



7th Annual
LEAD 2025
Enriching Experiences for Women in Hematology & Oncology



Practice-Changing Advances in Gastrointestinal Oncology

Shruti Patel MD & Christiana Mo, MD

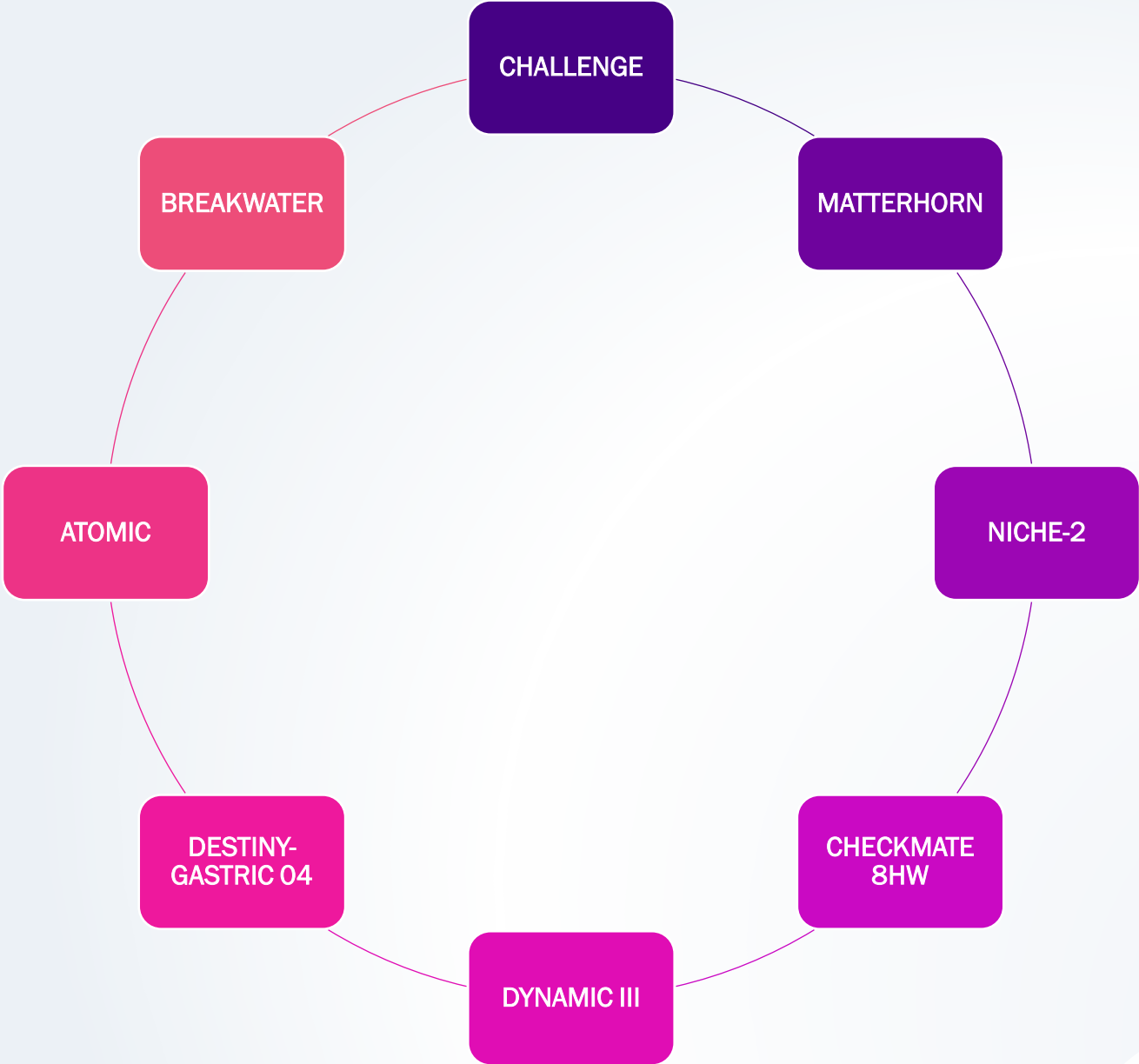
AGENDA



Christiana Mo, MD
University of Arizona



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MATTERHORN

PERIOPERATIVE IMMUNOTHERAPY IN RESECTABLE GEJ/GASTRIC ADENOCARCINOMA

THE EVOLUTION OF MANAGEMENT IN GEJ/GASTRIC CANCER

2006

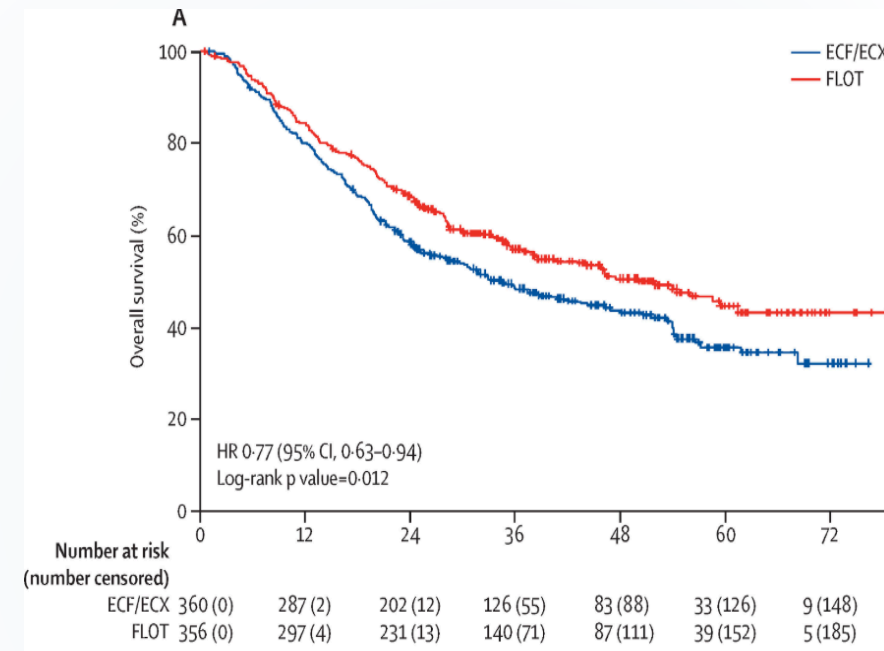
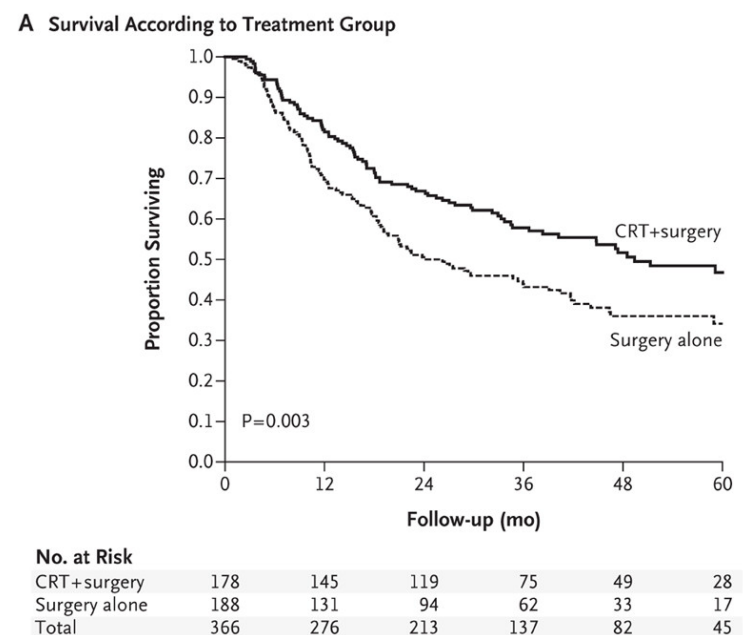
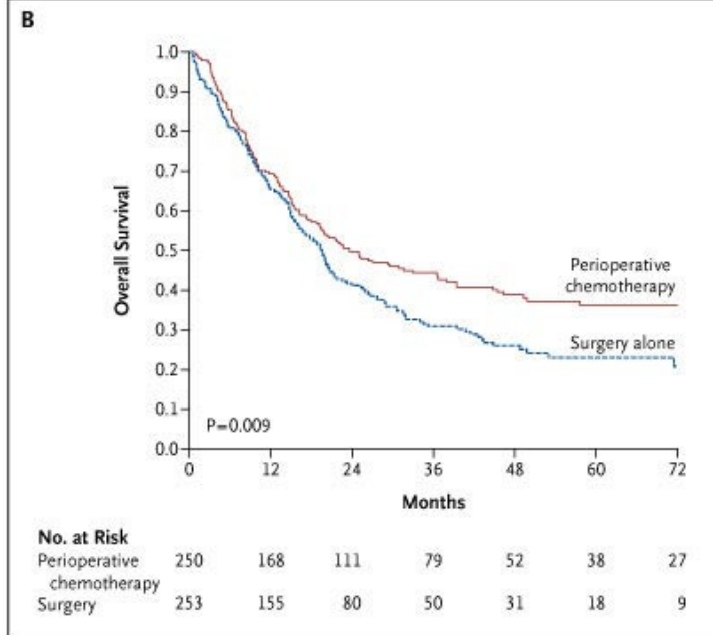
2012

