Therapeutic Developments in GI Cancers: 2023

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Co-Chair, NCI GI Steering Committee
August 5, 2023

Disclosures:

- Consultant:
  - Amgen
  - Elevation
  - General Electric
  - GSK
  - IGM
  - Merck
  - Natera
  - Pfizer
  - Seagen
  - Taiho

- Institutional Grants
  - Agenus
  - Gritstone
  - Hutchmed
  - Janssen
  - Merck
  - Pfizer
  - Sumitomo

Discussion Points:

- Gastric cancer: **VESTIGE**
- Pancreatic cancer: **NAPOLI 3**
- Metastatic anal cancer: **NCI9673 Part B**
- Rectal cancer:
  - **PROSPECT**
  - **PRODIGE23**
- MCRC
  - **LEAP-017**
  - **Destiny- CRC02**
  - **FRESCO-2**

Gastric Cancer

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EORTC-1707-GITCG

Adjuvant immunotherapy in patients with resected gastric cancer following preoperative chemotherapy and high risk for recurrence (N+ and/or R1) an open label randomized controlled phase II study: **the VESTIGE-TRIAL**

E. Smyth[1], M.E. Mauer, A. Chiara Cella, I. Ben-Aharon, G. Piessen, L. Wyrwicz, G. Al-Haidari, T. Fleitas-Kannonnikoff, V. Boige, R. Obermannova, M.K. Stahl, U.M. Martens, C. Gomez-Martin, P. Thuss-Patience, V. Arrazubi-Arrula, A. Avallone, K-K. Shiu, M. Collienne, A. Giraut, **F. Lordick**[2]

[1]Oxford Cancer, Oxford, United Kingdom. [2]University Cancer Center Leipzig (UCCL), Leipzig, Germany.

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VESTIGE: Main eligibility criteria & design

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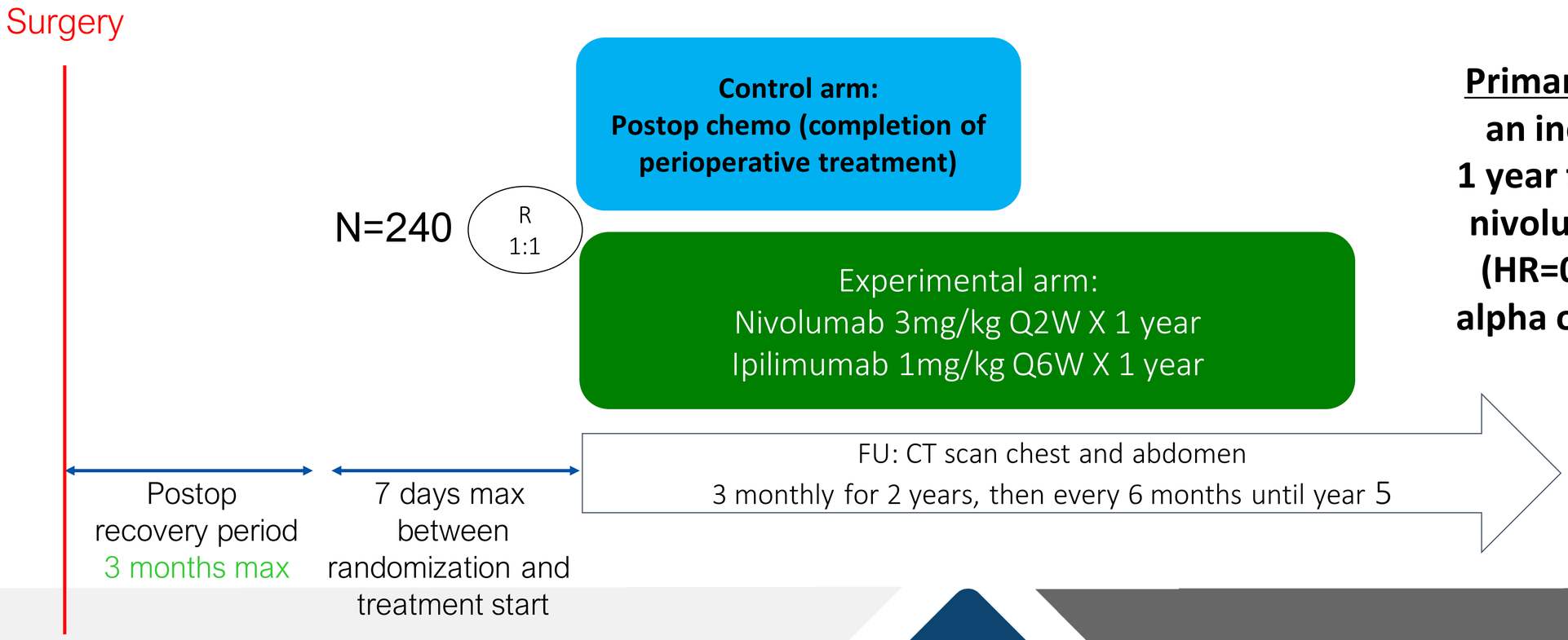
- Gastric or EGJ adenocarcinoma stage Ib-IV
- Completed pre-operative chemotherapy with a fluoropyrimidine/platin-containing regimen followed by surgery within 12 weeks prior to randomization
- Recovered from surgery
- ypN1-3 status according to current (8th) version of TNM classification system AND/OR
- R0 or R1 resection according to current (8th) version of TNM



<u>Primary objective:</u> to detect an increase in DFS rate at 1 year from 65% to 74% with nivolumab plus ipilimumab (HR=0.7) with a one-sided alpha of 10% and 80% power

Participating countries and accrual

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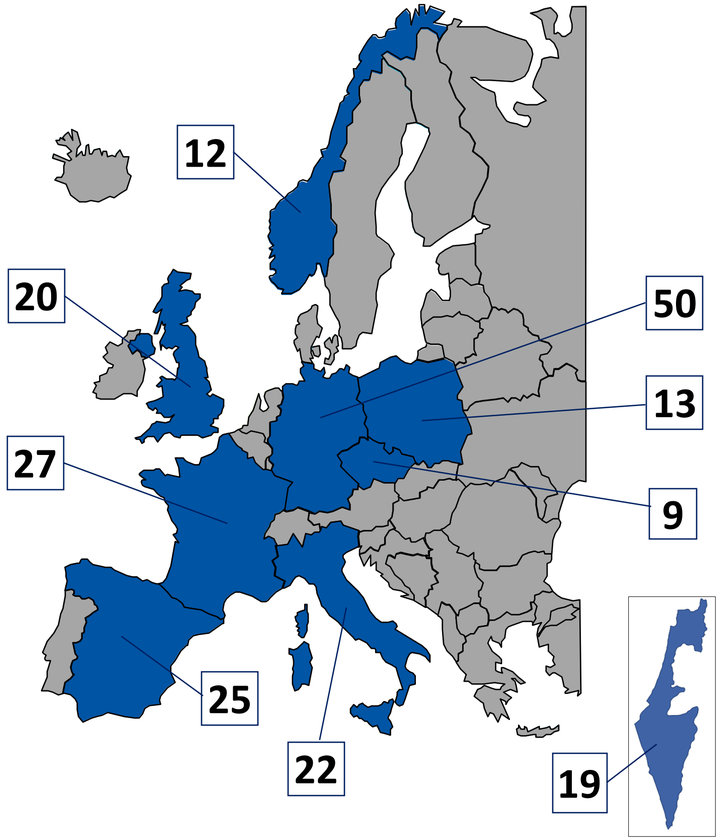
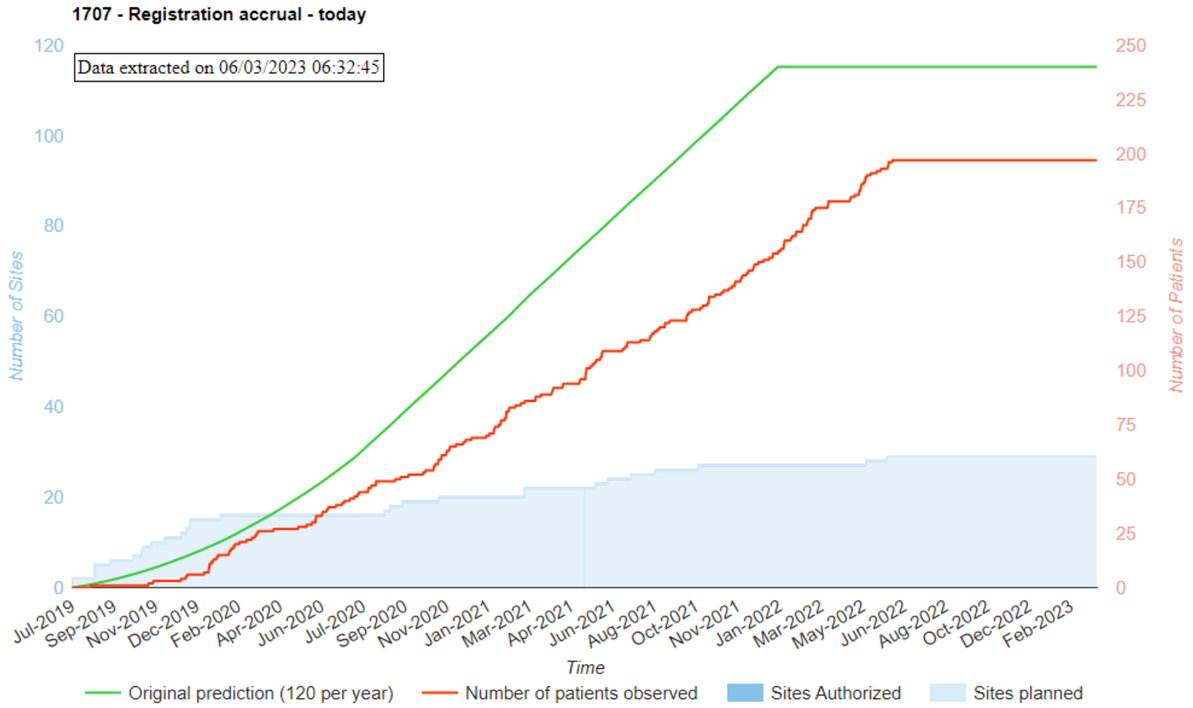
- 2019-2022: **197/240 patients randomized**



- 9 European Countries: 24 sites
- Including Israel and the UK



Unplanned interim analysis for protocol amendment in June 2022

Recruitment was prematurely terminated for futility per EORTC IDMC recommendation

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VESTIGE: Patient Baseline Characteristics

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	Treatment arm (ITT population)	
	CT (N=94)	**Nivo/Ipi (N=95)**
ypN stage, N (%)		
ypN0	4 (4.3)	2 (2.1)
ypN1	30 (31.9)	24 (25.3)
ypN2	24 (25.5)	20 (21.1)
ypN3	36 (38.3)	49 (51.6)
Pre-operative chemotherapy regimen, N (%)		
non-FLOT	7 (7.4)	8 (8.4)
FLOT	87 (92.6)	87 (91.6)
Neoadjuvant chemotherapy duration (weeks), Median (Range)	7.5 (5.0 – 12.0)	8.0 (5.0 - 10.0)

VESTIGE: Exposure to Treatment

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- A total of 136 out of 175 patients in the Safety population ended protocol treatment at the clinical cut-off date for the interim analysis.
  - For 39 patients, protocol treatment was still ongoing.

	Safety population – Treatment arm	
	CT (N=74)	Nivo/Ipi (N=62)
Reasons for Stopping treatment, N (%)		
Treatment completion	61 (82.4)	10 (16.1)
Progression of disease (PD)	0 (0.0)	23 (37.1)
Adverse Event	9 (12.2)	22 (35.5)
Patient's decision	4 (5.4)	7 (11.3)

VESTIGE: Primary Endpoint DFS- ITT

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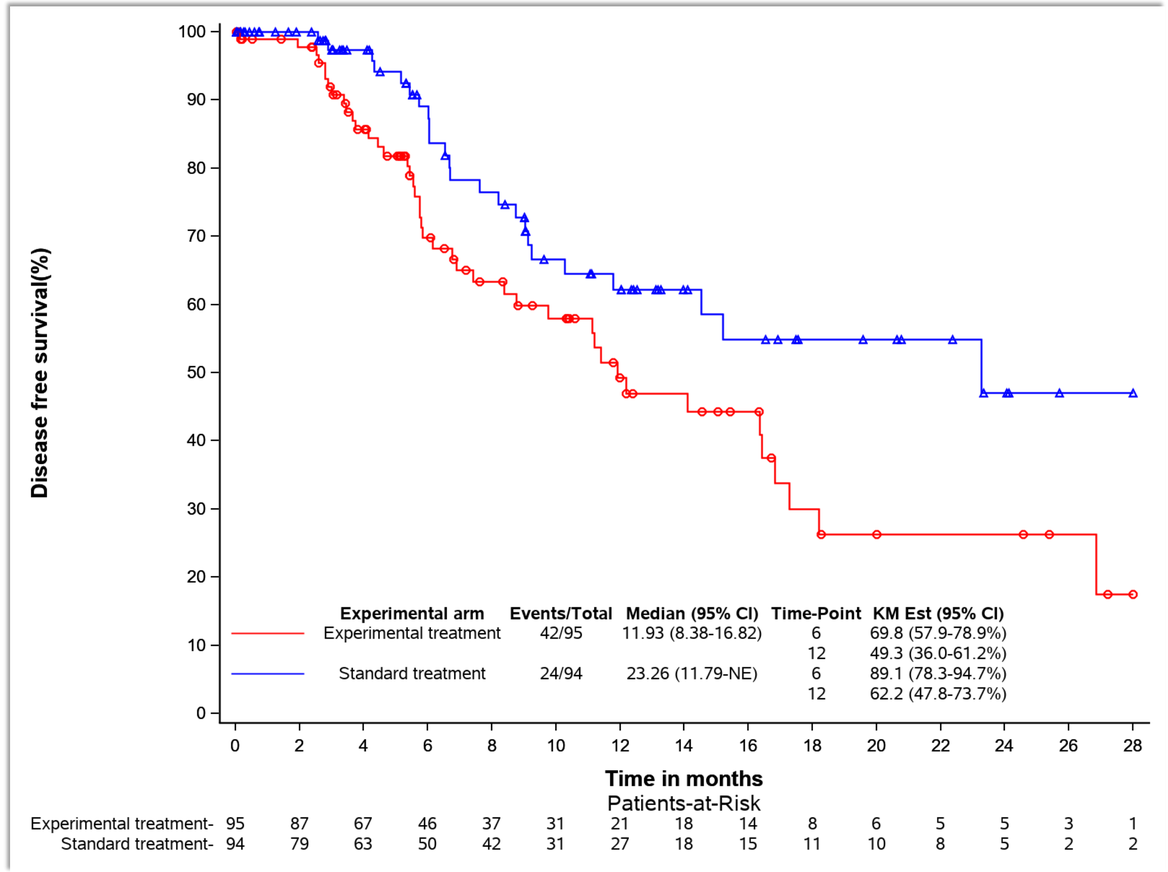

	CT am		Nivo/Ipi arm	
Median DFS(m) (95% CI)	23.26	(11.79 – NE)	11.93	(8.36- 16.82)
12m DFS % (95% CI)	62.2	(47.8-73.7)	49.3	(36.0- 61.2)

	Event/Total	Hazard Ratio (95% CI)^{Cox}	P-value
Nivo/Ipi arm	42/95	1.80 (1.09-2.98)	0.0195*
CT arm	24/94	Reference	

^{Cox}Cox model; *Logrank test

VESTIGE: Secondary Endpoint – OS - ITT

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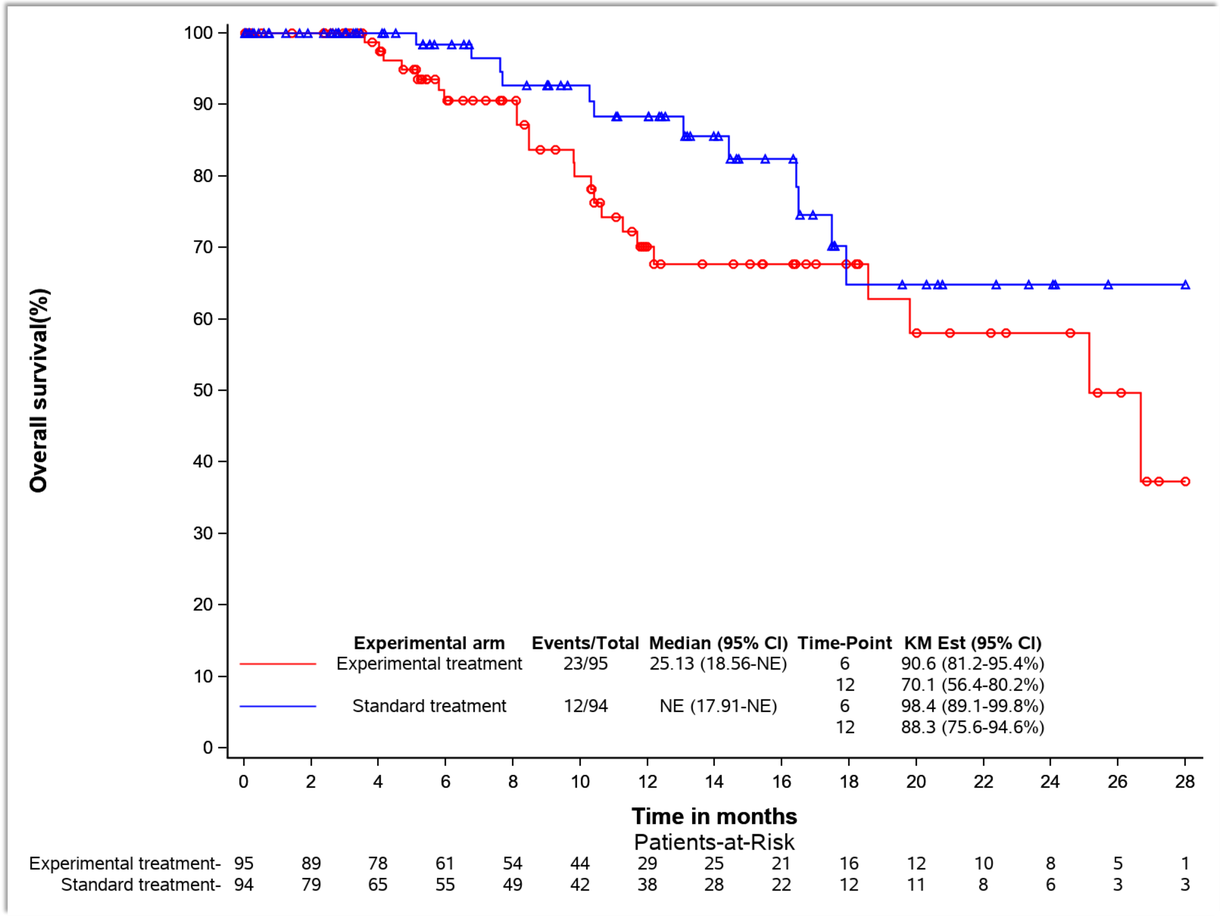


	Event/Total	Hazard Ratio (95% CI)[Cox]	P-value
Nivo/Ipi arm	23/95	1.79 (0.89-3.59)	0.0994*
CT arm	12/94	Reference	

[Cox]Cox model; *Logrank test

	CT am		Nivo/Ipi arm	
Median OS(m) (95% CI)	NE	(18.56 – NE)	23.13	(18.56- 16.NE)

Main cause of death	Treatment arm (ITT population)	
	CT (N=12)	Nivo/Ipi (N=23)
PD	9 (75.0)	21 (91.3)
Other	2 (16.7)	2 (8.7)
Missing	1 (8.3)	0 (0.0)

Pancreatic Cancer

2023 ASCO ANNUAL MEETING

NALIRIFOX versus nab-paclitaxel + gemcitabine in treatment-naive patients with mPDAC: additional results from the phase 3 NAPOLI 3 trial

