 event each of myocarditis and pneumonitis. [c]One death (acute myocarditis) was related to crossover treatment. [d]Includes events reported within 100 days of last dose of study therapy reported in ≥ 2% of patients.

Background

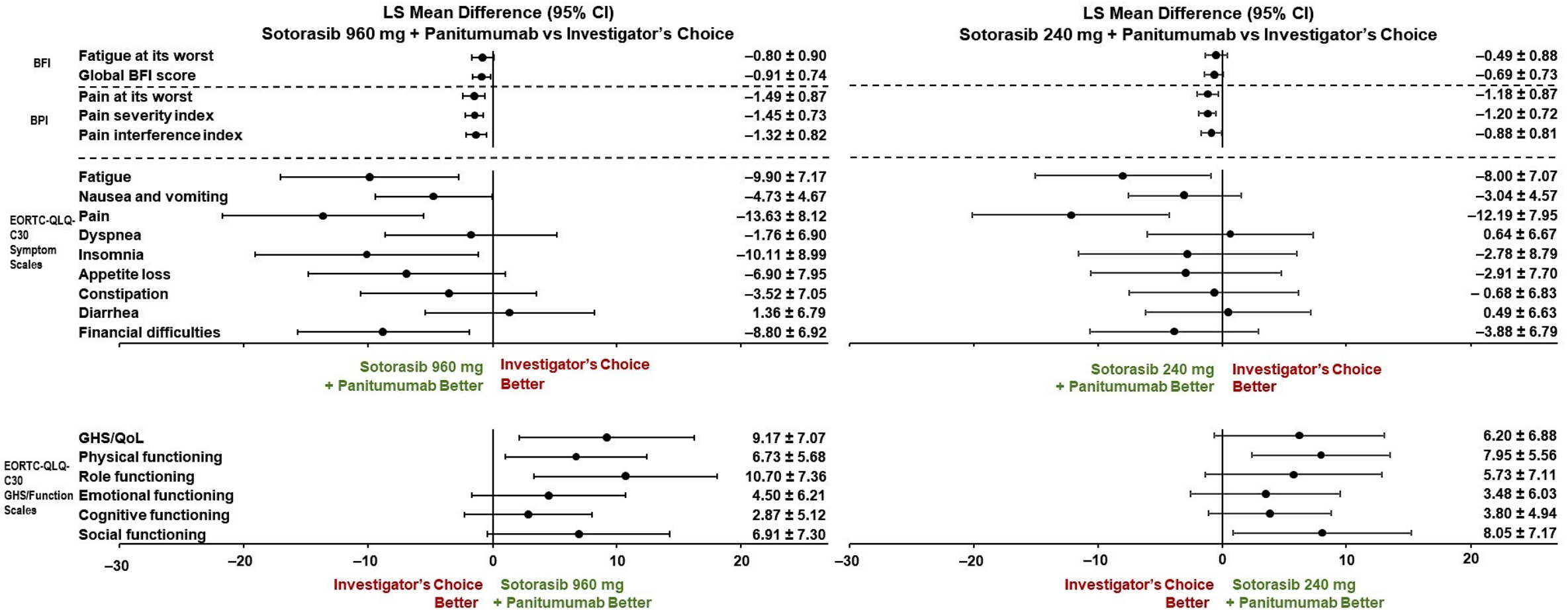
- CodeBreaK 300 (NCT05198934) was the first global phase 3 study to demonstrate the benefits of a $KRAS^{G12C}$ inhibitor in mCRC[1]
- In CodeBreaK 300, sotorasib 960 mg plus panitumumab demonstrated statistically and clinically significant benefit compared with SOC[1]
  - Median progression-free survival (PFS) of 5.6 months vs 2.2 months, HR = 0.49 (0.30 - 0.80), *P* = 0.006
  - Objective response rate (ORR) of 26.4%



Here, we present patient-reported outcomes (PROs) from the CodeBreaK 300 study

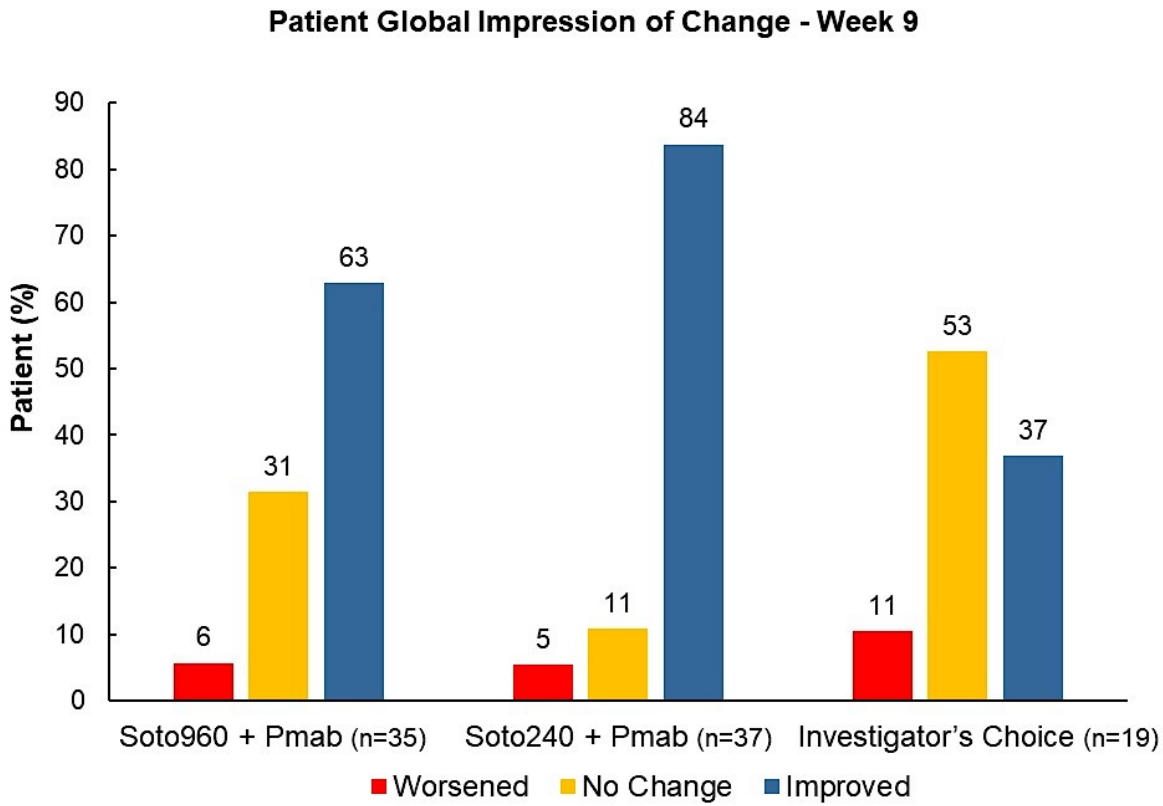
1. Fakih MG, et al. N Engl J Med 2023;389:2125-2139. HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; PK, pharmacokinetics; PRO, patient reported outcomes; QD, once a day; SOC, standard of care

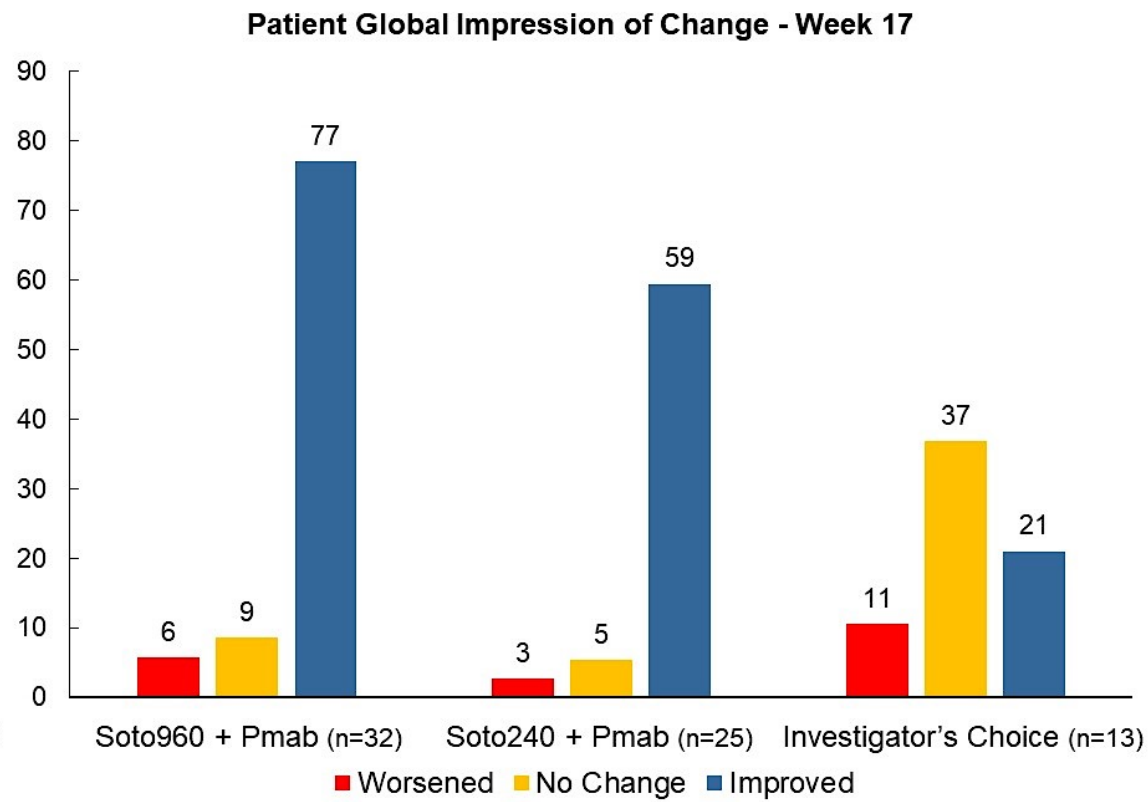
Change From Baseline to Week 8 Indicated an Improvement in Key PRO Scales for Sotorasib + Panitumumab Groups vs Investigator's Choice



Difference in mean change from baseline to week 8 between the treatment arms was assessed for scales of the BFI, BPI, and EORTC QLQ-C30 using a mixed models for repeated measures (MMRM). MMRM was based on change from baseline as the dependent variable, intercept, time, baseline score, treatment, treatment-by-time interaction, and randomization factors as fixed effects, and patient intercept and slope of time for the change from baseline as random effects, including multiple assessment at each time point (excluding follow-up after treatment). BFI, Brief Fatigue Inventory; BPI, Brief Pain Inventory; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core 30-item Quality of Life questionnaire; GHS/QoL, Global Health Status/Quality of Life; LS, least squares; PRO, patient reported outcomes

Patients' Perception of Overall Status at Weeks 9 and 17





- **Most patients in the sotorasib + panitumumab groups reported their overall status as "Improved"**
- **Most patients in the investigator's choice group reported their overall status as "No Change"**

PGI-C subcategories "(very) much worse" + "minimally worse" were combined into "Worsened" category; PGI-C subcategories "minimally improved" + "(very much) improved" were combined into "Improved" category. PGI-C, Patient Global Impression of Change; Pmab, panitumumab; Soto960, sotorasib 960 mg; Soto240, sotorasib 240 mg

Agenda

Module 1: Select Biomarker-Directed Approaches for CRC — Dr Ciombor

Module 2: HER2-Targeted Approaches for mCRC; Other Available and Emerging Therapeutic Strategies — Dr Strickler

HER2-Targeted Approaches for mCRC; Other Available and Emerging Therapeutic Strategies

John H. Strickler, MD
Associate Professor of Medicine
Duke University Medical Center

March 24, 2024

Disclosures

Advisory Committees	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, GSK, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Merck, Natera Inc, Pfizer Inc, Regeneron Pharmaceuticals Inc, Seagen Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Xilio Therapeutics
Contracted Research	AbbVie Inc, Amgen Inc, A*STAR D3, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Curegenix, Daiichi Sankyo Inc, Erasca, Genentech, a member of the Roche Group, GSK, Leap Therapeutics Inc, Lilly, Seagen Inc
Data and Safety Monitoring Boards/Committees	BeiGene Ltd, Seagen Inc
Stock Options — Private Company	Triumvira Immunologics

Case: Metastatic colorectal cancer

- 38 year old female, presents with intractable nausea and vomiting
- CT chest/ abd/ pelvis: multiple liver and lung metastases
- Flexible sigmoidoscopy: near obstructing rectosigmoid mass
- MRI pelvis: T4N+ rectosigmoid cancer
- Biopsy of liver mass: adenoca consistent with colorectal primary
- Treated with 8 cycles (4 months) FOLFOXIRI/bevacizumab→ stable disease as best response
- Remains symptomatic from rectosigmoid primary
- Struggling with progressive fatigue/ neuropathy
- Patient establishes care in my clinic

What should the patient be offered next?

Case: Metastatic colorectal cancer

Tissue NGS

- TP53 frameshift mutation
- APC truncation mutation
- NRAS amplification
- ERBB2 (HER2) amplification
- MSS
- TMB= 2.3 muts/Mb

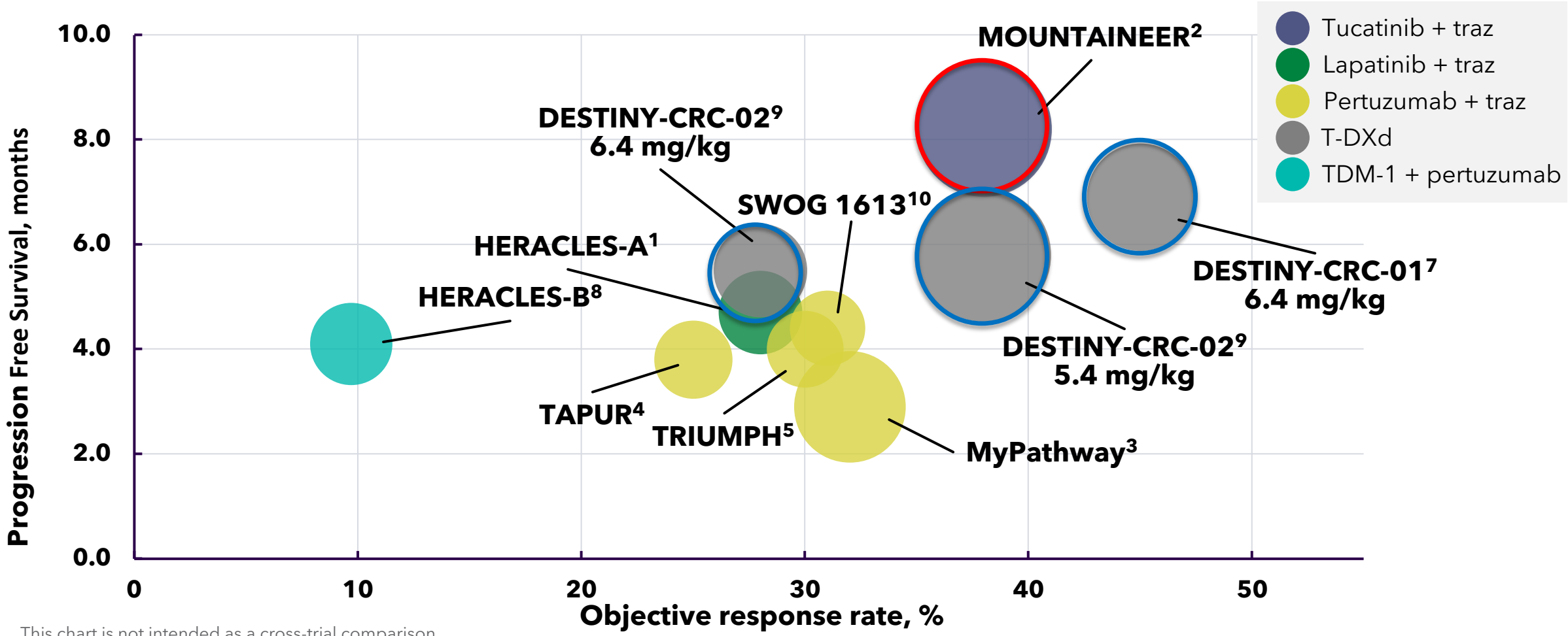
Blood NGS (ctDNA)

Alteration	MAF	Copy number
TP53	5.3%	
APC	4.2%	
ERBB2 amp		12.7
MSI-H not detected, TMB=7.2 muts/Mb		

Decision: Treat with anti-HER2 therapy

Therapeutic landscape for HER2+ metastatic CRC

Size of data point adjusted for sample size

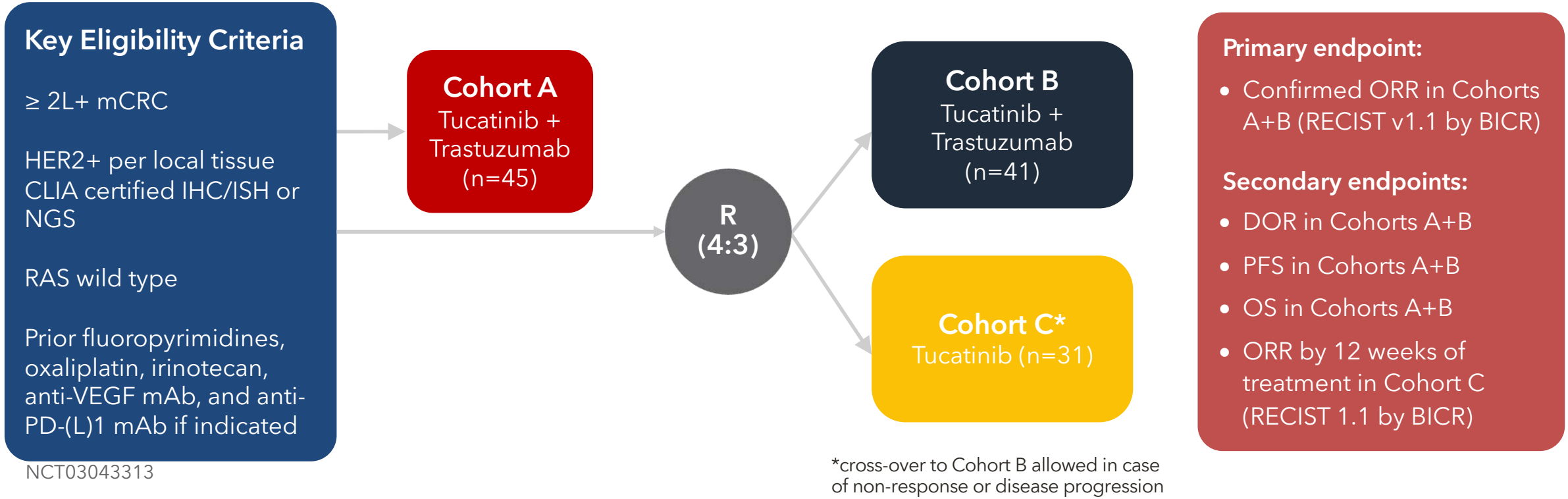


This chart is not intended as a cross-trial comparison.

CRC, colorectal cancer; HER2, human epidermal growth factor receptor 2; HER2+, HER2 gene amplification; T-DXd, trastuzumab-deruxtecan; TDM-1, trastuzumab emtansine; traz, trastuzumab.

1. Tosi F et al., Clin Colorectal Cancer 2020; 2. Strickler JH et al., Lancet Oncol. 2023; 3. Meric-Bernstam F et al., Lancet Oncol 2019; 4. Gupta et al., J Clinical Oncol. 2020; 5. Nakamura Y et al., Nature Medicine 2021; 6. Meric-Bernstam F et al., Ann Oncol. 2019; 7. Yoshino T et al., Nat. Commun. 2023. 8. Sartore-Bianchi A et al., ESMO Open 2020; 9. Raghav K et al., presented at ASCO Annual Meeting 2023, Chicago (USA), June 2-6, Oral Abstract 3501; 10. Raghav K et al., J Clin Oncol. 2023.

MOUNTAINEER: Tucatinib + Trastuzumab for HER2+ mCRC - Phase 2 Study Design



- Tucatinib is an oral, small molecule TKI that targets HER2
- Highly selective for the HER2 receptor
- Selectivity may improve tolerability (skin rash, diarrhea, etc.) compared to non-selective TKIs

Strickler JH et al. *Lancet Oncol.* 2023;24(5):496-508. Corti C et al. *ESMO Open.* 2021;6(2):100063. Moulder SL et al. *Clin Cancer Res.* 2017;23(14):3529-3536.

MOUNTAINEER: Tucatinib + Trastuzumab: Summary – Efficacy and Safety

Overview efficacy Tucatinib + Trastuzumab Cohorts A+B (n=84)[1]

Confirmed ORR, % (95% CI)	**38.1%** (27.7-49.3)
mDOR, months (95% CI)	**12.4 months** (8.5-25.5)
DCR, n (%)	**60** (71%)
PFS, months (95% CI)	**8.2 months** (4.2-10.3)
OS, months (95% CI)	**24.1 months** (20.3-36.7)

Overview safety Tucatinib + Trastuzumab Cohorts A+B (n=86)[2]

TEAEs, n (%)	Tucatinib + Trastuzumab
Any grade AEs	82 (95.3)
Tucatinib-related	63 (73.3)
Trastuzumab-related	58 (67.4)
Grade ≥3 AEs	33 (38.4)
Tucatinib-related	8 (9.3)
Trastuzumab-related	6 (7.0)
SAEs	19 (22.1)
Tucatinib-related	3 (3.5)
Trastuzumab-related	2 (2.3)
AEs leading to study treatment discontinuation[a,b]	5 (5.8)
AEs leading to tucatinib dose modification	22 (25.6)
Deaths due to AEs	0

[a] TEAEs leading to discontinuation of tucatinib included alanine aminotransferase increase (2.3%), COVID-19 pneumonia (1.2%), cholangitis (1.2%), and fatigue (1.2%);
[b] TEAEs leading to discontinuation of trastuzumab included alanine aminotransferase increase (2.3%) and COVID-19 pneumonia (1.2%).

