Fourth Annual
National General Medical Oncology Summit

Sunday, March 2, 2025

Moderator

Neil Love, MD

Faculty

Thomas A Abrams, MD
Prithviraj Bose, MD
Natalie S Callander, MD
Ramaswamy Govindan, MD
Shilpa Gupta, MD
Yelena Y Janjigian, MD
Ahmed Omar Kaseb, MD, CMQ
Samuel J Klempner, MD
Andrew T Kuykendall, MD
Christopher Lieu, MD
Stephen V Liu, MD
Thomas Martin, MD
Paul E Oberstein, MD, MS
Philip A Philip, MD, PhD
Kanwal Raghav, MD
Jonathan E Rosenberg, MD

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Co-Moderators

Maria Regina Flores, MD
Lucio N Gordan, MD
Maen Hussein, MD
Anjan J Patel, MD
Sumithra Vattigunta, MD
Faye Yin, MD

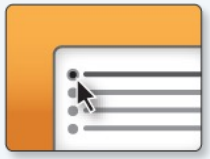
Disclosures for Moderator Neil Love, MD

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME/NCPD/ACPE activities from the following companies: AbbVie Inc, ADC Therapeutics, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Black Diamond Therapeutics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Clovis Oncology, Coherus BioSciences, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, Exact Sciences Corporation, Exelixis Inc, Genentech, a member of the Roche Group, Genmab US Inc, Geron Corporation, Gilead Sciences Inc, GSK, Hologic Inc, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Legend Biotech, Lilly, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Nuvalent, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Rigel Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, and Tesaro, A GSK Company.

Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the premeeting survey.

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

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

Clinicians Attending via Zoom

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

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

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from this weekend will be edited and developed into an enduring web-based video/PowerPoint program. An email will be sent to all attendees when the activity is available.

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Module 10: Colorectal Cancer

Optimizing the Care of Patients with Nonmetastatic Colorectal Cancer (CRC) — Dr Lieu

Recent Advances in the Management of Metastatic CRC — Dr Raghav

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Cancer Center

NCI-DESIGNATED CONSORTIUM
COMPREHENSIVE CANCER CENTER

Optimizing the Care of Patients with Nonmetastatic Colorectal Cancer (CRC)

Christopher Lieu, MD
Director, GI Medical Oncology
Associate Director for Clinical Research
University of Colorado

NCI Designated Comprehensive Cancer Center

Disclosures

Consulting Agreements	Amgen Inc, Pfizer Inc
Contracted Research	Genentech, a member of the Roche Group, Sanofi

Topics for Discussion

- ctDNA-based MRD monitoring in early-stage CRC
  - *What have the available studies taught us about MRD testing and treatment decision making?*

- Neoadjuvant checkpoint inhibition for MSI-H/dMMR resectable CRC
  - *Should immunotherapy go first?*

What Are the Potential Applications of ctDNA?

Minimal Residual Disease

Stage II Colon Cancer

DYNAMIC Study Design

ACTRN12615000381583

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op

R
2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo**
  (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

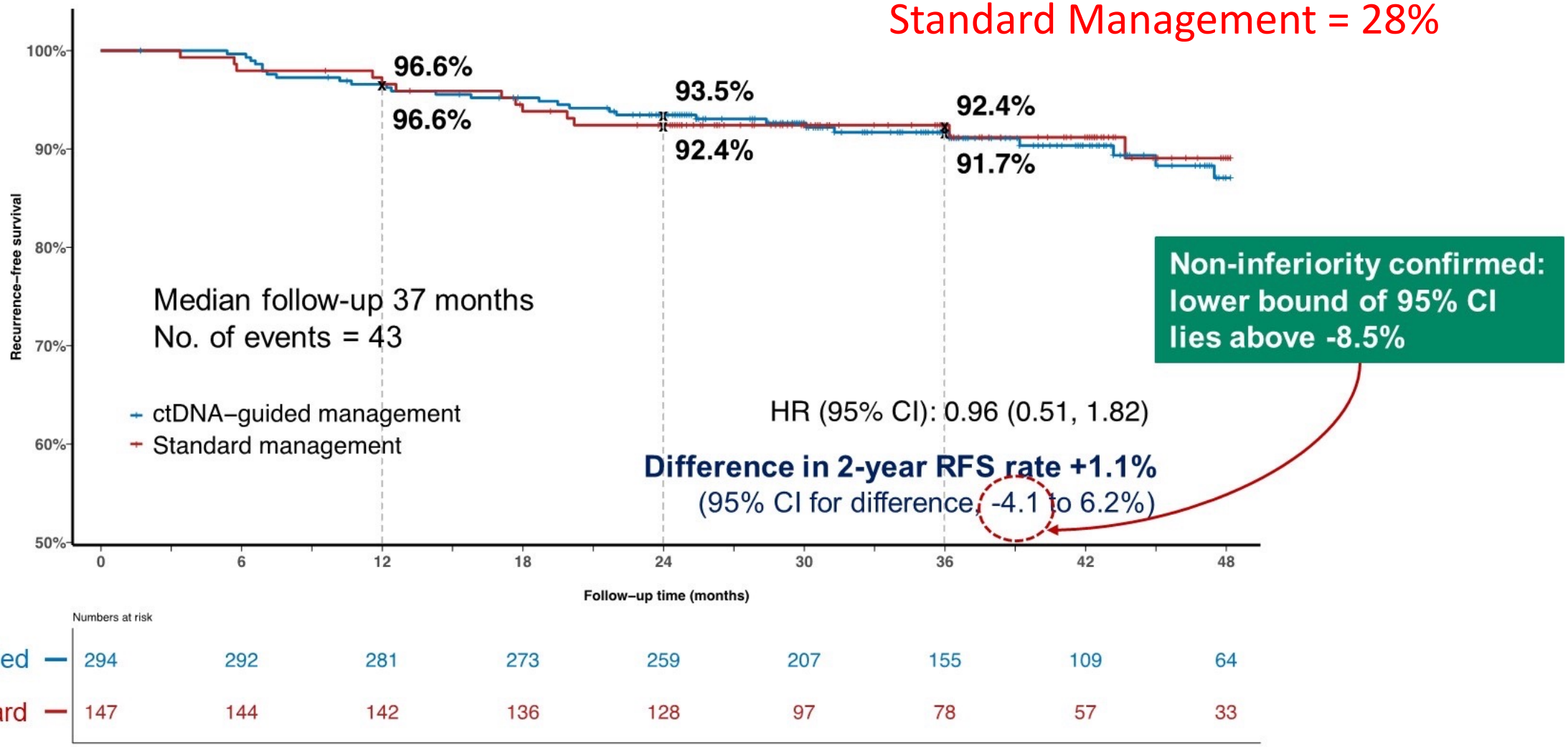
Tie et al. J Clin Oncol 40, 2022 (suppl 17; abstr LBA100)

Recurrence-Free Survival

CHEMOTHERAPY RECEIVED

ctDNA guided = 15%

Standard Management = 28%



Tie et al. J Clin Oncol 40, 2022 (suppl 17; abstr LBA100)

Take Home Point:

ctDNA can be considered in low-risk stage II colon cancer

If ctDNA is positive, who would not offer adjuvant chemotherapy?

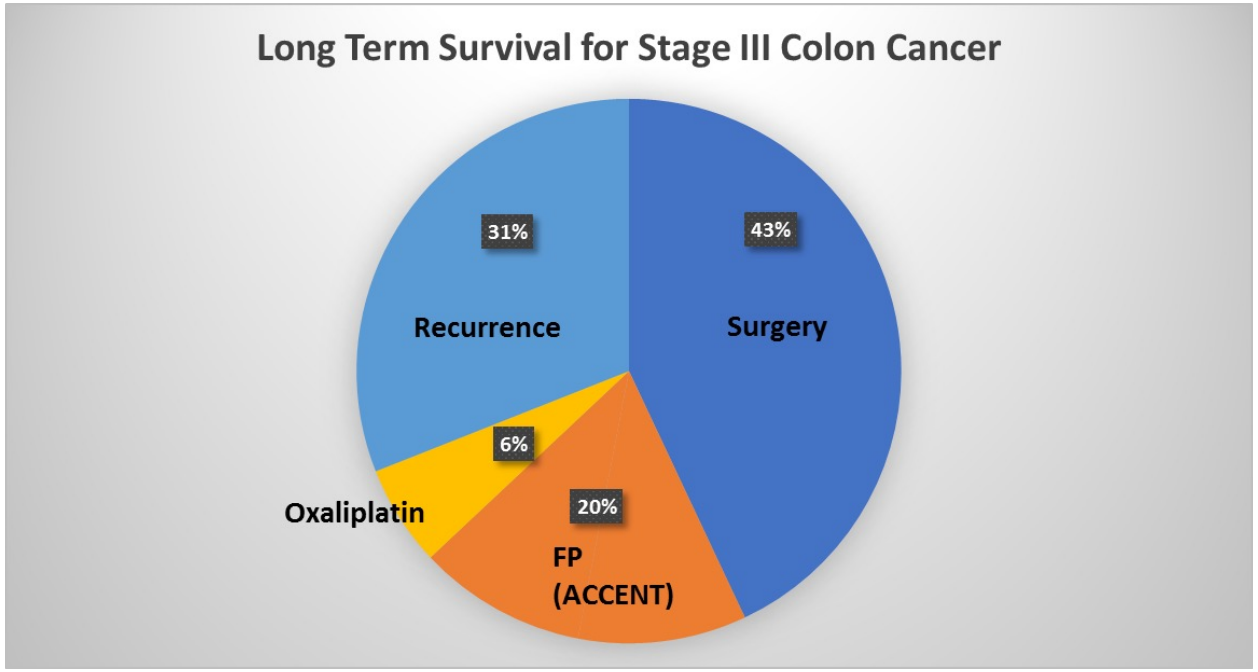
What Are the Potential Applications of ctDNA?

Minimal Residual Disease

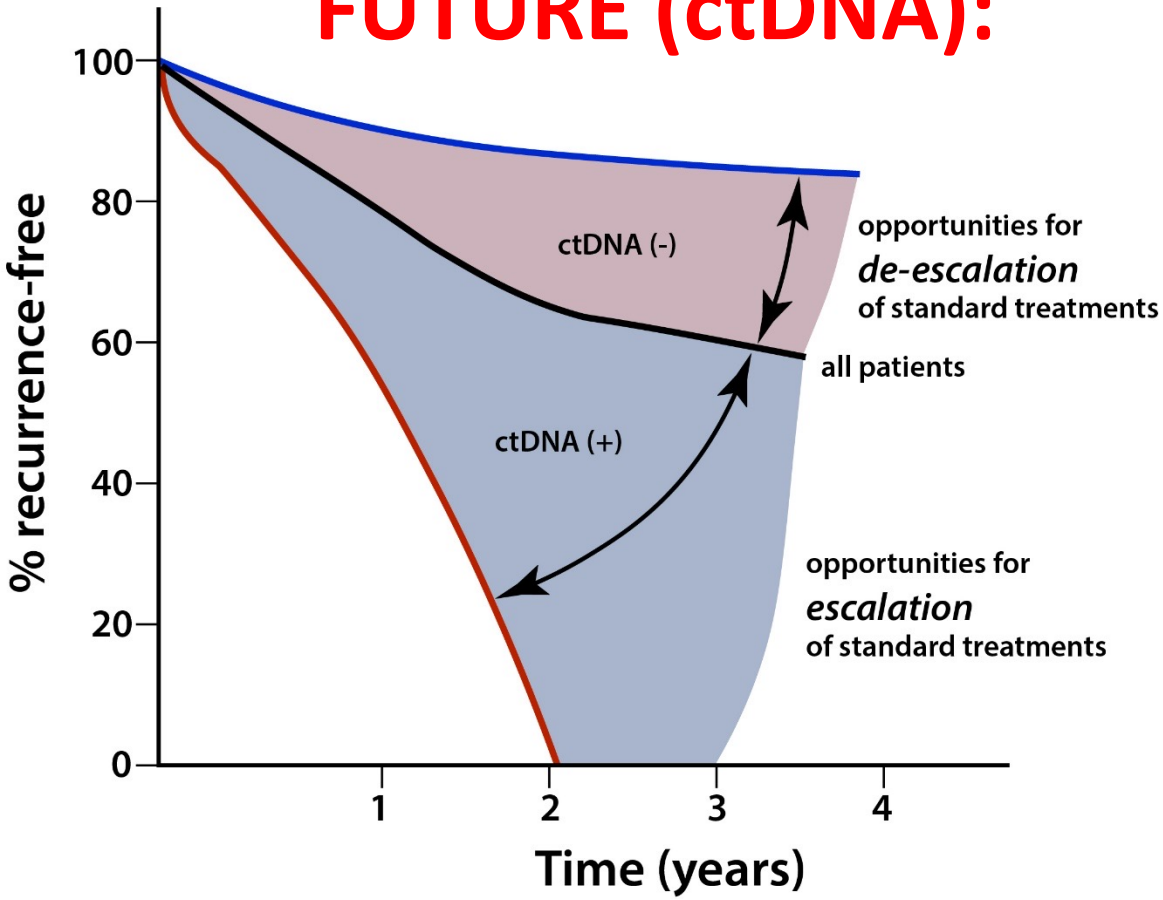
Stage III Colon Cancer

Adjuvant Therapy in Stage III CC: Room for Improvement

CURRENT (TNM):



FUTURE (ctDNA):

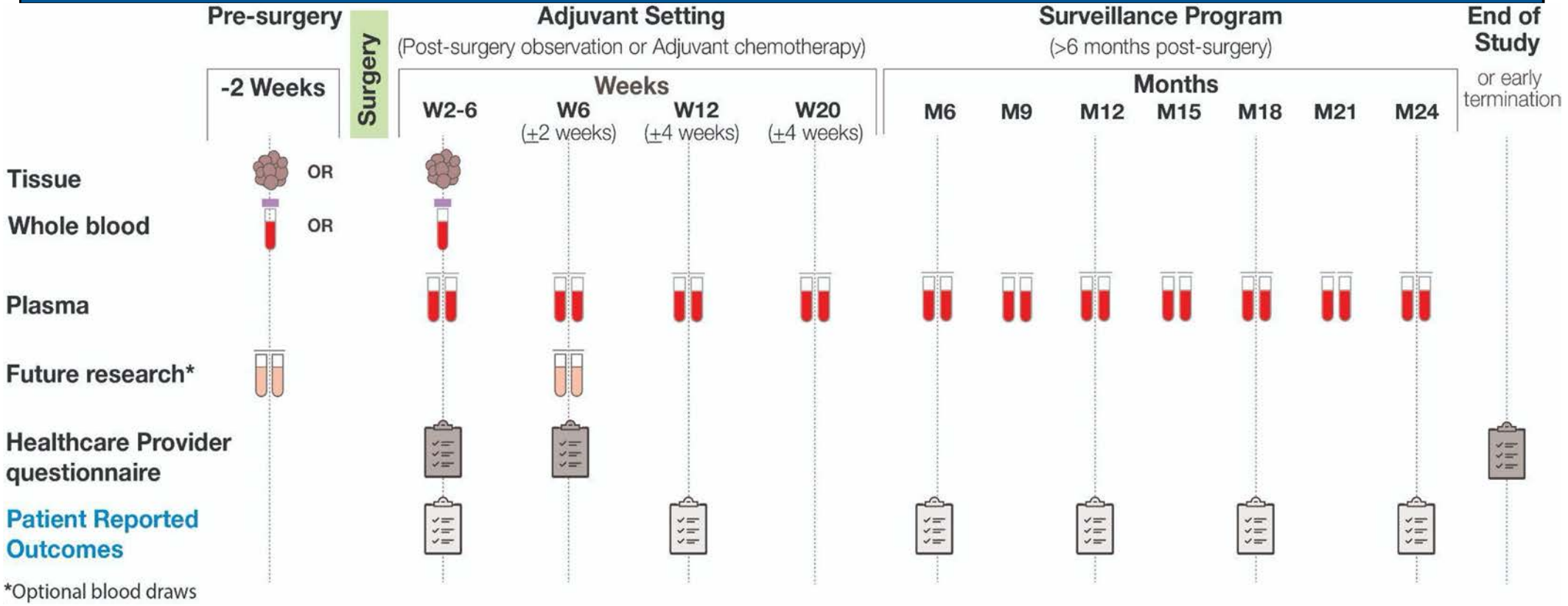


Sargent DJ et al. J Clin Oncol. 2009;27(12):1948-1955; André T et al. J Clin Oncol. 2015;33(35):4176-4187.

BESPOKE CRC: A Prospective, Case-Controlled Observational Study

Estimated enrollment (N = 2,000)

- Stage I-IV CRC or Stage IV CRC with oligometastatic disease eligible for post-operative systemic therapy

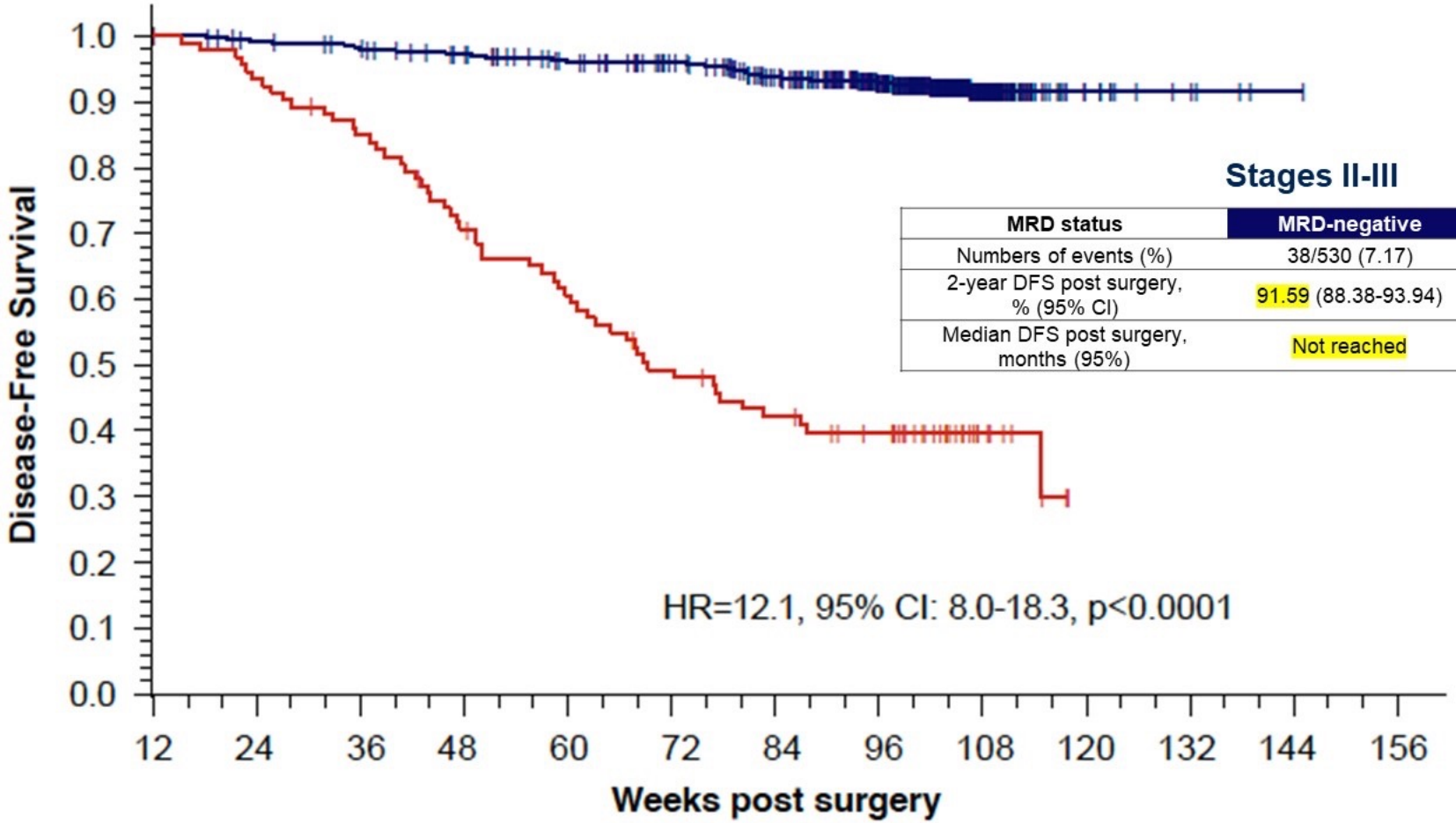


NCT04264702 Kasi PM et al. *BMJ Open* 2021;11:e047831.

ctDNA-positivity at MRD time point is predictive of inferior DFS

MRD window:
2-12 weeks post-surgery, before the start of adjuvant chemotherapy (ACT)

Surveillance window:
>2 weeks post-ACT or >12 weeks post-surgery if on observation



Stages II-III

MRD status	MRD-negative	MRD-positive
Numbers of events (%)	38/530 (7.17)	55/93 (59.14)
2-year DFS post surgery, % (95% CI)	91.59 (88.38-93.94)	29.86 (13.26-48.54)
Median DFS post surgery, months (95%)	Not reached	15.98 (13.77-20.22)

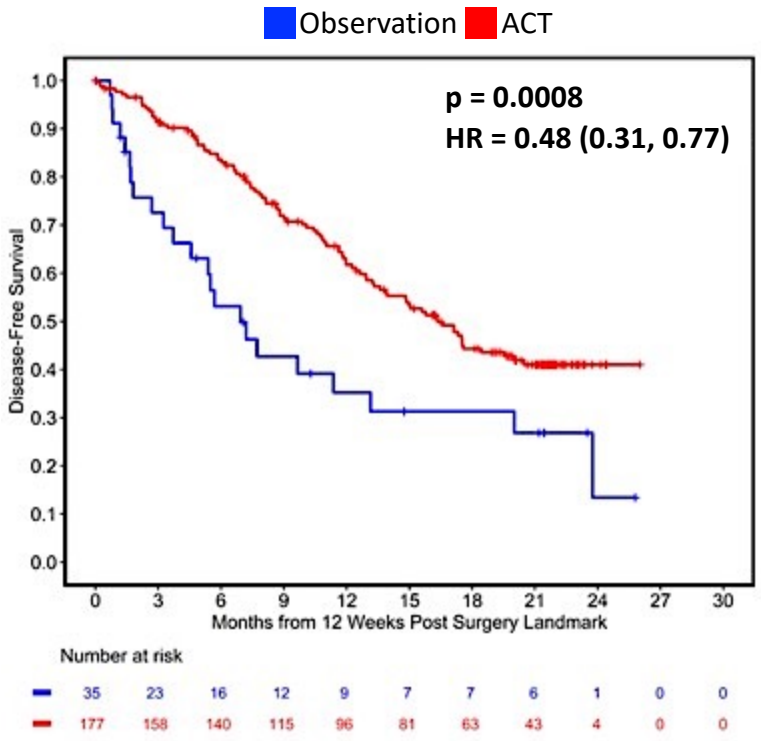
Number at Risk

MRD-negative	530	522	513	499	482	464	429	353	101	12	5	1	0
MRD-positive	93	87	78	64	54	43	36	30	8	0			

Kasi PM et al. J Clin Oncol 42, 2024 (suppl 3; abstr 54)

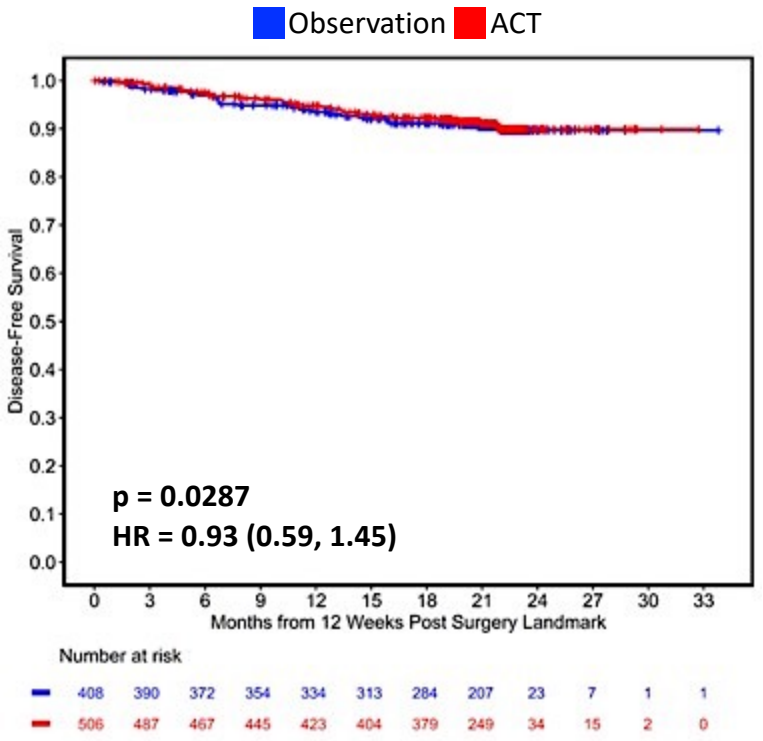
ctDNA-based MRD testing is predictive of the benefit of ACT

MRD-positive



Adjuvant strategy	ACT	Observation
Numbers of events (%)	96/177 (54.24)	29/35 (82.86)
2-year DFS post surgery, % (95% CI)	40.3 (33.3 - 48.9)	24.7 (13.2 - 46.3)
Median DFS post surgery, months (95%)	17.7 (14.6 - 21.4)	7.1 (4.6 - 21.4)

MRD-negative

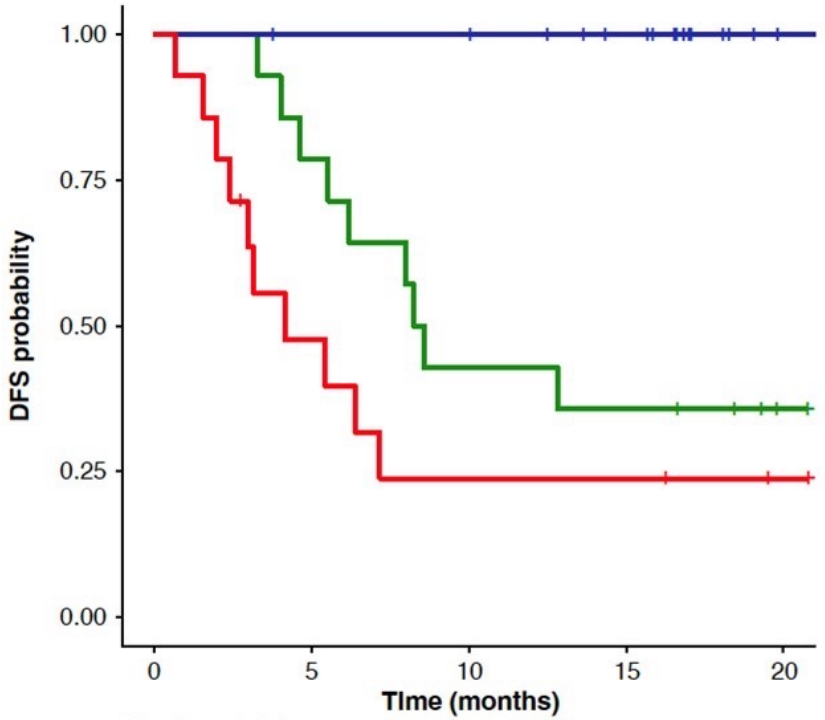


Adjuvant strategy	ACT	Observation
Numbers of events (%)	43/506 (8.50)	37/408 (9.07)
2-year DFS post surgery, % (95% CI)	89.7 (86.7- 92.9)	89.5 (86.2- 92.9)
Median DFS post surgery, months (95%)	Not reached	Not reached

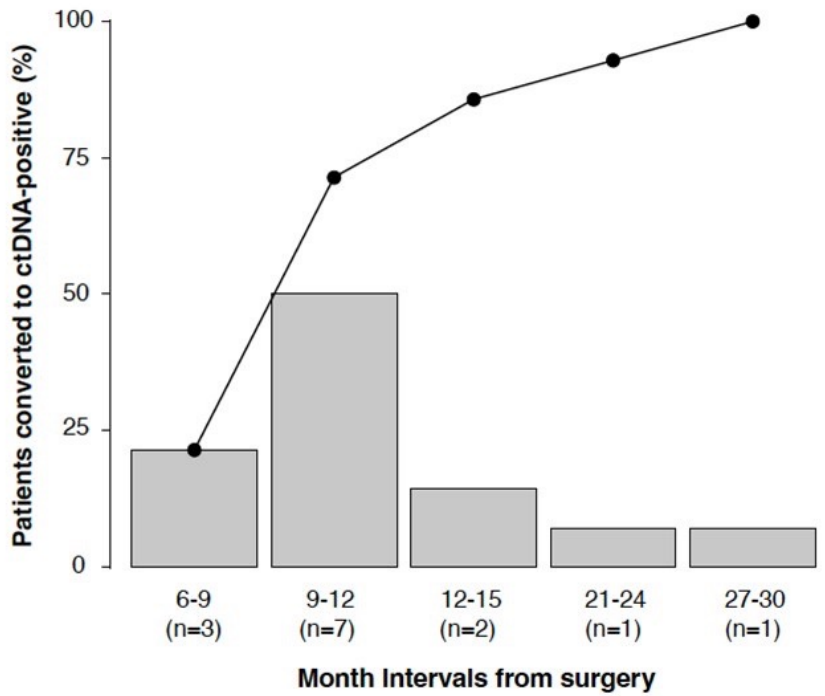
Shah P et al. 2025 ASCO GI; Abstract 15

Sustained ctDNA clearance is associated with superior DFS when compared to transient or no clearance

DFS by ctDNA clearance patterns



85% of patients with transient clearance develop molecular recurrence by the 15th month



Kasi PM et al. J Clin Oncol 42, 2024 (suppl 3; abstr 54)

Phase III CALGB/SWOG 80702 Study Design

Key eligibility criteria

- Resected adenocarcinoma of the colon without metastatic disease
- At least one pathologically confirmed positive lymph node or N1c disease as defined in AJCC version 7
- Patients ineligible if they use NSAIDs at any dose more than 2x / week or aspirin at more than 325 mg 3x / week. Low-dose aspirin not exceeding 100 mg/day *permitted*

Celecoxib versus Placebo

6 versus 12 treatments FOLFOX

Arm A **12 FOLFOX + Placebo daily**	**Arm B** **12 FOLFOX + Celecoxib 400 mg daily**
Arm C **6 FOLFOX + Placebo daily**	**Arm D** **6 FOLFOX + Celecoxib 400 mg daily**

Celecoxib/placebo continued for a total of 3 years from the day that study drug was initiated.

Target sample size = 2,500
Actual final accrual = 2,526

1,752 patients consented to biospecimen collection and had tumor tissue successfully banked

↓

1,197 patients had whole exome data successfully generated

↓

1,011 patients had sufficient plasma for ctDNA testing

↓

940 patients evaluable after excluding patients with plasma collected outside the immediate post-surgical time period

↓

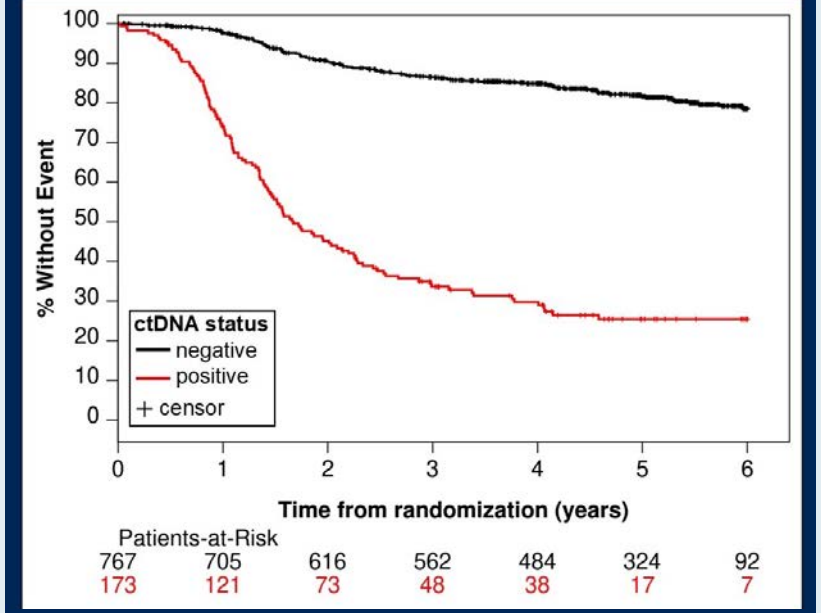
18.4% ctDNA positive

81.6% ctDNA negative

Nowak JA et al. Gastrointestinal Cancers Symposium 2025;Abstract LBA14.

Phase III CALGB/SWOG 80702: Survival by ctDNA Status

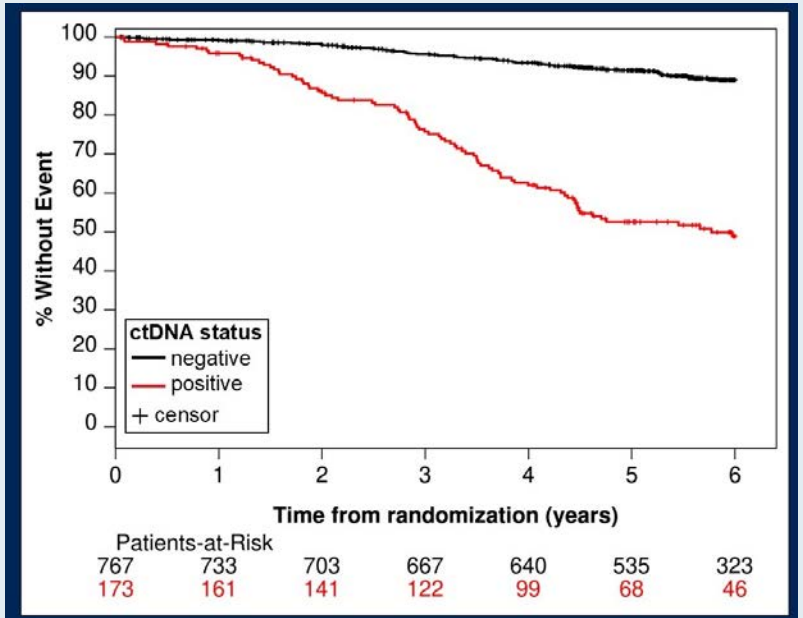
Disease-free survival



ctDNA Status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]
Negative	131/767	Reference	86.5 (84.0-89.1%)
Positive	118/173	7.14 (5.54-9.21)	33.7 (27.1-41.8%)
Logrank P-value: <0.0001[3]			

[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Log-rank test

Overall survival



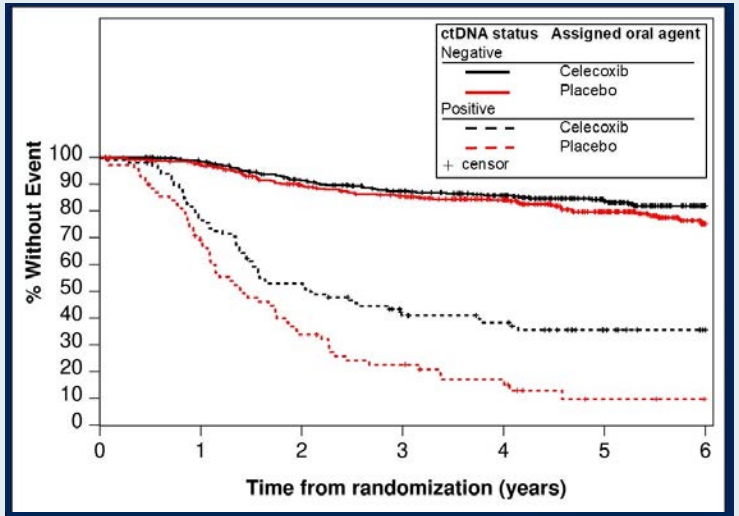
ctDNA Status	Events / Total	Hazard Ratio (95% CI)[1]	5 Year Survival Estimate (95% CI)[2]
Negative	77/767	Reference	91.5 (89.5-93.6%)
Positive	85/173	6.72 (4.91-9.18)	52.6 (45.3-61.0%)
Logrank P-value: <0.0001[3]			

[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Log-rank test

Nowak JA et al. Gastrointestinal Cancers Symposium 2025;Abstract LBA14.

Phase III CALGB/SWOG 80702: Survival by ctDNA Status and Celecoxib Use

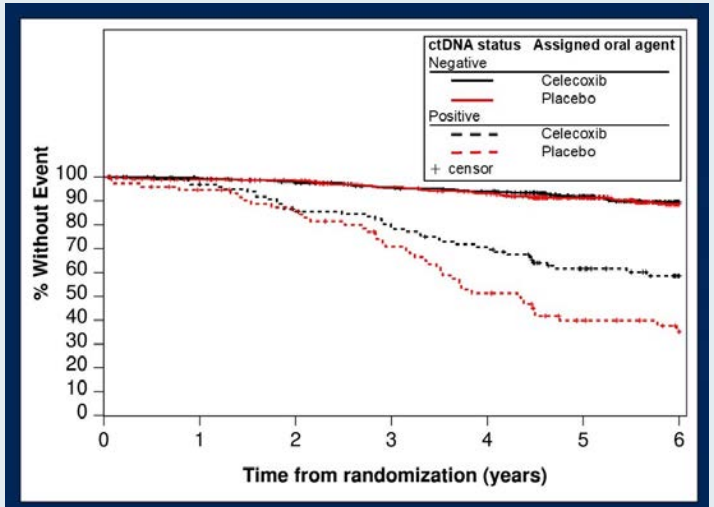
Disease-free survival



Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.1293[4]
Celecoxib	58/375	0.76 (0.54-1.08)	87.4 (84.0-91.0%)	
Placebo	73/392	Reference	85.6 (82.0-89.4%)	
Positive				0.0013[4]
Celecoxib	61/99	0.55 (0.39-0.80)	41.0 (32.2-52.2%)	
Placebo	57/74	Reference	22.6 (14.3-35.5%)	
Interaction P-value: 0.1359[3]				

[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test, [4] Log-rank test

Overall survival



Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	5 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.5098[4]
Celecoxib	36/375	0.86 (0.55-1.35)	91.8 (88.9-94.7%)	
Placebo	41/392	Reference	91.3 (88.4-94.3%)	
Positive				0.0135[4]
Celecoxib	41/99	0.58 (0.38-0.90)	61.6 (52.4-72.4%)	
Placebo	44/74	Reference	39.9 (29.6-53.8%)	
Interaction P-value: 0.2061[3]				

[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test, [4] Log-rank test

Nowak JA et al. Gastrointestinal Cancers Symposium 2025;Abstract LBA14.

Phase III CALGB/SWOG 80702: Summary and Conclusions

Endpoint	Comparison	Events / Total	Adjusted HR (95% CI)	Adjusted P-value	Adjusted Interaction P-value
Disease-free survival		247/930			0.4826
	ctDNA+: Celecoxib v Placebo (ref)		0.63 (0.43-0.92)	0.0167	
	ctDNA-: Celecoxib v Placebo (ref)		0.76 (0.53-1.08)	0.1262	
Overall survival		160/930			0.3873
	ctDNA+: Celecoxib v Placebo (ref)		0.63 (0.40-0.98)	0.0419	
	ctDNA-: Celecoxib v Placebo (ref)		0.84 (0.53-1.34)	0.4593	

Adjusted for ctDNA, age, sex, low dose aspirin usage, performance status, T stage, N stage, sidedness, days from surgery to blood draw, *KRAS*, *BRAF*, and MSI status

- In a subset of patients enrolled in CALGB/SWOG 80702, ctDNA status after surgery and prior to starting adjuvant therapy was highly prognostic of DFS and OS
- ctDNA status also appeared predictive of benefit of adjuvant celecoxib
- Sensitivity and subgroup analyses are ongoing
- Studies on the predictive value of ctDNA for 3 versus 6 months of adjuvant FOLFOX are underway

Nowak JA et al. Gastrointestinal Cancers Symposium 2025;Abstract LBA14.

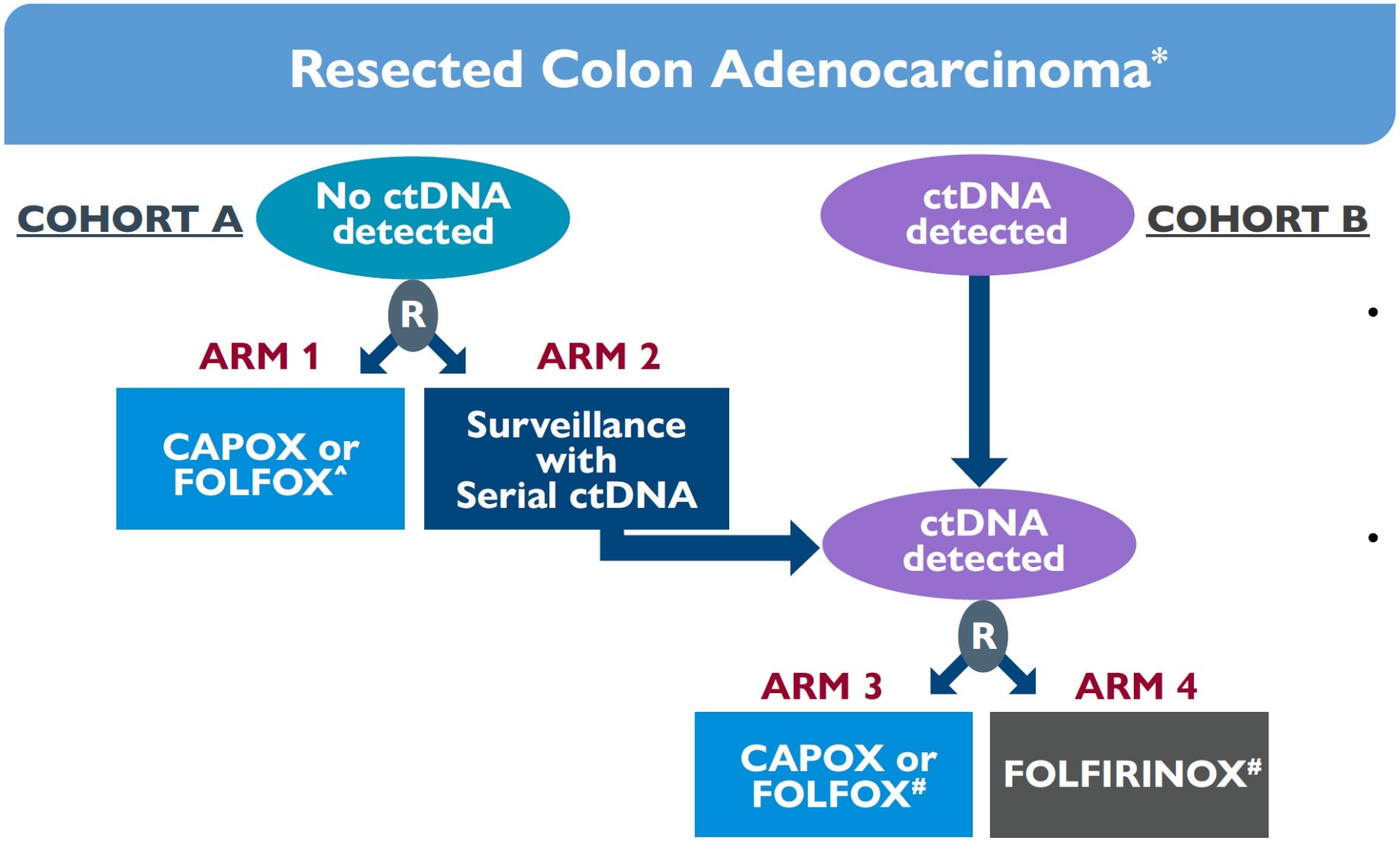
Take Home Points:
What have these studies taught us?

- ctDNA is easily the most prognostic test we have ever seen in colon cancer

- Stage II Colon Cancer:
  - ctDNA may be ready for primetime for low-risk stage II colon cancer
    - *If ctDNA is positive, who would not offer adjuvant chemotherapy?*

- Stage III Colon Cancer:
  - Ongoing studies are critically needed to determine if ctDNA can be used to guide the management of patients with stage III colon cancer

CIRCULATE North America: Stage III Colon Cancer Study
Amended Schema



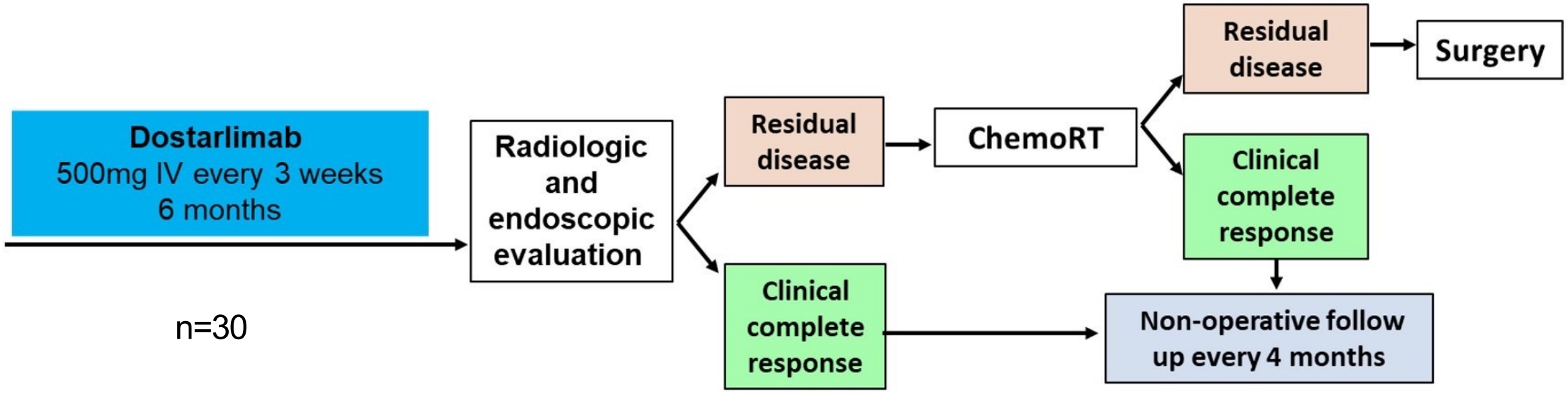
- Study population amended to include <u>all</u> patients with Stage IIB, IIC, and Stage III colon adenocarcinoma
- One dose of chemotherapy allowed while awaiting Step 2 randomization

PIs: Dasari and Lieu (NRG-GI008 – NCT0517416)

NRG ONCOLOGY™

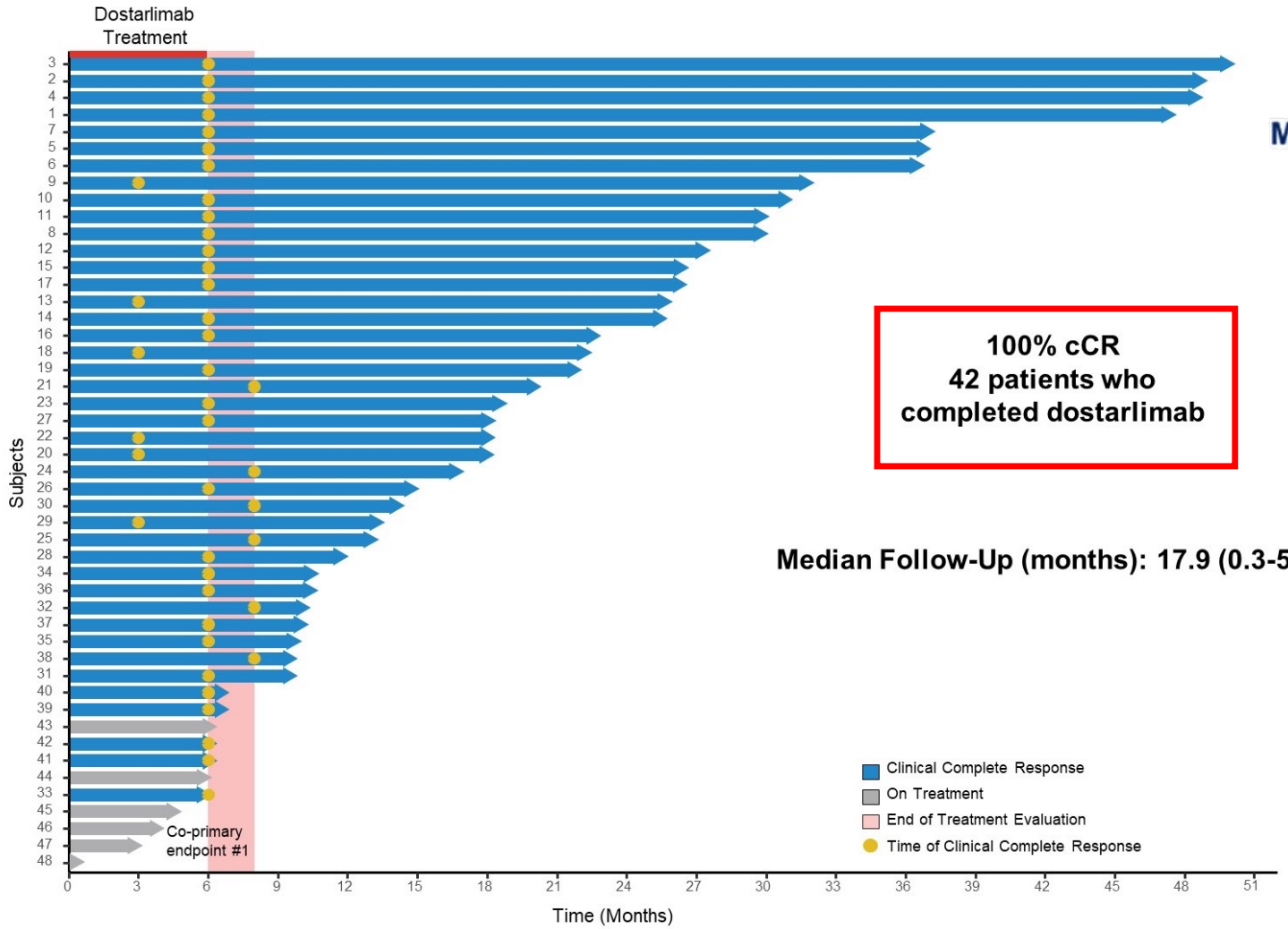
Immune checkpoint inhibitors for patients with non-metastatic CRC

Dostarlimab for MSI-H Stage II-III Rectal Cancer



- Primary endpoints
  - Overall response rate at 6 months per MSKCC regression criteria
  - pCR or cCR rate at 12 months
- Secondary endpoint
  - Safety and tolerability

Cercek A, et al. *N Engl J Med* 2022.