2017

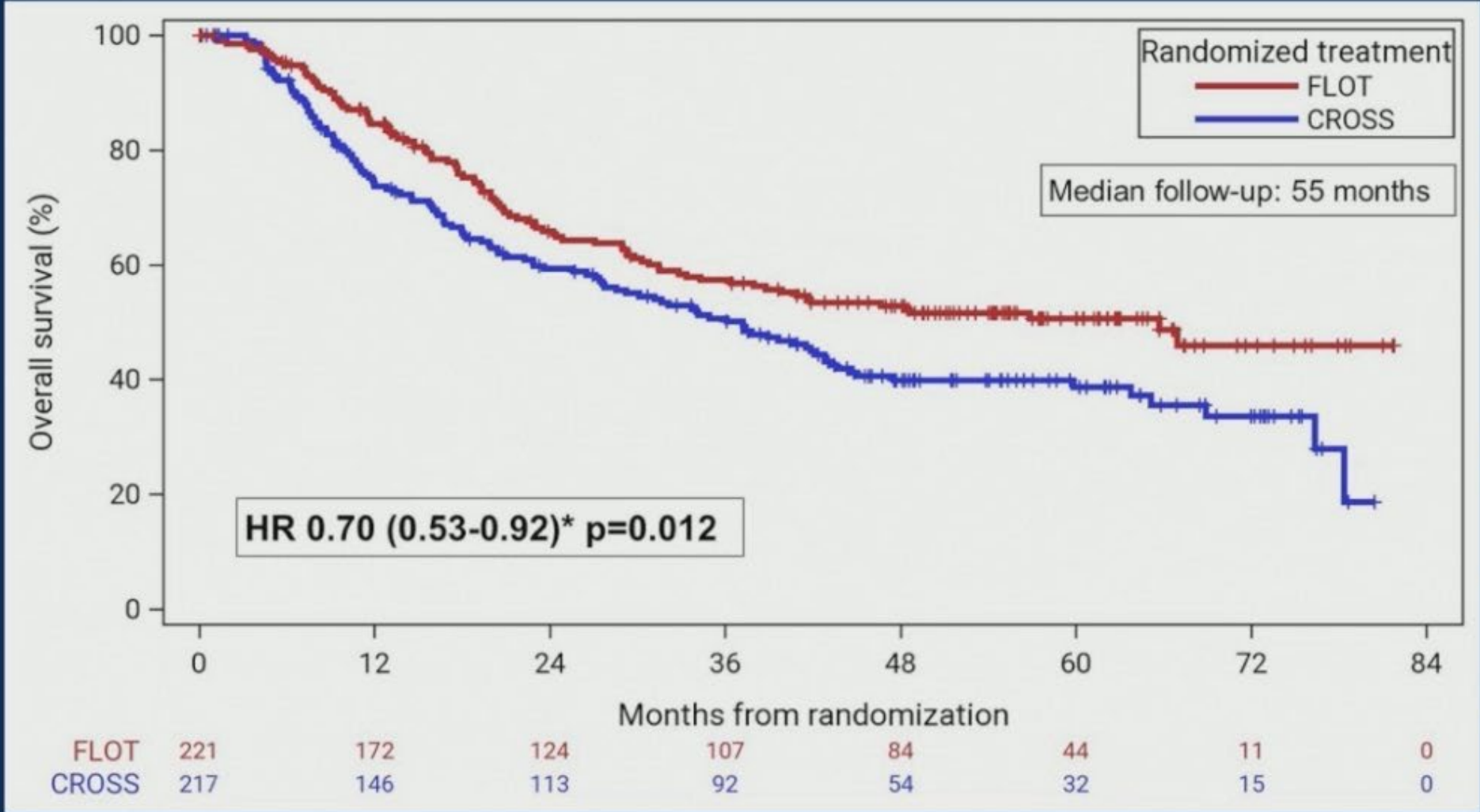
MAGIC

CROSS

FLOT-4



ESOPEC: Importance of Active Systemic Therapy



	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – n.e	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

ASCO Plenary 2024

MATTERHORN Study Design

4

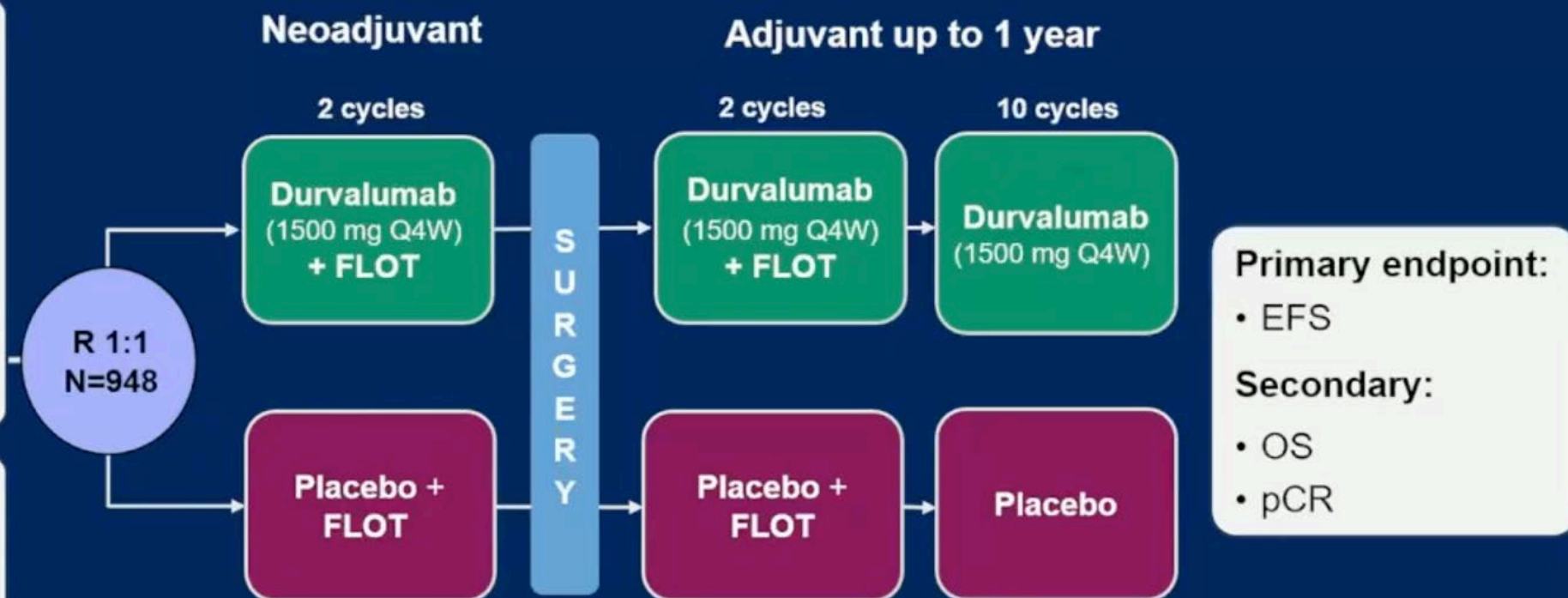
A global, Phase 3, randomized, double-blind, placebo-controlled study

Study population

- Gastric and GEJ adenocarcinoma
- Stage II to IVa
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrollment in Asia, Europe, North & South America

Stratification factors

- Asia vs non-Asia
- Clinical N+ vs N-
- PD-L1: TAP <1% vs TAP ≥1%*





Participant Disposition

	DFLOT	FLOT
Completed Surgery	91%	90%
R0 resection	92%	92%
Received any neoadjuvant txt	100%	99%
Received any adjuvant txt	77%	74%