AE, adverse event; CI, confidence interval; DCR, disease control rate; mDOR, median duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

1. Strickler JH et al. *Lancet Oncol.* 2023;24(5):496-508. 2. Strickler JH et al. 2022 ESMO GI Congress. Abstract LBA-2.

MOUNTAINEER: Results by testing modality

	Primary analysis*	Central IHC/FISH		Tissue NGS (PGDX)		Blood NGS (G360)	
		+	-	+	-	+	ND
PFS, mo (95% CI)	**8.2 mo** (4.2-10.3)	10.1 mo (4.2-15.2)	2.8 mo (1.2-6.3)	10.9 mo (7.0-20.7)	2.1 mo (1.3-nr)	8.1 mo (3.1-10.2)	10.9 mo (2.0-18.4)
ORR, % (95% CI)	**38.1%** (27.7-49.3)	40% (NR)	10% (0.3-44)	47.7% (32-63)	0% (0-45.9)	41.1% (28.1-55)	20% (4.3-48.1)
Duration of response, mo (95% CI)	**12.4 mo** (8.5-25.5)	16.4 mo (10.6-25.5)	--	15.3 mo (8.9-25.5)	--	12.4 mo (6.2-38.3)	--

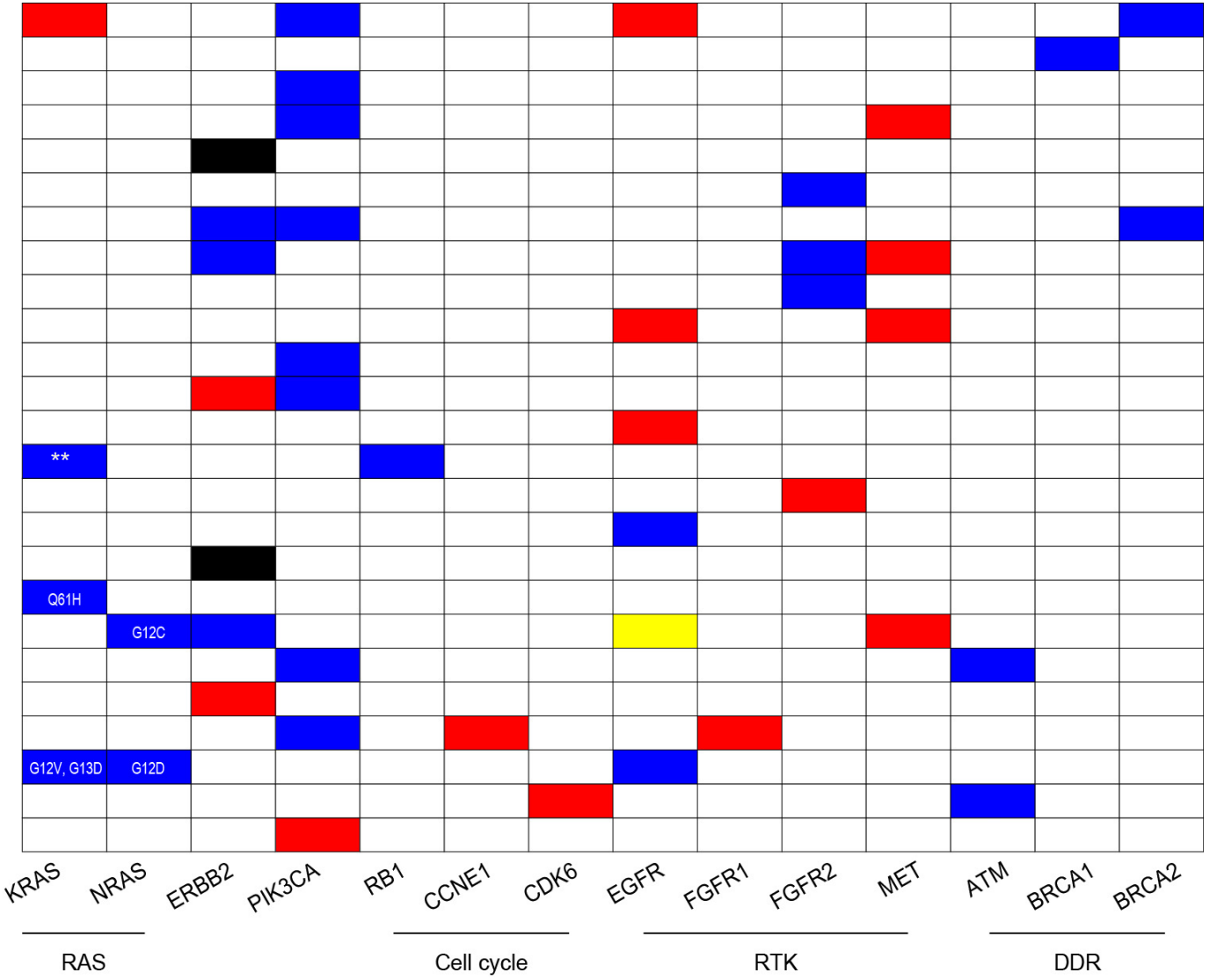
* Trial included patients with HER2+ result from any tissue-based assay (IHC, FISH, NGS)

Strickler JH et al., J Clin Oncol 41, 2023 (suppl 16; abstr 3528). Presented at 2023 ASCO Annual Meeting.

ctDNA NGS: Genomic Landscape of Acquired Alterations at Progression Timepoint or EOT

Response	PFS
PR	16.5
PR	15.2
PR	13.1
PR	12.6
PR	12.5
PR	10.3
PR	8.3
PR	8.3
SD	8.1
PR	8.1
PR	8
PR	6.8
SD	4.4
SD	3.1
SD	2.8
SD	2.7
SD	2.7
SD	2.6
SD	2.6
SD	2.6
SD	2.1
PD	2.1
PD	1.7
PD	1.5
PD	1.1

**KRAS G13C, G12C, I24N



n=31; 1 patient removed from analysis due to no detected alterations at baseline, leading to analysis set of 30; 23/30 showed alteration gains; 2/30 showed ERBB2 loss; 5/30 showed no alteration gains and no ERBB2 loss.

SNV/INDEL

Amplification

SNV/INDEL and amplification

Loss of amplification

Note: a single BLUE or YELLOW box can represent multiple SNV/INDEL detections in the same gene

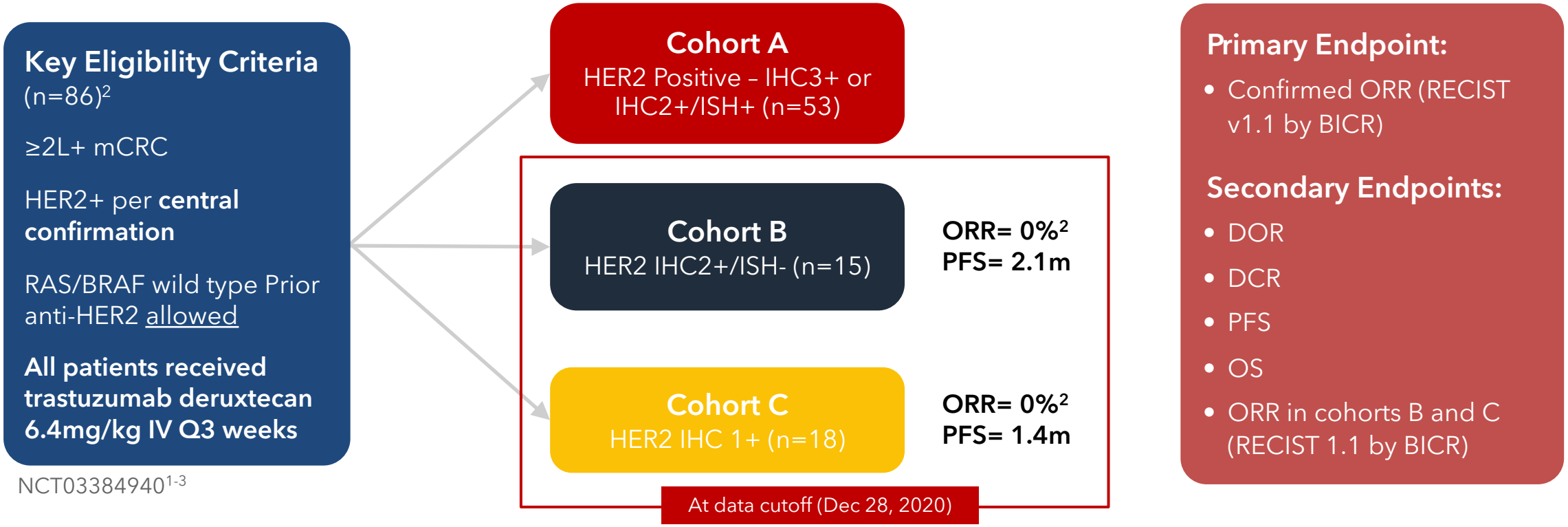
DDR: DNA Damage Response; EOT, end of treatment; PFS, progression-free survival; RTK: Receptor Tyrosine Kinase; SNV, single nucleotide variation

MADRID 2023 ESMO congress

Strickler et al.

Strickler JH et al. Annals of Oncology 34, 2023 (suppl_2): S410-S457. 2023 ESMO Annual Meeting.

DESTINY-CRC01: Trastuzumab deruxtecan (T-DXd; DS-8201a) for HER2+ mCRC - Phase 2 Study Design



1. Siena S et al. *Lancet Oncol.* 2021;22(6):779-789.
2. Yoshino T et al. 2021 ASCO Annual Meeting. Abstract 3505.
3. Yoshino T et al. *Nat Commun.* 2023;14(1):3332.

DESTINY-CRC01: Trastuzumab deruxtecan for HER2+ mCRC - Efficacy Outcomes

Cohort A, N=53 (response assessed by BICR)[1-3]

Confirmed ORR, % (95% CI)	45.3% (31.6-59.6)
mDOR, months (95% CI)[2]	7.0 months (5.8-9.5)
Disease control rate, % (95% CI)	83.0% (70.2-91.9)
PFS, months (95% CI)[2]	6.9 months (4.1-8.7)
OS, months (95% CI)[2]	15.5 months (8.8-20.8)

Data cutoff (Dec 28, 2020)

BICR, blinded independent central review; CI, confidence interval; HER2+, HER2 gene amplification; mCRC, metastatic colorectal cancer; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

1. Siena S et al. *Lancet Oncol.* 2021;22(6):779-789. 2. Yoshino T et al. 2021 ASCO Annual Meeting. Abstract 3505. 3. Yoshino T et al. *Nat Commun.* 2023;14(1):3332.

DESTINY-CRC01: Trastuzumab deruxtecan for HER2+ mCRC - Most Common TEAEs (≥ 10%)

(All cohorts, N=86)

Preferred term	Any grade	Grade ≥3
Patients with any TEAE	86 (100)	56 (65.1)
Nausea	53 (61.6)	5 (5.8)
Anemia	31 (36.0)	12 (14.0)
Fatigue	31 (36.0)	1 (1.2)
Decreased appetite	30 (34.9)	0
Platelet count decreased	28 (32.6)	8 (9.3)
Vomiting	27 (31.4)	1 (1.2)
Neutrophil count decreased	26 (30.2)	19 (22.1)
Diarrhea	23 (26.7)	1 (1.2)

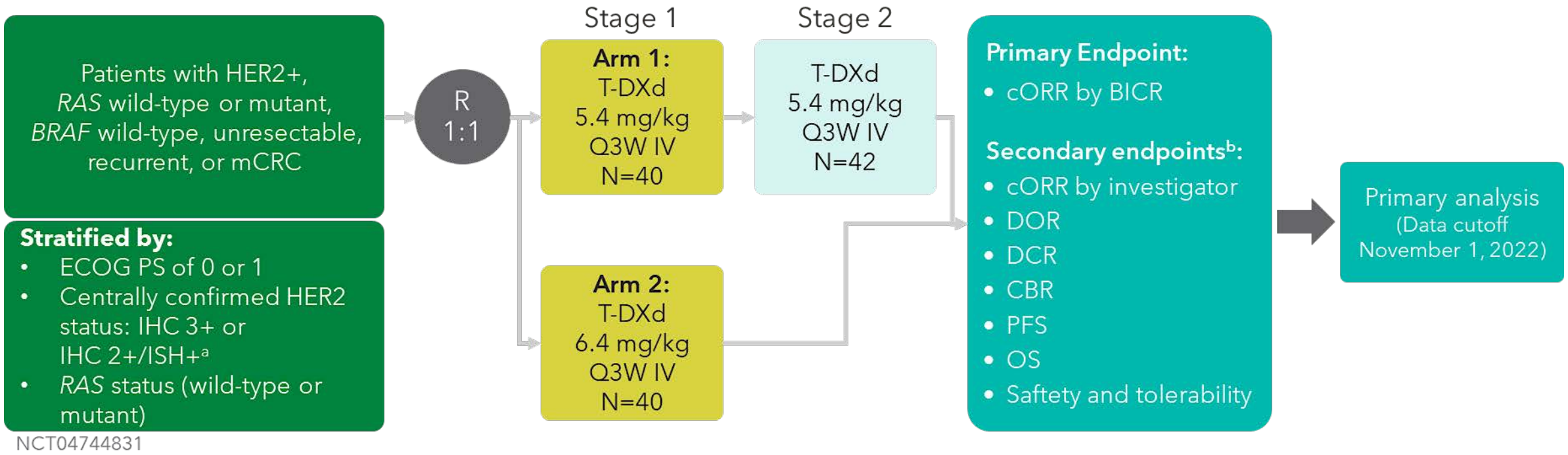
- Eight (9.3%) of 86 patients had interstitial lung disease or pneumonitis
  - Grade 2 = 4 patients
  - Grade 3 = 1 patient
  - Grade 5 = 3 patients
- Median time to onset date of interstitial lung disease or pneumonitis was 66.5 days
- 4 recovered, 1 did not recover and died of disease progression, and 3 died due to the AE

AE, adverse event; HER2, human epidermal growth factor receptor 2; HER2+, HER2 gene amplification; mCRC, metastatic colorectal cancer; TEAE, treatment-emergent adverse event.

Yoshino T et al. *Nat Commun.* 2023;14(1):3332.

DESTINY-CRC02 - Study Design

A randomized, blinded, 2-stage, 2-arm, multicenter, global, phase 2 study



NCT04744831

This study was not powered to statistically compare the two arms.

- Stage 1 (randomized) was followed by Stage 2 (nonrandomized), which enrolled an additional 42 patients

Raghav K et al. 2023 ASCO Annual Meeting. Abstract 3501.

DESTINY-CRC02: Trastuzumab deruxtecan for HER2+ mCRC - Efficacy Outcomes

	5.4 mg/kg Q3W (n = 82)	6.4 mg/kg Q3W (n = 40)
Confirmed ORR, % (95% CI)	37.8% (27.3-49.2)	27.5% (14.6-43.9)
mDOR, months (95% CI)	5.5 months (4.2-8.1)	5.5 months (3.7-NE)
Disease control rate, % (95% CI)	86.6% (77.3-93.1)	85.0% (70.2-94.3)
PFS, months (95% CI)	5.8 months (4.6-7.0)	5.5 (4.2-7.0)
OS, months (95% CI)	13.4 months (12.5-16.8)	NE (9.9-NE)
ILD/ Pneumonitis All grade, n (%) Grade 5, n (%)	 7 (8.4%) 0 (0%)	 5 (12.8%) 1 (2.6%)

Raghav K et al. 2023 ASCO Annual Meeting. Abstract 3501.

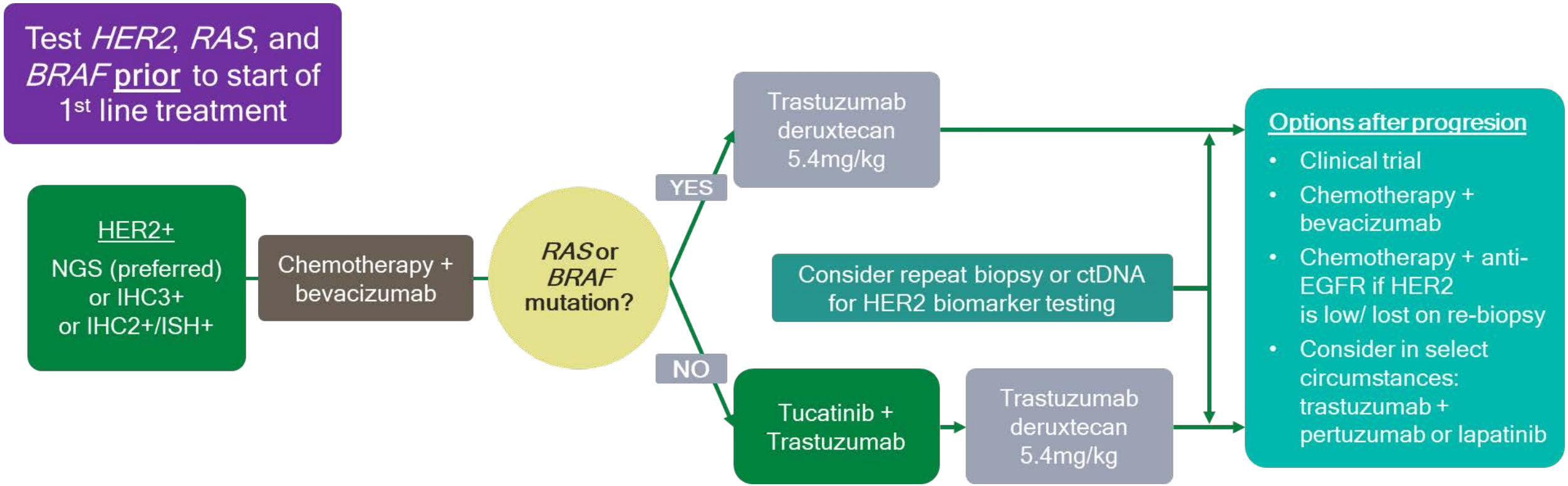
DESTINY-CRC02: Trastuzumab deruxtecan for HER2+ mCRC - Best ORR (BICR) by T-DXd 5.4 mg/kg subgroup

		ORR, % (n/N)	95% CI[a]
All patients (5.4 mg/kg)	**N = 82**	**37.8 (31/82)**	27.3-49.2
HER2 status	IHC 3+	**46.9 (30/64)**	34.3-59.8
	IHC 2+/ISH+	**5.6 (1/18)**	0.1-27.3
***RAS* status**	Wild-type	**39.7 (27/68)**	28.0-52.3
	Mutant[b]	**28.6 (4/14)**	8.4-58.1
ECOG PS	0	**39.1 (18/46)**	25.1-54.6
	1	**36.1 (13/36)**	20.8-53.8
Primary tumor site	Left colon[c]	**39.3 (24/61)**	27.1-52.7
	Right colon[d]	**33.3 (7/21)**	14.6-57.0
Prior anti-HER2 treatment	No	**36.9 (24/65)**	25.3-49.8
	Yes	**41.2 (7/17)**	18.4-67.1

[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All RASm responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.
Trastuzumab deruxtecan is not approved by EMA in mCRC.

Raghav K et al., presented at ASCO Annual Meeting 2023, Chicago (USA), June 2-6, Oral Abstract 3501.

Evidence-Based Algorithm for HER2+/ MSS mCRC



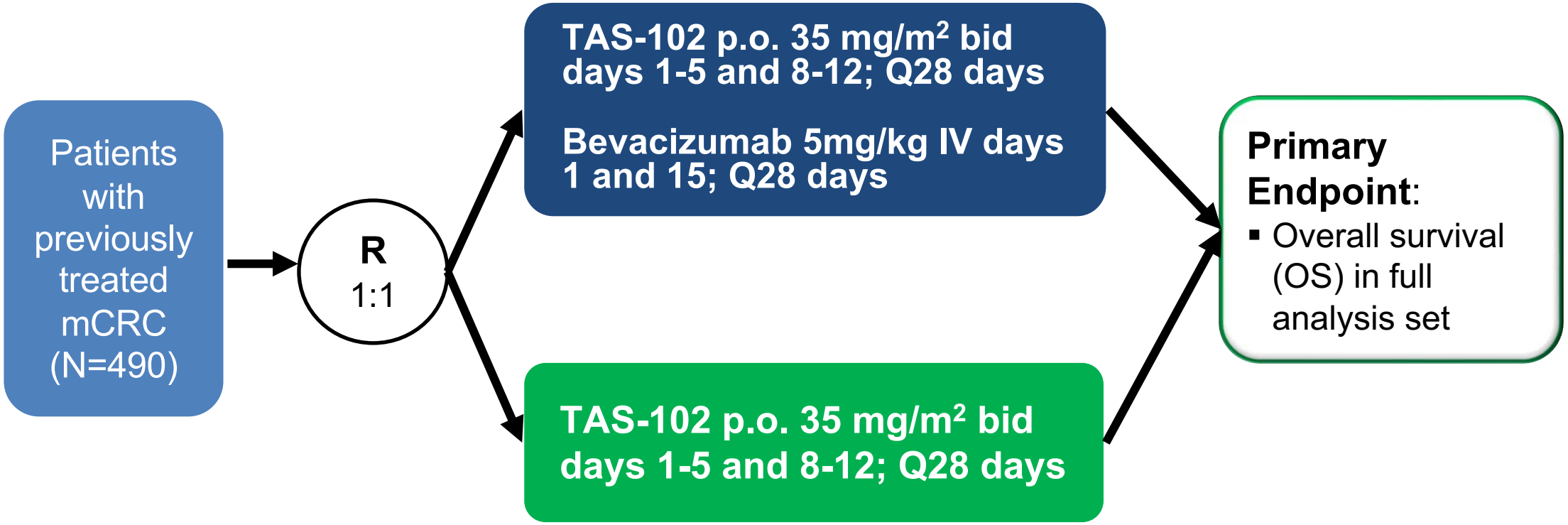
Treatment refractory colorectal cancer: ≥3rd line treatment options before 2023

	N	ORR (%)	Median PFS (months) (95% CI)	Median OS (months) (95% CI)
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)

*** 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.

SUNLIGHT: TAS-102 +/- bevacizumab



Secondary Endpoints	PFS, DCR, ORR, safety profile, QoL

Prager G et al. *NEJM.* 2023; 388: 1657-1667.