Eileen M O'Reilly,[1] Davide Melisi,[2] Teresa Macarulla,[3] Roberto A Pazo Cid,[4] Sreenivasa R Chandana,[5] Christelle De La Fouchardière,[6] Andrew Dean,[7] Igor Kiss,[8] Woo Jin Lee,[9] Thorsten O Goetze,[10] Eric Van Cutsem,[11] Scott Paulson,[12] Tanios Bekaii-Saab,[13] Shubham Pant,[14] Richard Hubner,[15] Zhimin Xiao,[16] Huanyu Chen,[16] Fawzi Benzaghou,[16] Zev A Wainberg[17]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Investigational Cancer Therapeutics Clinical Unit, Azienda Ospedaliera Universitaria Integrata, Verona, Italy; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]Hospital Universitario Miguel Servet, Zaragoza, Spain; [5]Cancer and Hematology Centers of Western Michigan, Grand Rapids, MI, USA; [6]Centre Léon Bérard, Lyon, France; [7]St John of God Subiaco Hospital, Subiaco, WA, Australia; [8]Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk University, Brno, Czechia; [9]National Cancer Center, Goyang, Republic of Korea; [10]Krankenhaus Nordwest, Frankfurt, Germany; [11]University Hospitals Gasthuisberg and KULeuven, Leuven, Belgium; [12]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [13]Mayo Clinic, Scottsdale, AZ, USA; [14]MD Anderson Cancer Center, Houston, TX, USA; [15]The Christie NHS Foundation Trust, Manchester, UK; [16]Ipsen, Cambridge, MA, USA; [17]University of California, Los Angeles, CA, USA

NAPOLI 3: Study design

N = 770

Key inclusion criteria

- Aged ≥ 18 years
- Confirmed PDAC not previously treated in the metastatic setting
- Metastatic disease diagnosed ≤ 6 weeks prior to screening
- ≥ 1 metastatic lesions measurable by CT/MRI according to RECIST v1.1
- ECOG PS of 0 or 1

R 1:1

Stratification

- ECOG PS 0/1
- Region
- Liver metastases

NALIRIFOX

Liposomal irinotecan 50 mg/m^2
+ **5-FU** 2400 mg/m^2
+ **LV** 400 mg/m^2
+ **oxaliplatin** 60 mg/m^2
Days 1 and 15 of a 28-day cycle[a]

Gem+NabP

Gem 1000 mg/m^2
+ **NabP** 125 mg/m^2
Days 1, 8, and 15 of a 28-day cycle

- Tumor assessment every 8 weeks per RECIST v1.1[b]
- Treatment until disease progression, unacceptable toxicity or study withdrawal
- AEs recorded and coded using MedDRA (v24.0); severity graded by NCI-CTCAE (v5.0)
- Follow-up every 8 weeks until death or study end[c]

Primary endpoint: OS

[a]Administered sequentially as a continuous infusion over 46 hours on days 1 and 15 of a 28-day cycle (dose delays and oxaliplatin discontinuation were permitted). [b]Until progressive disease. [c]The study was completed once all patients had discontinued the study treatment and at least 543 OS events had occurred in randomized patients.
5-FU, 5-fluorouracil; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; LV, leucovorin; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

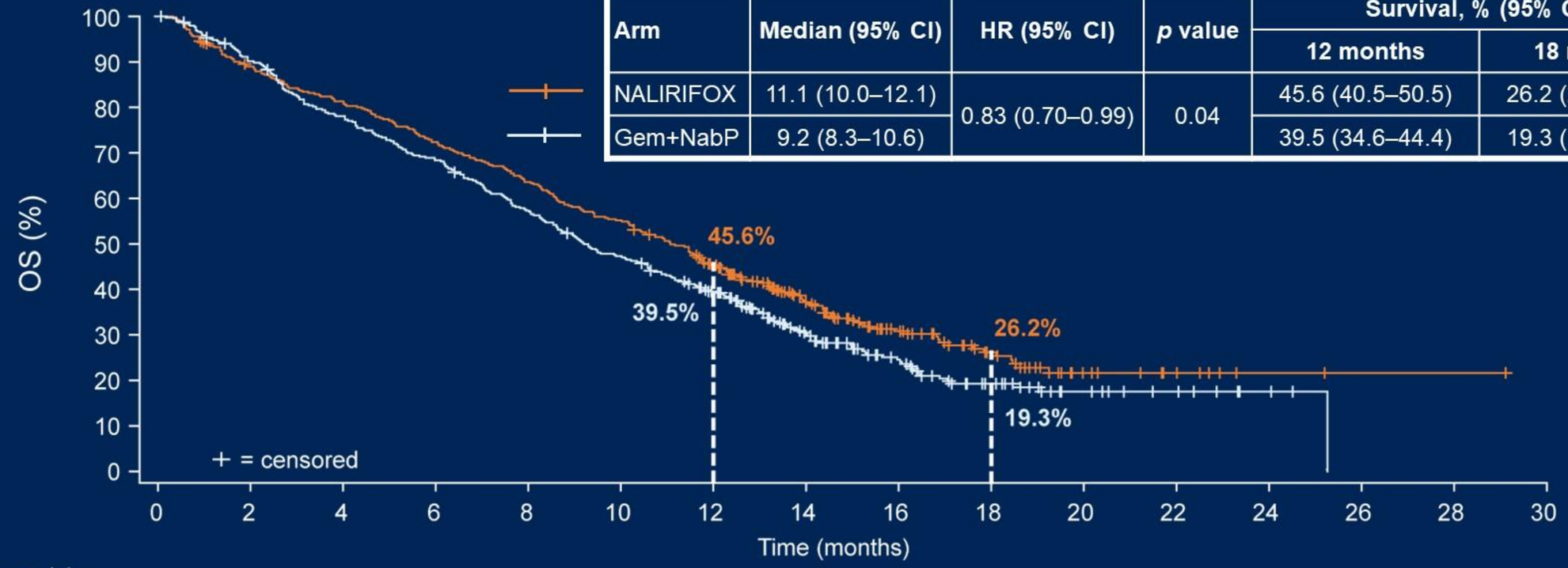
NAPOLI 3: Baseline characteristics (ITT population)

Characteristic	NALIRIFOX (n = 383)	Gem+NabP (n = 387)
Median (range) age, years	64.0 (20.0–85.0)	65.0 (36.0–82.0)
Men, %	53.3	59.4
White, %	82.2	83.7
ECOG performance status score, %		
0 / 1[a]	41.8 / 58.0	43.4 / 56.6
Number of metastatic sites, %		
1 / 2 / ≥ 3	29.8 / 31.3 / 38.9	35.7 / 27.9 / 36.4
Liver metastases, %	80.2	80.4
Geographic region, %		
North America	31.3	31.5
East Asia	2.9	2.8
Rest of the world	65.8	65.6
Main pancreatic tumor location		
Head	38.4	40.3
Other[b]	61.6	59.7
Baseline CA 19-9, %[c]		
< 37 U/mL	15.7	18.3
≥ 37 U/mL	83.8	81.7
Any prior anti-cancer therapy, %	5.7	7.0
Chemotherapy / radiotherapy / surgical procedure	3.7 / 2.6 / 4.7	4.1 / 1.6 / 6.5
Time from metastatic diagnosis at study entry until randomization, weeks, median (range)	3.0 (0.6–9.1)	3.6 (0.4–10.9)

[a]For one patient, ECOG 1 was reconsidered to be ECOG 2 after randomization. [b]Body, tail or unknown location. [c]Two patients (0.5%) from the NALIRIFOX arm had missing baseline CA 19-9 values.
CA 19-9, cancer antigen 19-9; ECOG, Eastern Cooperative Oncology Group; Gem, gemcitabine; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin.

NAPOLI 3: OS (ITT population)

Arm	Median (95% CI)	HR (95% CI)	*p* value	Survival, % (95% CI)	
				12 months	18 months
NALIRIFOX	11.1 (10.0–12.1)	0.83 (0.70–0.99)	0.04	45.6 (40.5–50.5)	26.2 (20.9–31.7)
Gem+NabP	9.2 (8.3–10.6)			39.5 (34.6–44.4)	19.3 (14.8–24.2)



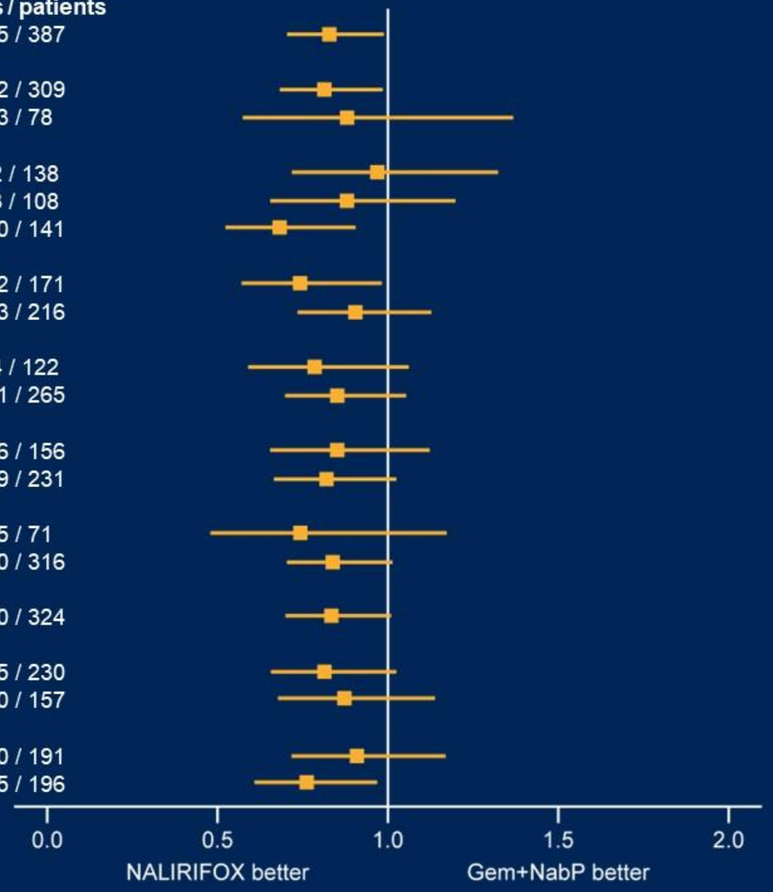
No. at risk:

NALIRIFOX	383	337	308	274	241	209	162	98	59	32	13	7	2	1	1	0
Gem+NabP	387	345	298	261	218	179	140	80	50	28	15	10	3	0	0	0

Hazard ratio and 95% CI based on a Cox proportional hazards regression model, stratified by ECOG PS (0 vs 1), region (North America vs ROW), liver metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival; ROW, rest of world.

NAPOLI 3: OS subgroup analyses (ITT population)

Subgroup	NALIRIFOX, events / patients	Gem+NabP, events / patients	HR (95% CI)
Overall	259 / 383	285 / 387	0.83 (0.70, 0.99)
Presence of liver metastases at baseline			
Yes	220 / 309	242 / 309	0.82 (0.68, 0.98)
No	39 / 74	43 / 78	0.89 (0.57, 1.37)
Number of metastatic sites			
1	75 / 114	92 / 138	0.98 (0.72, 1.32)
2	87 / 120	83 / 108	0.89 (0.65, 1.20)
≥ 3	97 / 149	110 / 141	0.69 (0.52, 0.90)
Baseline ECOG PS			
0	97 / 168	112 / 171	0.75 (0.57, 0.98)
1	162 / 215	173 / 216	0.91 (0.73, 1.13)
Region			
North America	85 / 120	94 / 122	0.79 (0.59, 1.06)
Rest of the world	174 / 263	191 / 265	0.86 (0.70, 1.05)
Main pancreatic tumor location			
Head	97 / 147	116 / 156	0.86 (0.65, 1.12)
Other	162 / 236	169 / 231	0.83 (0.67, 1.02)
Baseline CA 19-9			
< 37 U/mL	34 / 60	45 / 71	0.75 (0.48, 1.17)
≥ 37 U/mL	223 / 321	240 / 316	0.84 (0.70, 1.01)
Race			
White	218 / 315	240 / 324	0.84 (0.70, 1.01)
Sex			
Male	139 / 204	175 / 230	0.82 (0.66, 1.02)
Female	120 / 179	110 / 157	0.88 (0.68, 1.14)
Age			
< 65 years	127 / 193	130 / 191	0.92 (0.72, 1.17)
≥ 65 years	132 / 190	155 / 196	0.77 (0.61, 0.97)



CA 19-9, cancer antigen 19-9; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; HR, hazard ratio; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival.

NAPOLI 3: Selected any-cause TEAEs

	NALIRIFOX (n = 370)		Gem+NabP (n = 379)	
Any-cause TEAEs in ≥10% of patients, %[a]	Any grade	Grade 3–4	Any Grade	Grade 3–4
Hematologic				
Neutropenia[b] / febrile neutropenia	50.0 / 2.4	23.8 / 2.4	50.6 / 2.6	38.0 / 2.4
Anemia	26.2	10.5	40.4	17.4
Thrombocytopenia[c]	24.0	1.6	40.6	6.1
Non-hematologic				
Diarrhea	70.5	20.3	36.7	4.5
Nausea	59.5	11.9	42.7	2.6
Vomiting	39.7	7.0	26.4	2.1
Hypokalemia	31.6	15.1	12.9	4.0
Peripheral neuropathy[d]	32.9	6.7	30.9	8.7
Paresthesia	11.9	0.3	8.7	0.5
Pyrexia	10.5	0.8	23.0	1.6

[a]Grouped by system organ class (safety population). [b]Includes neutropenia and neutrophil count decreased. [c]Includes thrombocytopenia and platelet count decreased. [d]Includes peripheral neuropathy and peripheral sensory neuropathy.
Gem, gemcitabine; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; TEAE, treatment-emergent adverse event.

Metastatic Anal Cancer

NCI9673 (Part B): A multi-institutional ETCTN randomized phase II study of nivolumab with or without ipilimumab in refractory, metastatic squamous cell carcinoma of the anal canal (NCT02314169)

V.K. Morris[1], K.K. Ciombor[2], B. Polite[3], S. Mukherjee[4], J.C. Krauss[5], T. Shields[6], O. Aranha[7], J. Hays[8], S. Kazmi[9], B. Weinberg[10], K. Nguyen[11], A.B. Benson[12], C. Lieu[13], S. Iqbal[14], H. Hochster[15], L. Xiao[1], C. Eng[2]

[1]University of Texas – MD Anderson Cancer Center; [2]Vanderbilt-Ingram Cancer Center; [3]University of Chicago; [4]Roswell Park Cancer Institute; [5]University of Michigan; [6]Karmanos Cancer Institute; [7]Washington University School of Medicine; [8]The Ohio State University; [9]The University of Texas Southwestern Medical Center; [10]Georgetown University; [11]Yale University; [12]Northwestern University; [13]University of Colorado; [14]University of Southern California; [15]Rutgers University

NCI9673 (Part B) Study Design

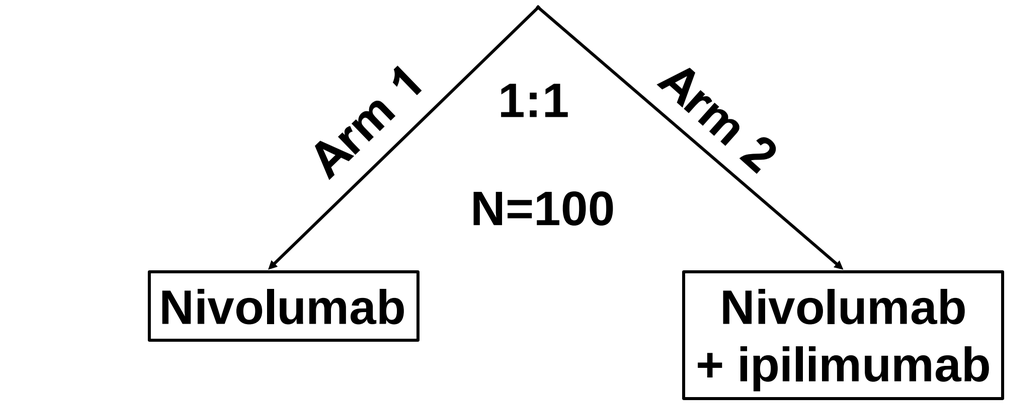
- **Primary Endpoint:**
  - **Progression-free survival (PFS)**

- **Secondary Endpoints:**
  - **Overall response (RECIST 1.1)**
  - **Overall survival (OS)**
  - **Safety/toxicity (CTCAE v5)**

- **Statistical Design:**
  - **H_0: Median $PFS_{Arm2} \leq PFS_{Arm1}$**
    H_a: Median $PFS_{Arm2} > PFS_{Arm1}$
  - **At a one-sided α=.10 and 90% power, 100 participants are needed to observe an improvement in median PFS from 4 to 7 months.**

Participants with:

- Unresectable or metastatic SCCA
- ≥1 prior line of systemic treatment



Study Treatment:

- **Nivolumab: 480 mg IV every 4 weeks**
- **Ipilimumab 1 mg/kg IV every 8 weeks (Arm 2 only)**

NCT02314169

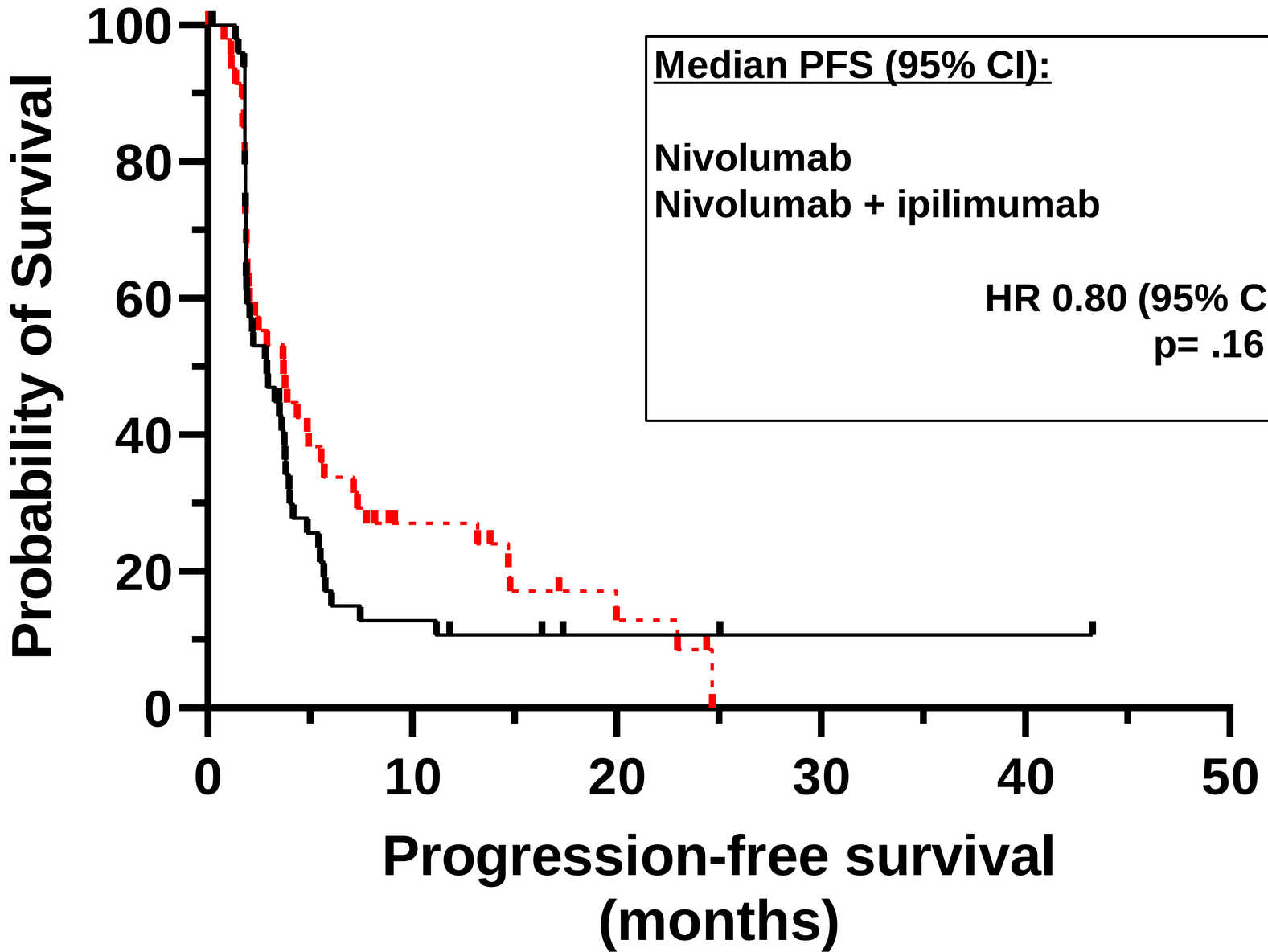
ETCTN
Experimental Therapeutics Clinical Trials Network
Team Driven. Cancer Therapy Focused.