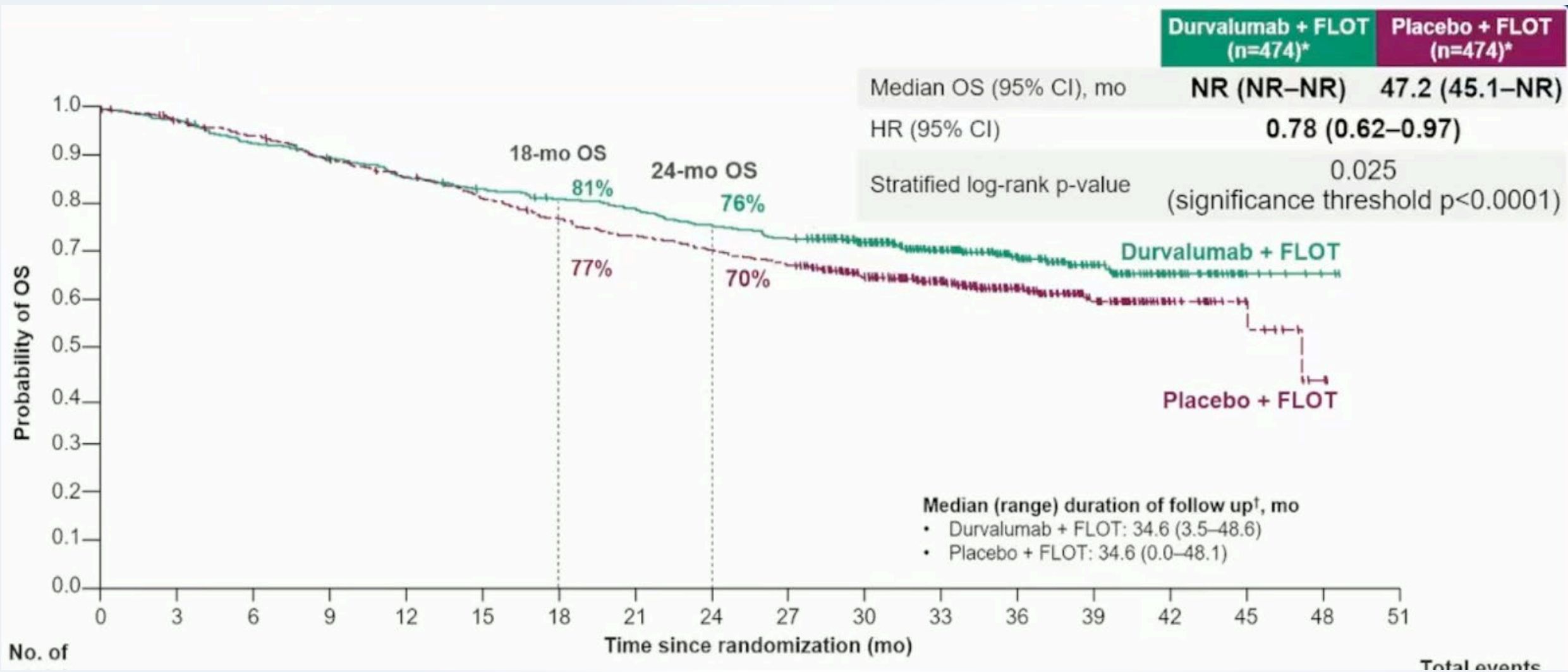
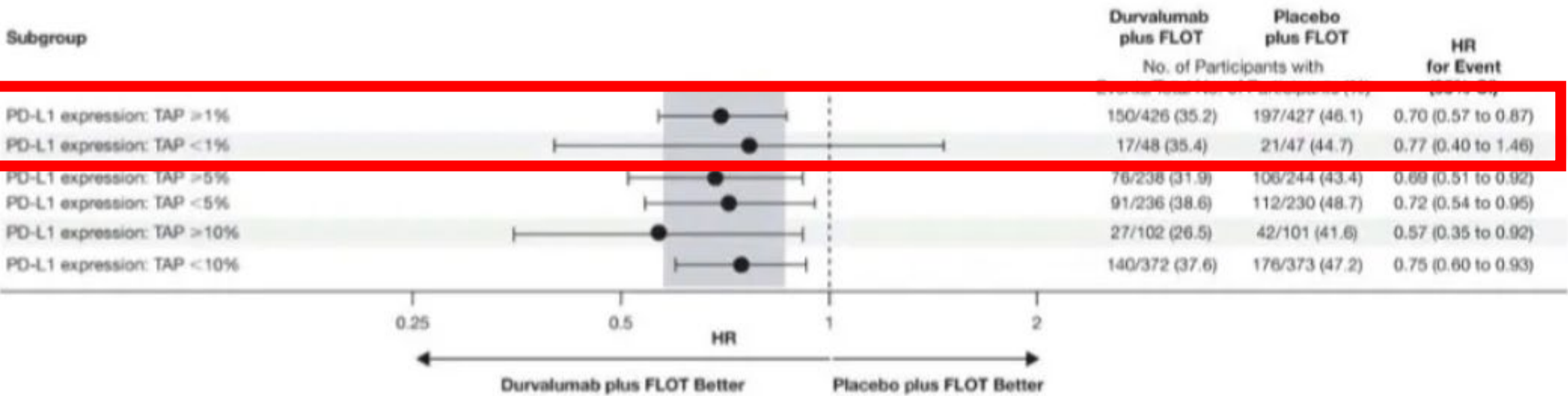
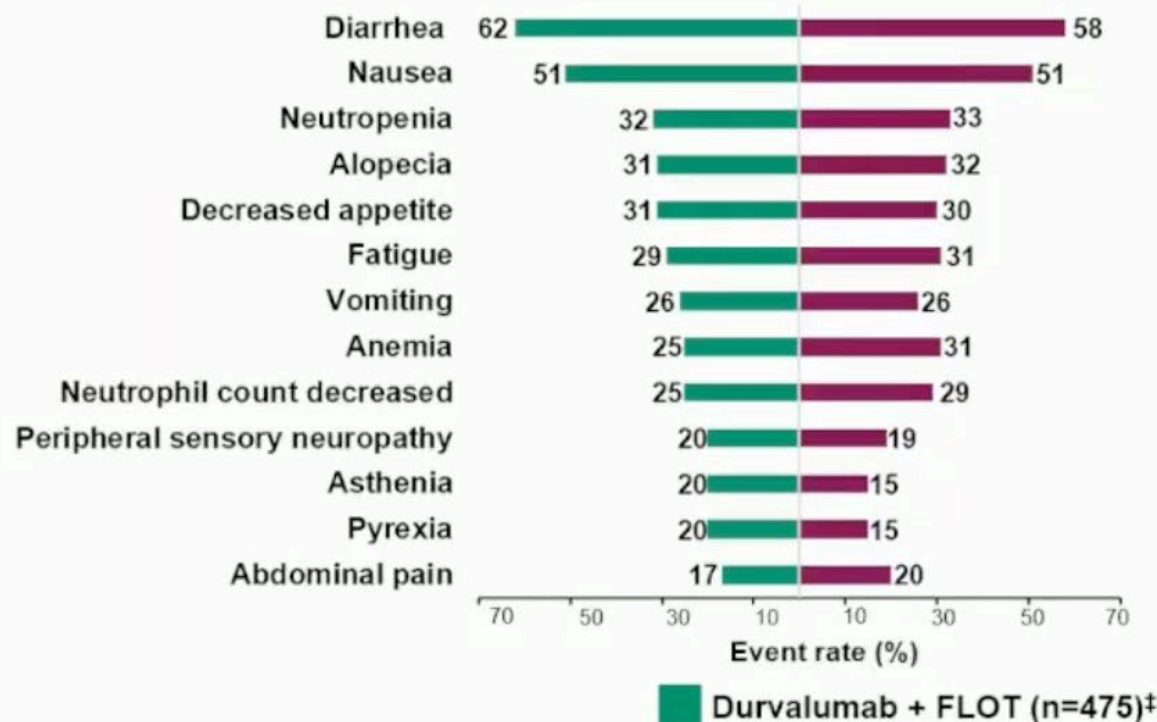


Figure S4. Event-Free Survival in Participant Subgroups by PD-L1 expression in the Full Analysis Set.

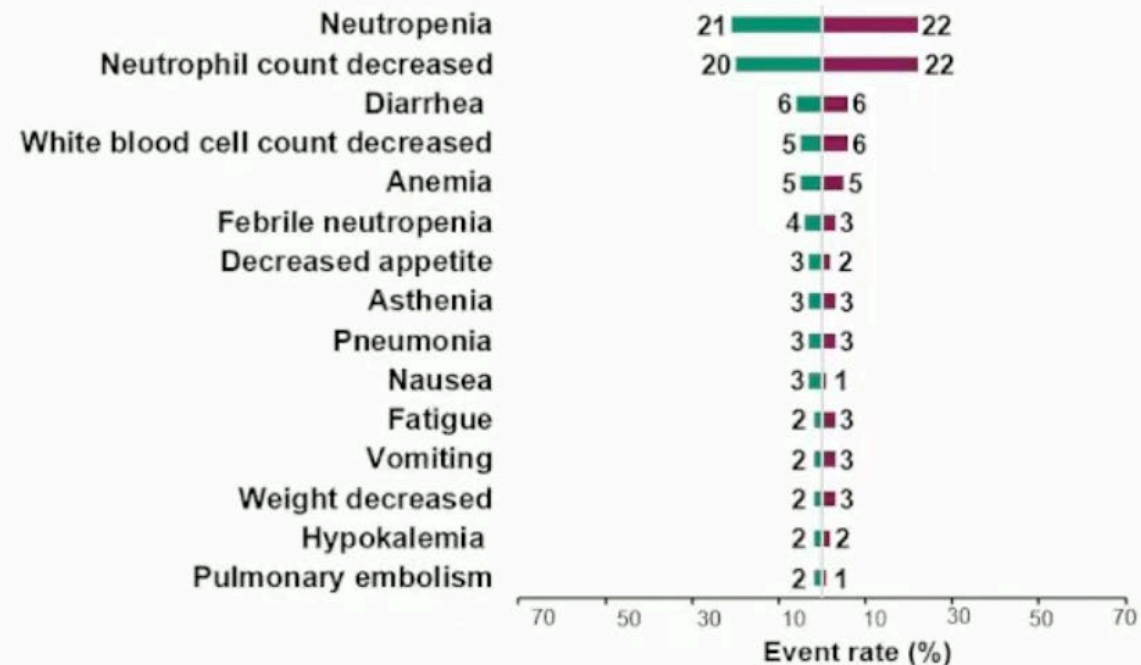


Common AEs: Balanced Between Cohorts, Aligned With Known Profiles of Durvalumab and FLOT

Most common AEs of any grade*



Most common maximum Grade 3 or 4 AEs†



A large teal circle on the left side of the slide.