SUNLIGHT: TAS-102 + bevacizumab improves survival

	TAS-102 + bev (95% CI)	TAS-102 (95% CI)	HR (95% CI) P-value
Overall Survival (full analysis set)	10.8 months (9.4-11.8)	7.5 months (6.3-8.6)	0.61 (0.49-0.77) P<0.001
Prior bevacizumab sub-population	9.0 months (8.3-10.8)	7.1 months (6.0-8.5)	0.72 (0.56-0.92) NR
PFS	5.6 months (4.5-5.9)	2.4 months (2.1-3.2)	0.44 (0.36-0.53) P<0.001
Prior bevacizumab sub-population	4.5 months (4.1-5.5)	2.2 months (2.1-3.4)	0.51 (0.41-0.63) NR
ORR	6.3%	0.9%	P=0.004
DCR	76.6%	47.0%	P<0.001

Prager G et al. *NEJM.* 2023; 388: 1657-1667.

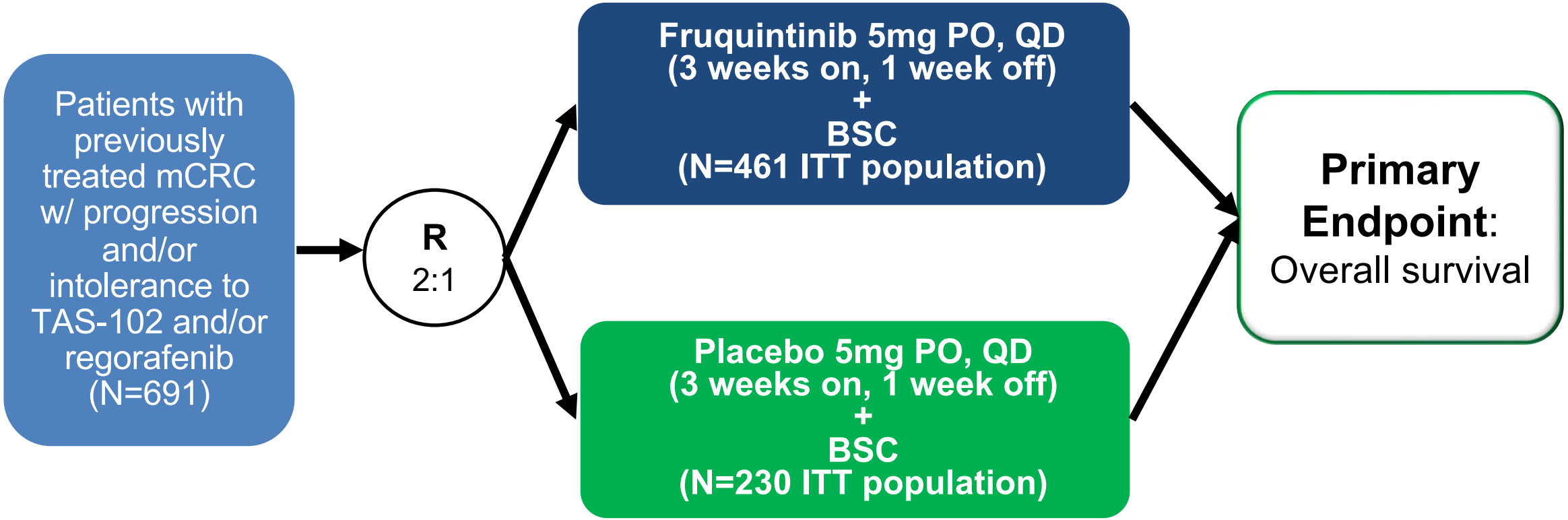
SUNLIGHT: Safety Summary

Adverse events occurring in at least 20% of patients that received TAS-102

	TAS-102 + bevacizumab (n=246)		TAS-102 (n=246)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	62.2%	43.1%	51.2%	32.1%
Nausea	37.0%	1.6%	27.2%	1.6%
Anemia	28.9%	6.1%	31.7%	11.0%
Asthenia	24.4%	4.1%	22.4%	4.1%
Fatigue	21.5%	1.2%	16.3%	3.7%
Diarrhea	20.7%	0.8%	18.7%	2.4%
Decreased appetite	20.3%	0.8%	15.4%	1.2%

Prager G et al. *NEJM.* 2023; 388: 1657-1667.

FRESCO-2: Fruquintinib vs placebo



Secondary Endpoints	PFS, DCR, ORR, Safety

Dasari A et al. *Lancet*. 2023 Jun 15:S0140-6736(23)00772-9.

FRESCO-2: Fruquintinib improves survival, PFS

	Fruquintinib (95% CI)	Placebo (95% CI)	HR (95% CI) P-value
Overall Survival	7.4 months (6.7-8.2)	4.8 months (4.0-5.8)	0.66 (0.55-0.80) P<0.0001
PFS	3.7 months (3.5-3.8)	1.8 months (1.8-1.9)	0.32 (0.27-0.39) P<0.0001
ORR	2% (0.6-3.1)	0% (0.0-1.6)	P=0.059
DCR	56% (50.9-60.1)	16% (11.6-21.5)	P<0.0001

Dasari A et al. *Lancet.* 2023 Jun 15:S0140-6736(23)00772-9.

FRESCO-2: Safety summary

Adverse events occurring in at least 20% of patients that received fruquintinib

	Fruquintinib (n=456)		Placebo (n=230)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension	37%	14%	9%	1%
Asthenia	34%	8%	23%	4%
Decreased appetite	27%	2%	17%	1%
Diarrhea	24%	4%	10%	0%
Hypothyroidism	21%	<1%	<1%	0%
Fatigue	20%	4%	16%	1%

Dasari A et al. *Lancet*. 2023 Jun 15:S0140-6736(23)00772-9.

Stacking up the 3L+ options for metastatic CRC

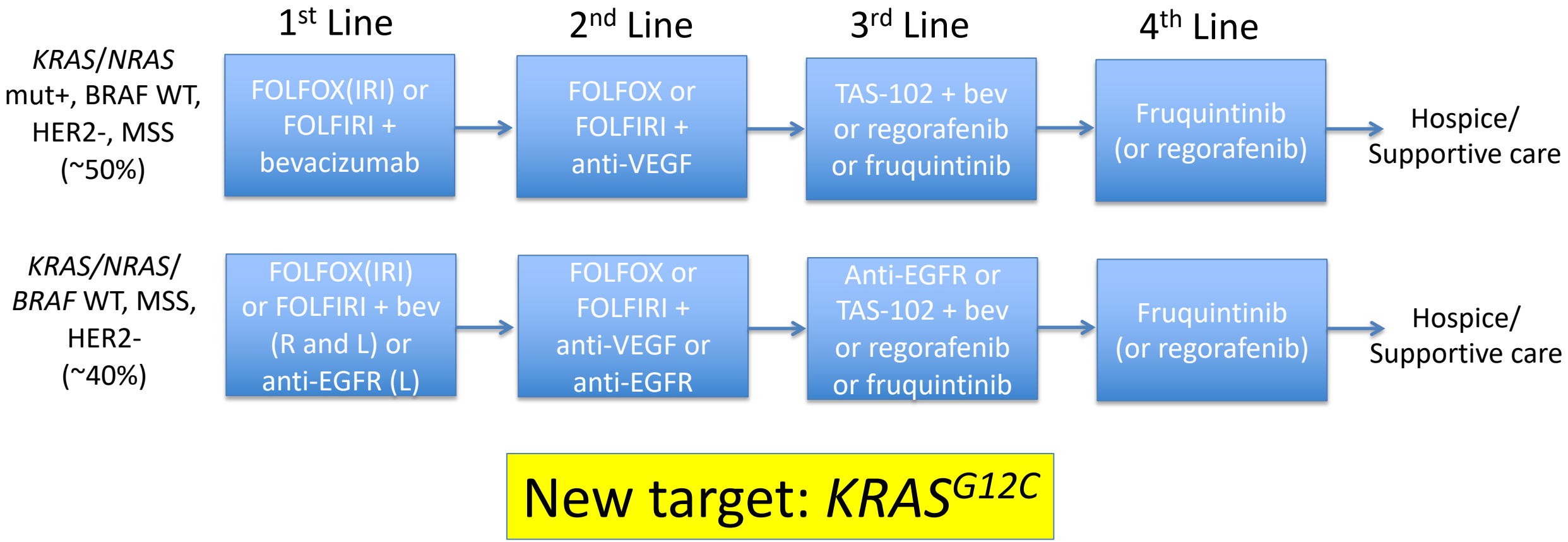
Agent	Regorafenib		TAS-102+bev		Fruquintinib	
Trial	**ReDOS**		**SUNLIGHT**		**FRESCO-2**	
	Escalating	Standard	TAS+Bev	TAS only	Fruquintinib	Placebo
Overall Survival	9.8	6.0	Overall 10.8 Prior bev 9.0	Overall 7.5 Prior bev 7.1	7.4	4.8
PFS	2.8	2.0	Overall 5.6 Prior bev 4.5	Overall 2.4 Prior bev 2.2	3.7	1.8

Factors that influence treatment choice:

- Prior therapies
- Comorbidities
- Tolerability
- Clinical activity
- Access (reimbursement)

Bekaii-Saab TS et al. *Lancet Oncol.* 2019; 20(8):1070-1082.
Prager G et al. *NEJM.* 2023; 388: 1657-1667.
Dasari A et al. *Lancet.* 2023 Jun 15:S0140-6736(23)00772-9.

How I manage metastatic CRC (ECOG 0-2)



New target: *KRAS*^{G12C}

Overview

Sunday, March 24th

Module 10: 7:30 AM – 8:20 AM — Multiple Myeloma

Module 11: 8:20 AM – 9:10 AM — Gastroesophageal Cancers

Module 12: 9:30 AM – 10:20 AM — Hepatobiliary Cancers

Module 13: 10:20 AM – 11:10 AM — Colorectal Cancer

Module 14: 11:10 AM – 12:00 PM — Pancreatic Cancer

Agenda

Module 1: Selection and Sequencing of Therapy for Patients with Metastatic Pancreatic Adenocarcinoma (PAD) — Dr Ko

Module 2: Biomarker-Based Strategies for Metastatic PAD; Novel Investigational Approaches — Dr O'Reilly

Agenda

Module 1: Selection and Sequencing of Therapy for Patients with Metastatic Pancreatic Adenocarcinoma (PAD) — Dr Ko

Module 2: Biomarker-Based Strategies for Metastatic PAD; Novel Investigational Approaches — Dr O'Reilly

Selection and Sequencing of Therapy for Patients with Metastatic Pancreatic Adenocarcinoma

Third Annual National General Medical Oncology Summit (Miami, FL)
March 24, 2024

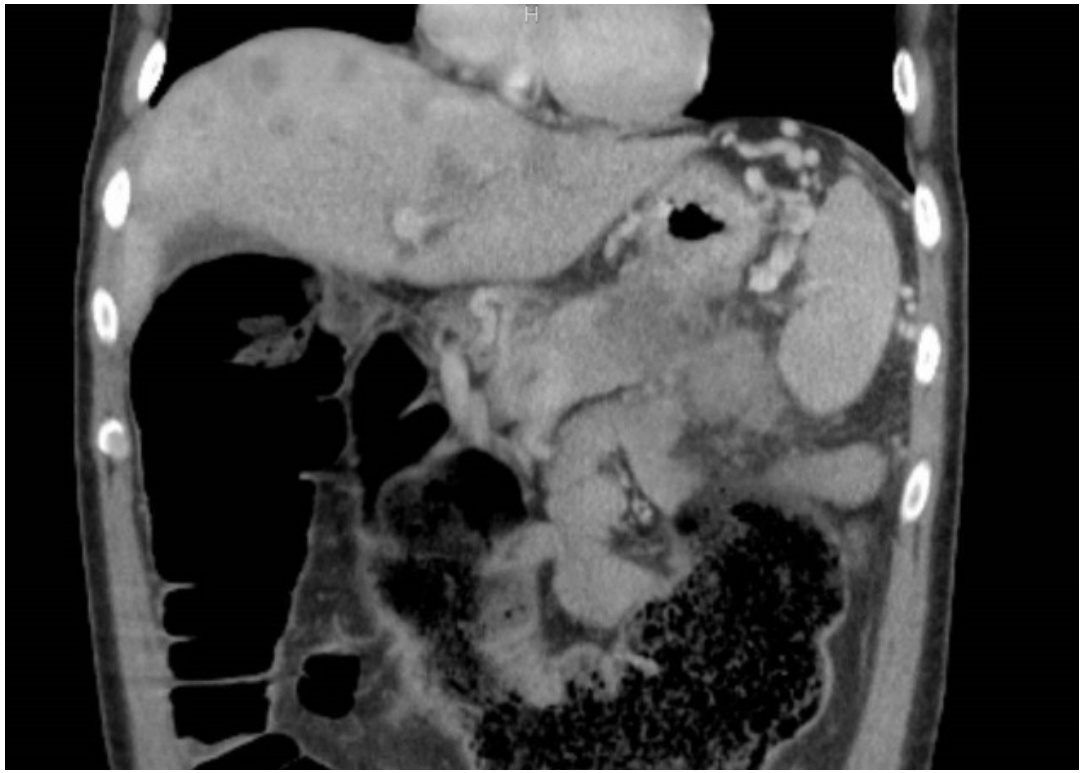
Andrew H. Ko, MD, FASCO
Professor of Clinical Medicine and Associate Chief
Division of Hematology/Oncology
University of California San Francisco

Disclosures

Advisory Committees (One-Time Advisory Boards)	Aadi Bioscience, Arcus Biosciences, Eisai Inc, FibroGen Inc, Genentech, a member of the Roche Group, Merus BV
Consulting Agreement	FibroGen Inc
Contracted Research (to Institution)	AbGenomics, Apexigen, Astellas, Bristol Myers Squibb, Celgene Corporation, Leap Therapeutics Inc, Merck, Verastem Inc
Data and Safety Monitoring Boards/Committees	Genentech, a member of the Roche Group, Grail Inc
Nonrelevant Financial Relationships	Pancreatic Cancer Action Network, Parker Institute for Cancer Immunotherapy

Case presentation

- A 72 yr old man who presents with abdominal pain and progressive fatigue
- Diagnostic CT shows a pancreatic body mass, retroperitoneal lymphadenopathy, and hepatic lesions up to 2 cm
- Core biopsy of one of the liver lesions demonstrated invasive adenocarcinoma
- Further molecular profiling reveals pathogenic mutations in the following:
  - KRAS (G12D)
  - CDKN2A
  - BRCA2
  - Tumor is microsatellite stable (MSS), with low TMB
- How can these results be used to guide therapeutic decision-making?

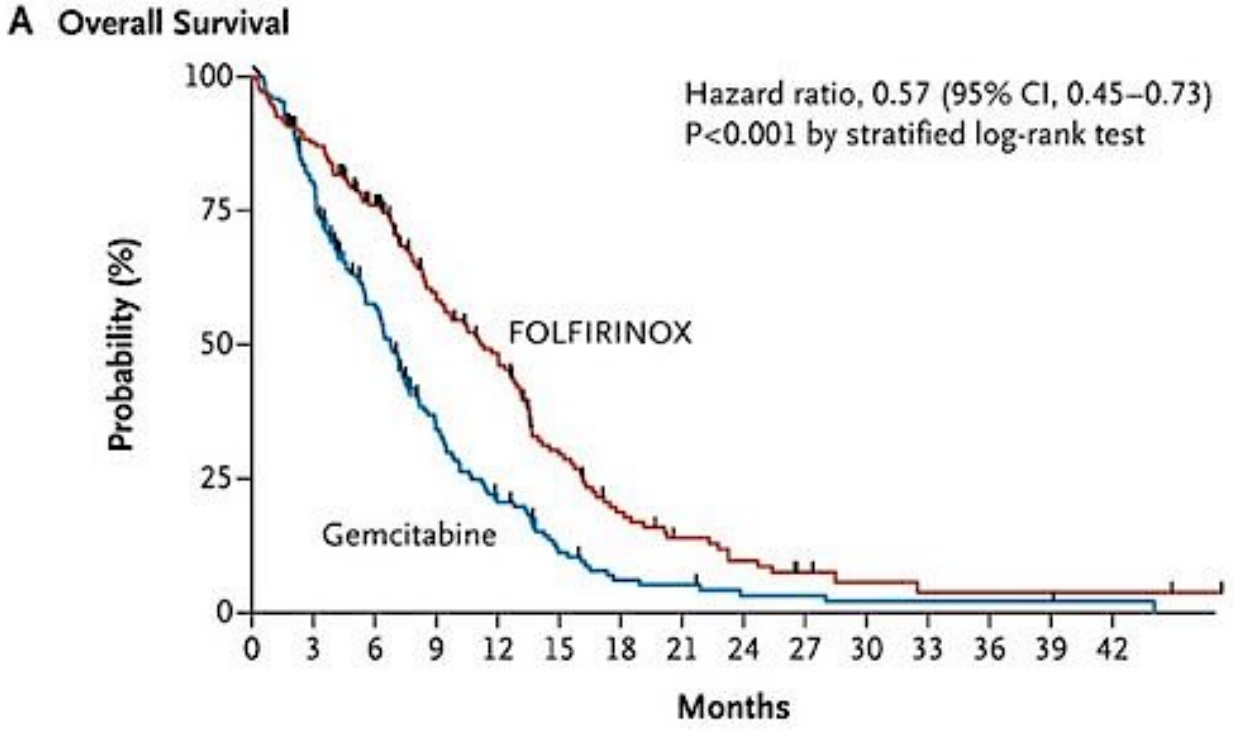


ECOG: Eastern Cooperative Oncology Group

Chemotherapy remains the mainstay of treatment for advanced/metastatic pancreatic cancer, but survival remains poor

FOLFIRINOX vs gemcitabine

(Conroy et al, *N Eng J Med* 2011; 364:1817-25)



N=342	FOLFIRINOX	Gemcitabine	
ORR	**31.6%**	9.4%	p<0.001
Median PFS (mos)	6.4	3.3	HR 0.47, p<0.001
Median survival (mos)	**11.1**	6.8	HR 0.57, p<0.001
1 year survival	**48.4%**	20.6%	

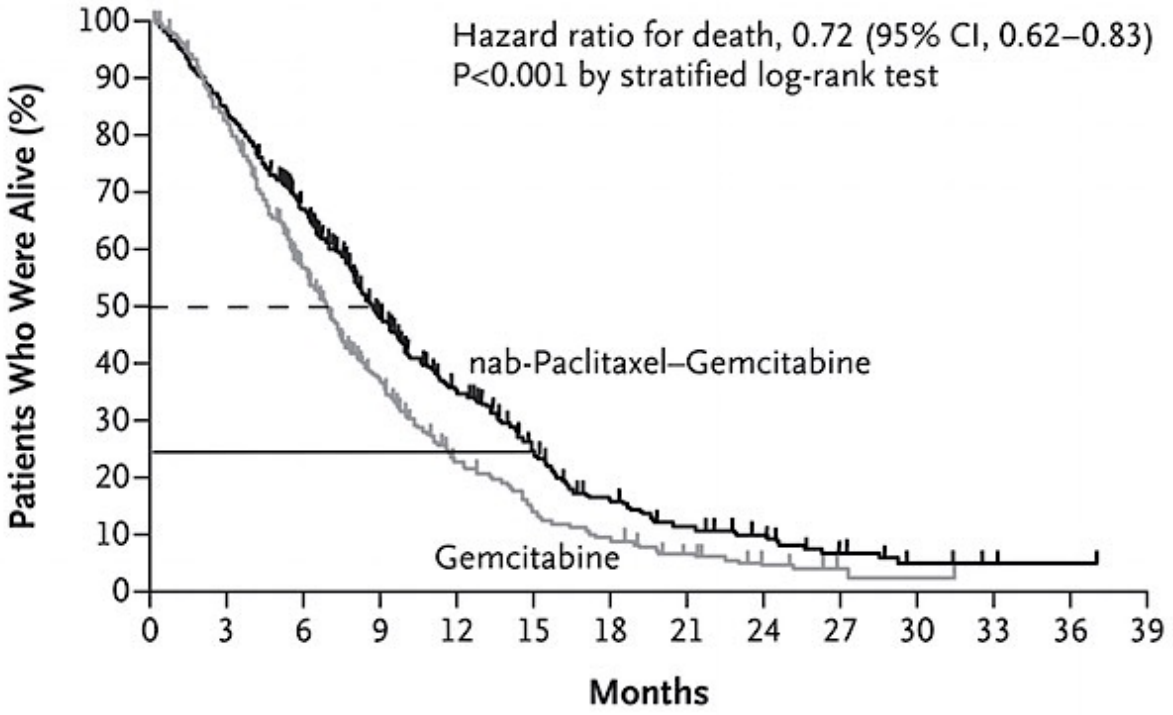
Contemporary FOLFIRINOX data for 1L met PDAC: OS = 14.4 months (SWOG 1313)

Philip et al, J Clin Oncol 2019; 37(13):1062-1069

Chemotherapy remains the mainstay of treatment for advanced/metastatic pancreatic cancer, but survival remains poor

Gemcitabine/albumin-bound paclitaxel (nab-paclitaxel) vs gemcitabine

Von Hoff, *N Engl J Med* 2013; 369:1691-703.