Progression-free survival

Median PFS (95% CI):

Nivolumab	2.9 months (1.9 – 4.0)
Nivolumab + ipilimumab	3.7 months (2.0 – 7.1)

HR 0.80 (95% CI, .52-1.2)
p= .16



Median follow-up: 22 months

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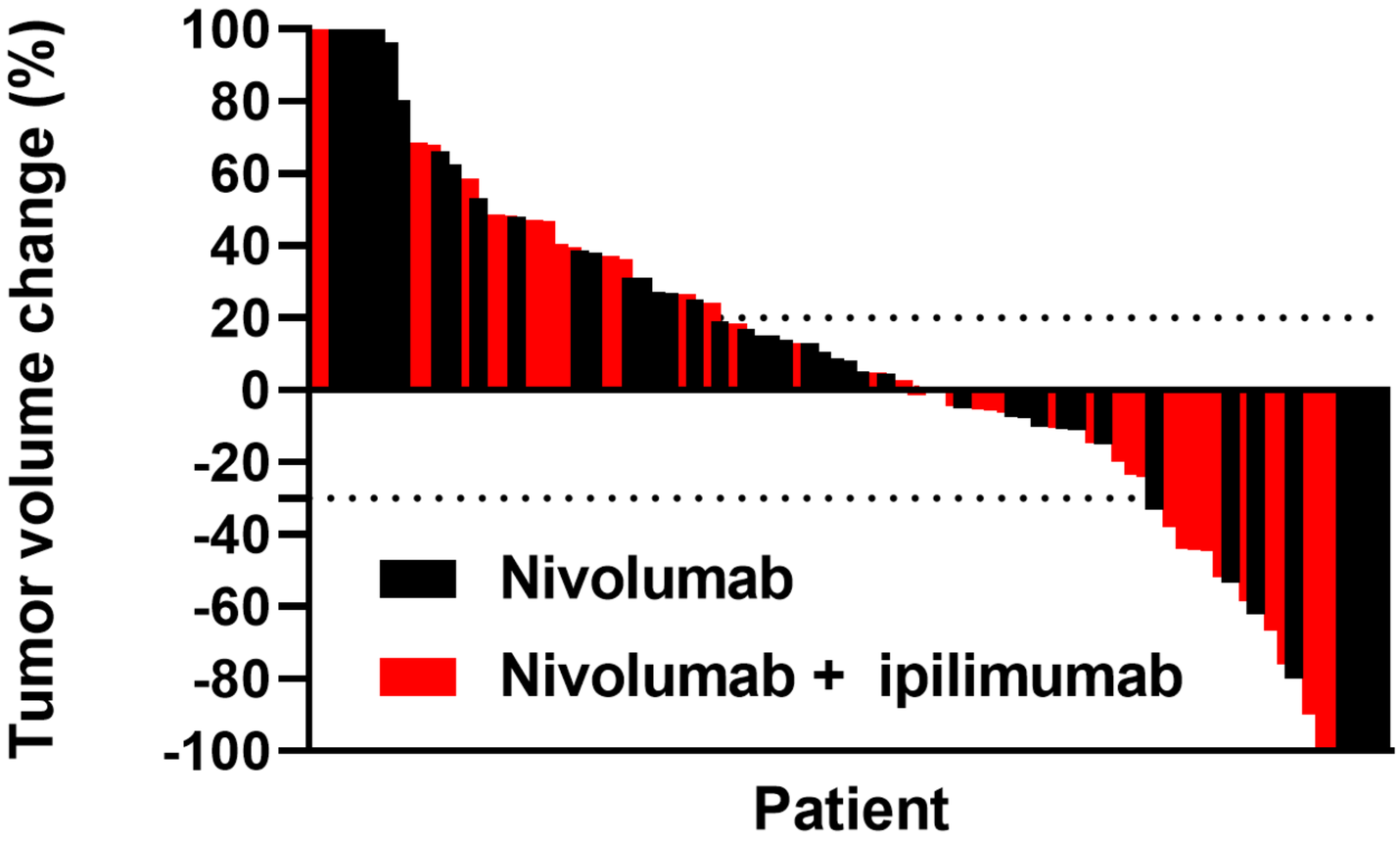
Response Assessment



Overall Response Rate (95% CI):

Nivolumab
17.4% (9.1-31)
Nivolumab + ipilimumab
21.5% (12-36)

Disease Control Rate (95% CI):

	Nivolumab (%)	Nivolumab + Ipilimumab (%)
Complete Response	3 (6.5)	2 (4.8)
Partial Response	5 (10.9)	7 (16.7)
Stable Disease	12 (21.7)	11 (26.2)
Progressive Disease	26 (56.5)	22 (52.3)

ETCTN
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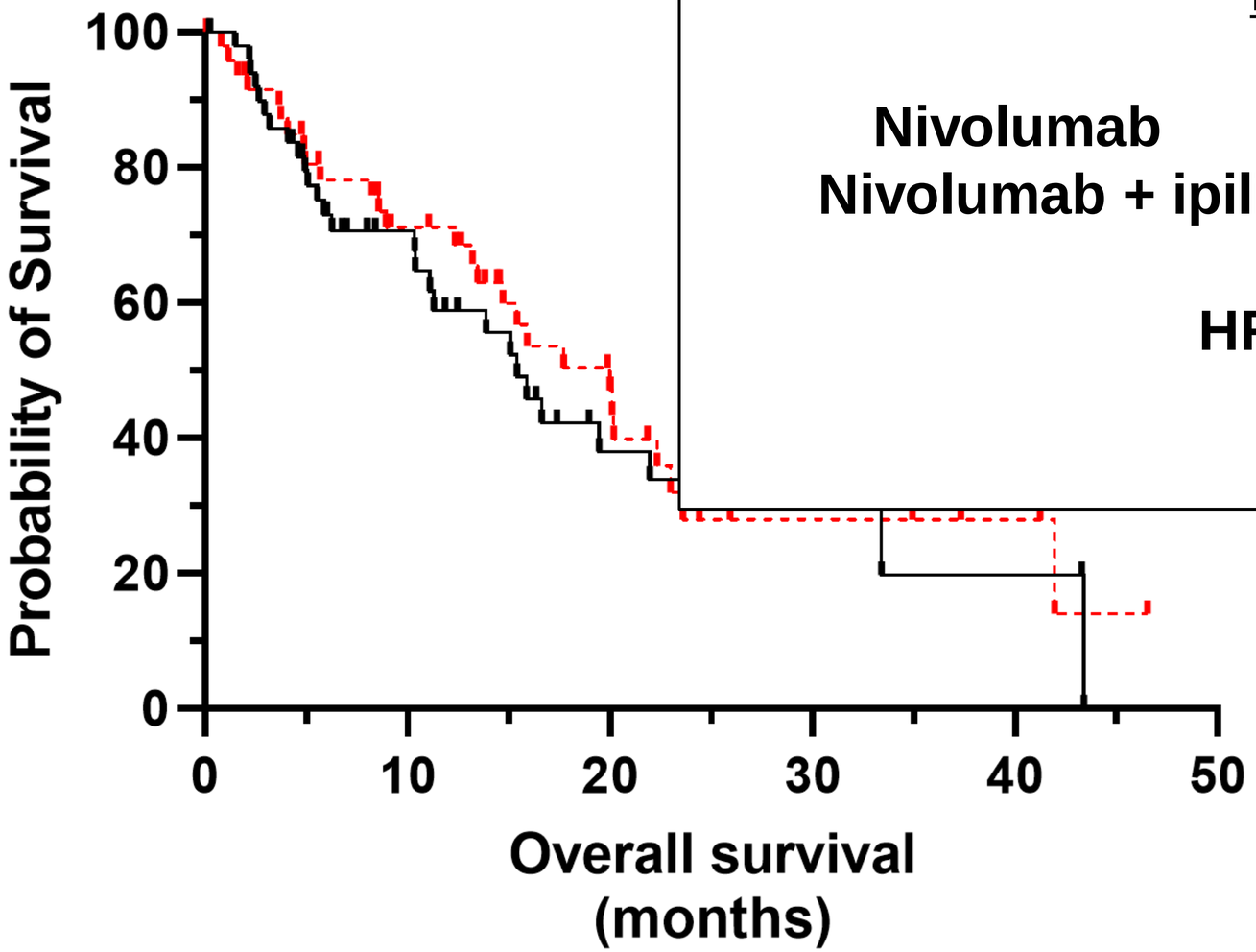
Overall survival

Median OS (95% CI):

Nivolumab	15.4 months (11.1 – NA)
Nivolumab + ipilimumab	20.0 months (13.5 – 23.6)

HR 0.86 (95% CI, .51-1.5)
p= .86

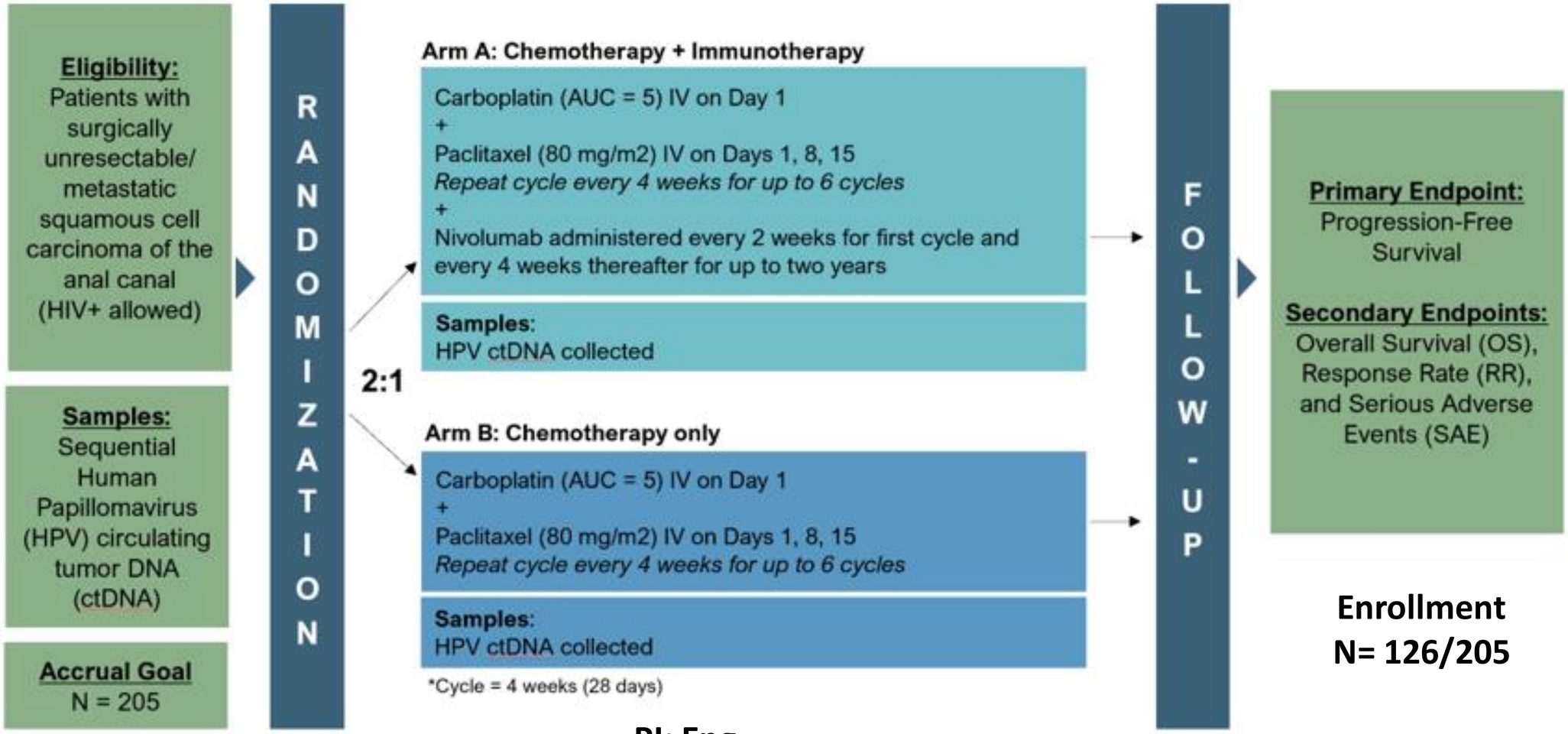


Safety/Toxicity Profile

- One grade 5 event (pneumonitis) occurred in a participant receiving nivolumab + ipilimumab.
- There were 4 grade 4 events in participants receiving nivolumab + ipilimumab: hyperglycemia (N=3) and diabetic ketoacidosis (N=1).
- There were 6 (12%) participants with grade 3 AEs attributed to nivolumab, and 12 (25%) participants with grades 3-5 AEs attributed to nivolumab + ipilimumab.

Grade ≥3 event	Nivolumab (N=52)	Nivolumab + ipilimumab (N=48)
Pneumonitis	0	4
Hyperglycemia	0	3
Hyponatremia	2	1
Abdominal pain	1	1
Elevated ALT	0	2
Adrenal insufficiency	0	1
Fatigue	0	1
Hypophysitis	0	1
Nephrotic syndrome	1	0

EA2176: Phase 3 Clinical Trial of Carboplatin and Paclitaxel +/- Nivolumab in Treatment-Naïve Metastatic Anal Cancer Patients



Enrollment
N= 126/205

PI: Eng

*HIV pts are eligible

Eng et al: JCO, 2022

2023 ASCO ANNUAL MEETING

Preoperative Chemotherapy with Selective Chemoradiation versus Chemoradiation for Locally Advanced Rectal Cancer:

The PROSPECT Trial (Alliance N1048)

D Schrag MD MPH Q Shi PhD MR Weiser MD MJ Gollub MD LB. Saltz MD BL Musher MD J. Goldberg MD T. Al Baghdadi MD KA Goodman MD RR McWilliams MD MSc JM Farma MD TJ George MD HF Kennecke MD A Shergill MD M Montemurro MD GD Nelson MS B Colgrove BS V Gordon MD AP Venook MD EM O'Reilly MD JA Meyerhardt MD MPH AC Dueck PhD E. Basch MD MSc GJ Chang MD HJ Mamon MD PhD

ClinicalTrials.gov Identifier: NCT01515787

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

NCI National Clinical Trials Network

PRESENTED BY: Deb Schrag MD MPH FASCO, Attending, Gastrointestinal Oncology Service, Memorial Sloan Kettering NY, NY USA