100% cCR
42 patients who completed dostarlimab

Median Follow-Up (months): 17.9 (0.3-50.5)

Most Common AEs

	All Grades	Grade 3 or 4
Dermatologic -no.(%)		
Pruritus	6 (13)	0 (0)
Rash / dermatitis	10 (21)	0 (0)
Gastrointestinal-no.(%)		
Diarrhea	4 (9)	0 (0)
Nausea	4 (9)	0 (0)
Constitutional-no.(%)		
Fatigue	5 (11)	0 (0)
Fever	3 (6)	0 (0)
Endocrine-no.(%)		
Hypothyroidism	5 (11)	0 (0)

Cercek et al. NEJM 2022, Cercek et al. ASCO 2024; Abstract LBA3512

Take Home Points:

Neoadjuvant immune checkpoint inhibition appears **ready for primetime for rectal dMMR/MSI-H**

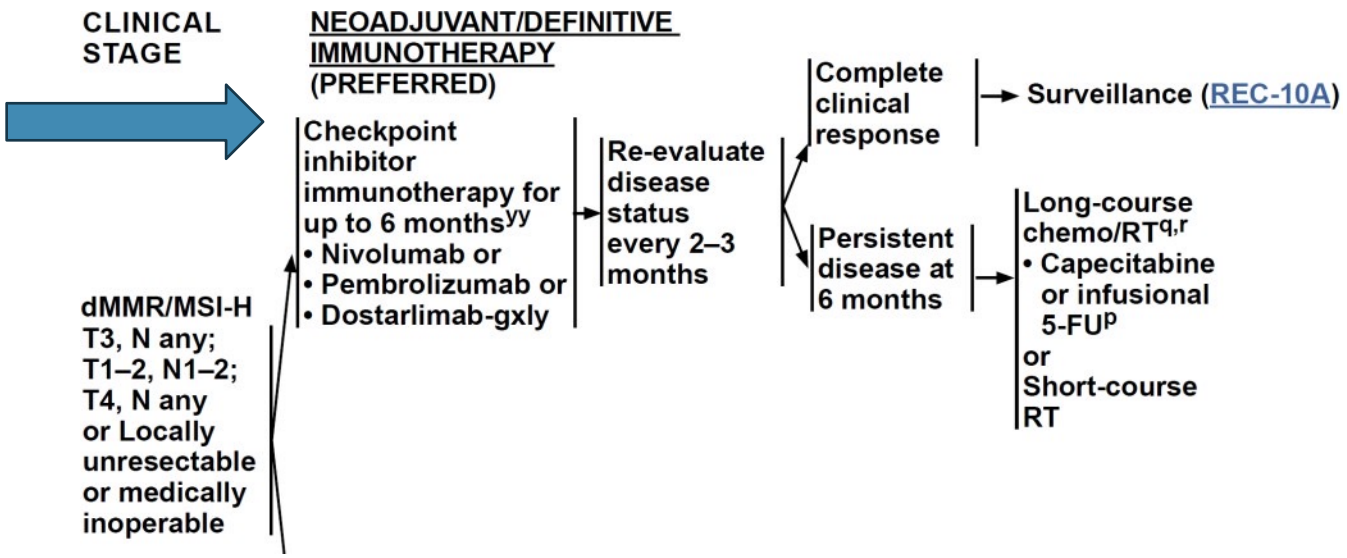
QUESTIONS:

What about stage I rectal cancer?

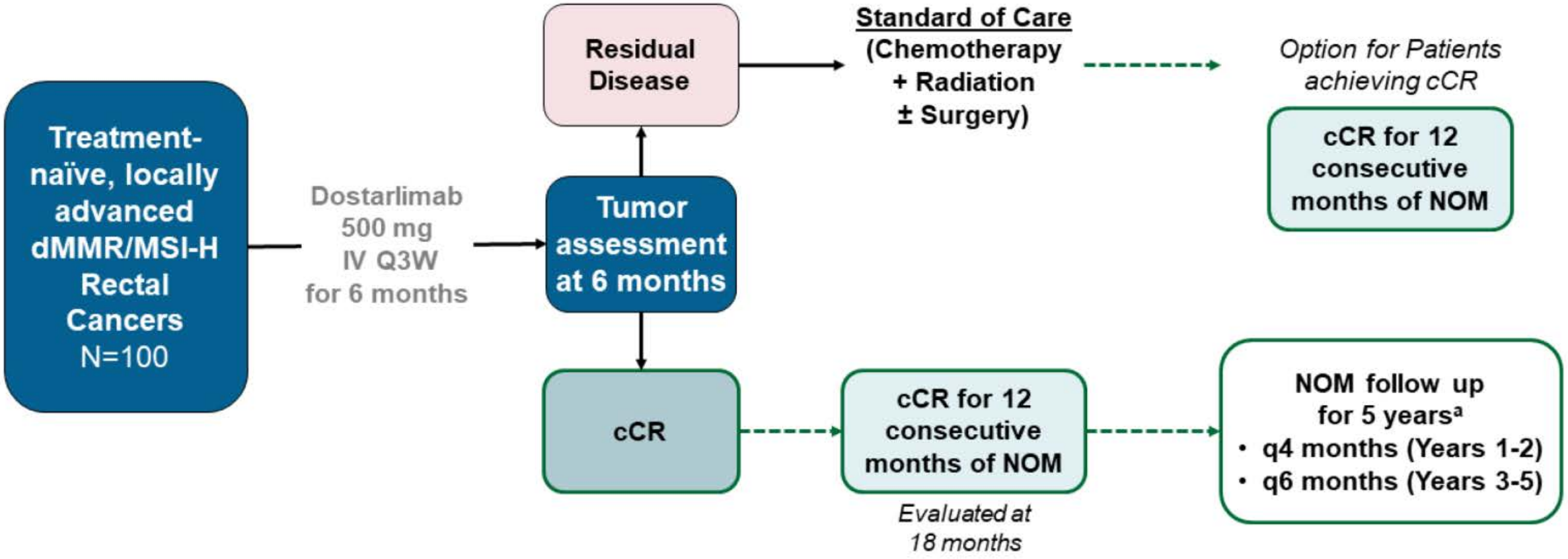
Should we be using nivo and ipi?

Does pCR mean cure?

What is the impact on pMMR/MSS patients?

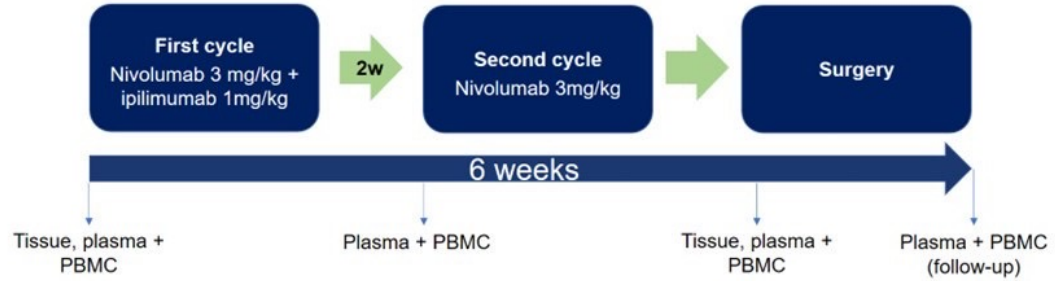


AZUR-1: Dostarlimab in dMMR/MSI-H Locally-Advanced Rectal Cancer



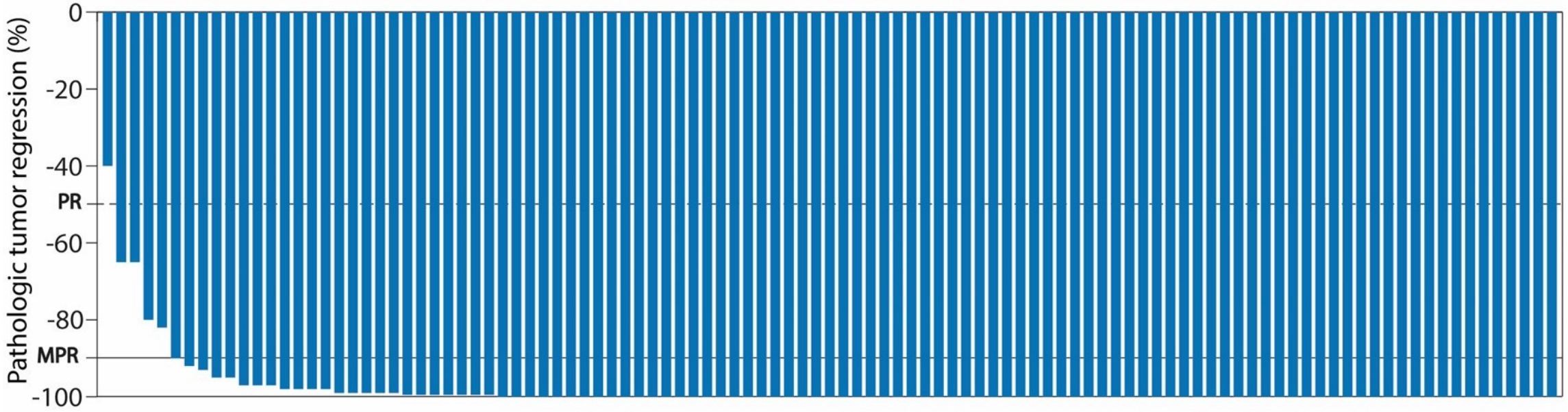
NCT05723562

NICHE-2 Study: Nivo/Ipi dMMR colon cancer



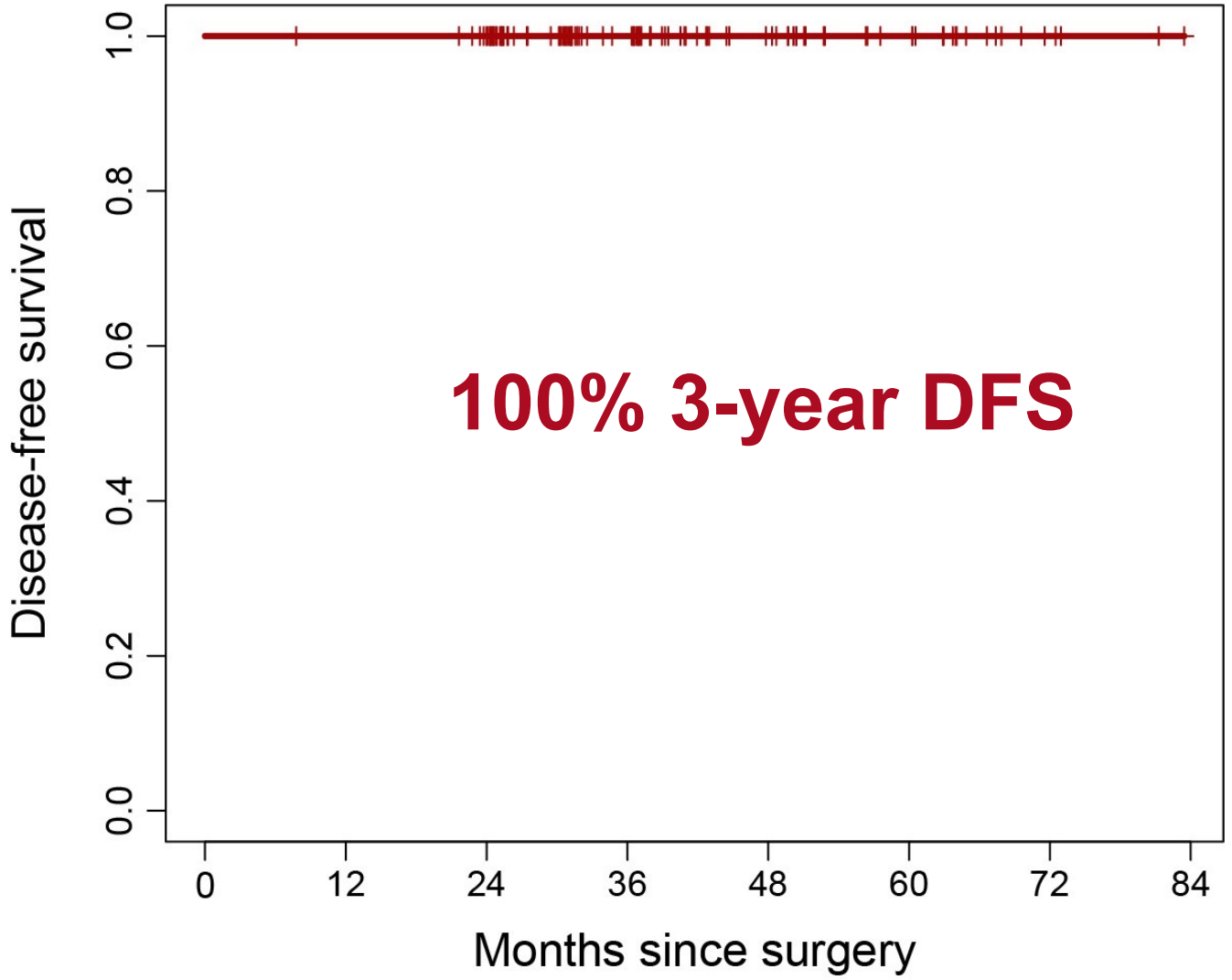
In locally advanced MMR-deficient colon cancers

- **95% MPR; 67% pCR**



Chalabi et al. ESMO 2022; Abstract LBA7.

Results – 3-year disease-free survival 100%



Number at risk

111	110	105	58	32	18	4

Median follow-up after surgery: 36.6 months (7.8 - 83.4)

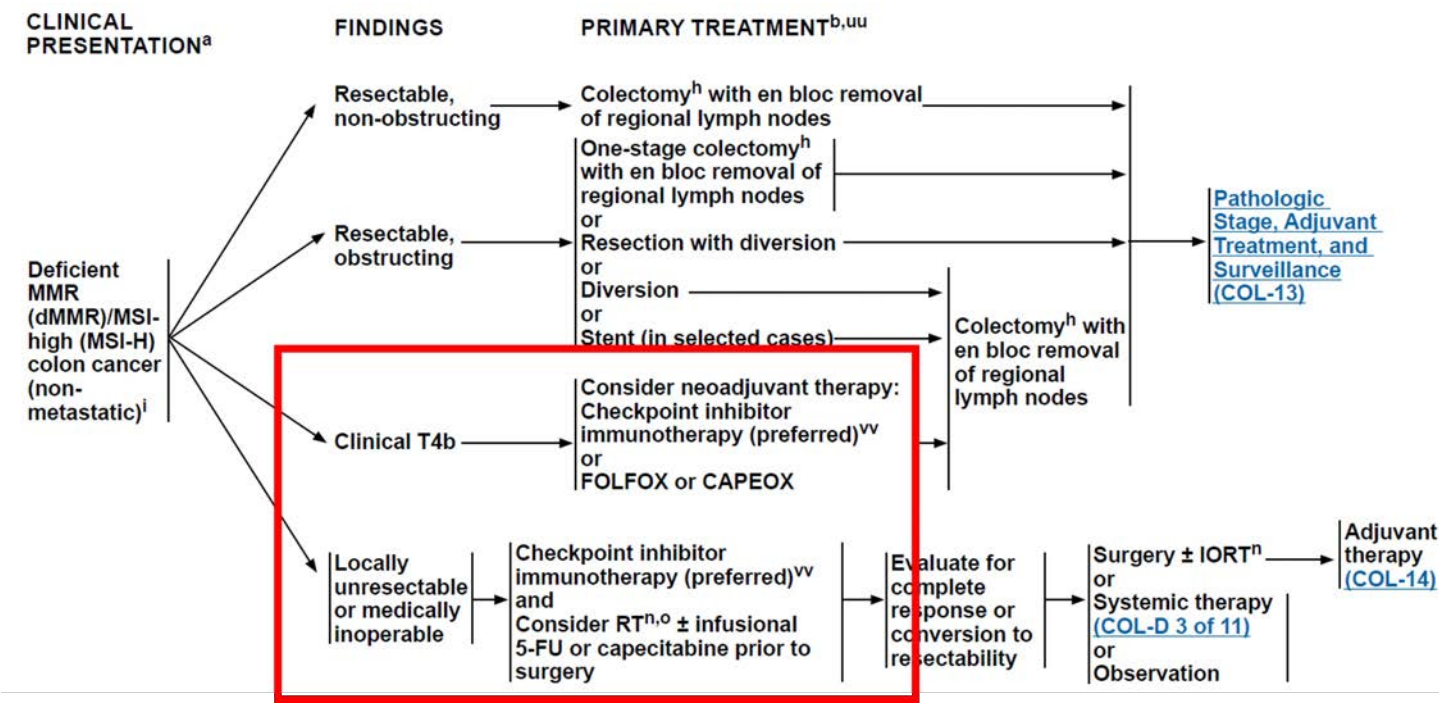
Chalabi et al. ESMO 2024; Abstract LBA24.

BARCELONA 2024 ESMO congress

Data cut-off: 11 September 2024

Take Home Points:

Neoadjuvant immune checkpoint inhibition should be considered for high-risk disease (T4b) colon cancer



QUESTIONS:

- Should we consider non-operative management for MSI-H/dMMR colon cancer?
- Are serial colonoscopies better or worse than a hemicolectomy?
- What is the best duration of immunotherapy prior to resection?
- What about adjuvant therapy?

AZUR-2: An Ongoing Phase III Study of Perioperative Dostarlimab for Untreated T4N0 or Stage III dMMR/MSI-H Resectable Colon Cancer

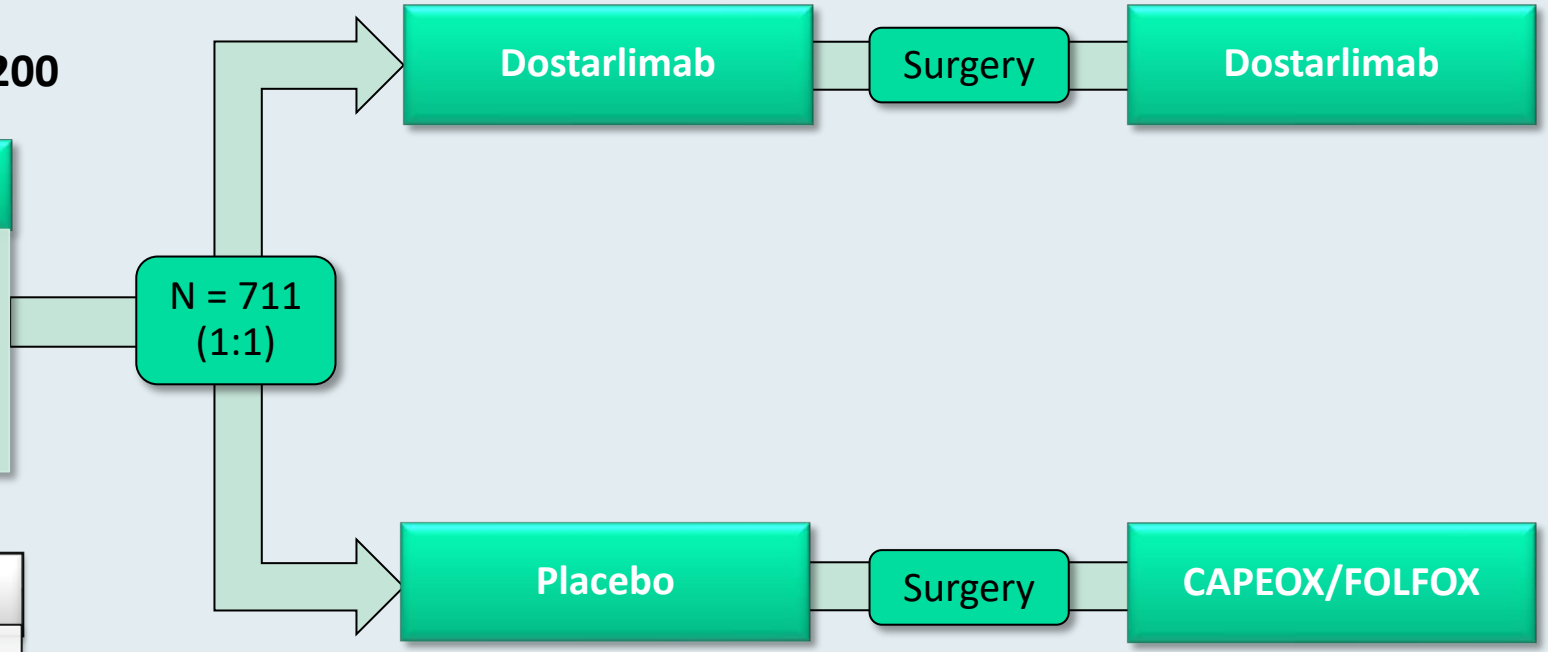
Trial identifier: NCT05855200

Key inclusion criteria

- Resectable T4N0 or Stage III colon adenocarcinoma
- dMMR or MSI-H tumor

Key exclusion criteria

- Prior chemotherapy, IO, biological or targeted therapy, RT, or surgery for colon cancer
- History of ILD or pneumonitis
- Allogeneic stem cell transplant
- Any major surgery or injury within 28 days of enrollment



Outcomes

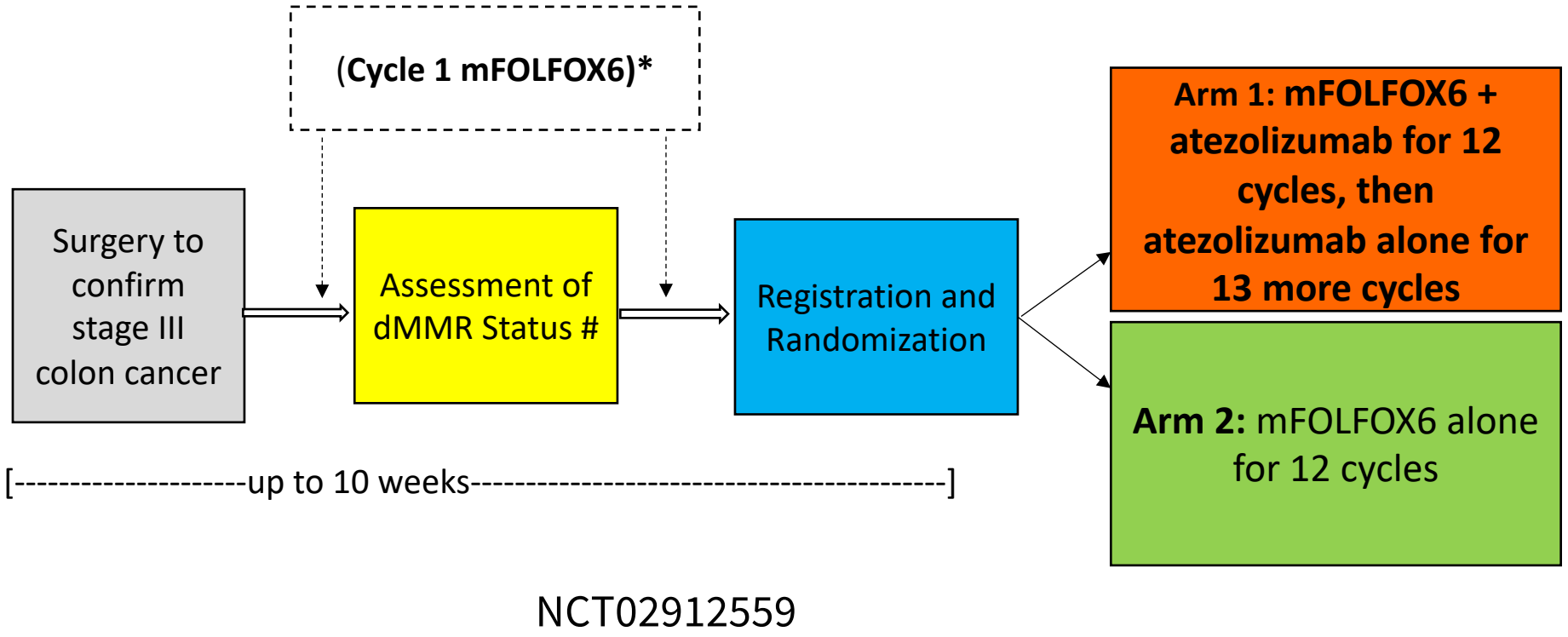
- Primary endpoint: EFS up to 5 years
- Key secondary endpoints: OS up to 5 years, pCR, safety

dMMR = defective mismatch repair; MSI-H = microsatellite instability high; IO = immunotherapy; RT = radiation therapy; ILD = interstitial lung disease; CAPEOX = capecitabine/oxaliplatin; FOLFOX = fluorouracil/leucovorin/oxaliplatin; EFS = event-free survival; OS = overall survival; pCR = pathological complete response

www.clinicaltrials.gov. Accessed January 2024.

RTP RESEARCH TO PRACTICE

Adjuvant PD-L1 for Stage III colon cancer: ATOMIC Study (A021502)



NCT02912559

Enrollment completed 2023

PI: Frank Sinicrope

Discussion Questions

- A patient presents with Stage II colorectal cancer (CRC) with high-risk features and undergoes R0 resection. Regulatory and reimbursement issues aside, what would be your preferred approach to adjuvant therapy?

- A patient presents with Stage IIA CRC with no high-risk features and undergoes R0 resection. A ctDNA assay ordered after surgery is negative, but repeat testing at 3 months is positive. What would you most likely recommend?

Discussion Questions

- In which situations, if any, would you recommend celecoxib to a patient with Stage II or III colon cancer?

- Regulatory and reimbursement issues aside, what would you most likely recommend as neoadjuvant therapy for a patient with dMMR locally advanced rectal cancer?

Module 10: Colorectal Cancer

Optimizing the Care of Patients with Nonmetastatic Colorectal Cancer (CRC) — Dr Lieu

Recent Advances in the Management of Metastatic CRC — Dr Raghav

Recent Advances in the Management of Metastatic CRC (mCRC)

Kanwal Raghav, MD

Associate Professor, Dept. Gastrointestinal Medical Oncology

Associate Vice President (AVP), Ambulatory Medical Operations

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

Disclosures

Advisory Committees and Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Eisai Inc, Guardant Health, Janssen Biotech Inc, Merck, Pfizer Inc
Data and Safety Monitoring Boards/Committees	AbbVie Inc, Pfizer Inc

Phase III KEYNOTE-177 Study: Long Term Results

Front-line Pembrolizumab versus chemotherapy for newly diagnosed MSI-H/dMMR mCRC

Primary Analysis

KEYNOTE-177

Eligibility Criteria (N = 307)

- Confirmed metastatic colorectal adenocarcinoma
- MSI-H/d-MMR (local testing)
- Not received prior systemic treatment for metastatic disease

R 1:1

Pembrolizumab (N = 153)

SOC (Chemo ± Bevacizumab/Cetuximab) (N = 154)

Dual Primary Endpoints
PFS and OS by BICR (Pembro vs. SOC)

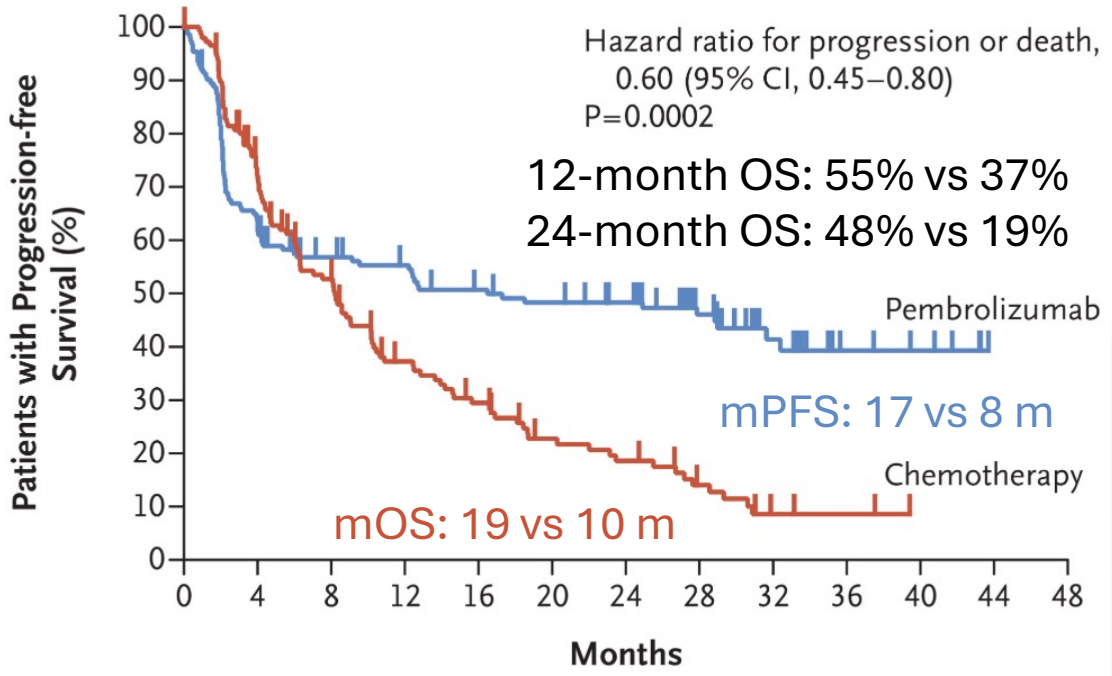


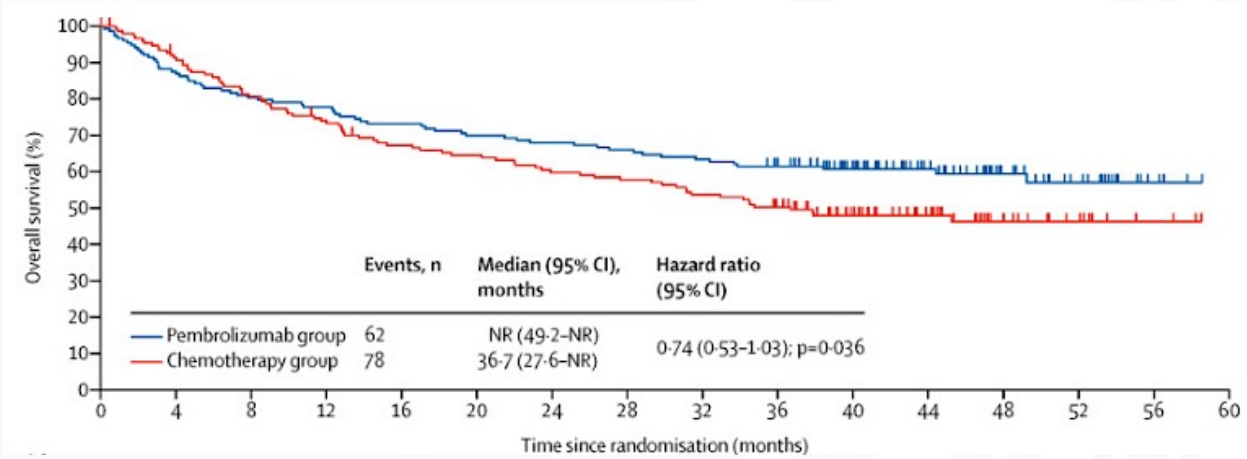
Table 2. Antitumor Activity in the Intention-to-Treat Population.

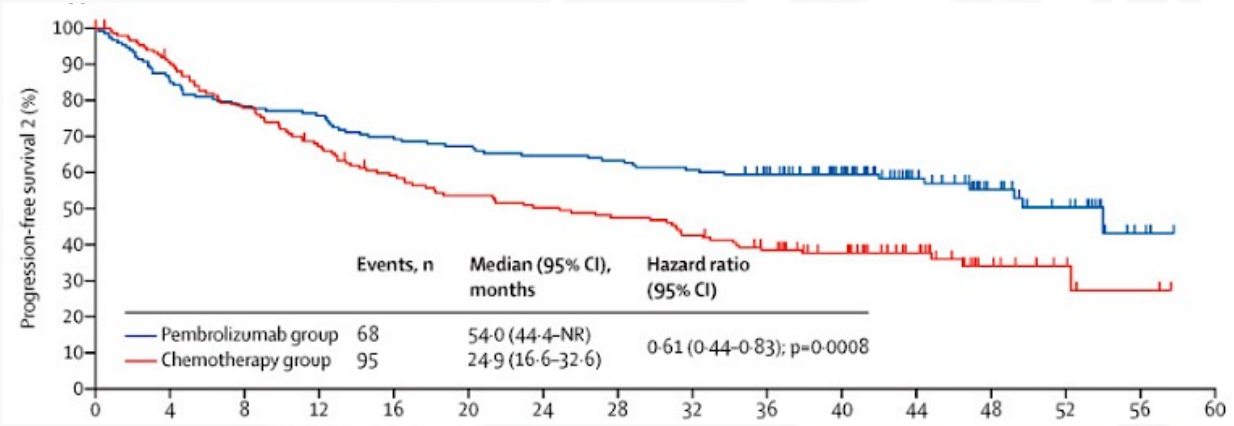
Variable	Pembrolizumab (N=153)	Chemotherapy (N=154)
Overall response*		
No. of patients	67	51
% (95% CI)	43.8 (35.8 to 52.0)	33.1 (25.8 to 41.1)
Best response — no. (%)†		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Progressive disease	45 (29.4)	19 (12.3)
Could not be evaluated or no assessment made‡	9 (5.9)	19 (12.3)
Median time to response (range) — mo	2.2 (1.8 to 18.8)	2.1 (1.7 to 24.9)
Median duration of response (range) — mo§	NR (2.3+ to 41.4+)	10.6 (2.8 to 37.5+)
Response duration of ≥24 months — %§	82.6	35.3

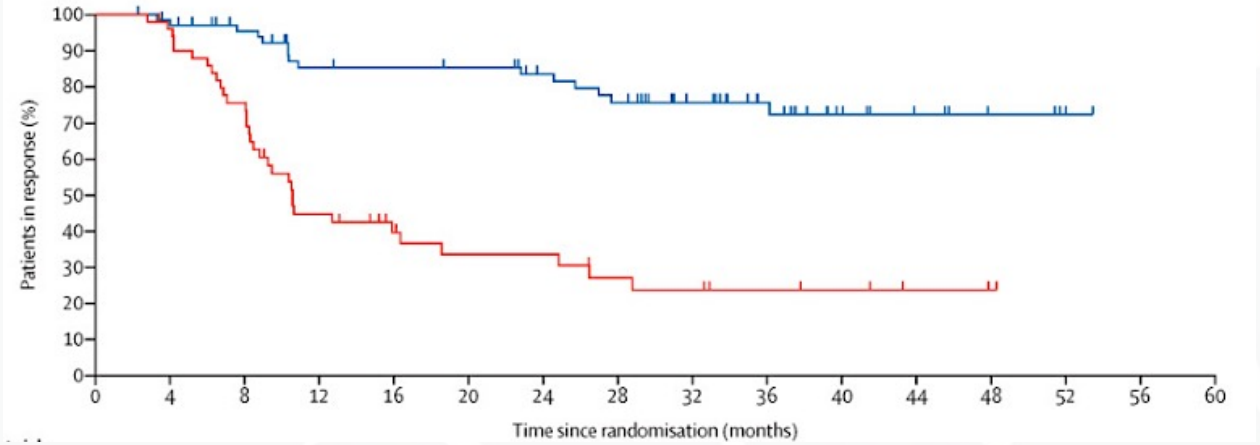
➢ Pembrolizumab improved PFS over chemotherapy as first-line therapy for MSI-H/dMMR mCRC.

Andre et. al. NEJM 2020

Final Analysis







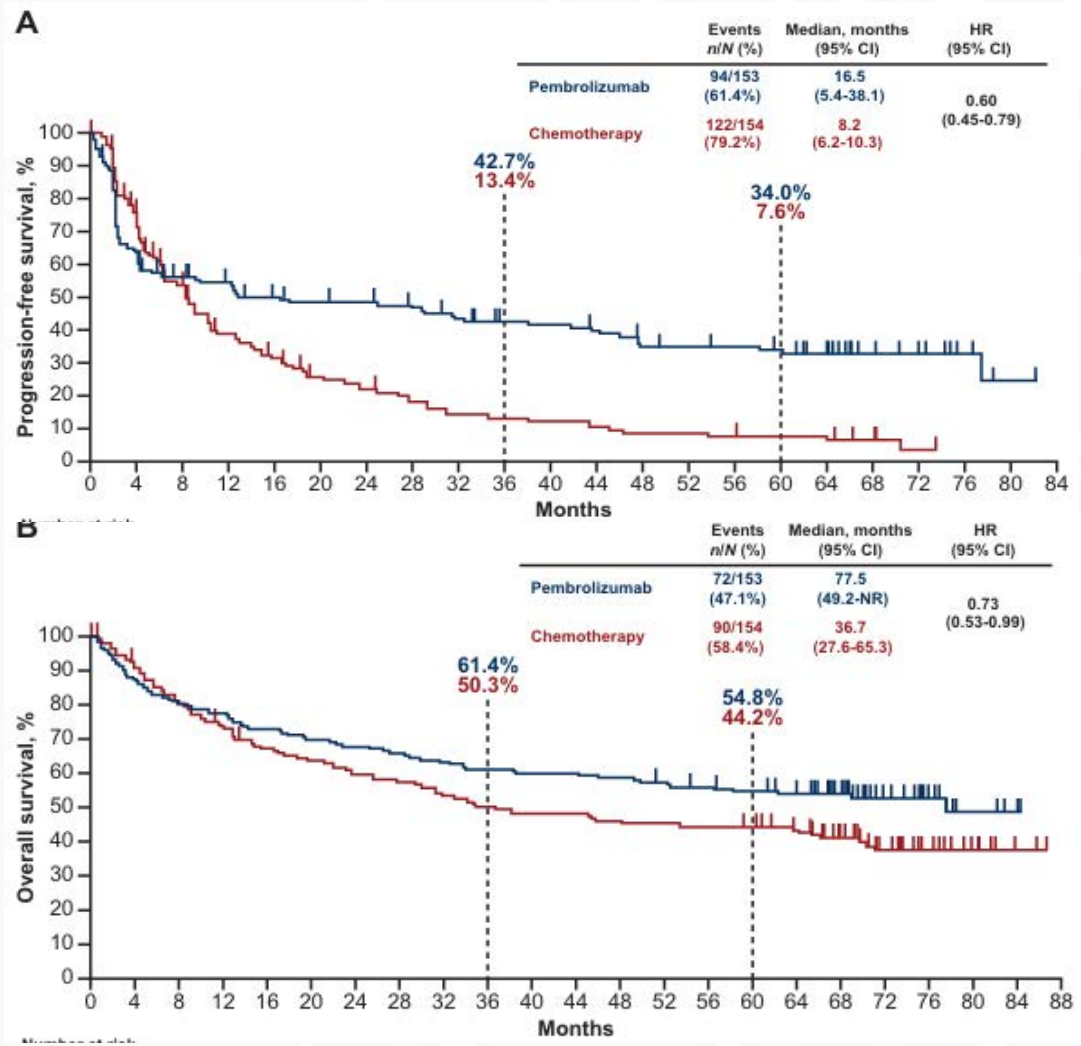
- First-line treatment with pembrolizumab versus chemotherapy did not result in a significant difference in survival of patients with MSI-H/d-MMR mCRC.
- 36% of patients in chemotherapy group met crossover criteria and received pembrolizumab + 24% of patients received off-study anti-PD-1/ PD-L1 therapies + 4% initially assigned to receive SOC refused treatment and had anti-PD1 off study.
- PFS benefit of pembrolizumab was maintained.
- Grade 3/4 TRAEs occurred in 56% versus 78% of patients receiving Pembrolizumab versus SOC, respectively.

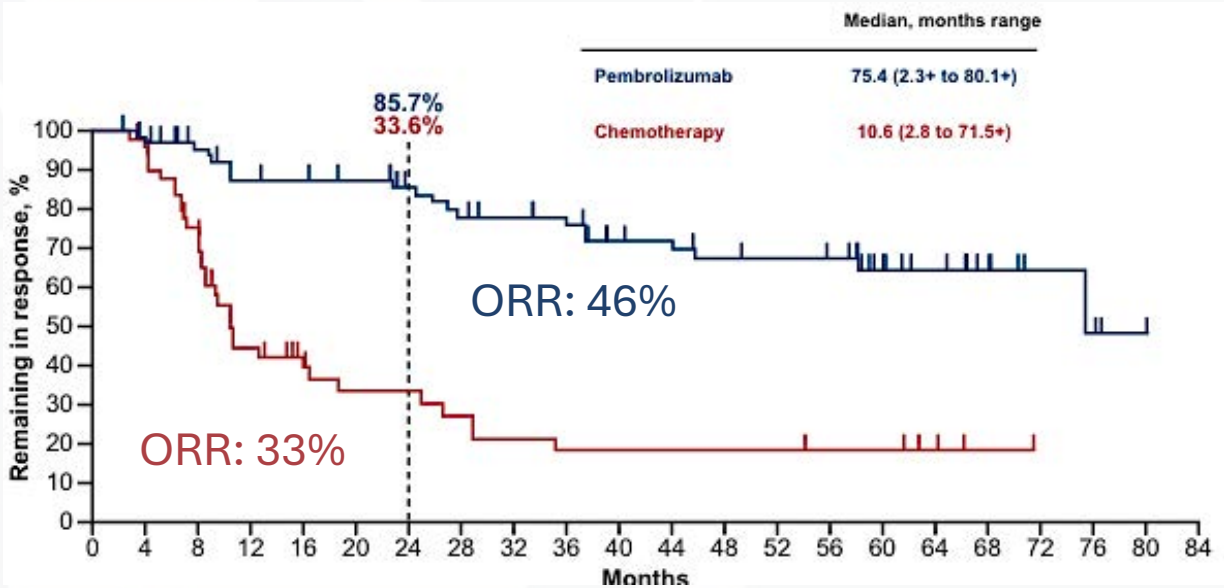
Diaz et. al. The Lancet Oncology 2022

Updated 5-Year Follow-up

Table 1. Subsequent anticancer therapy

	Pembrolizumab *n* = 153	Chemotherapy *n* = 154
No subsequent therapy	99 (64.7)	49 (31.8)
Any PD-(L)1 inhibitor therapy	20 (13.1)	96 (62.3)
On-protocol therapy with pembrolizumab[a]	12 (7.8)	57 (37.0)
Off-protocol therapies	8 (5.2)	39 (25.3)
Any therapy excluding PD-(L)1 inhibitor therapy	38 (24.8)	31 (20.1)





- First-line treatment with pembrolizumab versus chemotherapy results in a significant improvement of PFS and OS in survival of patients with MSI-H/d-MMR mCRC.
- 86% versus 34% of patients on pembrolizumab and chemotherapy arms, experienced a DOR of ≥ 24 months.
- Grade 3/4 TRAEs occurred in 22% versus 67% of patients receiving Pembrolizumab versus SOC, respectively.

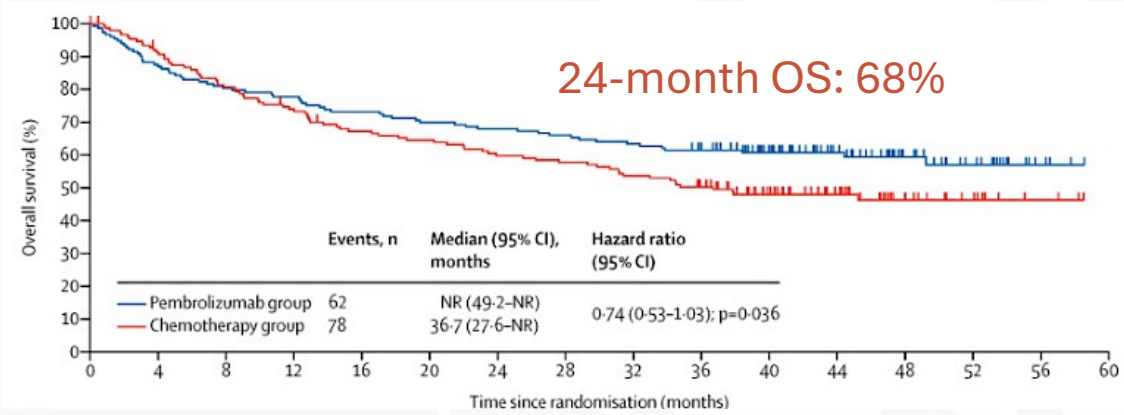
Andre et. al. Annals of Oncology 2025

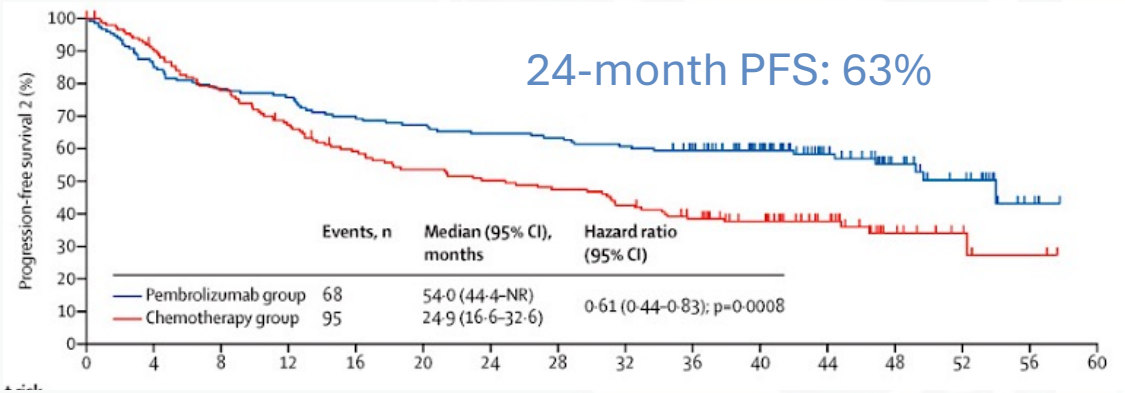
Phase III CheckMate 8HW Trial: Key Results

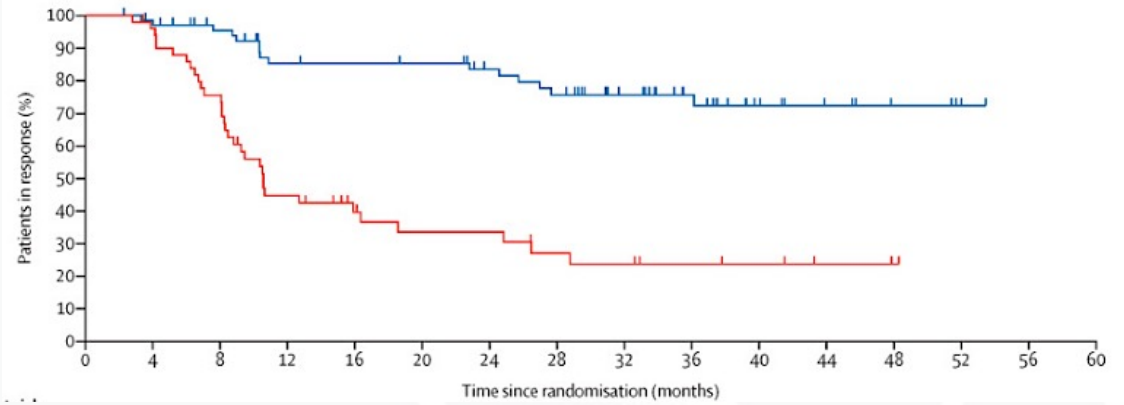
Nivolumab/Ipilimumab versus chemotherapy for patients with previously untreated MSI-H/dMMR mCRC

Background And Rationale

KEYNOTE-177



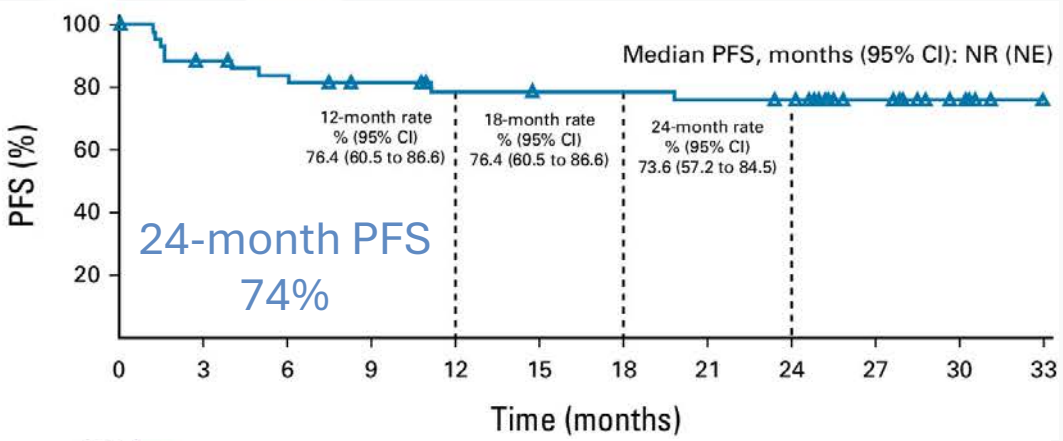


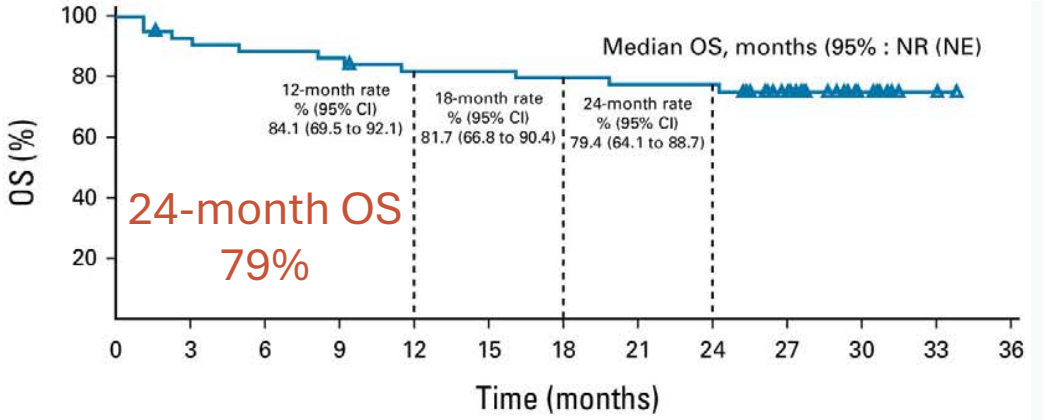


- Front-line pembrolizumab improved PFS over SOC chemotherapy in MSI-H/dMMR mCRC.