N=861	Gemcitabine/ nab-paclitaxel	Gemcitabine	
Median OS (months)	8.5	6.7	HR 0.72 (p<0.001)
One-year survival	35%	22%	
Median PFS (months)	5.5	3.7	HR 0.69 (p<0.001)
ORR	23%	7%	p<0.001

Contemporary gemcitabine/nab-paclitaxel data for 1L met PDAC: OS = 11.5 months (HALO-301)

van Cutsem et al, J Clin Oncol 2020; 38:3185-94.

Cross-study comparison: Phase III trials of FOLFIRINOX and gemcitabine/nab-paclitaxel

	FOLFIRINOX	Gemcitabine/nab-paclitaxel
Sample size	342	861
Locations	France	N America, Europe, Australia
Eligibility criteria, PS	ECOG 0-1	KPS 70-100
Survival, median (months) **% at one year**	11.1 months 48%	8.5 months 35%
Toxicity (grade 3/4)	Fatigue 23.6% Neutropenia 45.7% Neuropathy 9% Febrile neutropenia 5.4%	Fatigue 17% Neutropenia 38% Neuropathy 17% Febrile neutropenia 3%
Receipt of growth factor support	42.5%	26%
Poorer performance status patients?	N/A	Benefit maintained in KPS 70-80 pts
QoL data?	Yes	No

The direct head-to-head comparison of FOLFIRINOX vs. gemcitabine/nab-paclitaxel we've all been waiting for?

Phase III JCOG1611 (GENERATE) trial

N=527 (of originally planned 732)

Key inclusion criteria

- Metastatic or recurrent pancreatic cancer
- Adenocarcinoma or adenosquamous carcinoma
- ECOG PS of 0 or 1
- Aged 20–75 years
- No prior treatment for metastatic or recurrent disease
- UGT1A1 of WT, *6/-, or *28/-
- At least one measurable lesion (P2 portion)

R 1:1:1

Adjustment factors
Institution
ECOG PS 0/1
Metastatic/Recurrent

nab-PTX+GEM

Nab-paclitaxel 125 mg/m^2
Gemcitabine 1,000 mg/m^2
Days 1, 8, 15, every 4 weeks

mFOLFIRINOX

Oxaliplatin 85 mg/m^2
Irinotecan 150 mg/m^2
l-leucovorin 200 mg/m^2
Fluorouracil 2,400 mg/m^2
Days 1–3, every 2 weeks

S-IROX

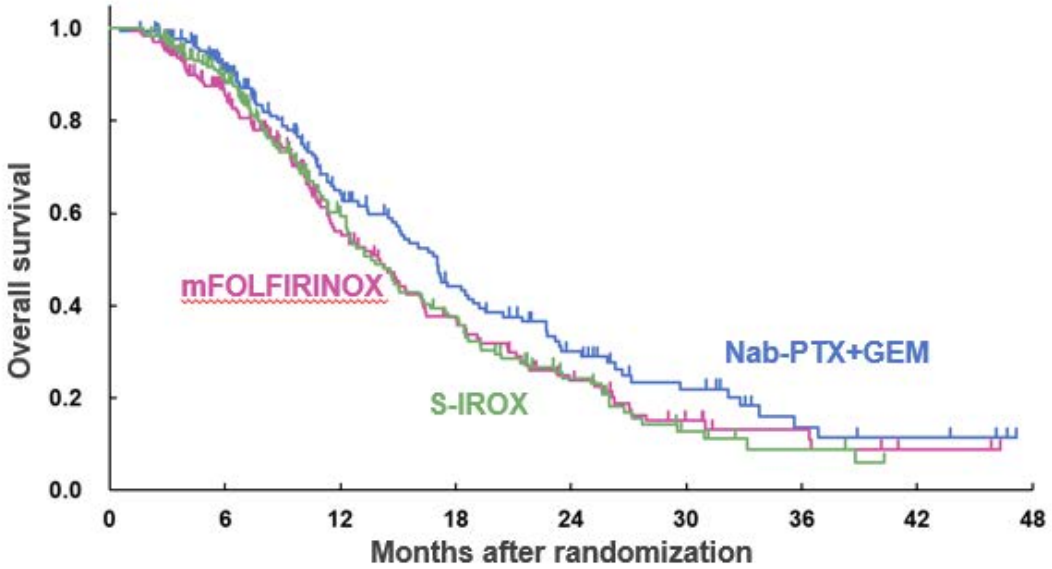
Oxaliplatin 85 mg/m^2
Irinotecan 150 mg/m^2
S-1 80 mg/m^2/day
Days 1–7, every 2 weeks

- Treatment until disease progression or unacceptable toxicity
- Tumor assessment every 6 weeks per RECIST v1.1
- Toxicities graded per CTCAE v4.0

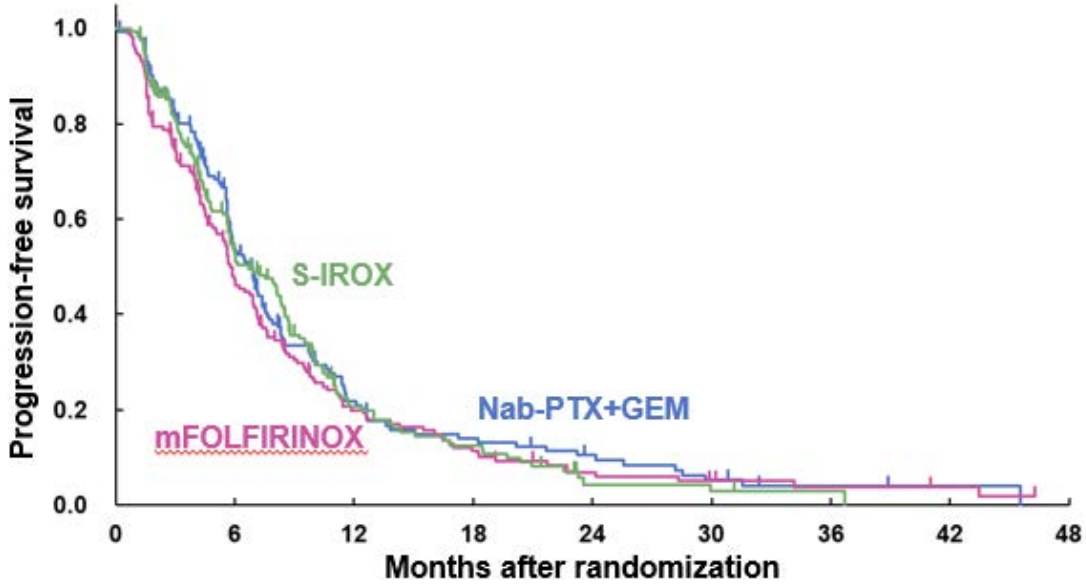
- **Primary endpoint = OS**

Ohba et al, ESMO Congress 2023 (abstract 1616O)

JCOG1611: Overall and progression-free survival *(updated May 2023)*



Arm	Median (95% CI)	HR (95% CI)*
Nab-PTX+GEM (n=176)	**17.0 (14.5–18.9)**	–
mFOLFIRINOX (n=175)	**14.0 (11.4–16.3)**	1.29 (0.98–1.70)
S-IROX (n=176)	13.6 (12.3–16.3)	1.29 (0.98–1.70)



Arm	Median (95% CI)	HR (95% CI)
Nab-PTX (n=176)	**6.7 (5.7–7.4)**	–
mFOLFIRINOX (n=175)	**5.8 (5.1–6.9)**	1.15 (0.91–1.45)
S-IROX (n=176)	6.7 (5.7–8.3)	1.07 (0.84–1.35)

Ohba et al, ESMO Congress 2023 (abstract 1616O)

Interpreting these JCOG1611 data

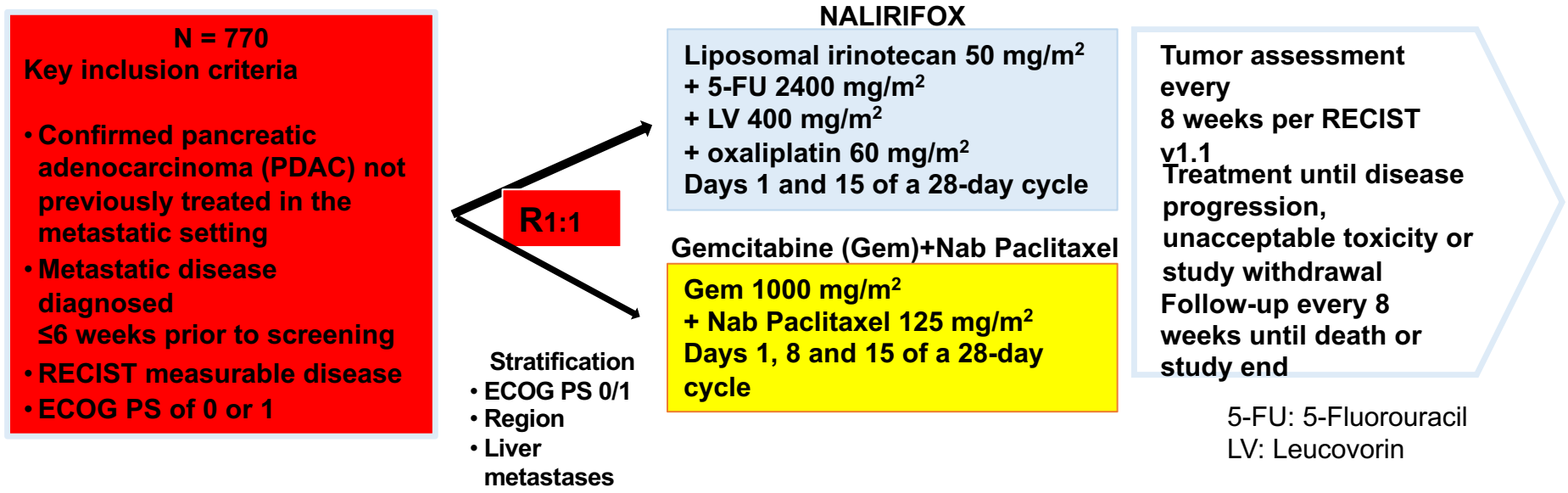
	FOLFIRINOX (n=175)	Gemcitabine/nab-paclitaxel (n=176)
Median OS	14.0 months	17.0 months
Median PFS	5.8 months	6.7 months
ORR	32.4%	35.4%
Toxicity (grade 3/4)	Neutropenia 51.5% Febrile neutropenia 8.8% Anorexia 22.8% Diarrhea 8.8%	Neutropenia 60.3% Febrile neutropenia 3.4% Anorexia 5.2% Diarrhea 1.1%
Subsequent treatment	63.4%	59.7%

Ohba, ESMO Congress 2023 (abstract 1616O)

- Trial terminated for futility after pre-planned interim analysis — unlikely that mFOLFIRINOX (or S-IROX) would prove to be superior to gemcitabine/nab-paclitaxel
- **Investigators conclude that gemcitabine/nab-paclitaxel should represent the 1L standard of care for metastatic PDAC**, given its numerical superiority in OS and overall better safety profile

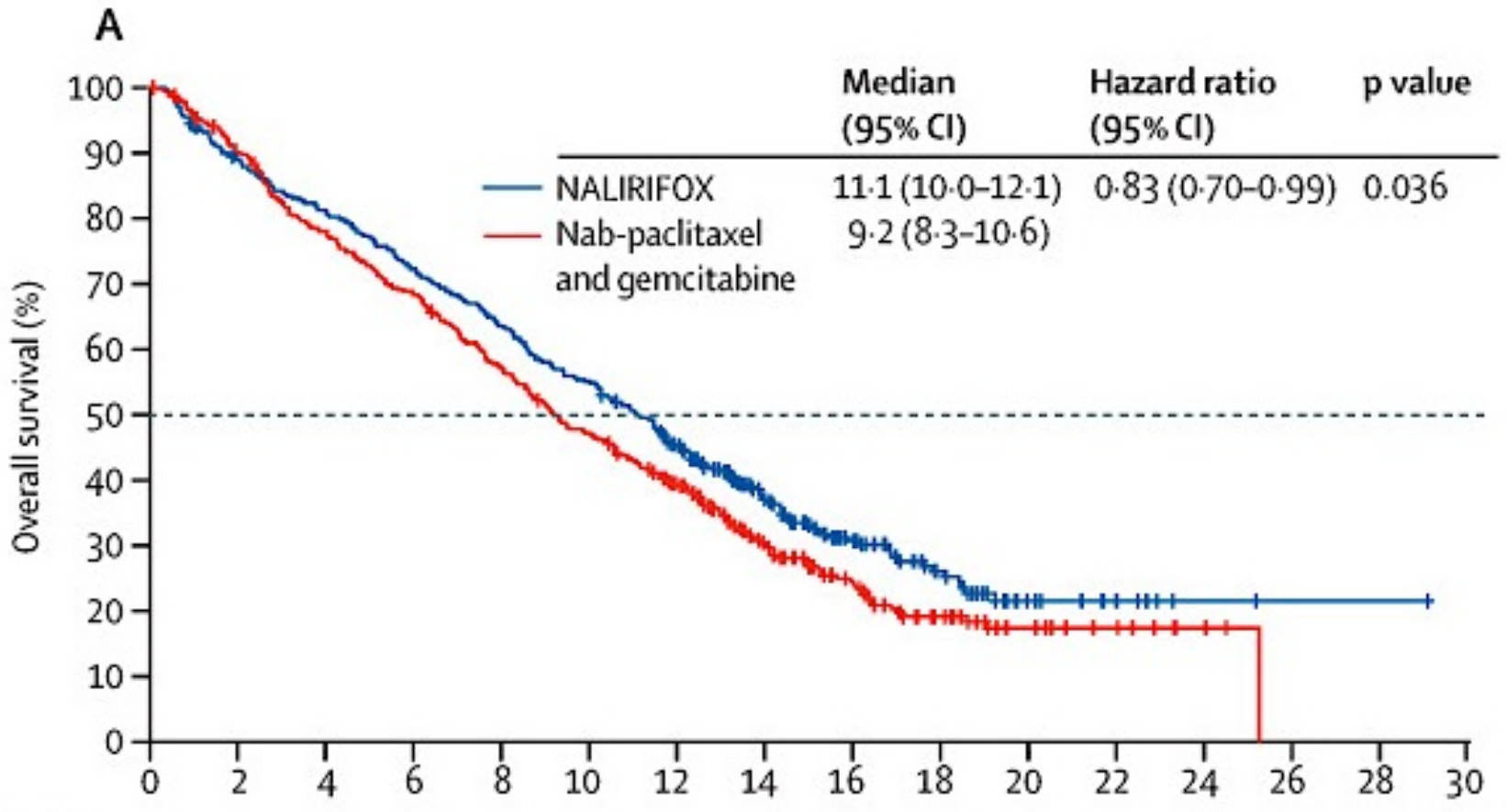
Adding to the confusion (possibly): Does the NAPOLI-3 trial establish a new 1L standard for metastatic pancreatic cancer?

- **Nanoliposomal irinotecan** = currently approved for use in 2L setting (following gemcitabine-based regimen)
- Prior phase I/II study looked at substituting this agent into FOLFIRINOX rx ("NALIRIFOX")
- Basis for international phase III NAPOLI-3 trial



Wainberg et al, Lancet 2023; 402:1272-81

NAPOLI-3 results



- **Median PFS, 7.4 vs 5.6 months (HR 0.69, p<0.0001)**
- **ORR 41.8 vs 36.2%**

Wainberg et al, Lancet 2023; 402:1272-81

Does NAPOLI-3 represent a substantial advance over FOLFIRINOX?

	NALIRIFOX (n=370)	FOLFIRINOX (n=171)
Median OS	**11.1 months**	**11.1 months**
1-yr OS	Not Reported (NR)	48.4%
Median PFS	7.4 months	6.4 months
ORR	41.8%	31.6 %
Grade 3/4 Adverse Events (AE)	Neutropenia 23.8% / fever and neutropenia (F&N) 2.4% Diarrhea 20.3% Peripheral sensory neuropathy (PSN) (3.2 + 3.5% + 0.3%)	Neutropenia 45.7% / F&N 5.4% Diarrhea 12.7% PSN 9.0%

So where exactly does this leave us in terms of selection of chemotherapy for our PDAC patients?

NAPOLI-3

NALIRIFOX > GEMCITABINE/NAB-PACLITAXEL

NALIRIFOX = FOLFIRINOX *(historic data)*

and yet…

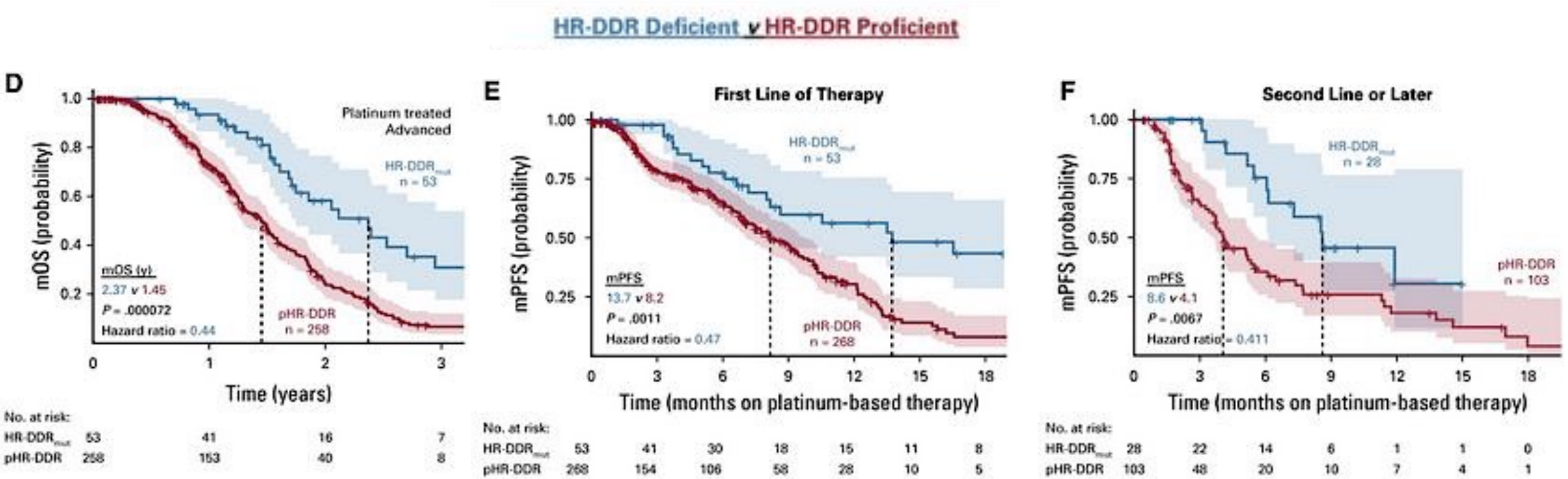
JCOG1611

GEMCITABINE/NAB-PACLITAXEL > FOLFIRINOX

(or at the very least equal)

- Can predictive biomarkers/genetic signatures allow for more rational decision-making?

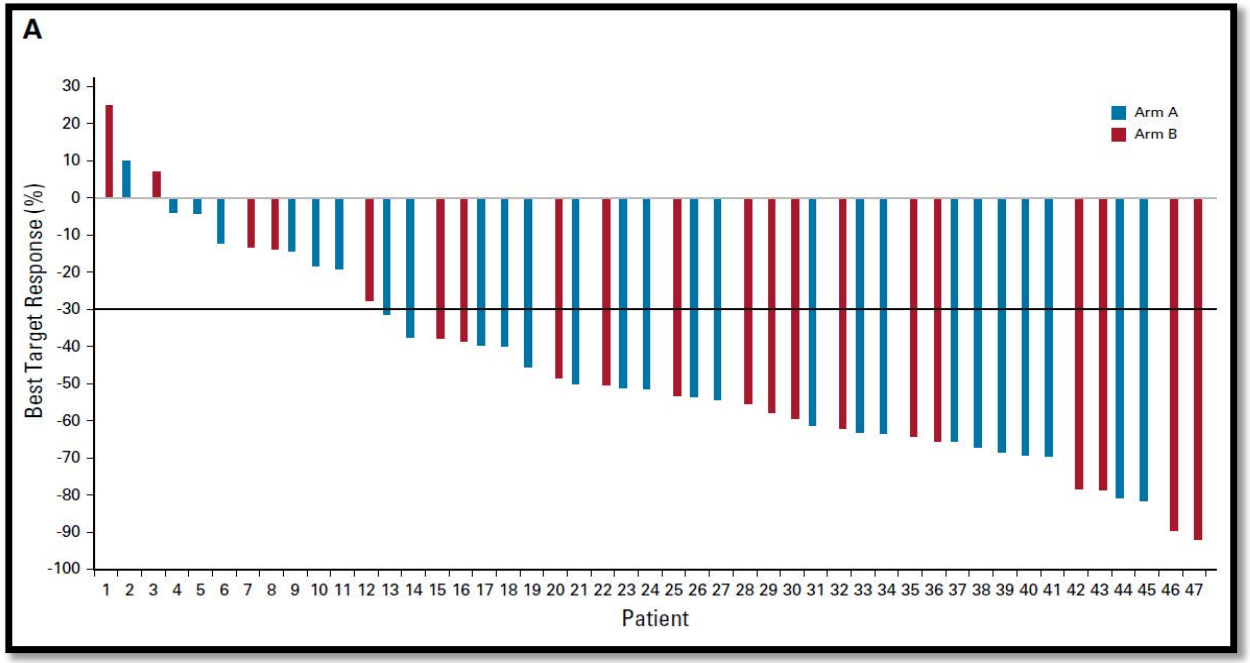
Multiple lines of evidence support platinum-based therapies in patients with HR-deficient PDAC (BRCA1/2, PALB2, etc.)