PROSPECT Study Summary

Recruitment 2012-2018 from 264 practice sites in the USA, Canada and Switzerland

Neoadjuvant Treatment for cT2N+, cT3N-, cT3N+ Rectal Cancer

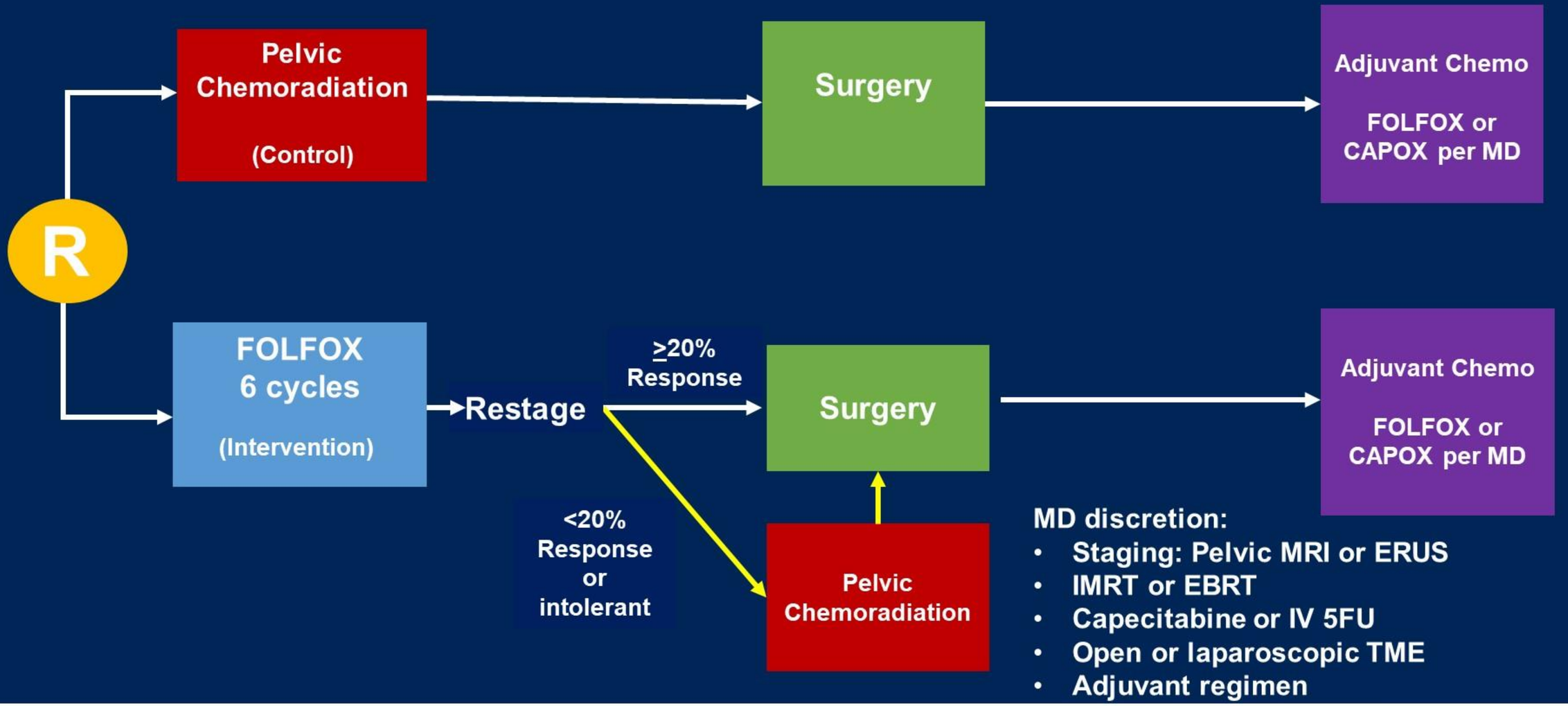
1:1

Pelvic Chemoradiation 5040cGy in 5.5 weeks

FOLFOX 6 cycles
Chemoradiation if poor response or FOLFOX not tolerated

Primary endpoint: Noninferior DFS

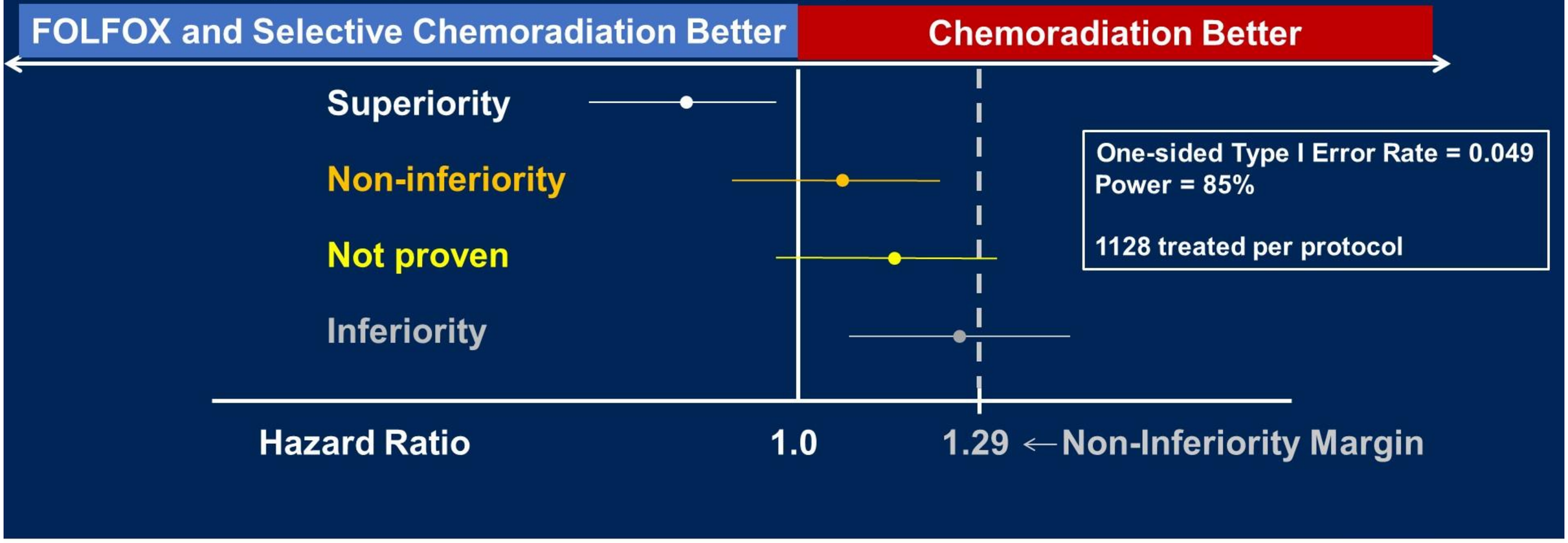
PROSPECT Study Full Schema



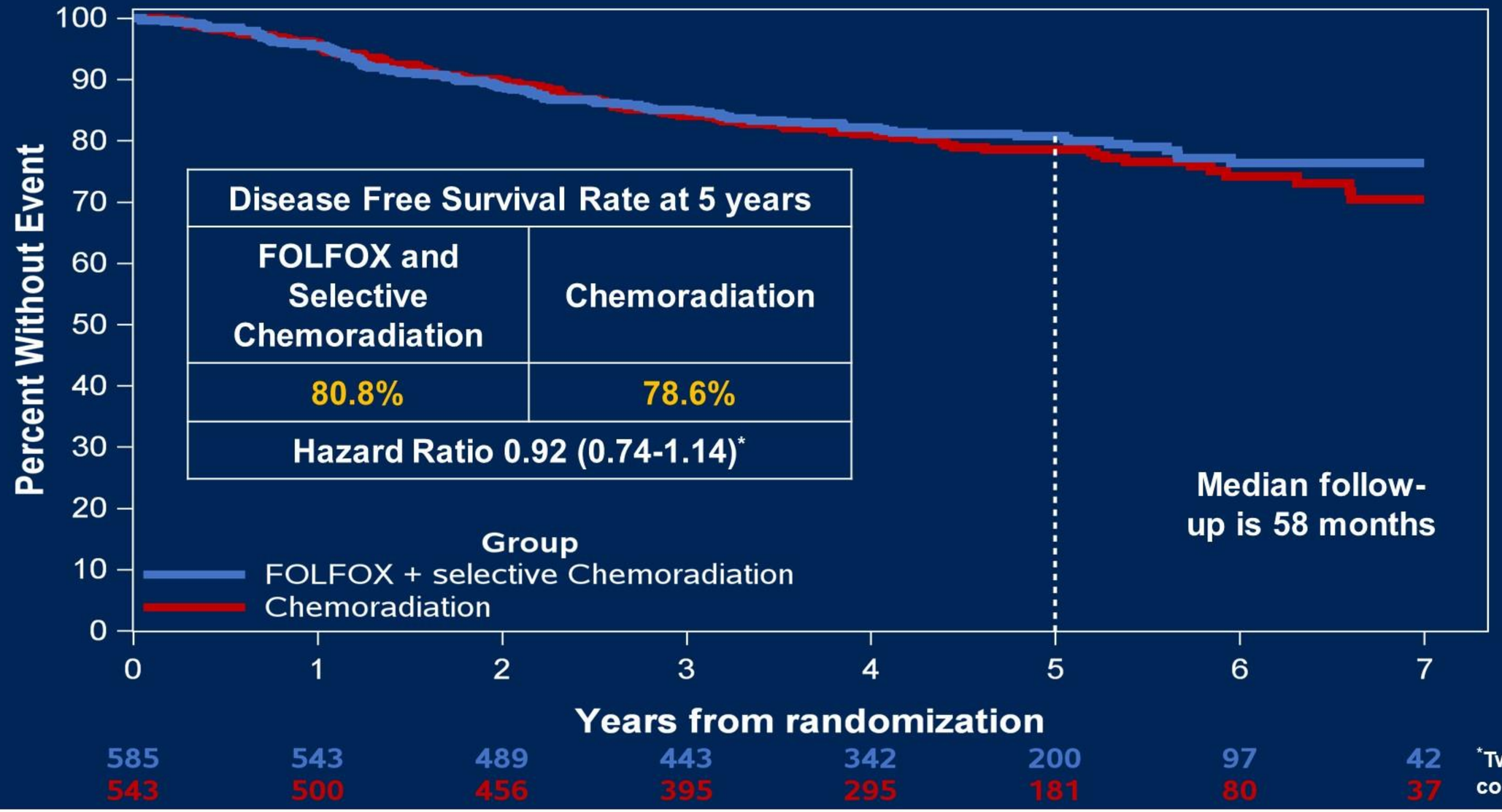
Non-inferiority Hypothesis for Disease Free Survival

Non-inferiority could be claimed if the upper limit of the two-sided 90.2% confidence interval of the hazard ratio (HR) did not exceed 1.29.

This corresponds to an absolute difference in 5-year DFS of <5%



PROSPECT: Disease Free Survival



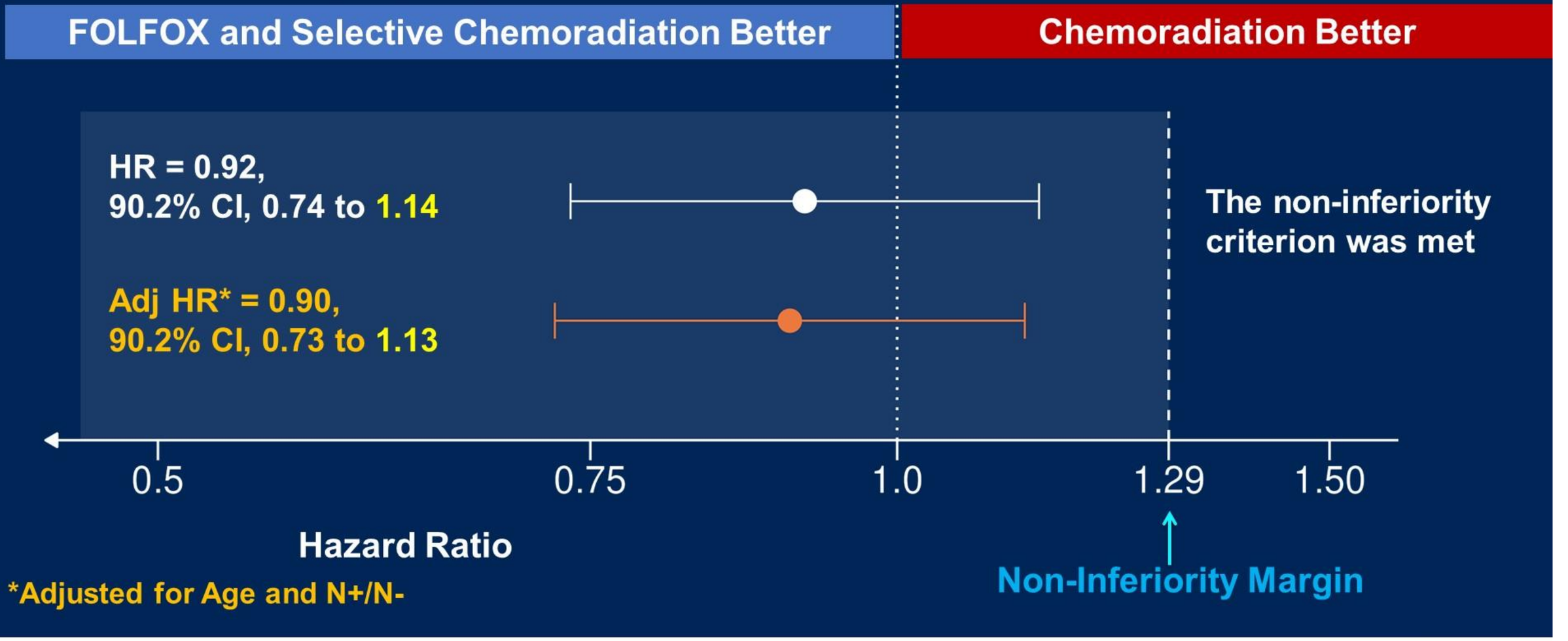
Disease Free Survival Rate at 5 years	
FOLFOX and Selective Chemoradiation	Chemoradiation
80.8%	78.6%
Hazard Ratio 0.92 (0.74-1.14)*	

Median follow-up is 58 months

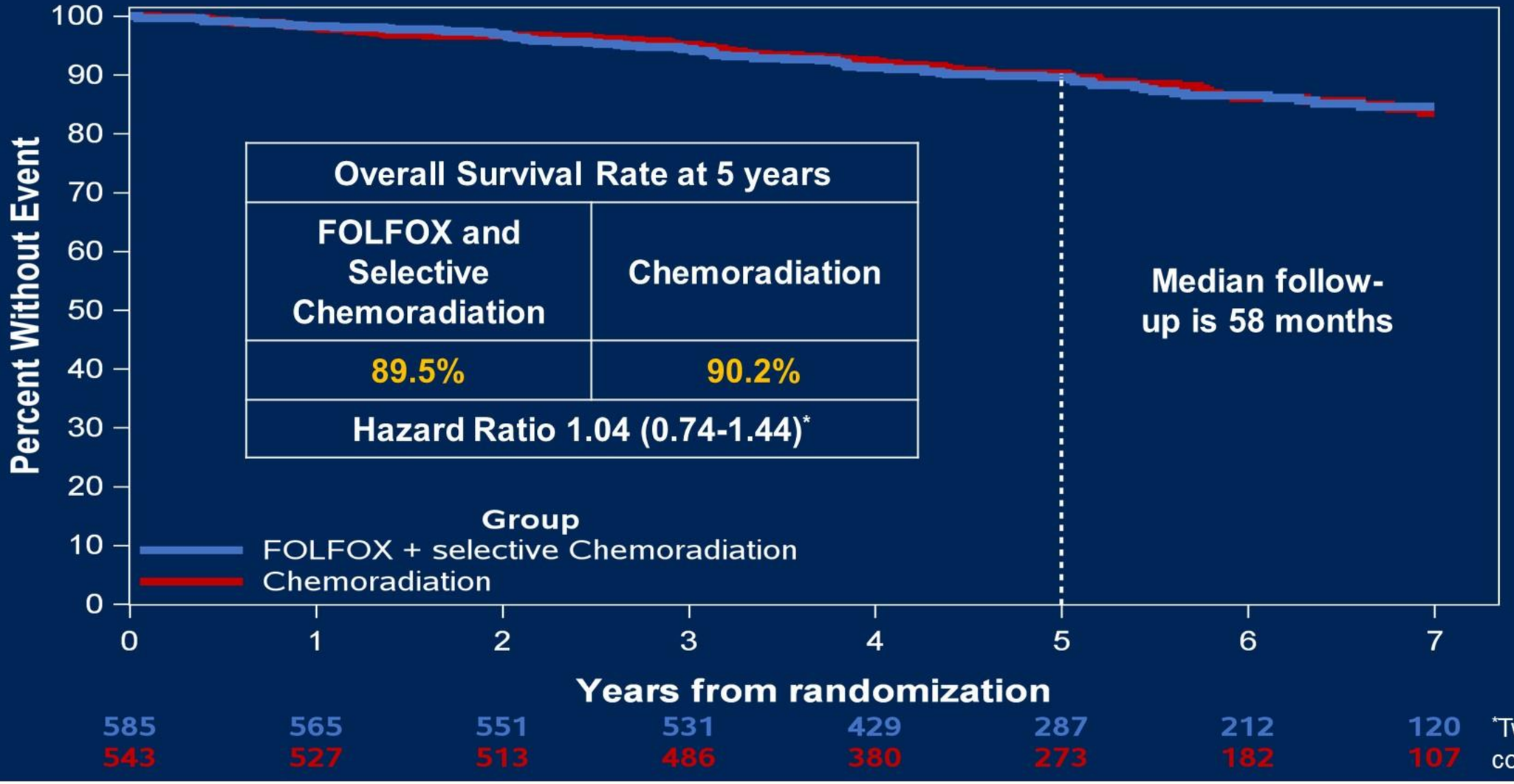
*Two-sided 90.2% confidence interval

PRESENTED BY: Deb Schrag MD MPH FASCO

PROSPECT: Disease Free Survival



PROSPECT: Overall Survival



*Two-sided 95% confidence interval

PROSPECT: Clinician-Reported Toxicity

Most severe toxicity during observation period based on CTCAE v. 4.0	FOLFOX and Selective Chemoradiation 12 weeks* 535 patients	Chemoradiation 6 weeks 510 patients
Neoadjuvant grade ≥3 adverse events	41%	23%
Adjuvant grade ≥3 adverse events	25%	39%

*22 weeks if also treated with chemoradiation

During Neoadjuvant treatment:
- More diarrhea in the RT group
- More neuropathy in the FOLFOX group

During Adjuvant treatment:
- More diarrhea in the RT group
- More neuropathy in the RT group

Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial.

T. Conroy, P-L. Etienne, E. Rio, L. Evesque, N. Mesgouez-Nebout, V. Vendrely, X. Artignan, O. Bouché, A. Boilève, M. Delaye, D. Gargot, V. Boige, N. Bonichon-Lamichhane, C. Louvet, C. de la Fouchardière, C. Morand, V. Pezzella, E. Rullier, F. Castan, and C. Borg

2023 ASCO ANNUAL MEETING

#ASCO23

PRESENTED BY: T Conroy, MD

PRODIGE 23 trial: trial design

MRI staging
Randomisation: 1/1
Stratification:
- center
- cT3 vs cT4
- cN0 vs cN+
- T extramural extension (≥5 vs. <5 mm)
- tumor location (cm from anal verge)

461 patients included

RANDOMIZE

SoC arm

Radiotherapy 50.4 Gy /5wks + capecitabine 1600 mg/m²/d 5 days/7 → 7 weeks → TME → mFOLFOX6, 12 cycles or capecitabine, 8 cycles*(6 months)

TNT arm

mFOLFIRINOX** 6 cycles, 3 months → Radiotherapy 50.4 Gy /5 wks + capecitabine 1600 mg/m²/d 5 days/7 → 7 weeks → TME → mFOLFOX6, 6 cycles or capecitabine, 4 cycles* (3 months)

Primary endpoint: DFS

****mFOLFIRINOX: At d1, Oxaliplatin 85 mg/m², Leucovorin 400 mg/m², Irinotecan 180 mg/m²; Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours (no bolus Fluorouracil)**

***according to center choice throughout the study; adjuvant chemotherapy was mandatory in both arms regardless of ypTNM stage.**

Tumor characteristics

Characteristics	TNT N=231	SoC N=230	p
Distance to anal verge			
≤5 cm	37.7%	36.1%	0.92
5.1-10 cm	49.3%	51.3%	
10.1-15 cm	13.0%	12.6%	
mrT stage			
T2/T3	1.3%/80.9%	0.9%/83.6%	0.70
T4	17.8%	15.6%	
cN stage			
N+	89.1%	90.0%	0.52
Predicted lateral margin			
≤1 mm	26.0%	27.7%	0.70

Cumulative incidence of rectal cancer recurrences

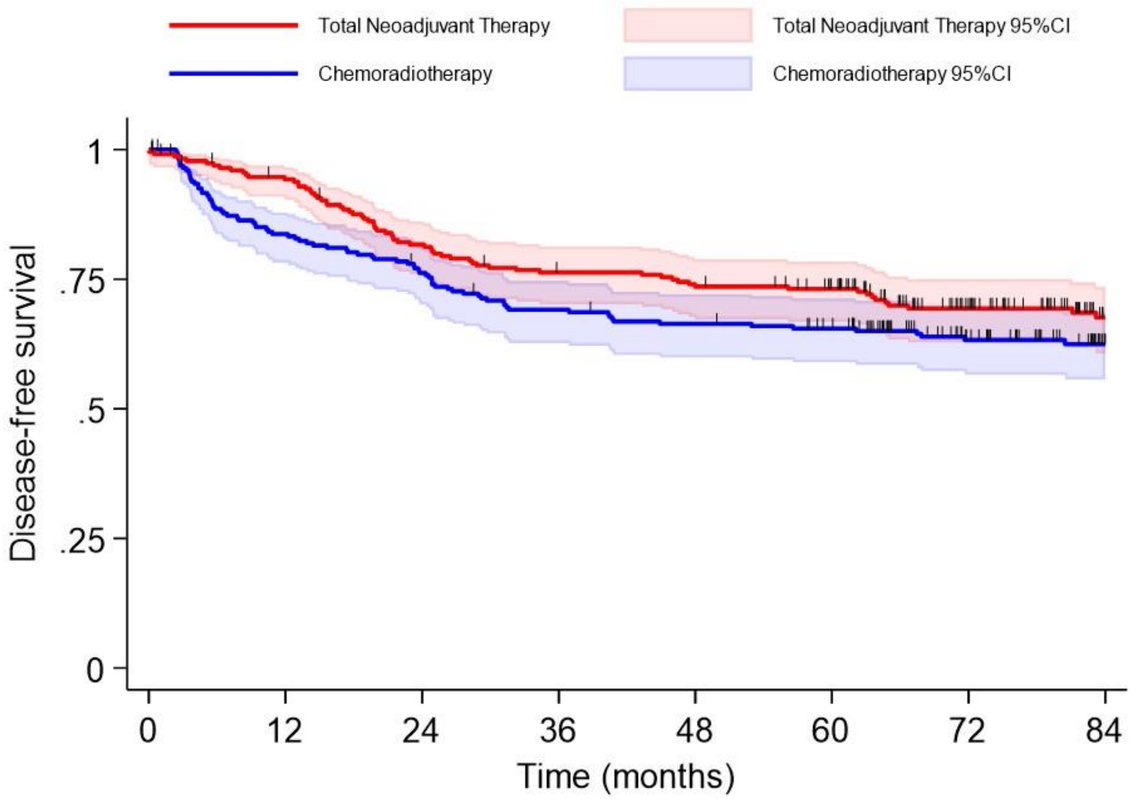
Results	TNT	SoC
Local		
At 5 years	4.7% [95%CI: 2.5-8.5]	6.4% [95%CI: 3.8-10.8]
At 7 years	5.3% [95%CI: 2.9-9.3]	8.1% [95%CI: 4.9-13.3]
Metastatic*		
At 5 years	18.4% [95%CI: 13.8-24.2]	26.6% [95%CI: 21.2-33.0]
At 7 years	20.7% [95%CI: 15.6-27.0]	27.7% [95%CI: 22.2-34.2]
Alive with metastases	19/44 (43%)	21/60 (35%)

*38% of the patients with metastatic disease were still alive at the time of the cut-off analysis

DFS events

	TNT	SoC	p-value
# events / N	72/231	83/230	
Type of first event			
Metastases	38 (52.8%)	54 (65.1%)	
Locoregional relapse	10 (13.9%)	10 (12%)	
Locoregional relapse + metastases	0 (0%)	2 (2.4%)	0.034
Death	10 (13.9%)	13 (15.7%)	
Second cancer	14 (19.4%)	4 (4.8%)	
Number of deaths	42 (18.2%)	56 (24.4%)	
Definitive stoma	32 (13.9%)	34 (14.4%)	ns

Disease-Free Survival



Number at risk

Total Neoadjuvant Therapy	231	211	182	168	162	152	107	67
Chemoradiotherapy	230	190	172	155	148	140	100	64

155 events

7-yr DFS rate:

- 67.6% [95%CI: 60.7-73.6] TNT arm
- 62.5% [95%CI: 55.6-68.6] SoC arm

5-yr DFS rate:

- 73.1% [95%CI: 66.8-78.4] TNT arm
- 65.5% [95%CI: 58.9-71.3] SoC arm

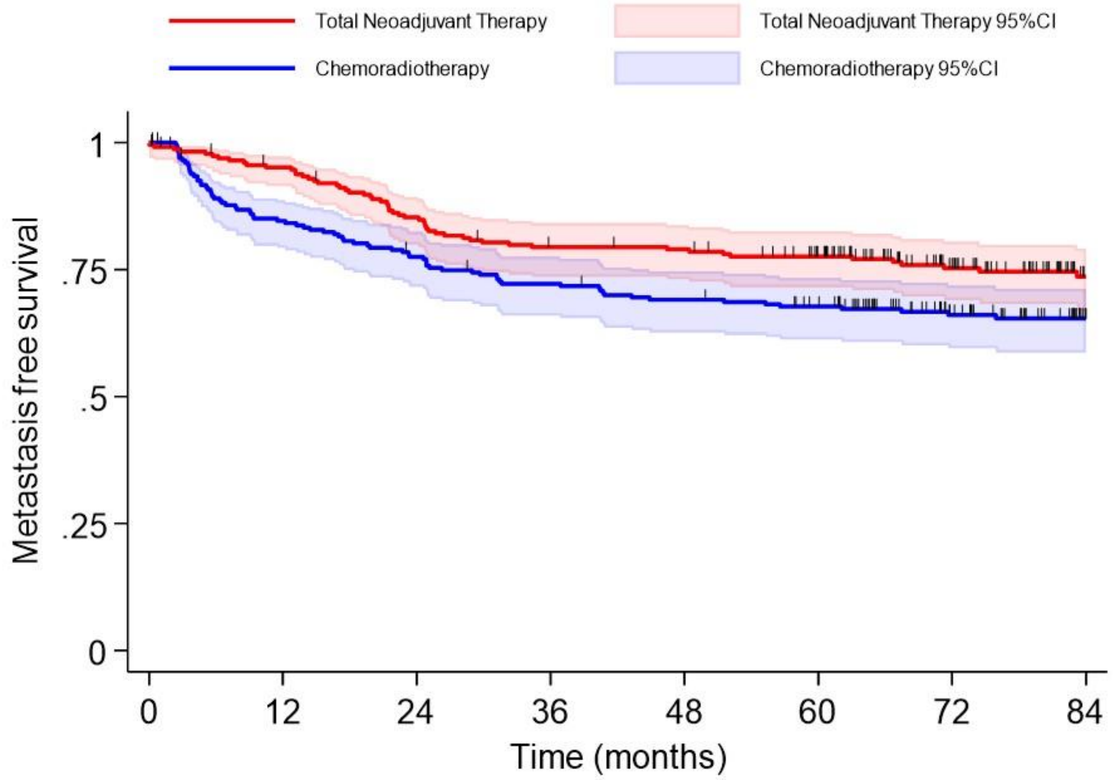
RMST (7-yr), months:

5.73 [0.05-11.41] DFS benefit for TNT arm

p=0.048

Metastasis-free Survival

At 5 years, the cumulative incidence of developing metastatic recurrences was 18.4% in the TNT arm vs 26.6% in the SoC arm.