My take on MATTERHORN

- Six negative trials, one positive trial
- PDL-1 biology is important despite blanket approval
- Taxane appears to be important part of the regimen
- EFS benefits with IO are real in patients with PDL-1+
- Need to await OS data

CHALLENGE

ADJUVANT EXERCISE IN LOCALIZED COLORECTAL CANCER

Physical activity and colorectal cancer

Gastrointestinal Cancer | August 01, 2006



Impact of Physical Activity on Cancer Recurrence and Survival in Patients With Stage III Colon Cancer: Findings From CALGB 89803

Authors: [Jeffrey A. Meyerhardt](#), [Denise Heseltine](#), [Donna Niedzwiecki](#), [Donna Hollis](#), [Leonard B. Saltz](#), [Robert J. Mayer](#), [James Thomas](#), [Heidi Nelson](#), [Renaud Whittom](#), [Alexander Hantel](#), [Richard L. Schilsky](#), and [Charles S. Fuchs](#) | [AUTHORS INFO & AFFILIATIONS](#)

Publication: Journal of Clinical Oncology • Volume 24, Number 22 • <https://doi.org/10.1200/JCO.2006.06.0863>

Gastrointestinal Cancer | August 01, 2006



Physical Activity and Survival After Colorectal Cancer Diagnosis

Authors: [Jeffrey A. Meyerhardt](#), [Edward L. Giovannucci](#), [Michelle D. Holmes](#), [Andrew T. Chan](#), [Jennifer A. Chan](#), [Graham A. Colditz](#), and [Charles S. Fuchs](#) | [AUTHORS INFO & AFFILIATIONS](#)

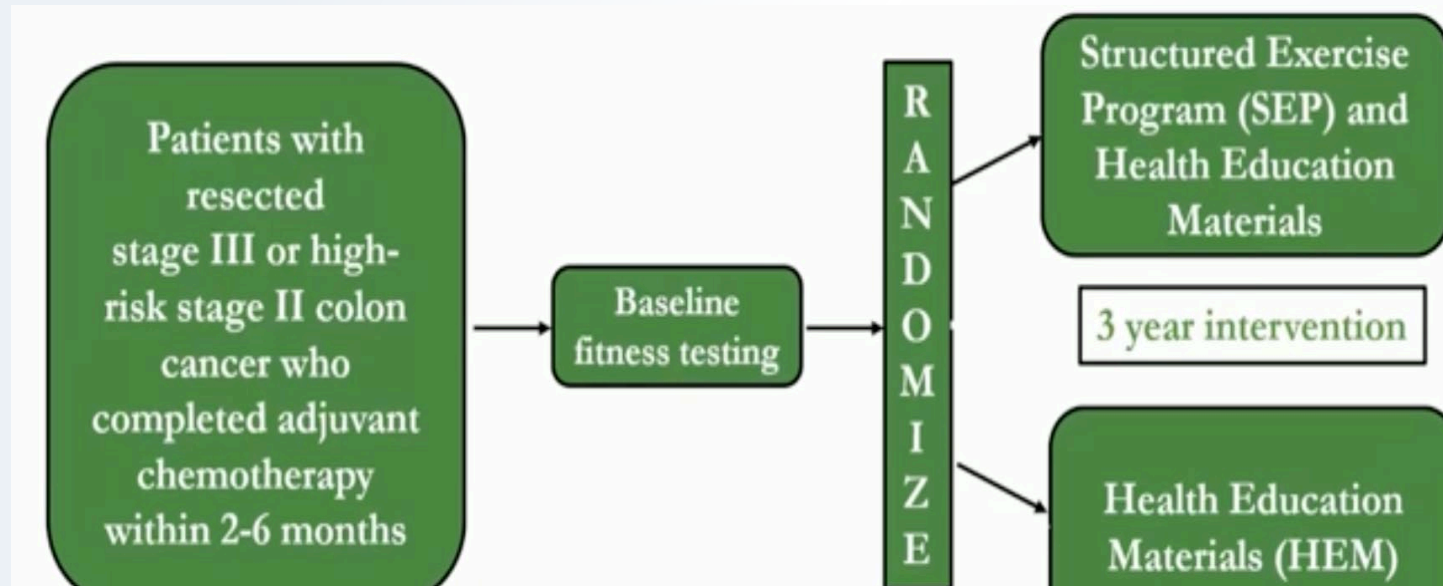
Publication: Journal of Clinical Oncology • Volume 24, Number 22 • <https://doi.org/10.1200/JCO.2006.06.0855>

CHALLENGE TRIAL

First RCT evaluating exercise as adjuvant treatment

Stage III or high-risk stage II colon cancer s/p adjuvant chemo

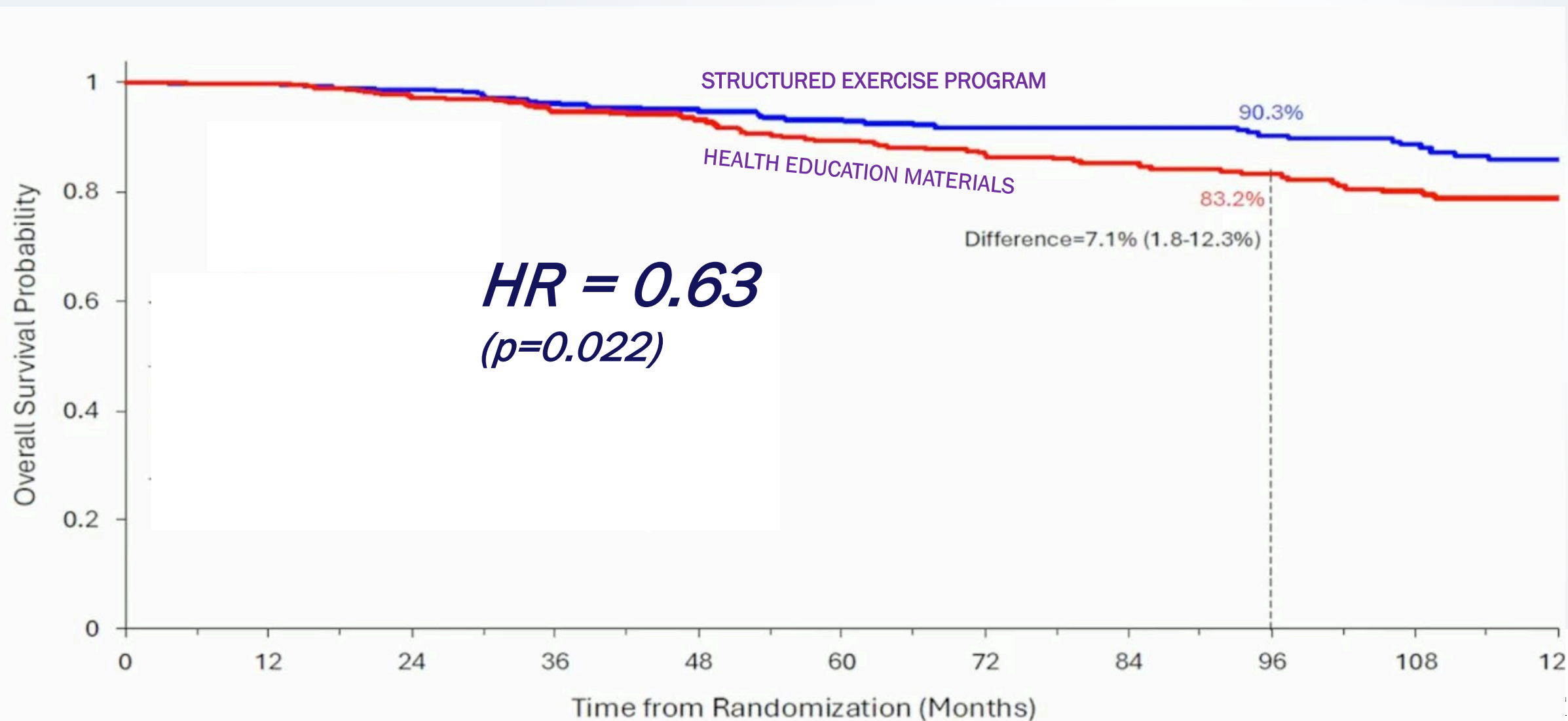
GOAL: target was to increase physical activity by 10 MET-hrs/week above baseline



What is a MET?

- 1 MET = the energy expenditure of a person at rest
- 1 hour of brisk walking = 4 MET-hours
 - +2.5 hours of brisk walking = goal of +10MET-hrs/week
- Physical Activity Consultants worked with patients to create an "exercise prescription" based on their preferred activities/ lifestyle
- Most patients could hit their target by adding 45-60 min brisk walk
 - 3-4 times per week

Overall survival results



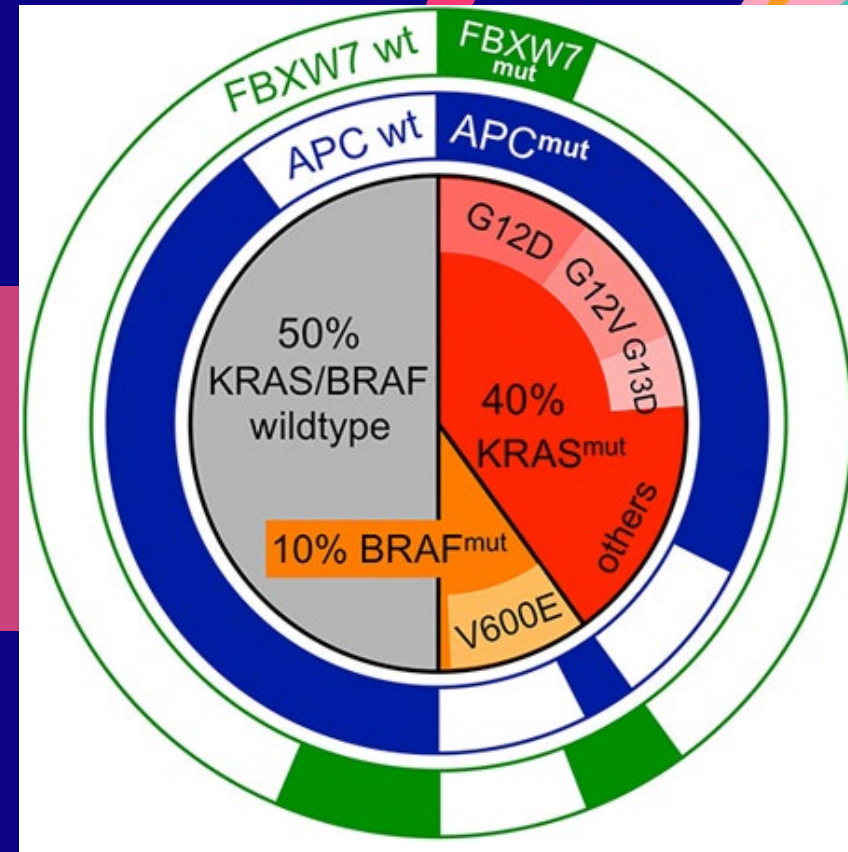
	Structured Exercise Program (n=445)	Health Education Materials (n=444)
DFS event	93 (21%)	131 (30%)
Recurrence	65 (15%)	81 (18%)
Local colon	12	12
Liver	16	29
Lung	20	19
Other	30	33
New Primary	23 (5%)	43 (10%)
Breast	2	12
Prostate	5	9
CRC	0	5
Other	17	17