CheckMate 142

First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/ Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study





- First-line dual immune-checkpoint inhibition showed prolonged and robust survival outcomes in MSI-H/dMMR mCRC.

Study Design and Primary Endpoint

CheckMate 8HW

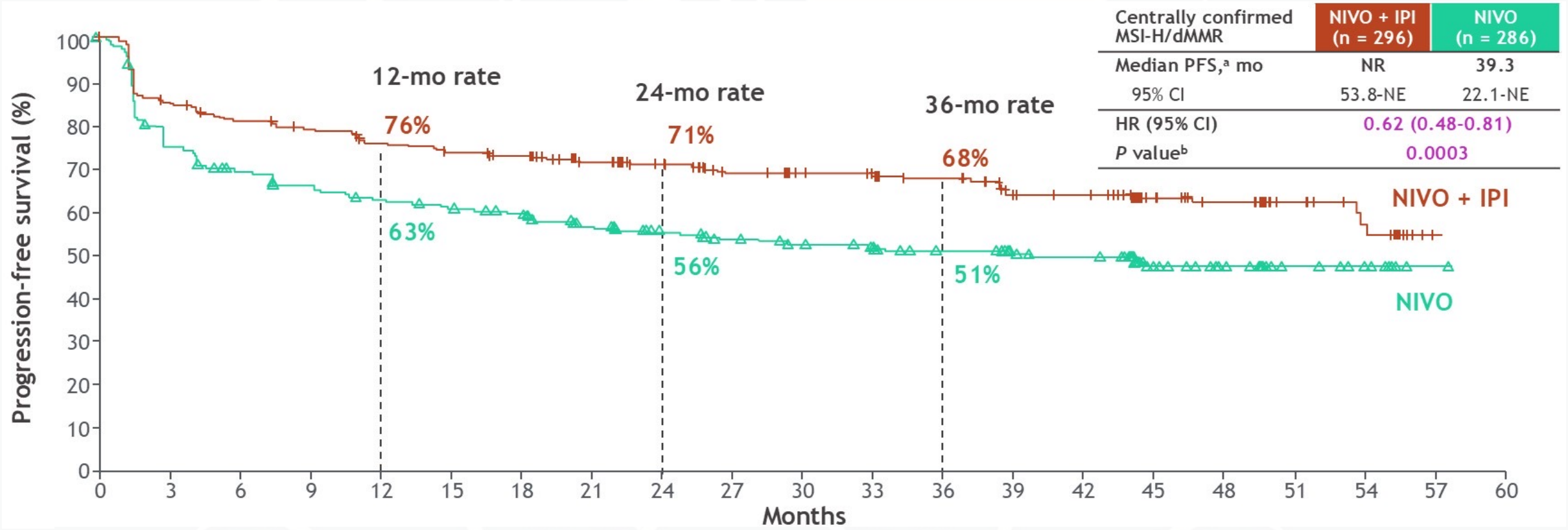
Eligibility Criteria (N = 839)

- Confirmed metastatic colorectal adenocarcinoma
- MSI-H/dMMR
- Immunotherapy-naïve
- Stratify by prior lines of therapy (0 vs 1 vs ≥2)

R 2:2:1

- NIVO (N = 353)
- NIVO + IPI (N = 354)
- SOC (Chemo ± Bev/Cetux) (N = 132)

Dual Primary Endpoints
(In centrally confirmed MSI-H/dMMR)
PFS by BICR (Nivo + Ipi vs. Nivo – all lines)

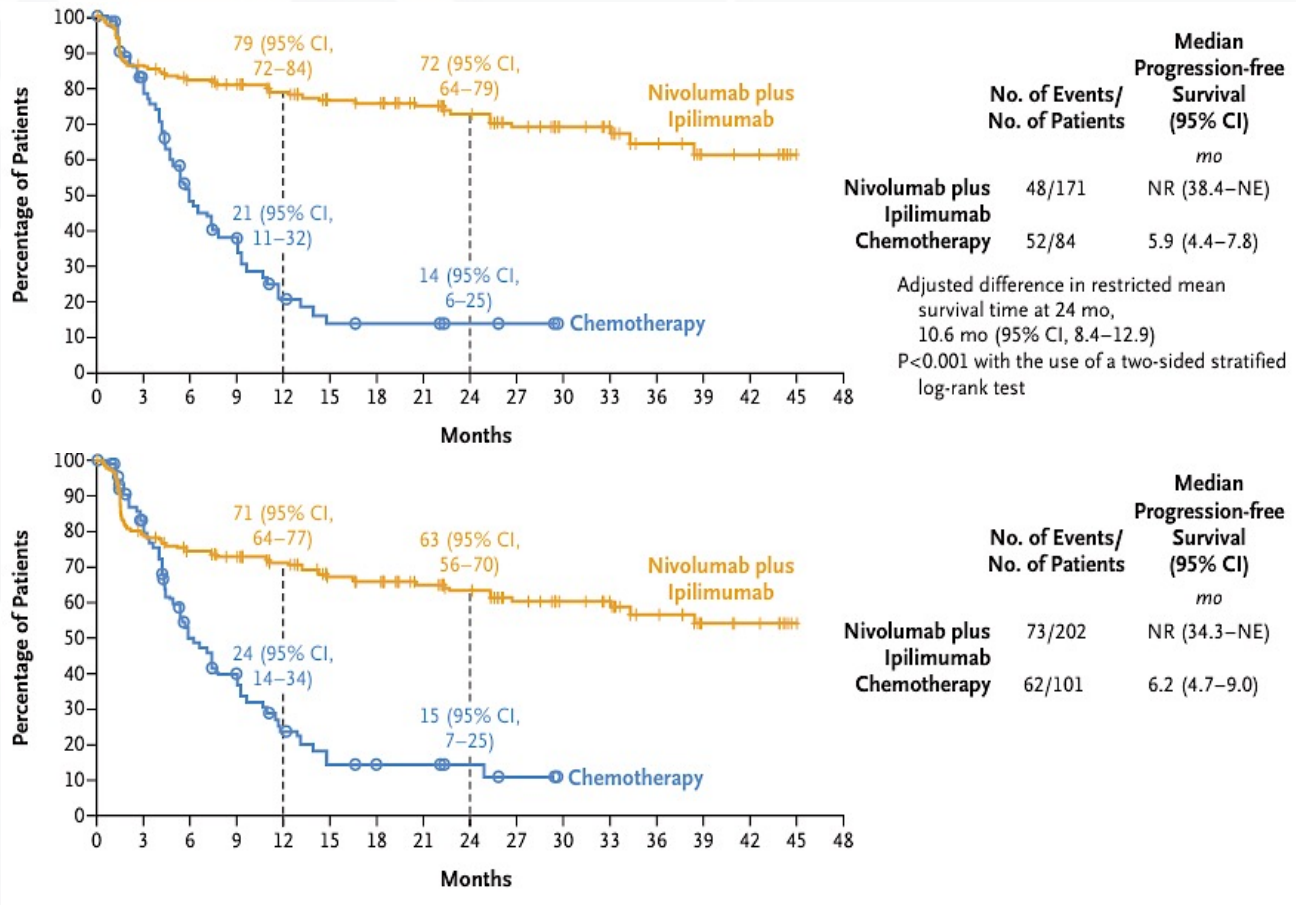


Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS,[a] mo	NR	39.3
95% CI	53.8-NE	22.1-NE
HR (95% CI)	0.62 (0.48-0.81)	
P value[b]	0.0003	

Andre et. al. NEJM 2024; Andre et. al. ASCO Gastrointestinal Cancers Symposium 2025

Other Key Results

	Nivo + Ipi (296)	Nivo (286)
Efficacy		
cORR (95%CI)	71% (65-76)	58% (52-64)
CR	30%	28%
PR	40%	30%
PD	10%	19%
Median TTR	2.8 months	2.8 months
Safety		
Grade ≥ TRAEs	22%	14%
Serious TRAEs	16%	7%
TRAEs with discontinuation	9%	4%



- PFS was longer with nivolumab plus ipilimumab versus nivolumab among patients with centrally confirmed MSI-H/dMMR mCRC.
- PFS was longer with upfront nivolumab plus ipilimumab than with chemotherapy among patients with MSI-H or dMMR mCRC.

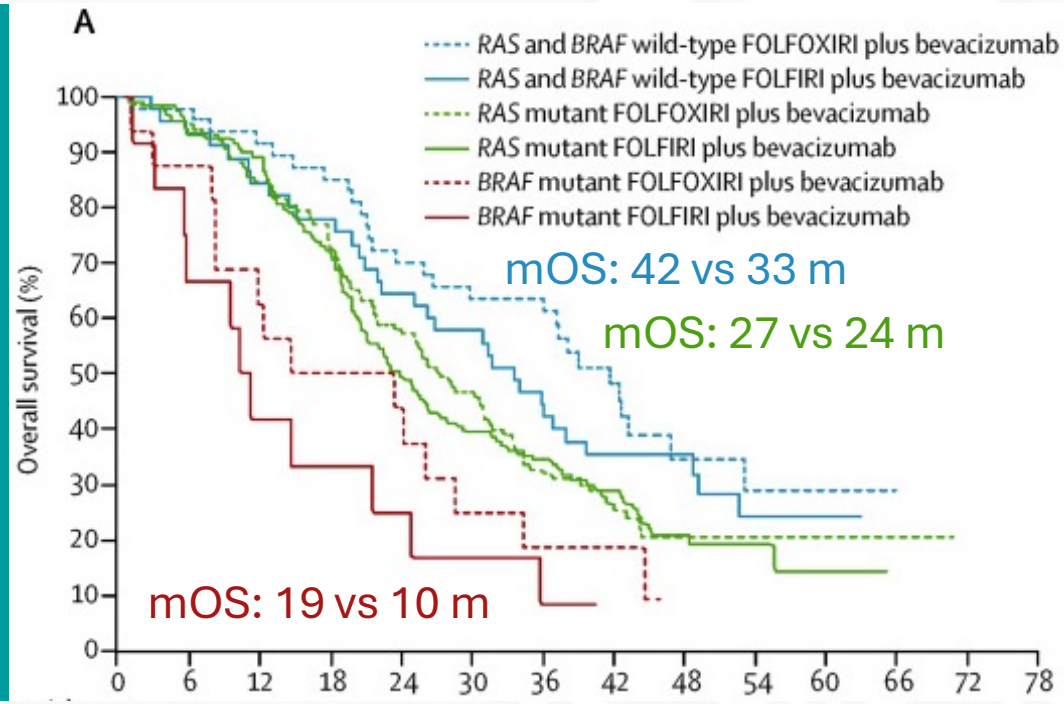
Andre et. al. NEJM 2024

Phase III BREAKWATER Trial: Primary Results

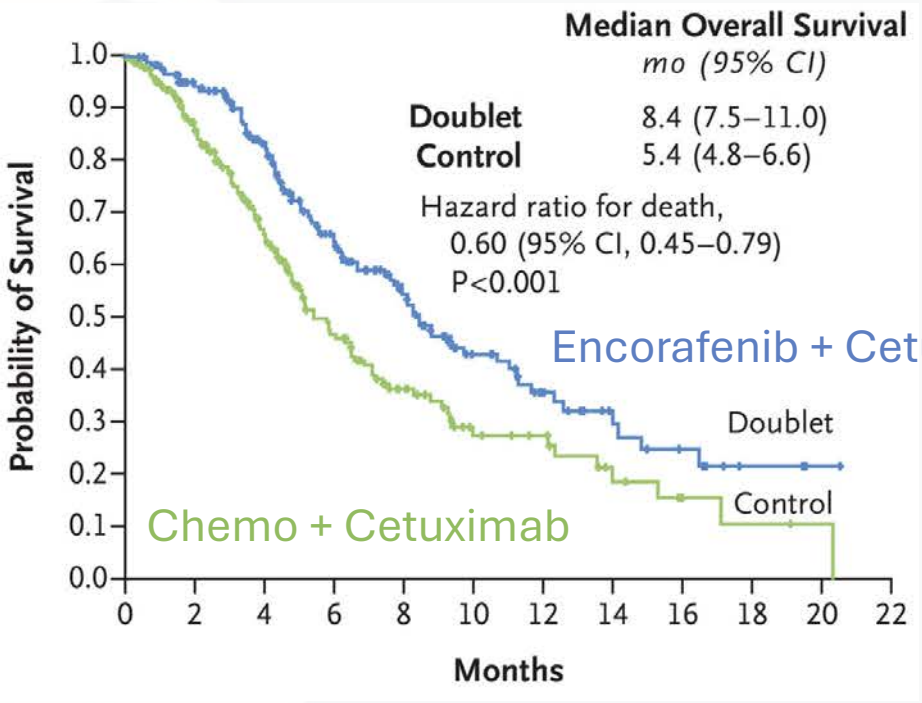
Encorafenib/Cetuximab with chemotherapy versus SOC chemotherapy for untreated BRAF V600E-mutant mCRC

Background And Rationale

TRIBE-2

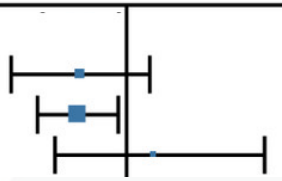


BEACON



- *BRAFV600* mutant mCRC is associated with poor prognosis with conventional therapies.
- Second-line dual BRAF-EGFR inhibition improves survival in *BRAFV600* mutant mCRC.

Subgroup	Doublets + Bev No. Events of Total (%)	FOLFOXIRI + Bev No. Events of Total (%)	HR (95% CI)	P
RAS and *BRAF* status				.337
RAS-BRAF wt	107 of 172 (62.2)	99 of 177 (55.9)	0.83 (0.63 to 1.10)	
RAS mut	316 of 430 (73.5)	289 of 422 (68.5)	0.82 (0.70 to 0.97)	
BRAF mut	43 of 54 (79.6)	53 of 61 (86.9)	1.11 (0.75 to 1.73)	



- Intensification of systemic cytotoxic therapy does not improve survival in *BRAFV600* mutant mCRC.

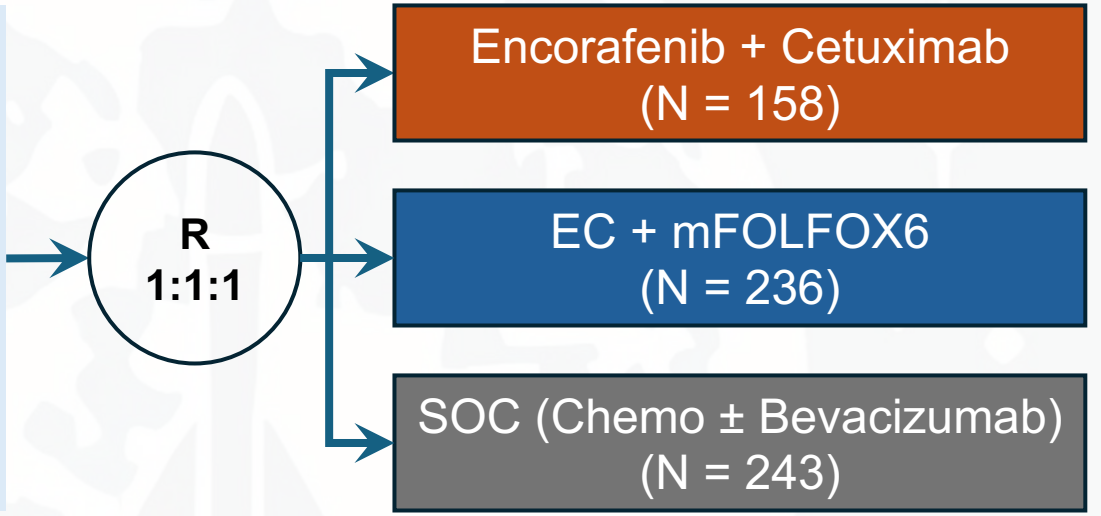
Cermolini et. al. The Lancet Oncology 2015; Cremolini et. al. JCO 2020

Study Design and Primary Endpoint

BREAKWATER

Eligibility Criteria (N = 637)

- Confirmed metastatic colorectal adenocarcinoma
- Measurable disease (RECIST 1.1)
- BRAF V600E mutant
- Not received prior systemic treatment for metastatic disease



Dual Primary Endpoints
PFS and ORR by BICR
(EC + Chemo vs. SOC)

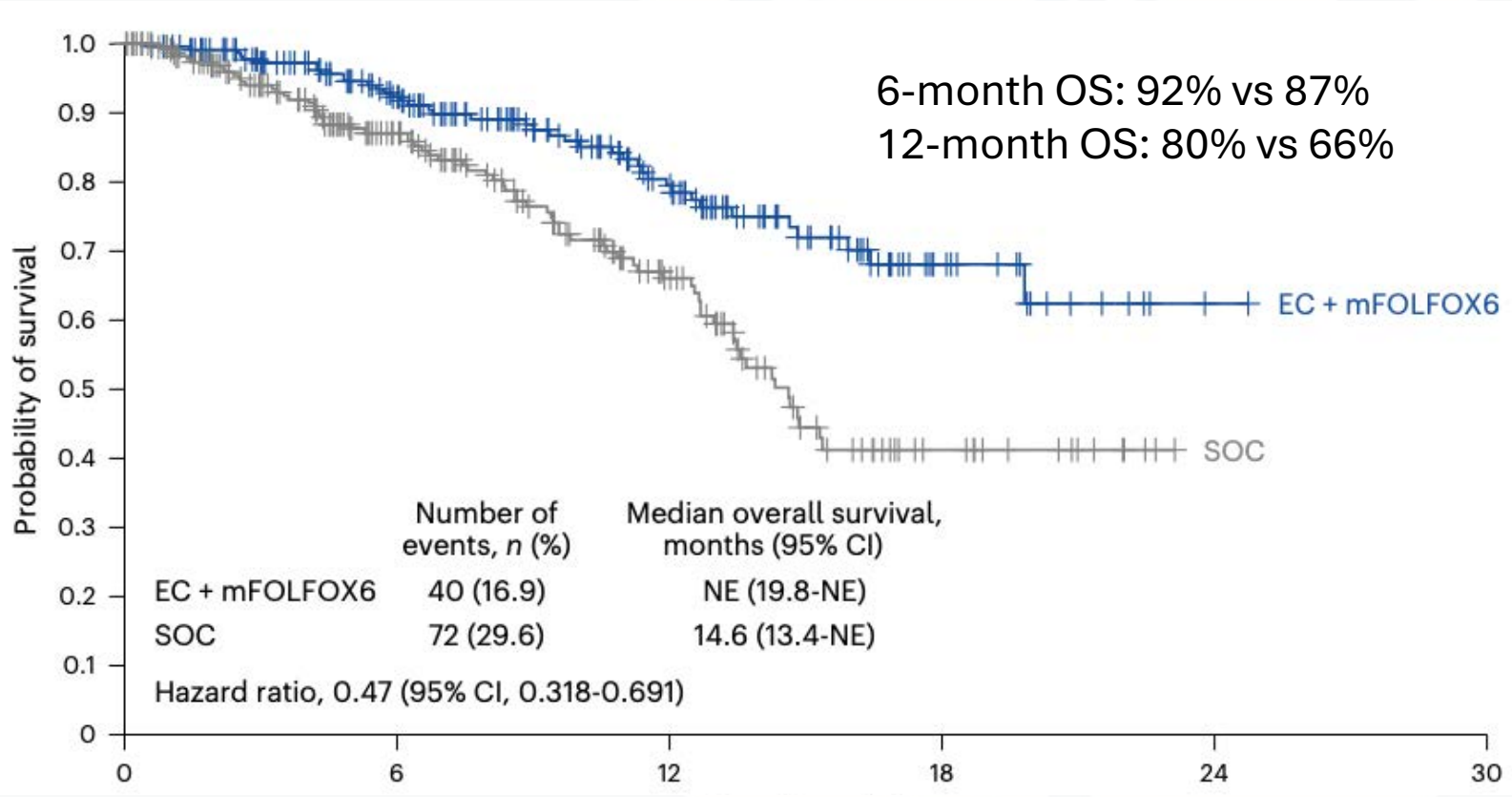
	EC+mFOLFOX6 (*n*=110)	SOC (*n*=110)
Confirmed best overall response, *n* (%)		
Complete response	3 (2.7)	2 (1.8)
Partial response	64 (58.2)	42 (38.2)
Stable disease	31 (28.2)	34 (30.9)
Confirmed objective response rate (95% CI), %[a]	60.9 (51.6–69.5)	40.0 (31.3–49.3)
Odds ratio (95% CI; 99.8% CI)[b]	2.443 (1.403–4.253; 1.019–5.855)	
One-sided *P* value	0.0008	

	EC+mFOLFOX6 (*n*=110)	SOC (*n*=110)
Median time to response (range), weeks	7.1 (5.7–53.7)	7.3 (5.4–48.0)
Estimated median duration of response (range), months	13.9 (8.5–NE)	11.1 (6.7–12.7)
Patients with a duration of response of ≥6 months, *n* (%)	46 (68.7)	15 (34.1)
Patients with a duration of response of ≥12 months, *n* (%)	15 (22.4)	5 (11.4)

- Addition of BRAF-targeted therapy to chemotherapy in front-line setting improved response rates and duration of response for *BRAFV600* mutant mCRC.

Kopetz et.al. Nature Medicine 2025

Other Key Results



- BRAF-targeted therapy + chemotherapy improved survival in front-line treatment of *BRAFV600* mutant mCRC, compared to SOC.
- 22% and 34% (21%-BRAF) patients received subsequent therapies.

- Grade 3/4 TRAEs occurred in 70% versus 54% of patients receiving EC+mFOLFOX6 versus SOC, respectively.

Table 3 | Most common all-causality treatment-emergent adverse events (≥10% of patients in any arm) by preferred term

	EC+mFOLFOX6 (*n*=231)		SOC (*n*=228)	
	Any grade	Grade≥3	Any grade	Grade≥3
Any adverse event	230 (99.6)	181 (78.4)	223 (97.8)	149 (65.4)
Nausea	118 (51.1)	6 (2.6)	110 (48.2)	7 (3.1)
Anemia	84 (36.4)	25 (10.8)	52 (22.8)	8 (3.5)
Diarrhea	79 (34.2)	3 (1.3)	107 (46.9)	8 (3.5)
Neutrophil count decreased	74 (32.0)	42 (18.2)	64 (28.1)	38 (16.7)
Decreased appetite	77 (33.3)	5 (2.2)	57 (25.0)	3 (1.3)
Vomiting	77 (33.3)	8 (3.5)	48 (21.1)	5 (2.2)
Asthenia	62 (26.8)	10 (4.3)	33 (14.5)	3 (1.3)
Pyrexia	60 (26.0)	4 (1.7)	31 (13.6)	1 (0.4)
Peripheral sensory neuropathy	57 (24.7)	13 (5.6)	49 (21.5)	5 (2.2)
Rash	57 (24.7)	2 (0.9)	6 (2.6)	0
Fatigue	56 (24.2)	6 (2.6)	57 (25.0)	6 (2.6)
Neuropathy peripheral	54 (23.4)	16 (6.9)	48 (21.1)	6 (2.6)
Arthralgia	51 (22.1)	2 (0.9)	8 (3.5)	0
Neutropenia	51 (22.1)	34 (14.7)	51 (22.4)	21 (9.2)
Alopecia	49 (21.2)	0	23 (10.1)	0
Constipation	47 (20.3)	1 (0.4)	44 (19.3)	1 (0.4)
Platelet count decreased	46 (19.9)	3 (1.3)	28 (12.3)	4 (1.8)
White blood cell count decreased	42 (18.2)	13 (5.6)	32 (14.0)	8 (3.5)
Lipase increased	46 (19.9)	34 (14.7)	22 (9.6)	12 (5.3)
Weight decreased	40 (17.3)	2 (0.9)	19 (8.3)	0
Skin hyperpigmentation	39 (16.9)	0	5 (2.2)	0
Abdominal pain	38 (16.5)	7 (3.0)	47 (20.6)	3 (1.3)
Dermatitis acneiform	35 (15.2)	2 (0.9)	1 (0.4)	0
Hypokalemia	30 (13.0)	4 (1.7)	22 (9.6)	7 (3.1)
Aspartate aminotransferase increased	29 (12.6)	2 (0.9)	25 (11.0)	3 (1.3)

Kopetz et.al. Nature Medicine 2025

Anti-HER2 Therapy: Key Findings

Trastuzumab plus Tucatinib/Pertuzumab and Trastuzumab Deruxtecan for previously treated HER2-positive mCRC

Trastuzumab + Tucatinib

MOUNTAINEER

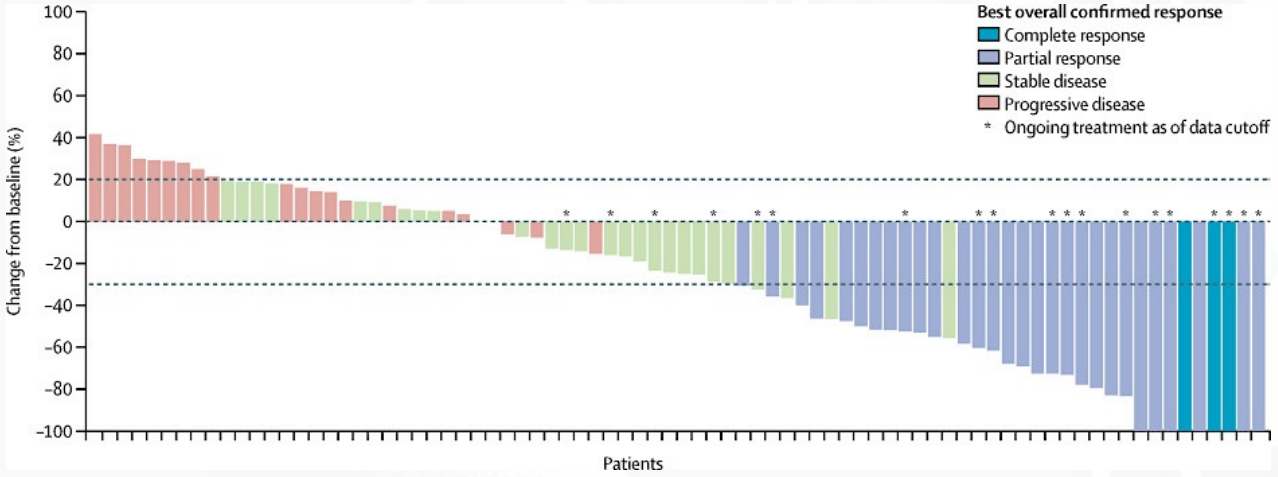
Eligibility Criteria (N = 117)

- Confirmed metastatic colorectal adenocarcinoma
- HER2-positive per local IHC/ISH/NGS testing
- *RAS*-WT
- Progression after receiving ≥2 lines of therapy

R 1:1

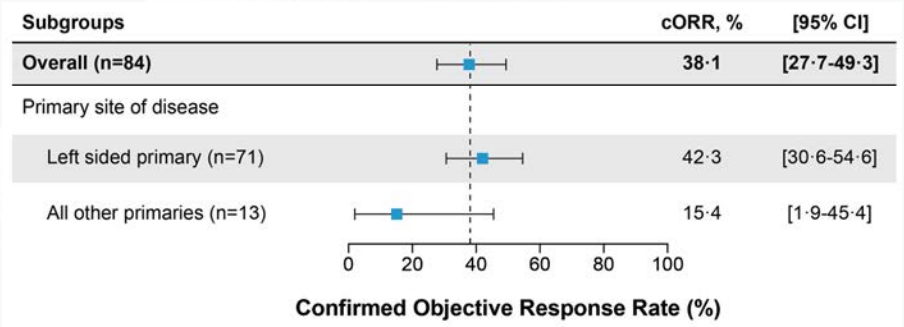
- Cohort A (N = 45) Trastuzumab + Tucatinib
- Cohort B (N = 41) Trastuzumab + Tucatinib
- Cohort C (N = 31) Tucatinib

Primary Endpoints
cORR (cohort A + B)
(Non-comparative randomization)



Responses		Tucatinib + Trastuzumab Cohorts A+B n=84[1]	Tucatinib Monotherapy Cohort C n=30	Tucatinib + Trastuzumab Post-Crossover n=28
Best overall response per BICR[a], n (%)	CR	3 (3.6)	0	0
	PR	29 (34.5)	1 (3.3)	5 (17.9)
	SD[b]	28 (33.3)	23 (76.7)	18 (64.3)
	PD	22 (26.2)	4 (13.3)	5 (17.9)
	Not available[c]	2 (2.4)	2 (6.7)	0
ORR per BICR, % (95% CI)[d]		**38.1 (27.7-49.3)[f]**	**3.3 (0.1-17.2)[g]**	**17.9 (6.1-36.9)[f]**
DCR[e] per BICR, n (%)		**60 (71.4)**	**24 (80.0)**	**23 (82.1)**

Responses	IHC 3+ (n=45)	IHC 2+/ISH+ (n=15)
Confirmed objective response rate†, % (95% CI)	46·7 (31·7–62·1)	20·0 (4·3–48·1)
Complete response, n (%)‡	3 (6·7)	0
Partial response, n (%)‡	18 (40·0)	3 (20·0)
Stable disease, n(%)‡,§	17 (37·8)	5 (33·3)
Progressive disease, n (%)‡	7 (15·6)	6 (40·0)
Not available, n (%)¶	0	1 (6·7)



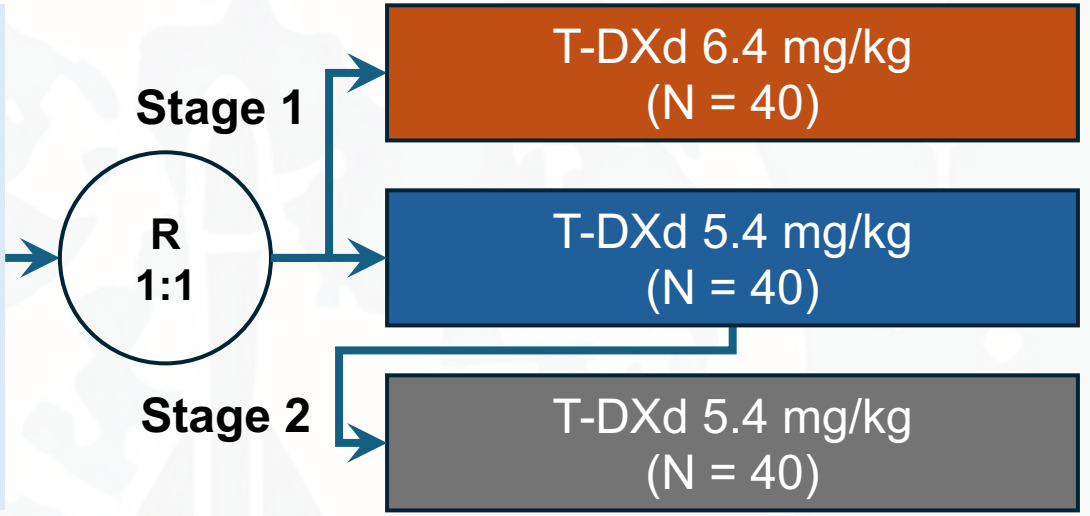
Strickler et. al. Lancet Oncology 2023; Strickler ASCO 2024

Trastuzumab Deruxtecan

DESTINY-CRC02

Eligibility Criteria (N = 120)

- Confirmed metastatic colorectal adenocarcinoma
- HER2-positive per central IHC/ISH testing
- *RAS*-WT or *RAS*-MUT
- Progression after receiving >2 lines of therapy

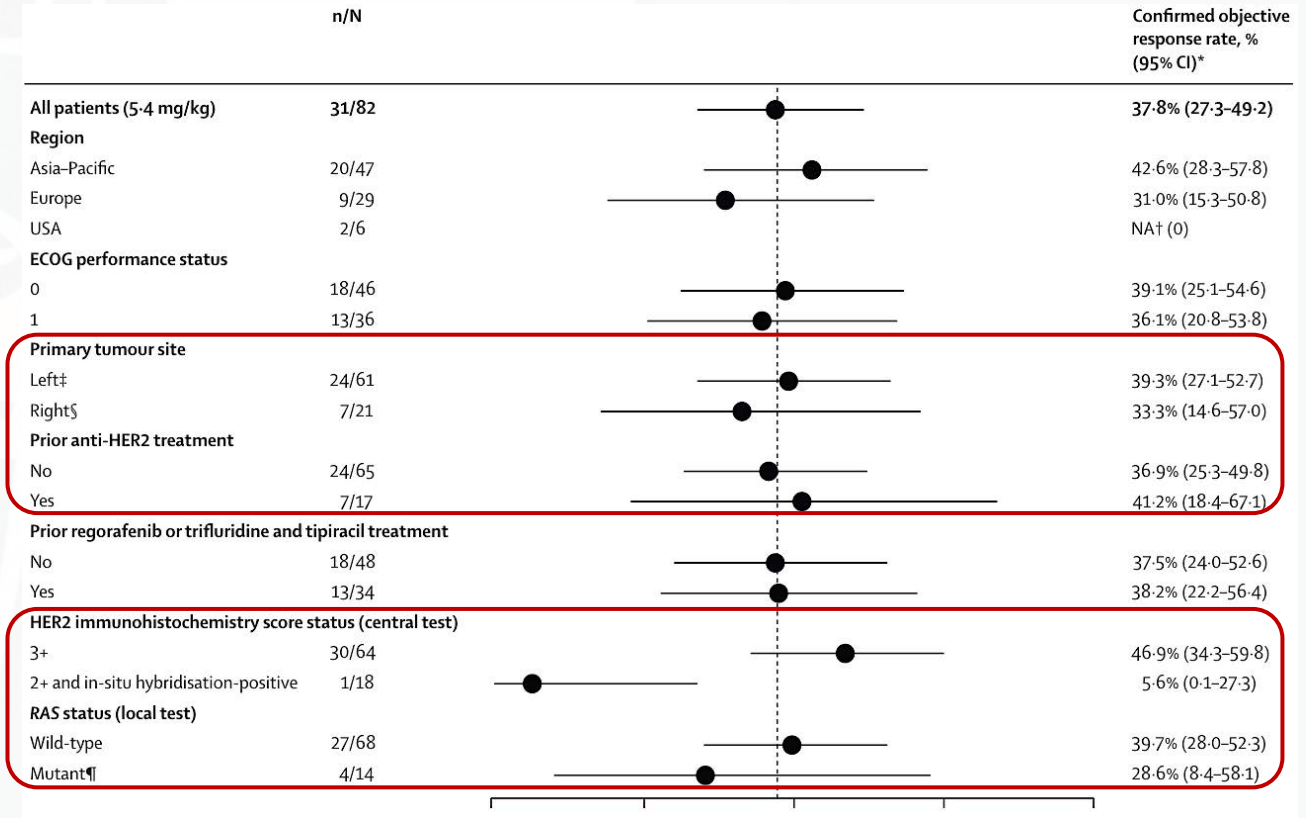


Dual Primary Endpoints
cORR by BICR

	Trastuzumab deruxtecan 5·4 mg/kg group (n=82)	Trastuzumab deruxtecan 6·4 mg/kg group (n=40)
Confirmed objective response rate* (% [95% CI)	31 (37·8% [27·3–49·2])	11 (27·5% [14·6–43·9])
Complete response	0	0
Partial response	31 (38%)	11 (28%)
Stable disease	40 (49%)	23 (58%)
Progressive disease	8 (10%)	4 (10%)
Not evaluable	3 (4%)	2 (5%)
Confirmed disease control rate* (% [95% CI])	71 (86·6% [77·3–93·1])	34 (85·0% [70·2–94·3])
Confirmed clinical benefit rate* (% [95% CI])	37 (45·1% [34·1–56·5])	13 (32·5% [18·6–49·1])
Median duration of response*, months (95% CI)	5·5 (4·2–8·1)	5·5 (3·7–NE)
Median progression-free survival*, months (95% CI)	5·8 (4·6–7·0)	5·5 (4·2–7·0)
Patients with events	54 (66%)	27 (68%)
Median overall survival, months (95% CI)	13·4 (12·5–16·8)	NE (9·9–NE)
Patients with events	26 (32%)	13 (33%)
Median follow-up, months (IQR)	8·9 (6·7–10·5)	10·3 (5·9–12·7)
Median treatment duration†, months (IQR)	5·5 (3·6–8·4)	4·9 (2·8–8·5)
Median total dose†, mg/kg (IQR)	37·8 (26·9–59·4)	40·8 (25·4–66·1)
Median cycles initiated† (IQR)	7·0 (5·0–11·0)	7·0 (4·0–11·0)

Data are n (%) except where otherwise stated. NE=not estimable. *Assessed by blinded independent central review. †Based on the total population treated with trastuzumab deruxtecan; 5·4 mg/kg, n=83; 6·4 mg/kg, n=39 (safety analysis set).

Table 2: **Antitumour activity endpoints**



Raghav et. al. Lancet Oncology 2024

Trastuzumab + Pertuzumab

S1613

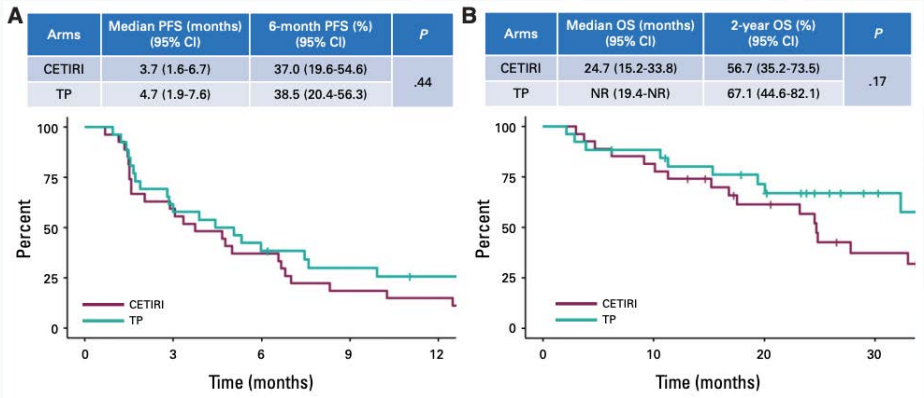
Eligibility Criteria (N = 54)

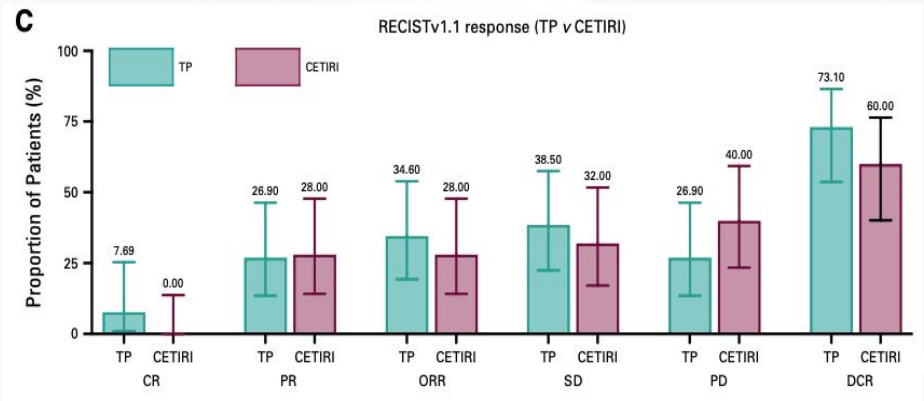
- Confirmed metastatic colorectal adenocarcinoma
- HER2-positive per central IHC/ISH testing
- *RAS/BRAF*-WT
- Progression after receiving 1 or 2 lines of therapy

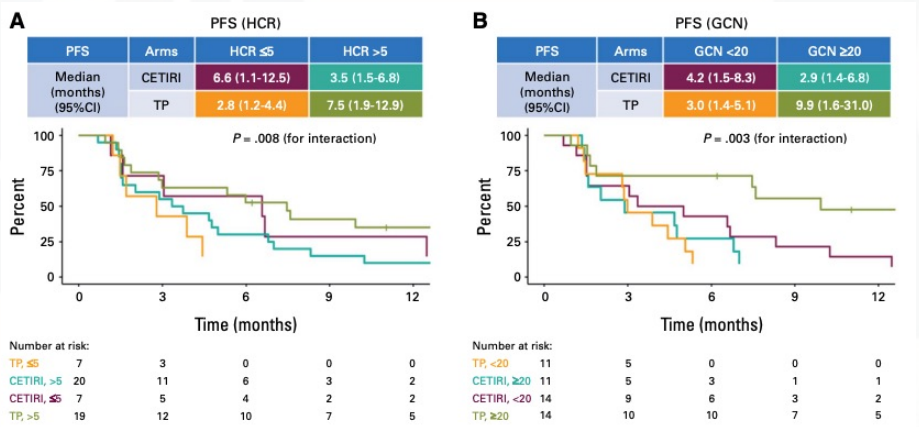
R 1:1

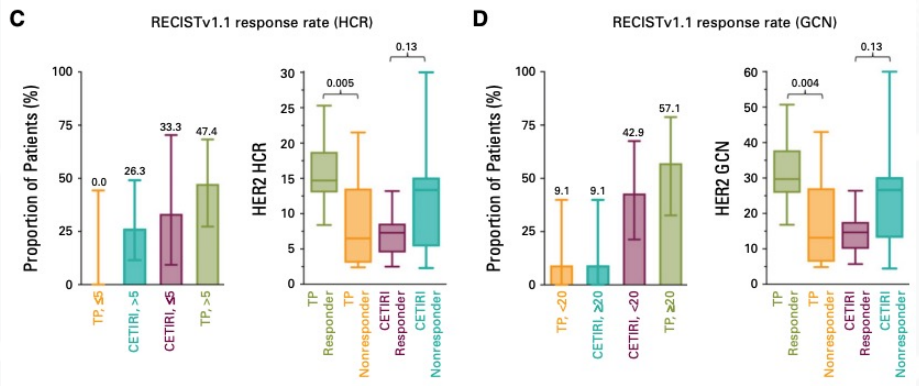
- Trastuzumab + Pertuzumab (N = 26)
- SOC (Cetux + Irinotecan) (N = 28)

Primary Endpoint
PFS









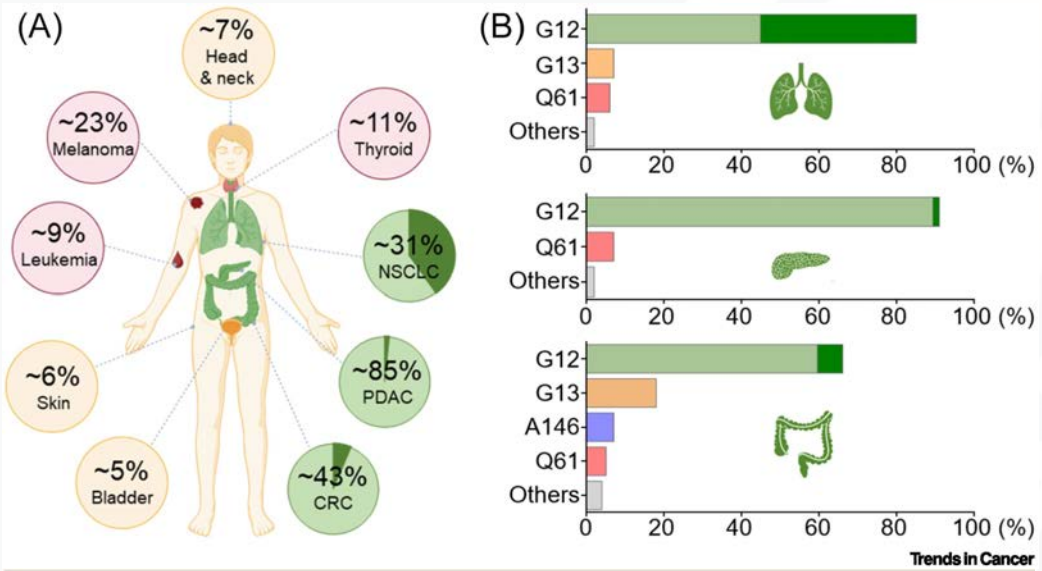
- TP appears to be a safe (Grade 3/4 TRAEs: 23% vs. 46%) and effective cytotoxic therapy free option for *RAS/BRAF*-WT, HER2-positive mCRC.
- Higher levels of *HER2* amplification ~ associated with greater benefit from TP vs. CETIRI