Number at risk

Total Neoadjuvant Therapy	231	213	190	175	173	159	115	72
Chemoradiotherapy	230	192	175	162	154	145	105	69

138 events

7-yr MFS:

- 73.6% [95%CI: 67.0-79.2] TNT arm
- 65.4% [95%CI: 58.7-71.3] SoC arm

5-yr MFS:

- 77.6% [95%CI: 71.5-82.5] TNT arm
- 67.7% [95%CI: 61.2-73.4] SoC arm

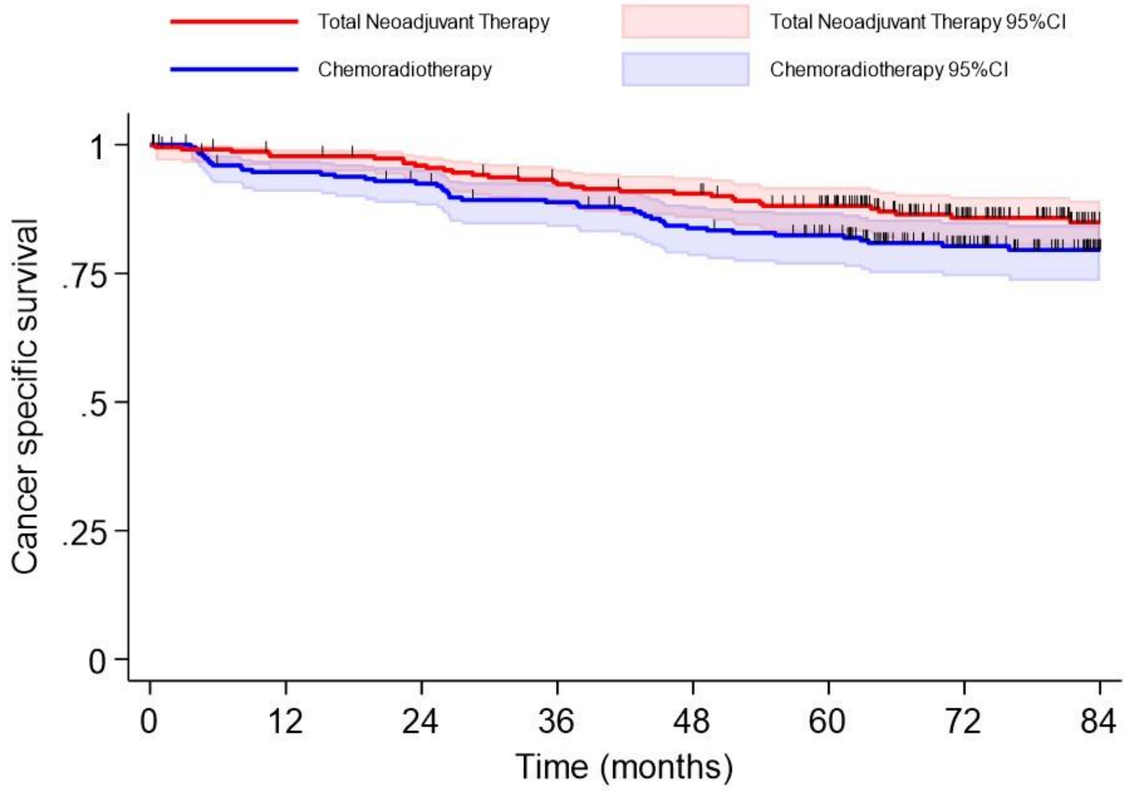
RMST (7-yr), months:

7.1 [1.65-12.63] MFS benefit for TNT arm

p=0.011

PRESENTED BY: T Conroy, MD

Cancer Specific Survival



Number at risk

Total Neoadjuvant Therapy	231	218	212	201	196	179	127	79
Chemoradiotherapy	230	213	206	196	182	171	125	79

80 events

7-yr CSS:

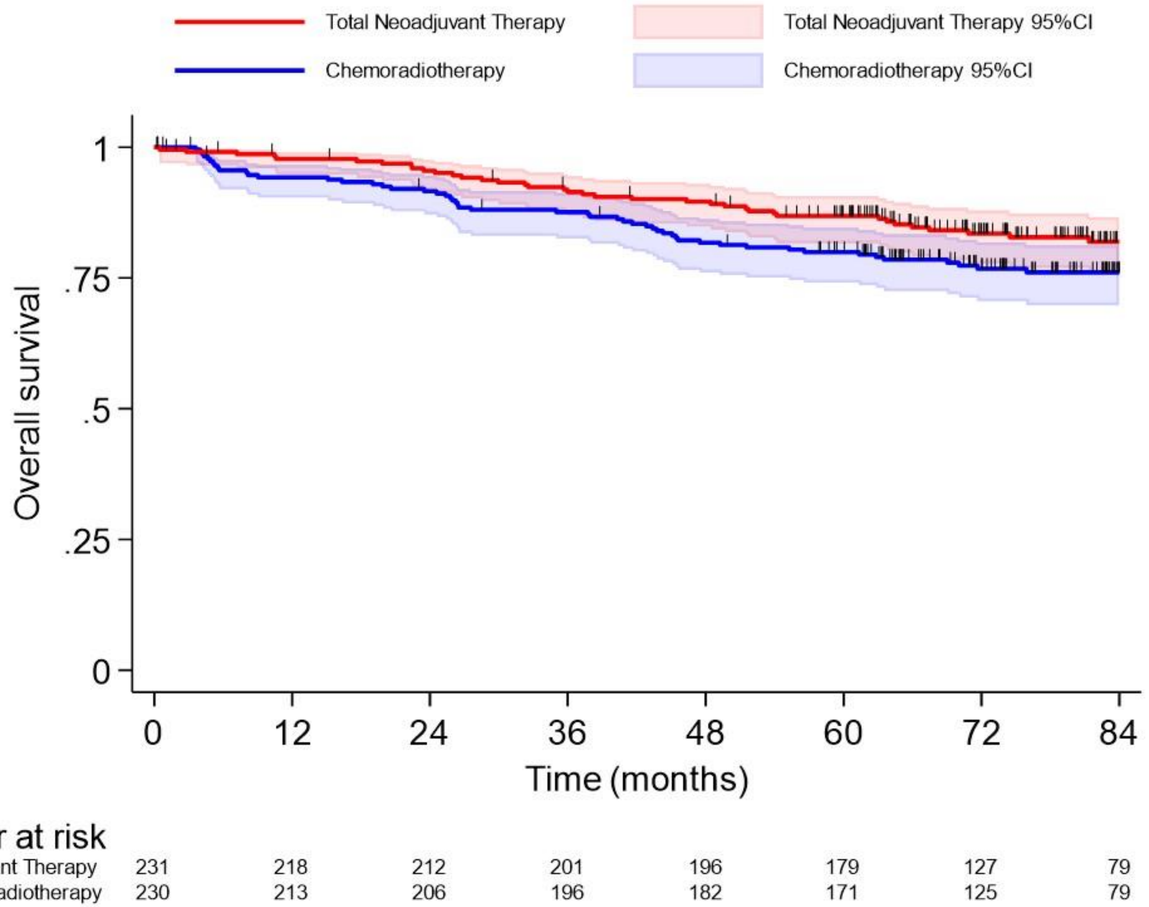
- 84.9% [95%CI: 79.1-89.2] TNT arm
- 79.6% [95%CI: 73.5-84.4] SoC arm

5-yr CSS:

- 88.1% [95%CI: 83.1-91.8] TNT arm
- 82.4% [95%CI: 76.7-86.8] SoC arm

RMST (7-yr), months: 3.84 [-0.02-7.71]
benefit for TNT arm
p = 0.051

Overall Survival



98 events.

7-yr OS:

- 81.9% [95%CI: 75.8-86.7] TNT arm
- 76.1% [95%CI: 69.8-81.3] SoC arm

5-yr OS:

- 86.9% [95%CI: 81.6-90.7] TNT arm
- 80.0% [95%CI: 74.1-84.6] SoC arm

RMST (7-yr), months:

4.37 [0.35-8.38] benefit for TNT arm

p=0.033

Metastatic Colorectal Cancer

LEAP-017 Study Design

Key Eligibility Criteria

- Unresectable and metastatic CRC that progressed on OR after OR could not tolerate standard treatment
- Not MSI-H/dMMR by local testing
- ECOG 0-1

R
1:1
N = 434

Pembrolizumab 400 mg IV Q6W[a]
+
Lenvatinib 20 mg PO QD[a]

Standard of Care (Investigator Choice)
Regorafenib 160 mg QD[b] Q4W
or
Trifluridine/tipiracil 35 mg/m^2 Q4W[c]

Stratification factor

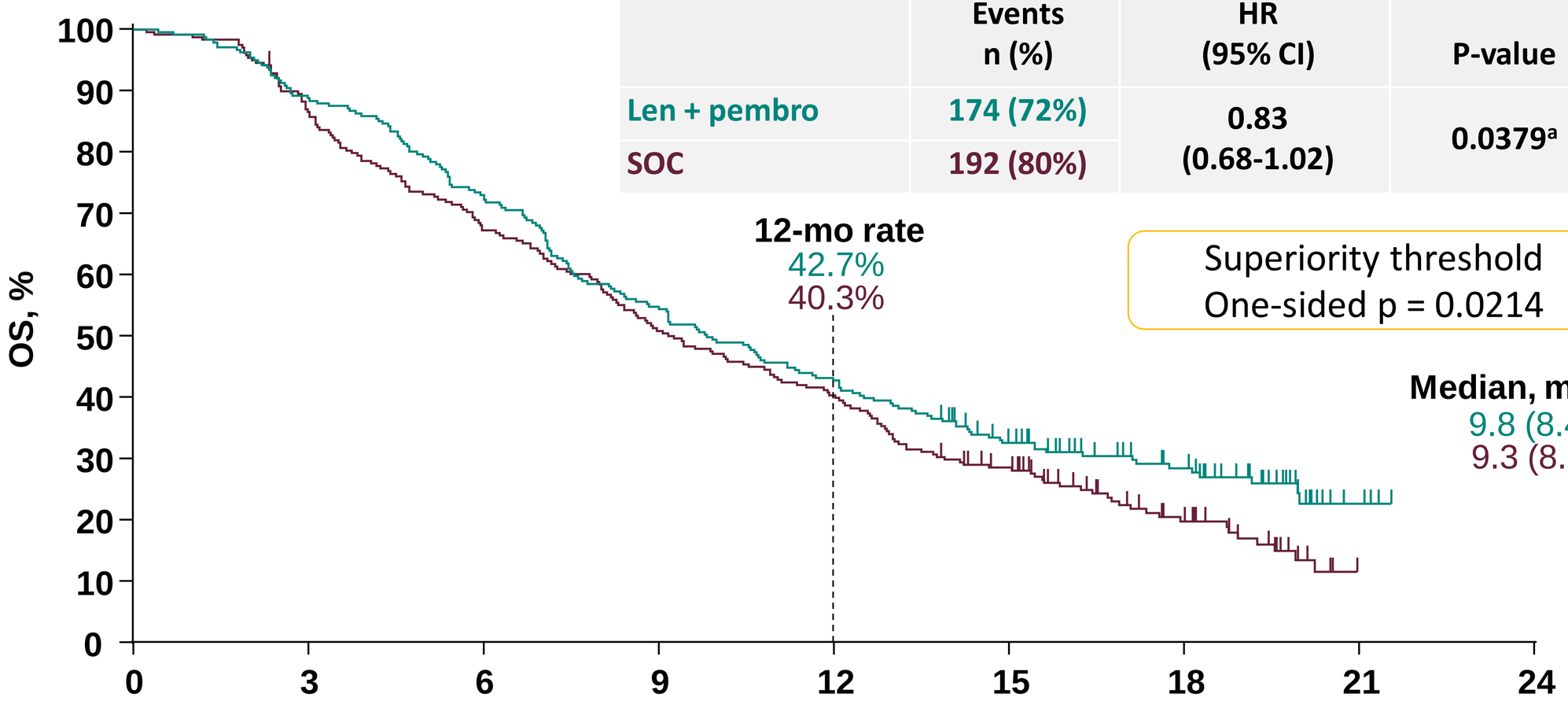
- Presence or absence of liver metastases

Primary endpoint: OS
Key secondary endpoints: PFS, ORR per RECIST, v1.1 by BICR

[a]Treatment with pembrolizumab continued until progression, up to 2 years, and with lenvatinib for >25 cycles until disease progression or treatment discontinuation; [b]On D1-21, no dose on d22-28 with cycle 1 dose escalation from 80 mg QD permitted as per local guidelines; [c]BID on d1-5 and d8-12, no doses on d6-7 or d13-28. Data cut-off February 20, 2023.

Overall Survival (FA)

	Events n (%)	HR (95% CI)	P-value
Len + pembro	174 (72%)	0.83 (0.68-1.02)	0.0379[a]
SOC	192 (80%)		



Superiority threshold
One-sided p = 0.0214

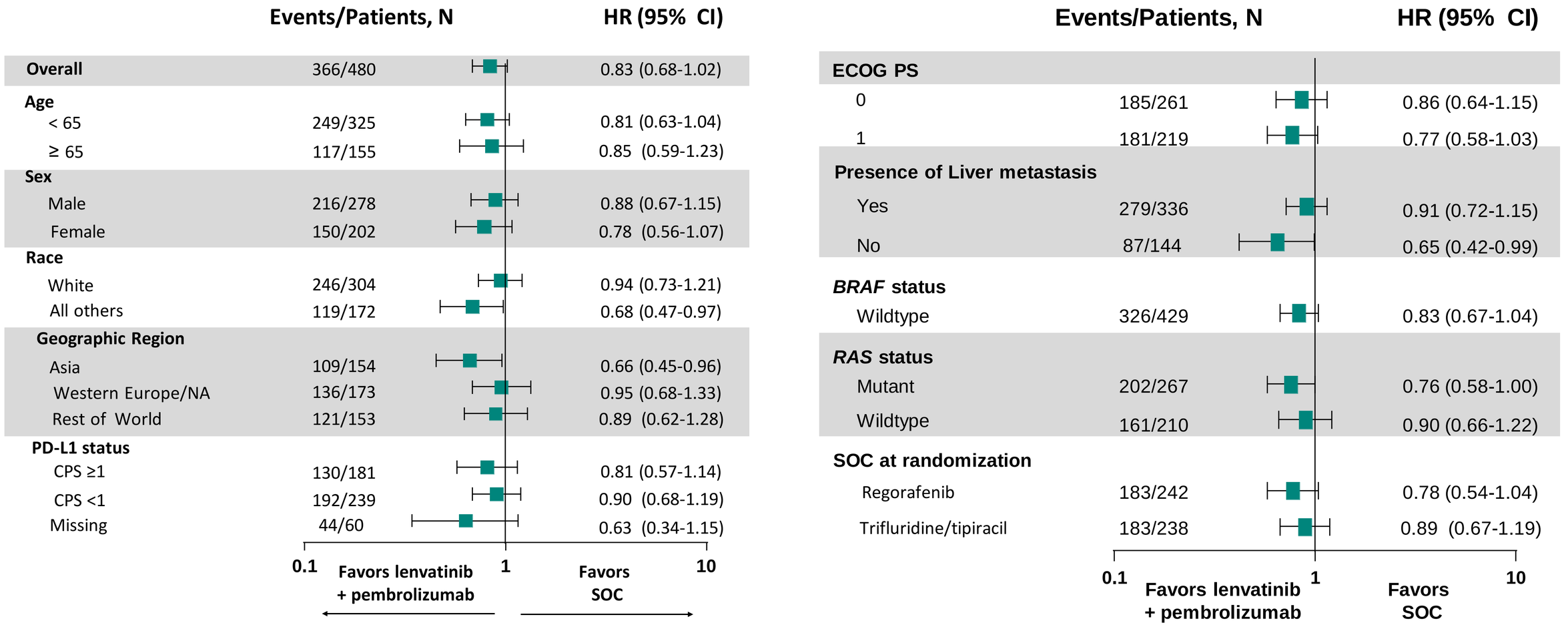
Median, mo (95% CI)
9.8 (8.4-11.6)
9.3 (8.2-10.9)

No. at Risk

Len + pembro	241	214	176	132	103	70	41	5	0
SOC	239	206	160	121	96	63	28	0	0

[a]OS did not meet pre-specified superiority threshold of one-sided p = 0.0214; Data cut-off February 20, 2023.

Overall Survival in Key Subgroups (FA)

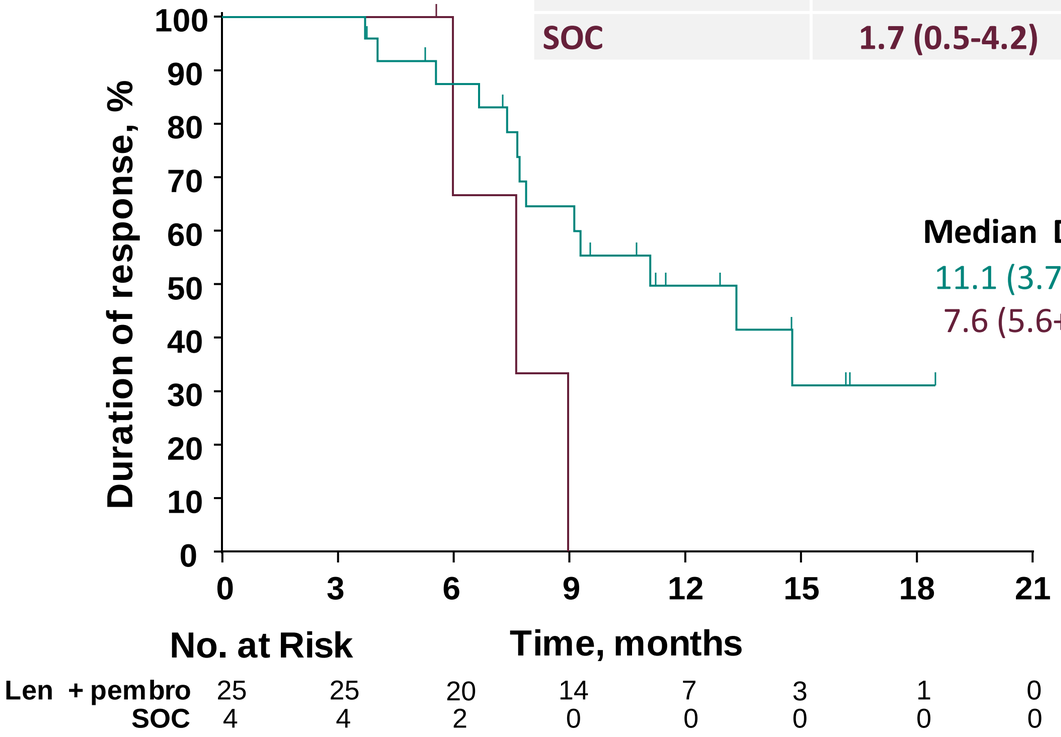


A subcategory with a number of participants <10% of the ITT population is not displayed in the plot; Data cut-off February 20, 2023.