Where does this stand as an "adjuvant" treatment?

Intervention	Disease	Absolute OS Gain
Adjuvant Exercise	Colon	7% at 8 years
Adjuvant Oxaliplatin	Colon	5% at 10 years
Adjuvant Osimertinib	NSCLC	8% at 5 years
Consolidation Durvalumab	NSCLC	10% at 5 years
Adjuvant Trastuzumab	Breast	5% at 5 years
Peri-op Pembrolizumab	TNBC	5% at 5 years
Adjuvant Pertuzumab	HER2 Breast	1.8% at 10 years

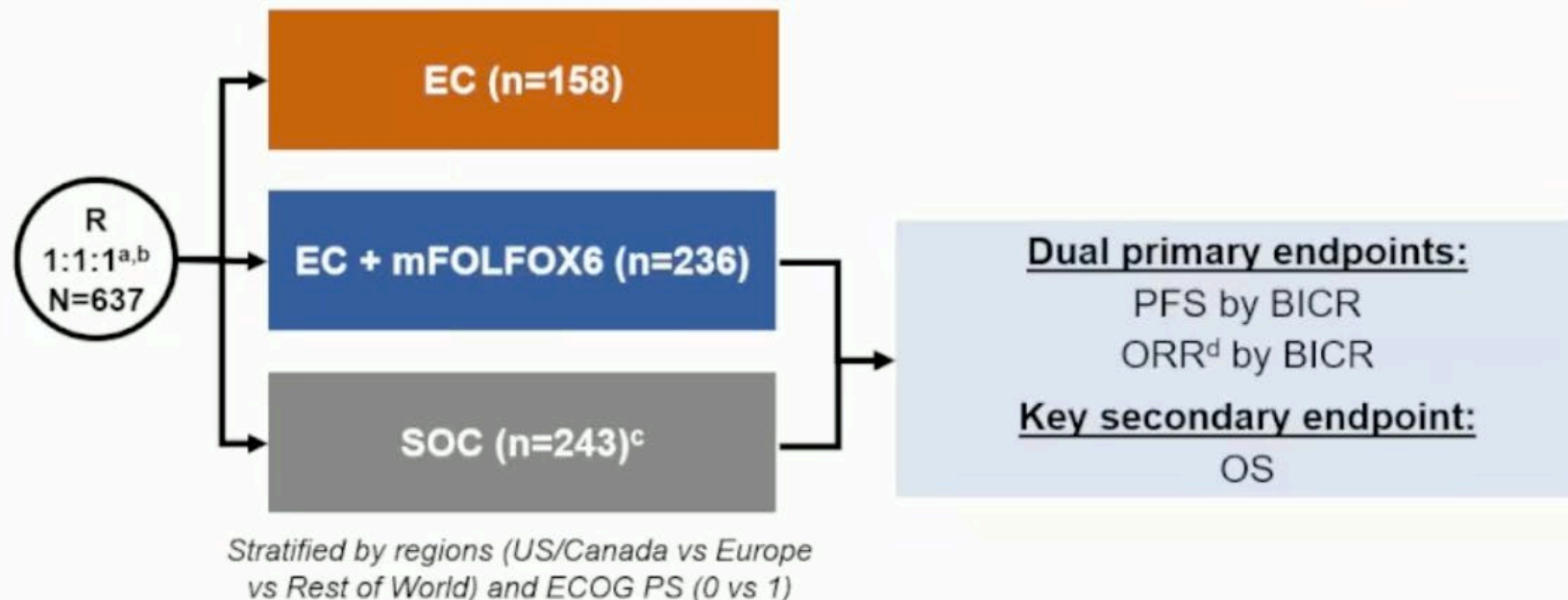
BREAKWATER

FIRST LINE TREATMENT OF
BRAF V600E METASTATIC COLORECTAL CANCER



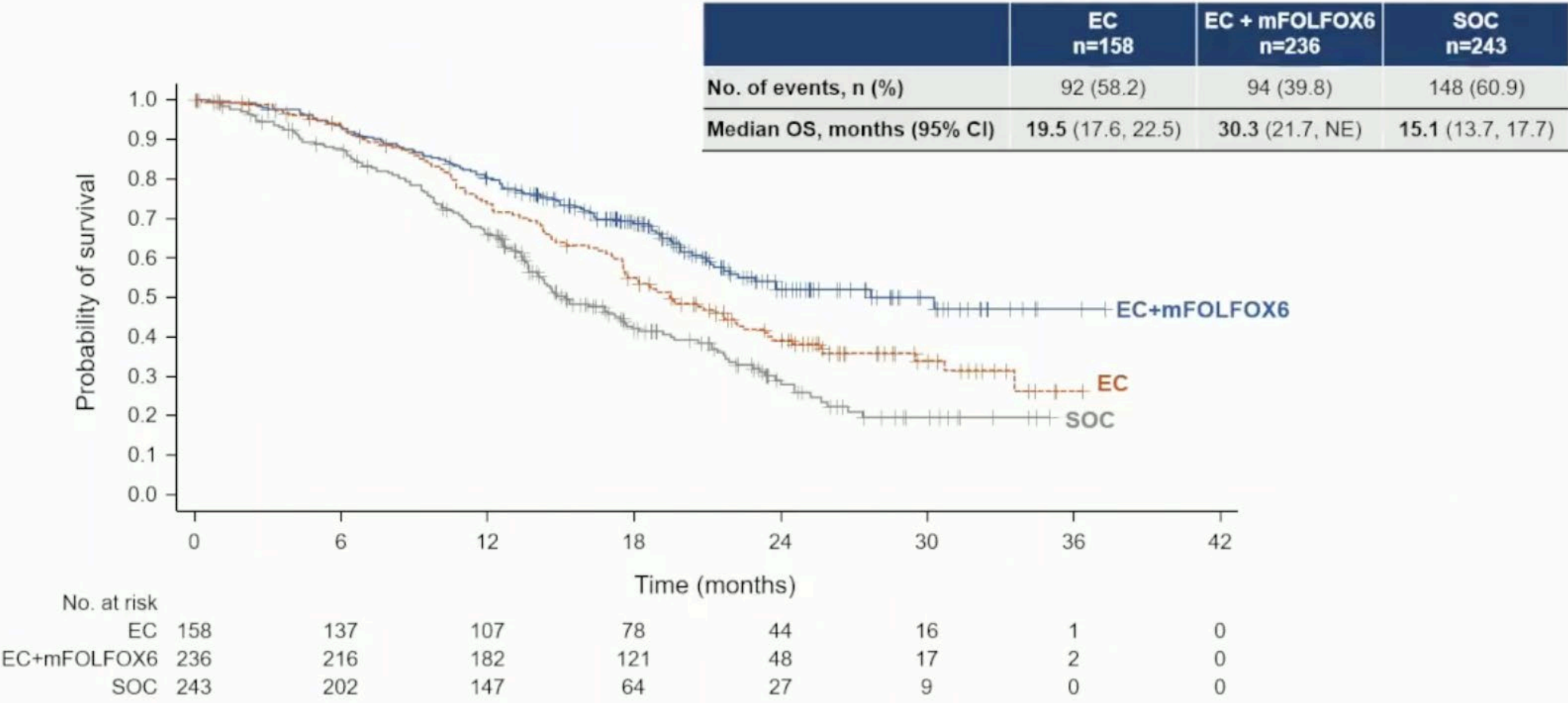
BREAKWATER: First-Line BRAF V600E mCRC

Inclusion criteria
• Age ≥16 years (or ≥18 years based on country) • No prior systemic treatment for metastatic disease • Measurable disease (RECIST 1.1) • BRAF V600E-mutant mCRC by local or central laboratory testing • ECOG PS 0 or 1 • Adequate bone marrow, hepatic, and renal function
Exclusion criteria
• Prior BRAF or EGFR inhibitors • Symptomatic brain metastases • MSI-H/dMMR tumors (unless patients were ineligible to receive immune checkpoint inhibitors due to a pre-existing medical condition) • Presence of a RAS mutation



We present the primary analysis of PFS by BICR and a second interim analysis of OS in the EC + mFOLFOX6 and SOC arms, the efficacy data in the EC arm, and safety data in all arms

OS (All Arms)



Data cutoff: January 6, 2025.
EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; SOC, standard of care.