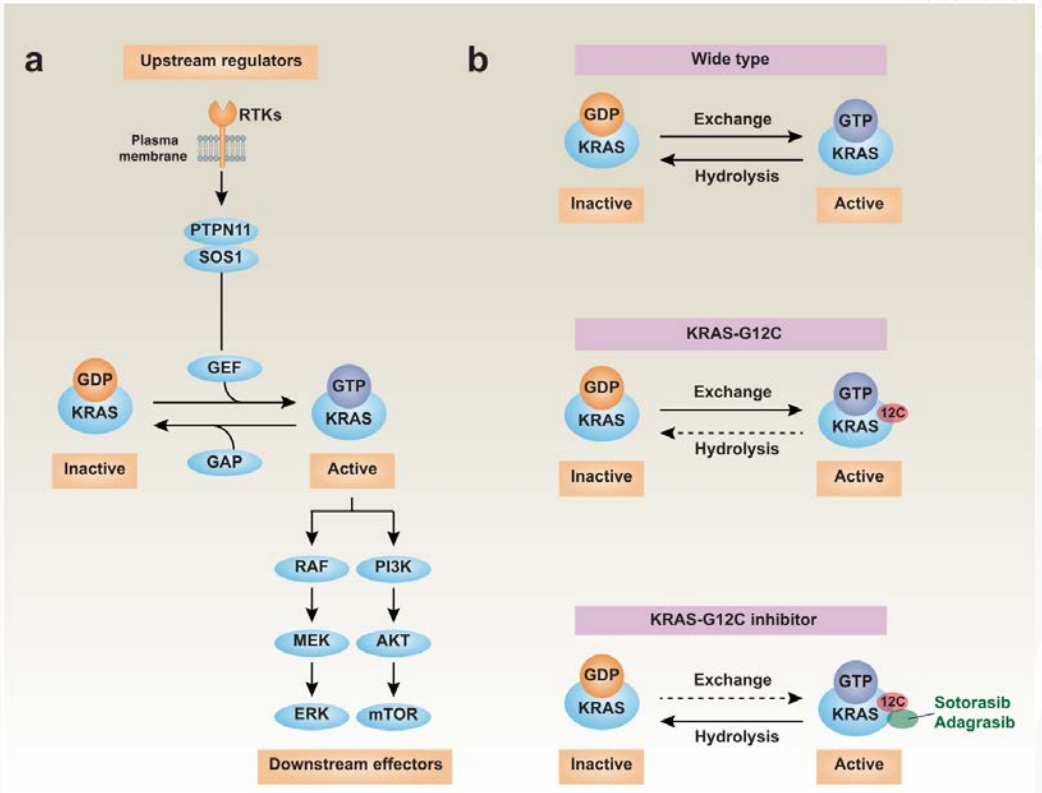
Raghav et.al. JCO 2025

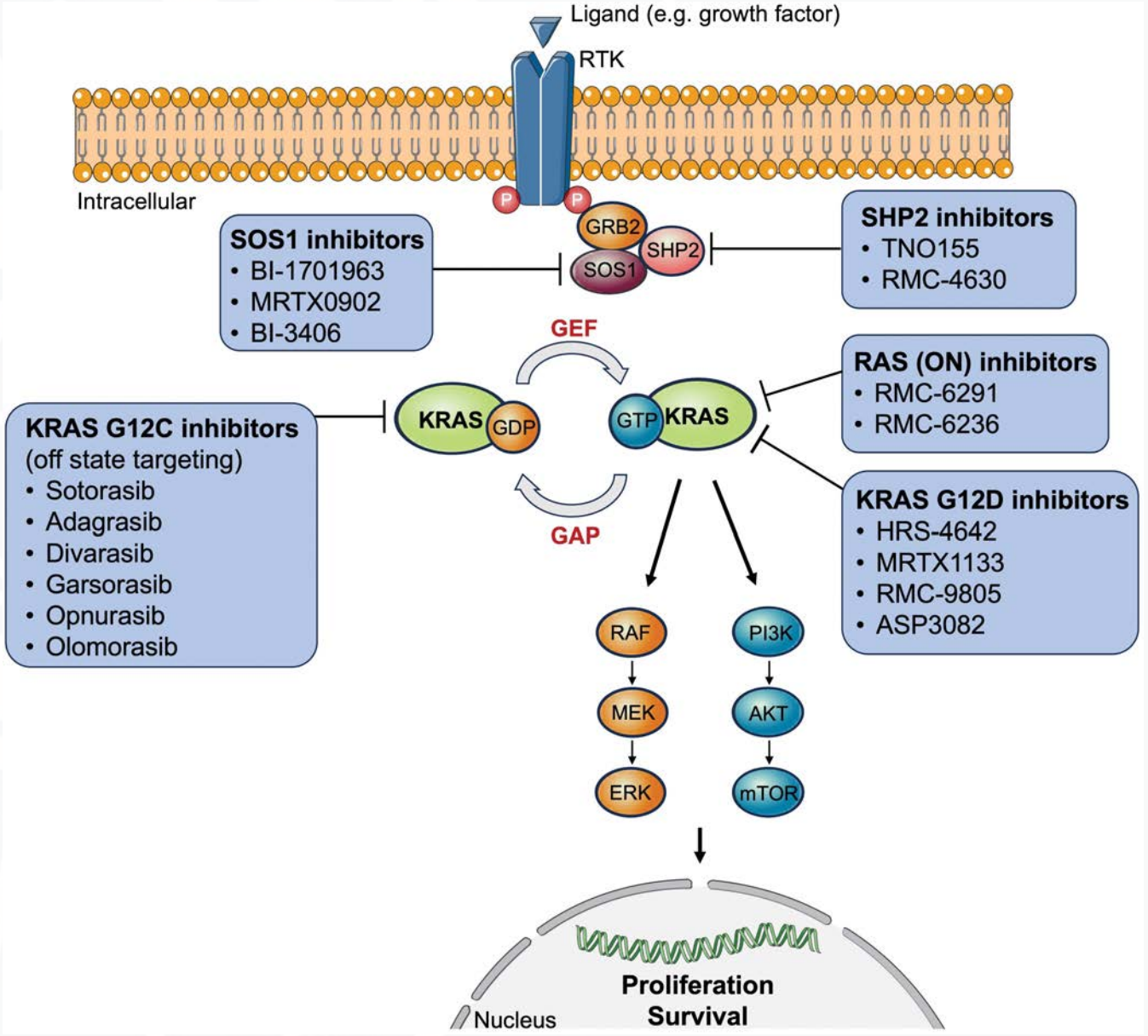
Anti-KRAS G12C Therapy: Emerging Data

Sotorasib plus Panitumumab and Adagrasib plus Cetuximab for previously treated KRAS G12C-mutated mCRC

Background And Rationale







Isermann et. al. Trends in Cancer 2025; Liu et. al. Cancer Gene Therapy 2022; Sreter et. al. Frontiers in Oncology 2024

Adagrasib

KRYSTAL-1

Eligibility Criteria (N = 76)

- Confirmed metastatic colorectal adenocarcinoma
- *KRASG12C* mutant
- No available SOC treatment (or ineligible or declined)

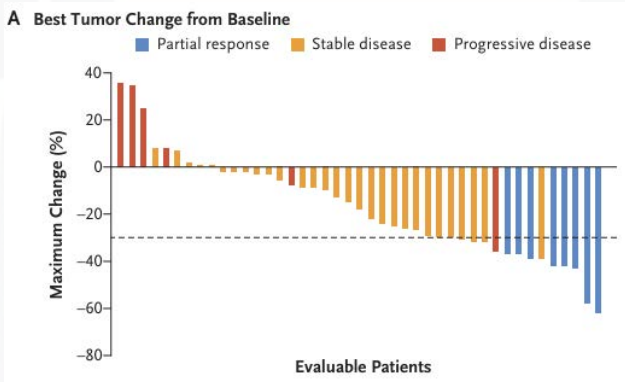
Adagrasib (N = 44)

Adagrasib + Cetuximab (N = 32)

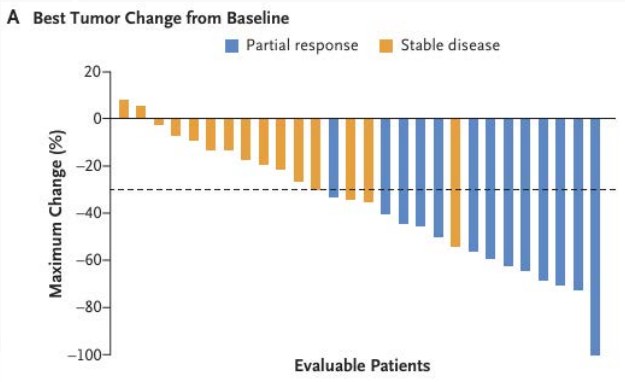
Primary Endpoints
ORR and Safety

Table 2. Overall Summary of Clinical Activity.*

Variable	Adagrasib Monotherapy (N=43)†	Adagrasib plus Cetuximab (N=28)‡
Objective response§		
Per blinded independent central review — no. of patients	10	13
% (95% CI)	23 (12–39)	46 (28–66)
As confirmed by investigator — no. of patients	8	13
% (95% CI)	19 (8–33)	46 (28–66)
Best overall response — no. (%)		
Complete response	0	0
Partial response	8 (19)	13 (46)
Stable disease	29 (67)	15 (54)
Progressive disease	6 (14)	0
Not evaluable	0	0
Median duration of response — mo	4.3	7.6
95% CI	2.3–8.3	5.7–NE
Median progression-free survival — mo¶	5.6	6.9
95% CI	4.1–8.3	5.4–8.1
Median overall survival — mo¶	19.8	13.4
95% CI	12.5–23.0	9.5–20.1



Adagrasib Monotherapy



Adagrasib + Cetuximab

- Updated (N = 94) treated with Adagrasib + Cetuximab: ORR 34.0%; DCR 85.1%, mDOR 5.8 months, mPFS 6.9 months and mOS 15.9 months.
- Grade 3/4 TRAEs occurred in 28% cases.

Yaeger et.al. NEJM 2022; Yaeger et. al. Cancer Discovery 2024

Sotorasib

CodeBreaK 300

Eligibility Criteria (N = 160)

- Confirmed metastatic colorectal adenocarcinoma
- *KRASG12C* mutant
- Progression after receiving at least one previous line of therapy for mCRC

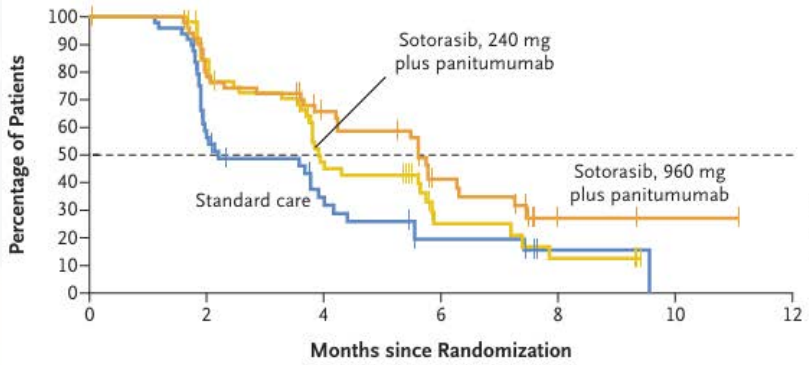
R 1:1:1

- Sotorasib 960 + Panitumumab (N = 53)
- Sotorasib 240 + Panitumumab (N = 53)
- SOC (Bev-TAS or Rego) (N = 54)

Primary Endpoint
PFS by BICR

Table 2. Efficacy According to Blinded Independent Central Review in the Intention-to-Treat Population.*

Variable	960-mg Sotorasib–Panitumumab (N=53)	240-mg Sotorasib–Panitumumab (N=53)	Standard Care (N=54)
Primary end point: progression-free survival			
Median (95% CI) — mo†	5.6 (4.2 to 6.3)	3.9 (3.6 to 5.7)	2.0 (1.9 to 3.9)
Hazard ratio (95% CI)‡	0.48 (0.30 to 0.78)	0.59 (0.37 to 0.95)	—
P value§	0.005	0.036	—
Secondary end points			
Best overall response — no. (%)			
Complete response	1 (1.9)	0	0
Partial response	13 (24.5)	3 (5.7)	0
Stable disease	24 (45.3)	33 (62.3)	25 (46.3)
Progressive disease	12 (22.6)	13 (24.5)	17 (31.5)
Noncomplete response or nonprogressive disease	0	2 (3.8)	1 (1.9)
Not assessed	2 (3.8)	1 (1.9)	11 (20.4)
No assessable disease at baseline¶	1 (1.9)	1 (1.9)	0
Percentage of patients with objective response (95% CI)‖	26.4 (15.3 to 40.3)	5.7 (1.2 to 15.7)	0.0 (0.0 to 6.6)
Difference in proportions**	27.0 (14.9 to 39.0)	5.5 (–0.7 to 11.8)	—
Percentage of patients with disease control (95% CI)‖††	71.7 (57.7 to 83.2)	67.9 (53.7 to 80.1)	46.3 (32.6 to 60.4)
Median duration of response (95% CI) — mo‡‡	4.4 (3.6 to not reached)	—	—
Median time to response (range) — mo‡‡	2.1 (1.9 to 3.9)	1.8 (1.7 to 1.9)	—



	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.48 (0.30–0.78)	0.005
Sotorasib, 240 mg plus Panitumumab	3.91	0.59 (0.37–0.95)	0.036
Standard Care	2.04		

- KRAS G12C + EGFR inhibition improved PFS in patients with refractory *KRAS G12C* mutant mCRC.
- Grade 3/4 TRAEs occurred in 36%, 30% versus 43% of patients receiving Soto960, Soto240 versus SOC, respectively.

Fakih et.al. NEJM 2023

Phase III FRESCO-2 Study:

Fruquintinib for patients with mCRC who have progressed on or are intolerant to approved standard therapies

Background And Rationale

FRESCO

Eligibility Criteria (N = 416)

- Confirmed metastatic colorectal adenocarcinoma
- Progressed on at least 2 lines of therapy
- May have received anti-VEGF therapy

R 2:1

Fruquintinib (N = 278)

Placebo (N = 138)

Primary Endpoint OS

- FRESCO: a randomized, double-blind, placebo-controlled, multicenter (28 hospitals in China), phase 3 clinical trial (December 2014 to May 2016)

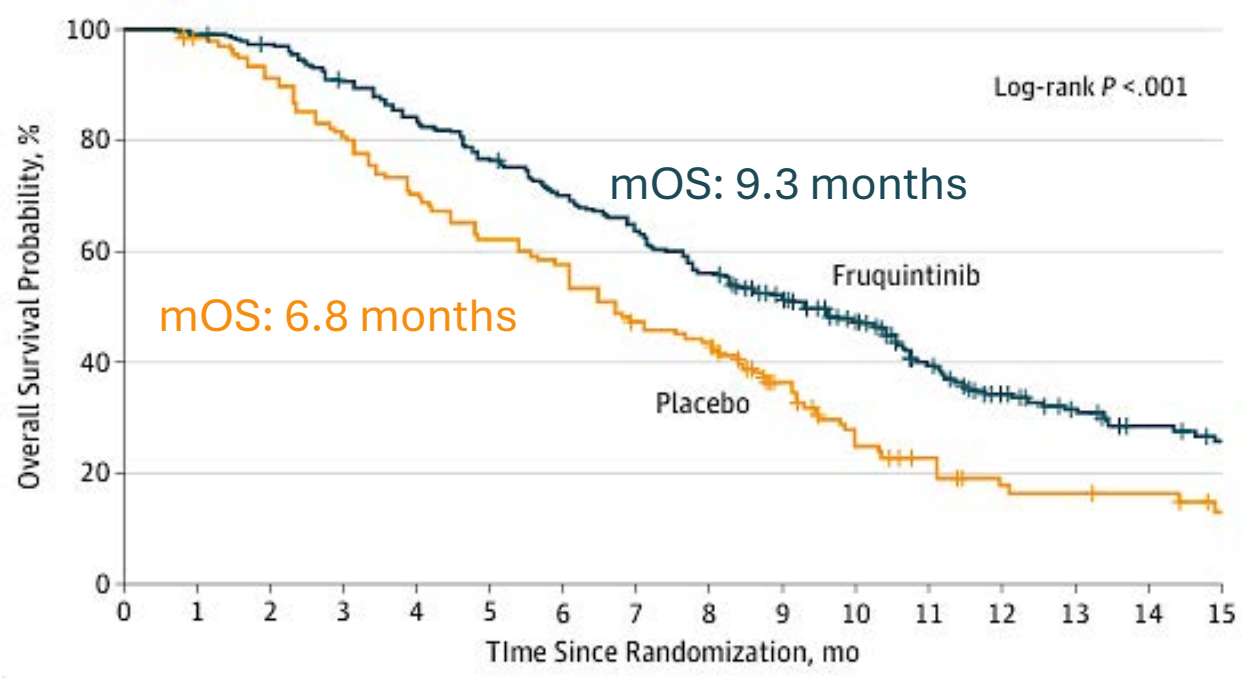


Figure 3. Subgroup Analyses for Overall Survival (Primary Outcome) in Patients With Metastatic Colorectal Cancer Receiving Fruquintinib vs Placebo (Intent-to-Treat Population)

Group	Fruquintinib, No. Deaths	Fruquintinib, No. Total	Placebo, No. Deaths	Placebo, No. Total	Hazard Ratio (95% CI)	P for Interaction
Age						
<65	151	228	88	110	0.56 (0.43-0.73)	.09
≥65	37	50	21	28	0.95 (0.55-1.63)	
Sex						
Men	108	158	77	97	0.52 (0.39-0.70)	.06
Women	80	120	32	41	0.85 (0.57-1.29)	
Number of prior treatment lines on metastatic disease						
≤3	146	221	86	107	0.64 (0.49-0.83)	.87
>3	42	57	23	31	0.53 (0.31-0.90)	
Previous chemotherapy lines						
2 or 3	126	190	80	98	0.60 (0.46-0.80)	.50
>3	62	88	29	40	0.67 (0.43-1.05)	
Prior use of VEGF inhibitors						
Yes	60	84	35	41	0.68 (0.45-1.03)	.72
No	128	194	74	67	0.60 (0.45-0.80)	
Primary tumor site at the time of diagnosis[a]						
Left side	141	214	91	115	0.56 (0.43-0.73)	.17
Right side	41	56	16	21	0.96 (0.53-1.75)	
Metastasis						
Single	5	13	2	4	1.03 (0.20-5.37)	.60
Multiple	183	265	107	134	0.61 (0.48-0.78)	
Liver metastasis						
Yes	134	185	85	102	0.59 (0.45-0.77)	.43
No	54	93	24	36	0.75 (0.46-1.21)	
Overall	188	278	109	138	0.62 (0.49-0.79)	

Li et. al. JAMA 2018

Study Design and Primary Endpoint

FRESCO-2

Eligibility Criteria (N = 934)

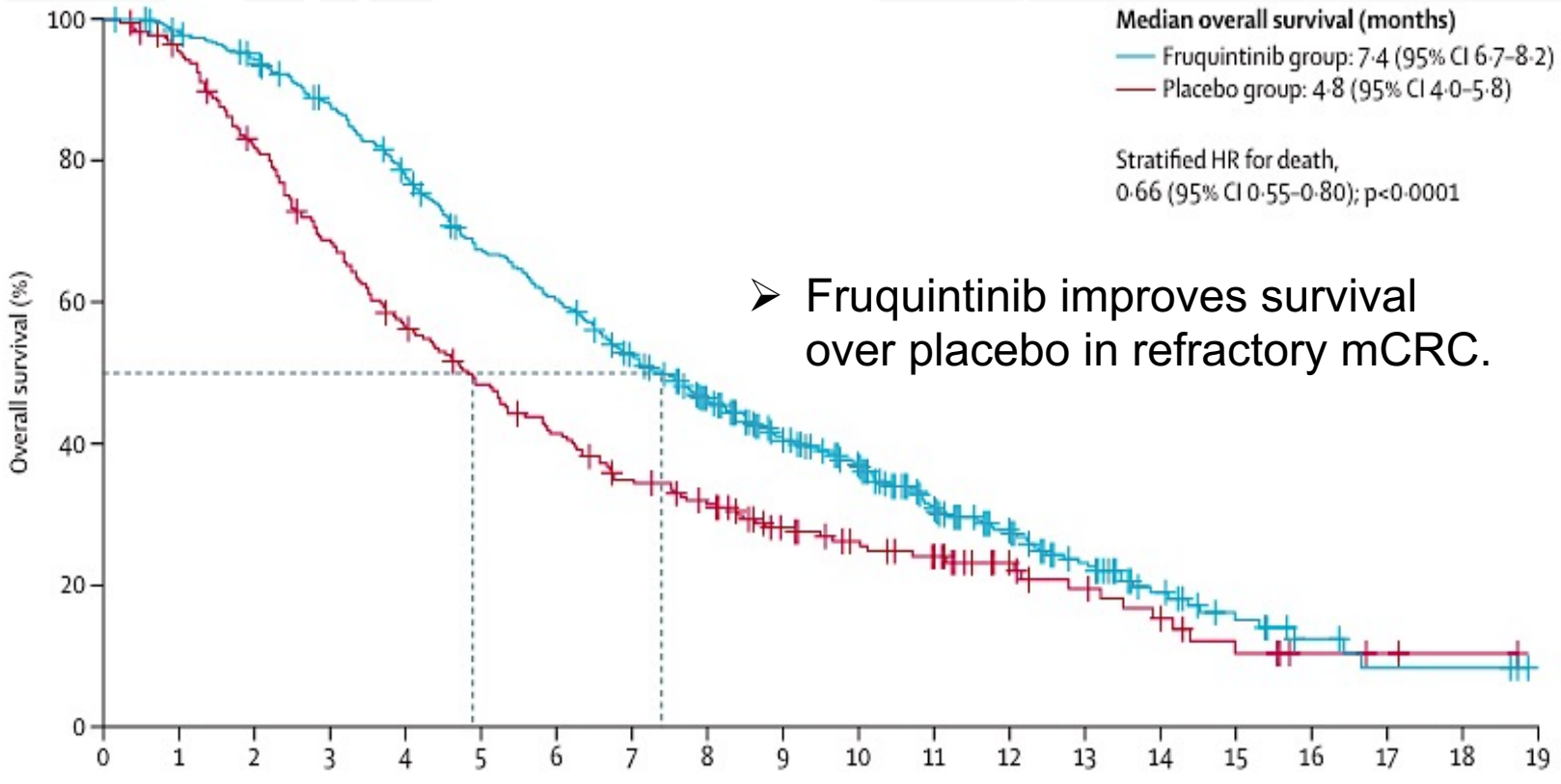
- Confirmed metastatic colorectal adenocarcinoma
- Progressed on all SOC therapies including anti-VEGF and anti-EGFR therapy and TAS-102 and/or Regorafenib

R 2:1

- Fruquintinib (N = 461)
- Placebo (N = 230)

Primary Endpoint
OS

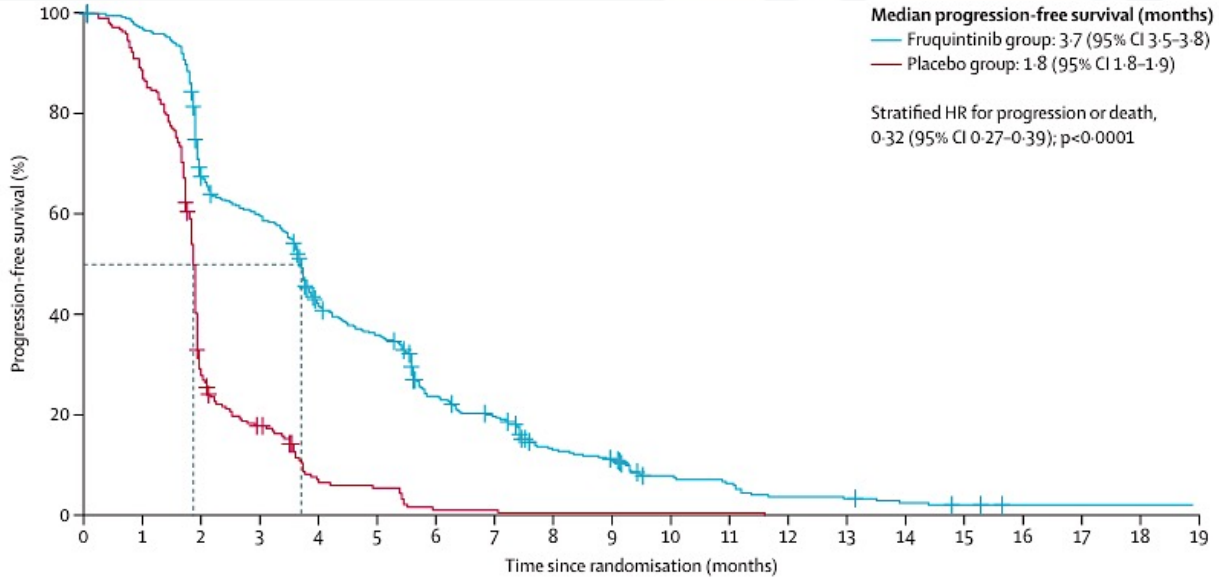
	Fruquintinib group (n=461)	Placebo group (n=230)
Region		
North America	82 (18%)	42 (18%)
Europe	329 (71%)	166 (72%)
Japan	40 (9%)	16 (7%)
Australia	10 (2%)	6 (3%)
Number of previous treatment lines in metastatic disease		
Median	4 (3–6)	4 (3–6)
≤3	125 (27%)	64 (28%)
>3	336 (73%)	166 (72%)
Previous therapies		
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%)



➢ Fruquintinib improves survival over placebo in refractory mCRC.

Dasari et.al. The Lancet 2023

Other Key Results



- Fruquintinib also improved PFS compared to placebo in a highly treatment refractory mCRC population, without any significant increase in ORR, but led to an increase in DCR.
- Grade 3/4 TRAEs occurred in 63% versus 50% of patients receiving Fruquintinib versus placebo, respectively.

	Fruquintinib group (n=461)	Placebo group (n=230)	Treatment effect	Two-sided p value
Antitumour activity endpoints				
Best overall response*				
Complete response	0	0	..	..
Partial response	7 (2%)	0	..	..
Stable disease	249 (54%)	37 (16%)	..	..
Progressive disease	139 (30%)	143 (62%)	..	..
Not evaluable	6 (1%)	1 (<1%)	..	..
NA†	60 (13%)	49 (21%)	..	..
Objective response rate	7 (2%, 0·6–3·1)	0 (0%, 0·0–1·6)	2% (0·4–2·7)	0·059
Disease control rate	256 (56%, 50·9–60·1)	37 (16%, 11·6–21·5)	39%‡ (32·8–46·0)	<0·0001
Duration of response, months				
Median	10·7 (3·9–NE)	0 (NA)	..	..
Range	2·1–16·9§	NA	..	..

	Fruquintinib group (n=456)		Placebo group (n=230)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Adverse events of special interest				
Any	368 (81%)	169 (37%)§	122 (53%)	44 (19%)§
Hypertension	175 (38%)	64 (14%)	20 (9%)	2 (1%)
Dermatological toxicity	157 (34%)	31 (7%)	27 (12%)	1 (<1%)
Thyroid dysfunction	123 (27%)	2 (<1%)	4 (2%)	0
Hepatic function abnormal	113 (25%)	38 (8%)	44 (19%)	21 (9%)
Infection	96 (21%)	30 (7%)	29 (13%)	13 (6%)
Proteinuria	80 (18%)	8 (2%)	12 (5%)	2 (1%)
Haemorrhage	65 (14%)	8 (2%)	22 (10%)	4 (2%)
Embolic and thrombotic events	21 (5%)	14 (3%)	5 (2%)	2 (1%)
Gastrointestinal perforation	16 (4%)	10 (2%)	1 (<1%)	1 (<1%)
Left ventricular ejection fraction decrease	5 (1%)	4 (1%)	6 (3%)	2 (1%)

Dasari et.al. The Lancet 2023

Discussion Question

- Regulatory and reimbursement issues aside, what is your most likely initial treatment recommendation for an asymptomatic, clinically stable 80-year-old patient with left-sided, pan-RAS wild-type, BRAF wild-type, HER2-negative, MSI-high mCRC?

Discussion Questions

- Regulatory and reimbursement issues aside, what would be your likely second-line treatment for a patient with RAS-mutant, MSS, HER2-positive mCRC who had experienced asymptomatic, low-volume disease progression on first-line FOLFOX/bevacizumab followed by maintenance bevacizumab? What about a patient with symptomatic, higher-volume disease?

Module 11: Urothelial Bladder Cancer

Management of Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Gupta

Optimizing the Treatment of Metastatic UBC — Dr Rosenberg

Module 11: Urothelial Bladder Cancer

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Cleveland Clinic

Management of Nonmetastatic Urothelial Bladder Cancer (UBC)

Shilpa Gupta, M.D.
Professor of Medicine
Cleveland Clinic Lerner College of Medicine at CWRU
Director, Genitourinary Oncology Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, OH

GMO'25
March 2, 2025

RTP RESEARCH TO PRACTICE

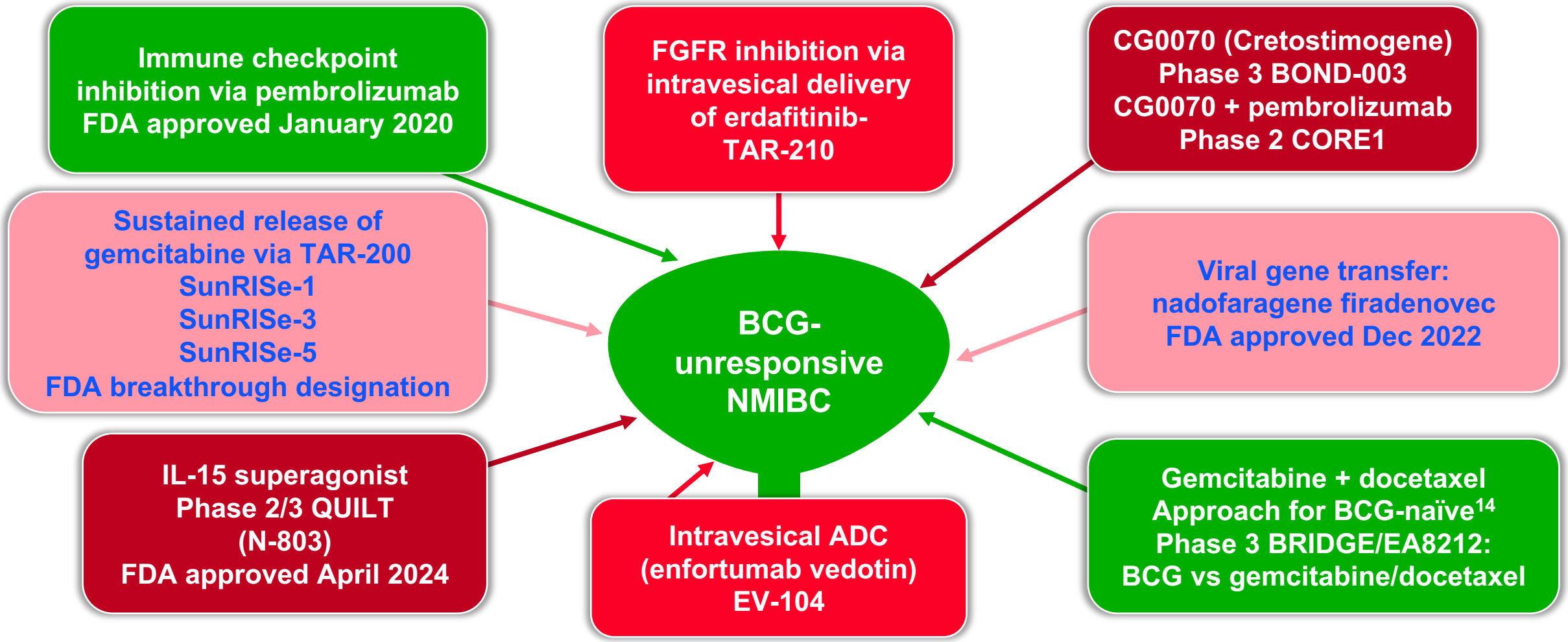
Unmet Needs in the Treatment of NMIBC and MIBC

- Only one-third of patients with NMIBC are given intravesical BCG
  - BCG shortages in the United States may affect access
- Close to half of patients with MIBC worldwide may not receive curative-intent therapy
- Patients who have undergone radical cystectomy for MIBC often have impaired HRQOL and a high risk of recurrence

- Development of effective, safe, and durable intravesical treatment remains a critical unmet clinical need for patients who want to avoid radical cystectomy
- Effective approaches post radical cystectomy are key to reducing the risk of recurrence

Tyson M et al. *J Clin Oncol*. 2019;37(suppl 15):e16012. 2. https://www.auanet.org/about-us/bcg-shortage-info.
Westergren DO et al. *J Urol*. 2019;202:905-912. Choi H et al. *Transl Androl Urol*. 2020;9:2997-3006. Roupret M et al. *Eur Urol*. 2021;79:62-79.

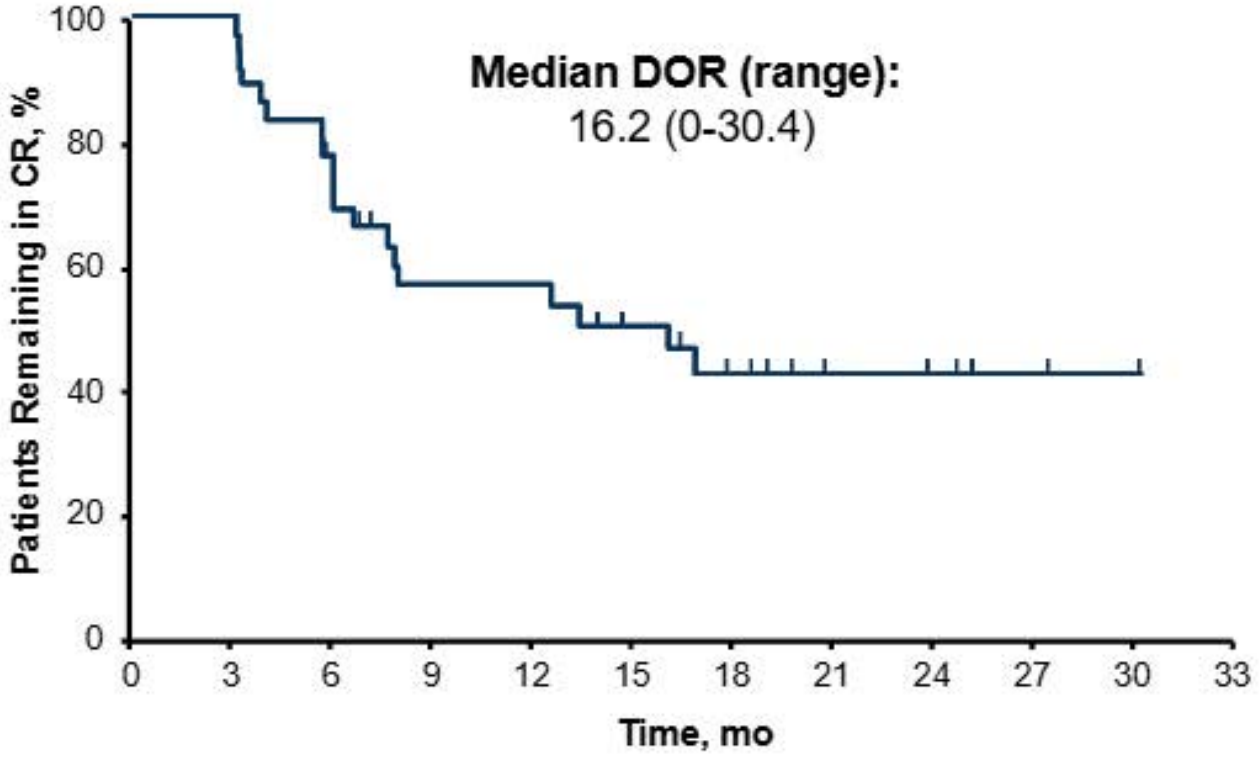
Treatment Approaches for High-Risk NMIBC Unresponsive to BCG



Balar AV et al. Lancet Oncol. 2021;22:919-930., Vilaseca A et al. AUA 2024, Tyson MD et al. AUA 2024.,Li R et al. J Clin Oncol. 2022, Daneshmand S et al. AUA 2023.. Necchi A et al. ESMO 2023. Jacob J et al. AUA 2024., Shore ND et al. J Clin Oncol. 2017; Boorjian SA et al. Lancet Oncol. 2021, Chamie K. NEJM Evidence. 2022, Kamat AM et al. J Clin Oncol. 2023, McElree IM et al. J Urol. 2022

KEYNOTE-057 Cohort A: Pembrolizumab Monotherapy for BCG-Unresponsive, High-Risk NMIBC

Cohort A: CIS ± Papillary Disease (High-Grade Ta or T1)



Best Response	Patients (N = 96)	
	n (%)	95% CI
CR	39 (40.6)	30.7-51.1
Non-CR	56 (58.3)	47.8-68.3
Progression to T2	0	N/A
NE	1 (1.0)	0-5.7

- Upstaging to ≥pT2 in 8.3% patients

Extended minimum follow-up of 26.3 mo
- Of 39 responders, 13 (33.3%) remained in CR ≥18 mo and 9 (23.1%) remained in CR ≥24 mo as of the data cutoff date
- No new safety risks were identified

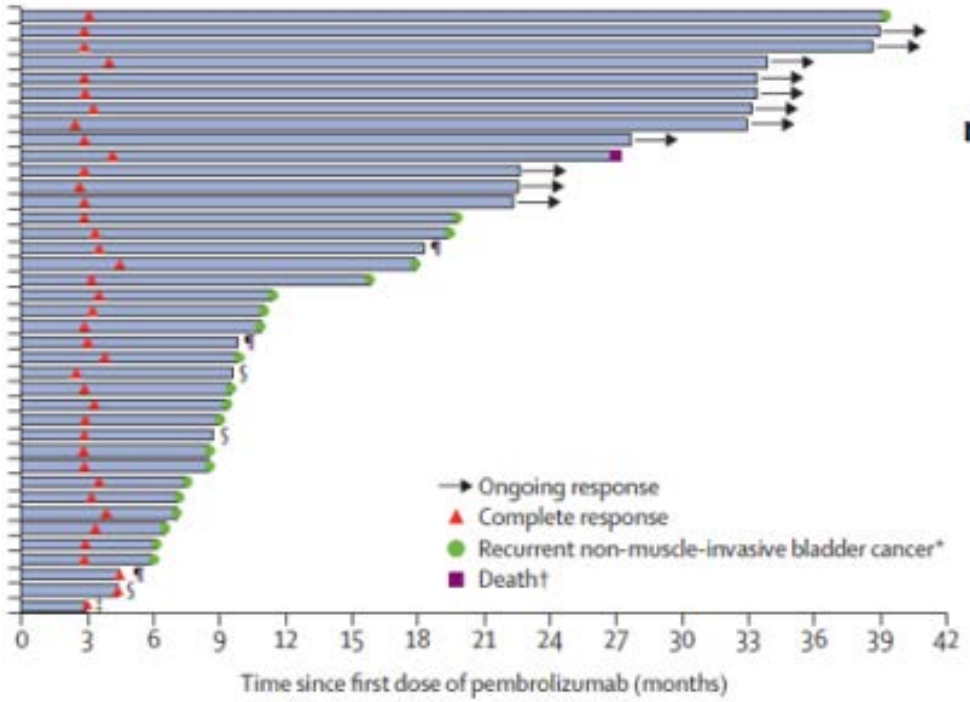
Pembrolizumab was FDA approved for the treatment of patients with BCG-unresponsive, high-risk NMIBC with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy

Balar AV et al. Lancet Oncol. 2021;22:919-930.

Keynote-057 Longer Follow-up

19% of all patients in CR for 12+ mos*
(18/96)

Efficacy of pembrolizumab drops



46% of responders in CR for 12+mos
(18/39 responders)

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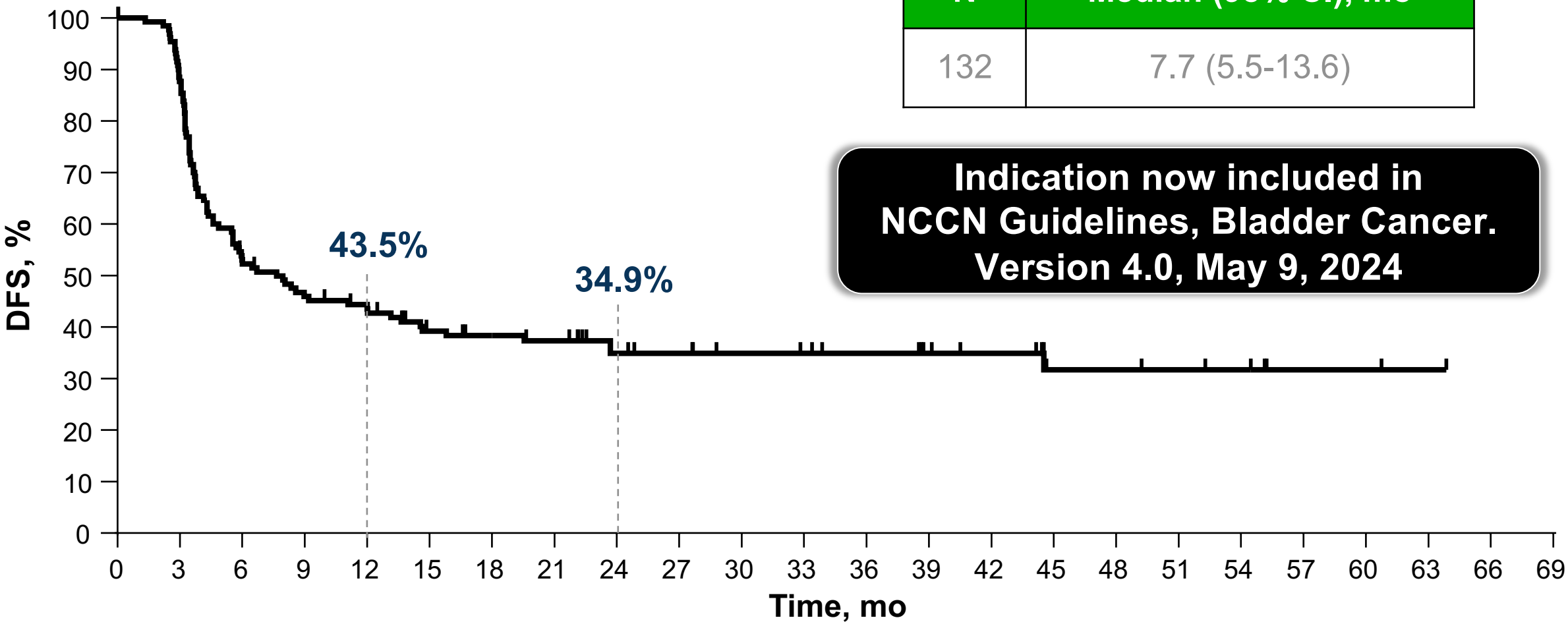
KEYNOTE-057 Cohort B: Pembrolizumab for Papillary High-Risk NMIBC

N	Median (95% CI), mo
132	7.7 (5.5-13.6)

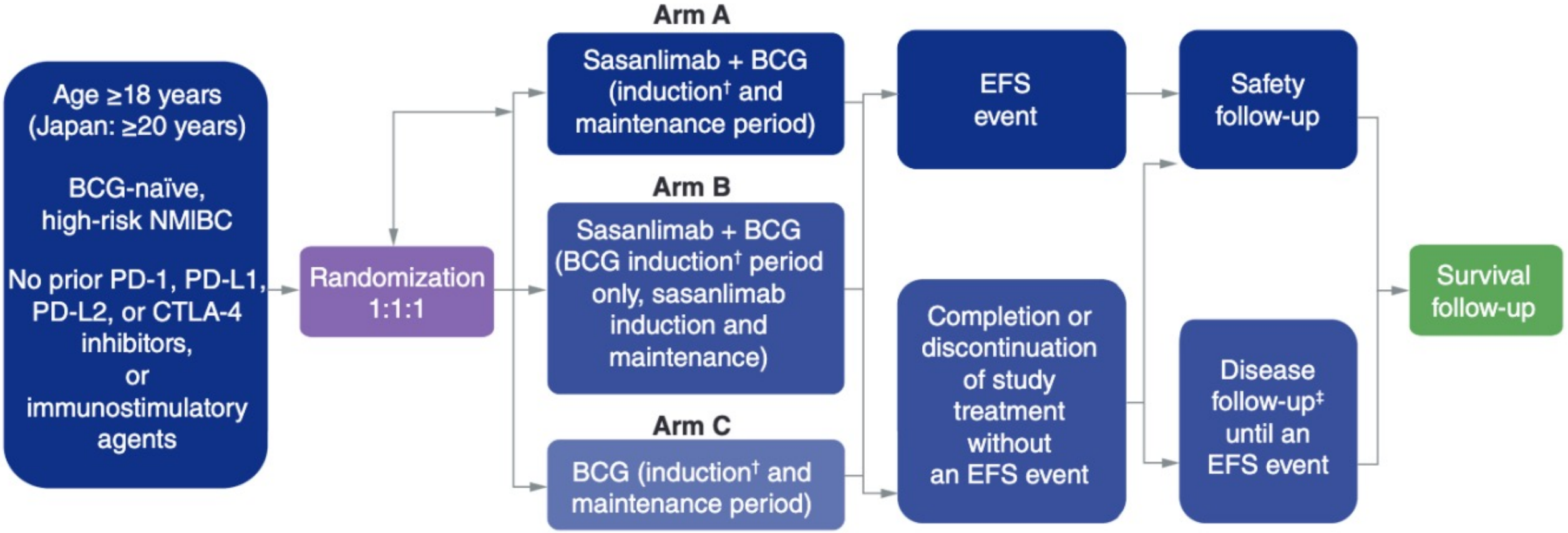


Indication now included in NCCN Guidelines, Bladder Cancer. Version 4.0, May 9, 2024

Cleveland Clinic

Necchi A et al. Lancet Oncol. 2024;S1470-2045:00178-5.

CREST: Ongoing Phase III Trial of Sasanlimab Combined with BCG versus BCG Monotherapy for Patients with BCG-Naïve High-Risk NMIBC



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Sasanlimab in Combination with BCG Improves Event-Free Survival in Patients with BCG-Naïve, High-Risk Non-Muscle Invasive Bladder Cancer

Press Release: January 10, 2025

Positive topline results were announced from the pivotal Phase 3 CREST trial evaluating sasanlimab, an investigational anti-PD-1 monoclonal antibody (mAb), in combination with Bacillus Calmette-Guérin (BCG) as induction therapy with or without maintenance in patients with BCG-naïve, high-risk non-muscle invasive bladder cancer. The study met its primary endpoint of event-free survival by investigator assessment, demonstrating a clinically meaningful and statistically significant improvement with sasanlimab in combination with BCG (induction and maintenance) as compared to BCG alone (induction and maintenance).

The overall safety profile of sasanlimab in combination with BCG was generally consistent with the known profile of BCG and data reported from clinical trials with sasanlimab. The profile of sasanlimab was also generally consistent with the reported safety profile of PD-1 inhibitors.

Results will be submitted for presentation at an upcoming medical congress.

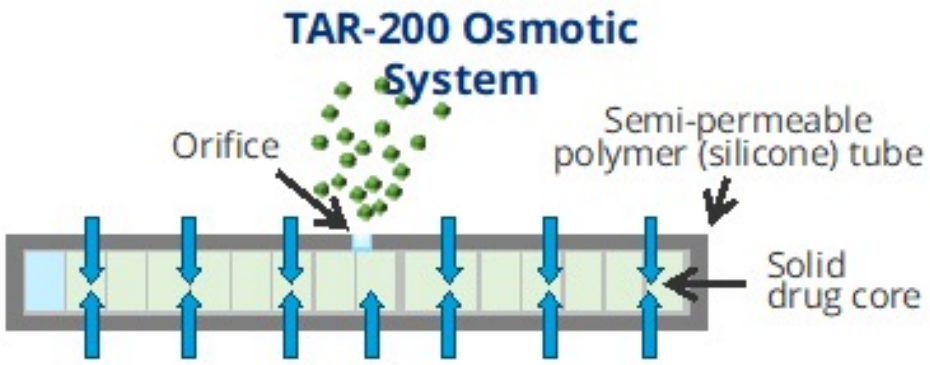
Key Ongoing Phase III Trials of antimPD-1/PD-L1 antibodies for BCG-naive NMIBC

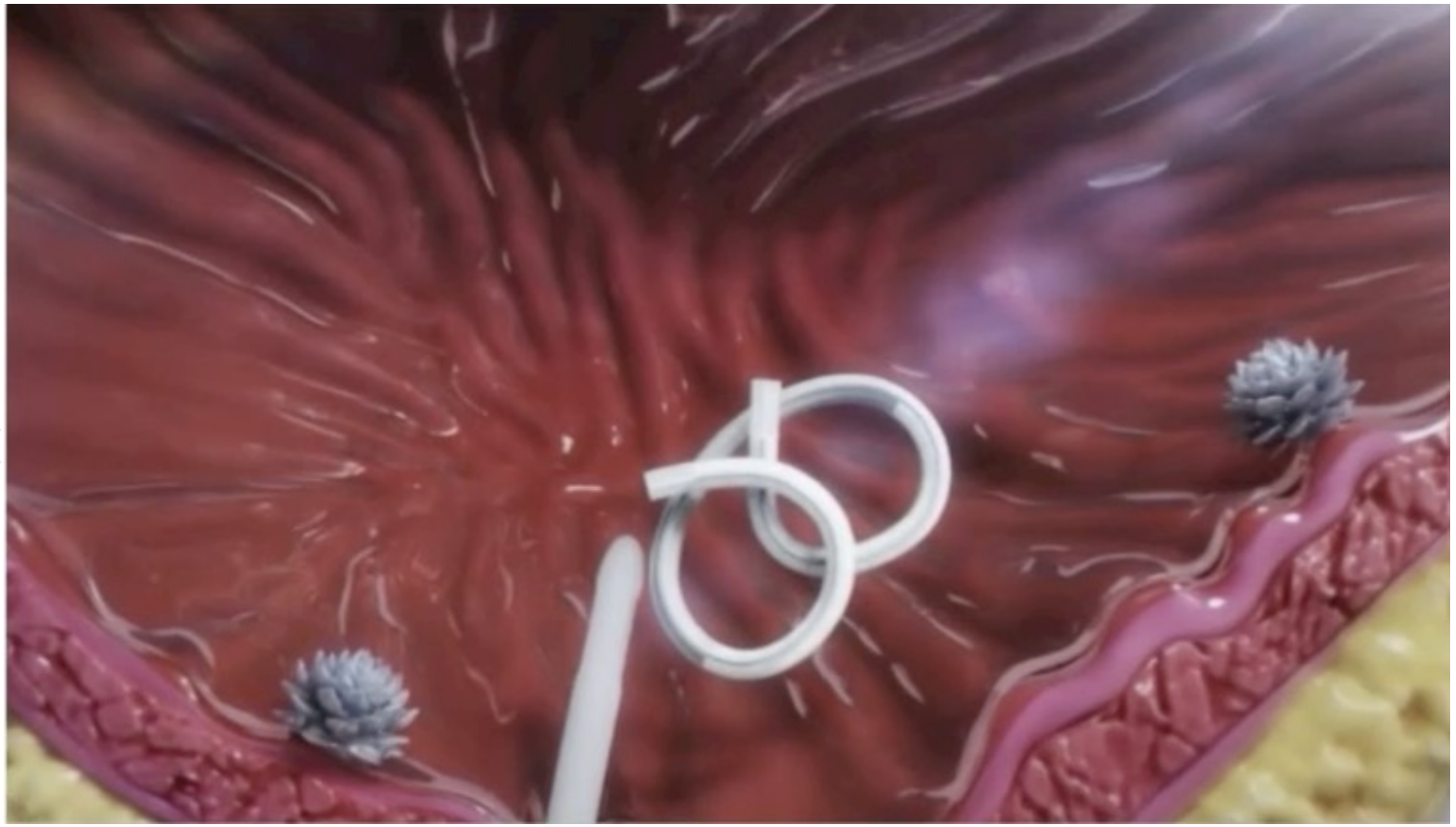
Protocol	n	Randomization
ALBAN (NCT03799835)	517	• Atezolizumab + BCG • BCG
POTOMAC (NCT03528694)	1,018	• Durvalumab + BCG • BCG
KEYNOTE-676 (NCT03711032)	1,397	• Pembrolizumab + BCG • BCG

BCG = Bacillus Calmette-Guérin

www.clinicaltrials.gov; Accessed March 2025.