Summary of Response at FA

RECIST v1.1, BICR

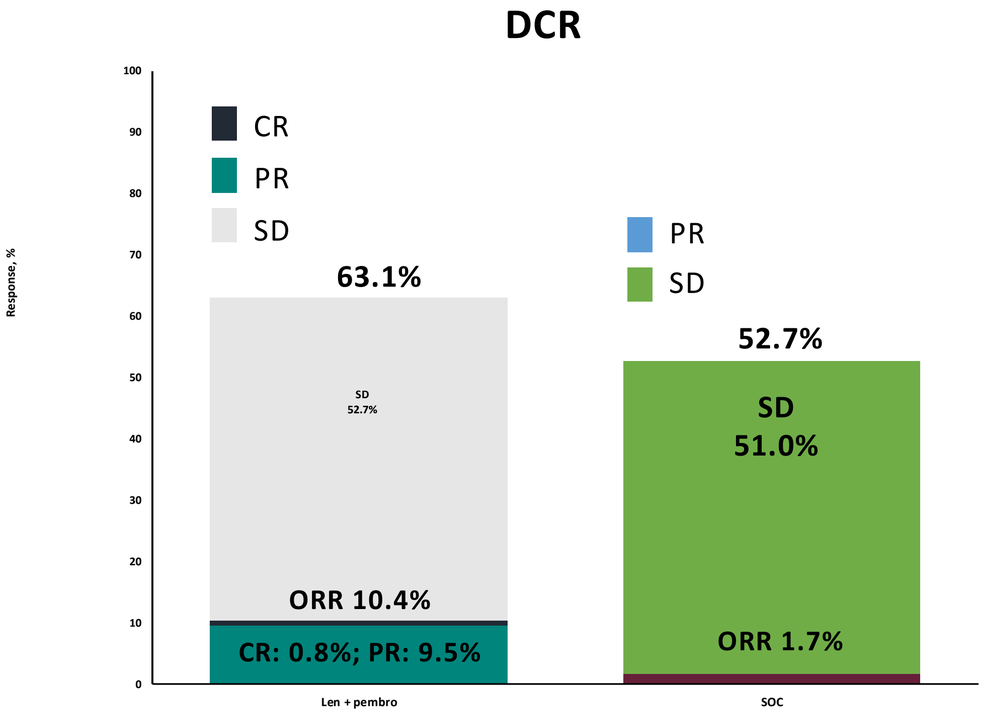
FA	ORR, % (95% CI)	% difference 95% CI)
Len + pembro	10.4 (6.8-14.9)	8.7 (4.7-13.5)
SOC	1.7 (0.5-4.2)	



Median DOR (range)

11.1 (3.7 to 18.5+)

7.6 (5.6+ to 9.0)



[a]ORR was not tested at IA; ORR at IA was 10.4% (95% CI, 6.8-14.9) and 1.7% (95% CI, 0.5-4.2) in the lenvatinib + pembrolizumab and SOC groups; median duration of study follow-up was 18.6 months (range, 14.0-22.5) at FA; Data cut-off February 20, 2023.

Summary and Conclusions

- While there was a trend toward longer OS with lenvatinib plus pembrolizumab versus SOC at FA, the combination did not meet the pre-specified threshold for statistical significance for the OS primary endpoint
  - HR (95% CI) = 0.83 (0.68 - 1.02), p = 0.0379, median OS: 9.8 vs 9.3 mo
- Trend toward improvement in key secondary endpoints of PFS and ORR was observed
  - PFS: HR (95% CI) = 0.69 (0.56 - 0.85)
  - ORR: observed difference (95% CI) = 8.7% (4.7% - 13.5%)
- No new safety signals were observed
- Novel therapeutic options for patients with previously treated non-MSI-H/dMMR mCRC remain an area of unmet need

2023 ASCO ANNUAL MEETING

T-DXd in Patients With HER2-Overexpressing/Amplified (HER2+) Metastatic Colorectal Cancer (mCRC): Primary Results From the Multicenter, Randomized, Phase 2 DESTINY-CRC02 Study

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

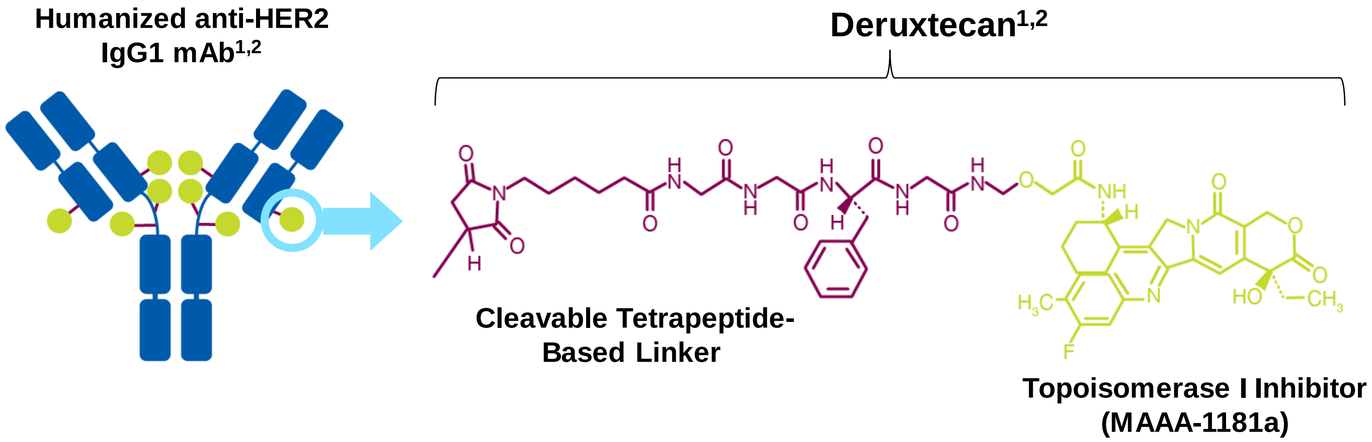
June 4, 2023

Additional authors: Salvatore Siena, Atsuo Takashima, Takeshi Kato, Marc Van Den Eynde, Maria Di Bartolomeo, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Christina Gravalos Castro, John Strickler, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Takayuki Yoshino

T-DXd Was Designed With 7 Key Attributes

An ADC composed of 3 components[1,2]:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:
  - A topoisomerase I inhibitor, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker



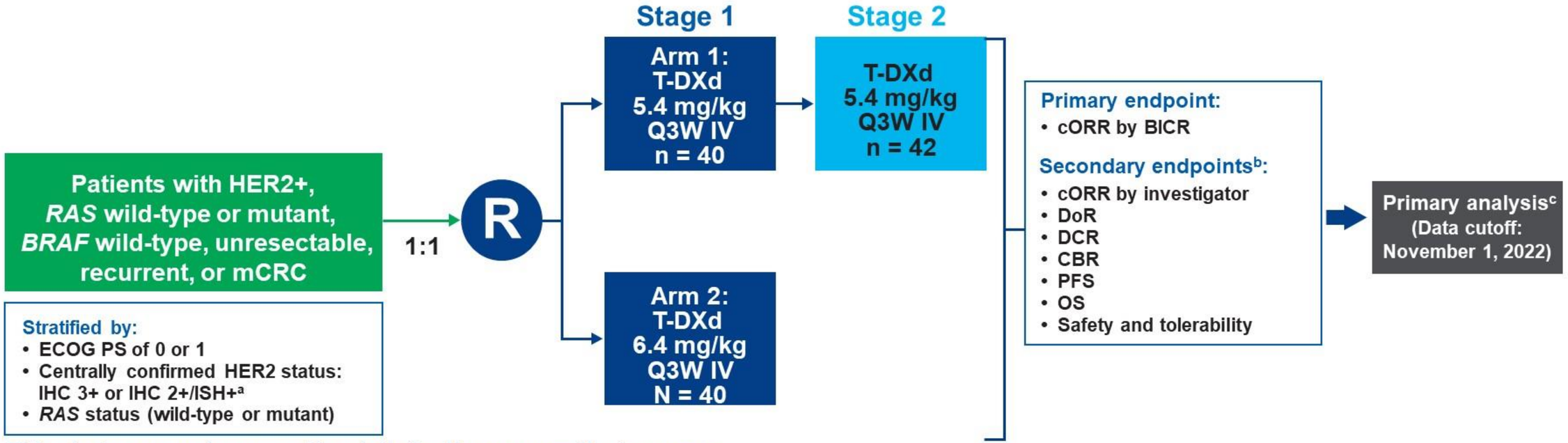
1. Payload MOA: topoisomerase I inhibitor[1,2,a]
2. High potency of payload[1,2,a]
3. High DAR ≈ 8
4. Payload with short systemic half-life[1,2,a]
5. Stable linker-payload[1,2,a]
6. Tumor-selective cleavable linker[1,2,a]
7. Membrane permeable payload[1,3,a]

ADC, antibody drug conjugate; DAR, drug-antibody ratio; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; MOA, mechanism of action; T-DXd, fam-trastuzumab deruxtecan-nxki.
[a]The clinical relevance of these features is under investigation.
References: **1.** Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. **2.** Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. **3.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046

DESTINY-CRC02 Study Design

A randomized, blinded, 2-stage, 2-arm, multicenter, global, phase 2 study (NCT04744831)

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



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

BICR, blinded independent central review; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Both investigators and patients were blind to treatments.
[a]HER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay (IUO). [b]Exploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator. [c]Primary analysis occurred ≥6 months after the last patient had been enrolled or when all patients discontinued from the study, whichever was earlier.

Baseline Characteristics (cont.)

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
HER2/*RAS* status, n (%)				
IHC 2+ ISH+/wild-type	7 (17.5)	5 (11.9)	12 (14.6)	6 (15.0)
IHC 2+ ISH+/mutant	1 (2.5)	5 (11.9)	6 (7.3)	0
IHC 3+/wild-type	27 (67.5)	29 (69.0)	56 (68.3)	28 (70.0)
IHC 3+/mutant	5 (12.5)	3 (7.1)	8 (9.8)	6 (15.0)
Liver metastases at baseline, n (%)	29 (72.5)	30 (71.4)	59 (72.0)	26 (65.0)
CNS metastases at baseline, n (%)	3 (7.5)	0	3 (3.7)	1 (2.5)
Primary tumor site, n (%)				
Left colon[a]	32 (80.0)	29 (69.0)	61 (74.4)	34 (85.0)
Rectum	15 (37.5)	12 (28.6)	27 (32.9)	19 (47.5)
Right colon[b]	8 (20.0)	13 (31.0)	21 (25.6)	6 (15.0)

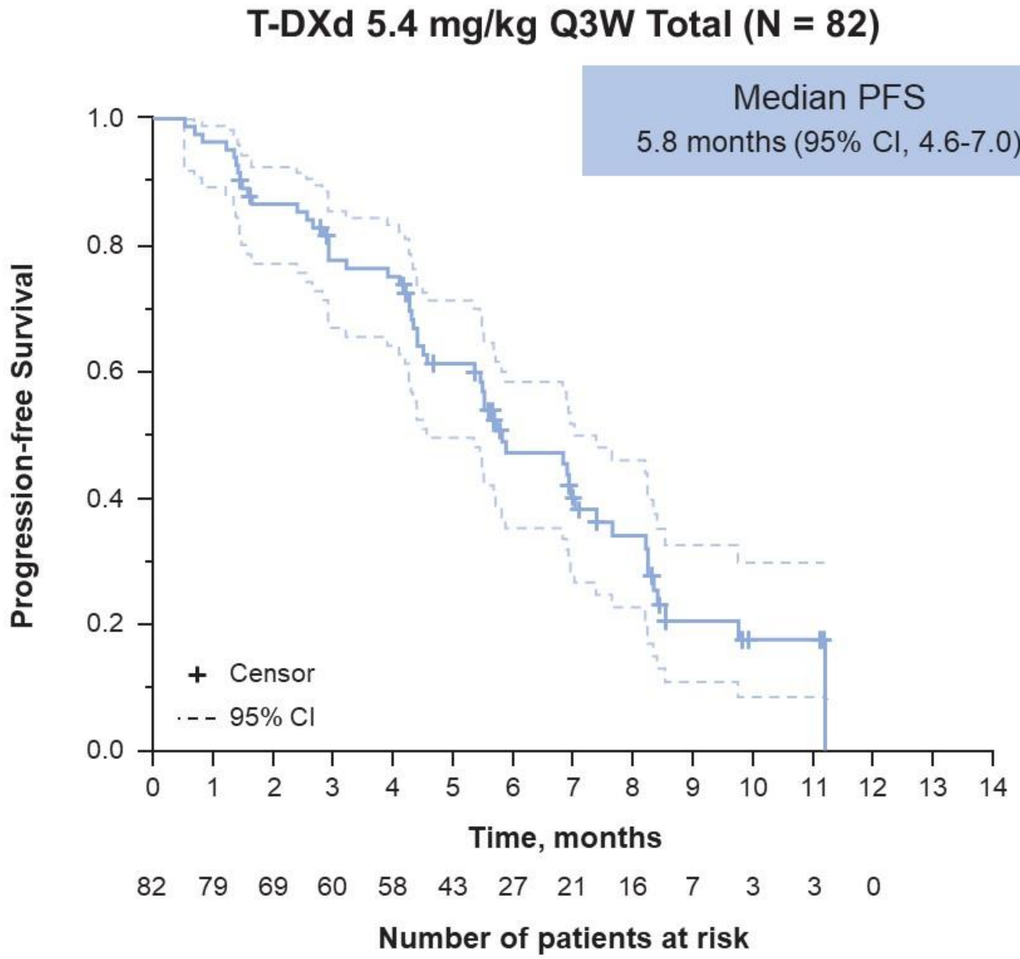
CNS, central nervous system; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
[a]Includes rectum, sigmoid, and descending. [b]Includes cecum, ascending, and transverse.

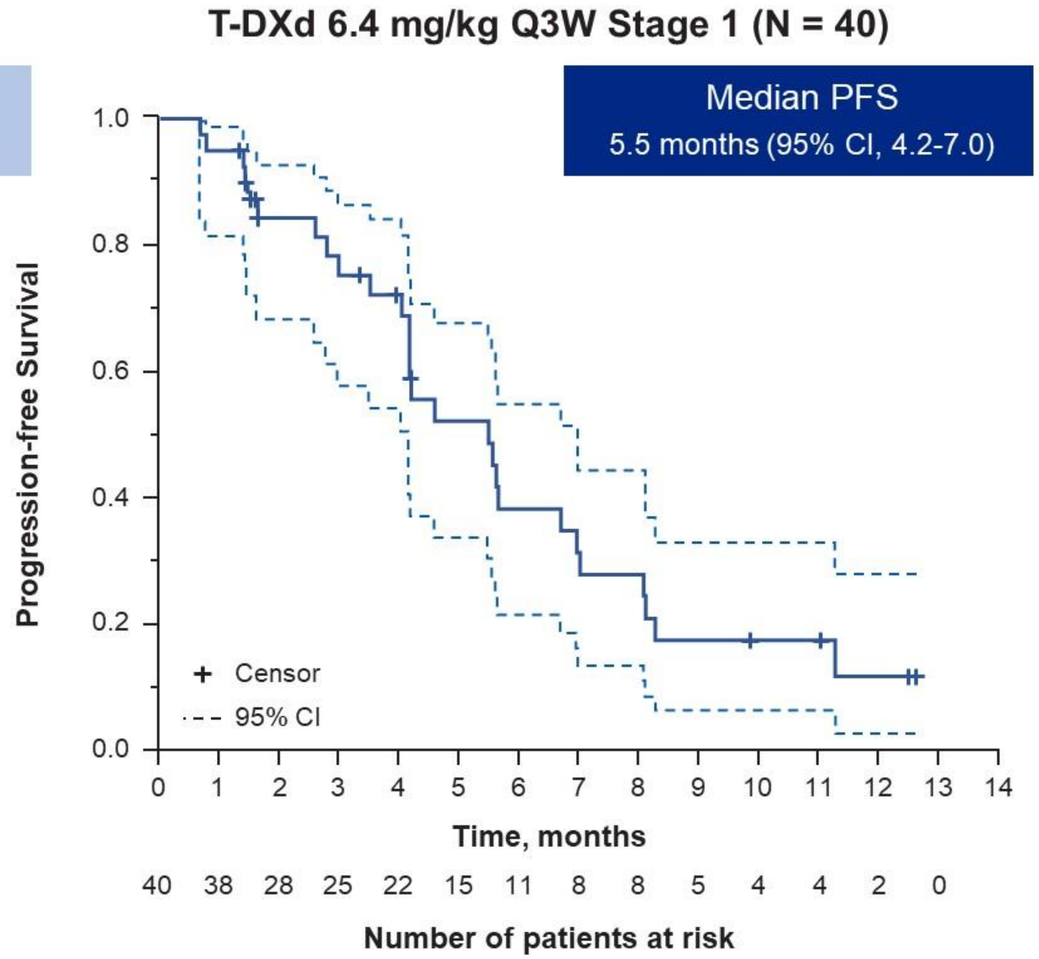
Efficacy Results

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; mo, month; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease; T-DXd, trastuzumab deruxtecan.