Golan et *al.* Br J Cancer 2014; Pishvaian et *al*. JCO Precision Onc 2019; Wattenberg et *al*. Br J Cancer 2020; Park et *al*. Clin Cancer Res 2020

This applies to both oxaliplatin (e.g. FOLFIRINOX, NALIRIFOX) *and* cisplatin-based (e.g. gemcitabine/cisplatin) regimens

Randomized phase II trial of **gemcitabine/cisplatin** +/- veliparib in PDAC patients with genomic *BRCA/PALB2* mutation

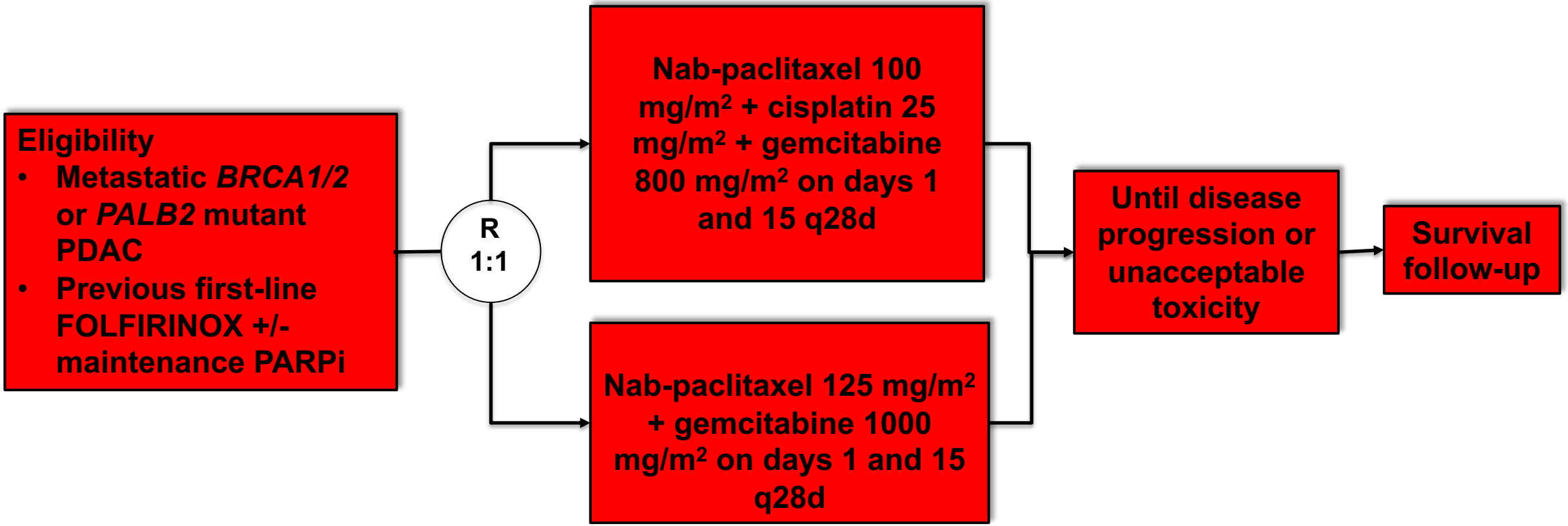


	Arm A (gem/cisplat + PARPi)	Arm B (gem/cisplat)
ORR	**74.1%**	**65.2%**
PFS	10.1 months	9.7 months
OS	15.5 months	16.4 months

O'Reilly et *al*. *J Clin Oncol* 2020;38:1378-88.

A022106: Phase II/III second-line NABPLAGEM vs. nab-paclitaxel/gemcitabine in *BRCA1/2* or *PALB2* mutant PDAC (PLATINUM)

(P.I.s, A. Ko and E. Tsang)

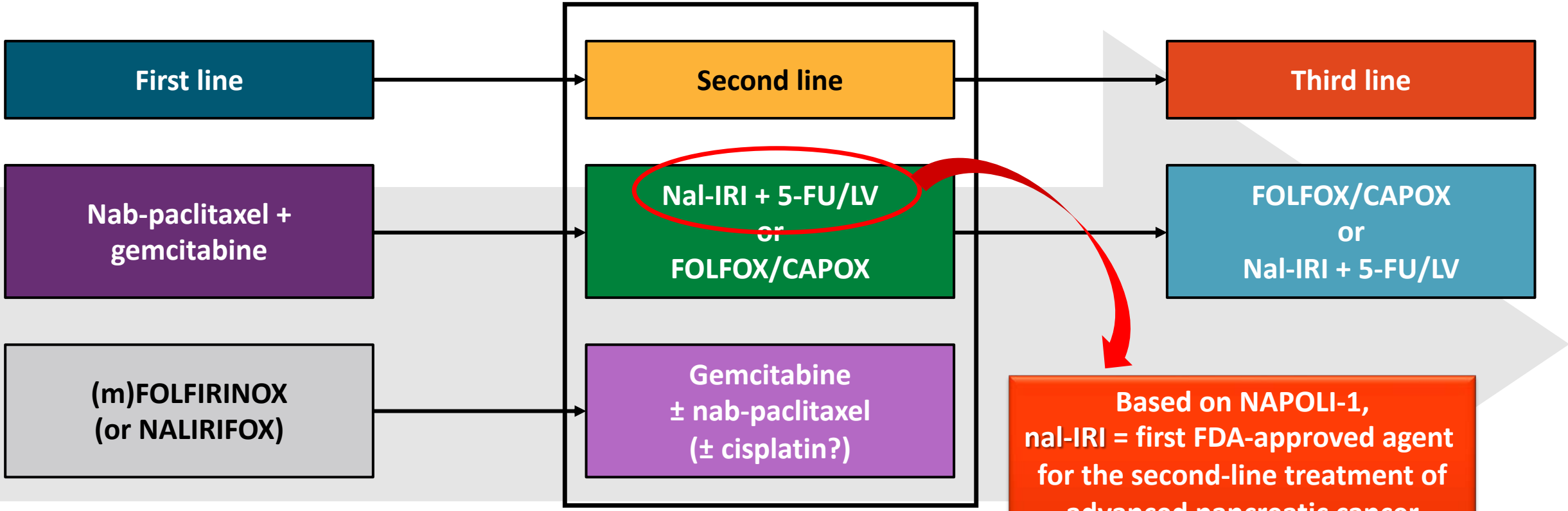


Primary endpoint

- **Phase II: Overall response rate per RECIST 1.1**
- **Phase III: Overall Survival**

NCT06115499

Sequencing therapy: What about second-line treatment?



Historically and in most clinical trials, ~50% or fewer patients go on to receive second-line therapy

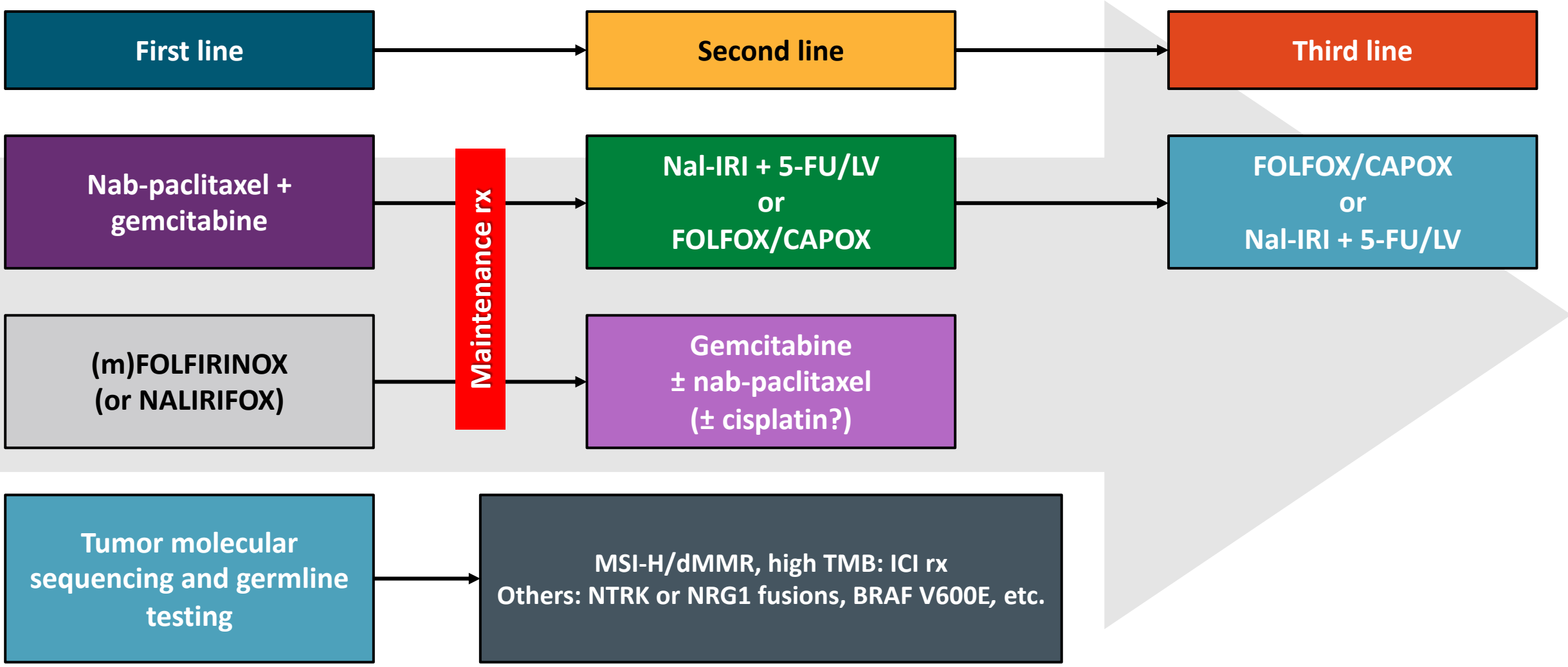
Based on NAPOLI-1, nal-IRI = first FDA-approved agent for the second-line treatment of advanced pancreatic cancer (post-gemcitabine-based rx)

Wang-Gillam et al, *Lancet* 2016

Sequencing therapy in advanced PDAC (2024)

Additional considerations:

(1) the role of maintenance rx; and (2) incorporating NGS/germline results



Maintenance therapy: “Kinder, gentler” treatment after achieving disease control on front-line therapy

1L chemotherapy	Maintenance recommendations (NCCN)
FOLFIRINOX	• Capecitabine • 5-FU/LV • FOLFIRI • FOLFOX
Gemcitabine/nab-paclitaxel	• Gemcitabine • Gemcitabine/nab-paclitaxel (modified schedule)
Platinum-based chemotherapy, BRCA1/2 or PALBs mutations	• PARP inhibitor (olaparib, rucaparib)

Examples of therapeutically actionable findings in pancreatic cancer

Molecular alteration	Incidence in pancreatic cancer	Treatment
Homologous recombination deficiency (e.g. BRCA1/2, PALB2 mutation)	10-15%	Platinum-based chemotherapy PARP inhibitor (e.g. olaparib, rucaparib) as **maintenance rx**
KRAS G12C mutation	2%	G12C inhibitors (e.g. adagrasib, sotorasib)
High microsatellite instability/ deficient mismatch repair	1-1.5%	Immune checkpoint inhibitors (e.g. pembrolizumab)
BRAF V600E mutation	<1%	RAF/MEK inhibitors (e.g. dabrafenib/trametinib)
NTRK fusion	<1%	TRK inhibitors (e.g. larotrectinib, entrectinib)

Outstanding issues in the treatment of metastatic pancreatic cancer

- Decisions are still made primarily on clinical criteria
  - Performance status and age
  - Co-morbid conditions
  - Risk of endobiliary stent complications (for tumors located in pancreatic head)
  - Organ function (including renal, hepatic, and bone marrow)
  - Convenience and patient preference

- Emerging evidence for molecular/genetic subtypes of pancreatic cancer that may help guide selection of therapy – but this still only applies to a small minority of patients

Agenda

Module 1: Selection and Sequencing of Therapy for Patients with Metastatic Pancreatic Adenocarcinoma (PAD) — Dr Ko

Module 2: Biomarker-Based Strategies for Metastatic PAD; Novel Investigational Approaches — Dr O'Reilly

Research To Practice

Pancreas Cancer 2024
Biomarker Based Strategies, Novel Therapeutics

Eileen M. O'Reilly, MD

Winthrop Rockefeller Endowed Chair, Memorial Sloan Kettering Cancer Center

Professor of Medicine, Weill Cornell Medicine

March 24th, 2024

Memorial Sloan Kettering Cancer Center

Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Autem Therapeutics, Berry Genomics, BioNTech SE, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Incyte Corporation, Ipsen Biopharmaceuticals Inc, J-Pharma Co Ltd, Merck, Merus, Neogene Therapeutics, Novartis, Servier Pharmaceuticals LLC, Tempus, Vector Pharma, Yiviva
Contracted Research	Agenus Inc, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, BioNTech SE, Bristol Myers Squibb, Digestive Care Inc, Elicio Therapeutics, Genentech, a member of the Roche Group, Helsinn Healthcare SA, Puma Biotechnology Inc, QED Therapeutics, Yiviva
Nonrelevant Financial Relationship	Parker Institute for Cancer Immunotherapy

Research To Practice

52-Year-Old Female

- 1 year history of progressive back pain; ↑ HbA1c
- Fm Hx g*BRCA2,* prostate ca
- CT Tail primary, liver, lymph nodes
- Ca 19-9 8,613, CEA 14.1
- mFOLFIRINOX x 8 cycles → PR
- Germline: *BRCA2*
  Somatic: *KRAS G12D, TP53, CDKN2A*

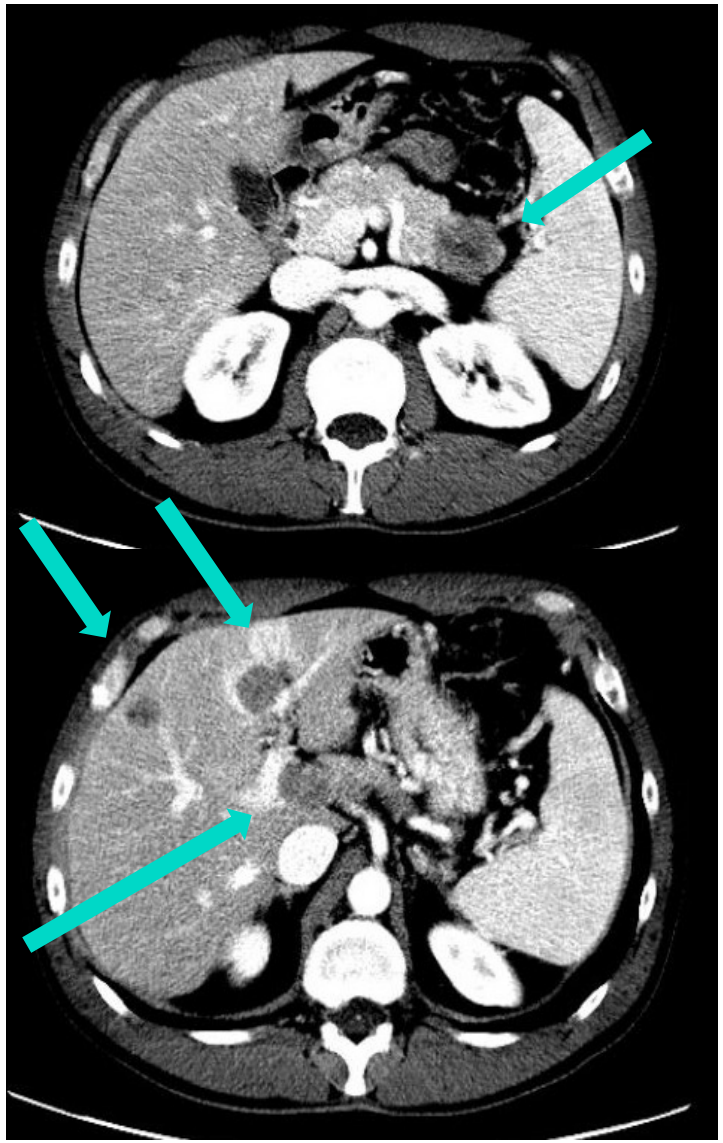
Maintenance therapy decision:

a) Continue chemotherapy

b) Treatment break

c) PARPi

d) KRAS inhibitor



Research To Practice

PDAC: Standard Therapy & Genomically Defined 2024 →

Germline (multigene panel), Somatic testing, ctDNA

Untreated mPDAC ECOG 0-1

- Clinical trial (preferred)
- (m)FOLFIRINOX
- NALIRIFOX
- Gemcitabine/nab-paclitaxel

- Maintenance
  - FOLFIRI
  - 5-FU/LV
  - Capecitabine

KRAS Mutated# (90%+)

- G12C (1%)
  Sotorasib*
  Adagrasib*

- G12D (35%), G12V (30%), G12R (15%)
  Allele specific
  Pan RAS/all RASi

  Small molecule
  Vaccines
  Protein degraders (PROTACs)
  Other

KRAS Wild-Type (4-8%)

- MAPKinase pathway
  Erlotinib
- *BRAF* V600E
  Dabrafenib/trametinib*
- HER2

- Fusions (0.3-0.5% each)
  RET, ALK, ROS, FGFR2/3, MET, NRG-1, NTRK*, BRAF*, ERBB4*

  Selpercatinib,
  Zenocutuzumab
  Entrectinib
  Larotrectinib
  Dabrafenib/trametinib

g/s*BRCA1/2* (+*RAD51C/D, PALB2*); MSI-H

- (m)FOLFIRINOX#
- Cisplatin/gemcitabine#
- NALIRIFOX#

- Maintenance
  Olaparib*
  Rucaparib**
- Ipilimumab/nivolumab?
- ATM/ATRi?

- Immune therapy
  Nivolumab,
  pembrolizumab
  Dostarlimab

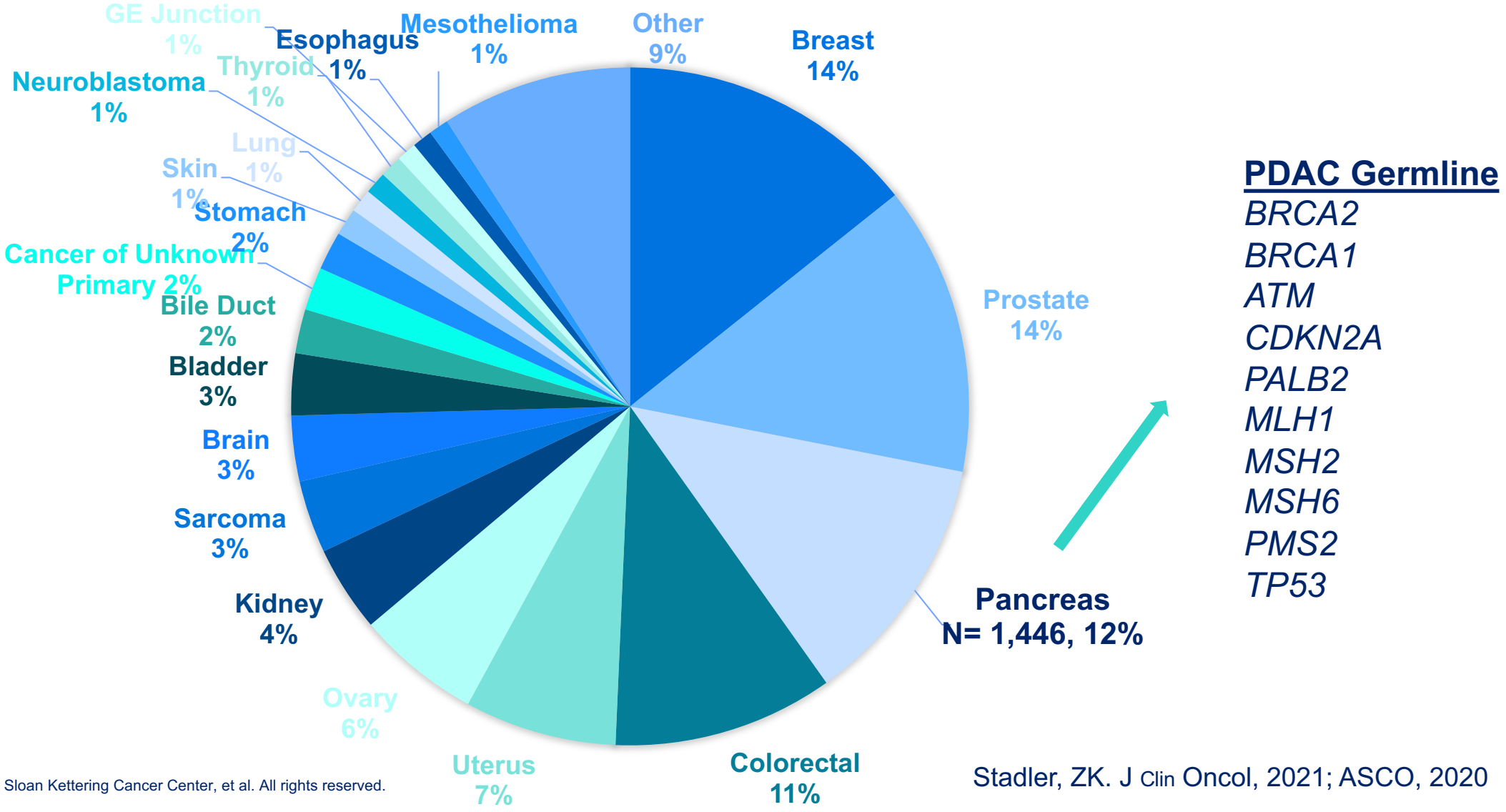
Other: CLDN 18.2; GATA6 (sub-typing), ADC's, multiple IO

#Guideline endorsed/not FDA approved; *Disease agnostic approvals; **Guideline endorsed

Synthetic Lethality Directed Therapy

Research To Practice

Germline Variants Pan-Cancer Cohort (N= 11,974)