TAR-200: A Novel Drug Delivery System for Sustained Local Release of Gemcitabine in the Bladder

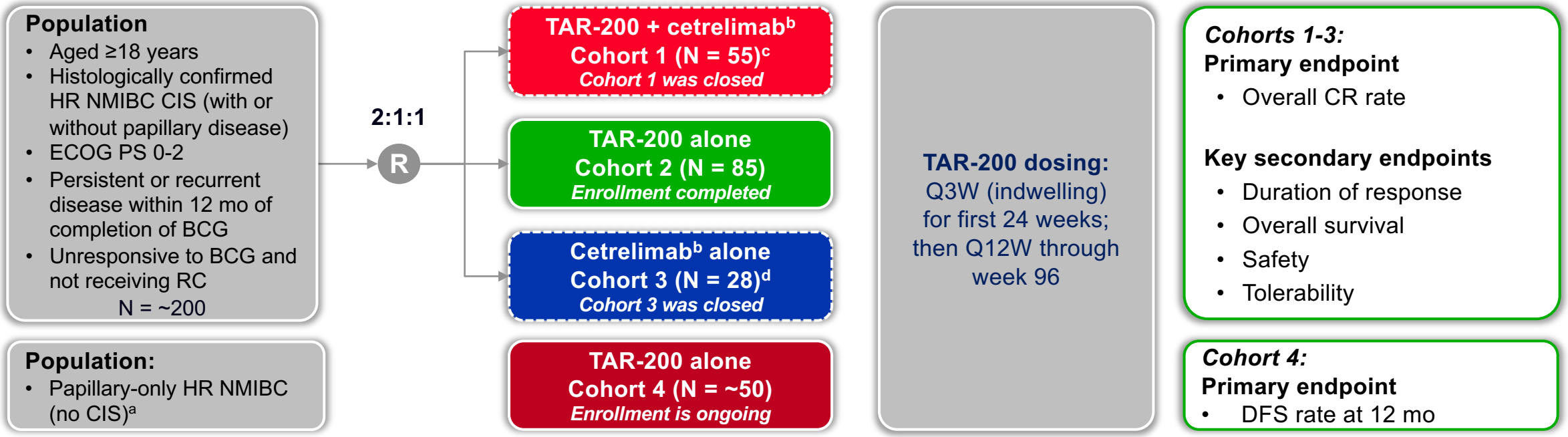




Grimberg DC, et al. *Eur Urol Focus* 2020;6:620-2; Daneshmand S, et al. *Urol Oncol* 2022;40:344.e1-344.e9; Tyson MD, et al. *J Urol* 2023:209:890-900.

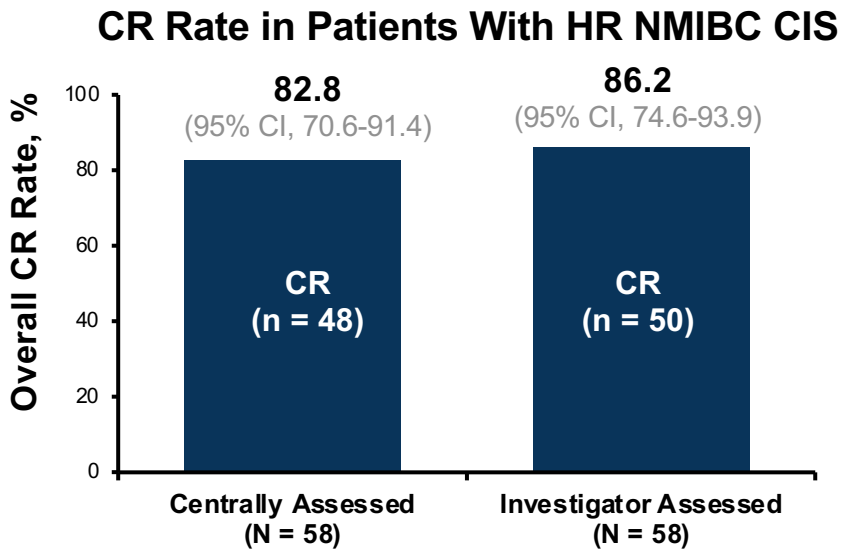
Courtesy of Sia Daneshmand, MD

SunRISe-1: TAR-200 in BCG-Unresponsive High-Risk NMIBC



- Response is determined by quarterly cystoscopy, quarterly central cytology, and central pathology at weeks 24 and 48 and as clinically indicated
- The study protocol did not allow retreatment for nonresponders consistent with US FDA gudance

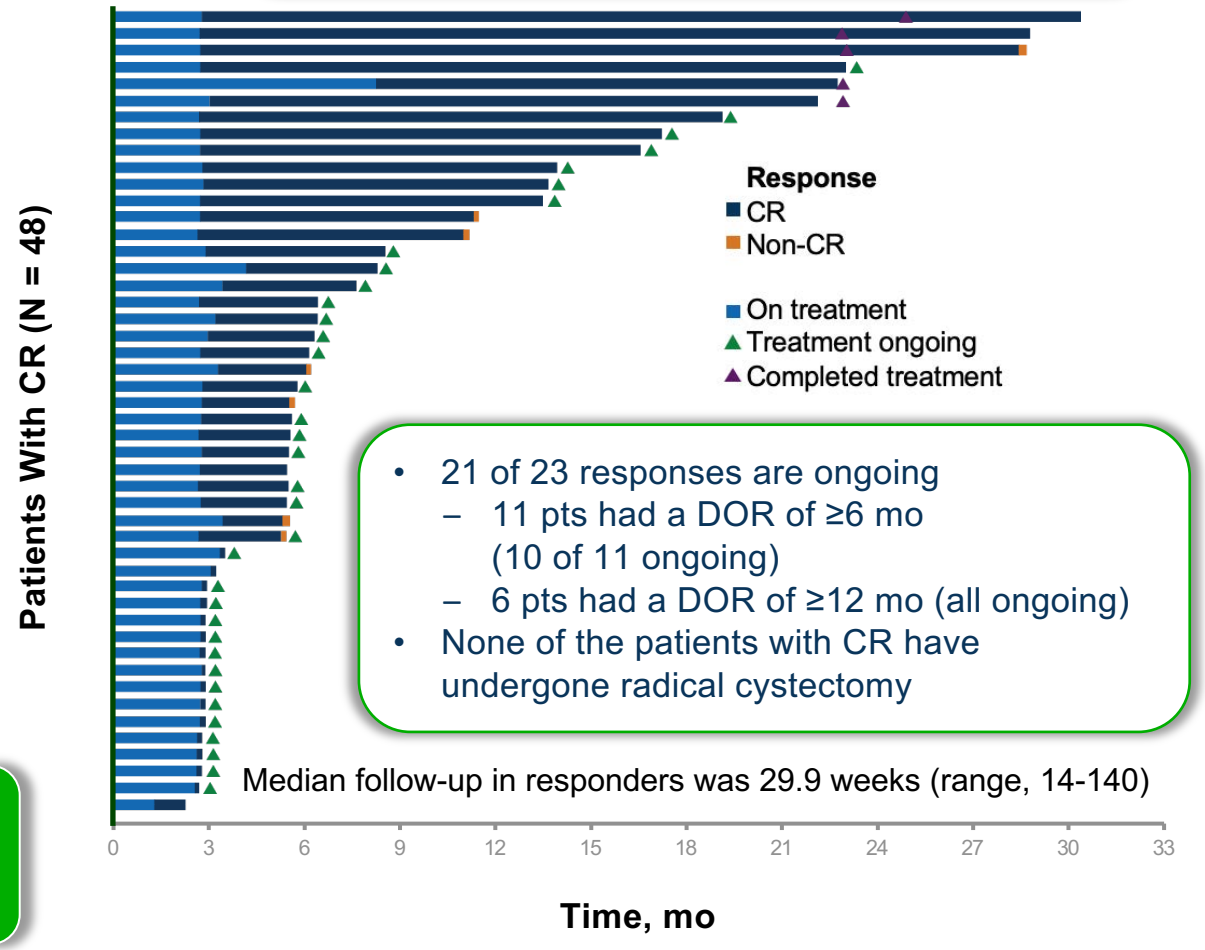
SunRISe-1: TAR-200 Monotherapy in BCG-Unresponsive, HR NMIBC (Cohort 2)



Landmark Time	DOR % (95% CI)
6 months	93% (61-99)
12 months	84% (49-96)

- TAR-200 was well tolerated; mainly low–grade 1 or 2 AEs
- TAR-200–related SAEs, grade ≥3 AEs, and discontinuations were infrequent

FDA Breakthrough Therapy Designation



- 21 of 23 responses are ongoing
  - 11 pts had a DOR of ≥6 mo (10 of 11 ongoing)
  - 6 pts had a DOR of ≥12 mo (all ongoing)
- None of the patients with CR have undergone radical cystectomy

Median follow-up in responders was 29.9 weeks (range, 14-140)

Cleveland Clinic

Daneshmand S et al. AUA 2023, Necchi A et al. ESMO 2023, 4. Jacob J et al. AUA 2024.

New Drug Application initiated with U.S. FDA for TAR-200, the first and only intravesical drug releasing system for patients with BCG-unresponsive high-risk non-muscle-invasive bladder cancer

Press Release: January 15, 2025

The manufacturer announced it has initiated the submission of an original New Drug Application with the U.S. Food and Drug Administration (FDA) for TAR-200 for the treatment of patients with Bacillus Calmette-Guérin (BCG)-unresponsive high-risk non-muscle-invasive bladder cancer (HR-NMIBC) with carcinoma in situ (CIS), with or without papillary tumors.

The submission of this innovative intravesical drug releasing system is supported by data from the Phase 2b SunRISe-1 registration study. Data collected through the second quarter of 2024 and presented at the European Society for Medical Oncology (ESMO) 2024 Congress as a late-breaking oral presentation showed an 83.5 percent complete response (CR) rate and highly durable CRs without the need for reinduction – at a median follow-up of nine months, 82 percent of responders maintained response. At data cutoff in May 2024, safety and tolerability data presented at ESMO demonstrated a low occurrence of Grade 3 or higher treatment-related adverse events (TRAEs) (9 percent); five patients had TRAEs leading to discontinuation (6 percent) and no treatment-related deaths were reported.

https://www.jnj.com/media-center/press-releases/new-drug-application-initiated-with-u-s-fda-for-tar-200-the-first-and-only-intravesical-drug-releasing-system-for-patients-with-bcg-unresponsive-high-risk-non-muscle-invasive-bladder-cancer

Phase 3 SunRISe-3: BCG-Naïve, High-Risk NMIBC

Key Eligibility Criteria

- Patients with histologically confirmed high-risk NMIBC (high-grade Ta, any T1, or CIS)[a]
- BCG-naïve (no prior BCG, or last exposure >3 y prior to randomization)
- Age ≥18 y
- ECOG PS 0-2

N = 1,050

1:1:1

R

Group A (n = 350)
TAR-200 (**gemcitabine** 225 mg Q3W [induction phase] and Q12W [maintenance phase]) + **cetrelimab**

Group B (n = 350)
BCG (QW for 6 wk [induction] and QW for 3 wk at weeks 12, 24, 48, 72, and 96 [maintenance])

Group C (n = 350)
TAR-200 (**gemcitabine** 225 mg Q3W [induction phase] and Q12W [maintenance phase])

- **Primary endpoint:** EFS (time from randomization to first occurrence of HR disease, progression,[b] or any-cause death, whichever occurs first[c])
- **Secondary endpoints:** Overall CR rate (CIS only)[d]/duration of CR,[e] RFS, TTP, OS, cancer-specific survival, safety and tolerability, patient-reported outcomes

Phase 3 SunRISe-5: Recurrent, HR NMIBC After BCG

Key Eligibility Criteria

- Histologically confirmed, papillary-only HR NMIBC (high grade Ta or any T1), recurrent within the first year of last dose of BCG
- No CIS at time of papillary recurrence
- RC refusing or ineligible
- ECOG PS <3

Stratification Factors

- T-stage
- Prior BCG

N = ~250

1:1

R

Group A (n = ~125)
TAR-200 monotherapy
Q3W during an induction phase
Q12W during a maintenance phase

Crossover
Patients in Group B may receive TAR-200 after positive study result at any planned analyses

Group B (n = ~125)
Intravesical gemcitabine
OR
Intravesical mitomycin
Weekly during an induction phase
Monthly during a maintenance phase

Primary endpoint

- Disease-free survival

Key secondary endpoints

- Recurrence-free survival
- Time to next intervention
- Time to progression
- Time to disease worsening
- Overall survival
- Safety and tolerability
- PROs/HRQOL

- Disease-free survival is defined as time from randomization to first recurrence of HR NMIBC (high grade Ta, any T1 or CIS), progression, or any cause death, whichever occurs first

The study will evaluate whether TAR-200 will prolong disease-free survival when compared with intravesical chemotherapy in patients with papillary-only HR NMIBC recurrent after BCG therapy who refuse or are unfit for RC

Key Efficacy and Safety Outcomes of Novel Therapies for the Treatment of HR NMIBC

Trial	BOND-003[1]	CORE-001[2]	SunRISe-1[3]	QUILT 3.032[4]	NCT02773849[5]	Keynote-057[6,7]	SWOG S1605[8]
Intervention	Cretostimogene	Cretostimogene + pembrolizumab	TAR-200	N-803+BCG	Nadofaragene	Pembrolizumab	Atezolizumab
Mechanism	Oncolytic immunotherapy	Oncolytic immunotherapy + checkpoint inhibitor	Chemotherapy	IL-15 superagonist + BCG	Gene therapy secreting IFN	Checkpoint inhibitor	Checkpoint inhibitor
Delivery	Intravesical	Intravesical + intravenous	Intravesical	Intravesical	Intravesical	Intravenous	Intravenous
Stage	Phase 3 (enrollment completed)	Phase 2 ongoing	Phase 2 (enrollment completed)	FDA approved April 22, 2024	FDA approved	FDA approved (CIS)	Phase 2 (enrollment completed)
Sample size	N = 112	N = 35	N = 85 (48)	N = 77	N = 98	N = 96 (A) N = 132 (B)	N = 129
DOR ≥12m or 12-m K-M DOR estimates	83%	88%	74.6%	58%	46%	19% (A) 43.5% (B)	56%
Safety	0% grade 3-4 TRAE	4 pt pembro-related discontinuation	8.2% TRAE	16% SAE 7% discontinuation	4% grade 3-4 TRAE; 3% discontinuation	A: 11% grade 3 TRAE; 2% grade 4 TRAE; 11% discontinuation	16% grade 3-5 TRAE

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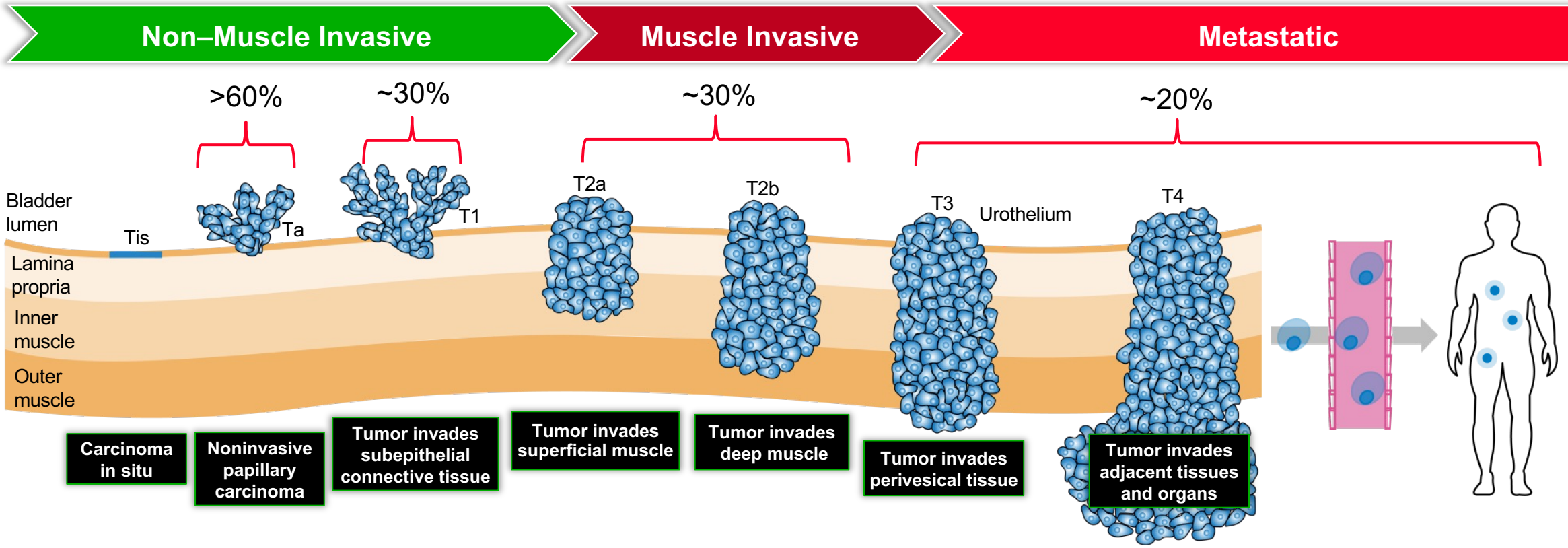
FGFR Mutations Are Frequently Observed in Bladder Cancer



FGFR inhibitors can be effective across the disease spectrum

Cleveland Clinic

Knowles MA et al. *Nat Rev Cancer*. 2015;15:25-41.

TAR-210 Erdafitinib Intravesical Delivery First-in-Human Phase 1 Trial

Molecular Eligibility

FGFR alterations:

- Flexible molecular eligibility strategy used
  - Local or central fresh/ archival **tissue-based** testing by NGS or PCR

or

  - Central **urine cell-free DNA** NGS testing

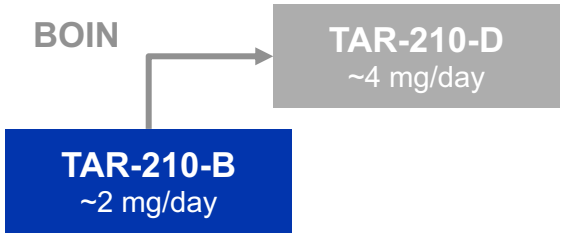
HR NMIBC (Cohort 1)

- Recurrent, high-grade Ta/T1, papillary only, no CIS
- BCG-experienced/unresponsive and not undergoing radical cystectomy
- TURBT with complete resection of all visible disease prior to treatment

IR NMIBC (Cohort 3)

- Recurrent, history of low-grade only Ta/T1 disease
- **Visible target lesions** prior to treatment (chemoablation design)

Part 1: Dose Escalation



- Placement every 3 months

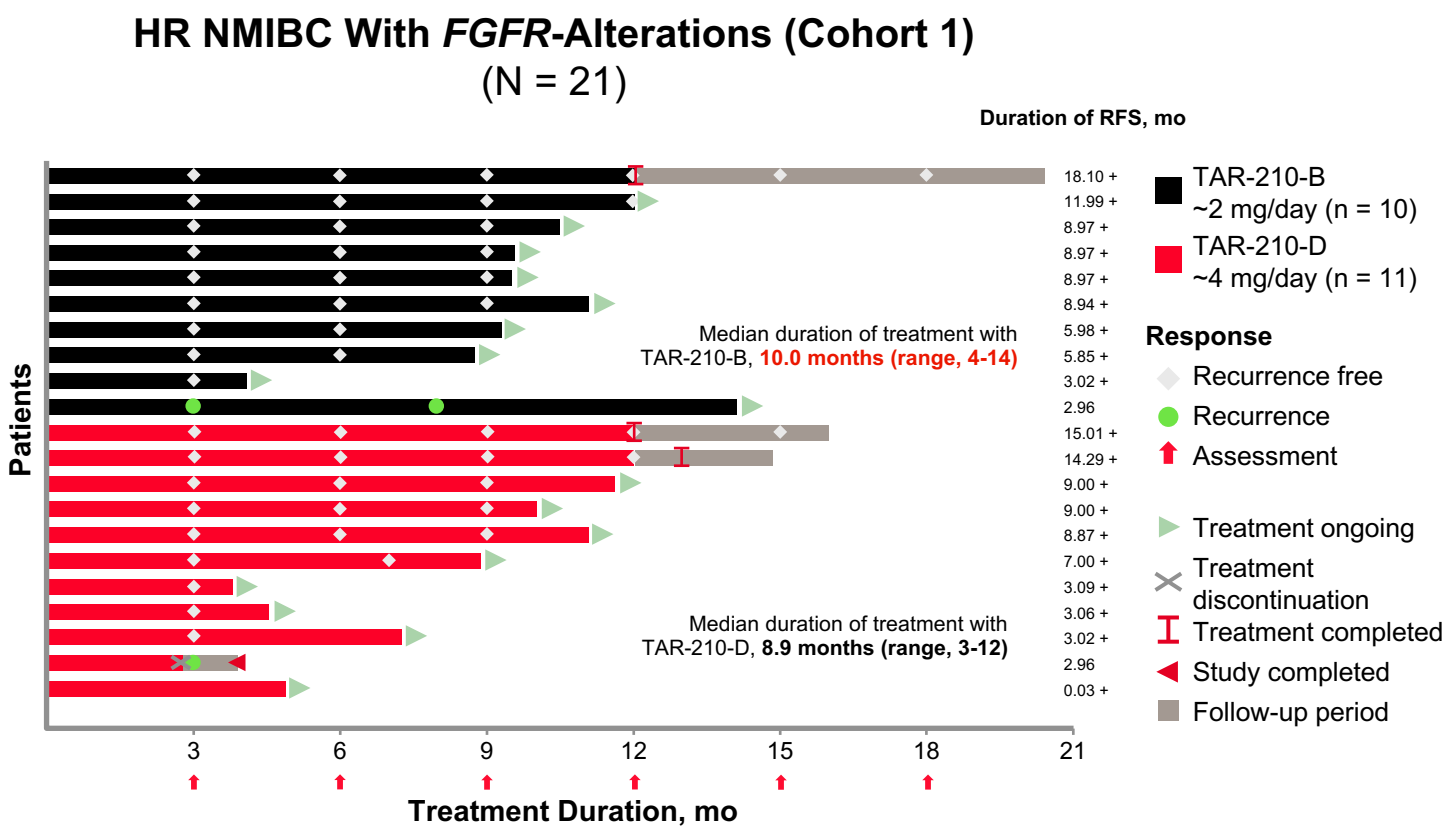
Part 2: Dose Expansion

- Expansion of both dose levels

Response assessed every 3 months with continued treatment for up to 1 year if recurrence free (cohort 1) or complete response (cohort 3)

Liu S, Yuan Y. *J R Stat Soc Ser C Appl Stat*. 2015;64:507-523, Yuan Y et al. *Clin Cancer Res*. 2016;22:4291-4301. Vilaseca A et al. AUA 2024. Abstract PD48-02.

TAR-210 HR NMIBC (Cohort 1): Response Rate



- **90% estimated 12-month RFS rate[a]** (n = 21)
  - Median RFS was not estimable
  - 2 of 21 patients have recurred
  - Median duration of follow-up 8.9 months
- No difference observed in RFS between the TAR-210 dose levels

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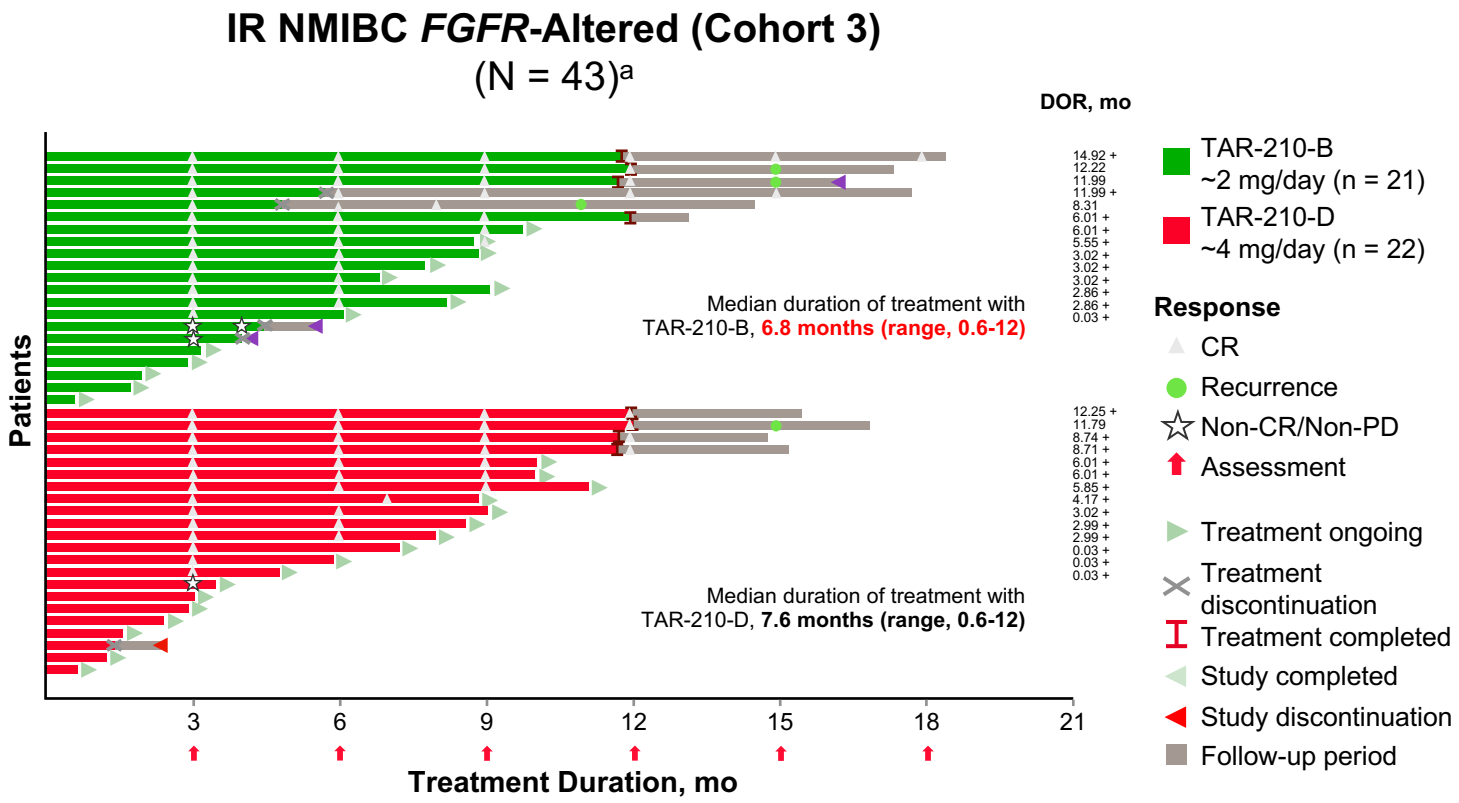
TAR-210 IR NMIBC (Cohort 3): Response Rate



- Overall, 31 patients were evaluable for response[b]
- **90% CR rate**, with 28/31 patients achieving a CR at week 12
  - Overall, **100% of patients achieved a clinical response**; 3 patients had a non-CR/non-PD response
- Consistent CR rate across both doses
- 86% (24/28) of CRs are ongoing at time of clinical cutoff

Durable Response Rate at Specific Landmarks[c]	% (95% CI)
6 months	100 (100-100)
9 months	89 (43-98)

Phase 3 MoonRISe-1 Underway[2]: TAR-210 vs IV chemotherapy in IR NMIBC with susceptible *FGFR* alterations

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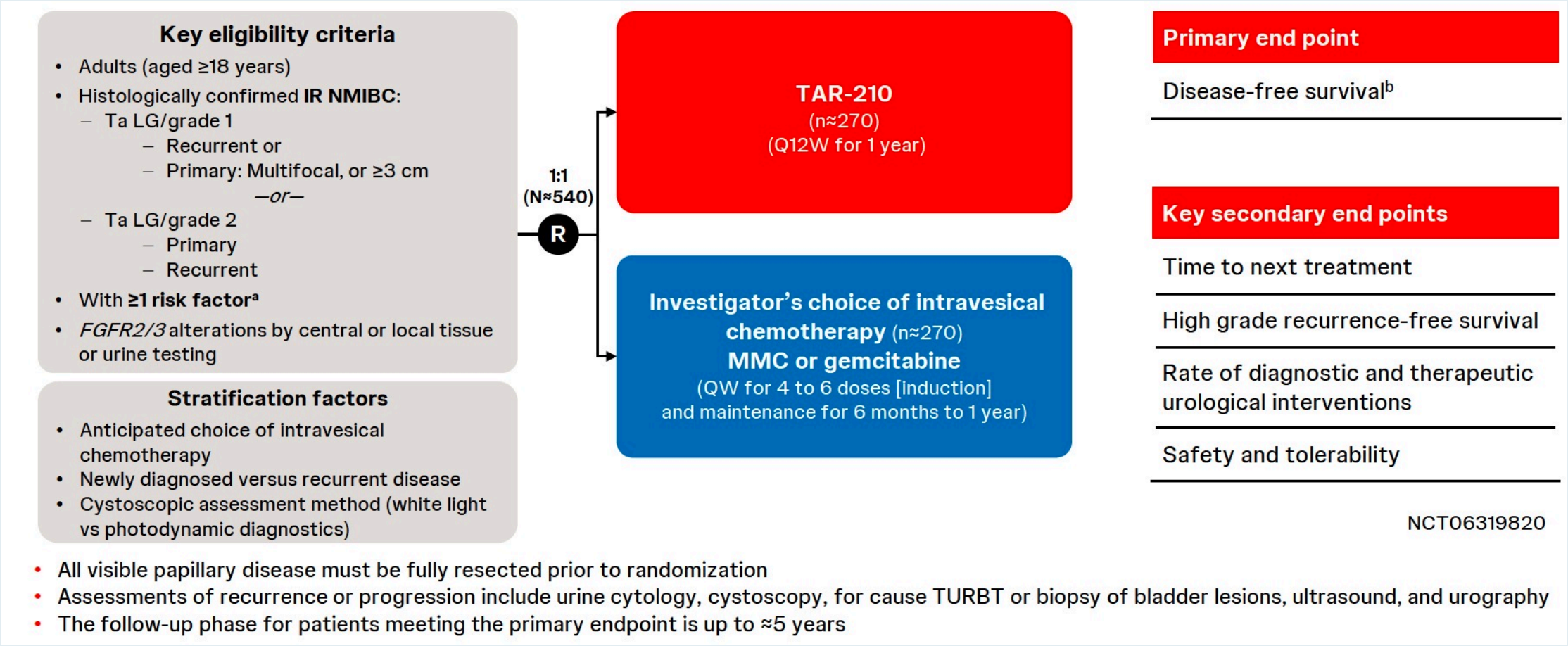
Phase III MoonRISe-1: Study Design



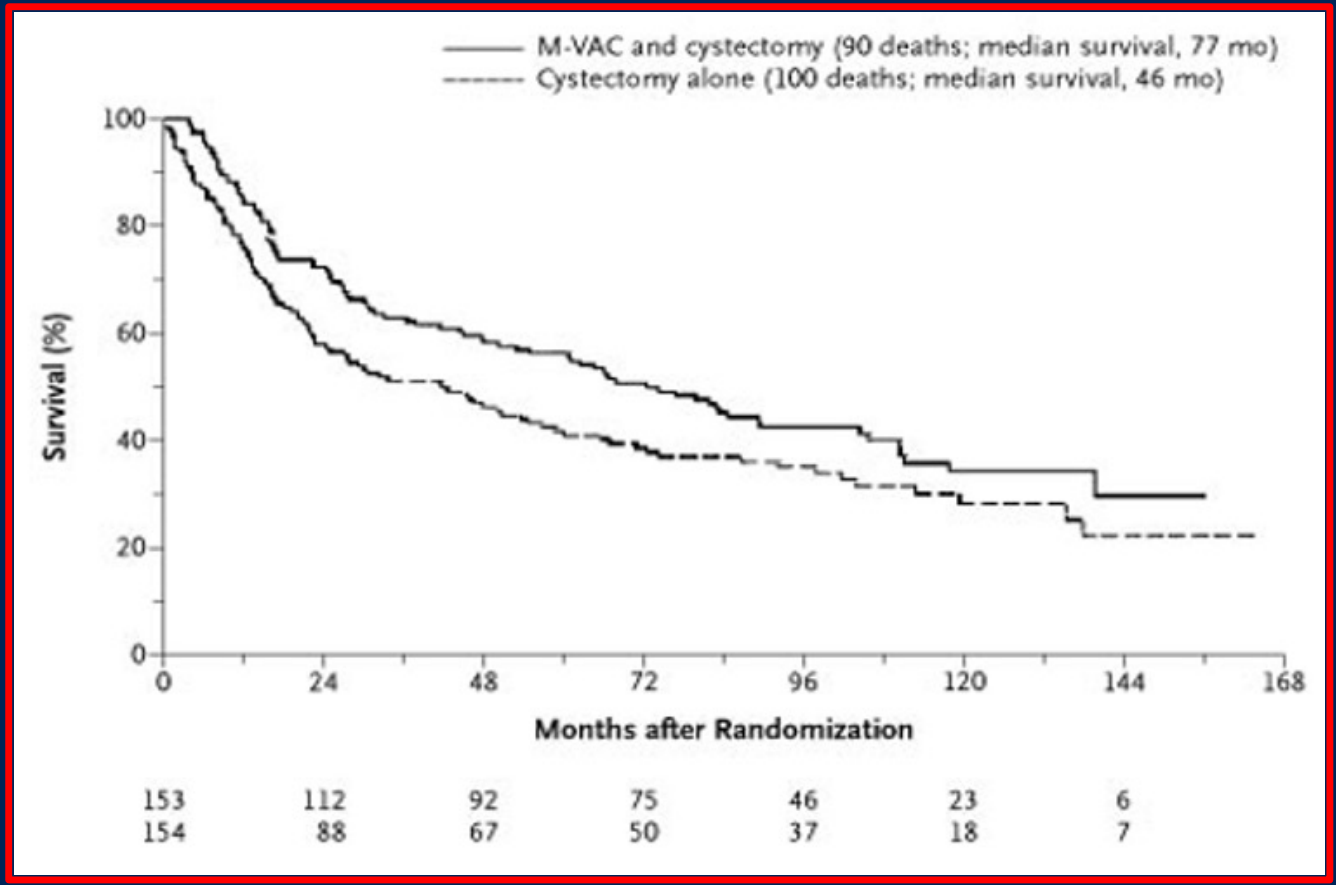
- All visible papillary disease must be fully resected prior to randomization
- Assessments of recurrence or progression include urine cytology, cystoscopy, for cause TURBT or biopsy of bladder lesions, ultrasound, and urography
- The follow-up phase for patients meeting the primary endpoint is up to ≈5 years

Vilaseca A et al. AUA 2024;Abstract PD48-02

MIBC has a huge societal burden

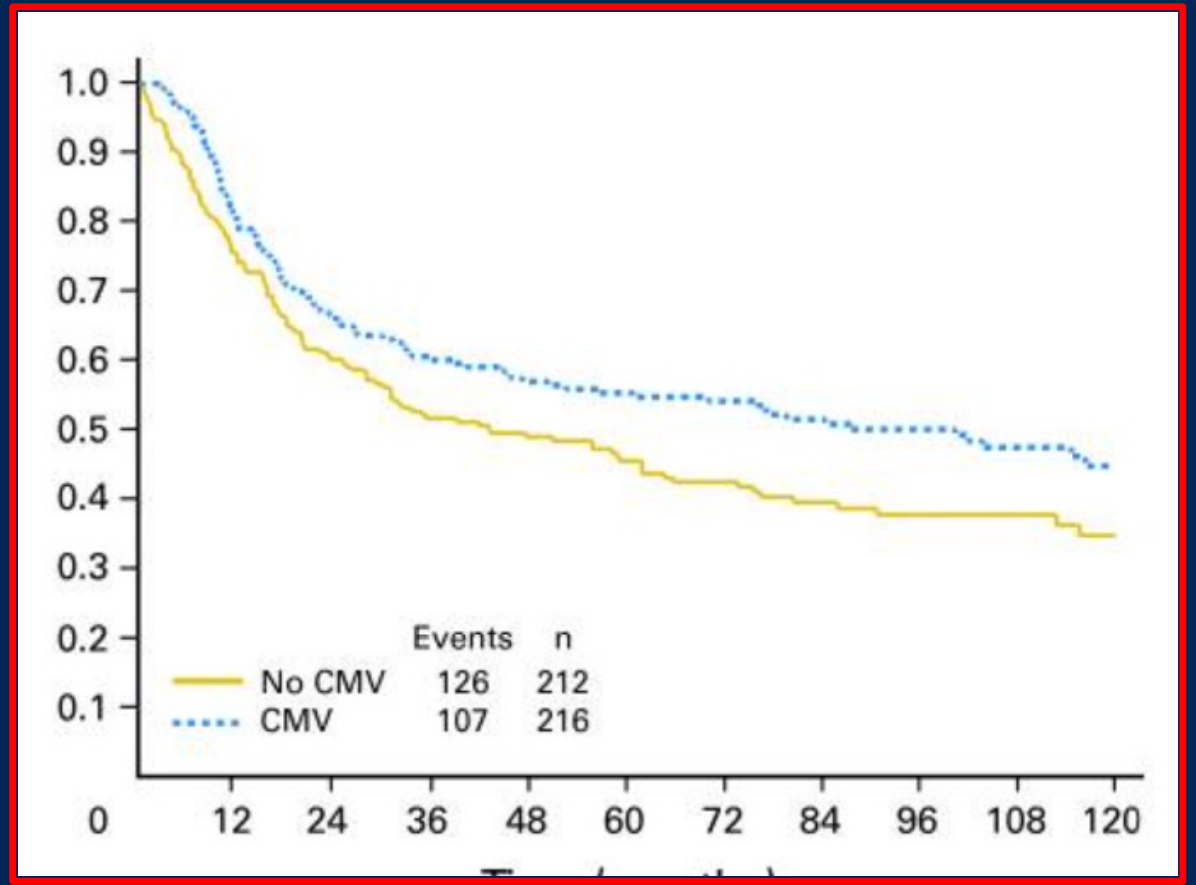
- Globally, over 550,000 new cases of bladder cancer occur annually
- The annual cost of bladder cancer in the US is ~ $5 billion
- Surgery has 2-13% mortality and significant impact on patients' QOL
- High risk of recurrence necessitates lifelong monitoring
- Racial and gender disparities

Neoadjuvant cisplatin-based chemotherapy (NAC) prior to RC improves survival in cisplatin-eligible MIBC patients



SWOG 8710

Grossman HB et al. NEJM 2003

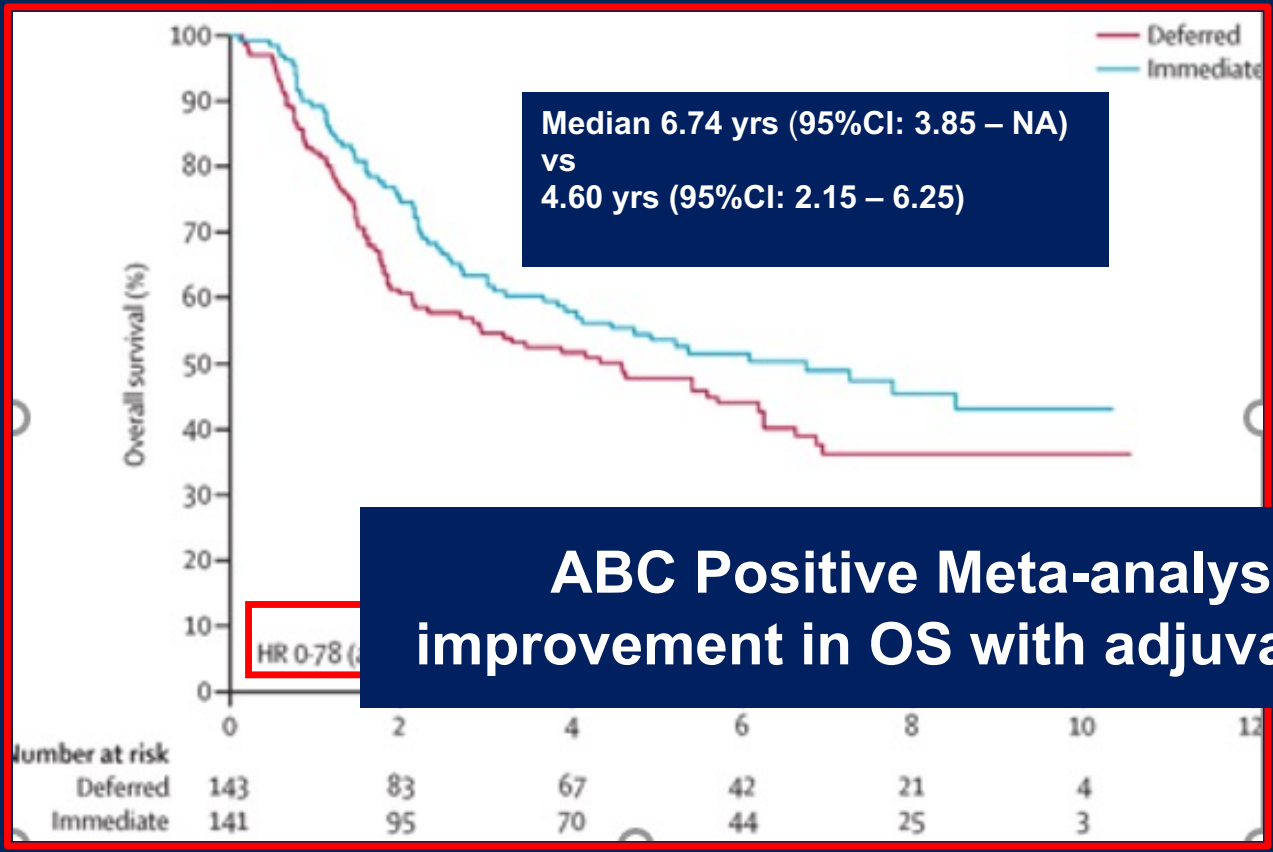


BA06 EORTC 30894

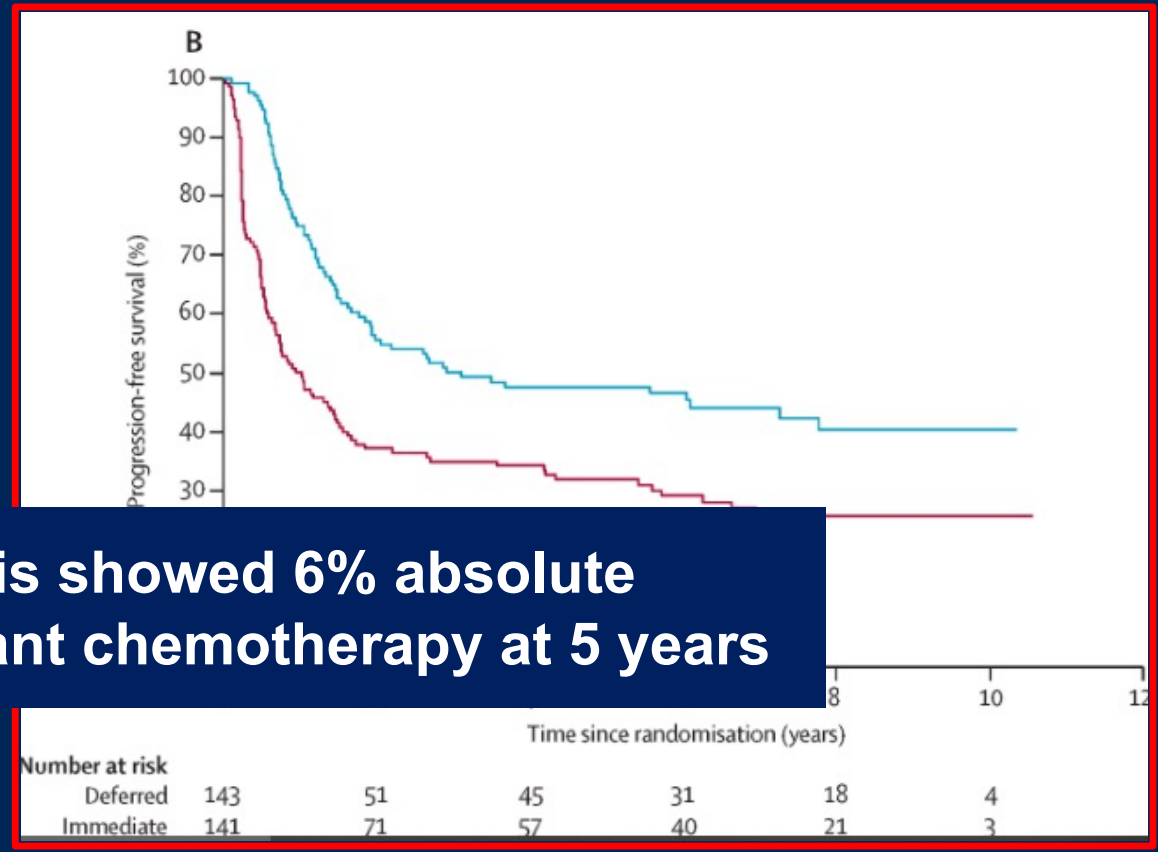
J Clin Oncol, 2011

ABC metaanalayis collaboration Vale CL eta l. European urology 2005, Yin M et al. Oncologist 2016, Galsky MD Cancer 2015, Flaig T el al. CCR 2021

Adjuvant therapy ultimate goal: Improve DFS, OS



Median 6.74 yrs (95%CI: 3.85 – NA)
vs
4.60 yrs (95%CI: 2.15 – 6.25)



ABC Positive Meta-analysis showed 6% absolute improvement in OS with adjuvant chemotherapy at 5 years

EORTC 30994: Immediate versus deferred chemotherapy (Investigator's choice MVAC, dd-MVAC,GC) after RC in patients with pT3–pT4 or N+ M0 Bladder Cancer

Sternberg CN et al, Lancet Oncol. 2015, ABC Metaanalysis European Urology 2022,

Completed Adjuvant IO trials in high-risk MIUC

High risk MIUC: if received NAC- ypT2-T4a/ypN+ or pT3-T4a/pN+ if not eligible for or declined adjuvant cisplatin-based chemotherapy