Safety Summary

Patients, n (%)	EC n=153	EC + mFOLFOX6 n=232	SOC n=229
Duration of treatment, median (range), weeks	27.0 (2.0-153.6)	49.8 (1.3-161.9)	25.9 (2.0-150.0)
All causality			
TEAE	149 (97.4)	232 (100)	227 (99.1)
Grade 3 or 4 TEAE	65 (42.5)	189 (81.5)	153 (66.8)
Grade 5 TEAE	4 (2.6)	10 (4.3)	10 (4.4)
Serious TEAE	46 (30.1)	107 (46.1)	89 (38.9)
TEAE leading to permanent discontinuation of any study treatment	20 (13.1)	62 (26.7)	40 (17.5)
TEAE leading to dose reduction of any study treatment	16 (10.5)	152 (65.5)	124 (54.1)
TEAE leading to dose interruption of any study treatment	63 (41.2)	212 (91.4)	168 (73.4)
Treatment-related			
AE related to any drug	136 (88.9)	232 (100)	217 (94.8)
Grade 3 or 4 TRAE	24 (15.7)	177 (76.3)	134 (58.5)
Grade 5 TRAE	0	0	1 (0.4) ^a
Serious AE related to any drug	10 (6.5)	45 (19.4)	50 (21.8)

EC+mFOLFOX
almost doubled
OS

EC alone is less
toxic than SOC

ALL patients
need NGS
testing

Would still use
IO dual
checkpoint in
MSI-H
BRAFV600E
mutated mCRC

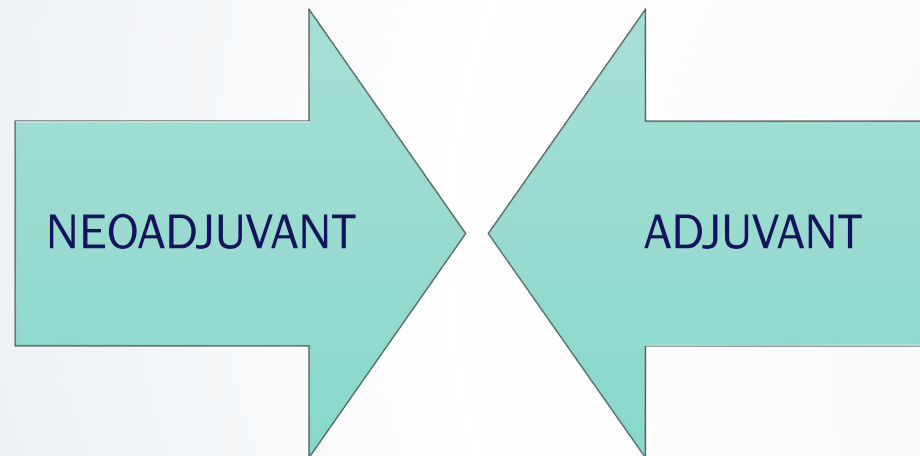
**My take on
BREAKWATER**

ATOMIC VS NICHE-2

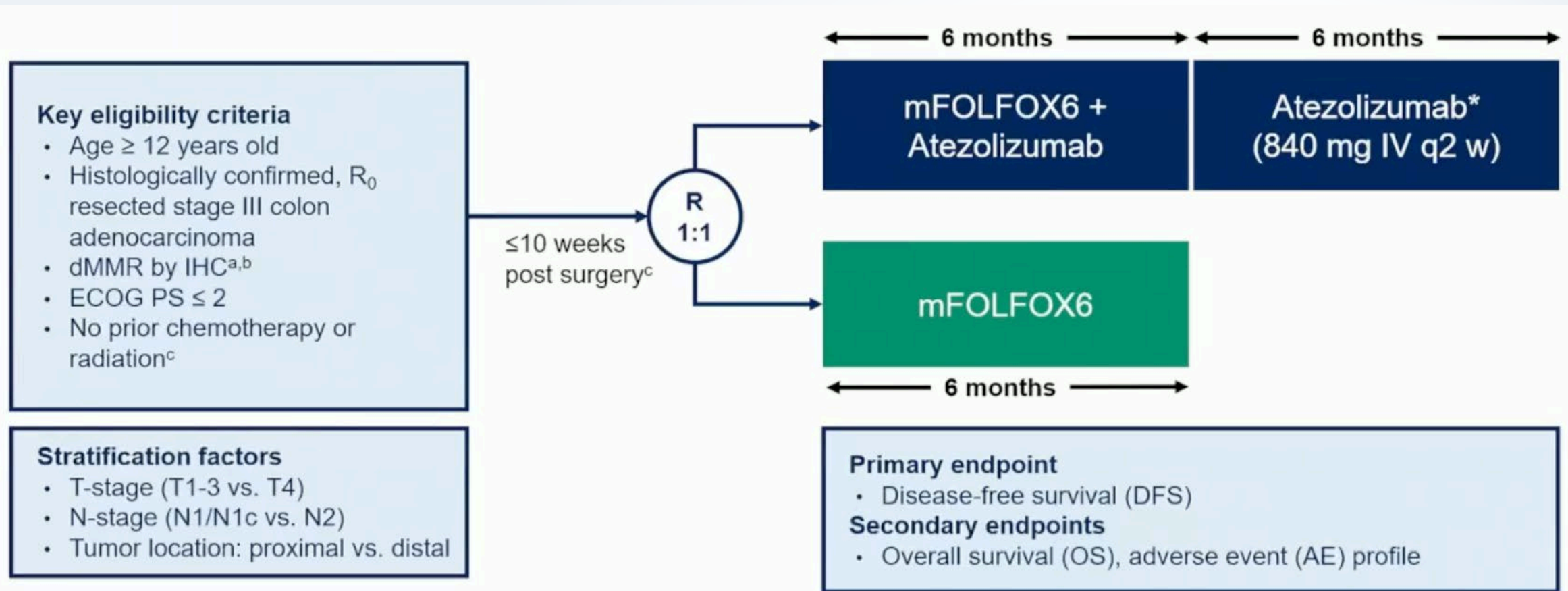
IMMUNOTHERAPY IN RESECTABLE HIGH RISK MSI-HIGH CRC

HOW DO WE REDUCE RECURRENCE IN STAGE III CRC

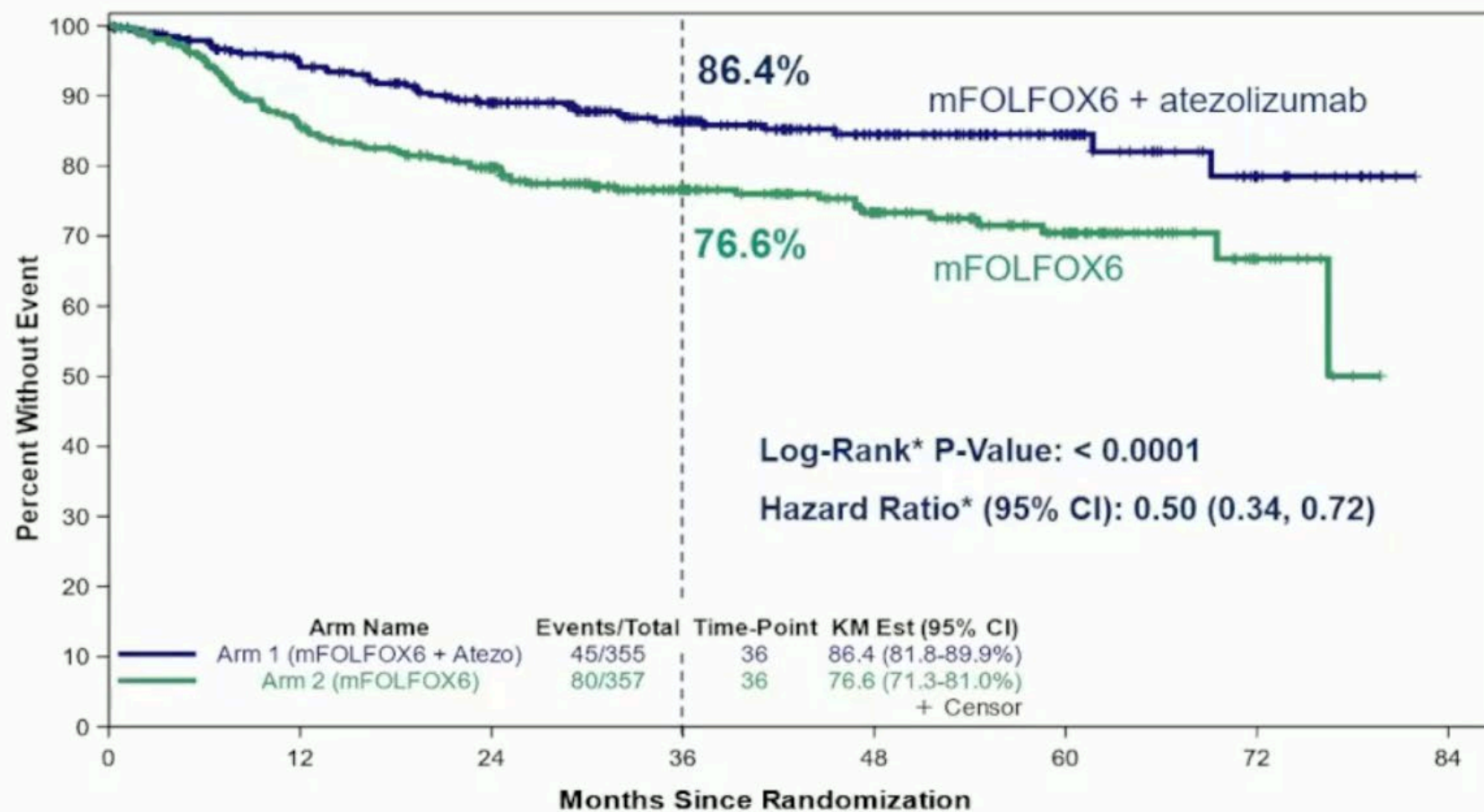
- Approximately 35% of stage III colon cancer patients will experience recurrence after adjuvant chemo
- Standard adjuvant chemotherapy for stage III tumors consists of a fluoropyrimidine + oxaliplatin regardless of MMR status
- 15% of colon cancers have deficient MMR and may display resistance to fluoropyrimidines