PDAC Germline

BRCA2
BRCA1
ATM
CDKN2A
PALB2
MLH1
MSH2
MSH6
PMS2
TP53

Stadler, ZK. J Clin Oncol, 2021; ASCO, 2020

Research To Practice

Survival Outcome *BRCA1* vs *BRCA2*

N= 234

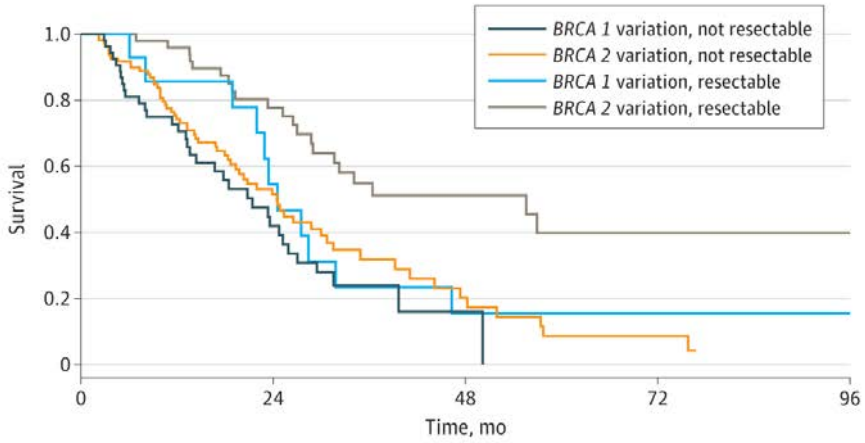
BRCA2 (N= 165)

- More common
- Improved outcome
- Better platinum response

BRCA1 (N= 69)

- More *TP53* mutations
- Less immunogenic

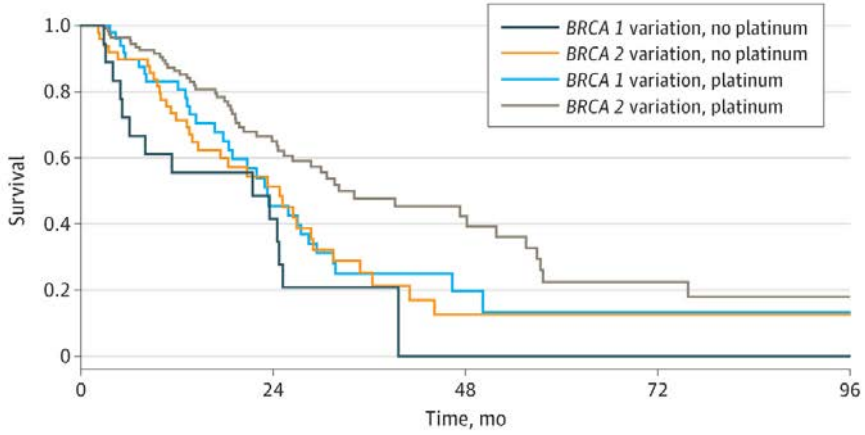
Outcome by Surgery or Not



No. at risk

BRCA 1 variation, not resectable	54	15	2	0	0
BRCA 2 variation, not resectable	115	32	7	2	0
BRCA 1 variation, resectable	15	7	2	2	1
BRCA 2 variation, resectable	50	30	10	5	3

Outcome by Platinum



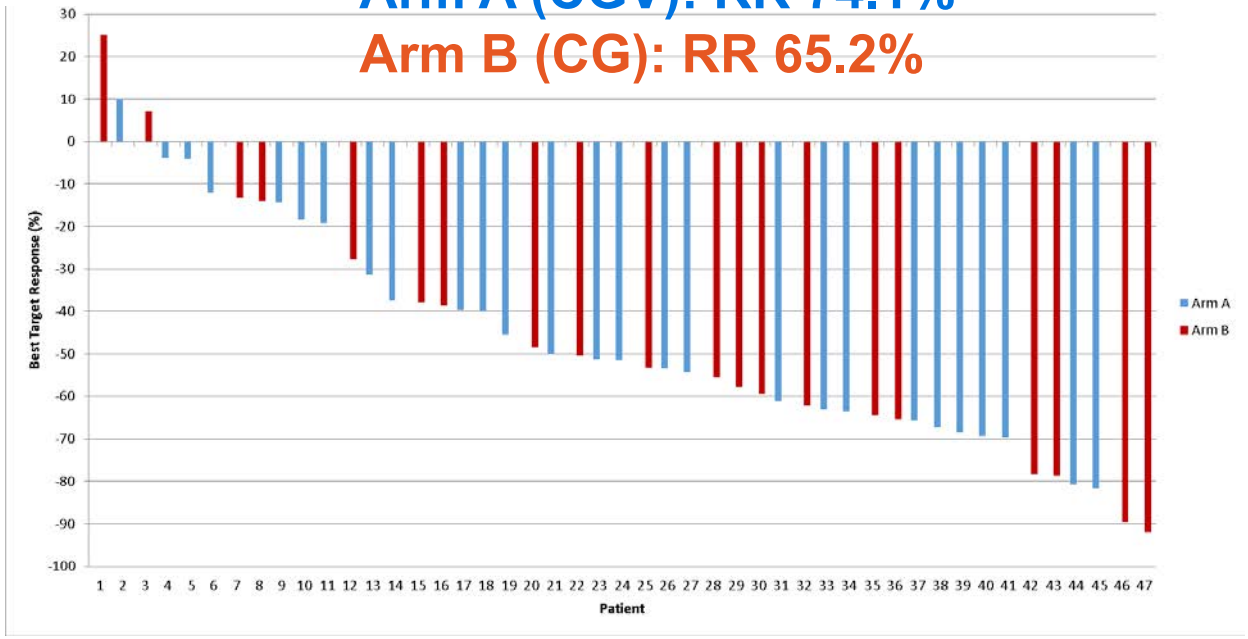
No. at risk

BRCA 1 variation, no platinum	18	6	0	0	0
BRCA 2 variation, no platinum	53	17	3	2	1
BRCA 1 variation, platinum	51	16	4	2	1
BRCA 2 variation, platinum	112	45	14	5	2

Boursi, B….Reiss, K. JAMA Network Open, 2023
Golan, T…Gallinger, S. Gastroenterology, 2021

Research To Practice

Cisplatin/Gem +/- Veliparib g*BRCA1/2, PALB2*: Randomized Phase II Advanced PDAC



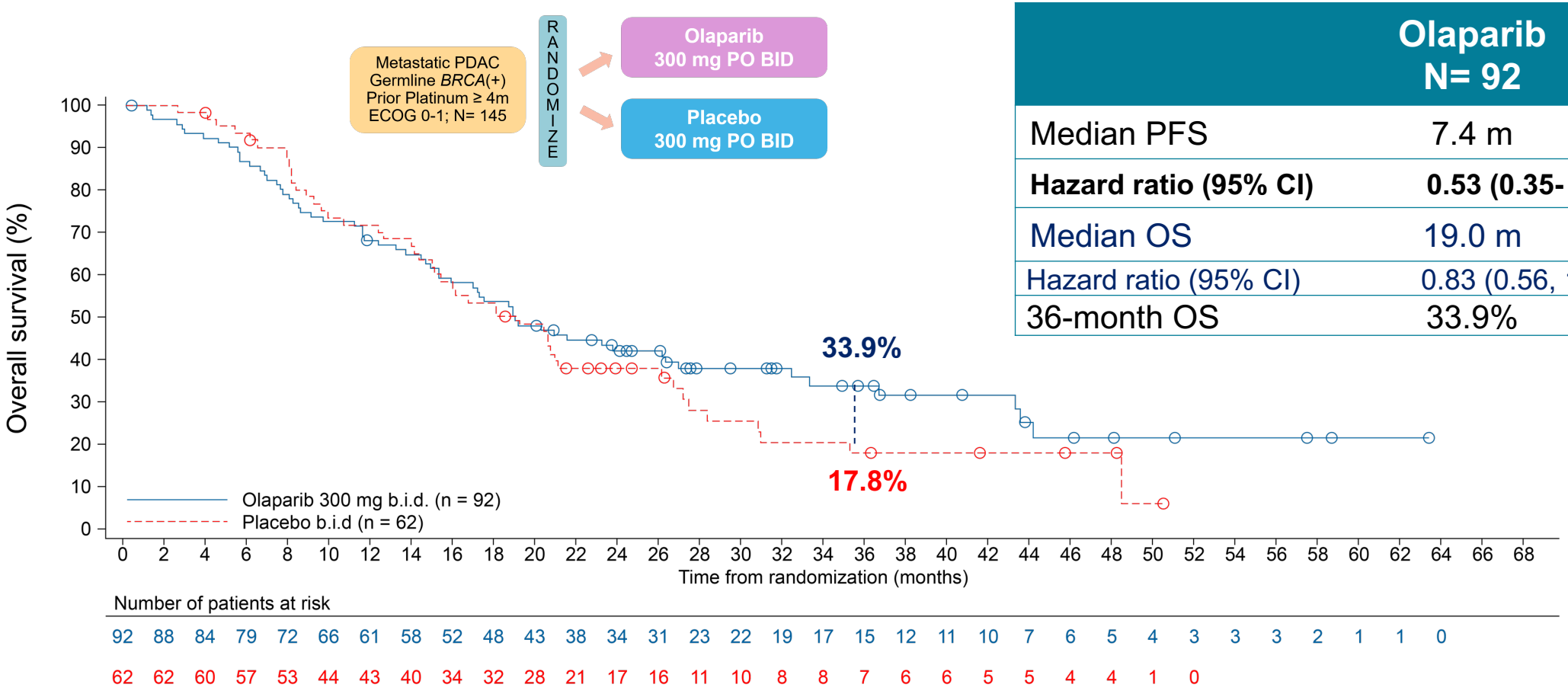
	Cis, Gem, V N= 27	Cis, Gem N= 23
Response Rate	74%	65%
Overall Survival	15.5 m	16.4 m
Combined Arms (N= 50)		
2-Year OS	31% (CI 17.8%- 44.4%)	
3-Year OS	18% (CI:8.1%- 30.7%)	
Platinum → PARPi	23 m (CI: 6.5- 53.9)	

- Defines a standard regimen *BRCA1/2, PALB2*

O'Reilly, EM…Kelsen, DP. J Clin Oncol, 2020

Research To Practice

POLO g*BRCA1/2*: Maintenance Olaparib vs Placebo



	Olaparib N= 92	Placebo N= 62
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%

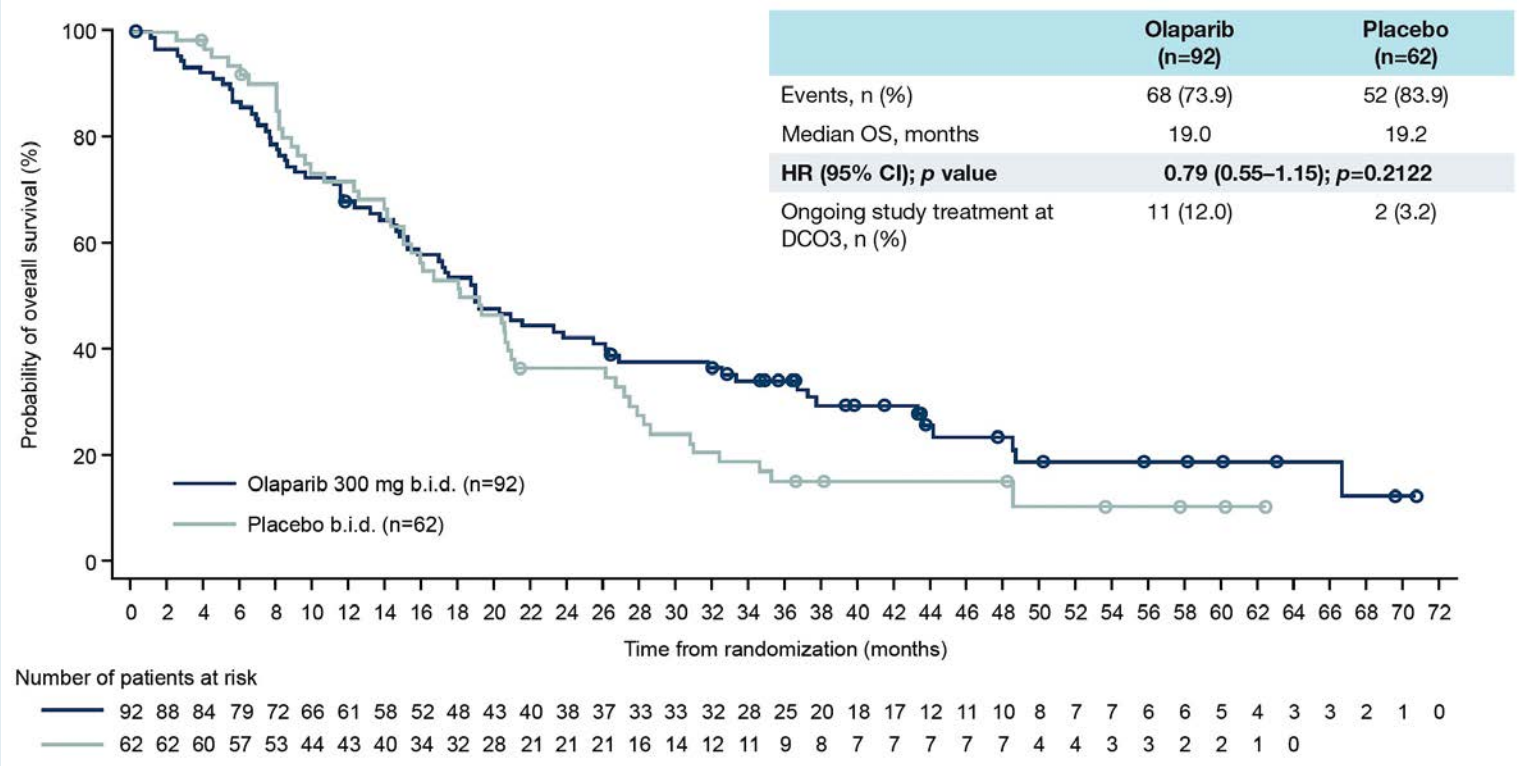
Golan, T. New Eng J Med, 2019
Kindler, H. J Clin Oncol, 2022

POLO: Extended Exploratory Analysis

Table 1. Summary of key secondary endpoints at DCO3

Secondary endpoint, median, months	Olaparib (n=92)	Placebo (n=62)	HR (95% CI)
OS	19.0	19.2	0.79 (0.55–1.15)
Investigator-assessed PFS	6.7	3.7	0.50 (0.34–0.75)
TDT	7.5	3.8	0.44 (0.30–0.65)
TFST	9.0	5.3	0.48 (0.32–0.70)
TSST	14.9	9.6	0.59 (0.41–0.86)

CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TDT, time to discontinuation of study treatment; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.



	Olaparib (n=92)	Placebo (n=62)
Events, n (%)	68 (73.9)	52 (83.9)
Median OS, months	19.0	19.2
HR (95% CI); *p* value	**0.79 (0.55–1.15); *p*=0.2122**	
Ongoing study treatment at DCO3, n (%)	11 (12.0)	2 (3.2)

Hammel P et al. ESMO 2022;Abstract 1298P.

POLO: Extended Safety Results

Table 2. Safety results at DCO1 (PFS analysis; January 2019), DCO2 (final OS analysis; July 2020) and DCO3 (extended OS analysis; July 2021)

Event, n (%)	DCO1		DCO2		DCO3	
	Olaparib (n=91)[a]	Placebo (n=60)[a]	Olaparib (n=90)	Placebo (n=61)	Olaparib (n=90)	Placebo (n=61)
Any AE	87 (95.6)	56 (93.3)	89 (98.9)	56 (91.8)	89 (98.9)	56 (91.8)
Grade ≥3 AE	36 (39.6)	14 (23.3)	44 (48.9)	15 (24.6)	44 (48.9)	15 (24.6)
Serious AE	22 (24.2)	9 (15.0)	28 (31.1)	10 (16.4)	28 (31.1)	10 (16.4)
AE leading to dose interruption	32 (35.2)	3 (5.0)	37 (41.1)	4 (6.6)	38 (42.2)	4 (6.6)
AE leading to dose reduction	15 (16.5)	2 (3.3)	16 (17.8)	3 (4.9)	16 (17.8)	3 (4.9)
AE leading to discontinuation	5 (5.5)	1 (1.7)	8 (8.9)	1 (1.6)	8 (8.9)	1 (1.6)

Hammel P et al. ESMO 2022;Abstract 1298P.

Research To Practice

Ipilimumab/Nivo: HR-Driven PDAC/Biliary Cancers (N= 12)

Patient No./gender/ age, y	Diagnosis	Germline variant	Best response	Duration of response, mo	PD-L1 combined positive score, %	TMB, mt/Mb	Somatic status[b]	Previous therapies
1/M/60s	PDAC	*BRCA1*	CR[c]	41.6	NA	4	Biallelic	Resection and adjuvant gemcitabine/ capecitabine
2/M/70s	CCA	*BRCA1*	CR[c]	39.9	0	8	Biallelic	Gemcitabine/cisplatin
3/M/50s	PDAC	*RAD51C*	CR[c]	26.4	NA	8	Biallelic	FOLFIRINOX, olaparib, liposomal irinotecan/5-fluorouracil, and gemcitabine/nab-paclitaxel/cisplatin
4/M/70s	AMP	*BRCA2*	CR[d]	11.5	2	NA	Biallelic	Resection, adjuvant gemcitabine/cisplatin, and olaparib
5/M/40s	PDAC	*BRCA1*	PR	7.3	NA	NA	Biallelic	Gemcitabine/cisplatin/nab-paclitaxel and olaparib
10/F/50s	PDAC	*ATM*	SD	4.1	NA	NA	Monoallelic	FOLFIRINOX, gemcitabine/nab-paclitaxel, and olaparib
6/F/70s	PDAC	*BRCA1*	SD	3.5	NA	5	Biallelic	Neoadjuvant gemcitabine/cisplatin and resection
12/F/60s	PDAC	*BRCA2*	PD	2.6	NA	4	NA	Neoadjuvant FOLFIRINOX, resection, and gemcitabine/nab-paclitaxel
7/M/60s	PDAC	*BRCA2*	PD	2.3	NA	3	NA	Resection, adjuvant gemcitabine/cisplatin, FOLFIRINOX, and olaparib
9/F/50s	PDAC	*RAD51D*	PD	2.0	0	6	NA	Gemcitabine/nab-paclitaxel, FOLFIRINOX, and olaparib
8/F/60s	PDAC	*BRCA2*	PD	1.8	0	3	Monoallelic	Gemcitabine/cisplatin/nab-paclitaxel
11/M/60s	PDAC	*BRCA2*	PD	1.3	NA	3	Biallelic	FOLFIRINOX and olaparib

Terrero, G…Hosein, P. JAMA Onc, 2022

Research To Practice

Selected Ongoing Trials in HRD/ *BRCA* in PDAC

APOLLO EA2192:
Adjuvant Olaparib vs Placebo

- Resected; completed all standard therapy
- N= 152; Primary endpoint: RFS (22 → 44 months; 90% power, HR 0.5)

SWOG/Alliance S2001:
Maintenance Olaparib +/- Pembrolizumab

- *BRCA1/2, PALB2* germline/somatic > 4 m platinum therapy
- N= 88; Primary endpoint: PFS (HR 0.6; 7→ 11.7 m)

PLATINUM A022106
Randomized phase II/III 2L: Cisplatin/gemcitabine/nab-paclitaxel vs Cisplatin/gemcitabine

- g/s*BRCA1/2, PALB2*
- N= 100; Primary endpoint ORR (phase II); OS (phase III)

NCT04858334 Reiss Binder (PI)
NCT04548752 Chung, Pishvaiain (PI)
NCT06115499 Ko, Tsang (PI)

KRAS Mutated PDAC

Research To Practice

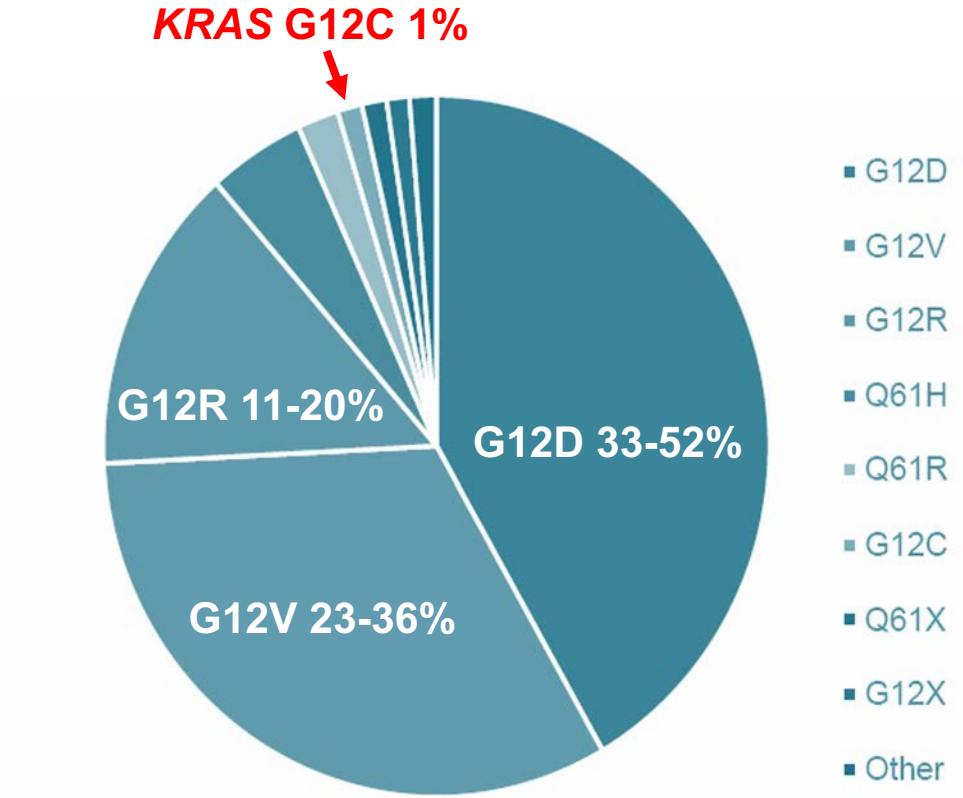
KRAS Biology and *KRAS* Mutations in PDAC