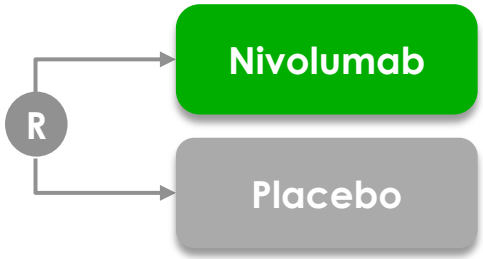
IMvigor010

Primary endpoint:
DFS

Key secondary endpoints:
OS, DSS, distant metastasis-free survival, NUTRFS

Did not meet primary endpoint

CheckMate -274



Primary endpoint:
DFS

Key secondary endpoints:
OS, NUTRFS, DSS

DFS Improvement
OS not statistically significant

AMBASSADOR

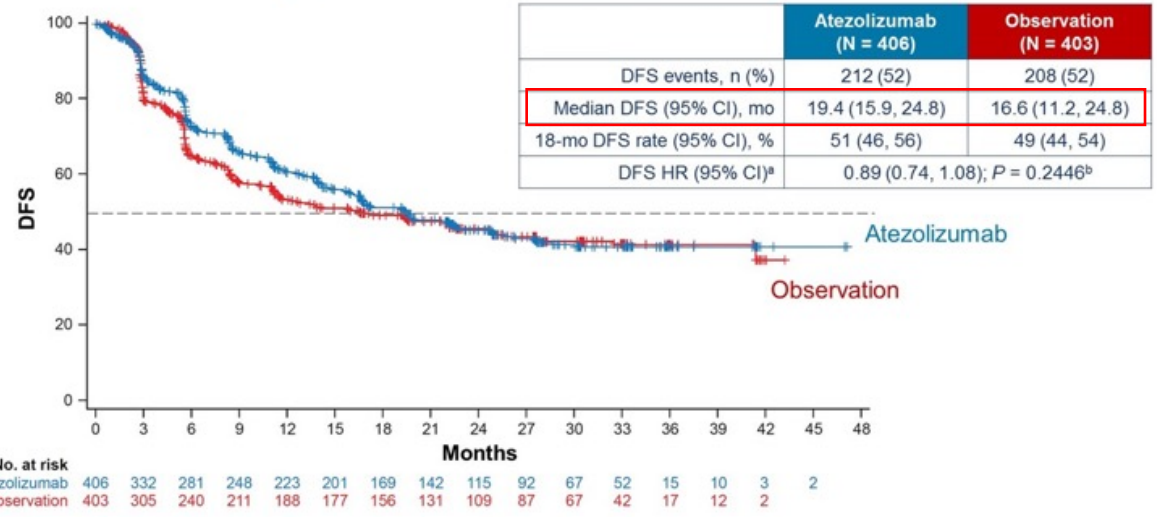
Coprimary endpoints:
DFS and OS

Key secondary endpoints:
OS and DFS in PD-L1–positive and PD-L1–negative patients

DFS Improvement
No OS improvement

IMvigor 010: No DFS or OS improvement with atezolizumab

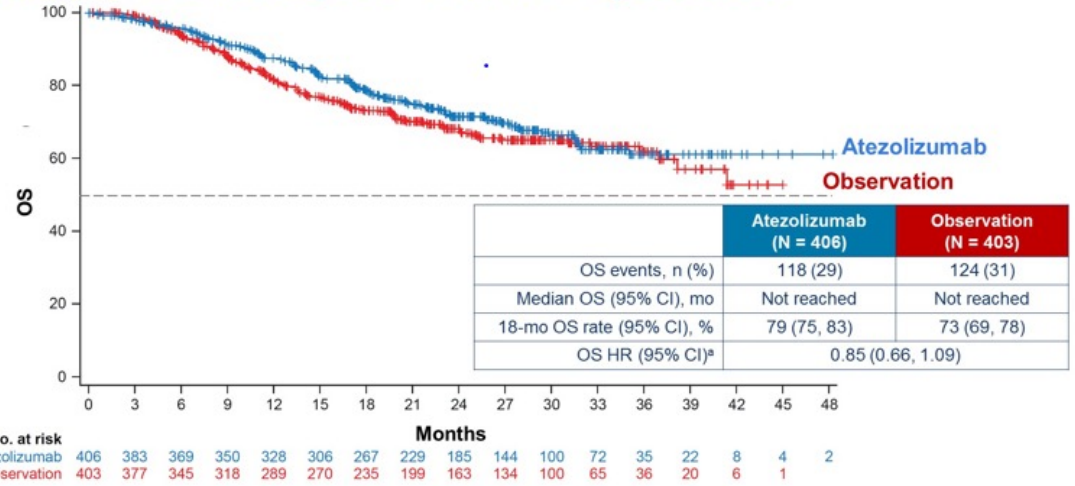
DFS in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

Interim OS Analysis in ITT Population

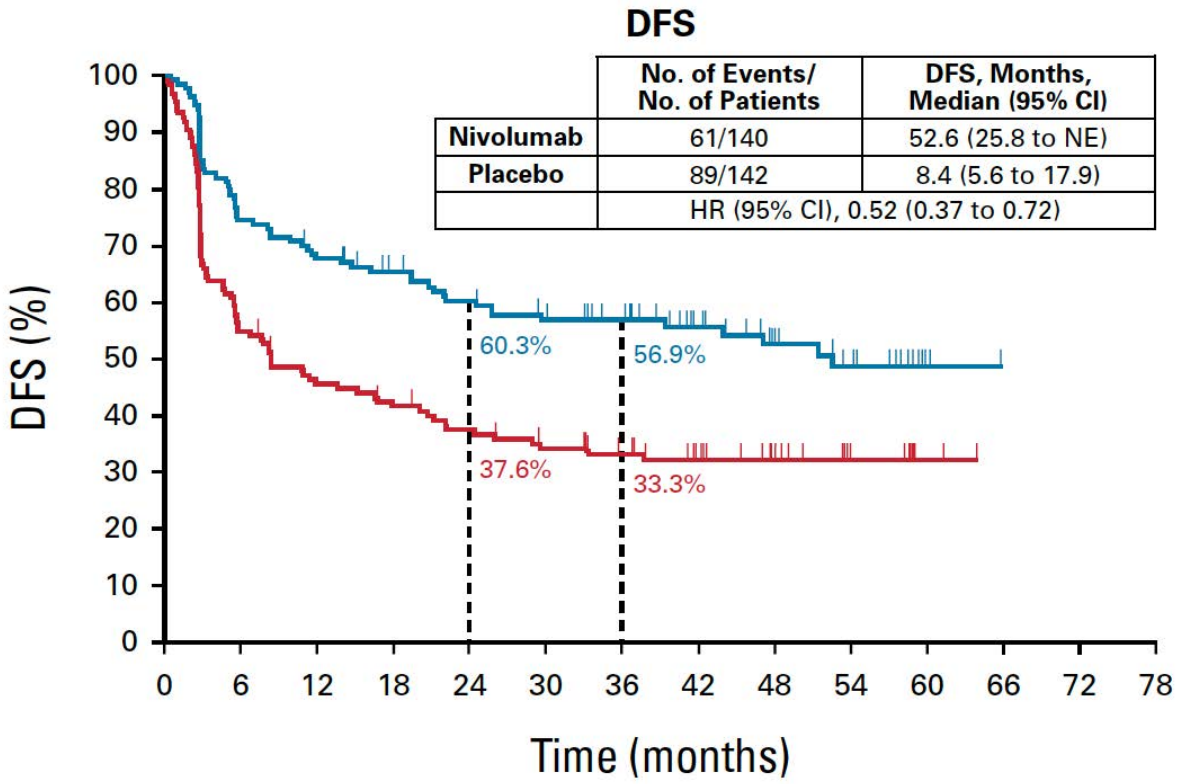


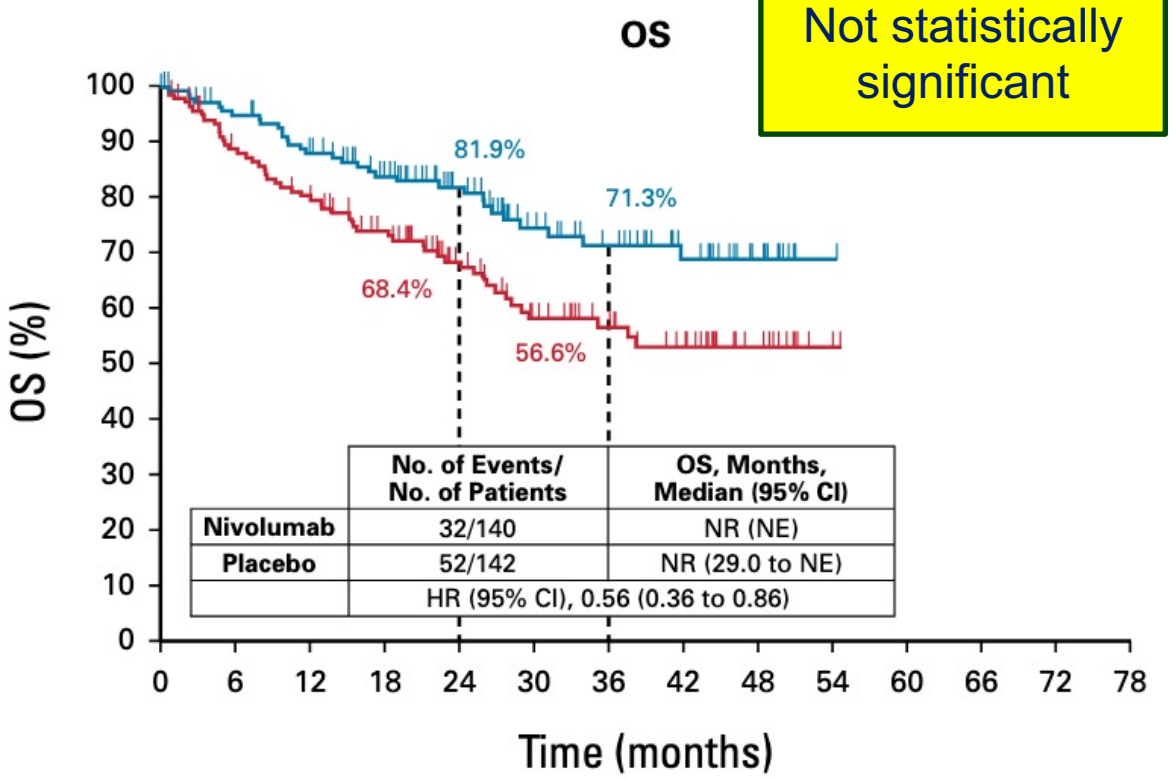
	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). [a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

Bellmunt J et al. Lancet 2021

CheckMate 274: 3 year DFS and 1st OS data





Not statistically significant

Galsky MD et al. JCO 2024

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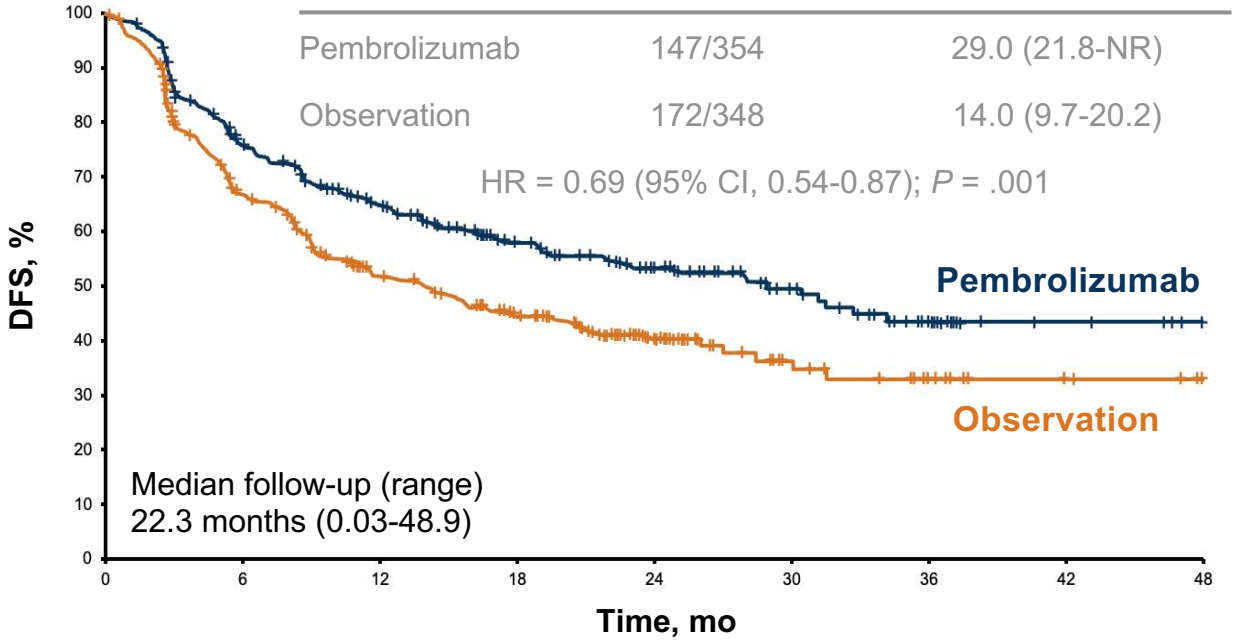
AMBASSADOR: DFS Benefit with Pembrolizumab

DFS (ITT Population)

	Events/Total, n	Median (95% CI), mo
Pembrolizumab	147/354	29.0 (21.8-NR)
Observation	172/348	14.0 (9.7-20.2)

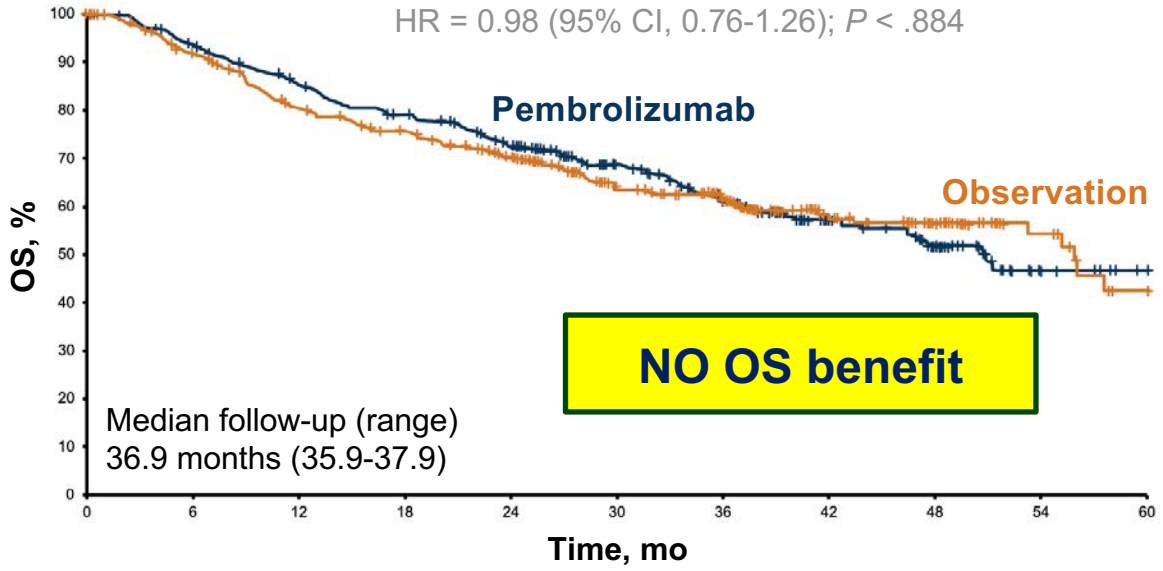
HR = 0.69 (95% CI, 0.54-0.87); *P* = .001



Overall Survival

	Events/Total, n	Median (95% CI), mo
Pembrolizumab	131/354	50.9 (43.8-NR)
Observation	126/348	55.8 (53.3-NR)

HR = 0.98 (95% CI, 0.76-1.26); *P* < .884



Apolo AB et al. NEJM 2024

Apolo AB et al. ASCO GU 2024.

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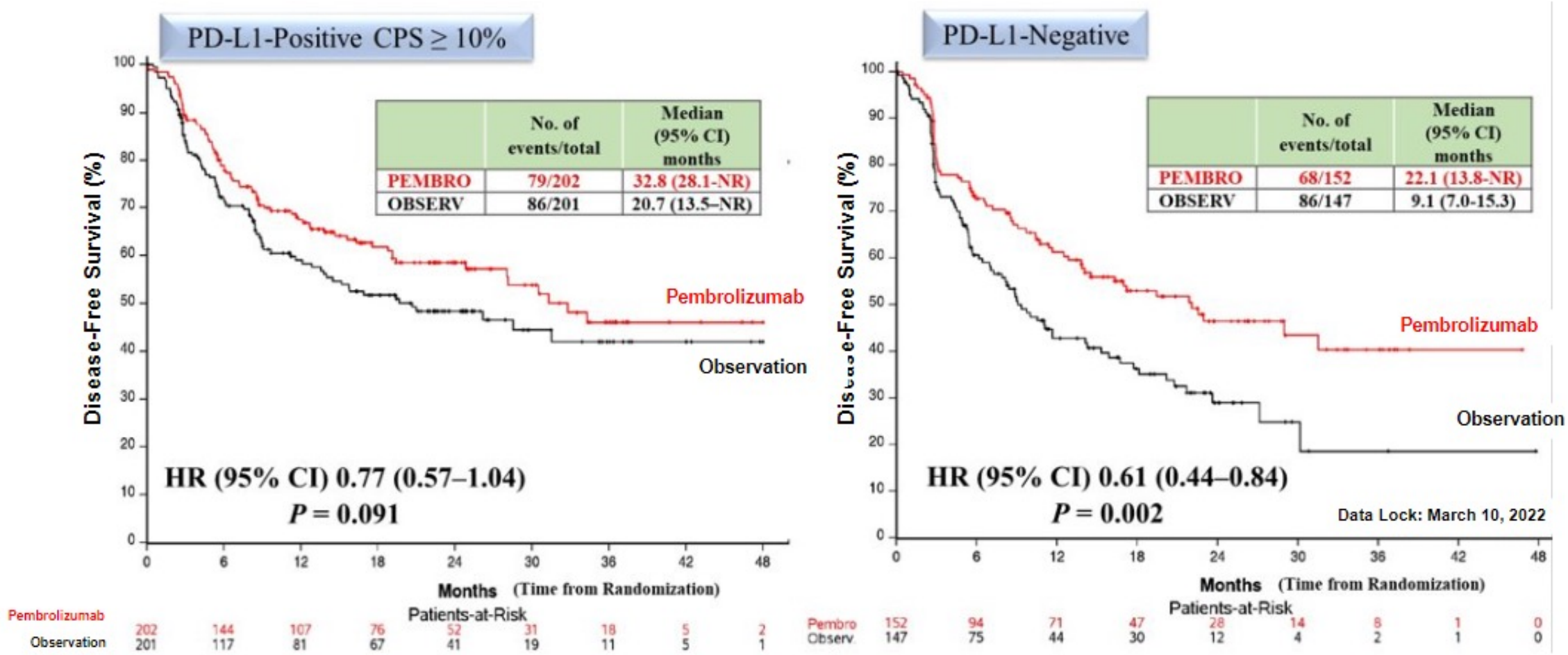
AMBASSADOR: Patients with PD-L1+ tumors did worse

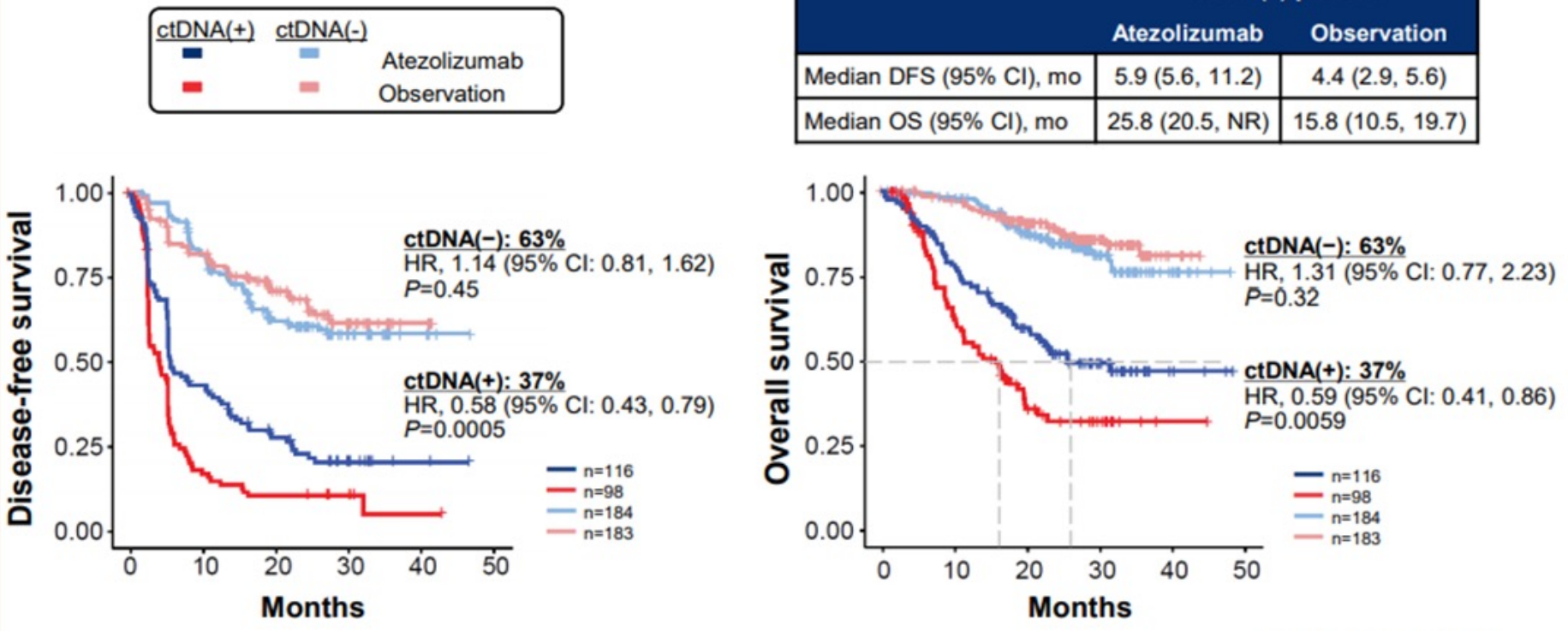


CI, confidence interval; CPS, combined positive score; DFS, disease-free survival; HR, hazard ratio; NR, not reached.

Improved OS, DFS with atezolizumab in ctDNA+ patients in IMvigor010

ctDNA(+) patients in the BEP had improved DFS and OS with atezolizumab vs observation

	ctDNA(+) patients	
	Atezolizumab	Observation
Median DFS (95% CI), mo	5.9 (5.6, 11.2)	4.4 (2.9, 5.6)
Median OS (95% CI), mo	25.8 (20.5, NR)	15.8 (10.5, 19.7)



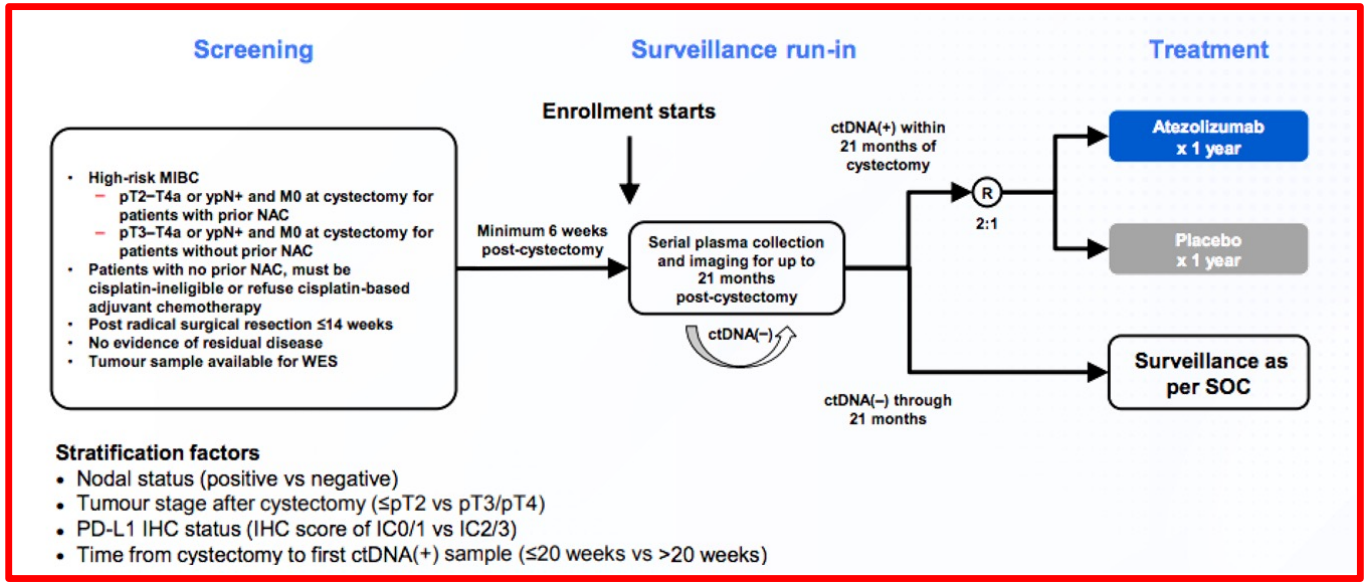
NR, not reached.

Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYIlE 10

Powles T et al. Nature 2021

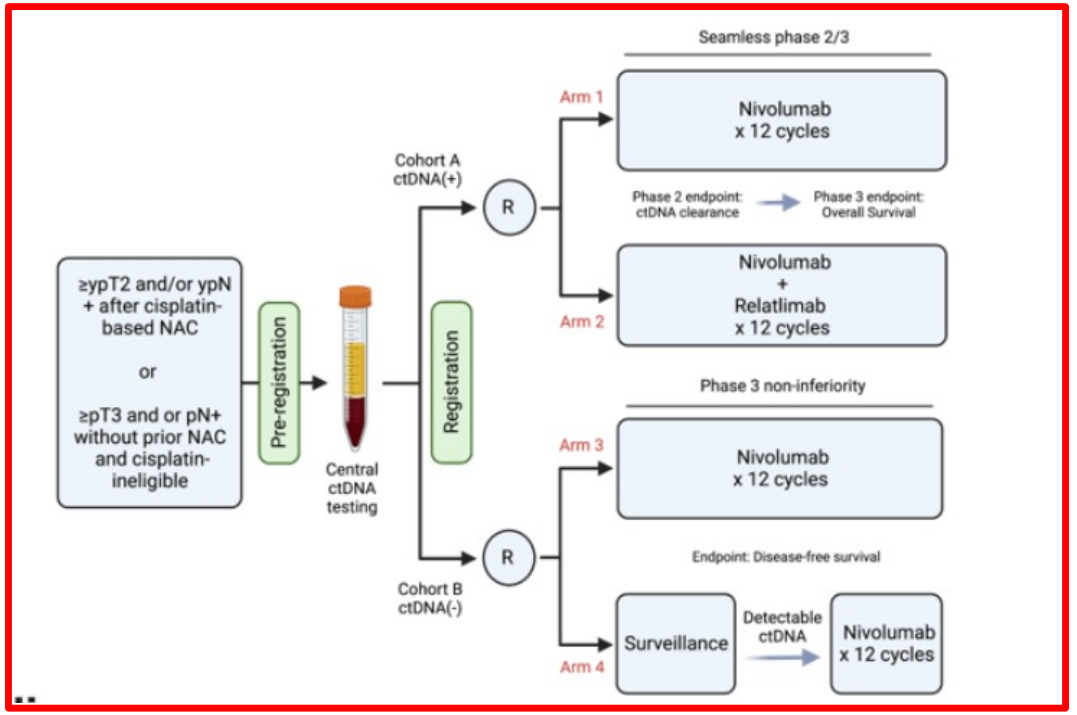
ctDNA guided adjuvant IO trials

IMvigor011



Only ctDNA+ patients randomized to atezolizumab vs placebo

MODERN



ctDNA- patients get randomized to immediate nivolumab vs when become ctDNA+

Ongoing Phase 3 Peri-operative IO-based Trials in MIBC

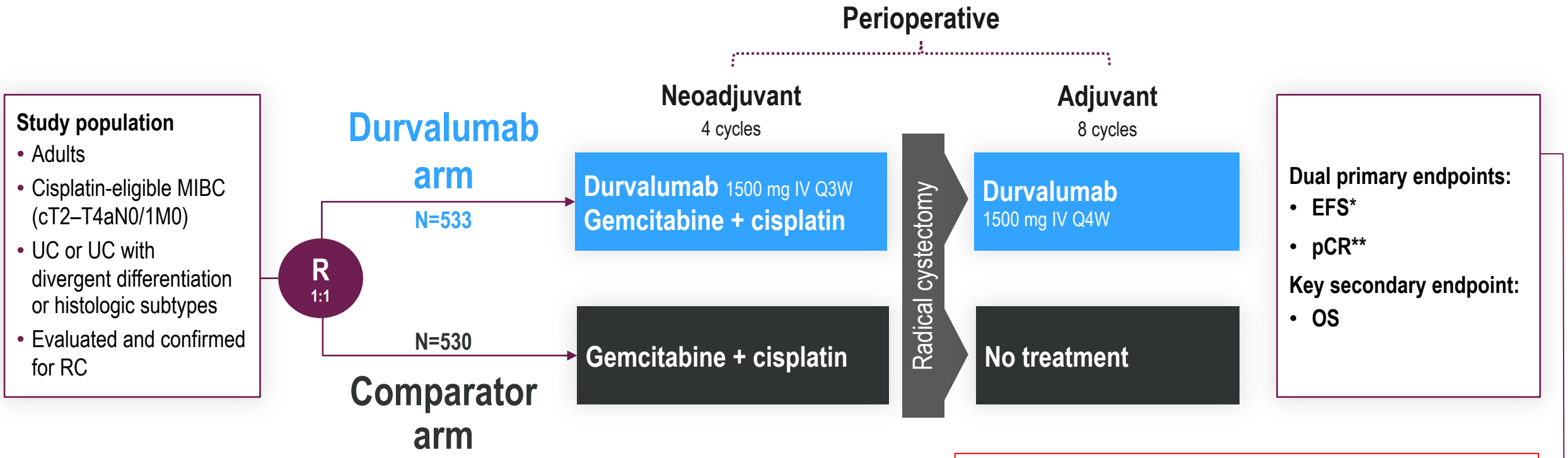
CISPLATIN ELIGIBLE

CISPLATIN-INELIGIBLE

Clinical Trial	N	Treatment Arms	Eligibility
KEYNOTE-866	870	Pembro + GC vs GC	T2-4aN0M0
KEYNOTE-B15/EV-304	784	Pembro +EV vs GC	T2-T4aN0M0 T1-T4aN1M0
NIAGARA	1050	Durva+ GC vs GC	T2-4aN1M0
ENERGIZE	1200	Nivo + GC vs GC	T2-4aN0M0
KEYNOTE-905/ EV-303	836	RC vs Pembro+EV vs Pembro	T2-4aN0M0
VOLGA	830	RC vs Druva/Tremi+EV vs Durva+EV	T2-4aN0M0

Primary Endpoints pCR, EFS
Adjuvant IO in experimental arm
NO adjuvant IO in control arm

NIAGARA: Study Design



Stratification factors

Clinical tumour stage (T2N0 vs >T2N0)

Renal function (CrCl ≥60 mL/min vs ≥40–<60 mL/min)

PD-L1 status (high vs low/negative expression)

Gemcitabine/cisplatin dosing

CrCl ≥60 mL/min: Cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2 Day 1, then gemcitabine 1000 mg/m^2 Day 8, Q3W for 4 cycles

CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m^2 + gemcitabine 1000 mg/m^2 Days 1 and 8, Q3W for 4 cycles

EFS defined as:

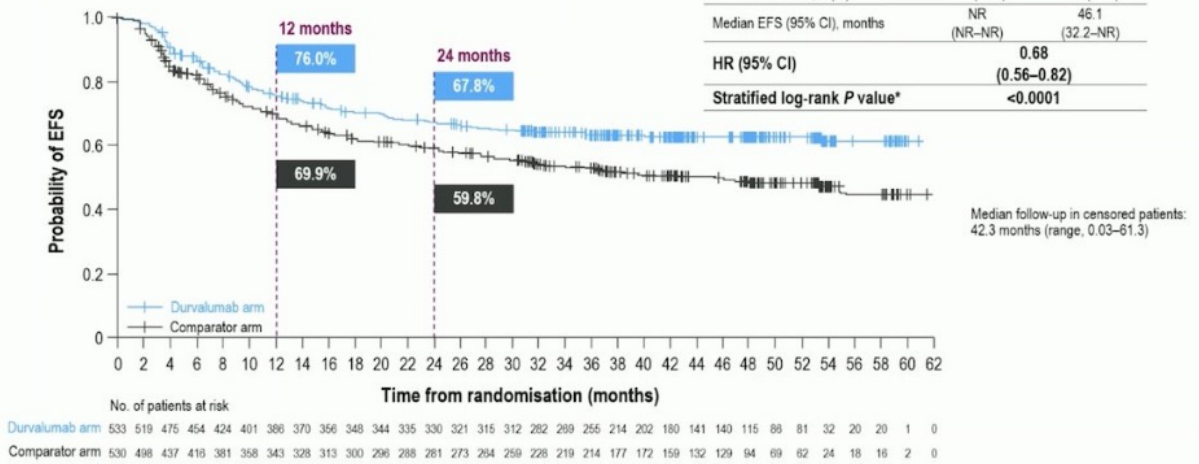
- Progressive disease that precluded RC
- Recurrence after RC
- Date of expected surgery in patients who did not undergo RC
- Death from any cause

Other endpoints (not reported here):
DFS, DSS, MFS, HRQoL, 5-year OS

Powles T et al. ESMO 2024;Abstract LBA5

*Evaluated by blinded independent central review or central pathology review (if a biopsy was required for a suspected new lesion).**Evaluated by blinded central pathology review.
ClinicalTrials.gov, NCT03732677; EudraCT number, 2018-001811-59. CrCl, creatinine clearance; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival; HRQoL, health-related quality of life; IV, intravenous; MFS, metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomised; RC, radical cystectomy; UC, urothelial carcinoma..

NIAGARA: Event-free Survival by Blinded Independent Central Review (ITT)

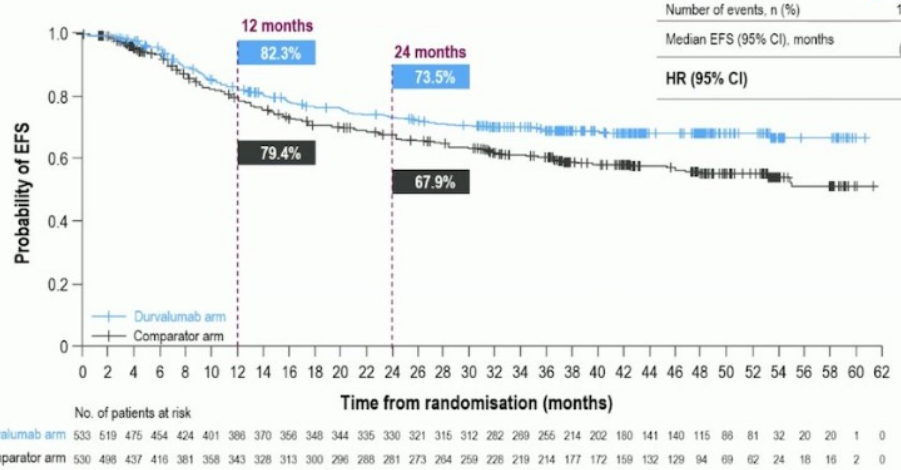


	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS (95% CI), months	NR (NR–NR)	46.1 (32.2–NR)
HR (95% CI)	0.68 (0.56–0.82)	
Stratified log-rank *P* value*	<0.0001	

Median follow-up in censored patients: 42.3 months (range, 0.03–61.3)

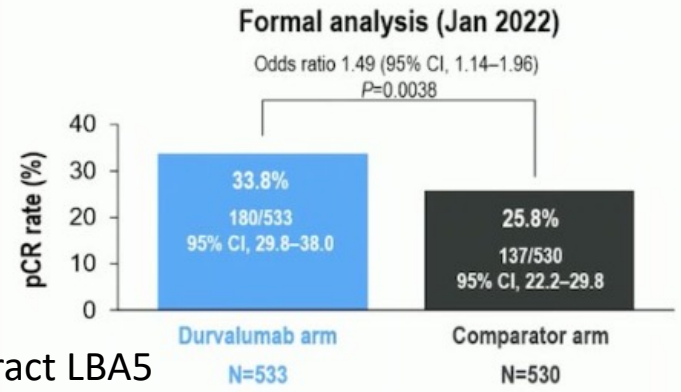
NIAGARA: Event-free Survival Sensitivity Analysis

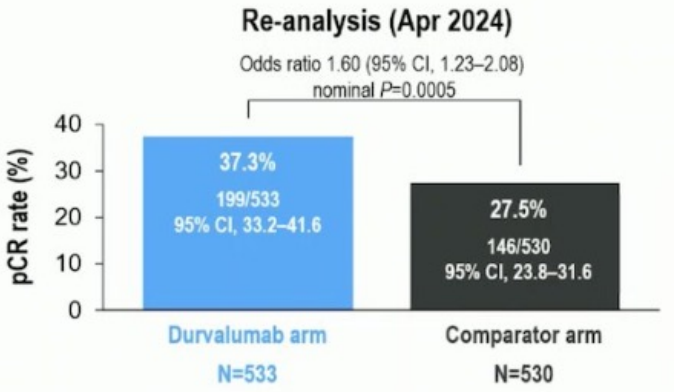
Patients who did not undergo RC were censored



	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	147 (27.6)	186 (35.1)
Median EFS (95% CI), months	NR (NR–NR)	NR (53.2–NR)
HR (95% CI)	0.69 (0.56–0.86)	

NIAGARA: Pathologic Complete Response (ITT)





Powles T et al. ESMO 2024;Abstract LBA5

Conclusions

- Treatments for NMIBC and MIBC are rapidly evolving and improvement in outcomes seen with immunotherapy and novel therapies

- Unmet need to identify valid biomarkers to select patients for the most appropriate treatment, spare unnecessary toxicity and allow bladder preservation

Discussion Questions

- What is your global perspective on the overall efficacy and tolerability of the TAR-200 delivery system? How would you compare the tolerability of TAR-200 to standard chemotherapy? In which settings would you like to utilize TAR-200 alone or with cetrelimab?

Discussion Questions

- What is your global perspective on the TAR-210 erdafitinib intravesical delivery system for patients with NMIBC and an FGFR alteration? How would you compare the tolerability of TAR-210 to standard erdafitinib administration? If this strategy were available, for which patients would you use it?

Module 11: Urothelial Bladder Cancer

Management of Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Gupta

Optimizing the Treatment of Metastatic UBC — Dr Rosenberg

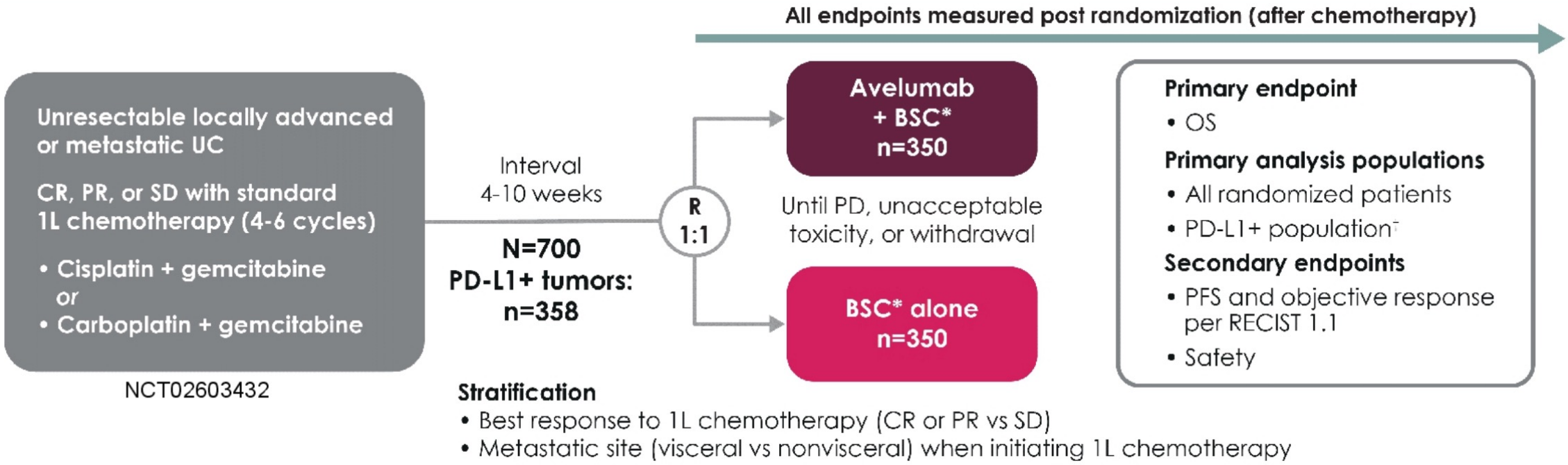
Optimizing the Treatment of Patients with Metastatic Urothelial Cancer

Jonathan Rosenberg, MD
Chief, Genitourinary Oncology Service
Enno Ercklentz Chair
Department of Medicine
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College

Disclosures

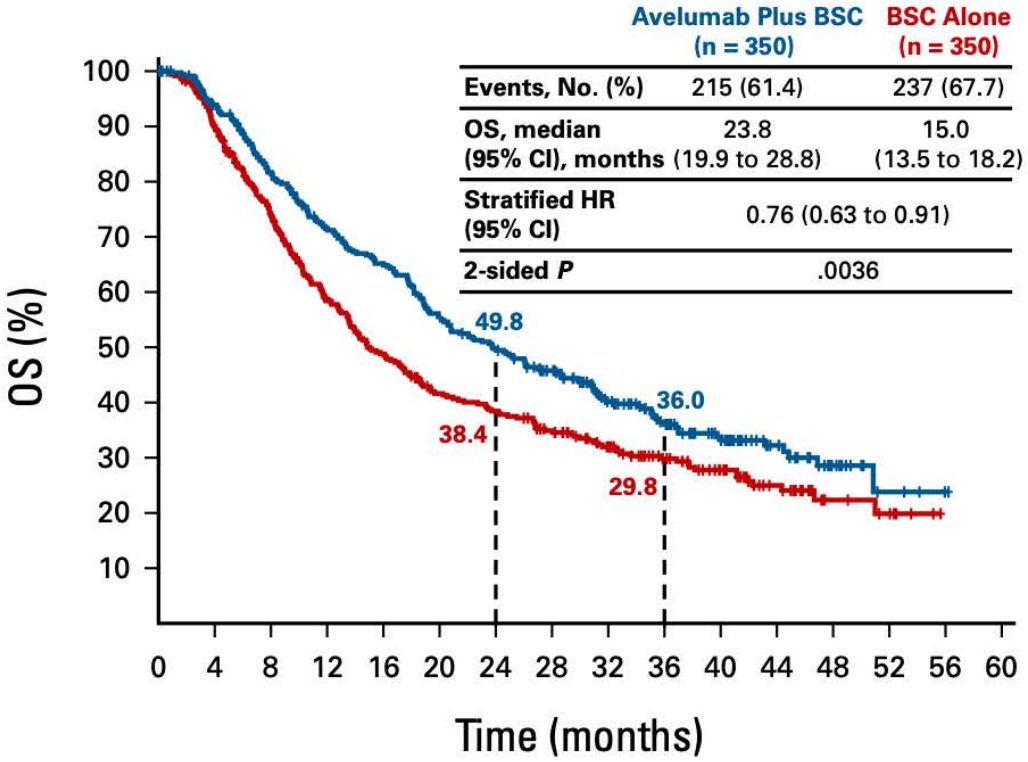
Advisory Committees	Astellas, Seagen Inc, Tyra Biosciences Inc
Consulting Agreements	Aadi Bioscience, Aktis Oncology, Alligator Bioscience, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, EMD Serono Inc, Genentech, a member of the Roche Group, Generate Biomedicines, Gilead Sciences Inc, Hengrui Therapeutics Inc, Imvax Inc, Janssen Biotech Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Pfizer Inc, Samsung Bioepis, Seagen Inc, Tyra Biosciences Inc
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Seagen Inc

Avelumab Maintenance Therapy



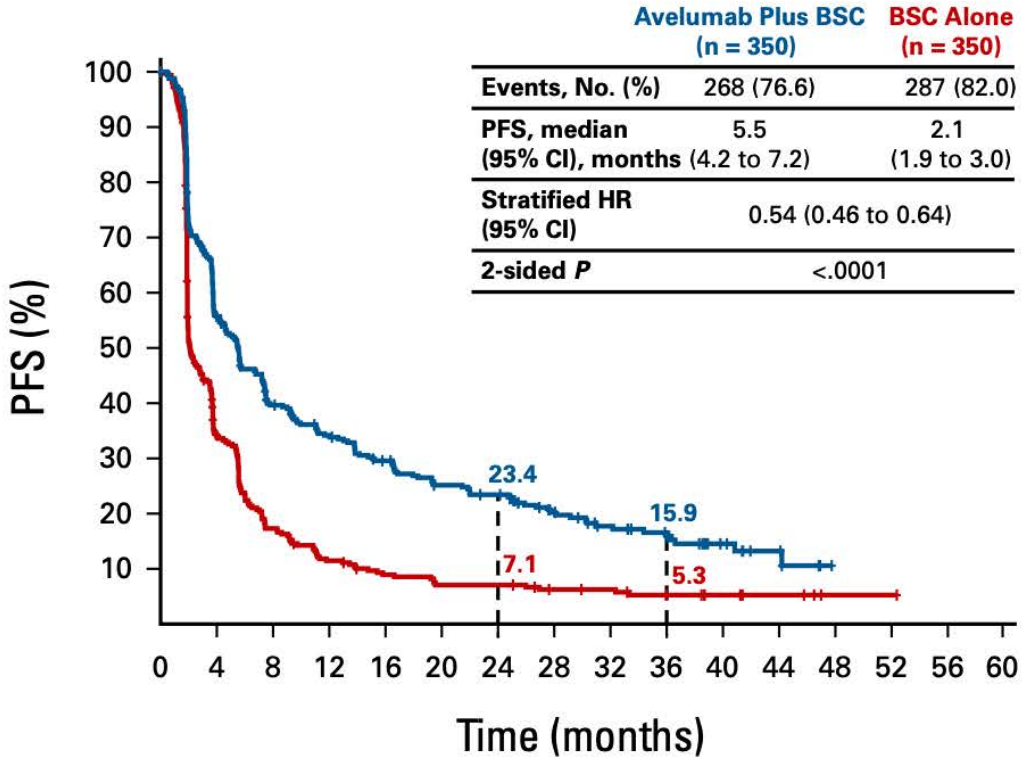
Powles T et al. ASCO GU 2022;Abstract 487.

Avelumab Maintenance Therapy – Survival Outcomes



No. at risk:

Avelumab plus BSC	350	318	274	237	216	183	164	140	99	74	53	31	13	4	1	0
BSC alone	350	304	243	190	158	131	121	103	82	62	46	27	10	7	0	

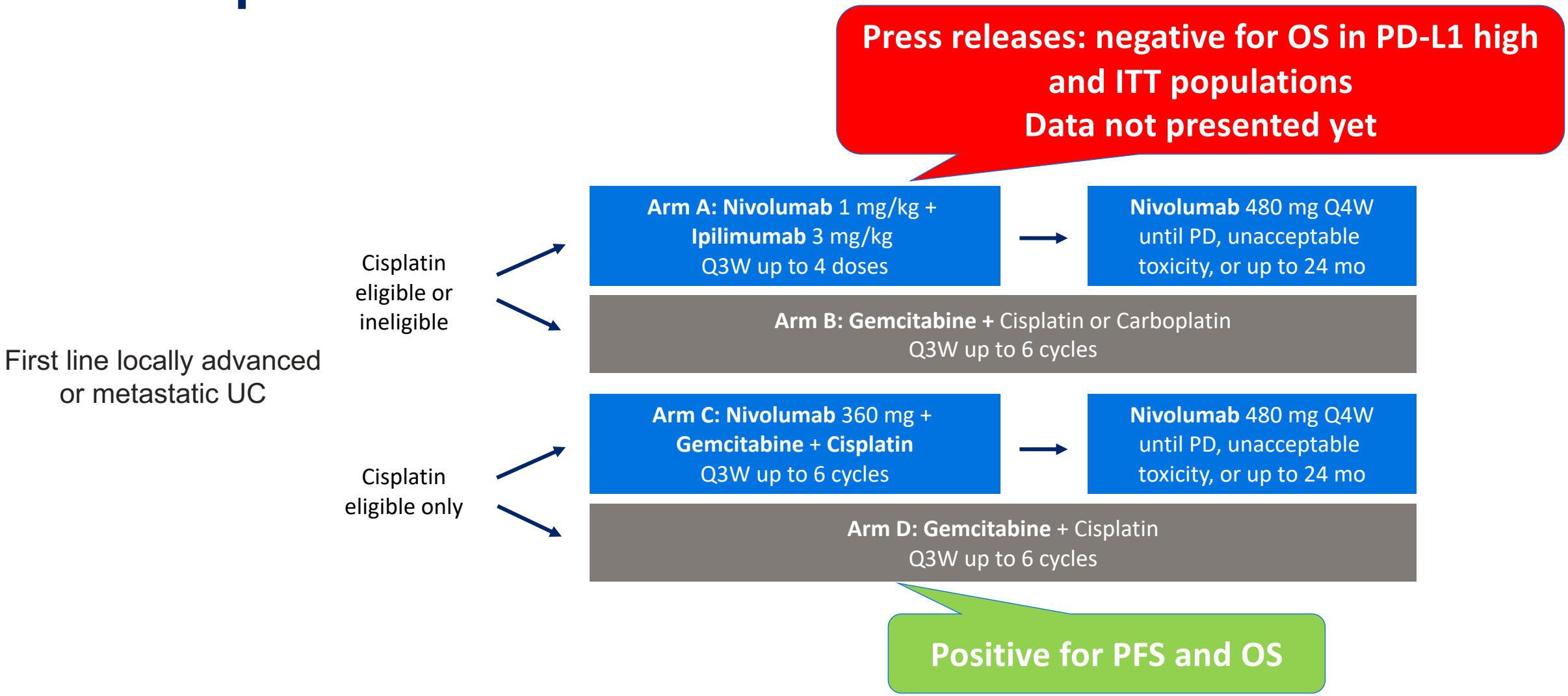


No. at risk:

Avelumab plus BSC	350	182	126	105	88	73	67	43	32	25	12	6	0			
BSC alone	350	101	51	33	24	19	19	14	13	9	6	4	1	1	0	

Powles T et al. *J Clin Oncol*. 2023;41(19):3486-3492.