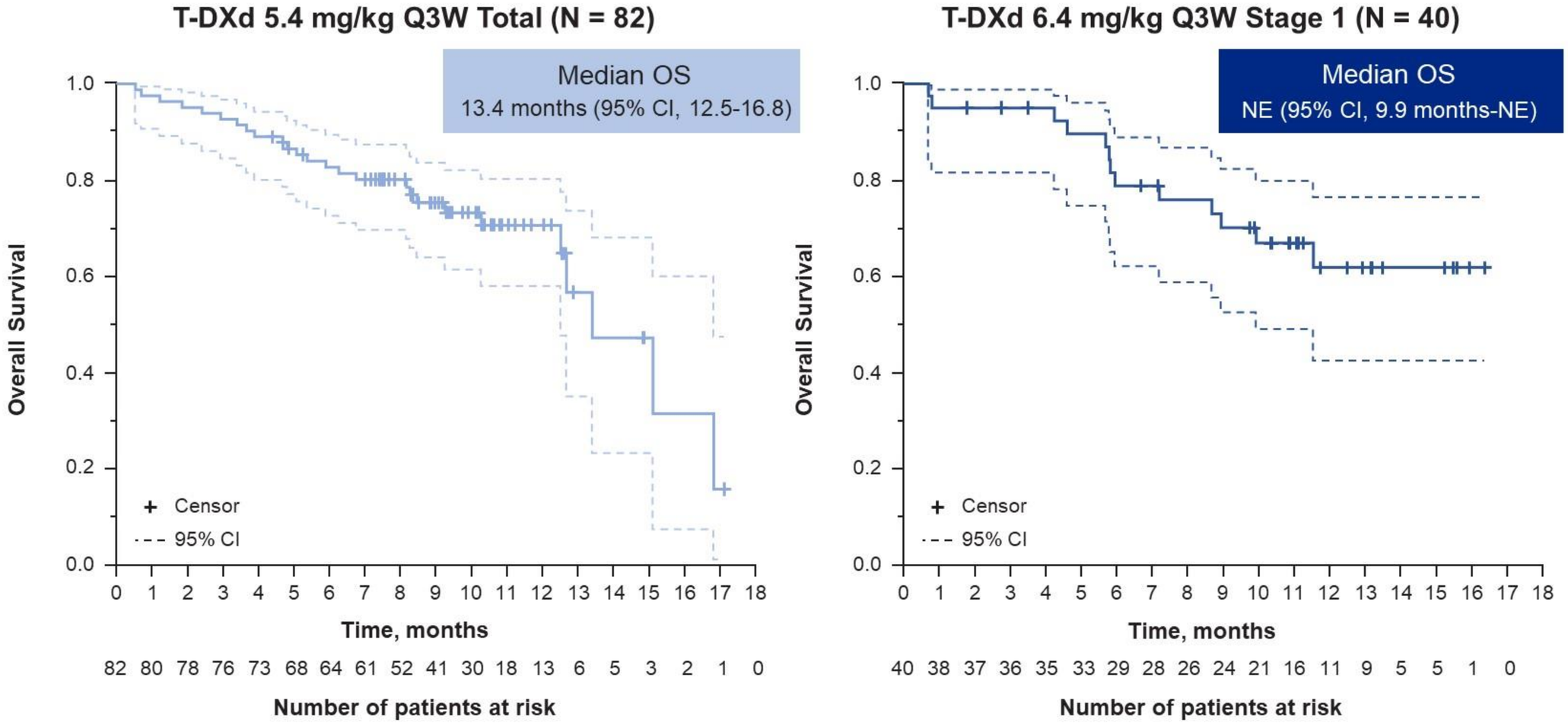
Median Progression-Free Survival by BICR





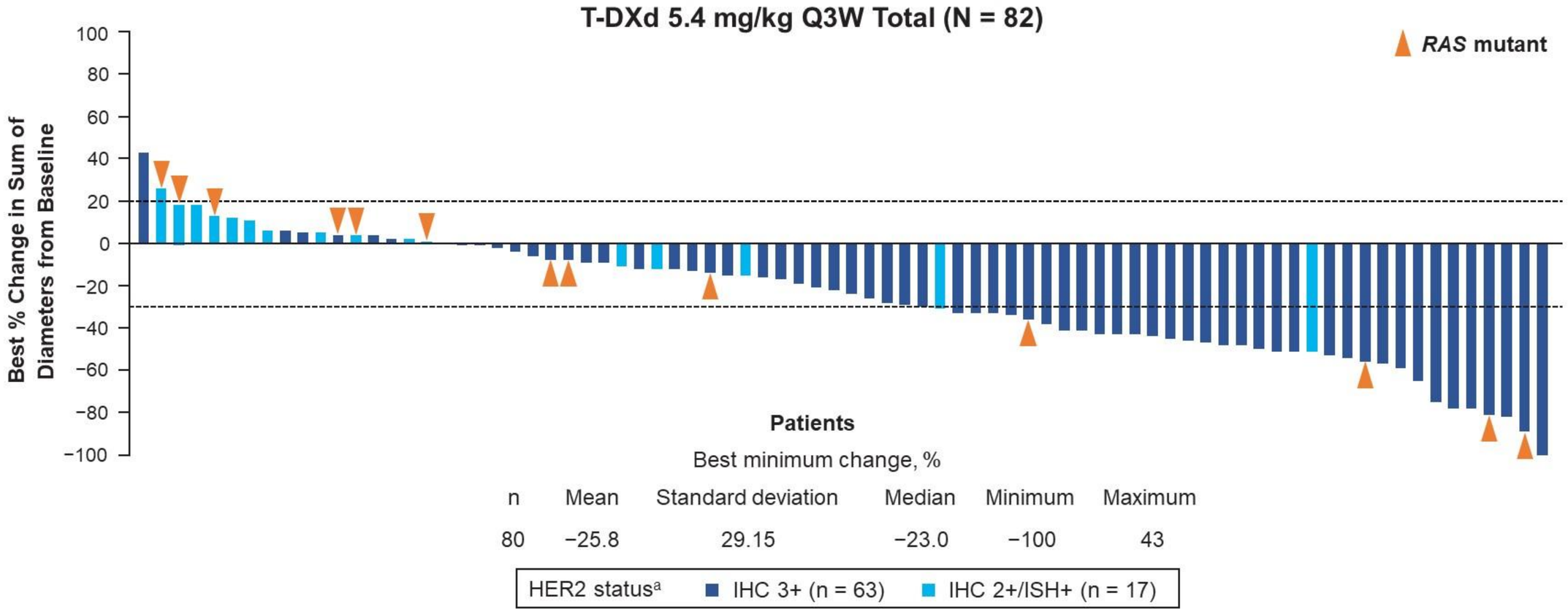
BICR, blinded independent central review; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Median Overall Survival



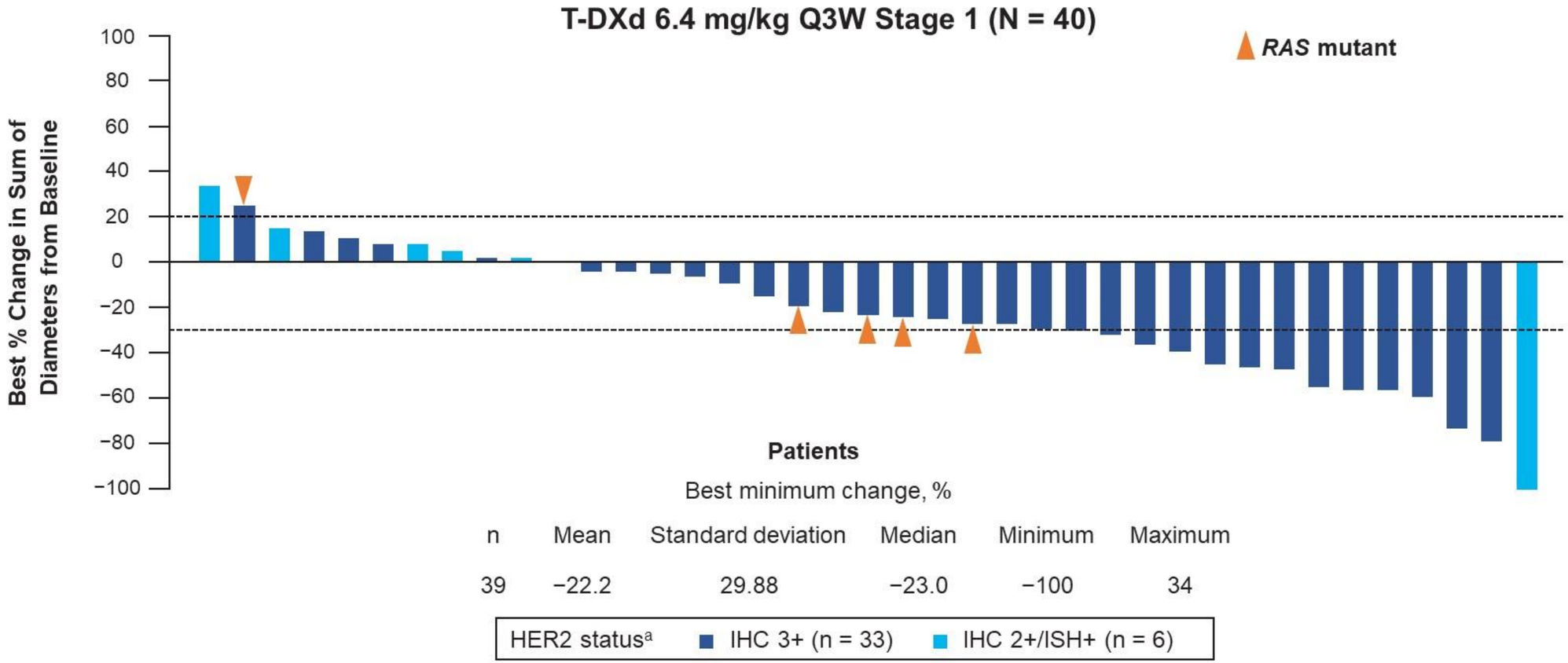
NE, not evaluable; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Best Percentage Change in Sum of Diameters by BICR for T-DXd 5.4 mg/kg



BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.
[a]HER2 status was assessed by central laboratory.

Best Percentage Change in Sum of Diameters by BICR for T-DXd 6.4 mg/kg



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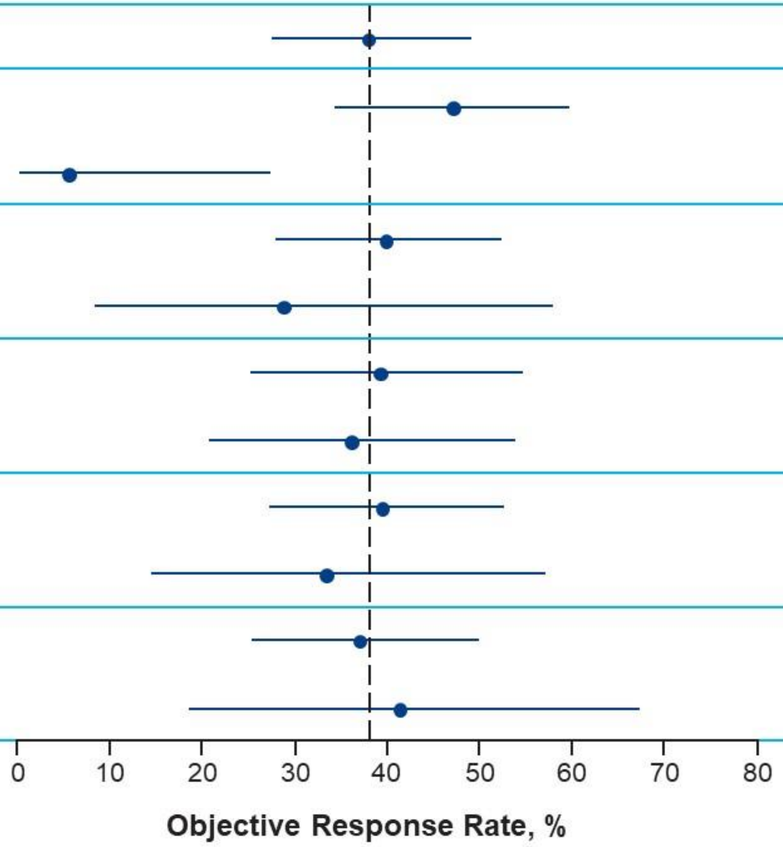
Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.
[a]HER2 status was assessed by central laboratory.

Best Overall Response by BICR by Subgroup With T-DXd 5.4 mg/kg

		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



BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All *RAS*m responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.

Adjudicated Drug-Related ILD/Pneumonitis by Independent Adjudication Committee

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
Any grade	4 (9.8)	3 (7.1)	7 (8.4)	5 (12.8)
Grade 1	1 (2.4)	0	1 (1.2)	2 (5.1)
Grade 2	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	1 (2.6)[b]

ILD, interstitial lung disease; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.
[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

FRESCO-2 Study Design

Patient Eligibility

- Prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if *RAS* wild type, an anti-EGFR therapy
- Progression on, or intolerance to, TAS-102 and/or regorafenib
- Prior treatment with an immune checkpoint inhibitor or BRAF inhibitor if indicated

R 2:1

N=687

Fruquintinib 5 mg PO, QD
(3 weeks on, 1 week off)
+
BSC
(N=458)

Placebo 5 mg PO, QD
(3 weeks on, 1 week off)
+
BSC
(N=229)

Treatment until progression or unacceptable toxicity

Stratification Factors

- Prior therapy (TAS-102 vs regorafenib vs TAS-102 and regorafenib)
- *RAS* mutational status (wild-type vs mutant)
- Duration of metastatic disease (≤18 months vs >18 months)

Mechanism of action: Highly selective oral tyrosine kinase inhibitor of VEGFRs-1, -2, and -3

Note: To ensure the patient population is reflective of clinical practice, the number of patients treated with prior regorafenib was limited to 344 patients (50%)

BSC, best supportive care.
NCT04322539.

PARIS 2022 ESMO congress

Dasari A …..Eng et al. ESMO 2022; Dasari et al: Lancet, June 15, 2023

Fast Facts about FRESCO-2

- Approved in China (2018)
- Only phase III trial opened at that time
- Due to lack of trials, we wanted to be able to offer to all possible patients
- Placebo arm due to no other treatments available after lonsurf and/or rego
- Completed enrollment quicker than expected despite COVID-19
  - Unmet need
- Supply chain issue resulted in ↓ tubes for ctDNA correlatives

Patient and Disease Characteristics

ITT Population

Enrollment: Sep 2020 to Dec 2021

Data Cutoff: 24 June 2022

Characteristic, n (%)		Fruquintinib (N=461)	Placebo (N=230)
Age, y	Median (range)	64 (25, 82)	64 (30, 86)
	≥ 65	214 (46.4)	111 (48.3)
Sex	Female	216 (46.9)	90 (39.1)
	Male	245 (53.1)	140 (60.9)
Region	North America	82 (17.8)	42 (18.3)
	Europe	329 (71.4)	166 (72.2)
	Asia Pacific	50 (10.8)	22 (9.6)
ECOG PS	0	196 (42.5)	102 (44.3)
	1	265 (57.5)	128 (55.7)
Primary site at 1st diagnosis	Colon left	192 (41.6)	92 (40.0)
	Colon right	97 (21.0)	53 (23.0)
	Colon left and right	4 (0.9)	2 (0.9)
	Colon unknown	25 (5.4)	13 (5.7)
	Rectum only	143 (31.0)	70 (30.4)
Liver metastases	Yes	339 (73.5)	156 (67.8)

Characteristic, n (%)		Fruquintinib (N=461)	Placebo (N=230)
Duration of metastatic disease	≤ 18 mo	37 (8.0)	13 (5.7)
	> 18 mo	424 (92.0)	217 (94.3)
RAS status	WT	170 (36.9)	85 (37.0)
	Mutant	291 (63.1)	145 (63.0)
BRAF V600E mutation	No	401 (87.0)	198 (86.1)
	Yes	7 (1.5)	10 (4.3)
	Other/Unknown	5 (11.5)	22 (9.6)
Number of previous treatment lines in metastatic disease			
Median		4 (3–6)	4 (3–6)
≤3		125 (27%)	64 (28%)
>3		336 (73%)	166 (72%)
Previous therapies			
VEGF inhibitor		445 (97%)	221 (96%)
EGFR inhibitor		180 (39%)	88 (38%)
Immune checkpoint inhibitor		21 (5%)	11 (5%)
BRAF inhibitor		9 (2%)	7 (3%)
Previous trifluridine–tipiracil or regorafenib			
Trifluridine–tipiracil		240 (52%)	121 (53%)
Regorafenib		40 (9%)	18 (8%)
Both		181 (39%)	91 (40%)

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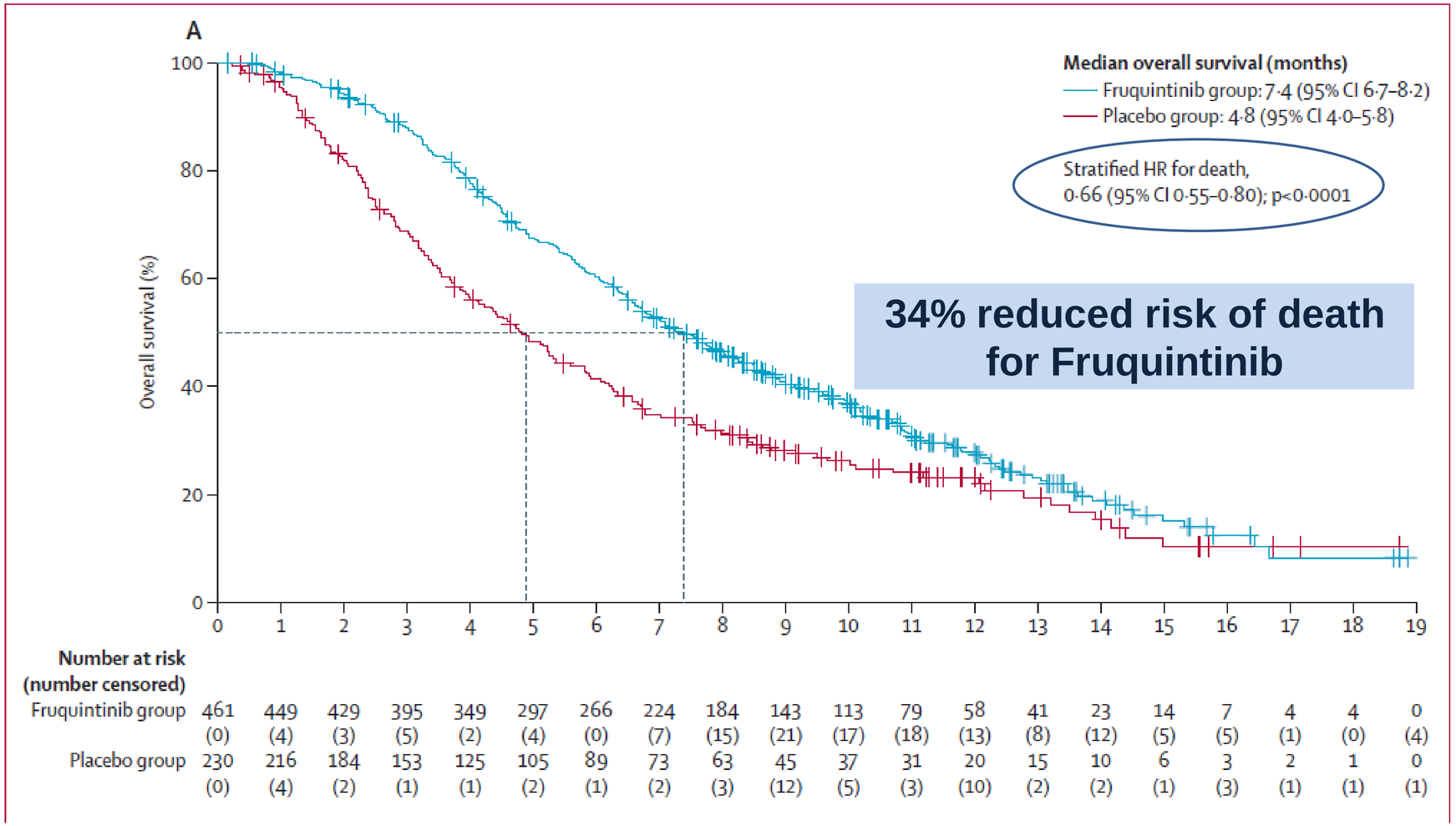
FRESCO-2: Primary Endpoint - OS