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 AV. Nature. 2012
Guo S. Br J Cancer. 2020
Singhi AD. Gastroenterology. 2019
Cancer Genome Atlas Research Network Cancer Cell, 2017
cbioportal.mskcc.org (A. Varghese), 2021
Johnson C. Cancer Discov. 2022
Hofmann MH. Cancer Discov. 2022

Research To Practice

KRAS Allele and Outcome in PDAC

KRAS mutation status prognostic

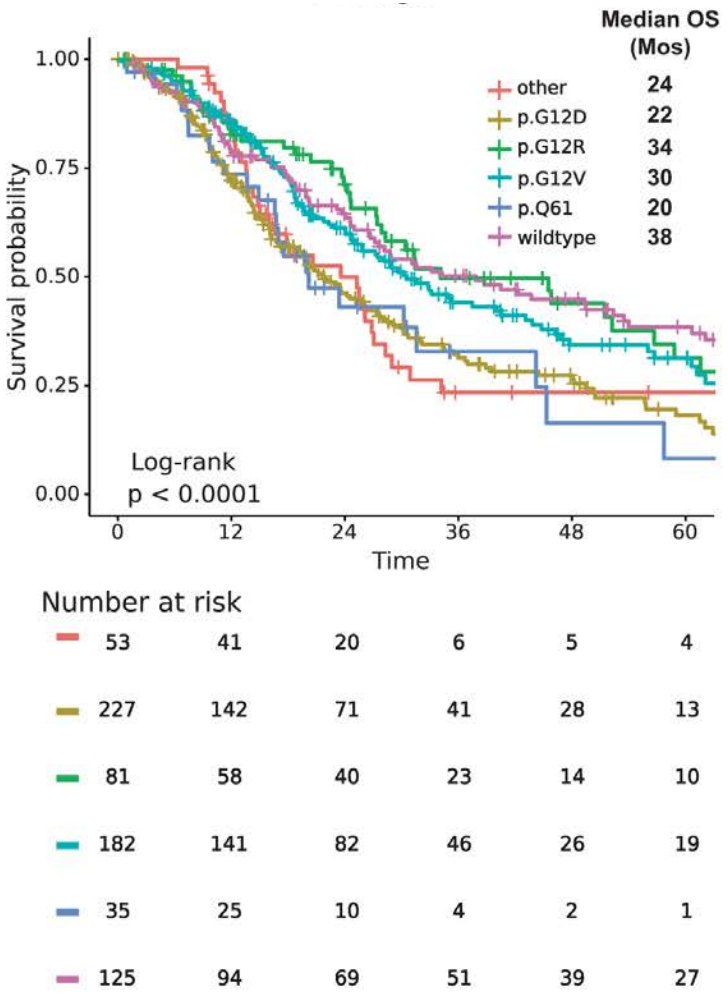
KRAS G12R similar to *KRAS*^{wt}

KRAS G12R G1-2 cancers

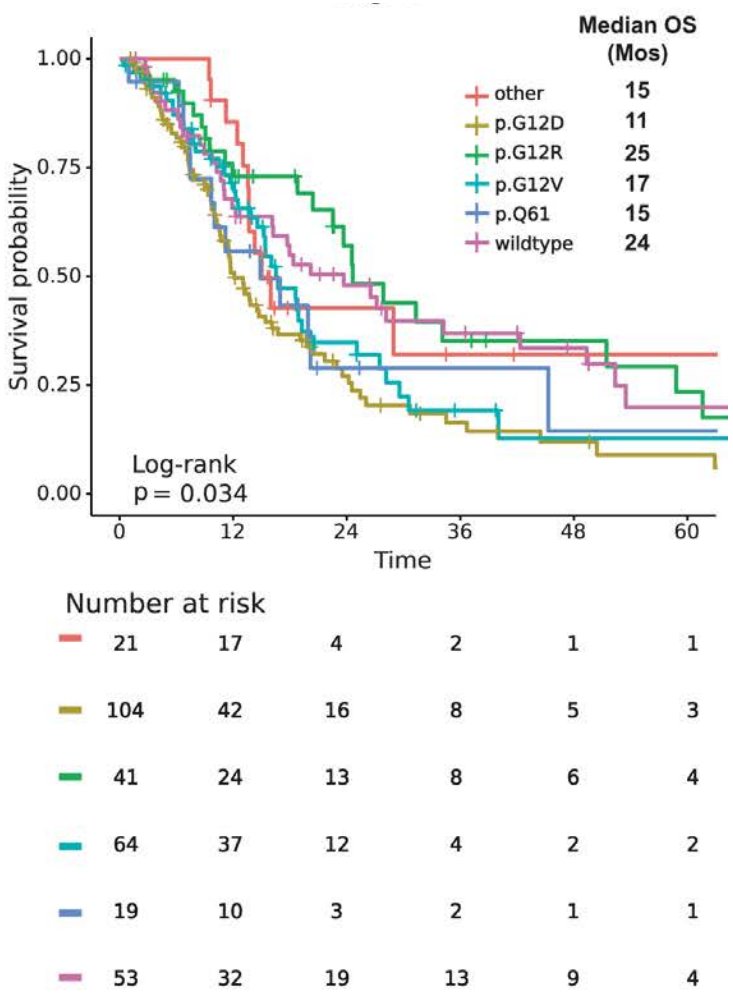
KRAS G12D enriched M1 disease

External validation cohort:
PanCAN Know Your Tumor (N= 408)

All patients: OS (N= 703)



Stage IV only: OS (N= 302)

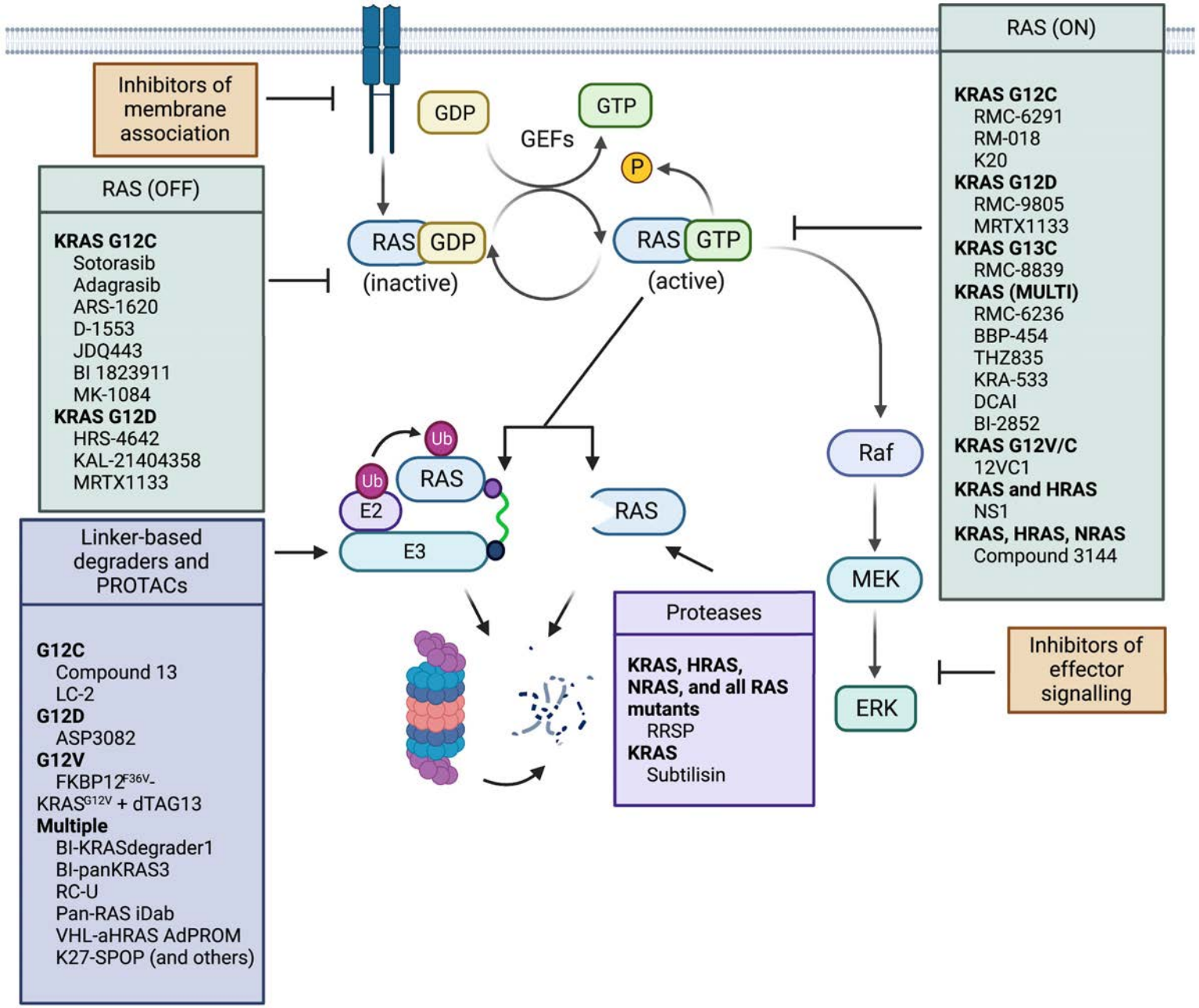


Abdelrahman, Y… Zhao, D. NPJ Precision Oncology, 2024

Research To Practice

KRAS Therapeutics

- Direct inhibition
  RAS ‘off’ vs ‘on’
- Linker-based degraders
  PROTAC’s
- Proteases
- Indirect downstream inhibitors
  e.g., SOS1, shP2
- *KRAS* vaccines



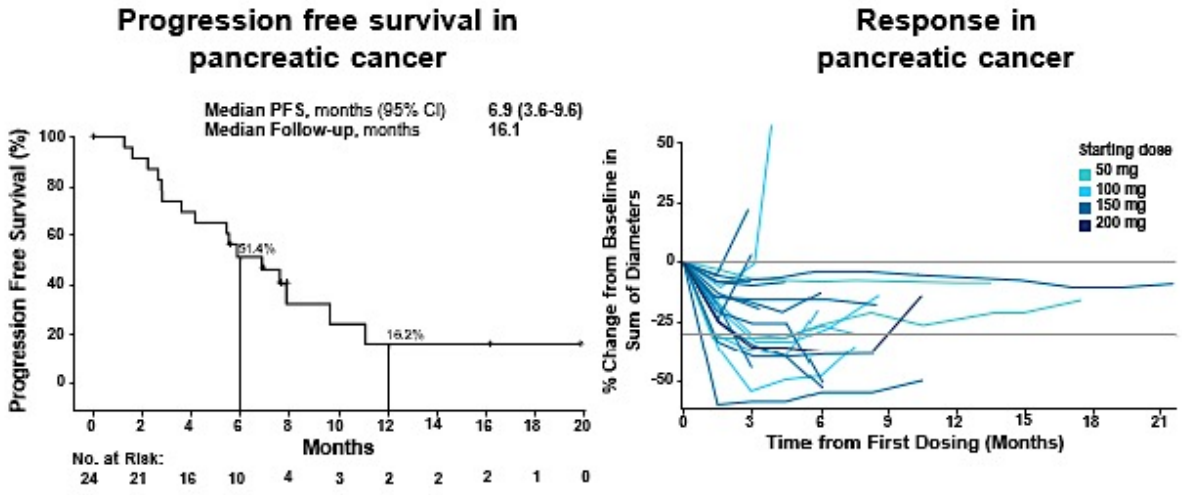
Esacher, TE, Sactchell, KJF. Mol Therapy, 2023

Research To Practice

KRAS G12C (Glycine → Cysteine): PDAC Summary Data

	N	Response Rate	Disease Control	Median PFS	Median OS
Sotorasib (CodeBreaK 100)	38	21% (8/38)	84% (32/38)	4 m	6.9 m
Adagrasib (KRYSTAL-1)	21	33% (7/21)	81% (17/21)	5.4 m	8 m
Divarasib	7	43% (3/7)	100% (7/7)	-	-
Olomorasib (LY3537982)	24	42% (10/24)	92% (22/24)	6.9 m	-
Glecirasib (JAB-21822)	31	42% (13/31)	93.5% (29/31)	5.6 m	10.7 m

Olomorasib (covalent GDP-G12Ci)



Stickler, J. New Engl J Med, 2023
Bekaii-Saab, T…Pant, S. J Clin Oncol, 2023
Sacher, A. New Engl J Med, 2023
Murciano-Goroff, Y. AACR, 2023
Hollebecque, A. Gastrointestinal Cancers Symposium, 2024
Li, J. Gastrointestinal Cancers Symposium, 2024

Research To Practice

Targeting RAS in PDAC: Selected Trials

RMC-6236 (pan/All *RAS*) – molecular 'glue' (Triple Meeting, ESMO 2023)

- First-in-class, orally bioavailable, tri-complex *RAS*^{multi} (ON) inhibitor
- Binds intracellular chaperone protein: cyclophilin A – engages RAS to form RAS selective tri-complex
- Dose-dependent, suppression RAS pathway xenografts (PDAC, CRC, NSCLC), G12X (D,V, R)
- Preclinical: anti-tumor immunity; additive with IO

ASP3082 (G12D) – degrader

- First in class: G12D protein degrader
- Binds directly *KRAS* G12D protein + E3 protein, forms ternary complex
- Preclinical: Dose-dependent inhibition PDAC *KRAS* G12D tumors

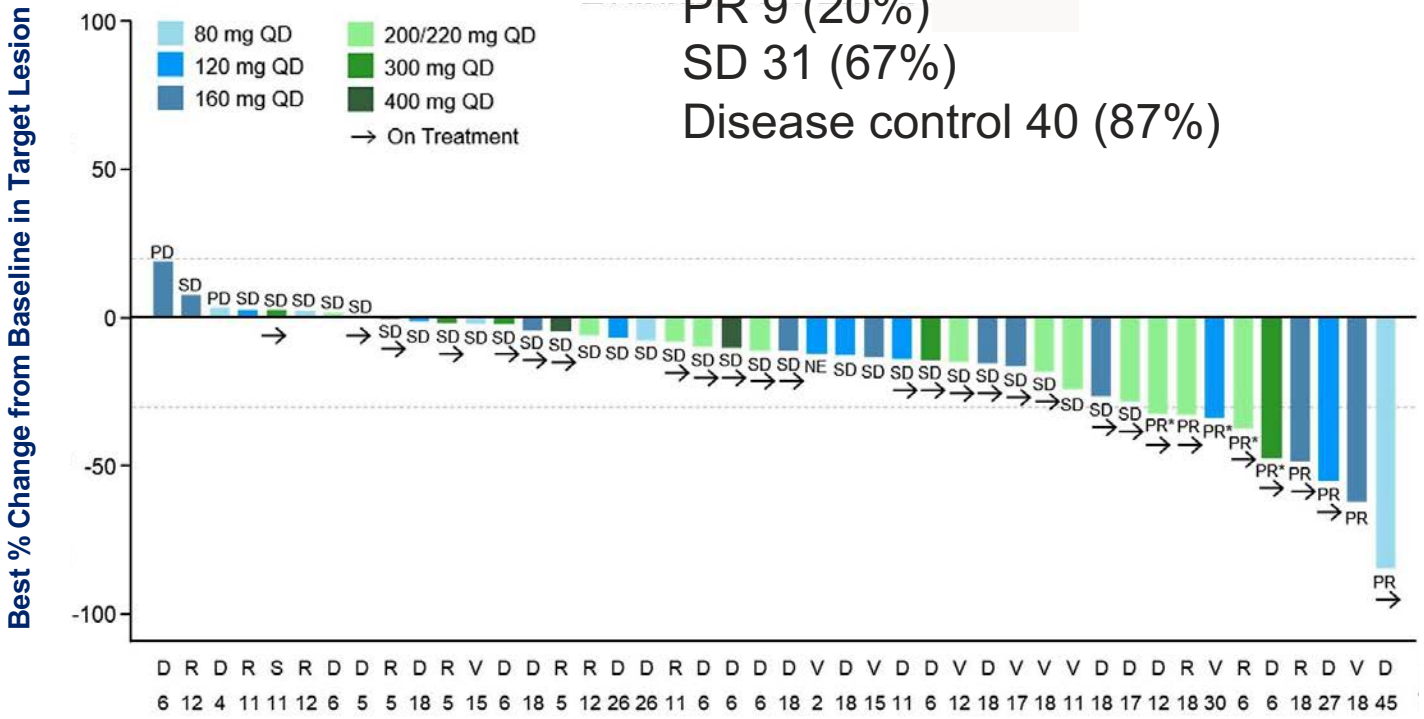
RMC-9805 (G12D)

- Mutant-select, covalent, oral *KRAS* G12D 'On' inhibitor
- Combination data with IO

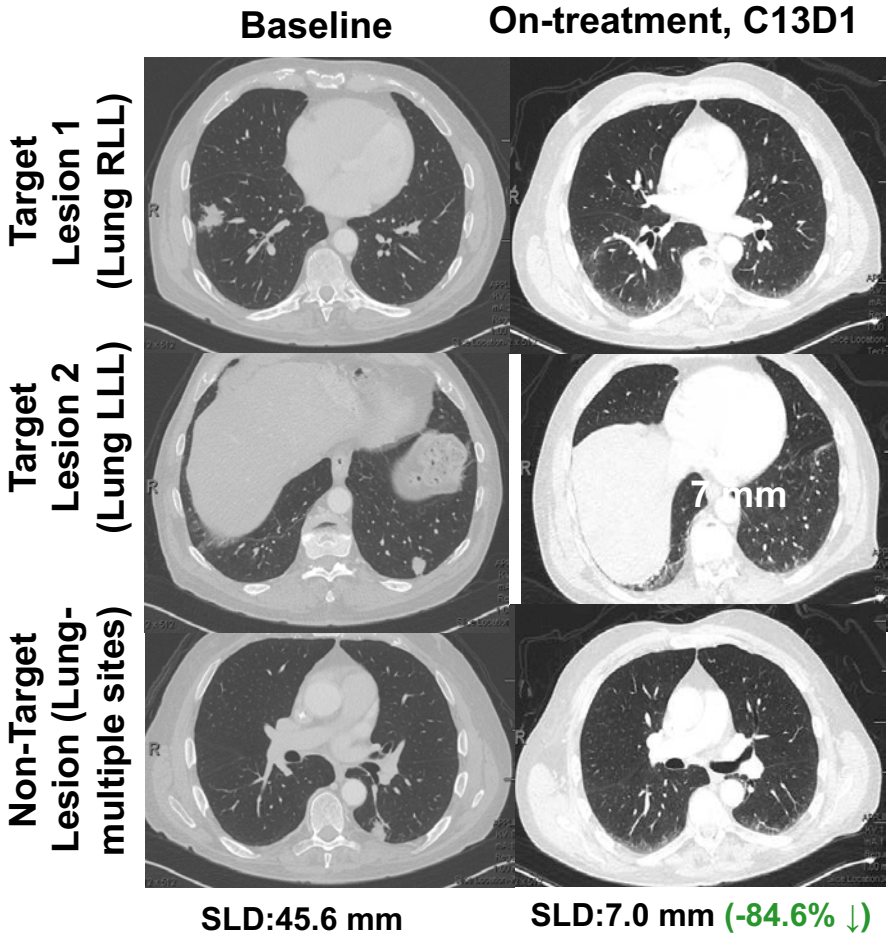
Singh M. AACR 2022, Koltun E et al. AACR 2022. Abstract 3597
NCT05379985
NCT05382559
NCT06040541

Research To Practice

RMC-6236 PDAC *KRAS* G12X Best Response (N= 46)



PR 9 (20%)
SD 31 (67%)
Disease control 40 (87%)



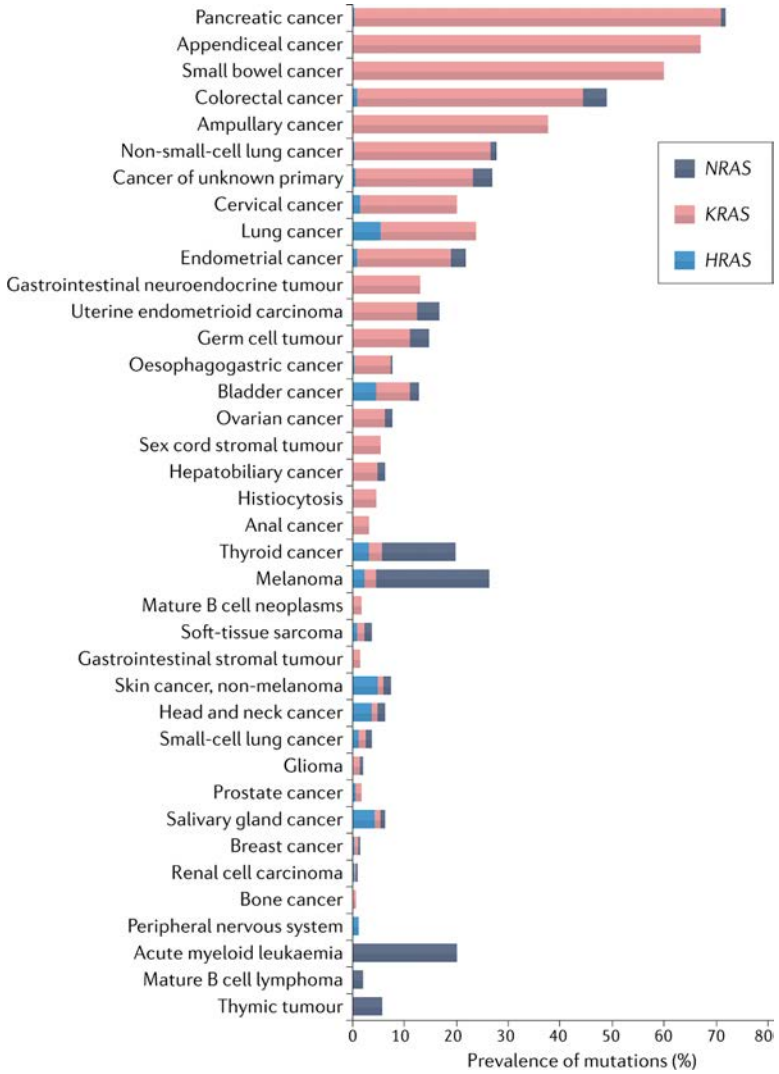
Arbour, K…Spira, A. ESMO, 2023
Spira, A.. Hong, DS. AACR-NCI-EORTC, 2023