CheckMate 901: two phase 3 trials of immune checkpoint blockade



Galsky. ASCO 2018. Abstr TPS539. NCT03036098.

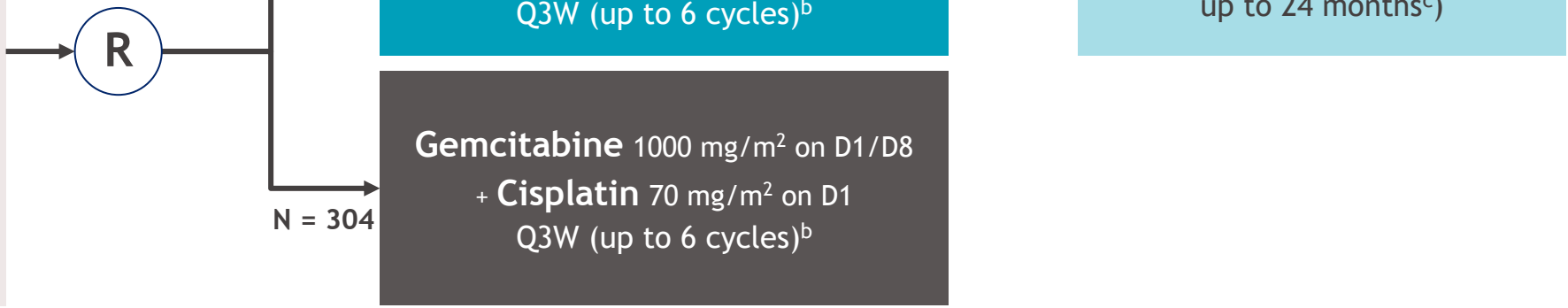
CheckMate 901: Study design

Does Nivolumab improve outcomes when added to gemcitabine-cisplatin?

Key inclusion criteria

- Age ≥ 18 years
- Previously untreated unresectable or mUC involving the renal pelvis, ureter, bladder, or urethra
- Cisplatin eligible
- ECOG PS of 0-1

Stratification factors:
- Tumor PD-L1 expression (≥ 1% vs < 1%)
- Liver metastases (yes vs no)



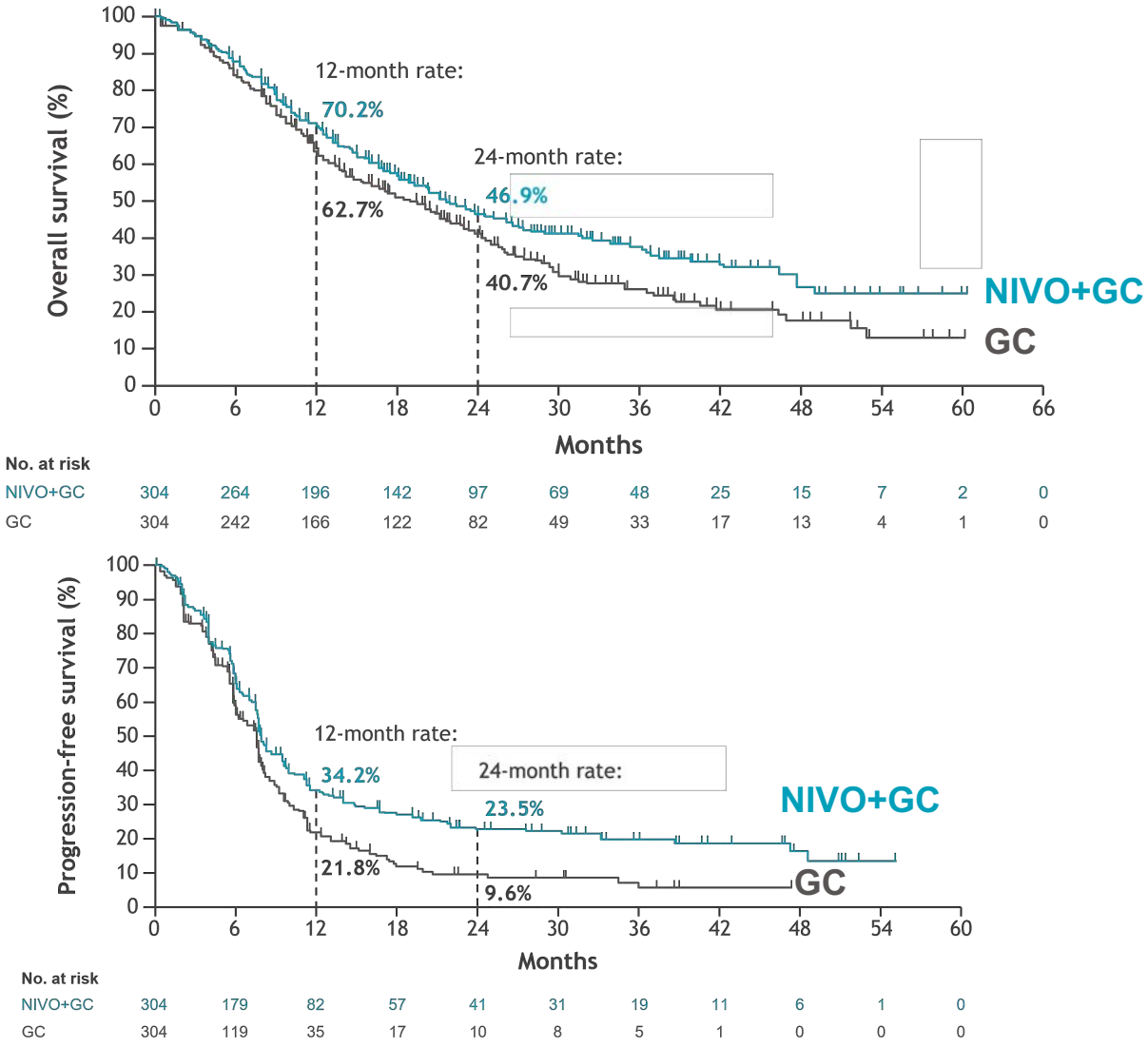
Median (range) study follow-up, 33.6 (7.4–62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

Avelumab or pembrolizumab was subsequently administered before disease progression in 2.0% of the patients in the nivolumab-combination group and in 14.5% of those in the gemcitabine–cisplatin group.

Adapted from M van der Heijden; ESMO LBA7 2023

Nivolumab improves progression-free and overall survival when added to gemcitabine and cisplatin chemotherapy



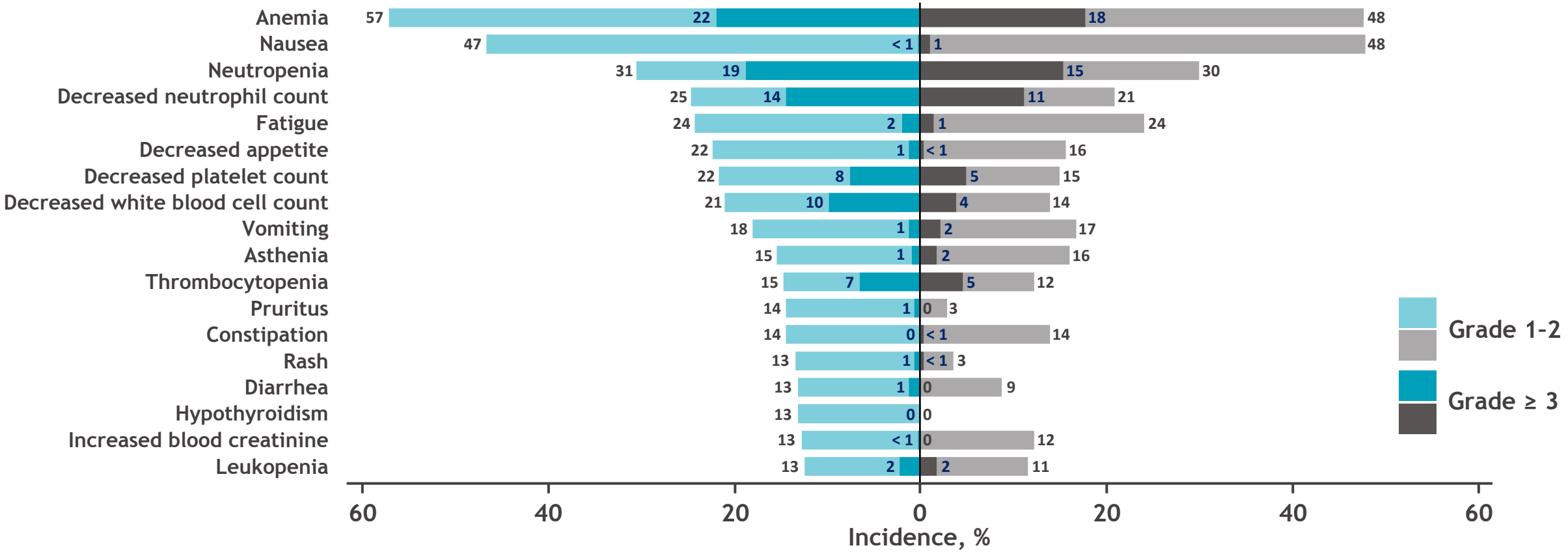
Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7–22.4)
HR (95% CI), 0.78 (0.63–0.96) *P* = 0.0171		

Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	211/304	7.9 (7.6-9.5)
GC	191/304	7.6 (6.1–7.8)
HR (95% CI), 0.72 (0.59–0.88) *P* = 0.0012		

Adapted from M van der Heijden; ESMO LBA7 2023

CheckMate 901: Treatment-related AEs in all treated patients

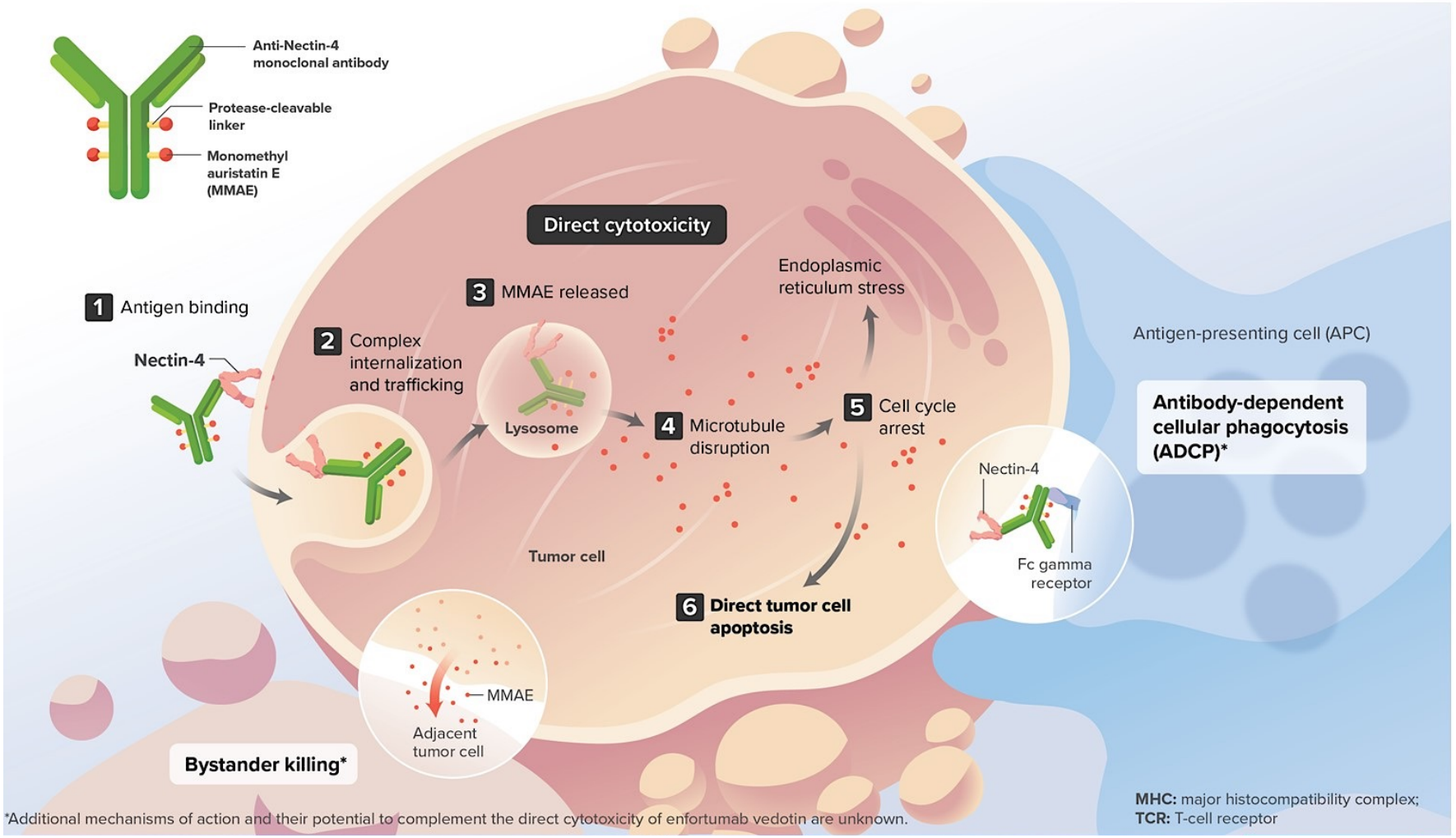
	NIVO+GC (n = 304)		GC (n = 288)	
Treatment-related AE, %[a]	Any grade	Grade ≥ 3[b]	Any grade	Grade ≥ 3[b]
Any	97	62	93	52
Leading to discontinuation	21	11	17	8



Adapted from M van der Heijden; ESMO LBA7 2023

Modest increase in grade ≥3 toxicity

Enfortumab vedotin: Nectin-4 directed ADC



Targets Nectin-4 which is highly expressed in urothelial cancers

IgG1 monoclonal antibody with intact Fc receptor

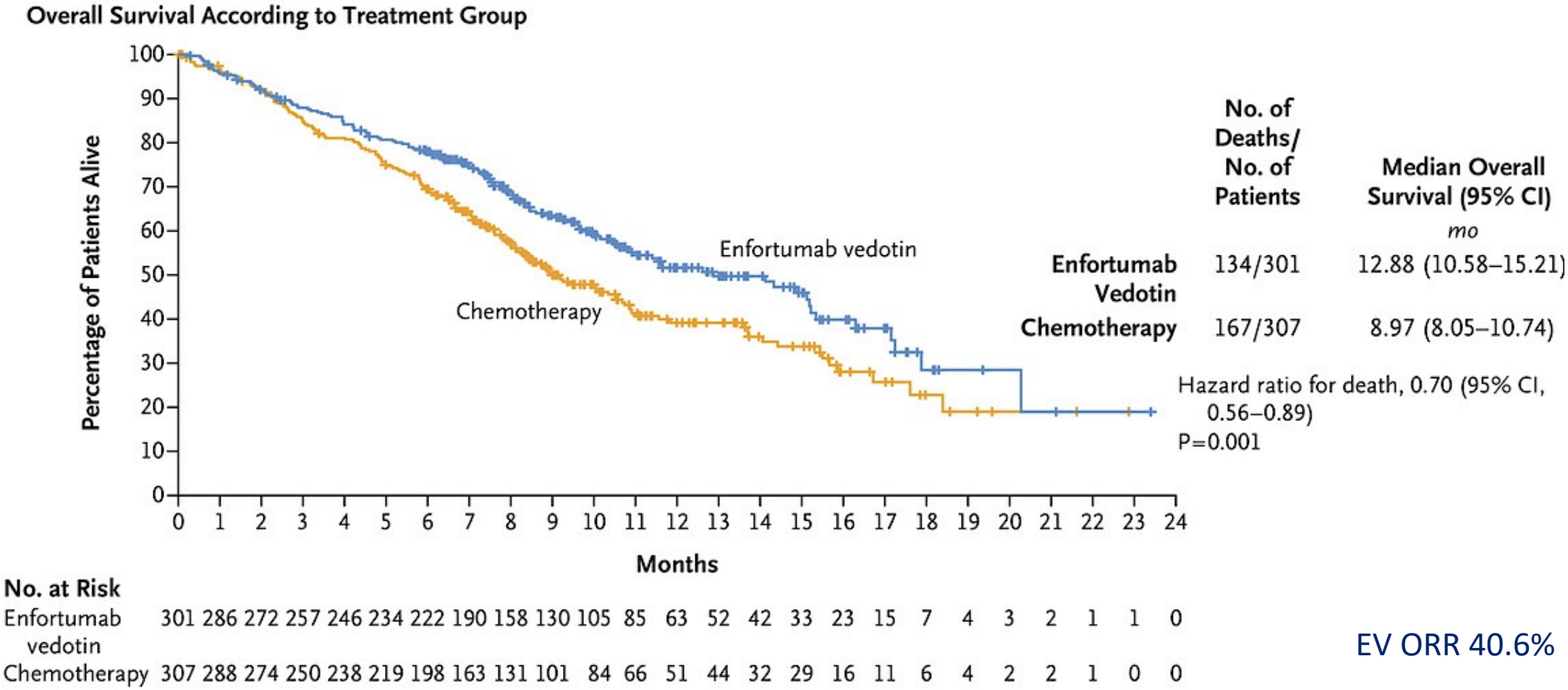
Drug : antibody ratio ~3.8

Cleavable drug linker: maleimidocaproyl valine-citrulline-p-aminobenzyloxycarbonyl

Improves OS in platinum- and immunotherapy-treated patients

Rosenberg, et al. J Clin Oncol. 2019; 37(29):2592-2600
Powles, et al. NEJM. 2021; 384:1125-1135

EV-301: EV improves survival compared to standard chemotherapy in platinum and ICB refractory patients

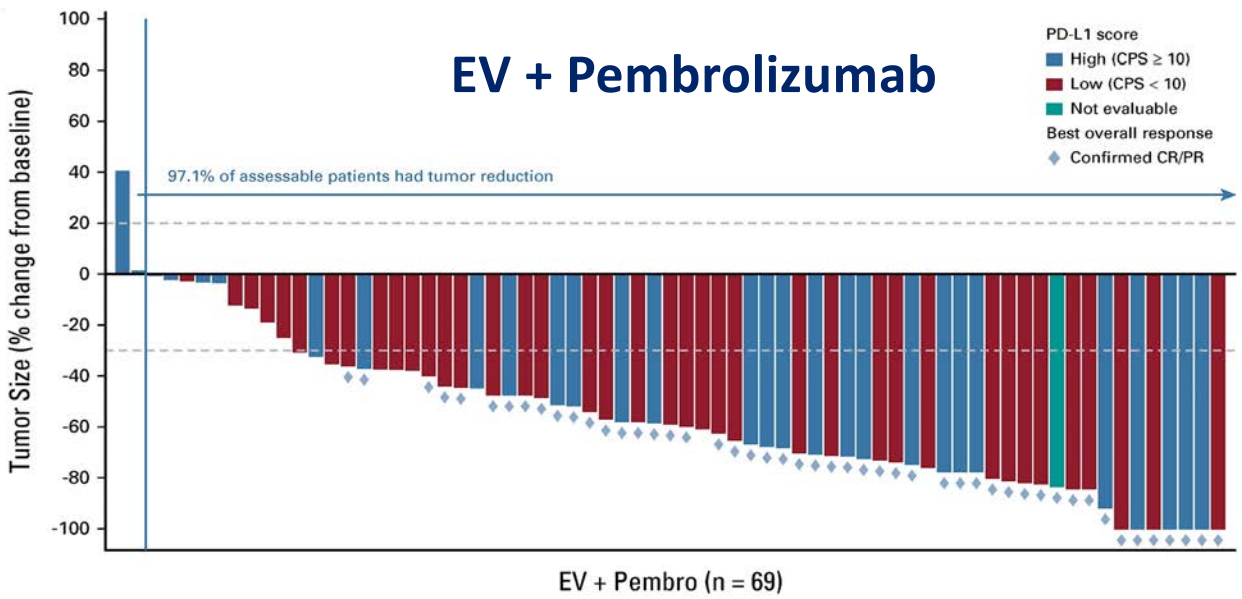


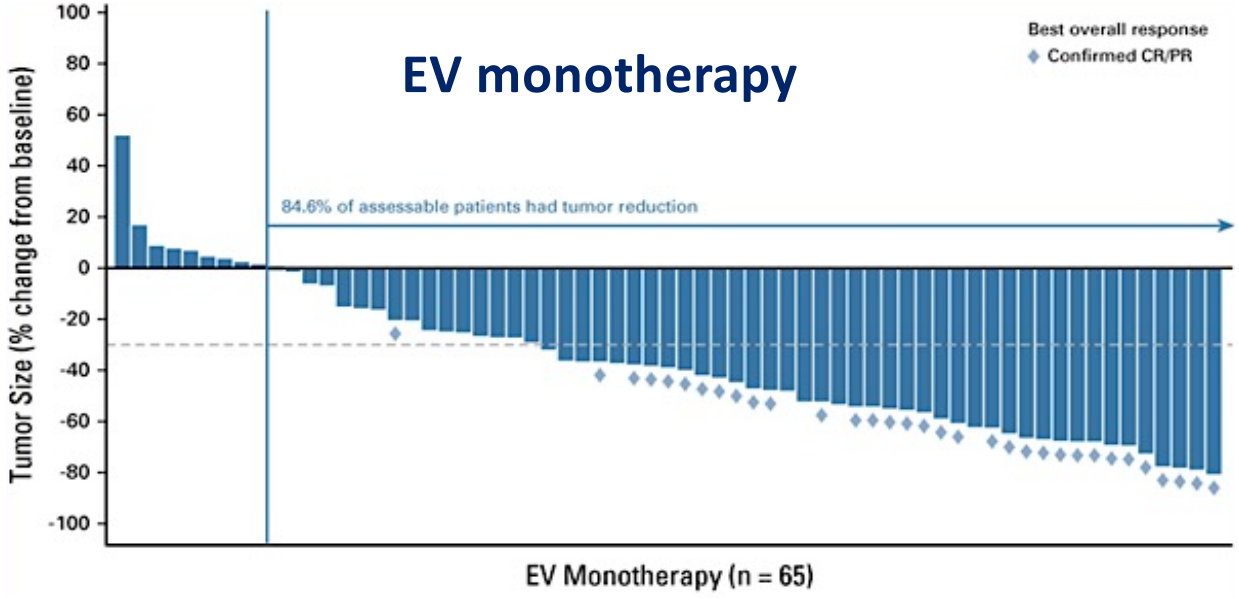
EV ORR 40.6%

PFS 5.55 vs. 3.71 months; HR 0.62; 95% CI, 0.51 to 0.75; P<0.001

Powles, Rosenberg, et al. *NEJM* 2021

EV-103 Cohort K: 1st-line EV +/- pembrolizumab





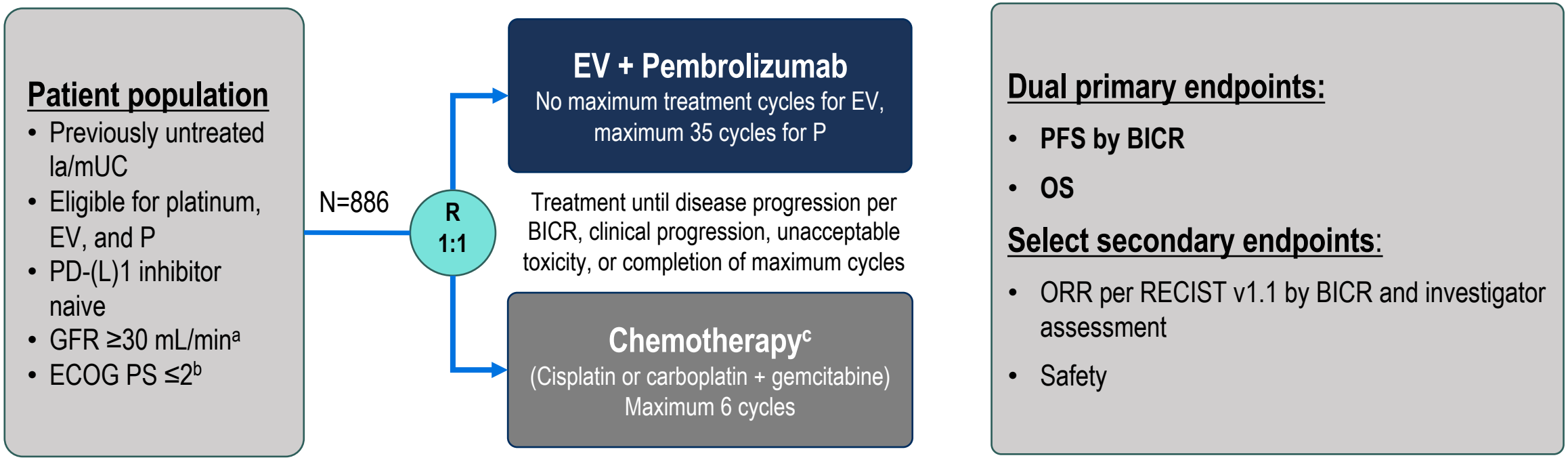
EV/Pembro activity independent of PD-L1 status

- 27/44 (61.4%) cORR in CPS<10
- 21/31 (67.7%) cORR in CPS≥10

O'Donnell et al. *JCO* 2023 41(25):4107-4117.

	EV+Pembro (N=76)	EV Monotherapy (N=73)
Confirmed ORR (95% CI)	**64.5% (52.7-75.1)**	**45.2% (33.5-57.3)**
Complete response	10.5%	4.1%
Partial response	53.9%	41.1%
Progressive disease	7.9%	9.6%
Not evaluable or no assessment	5.3%	10.9%
PFS	Not reached	8.0 months
Duration of response	Not reached	13.2 months

EV-302/KEYNOTE-A39 (NCT04223856)



Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

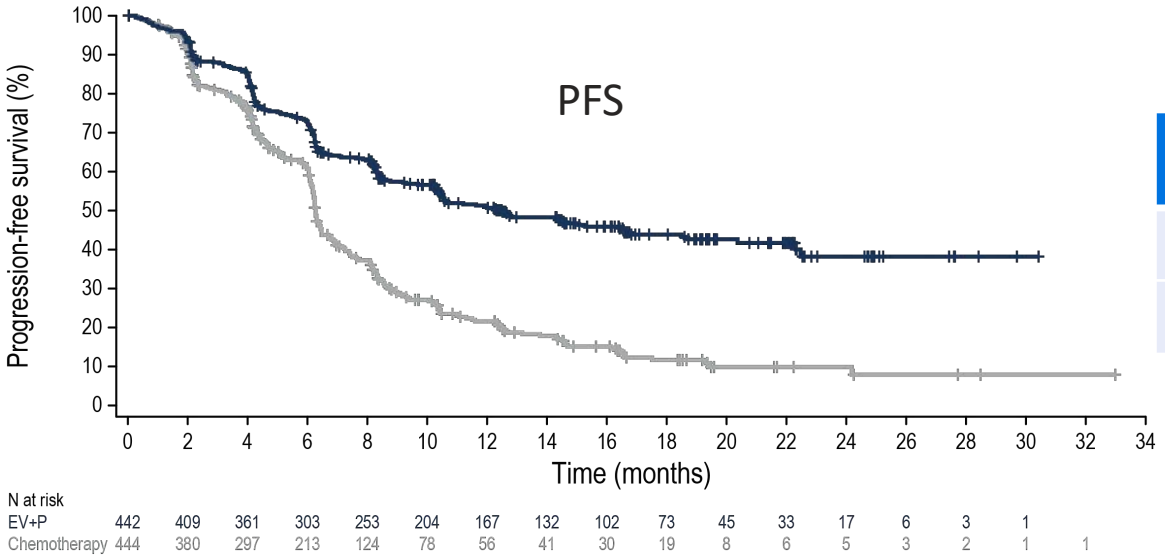
Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

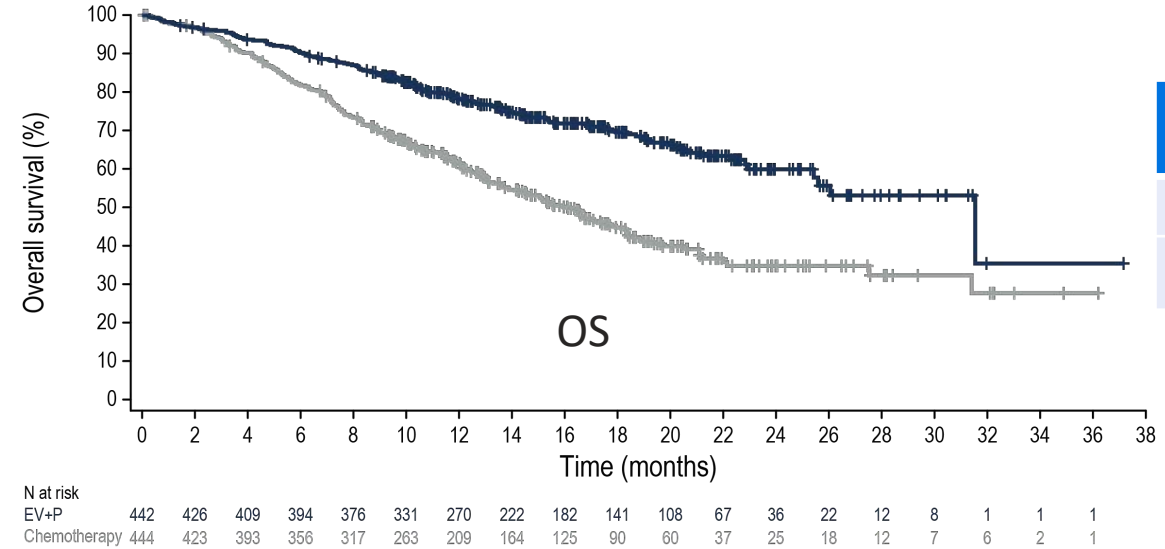
Adapted from Powles et al. ESMO 2023 LBA6

Trial amended to allow avelumab maintenance

EV-302: EV+P reduces risk of progression or death by 55% and death by 53%



	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)

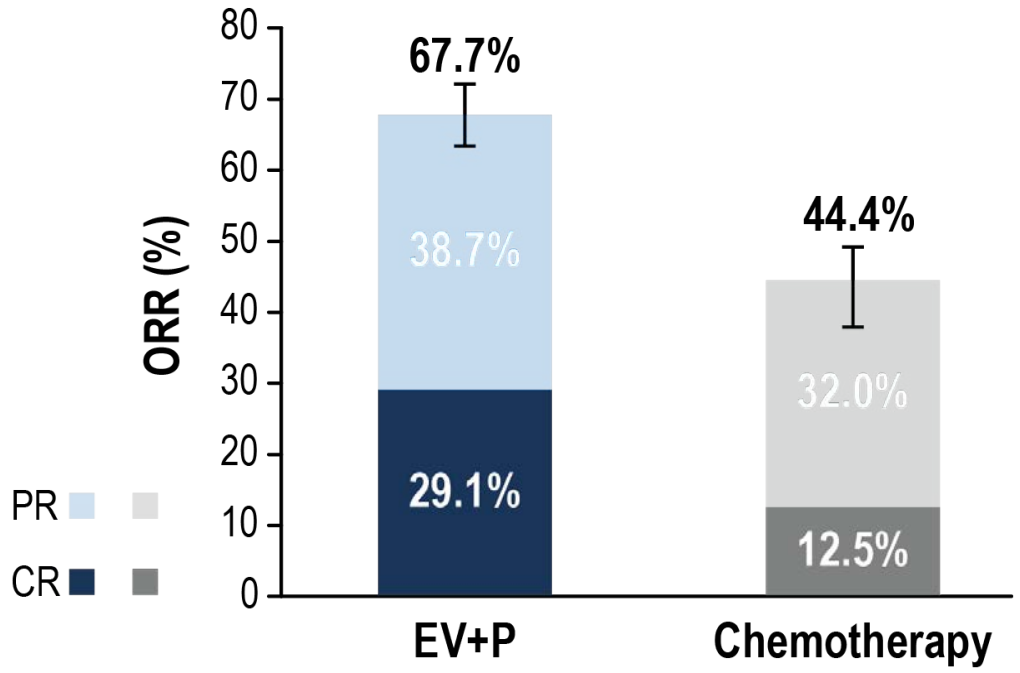


	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Adapted from Powles et al. ESMO 2023 LBA6

EV-302: Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



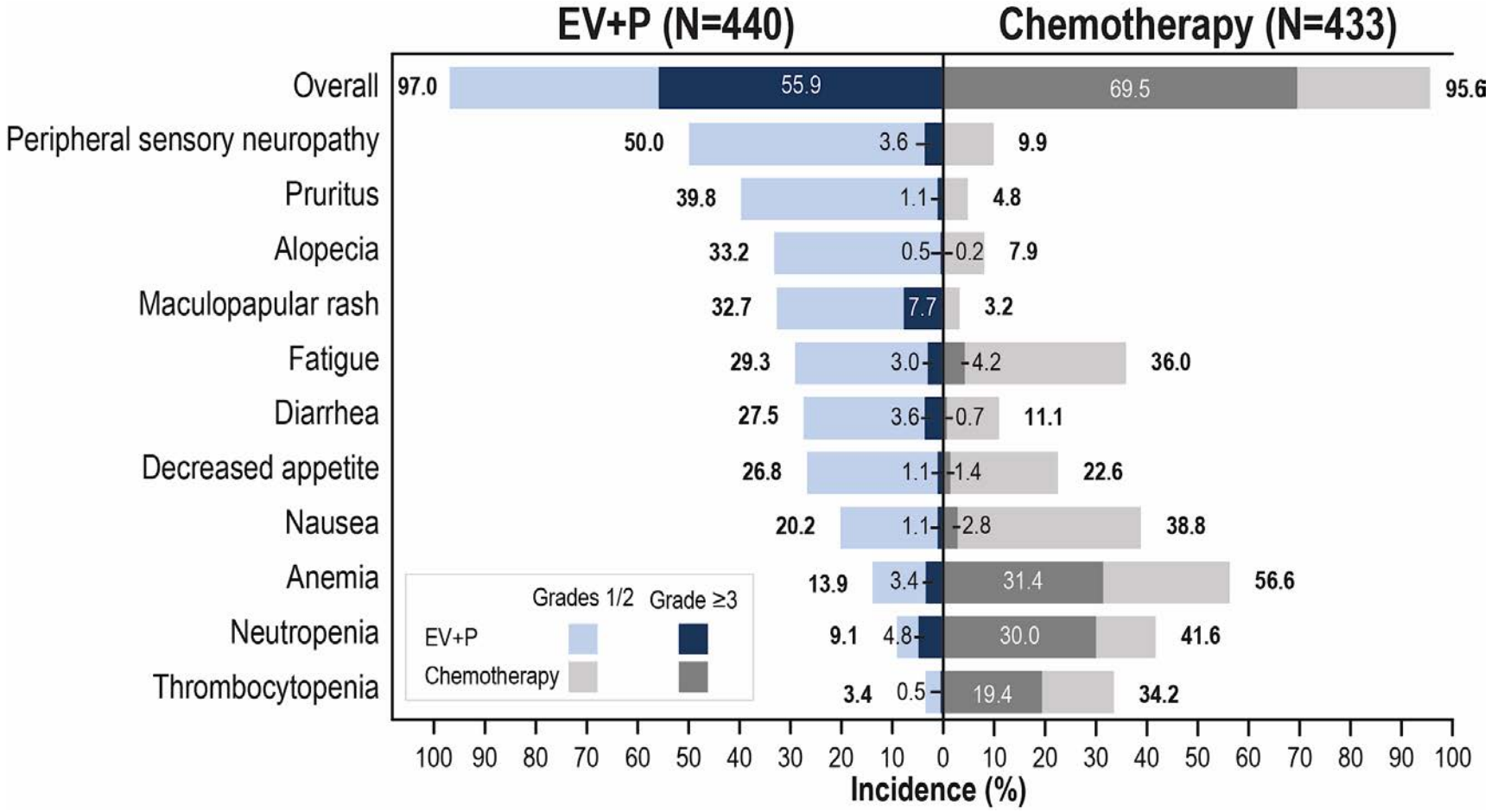
	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)
Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

EV+P ORR is remarkably consistent across studies

Adapted from Powles et al. ESMO 2023 LBA6

EV-302: Treatment-related adverse events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:

- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)

- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)

- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

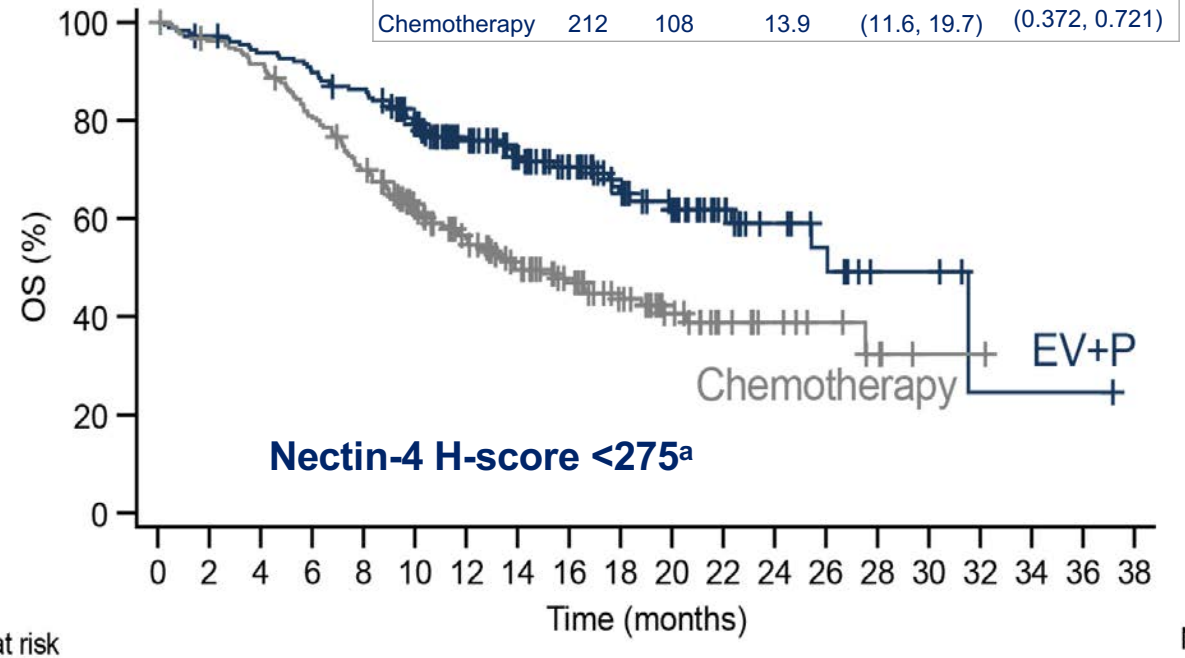
Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

Adapted from Powles et al. ESMO 2023 LBA6

Nectin-4 expression does not predict outcome compared to chemotherapy, though low levels may have a negative prognostic effect

OS Benefit with EV+P in Both <275 and ≥275 Nectin-4 H-Score Subgroups

	N	Events	Median (months)	95% CI	Stratified HR (95% CI)
EV+P	177	57	26.1	(22.3, –)	0.518 (0.372, 0.721)
Chemotherapy	212	108	13.9	(11.6, 19.7)	

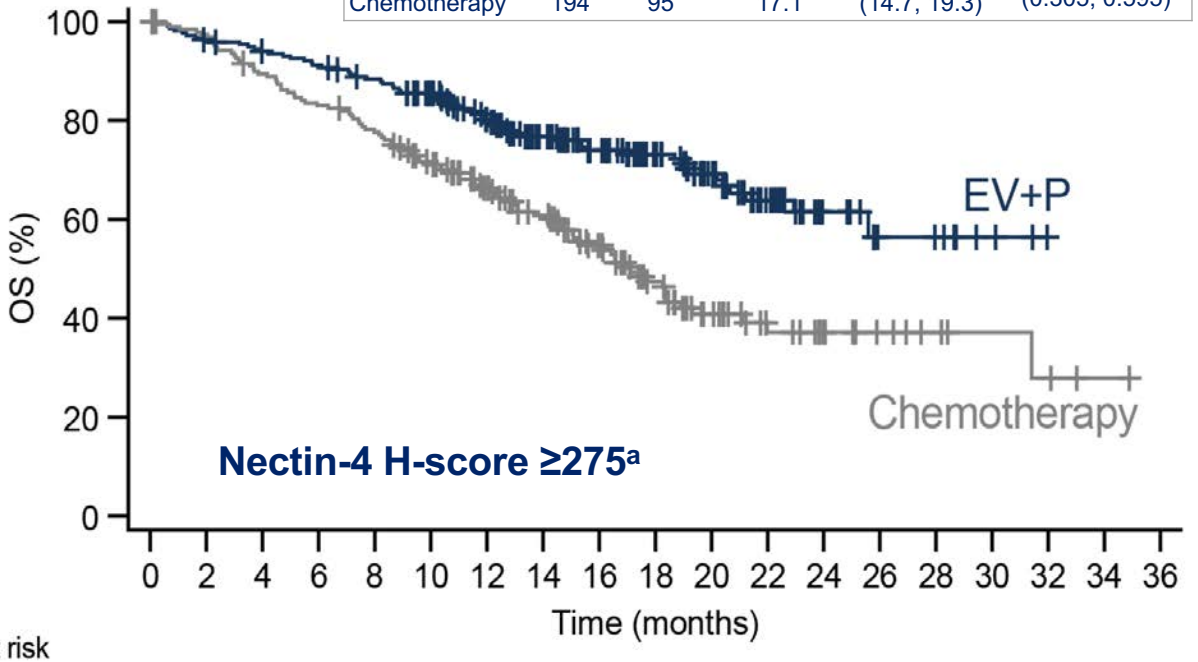


Nectin-4 H-score <275[a]

No. at risk

EV+P	177	171	164	157	150	128	102	81	64	46	36	24	15	11	4	4	1	1	1
Chemotherapy	212	202	192	169	145	114	87	66	50	36	24	15	10	7	4	1	1		

	N	Events	Median (months)	95% CI	Stratified HR (95% CI)
EV+P	217	62	–	(25.6, –)	0.426 (0.305, 0.595)
Chemotherapy	194	95	17.1	(14.7, 19.3)	



Nectin-4 H-score ≥275[a]

No. at risk

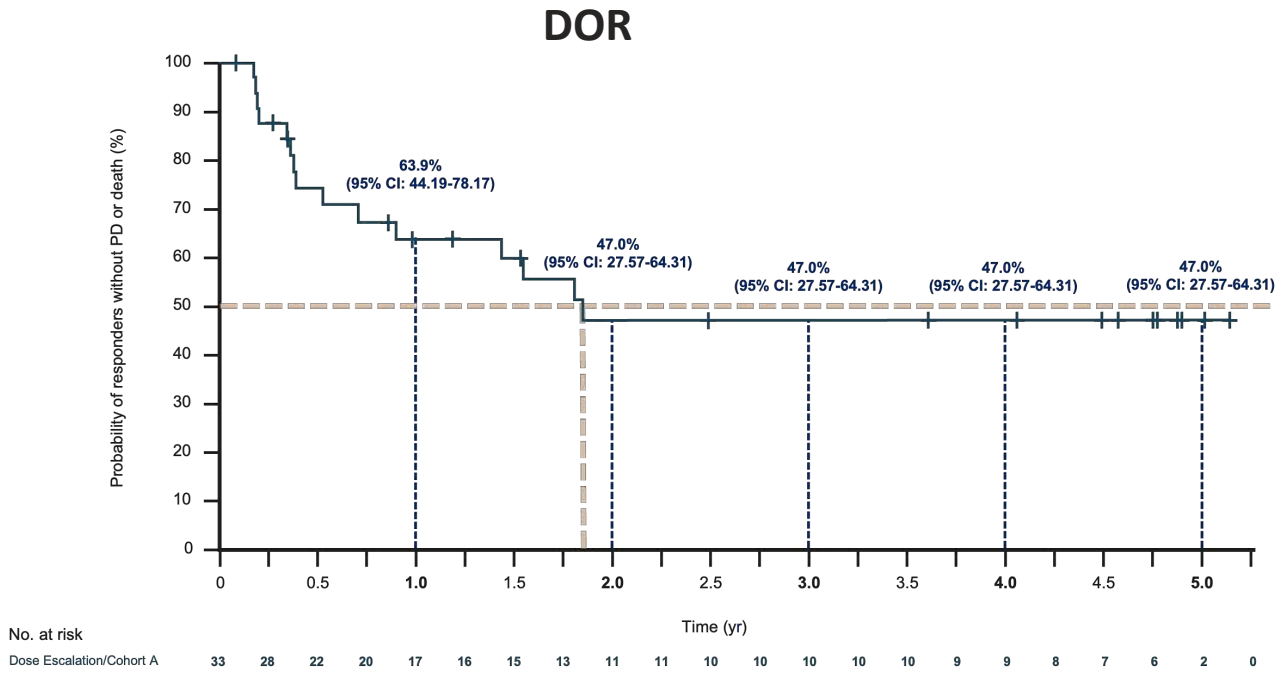
EV+P	217	208	201	195	186	169	144	121	103	81	59	35	17	8	7	3			
Chemotherapy	194	184	168	156	145	126	103	86	65	46	30	19	13	9	6	4	3	1	

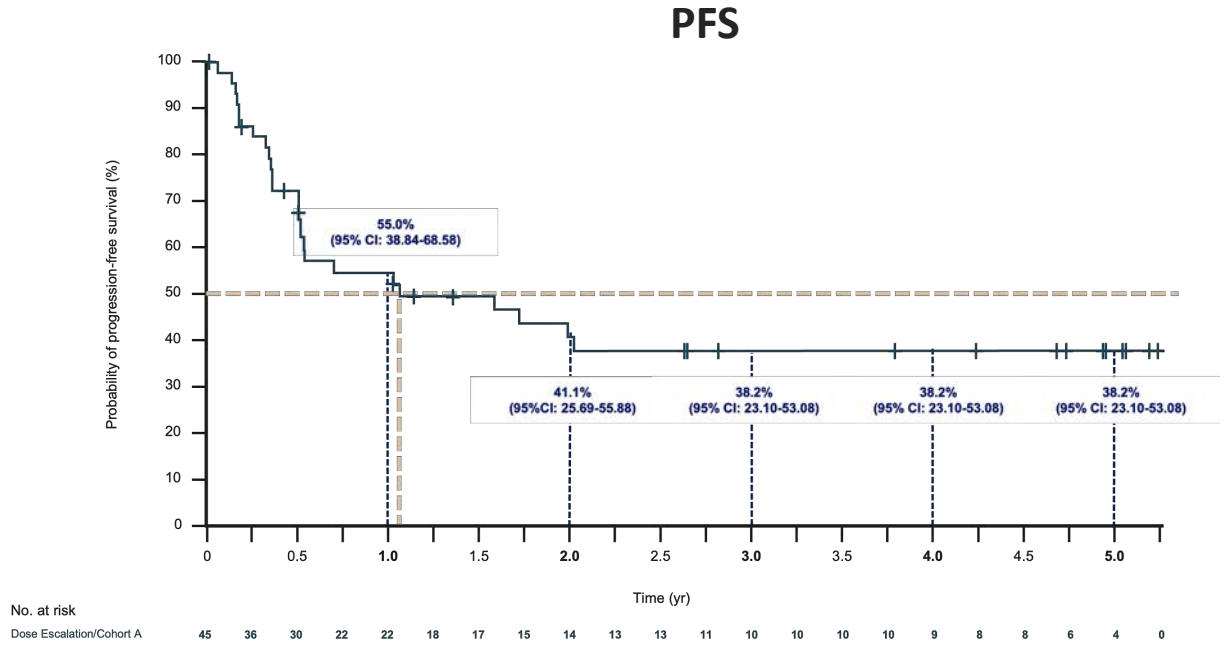
Powles et al. Annals of Oncology (2024) 35 (suppl_2): S1135-S1169.

Data cutoff: 8 August 2023.
EV, enfortumab vedotin; P, pembrolizumab.
[a]The median Nectin-4 H-score was 275 across patients in both arms.