ATOMIC – ADJUVANT

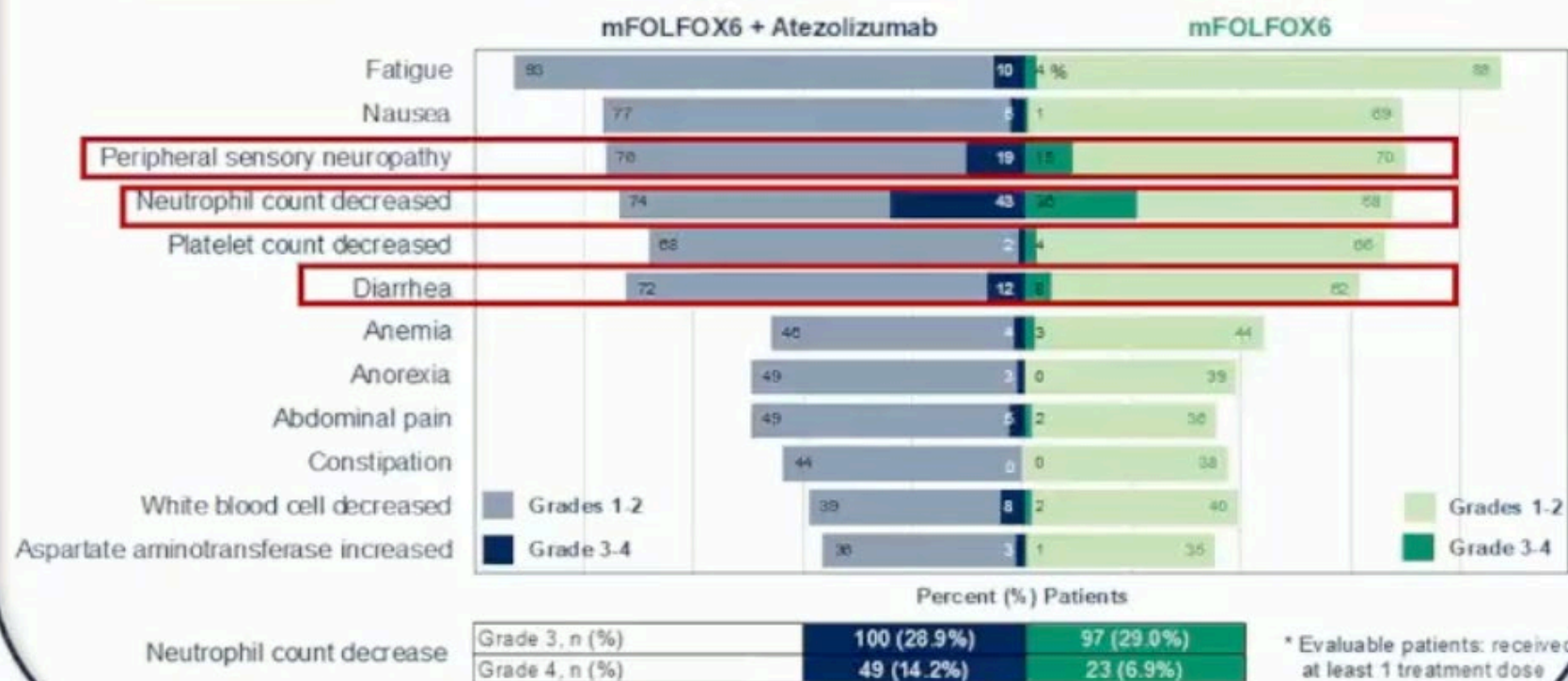


Primary Endpoint: DFS



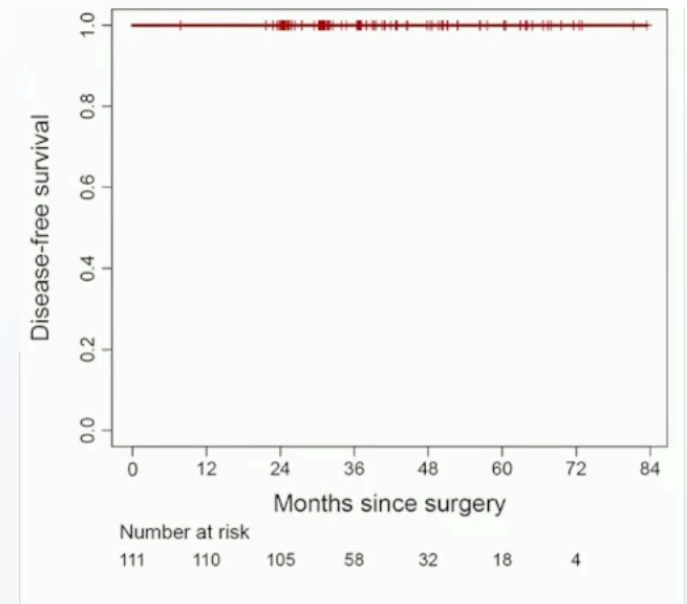
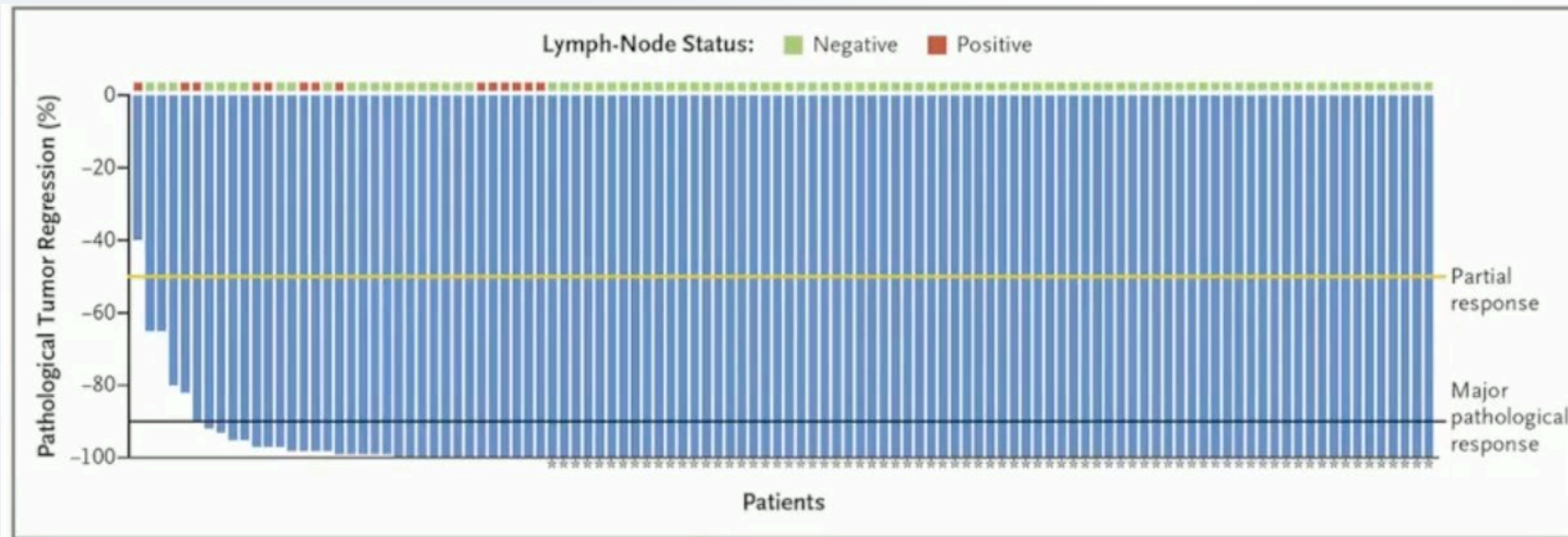
SAFETY AND TOLERABILITY

Characteristics	mFOLFOX6 + Atezo (N=346)*	mFOLFOX6 (N=334)*
Median treatment duration	5.5 months (mFOLFOX6); 10.9 months (Atezo)	5.4 months
Any Grade AE, % (n)	100% (346)	95.1% (329)
Treatment-related	99.7% (345)	94.2% (326)
Grade 3-4 AE, % (n)	83.8% (290)	69.1% (239)
Treatment-related	72.3% (250)	59.2% (205)
Grade 5 AE, % (n)	1.7% (6)	0.6% (2)
Treatment-related	0.6% (2)*	0.0% (0)



NICHE-2 – NEOADJUVANT

- Deep pathologic responses in 95% patients with 2 cycles of neoadjuvant immunotherapy
 - 65% of patients with cT4 tumors
- 3-year DFS 100%