KRAS Directed Immunotherapy

Research To Practice

Targeting m*KRAS* in PDAC with TCR Therapies

- Mutant KRAS promising public neoantigen target in PDAC
- HLA C*08:02 restricted
  G12D *KRAS* TCR → PR in PDAC, CRC
- Adoptive therapy challenges:
  - Select HLA's
  - Select mutations
  - Logistics
  - Potential CRS
  - Cost, resources, time



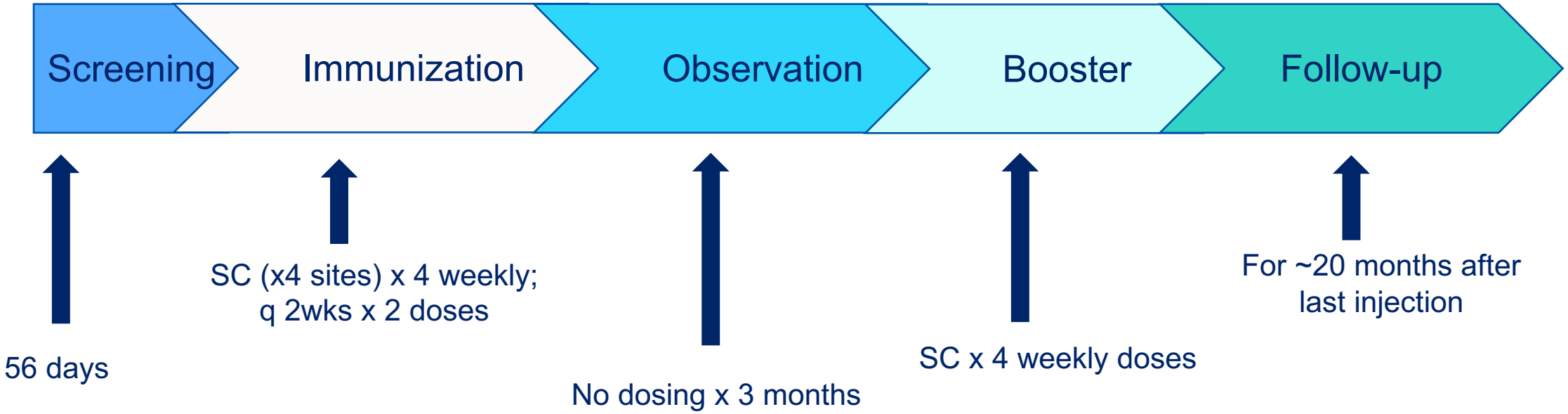
Leidner R et al. *N Engl J Med.* 2022;386(22):2112-2119; Tran E et al. *N Engl J Med.* 2016;375(23):2255-2262; Liu H et al. *Nature.* 2014;507(7493):519-522; Moynihan KD et al. *Nat Med.* 2016;22(12):1402-1410; Ma L et al. *Science.* 2019;365(6449):162-168.
cbioportal TCGA, MSK IMPACT Cohorts, 2022

Research To Practice

Phase I: ELI-002 2P KRAS G12D/R Vaccine

- First in human, phase 1/2 ELI-002 in *KRAS/NRAS* mutated PDAC, solid tumors with MRD(+ctDNA), elevated biomarkers (Ca 19-9/CEA)

- Determine MTD (if MTD) or RP2D, safety, ctDNA clearance, Immunogenicity



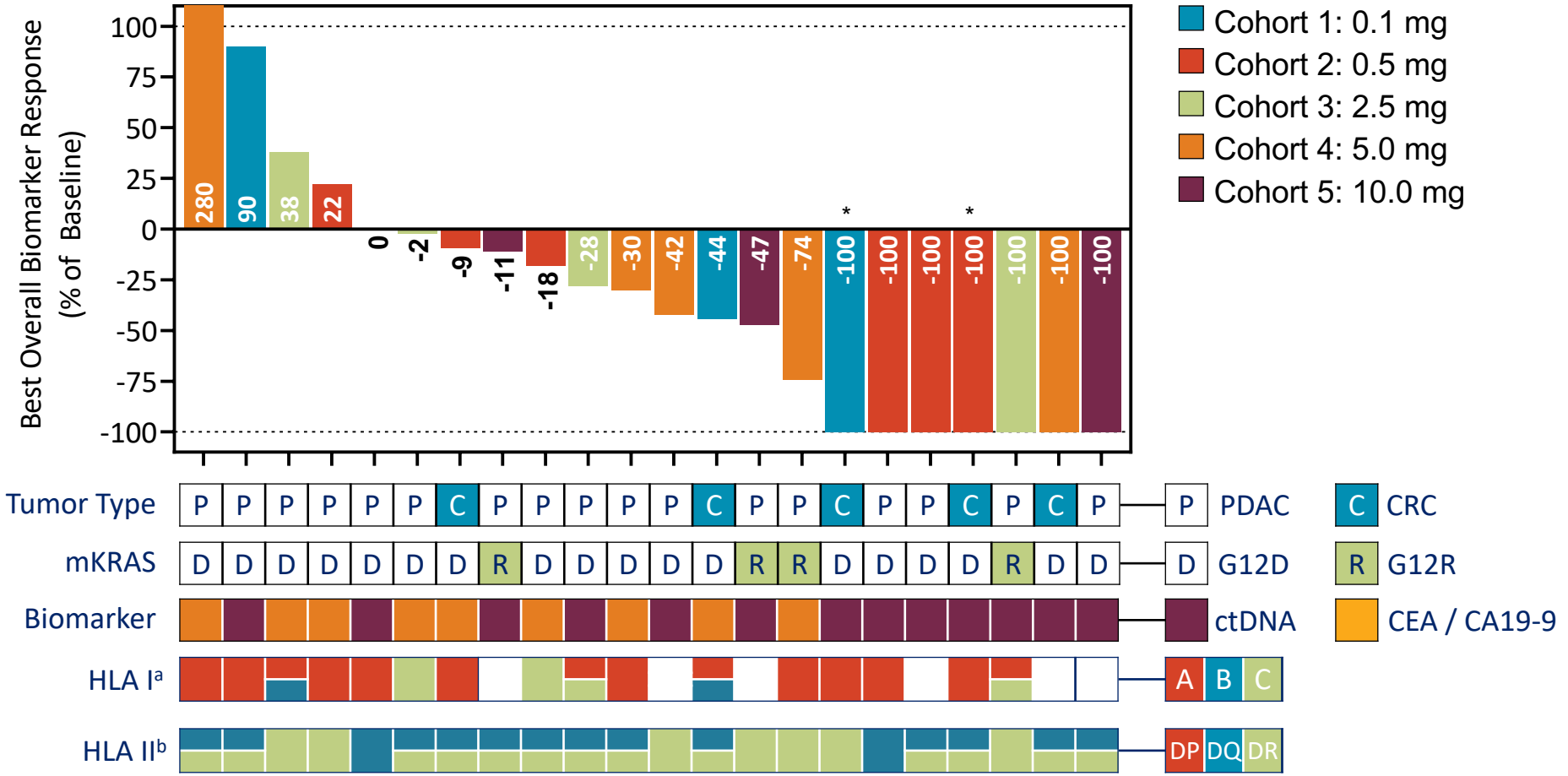
Pant S…O'Reilly EM et al. ASCO 2022. Abstract TPS2701. NCT04853017
O'Reilly EM…Pant S et al. ASCO 2023. Abstract 2528

Research To Practice

Phase I: Biomarker (CEA, Ca 19-9, ctDNA) Reduction/Clearance

Reduction = % decrease from baseline
- 17/22 (77%)

Clearance = 0 MTM/mL on ctDNA assay
- 7/22 (32%)



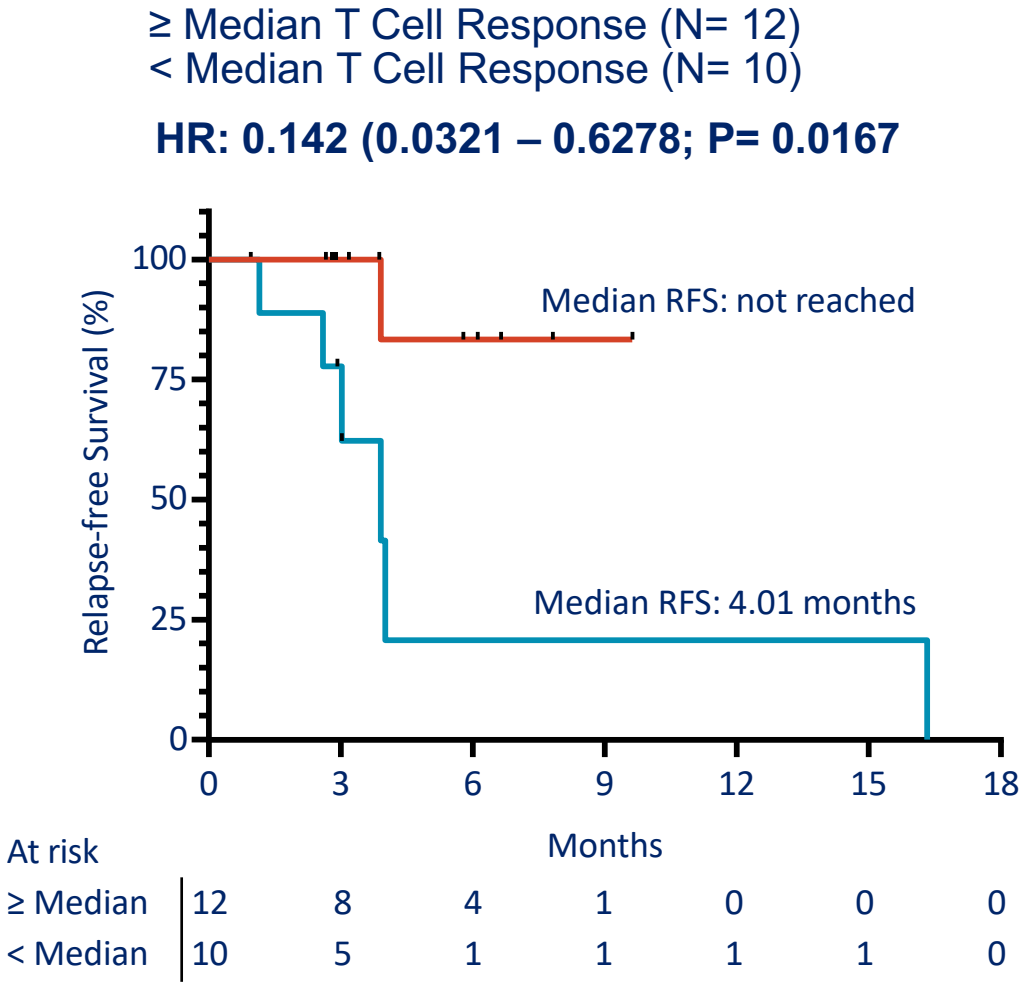
T cell responses 87%; dose response
Average change 56 x > baseline

O'Reilly EM…Pant S et al. ASCO 2023. Abstract 2528
Wainberg, Z…O'Reilly, EM. AACR Pancreas, 2023
Pant, S…Haqq, C, O'Reilly, EM.. Nature Med, 2024

Research To Practice

Median RFS >Median T cell Response Correlates with Outcome

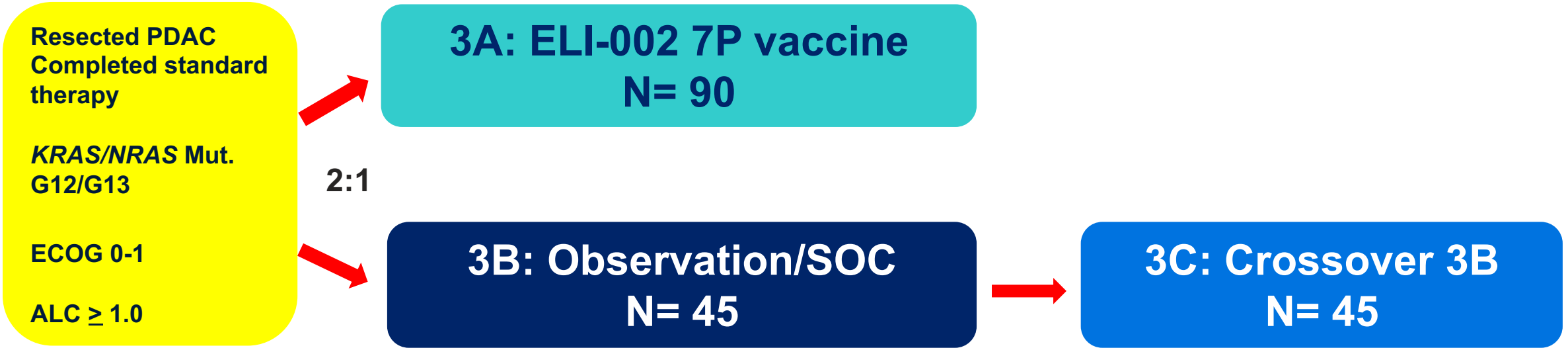
- Strength T cell response to ELI-002 2P strongly correlated with RFS/death
- At median f/up 7.6 m:
  For ≥ median T cell response: Not reached
  For < median T cell response: med RFS 4.01 m
- Median OS 16.3 m



Pant, S…Haqq, C, O'Reilly, EM.. Nature Med, 2024

Research To Practice

AMPLIFY-201 7P: Randomized Phase II Trial PDAC (ongoing)



Primary endpoint: Disease-free survival (investigator)
Secondary: Biomarker reduction & clearance, 1-year DFS, median OS, safety, ORR (crossover)
Exploratory: Immunogenicity ELI-002 7P to baseline
Stratification: N0 vs N1
*7-Peptide: G12D, G12V, G12R, G12C, G12A, G12S, G13D

Wainberg, Z…O'Reilly, EM. Trials In Progress, Gastrointestinal Cancers Symposium, 2024
NCT05726864

Research To Practice

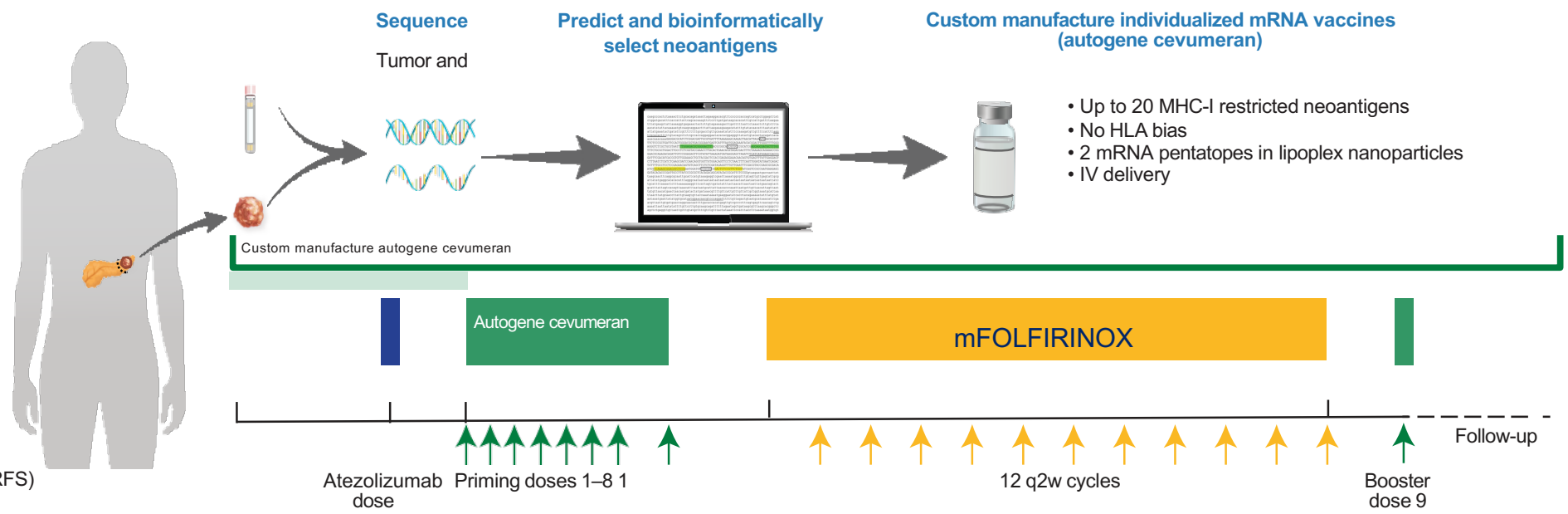
Personalized Neoantigen Vaccines: Phase I Trial Autogene Cevumeran in Resected PDAC

Investigator-initiated single-center phase I Target accrual: 20 patients

Eligible patients with PDAC:
- All surgically resectable
  - No borderline resectable
  - No locally advanced/metastatic
  - No neoadjuvant therapy

Primary endpoint: Safety

Other endpoints:
- Immunogenicity
- Feasibility
- 18-month recurrence-free survival (RFS)

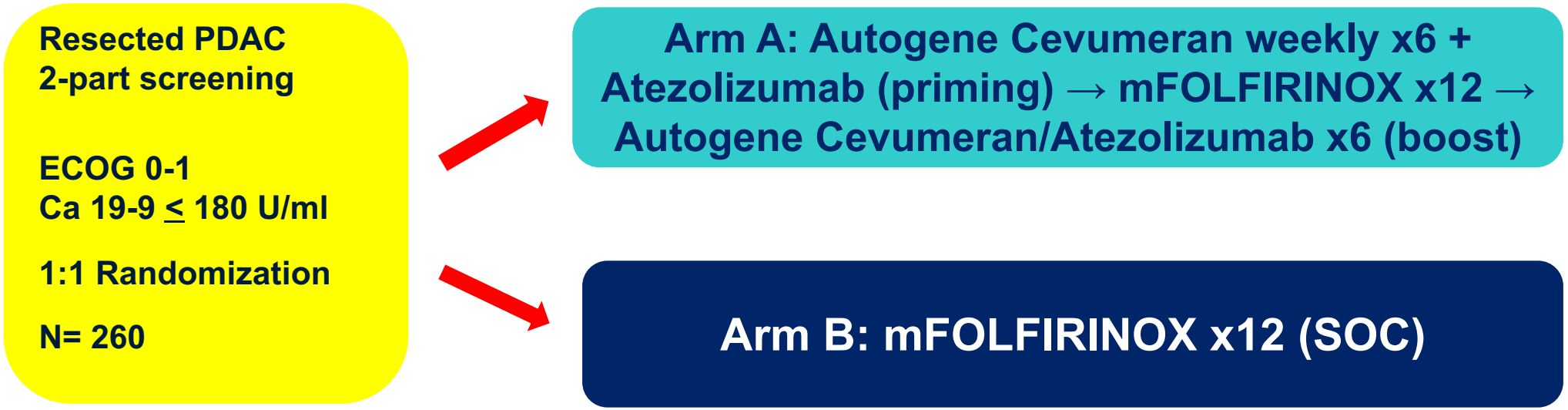


Vaccination: safe, feasible, in clinically relevant timeline
Personalized mRNA vaccine expands neoantigen specific T cells; Highly immunogenic in 50%
Immunity adjudicated: Elispot, T cell expansion; Immune responder required both (+)
mRFS: Not Reached (N= 8) vs 13.7 m (N= 8) immune-responders vs non-responders, HR 0.08, p= 0.03

Rojas, L…. Balachandran, V. Nature, 2023

Research To Practice

Randomized Phase II: mFOLFIRINOX +/- Personalized Neoantigen Vaccine (mRNA) + Atezolizumab (ongoing)



Primary endpoint: Disease-free survival (investigator)
Secondary: DFS @12, 24, 26 m; OS, OS @3, 5 years; Safety
Exploratory: QoL; QLQ-C30, EORTC PAN-26, PRO-CTCAE; PK; Immunogenicity
Stratification: R0 vs R1, N0 vs N1

G044479
NCT05968326

Third Annual National General Medical Oncology Summit

“What I Tell My Patients”
Sixteenth Annual RTP-ONS NCPD Symposium Series
ONS Congress, Washington, DC— April 24 to 28, 2024

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

RTP
RESEARCH TO PRACTICE

The Annual
National General Medical Oncology Summit

Sunday, March 24, 2024

Moderator

Neil Love, MD

Faculty

Ghassan Abou-Alfa, MD, MBA
Natalie S Callander, MD
Kristen K Ciombor, MD, MSCI
Richard S Finn, MD
Yelena Y Janjigian, MD
Samuel J Klempner, MD
Andrew H Ko, MD
Eileen M O'Reilly, MD
Paul G Richardson, MD
John Strickler, MD

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually.
The survey will remain open up to 5 minutes after the meeting ends.

To Claim CME, ACPE or NCPD Credit
In-person attendees: Please refer to the program syllabus for the CME credit link or QR code.
Online/Zoom attendees: The CME credit link is posted in the chat room.