Duration of response and progression free survival in EV-103 Cohort A/DE at median follow-up of 5 years

Responses durable after 2 years

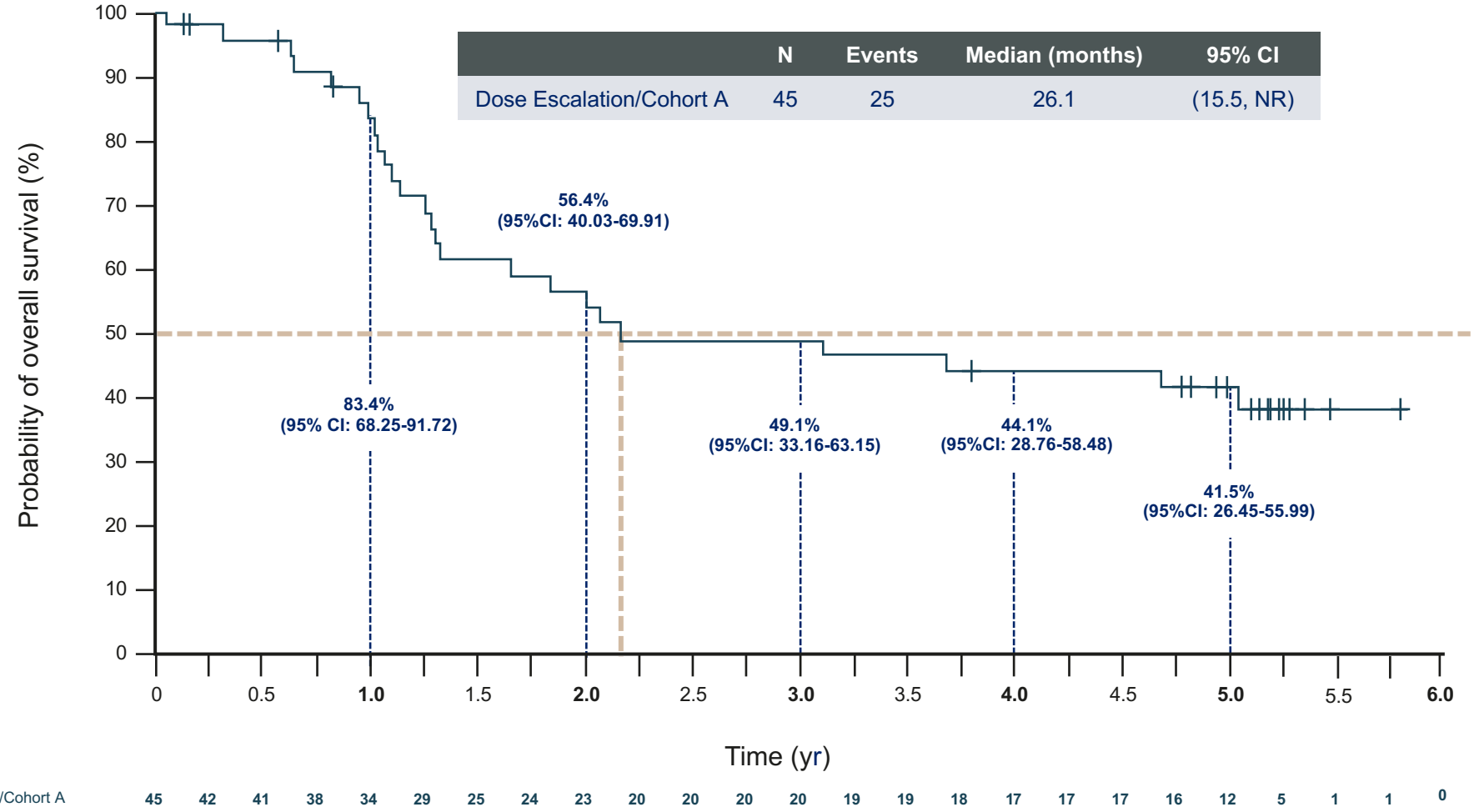




	N	Events	Median (months)	95% CI
DOR	33	15	22.1	(8.4, NR)
PFS	45	25	12.7	(6.1, NR)

Gupta S et al. ASCO 2023;Abstract 4505.

In this cisplatin-ineligible cohort, K-M estimate of 41.9% of patients were alive at 5 years follow-up



	N	Events	Median (months)	95% CI
Dose Escalation/Cohort A	45	25	26.1	(15.5, NR)

No. at risk

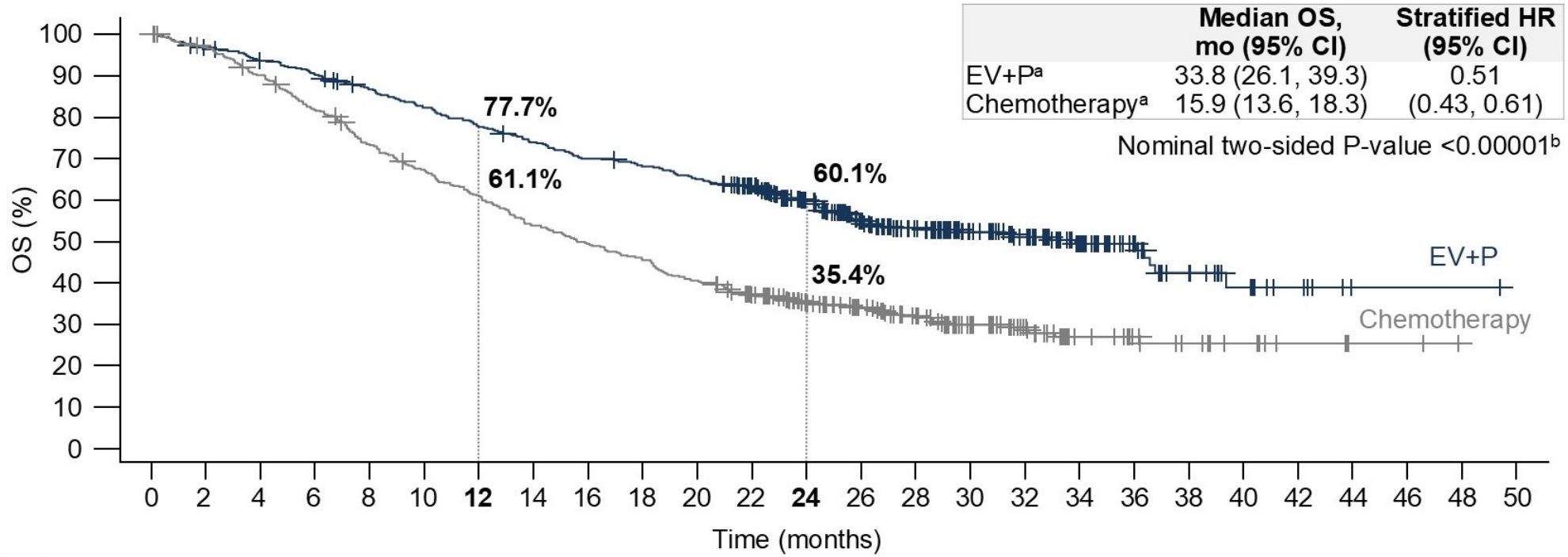
Dose Escalation/Cohort A	45	42	41	38	34	29	25	24	23	20	20	20	20	19	19	18	17	17	17	16	12	5	1	1	0

Gupta S et al. ASCO 2023;Abstract 4505.

EV-302: median 2.5 years follow-up

OS in the Overall Population

Risk of death was reduced by almost 50%



	Median OS, mo (95% CI)	Stratified HR (95% CI)
EV+P[a]	33.8 (26.1, 39.3)	0.51
Chemotherapy[a]	15.9 (13.6, 18.3)	(0.43, 0.61)

Nominal two-sided P-value <0.00001[b]

No. at risk																								
EV+P	442	426	409	394	375	356	336	319	302	293	280	252	206	161	133	102	79	52	32	19	11	6	1	1	1
Chemotherapy	444	423	393	356	317	290	263	233	214	197	176	148	121	102	81	59	43	24	18	13	9	5	2	2	

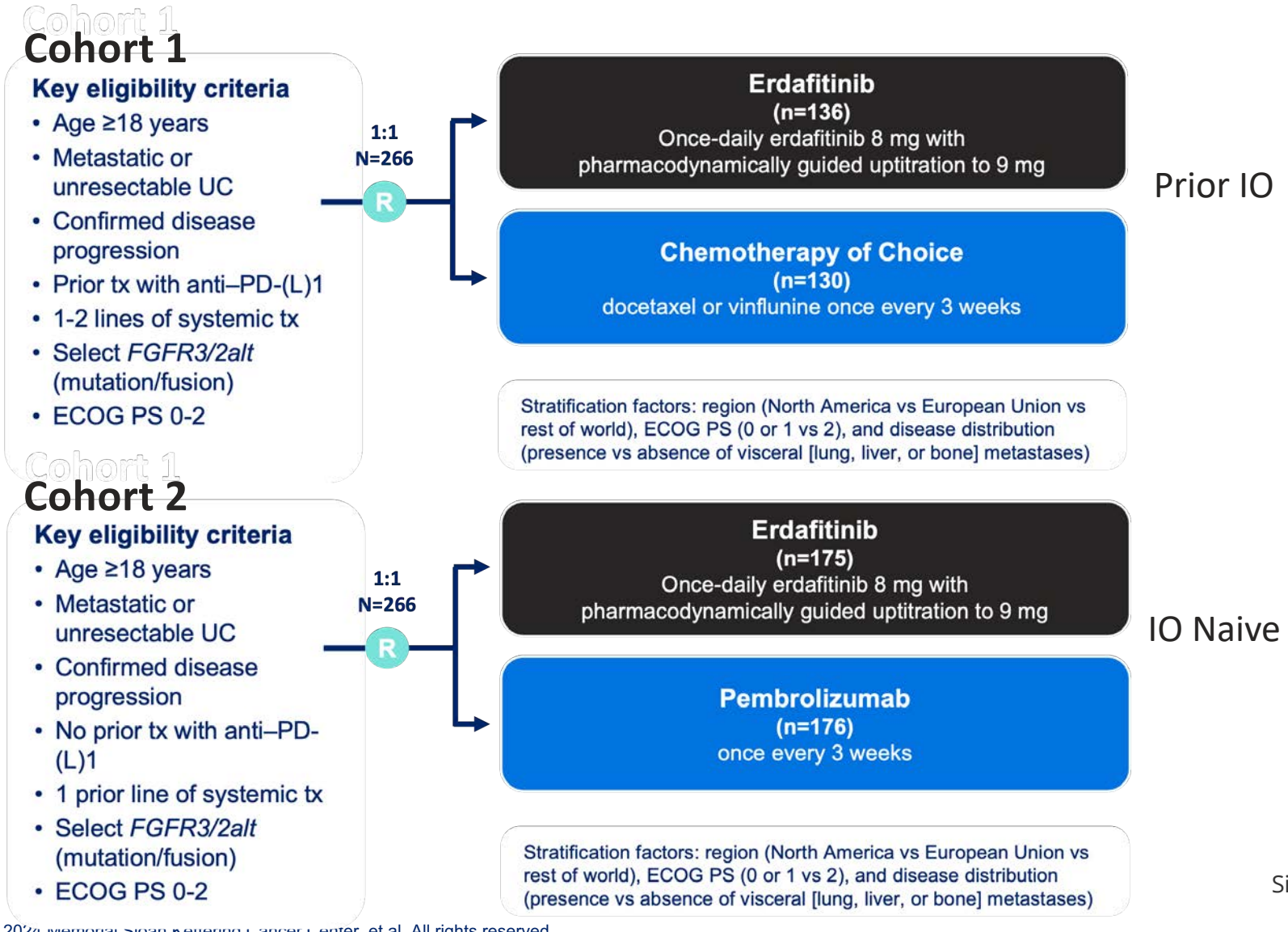
Data cutoff: August 8, 2024.

EV, enfortumab vedotin; P, pembrolizumab; OS, overall survival.

[a]Events/N were 203/442 for EV+P and 297/444 for chemotherapy. [b]P-value is nominal and descriptive.

Powles T et al. ASCO GI 2025;Abstract 664.

Targeting FGFR3: Phase 3 THOR Study: 2 cohorts



Primary end point:

- OS

Key secondary end points:

- PFS
- ORR
- Safety

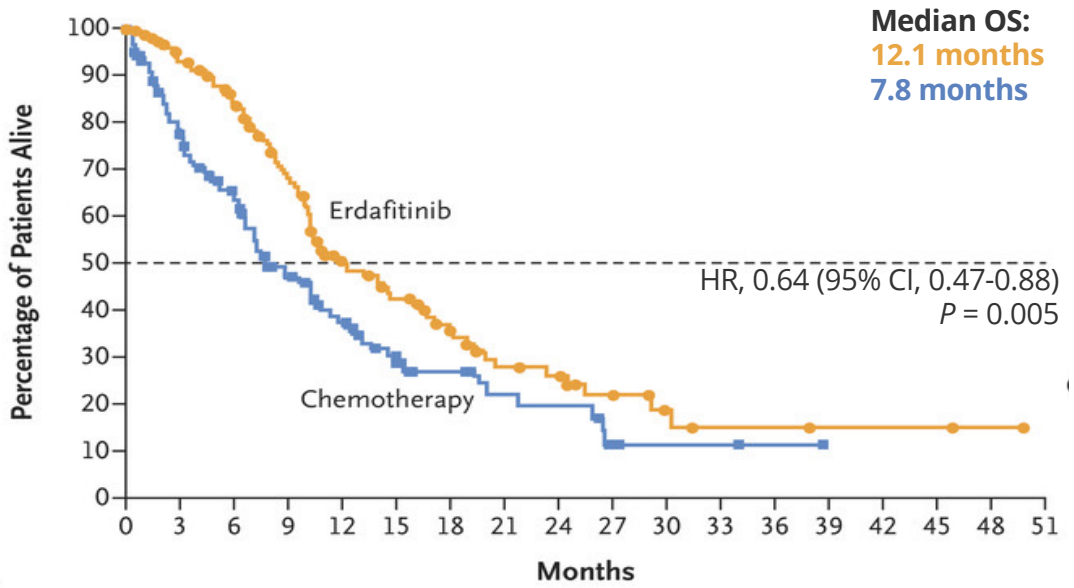
Loriot Y et al. N Engl J Med 2023; 389:1961-1971

Siefker-Radtke et al. Annals of Oncology 2024 (35): 107-117.

NCT03390504

Erdafitinib in FGFR3 or FGFR2 mutated refractory mUC

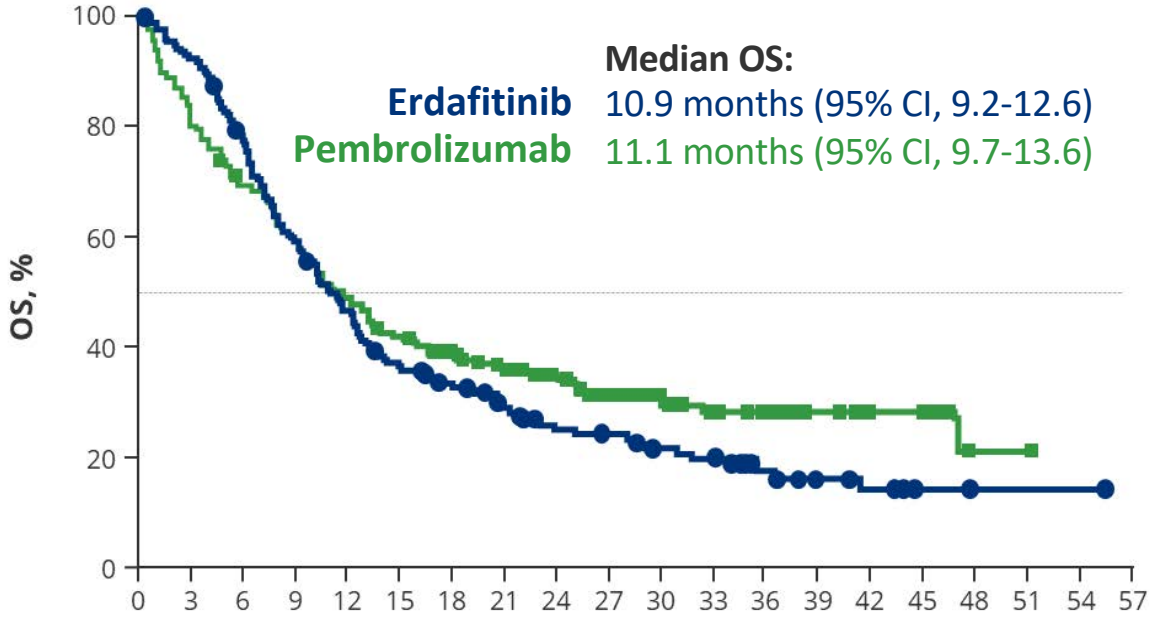
Cohort 1: Erdafitinib improves survival compared to taxane or vinflunine in IO-experienced patients



No. at Risk (no. with censored data)																		
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
	(0)	(10)	(20)	(25)	(35)	(39)	(44)	(47)	(48)	(52)	(55)	(56)	(56)	(57)	(57)	(57)	(58)	(59)
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0
	(0)	(17)	(25)	(30)	(35)	(41)	(45)	(47)	(47)	(49)	(50)	(50)	(51)	(52)	(52)	(52)	(52)	(52)

Loriot Y et al. N Engl J Med 2023; 389:1961-1971

Cohort 2: Erdafitinib does not improve survival compared to pembrolizumab in IO-naïve patients



No. at risk																			
Erdafitinib	175	160	131	100	78	60	52	41	30	28	23	21	13	9	7	2	1	1	1	0
Pembrolizumab	176	148	119	103	84	72	60	52	43	34	29	23	19	11	8	8	1	1	0	0

Siefker-Radtke et al. Ann Oncol 2024 (35): 107-117.

Adverse events associated with erdafitinib treatment

Hyperphosphatemia is on-target effect and requires monitoring for dose up-titration at 14-21 days

Gastrointestinal toxicity is common, including **stomatitis, dry mouth, and dysgeusia**

Skin and nail toxicity are frequent

Grade 3 **central serous retinopathy** (in 2.2%) and other eye disorders (in 2.2%) were uncommon but require monitoring per package insert

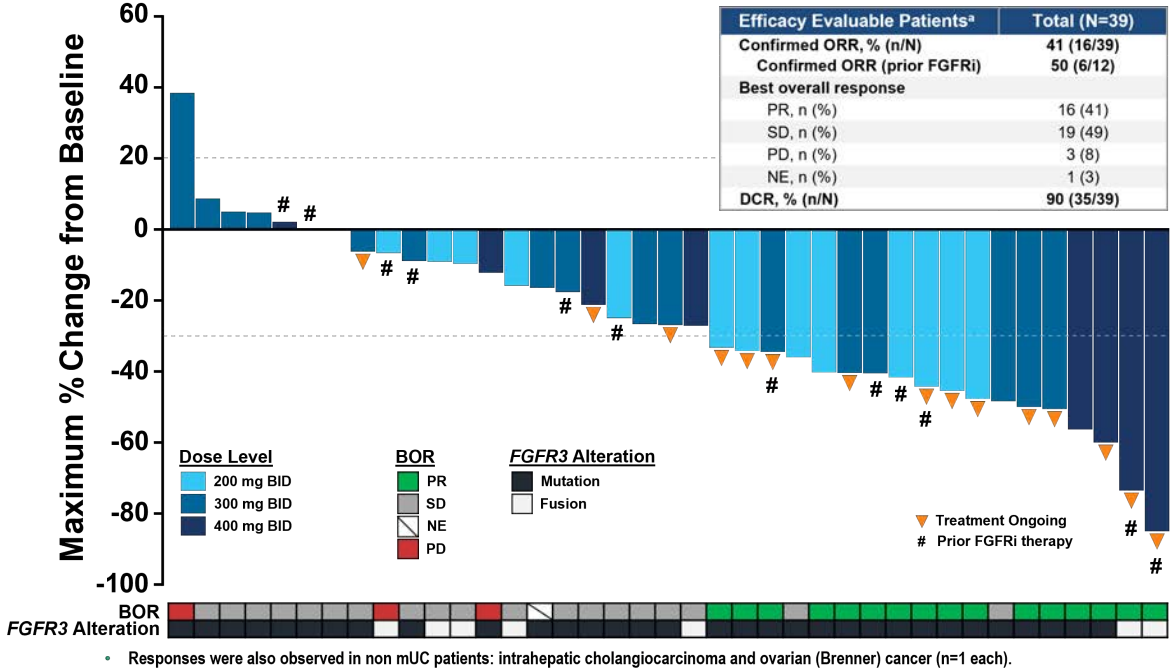
Table 2. Adverse Events in the Safety Population.*

Event	Erdafitinib (N=135)				Chemotherapy (N=112)			
	Any Grade	Grade 1	Grade 2	Grade ≥3	Any Grade	Grade 1	Grade 2	Grade ≥3
	number (percent)							
Hyperphosphatemia	108 (80.0)	70 (51.9)	31 (23.0)	7 (5.2)	0	0	0	0
Diarrhea	84 (62.2)	49 (36.3)	31 (23.0)	4 (3.0)	19 (17.0)	7 (6.2)	9 (8.0)	3 (2.7)
Stomatitis	65 (48.1)	22 (16.3)	32 (23.7)	11 (8.1)	14 (12.5)	4 (3.6)	8 (7.1)	2 (1.8)
Dry mouth	53 (39.3)	45 (33.3)	8 (5.9)	0	4 (3.6)	4 (3.6)	0	0
Palmar–plantar erythrodysesthesia syndrome	41 (30.4)	6 (4.4)	22 (16.3)	13 (9.6)	1 (0.9)	0	1 (0.9)	0
Dysgeusia	37 (27.4)	28 (20.7)	8 (5.9)	1 (0.7)	8 (7.1)	5 (4.5)	3 (2.7)	0
Alanine aminotransferase increased	37 (27.4)	24 (17.8)	9 (6.7)	4 (3.0)	4 (3.6)	2 (1.8)	1 (0.9)	1 (0.9)
Constipation	36 (26.7)	24 (17.8)	12 (8.9)	0	31 (27.7)	13 (11.6)	16 (14.3)	2 (1.8)
Decreased appetite	36 (26.7)	18 (13.3)	14 (10.4)	4 (3.0)	23 (20.5)	10 (8.9)	10 (8.9)	3 (2.7)
Anemia	35 (25.9)	10 (7.4)	15 (11.1)	10 (7.4)	36 (32.1)	8 (7.1)	19 (17.0)	9 (8.0)
Alopecia	34 (25.2)	29 (21.5)	4 (3.0)	1 (0.7)	27 (24.1)	16 (14.3)	11 (9.8)	0
Dry skin	31 (23.0)	23 (17.0)	6 (4.4)	2 (1.5)	5 (4.5)	4 (3.6)	1 (0.9)	0
Onycholysis	31 (23.0)	9 (6.7)	14 (10.4)	8 (5.9)	1 (0.9)	0	1 (0.9)	0
Weight decreased	30 (22.2)	12 (8.9)	15 (11.1)	3 (2.2)	3 (2.7)	3 (2.7)	0	0
Aspartate aminotransferase increased	29 (21.5)	21 (15.6)	5 (3.7)	3 (2.2)	3 (2.7)	2 (1.8)	1 (0.9)	0
Onychomadesis	28 (20.7)	9 (6.7)	17 (12.6)	2 (1.5)	2 (1.8)	1 (0.9)	1 (0.9)	0
Nail discoloration	24 (17.8)	16 (11.9)	7 (5.2)	1 (0.7)	2 (1.8)	1 (0.9)	1 (0.9)	0
Dry eye	23 (17.0)	20 (14.8)	3 (2.2)	0	2 (1.8)	1 (0.9)	1 (0.9)	0
Asthenia	20 (14.8)	6 (4.4)	12 (8.9)	2 (1.5)	28 (25.0)	9 (8.0)	15 (13.4)	4 (3.6)
Nausea	20 (14.8)	10 (7.4)	8 (5.9)	2 (1.5)	27 (24.1)	15 (13.4)	10 (8.9)	2 (1.8)
Neutropenia	0	0	0	0	22 (19.6)	1 (0.9)	5 (4.5)	16 (14.3)
Fatigue	20 (14.8)	12 (8.9)	8 (5.9)	0	21 (18.8)	13 (11.6)	4 (3.6)	4 (3.6)

* Listed are adverse events (of any cause) that emerged or worsened during treatment, according to preferred term and highest grade, and that were reported in more than 15% of the patients in either treatment group.

FGFR3 selective FGFR inhibitors

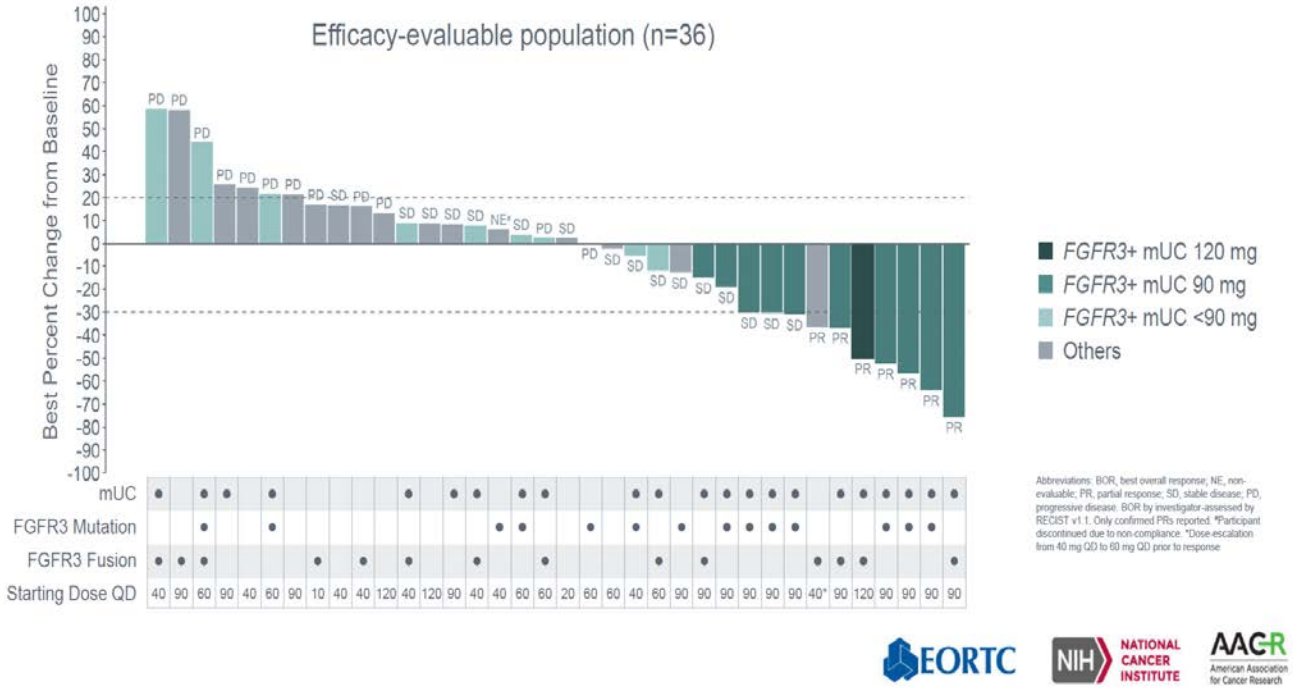
LOXO-435: NCT05614739



Efficacy Evaluable Patients[a]	Total (N=39)
Confirmed ORR, % (n/N)	41 (16/39)
Confirmed ORR (prior FGFRi)	50 (6/12)
Best overall response	
PR, n (%)	16 (41)
SD, n (%)	19 (49)
PD, n (%)	3 (8)
NE, n (%)	1 (3)
DCR, % (n/N)	90 (35/39)

- Responses were also observed in non mUC patients: intrahepatic cholangiocarcinoma and ovarian (Brenner) cancer (n=1 each).

Tyra300: NCT05544552



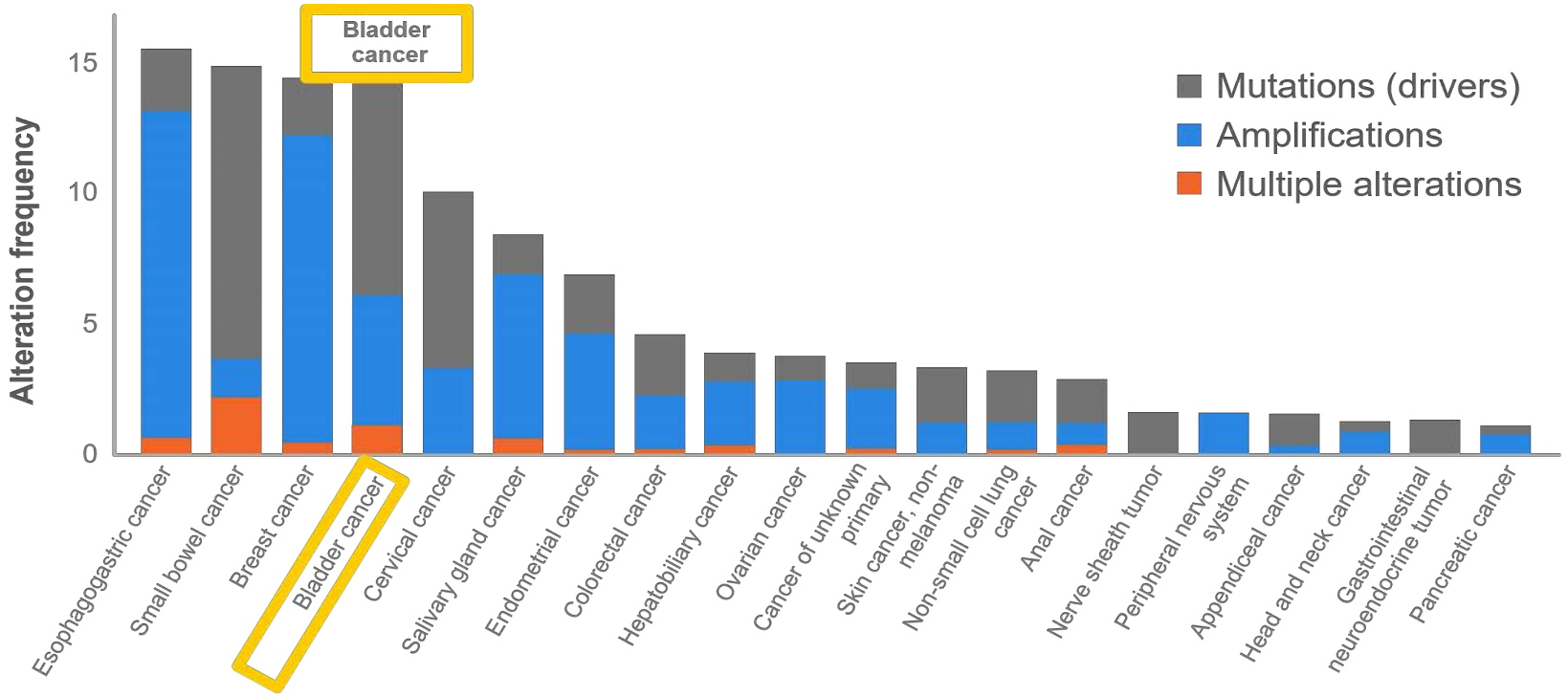
Confirmed ORR 41% at doses ≥200 mg BID

6/11 PR at doses ≥90mg daily

Iyer et al. *J Clin Oncol* 43, 2025 (suppl 5; abstr 662)

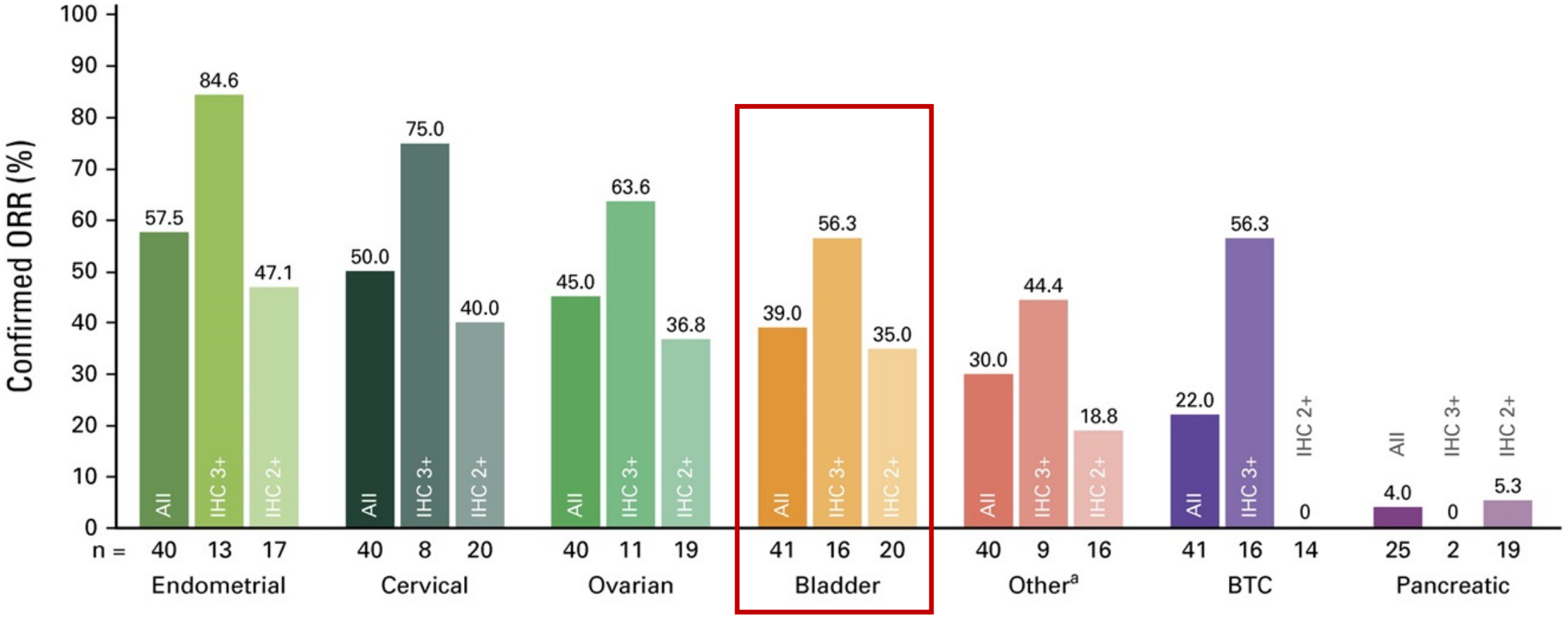
Zhang et al. *European Journal of Cancer* 211S1 (2024) 114563

Frequency of *HER2* alterations is high in bladder cancer



- Mutations
  - 5-11% (higher frequency than breast and other cancer types)
- Amplifications
  - 6-9%
  - Can co-exist with mutations in a subset of tumors
- Overexpression in about 25-40% of UC tumors

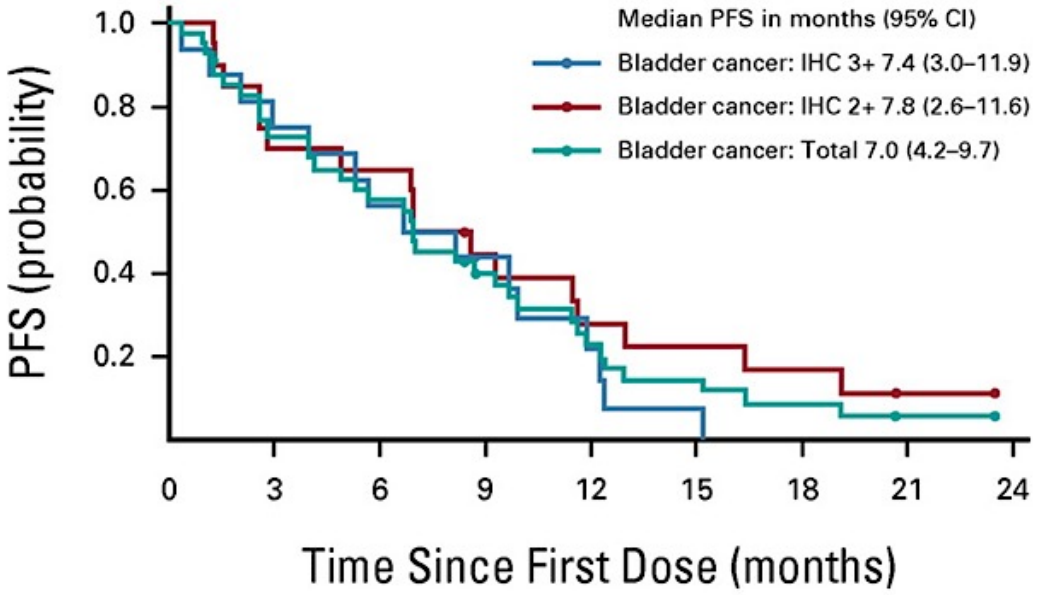
DESTINY-PanTumor02: Trastuzumab Deruxtecan (T-DXd) leads to high response rates in HER2+ urothelial cancer



ORR 39%

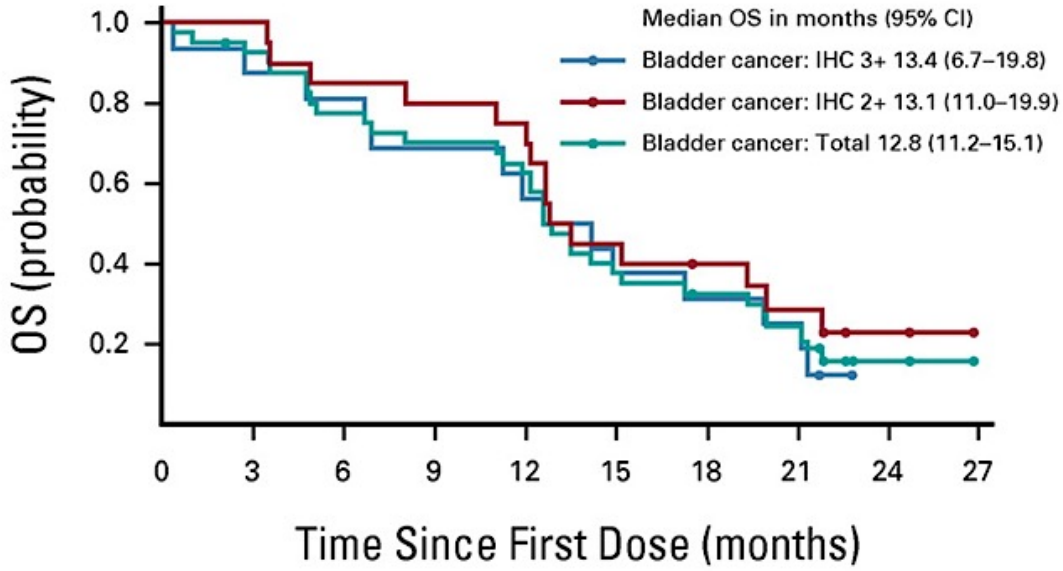
Meric-Bernstam F. et al. *J Clin Oncol*. 2024 Jan 1;42(1):47-58.

T-DXd outcomes by HER2 status in mUC



No. at risk:									
Bladder cancer: IHC 3+	16	12	9	6	3	1	0		
Bladder cancer: IHC 2+	20	14	13	8	5	4	3	1	0
Bladder cancer: Total	41	29	23	14	8	5	3	1	0

PFS



No. at risk:										
Bladder cancer: IHC 3+	16	14	13	11	9	6	5	4	0	
Bladder cancer: IHC 2+	20	20	17	16	15	9	7	5	2	0
Bladder cancer: Total	41	37	31	28	25	15	12	9	2	0

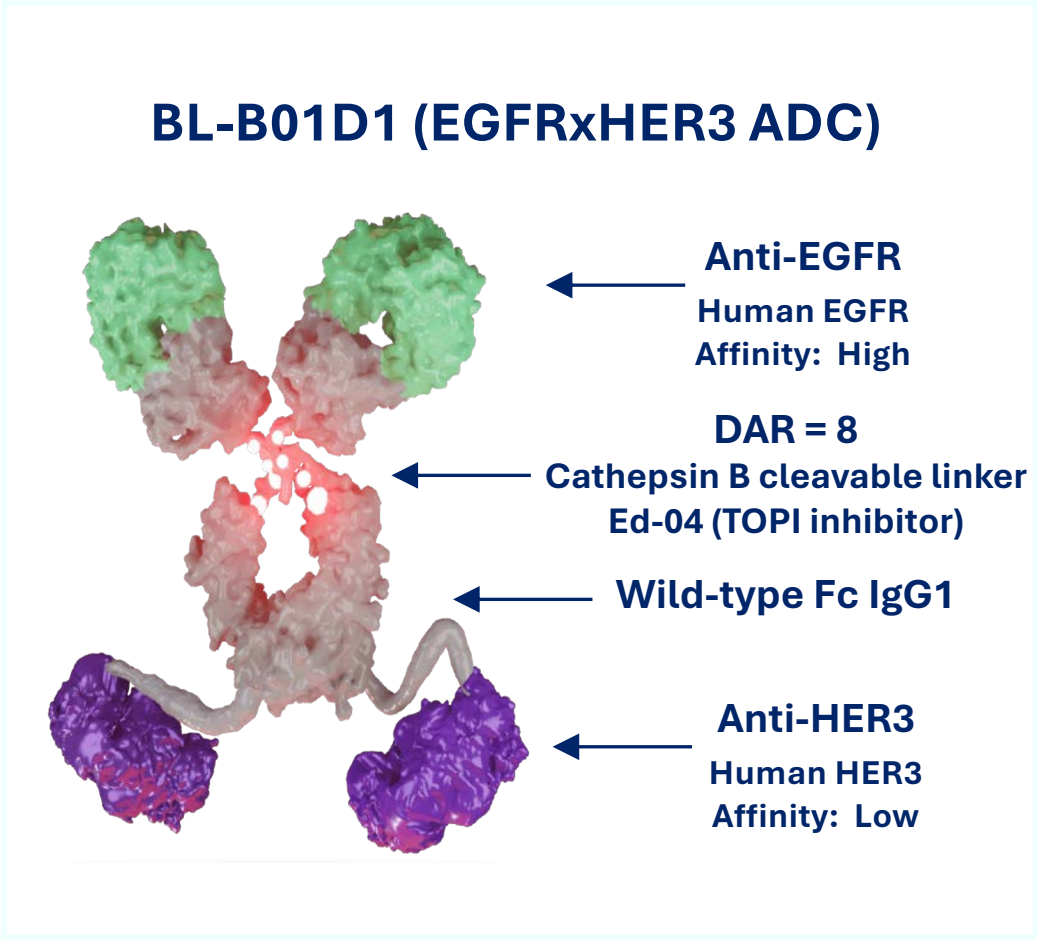
OS

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

Novel ADCs against other targets in urothelial cancer

- Nectin-4 may still be a valid target after POD on EV
  - Radiopharmaceuticals
  - ADCs with other payloads (LY4101174, LY4052031, IPH4502)
- HER2-targeted ADC T-DXd already approved in UC
  - Disitamab vedotin has high activity
- While sacituzumab govitecan did not improve OS in TROPiCS-04, TROP2 remains a valid target for UC therapy
  - Sacituzumab tirumotecan (MK-2870)
  - Datopotamab deruxtecan

Bispecific antibody drug conjugate targeting EGFR and HER3



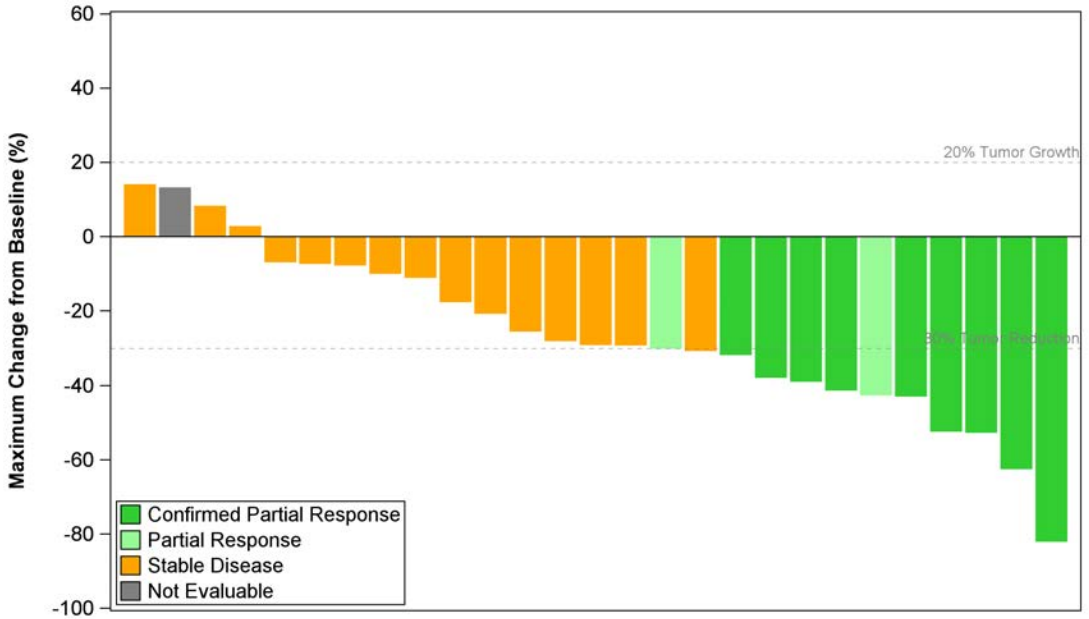
- Anti-EGFR antibody is derived from cetuximab — high affinity antibody
- Two HER3 single-chain fragment variable (scFv) with lower affinity
- Anti-EGFR antibody is fused to anti-HER3 scFvs with a glycine-serine linker
- Tetrapeptide-based cathepsin cleavable linker
  - Cytotoxic is Ed-04, a camptothecin derivative inhibitor of topoisomerase 1
- Drug-to-antibody ratio of 8

Ma, et al. *Lancet Oncology* 2024; 25:901-911
Wan et al. Cancer Res 2023; 83(7_Suupl) Abstract 2642

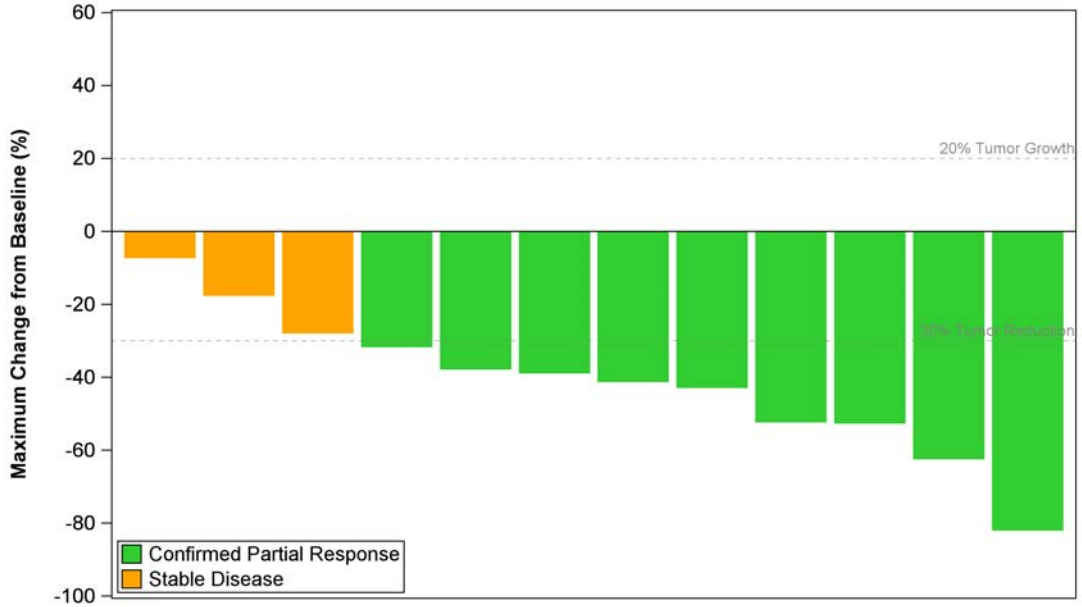
mUC Patients treated at 2.2 mg/kg d1 and d8 q3 weeks

- Majority of patients had tumor reductions
- At 2.2mg/kg dose level, ORR 40.7%, and 75% in one prior line of therapy (n=12)
- Activity appears higher in 2nd line population, but limited sample size

All patients



2nd-line only



Discussion Questions

- Regulatory and reimbursement issues aside, in which line of therapy would you generally offer targeted treatment to a patient with HER2-positive metastatic urothelial bladder cancer (mUBC)?

- Regulatory and reimbursement issues aside, what would you generally recommend as second-line therapy for a patient with HER2-positive (IHC 3+) mUBC whose disease progresses on first-line enfortumab vedotin/pembrolizumab? How, if at all, would your approach vary by agent(s) received and patient performance status?

Discussion Question

- Have you or would you administer trastuzumab deruxtecan to a patient with HER2-low (IHC 1+ or 2+) mUBC?

Discussion Questions

- Regulatory and reimbursement issues aside, what would you generally recommend as second-line therapy for a patient with mUBC with an FGFR3 mutation whose disease progresses on first-line enfortumab vedotin/pembrolizumab? How, if at all, would your approach vary by agent(s) received and patient performance status?

- What adverse events are commonly associated with erdafitinib? How can they be prevented and how should they be managed when they occur?

We are taking a short break!

The program will resume at 9:45 AM ET

Up Next…

Drs Natalie S Callander and Thomas Martin discuss the management of multiple myeloma

RTP
RESEARCH
TO PRACTICE