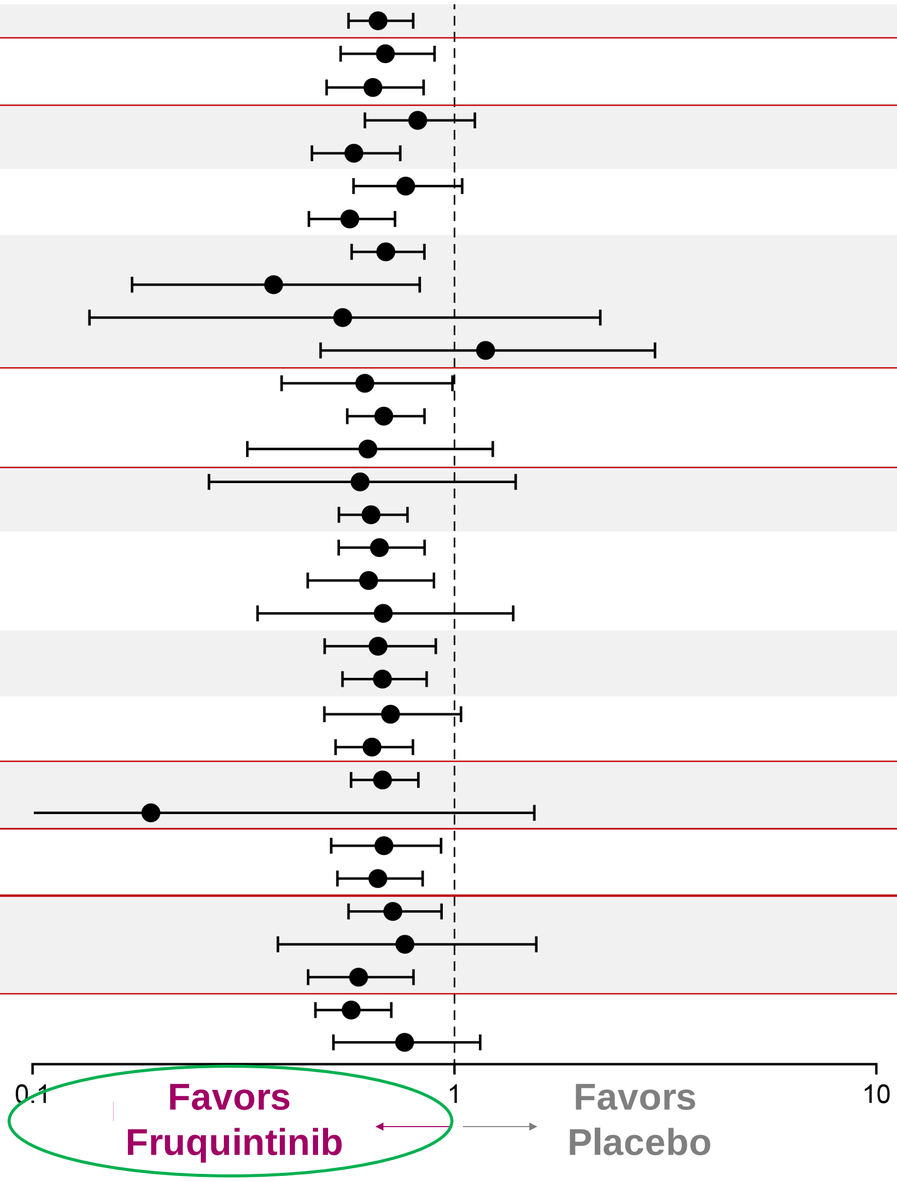


Dasari…Eng et al: The Lancet, 2023

OS Subgroup Analysis

ITT Population

Subgroup		Fruquintinib n/N	Placebo n/N	HR (95% CI)
ITT population		317/461	173/230	0.662 (0.549, 0.800)
Age	< 65	171/247	89/119	0.694 (0.534, 0.903)
	≥ 65	146/214	84/111	0.648 (0.494, 0.851)
Sex	Female	149/216	61/90	0.828 (0.609, 1.125)
	Male	168/245	112/140	0.584 (0.456, 0.749)
ECOG PS	0	121/196	67/102	0.775 (0.573, 1.050)
	1	196/265	106/128	0.571 (0.499, 0.728)
Race	Caucasian	260/367	145/192	0.696 (0.567, 0.854)
	Asian	24/43	14/18	0.377 (0.171, 0.833)
	African American	7/13	5/7	0.550 (0.135, 2.231)
	Other	26/38	9/13	1.199 (0.478, 3.008)
Region	North America	50/82	29/42	0.620 (0.387, 0.995)
	Europe	237/329	130/166	0.688 (0.554, 0.855)
	Asia Pacific	30/50	14/22	0.631 (0.321, 1.241)
Duration of metastatic disease	≤ 18 mo	30/37	8/13	0.605 (0.260, 1.406)
	> 18 mo	287/424	165/217	0.642 (0.529, 0.779)
Primary tumor site at 1st diagnosis	Colon	195/279	109/137	0.672 (0.528, 0.855)
	Rectum	99/143	49/70	0.633 (0.446, 0.900)
	Colon and Rectum	23/39	15/23	0.686 (0.339, 1.388)
RAS status	WT	119/170	62/85	0.667 (0.489, 0.909)
	Mutant	198/291	111/145	0.683 (0.539, 0.865)
# of prior treatment lines in metastatic disease	≤ 3	80/125	45/64	0.714 (0.488, 1.043)
	>3	237/336	128/166	0.645 (0.519, 0.802)
Prior VEGFi	Yes	306/445	167/221	0.683 (0.565, 0.827)
	No	11/16	6/9	0.193 (0.024, 1.557)
Prior EGFRi	Yes	127/180	64/88	0.689 (0.507, 0.936)
	No	190/281	109/142	0.666 (0.524, 0.846)
Prior TAS-102 and Regorafenib	TAS-102	165/240	88/121	0.723 (0.557, 0.938)
	Regorafenib	25/40	12/18	0.772 (0.379, 1.573)
	Both	127/181	73/91	0.600 (0.447, 0.805)
Liver metastases	Yes	255/339	132/156	0.576 (0.465, 0.713)
	No	62/122	41/74	0.771 (0.513, 1.158)



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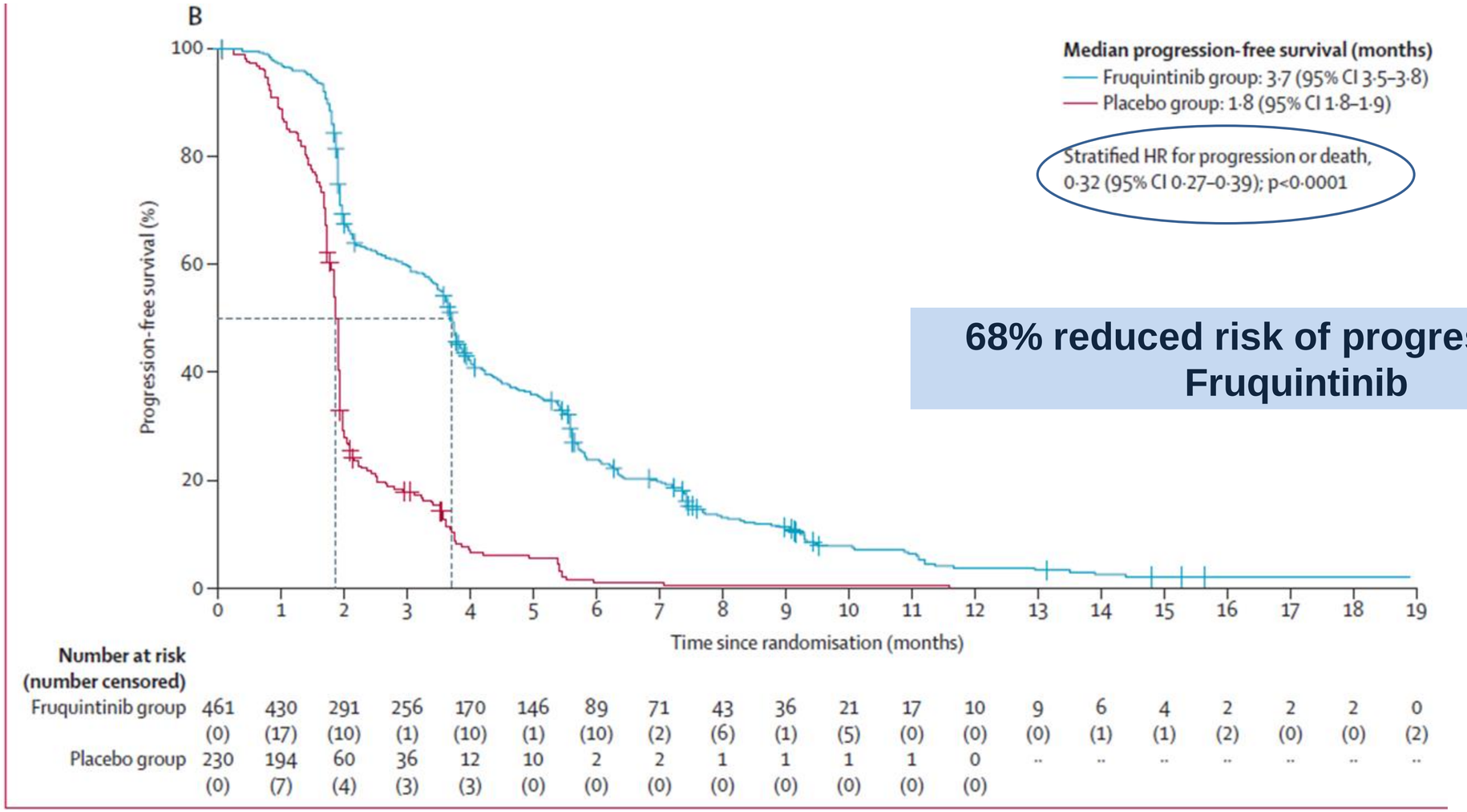
FRESCO-2: PFS



68% reduced risk of progression for Fruquintinib

Dasari…Eng et al: The Lancet, 2023

Analysis of Fruquintinib Adverse Events of Special Interest from The Phase 3 FRESCO-2 study

Table 3: Treatment-emergent AESIs (any grade, PT occurring in ≥5% patients)

AESI category, n (%)* PT	Fruquintinib (n=456)		Placebo (n=230)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension†	179 (38.4)	65 (14.0)	20 (8.7)	2 (0.9)
Hypertension	168 (36.8)	62 (13.6)	20 (8.7)	2 (0.9)
Dermatological toxicity	157 (34.4)	31 (6.8)	27 (11.7)	1 (0.4)
Palmar-plantar erythrodysesthesia syndrome	88 (19.3)	29 (6.4)	6 (2.6)	0
Liver function test abnormality	113 (24.8)	38 (8.3)	44 (19.1)	21 (9.1)
AST increased	48 (10.5)	10 (2.2)	11 (4.8)	3 (1.3)
ALT increased	47 (10.3)	14 (3.1)	9 (3.9)	1 (0.4)
Blood bilirubin increased	36 (7.9)	11 (2.4)	11 (4.8)	6 (2.6)
Thyroid dysfunction	123 (27.0)	2 (0.4)	4 (1.7)	0
Hypothyroidism	94 (20.6)	2 (0.4)	1 (0.4)	0
Thyroid-stimulating hormone increased	32 (7.0)	0	3 (1.3)	0
Infection	96 (21.1)	30 (6.6)	29 (12.6)	13 (5.7)
Proteinuria	80 (17.5)	8 (1.8)	12 (5.2)	2 (0.9)
Hemorrhage	65 (14.3)	8 (1.8)	22 (9.6)	4 (1.7)

Analysis of Fruquintinib Adverse Events of Special Interest from The Phase 3 FRESCO-2 study

Table 4: Selected treatment-emergent AESIs leading to dose reduction and dose discontinuation

PT, n (%)	Patients with AESI PT leading to dose reduction				Patients with AESI PT leading to dose discontinuation			
	Fruquintinib (n=456)		Placebo (n=230)		Fruquintinib (n=456)		Placebo (n=230)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension	17 (3.7)	15 (3.3)	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)	0	0
Palmar-plantar erythrodysesthesia syndrome	24 (5.3)	14 (3.1)	0	0	3 (0.7)	2 (0.4)	0	0
AST increased	1 (0.2)	0	0	0	0	0	1 (0.4)	0
ALT increased	2 (0.4)	1 (0.2)	0	0	1 (0.2)	1 (0.2)	1 (0.4)	0
Blood bilirubin increased	6 (1.3)	0	0	0	1 (0.2)	0	0	0
Proteinuria	8 (1.8)	2 (0.4)	1 (0.4)	1 (0.4)	4 (0.9)	1 (0.2)	0	0

PRESENTED BY: Cathy Eng, MD, FACP, FASCO

Circulating Tumor DNA (ctDNA)

2023 ASCO ANNUAL MEETING

Circulating tumor DNA dynamics as an early predictor of recurrence in patients with radically resected colorectal cancer: Updated results from GALAXY study in the CIRCULATE-Japan

Eiji Oki[1], Daisuke Kotani[2], Yoshiaki Nakamura[2], Saori Mishima[2], Hideaki Bando[2], Hiroki Yukami[3], Koji Ando[4], Masaaki Miyo[5], Jun Watanabe[6], Keiji Hirata[7], Naoya Akazawa[8], Kun-Huei Yeh[9], George Laliotis[10], Shruti Sharma[10], Minetta C. Liu[10], Hiroya Taniguchi[11], Ichiro Takemasa[5], Takeshi Kato[12], Masaki Mori[13], Takayuki Yoshino[2]

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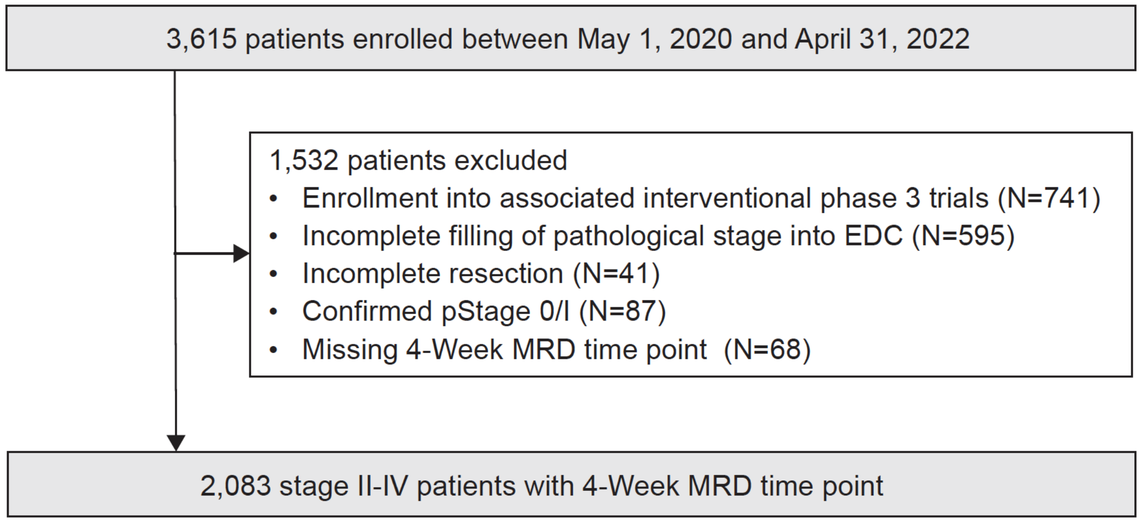
Background and Consort diagram

- Postoperative circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) is reported to be associated with a high risk of recurrence (Kotani D et al. Nature Med 2023)
- Here, we present an updated analysis and the lead time interval (LTI) of ctDNA positivity to radiographic recurrence in patients (pts) with radically resected colorectal cancer (CRC), stage II-IV in the observational GALAXY study (UMIN000039205).



Median follow-up: 496 days

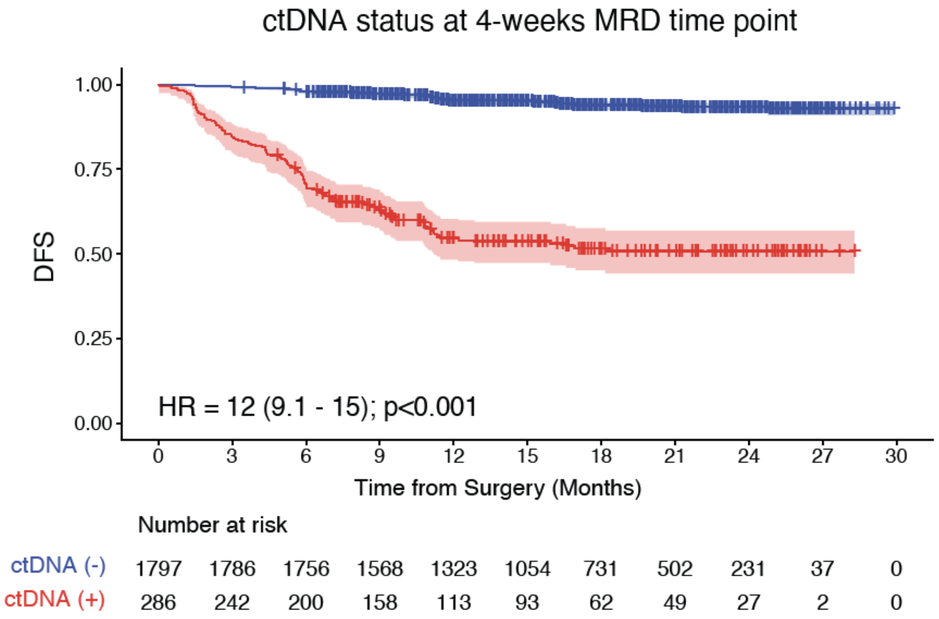
Data cut-off: November 10, 2022

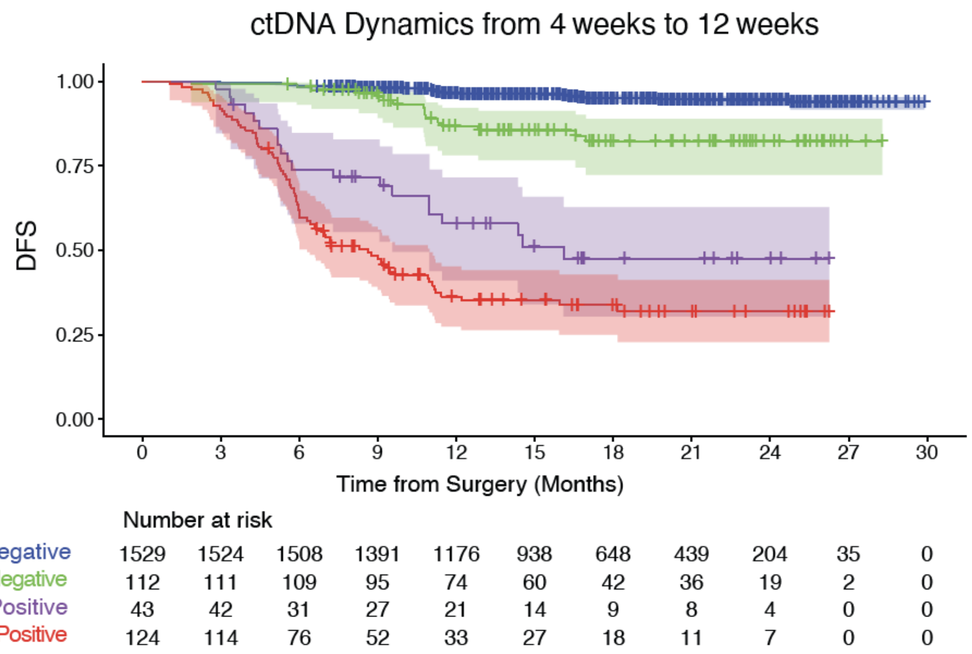
Characteristic	N = 2,083[1]
Gender	
Male	1,125 (54%)
Female	958 (46%)
Age	69 (25 - 95)
Tumor Location	
Left	1,447 (70%)
Right	477 (22%)
Unclassified	159 (8%)
Pathologic Stage	
II	736 (35%)
III	902 (43%)
IV	114 (6%)
Unclassified	331 (16%)
MSI Status	
MSS	1,775 (85%)
MSI-H	207 (10%)
Unclassified	101 (5%)
Follow up (months)	16.3 (0.8 - 30)
Lead Time (months)	4.7 (0 - 17.3)

Characteristic	N = 2,083[1]
BRAF Status	
BRAF wt	1,830 (88%)
BRAF V600E	169 (8%)
Unclassified	84 (4%)
RAS Status	
RAS wt	1,150 (55%)
RAS mut	856 (41%)
Unclassified	77 (4%)
Post-surgery treatment	
Observation	1,376 (66%)
ACT	707 (34%)
ctDNA status MRD time point	
ctDNA negative	1,797 (86%)
ctDNA positive	286 (14%)
ctDNA clearance from 4 to 12 weeks	
Clearance	112 (47%)
No Clearance	124 (53%)

[1]n (%); Median (Range)

ctDNA dynamics between weeks 4 and 12 post surgery is prognostic of DFS





Dynamics	ctDNA Negative	ctDNA Positive
Events (n)	96/1797 (5.3%)	130/286 (45.5%)
18M - DFS	93.9 (92.5 - 95)	51.6 (45.2 - 57.6)
HR	Reference	12
95% CI	Not applicable	9.1 - 15
P	Not applicable	<0.001

Dynamics	Persistently Negative	Converted Negative	Converted Positive	Persistently Positive
Events (n)	69/1529 (4.5%)	16/112 (14.3%)	20/43 (46.5%)	78/124 (62.9%)
18M - DFS	94.9 (93.5 - 96)	82.2 (72.3 - 88.9)	47.4 (30.4 - 62.7)	33.8 (25 - 42.8)
HR	Reference	3.5	14.5	25.4
95% CI	Not applicable	1.9 - 5.8	8.8 - 23.8	18.3 - 35.3
P	Not applicable	<0.001	<0.001	<0.001

Conclusions:

- Gastric cancer: Nivo/ipi has no role in the adjuvant setting **(VESTIGE)**
- Pancreatic cancer: Nalirifox has demonstrated an improvement in OS **(NAPOLI 3)**
- Metastatic anal cancer: Nivo/Ipi has no role in the refractory setting **(NCI9673 Part B)**
- Rectal cancer: Omission of XRT of mid-high lying rectal cancer results in non-inferiority of DFS **(PRODIGE23)**
- MCRC
  - Lenvatinib + pembrolizumab did not demonstrate OS vs. the SOC **(LEAP-017)**
  - The recommended dose of Deruxtecan is 5.4 mg/kg **(Destiny- CRC02)**
  - Fruquintinib is a selective oral TKI against VEGFR 1,2, and 3 demonstrating OS in refractory disease **(FRESCO-2)**