Efficacy of neoadjuvant IO in dMMR colon cancer

	Treatment regimen and duration	No. of patients	pCR/cCR* rate
Chalabi et al, NEJM 2024 (NICHE-2)	Nivolumab + ipilimumab 4 weeks	115	68%
Xu et al, ASCO 2024	Sintilimab +/- IBI310 6 weeks	101 (49 vs 52)	78% vs 47%
De Gooyer et al, NatMed 2024 (NICHE-3)	Nivolumab + Relatlimab 8 weeks	59	68%
Hu et al, Lanc Gastr Hepat 2022 (PICC)	Toripalimab +/- celecoxib 12 weeks	34	88% (+celec) 65% (-celec)
Shiu et al, ASCO 2024 (NEOPRISM)	Pembrolizumab 6 weeks	32	58%
DelaFouchardiere et al, ESMO2024 (IMHOTEP)	Pembrolizumab 4-8 weeks	77	47% (1 cycle) 68% (2 cycles)
Cercek et al, NEJM 2025	Dostarlimab 6 months	22	82%*

- High pCR rates across studies with IO alone
- pCR/near pCR associated with an excellent 3-year DFS

CHECKMATE 8HW

DOUBLE IMMUNOTHERAPY IN MSI-H/DMMR UNRESECTABLE OR METASTATIC CRC

CHECKMATE 8HW

There has been significant advances in role of immunotherapy for MSI-H/dMMR colon cancer in the recent years

Since the first approval for pembrolizumab for unresectable or metastatic MSI-H colon cancer in 2020 based on KEYNOTE-117, immunotherapy has been very effective for this patient population

The question now – **is dual checkpoint inhibition better than single checkpoint inhibition?**

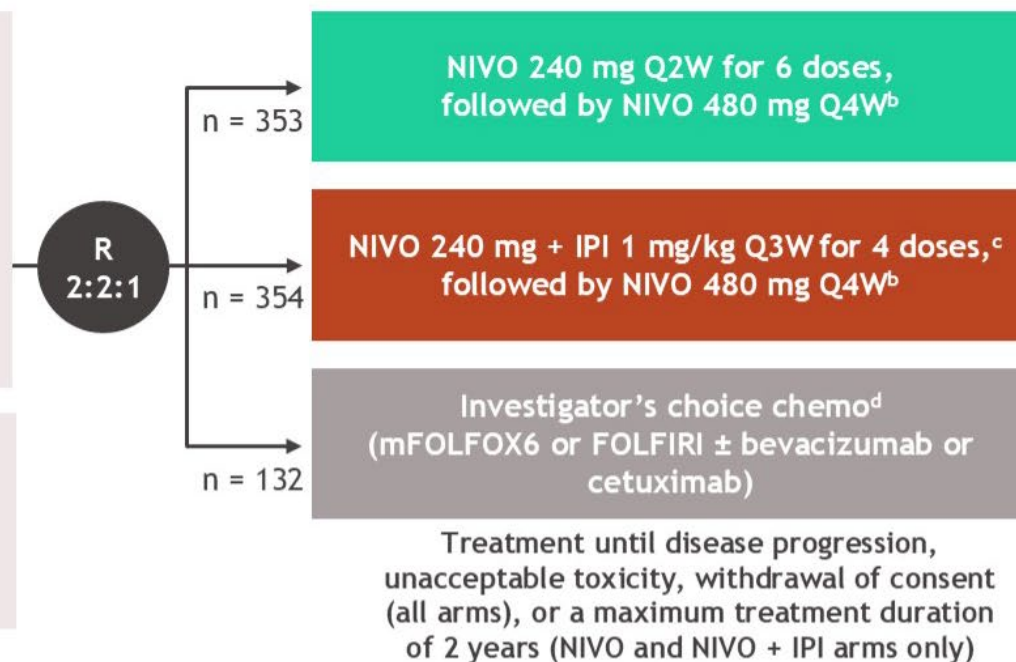
CHECKMATE 8HW Study Design

Key eligibility criteria:

- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- Immunotherapy-naïve
- ECOG PS 0 or 1

Stratification factors:

- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)



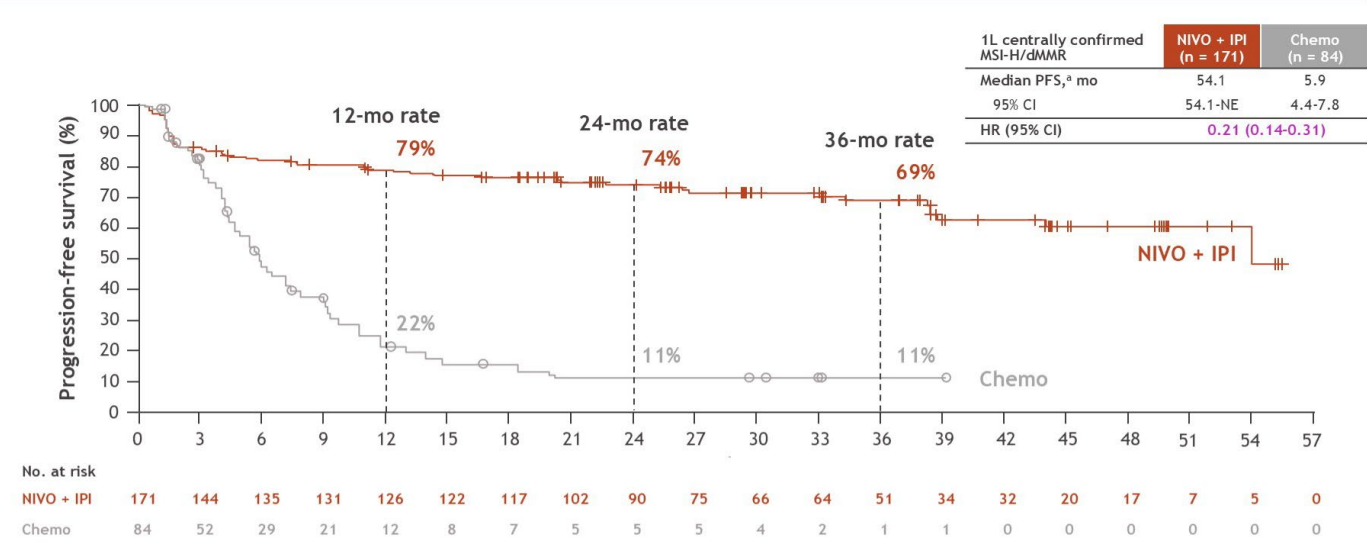
Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status^e:

- PFS by BICR^f (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR^f (NIVO + IPI vs NIVO across all lines)

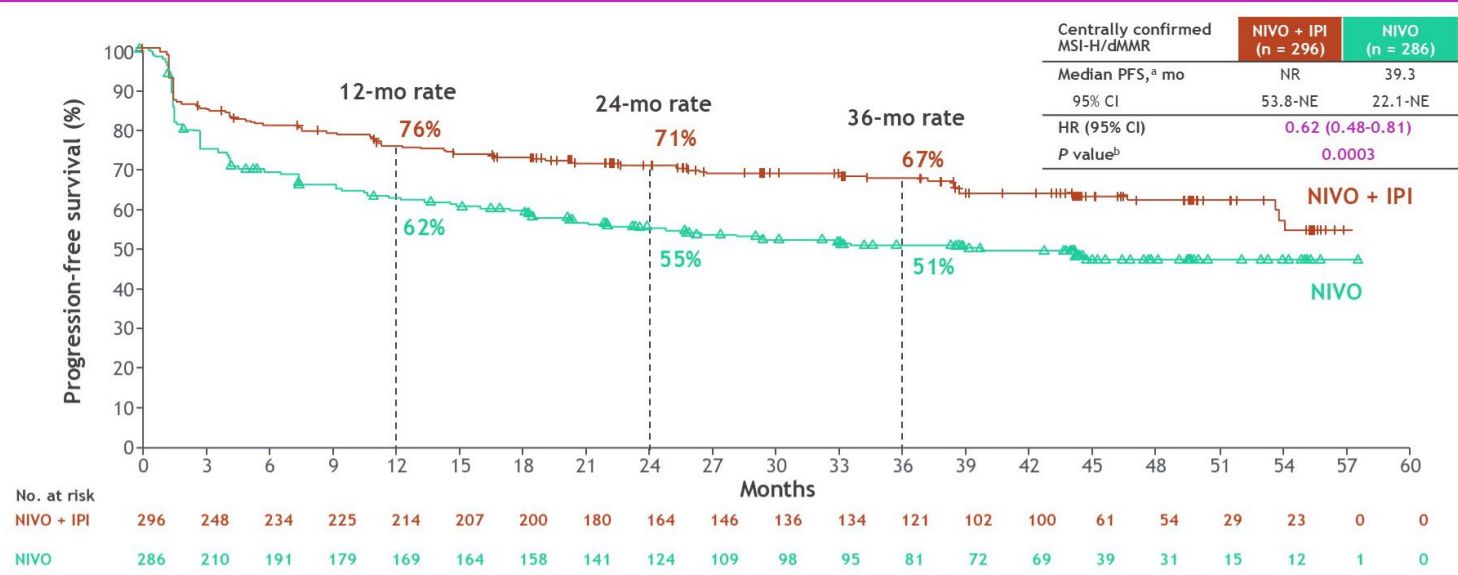
Other select endpoints:

- Safety
- PFS2; ORR by BICR^f; HRQoL; OS

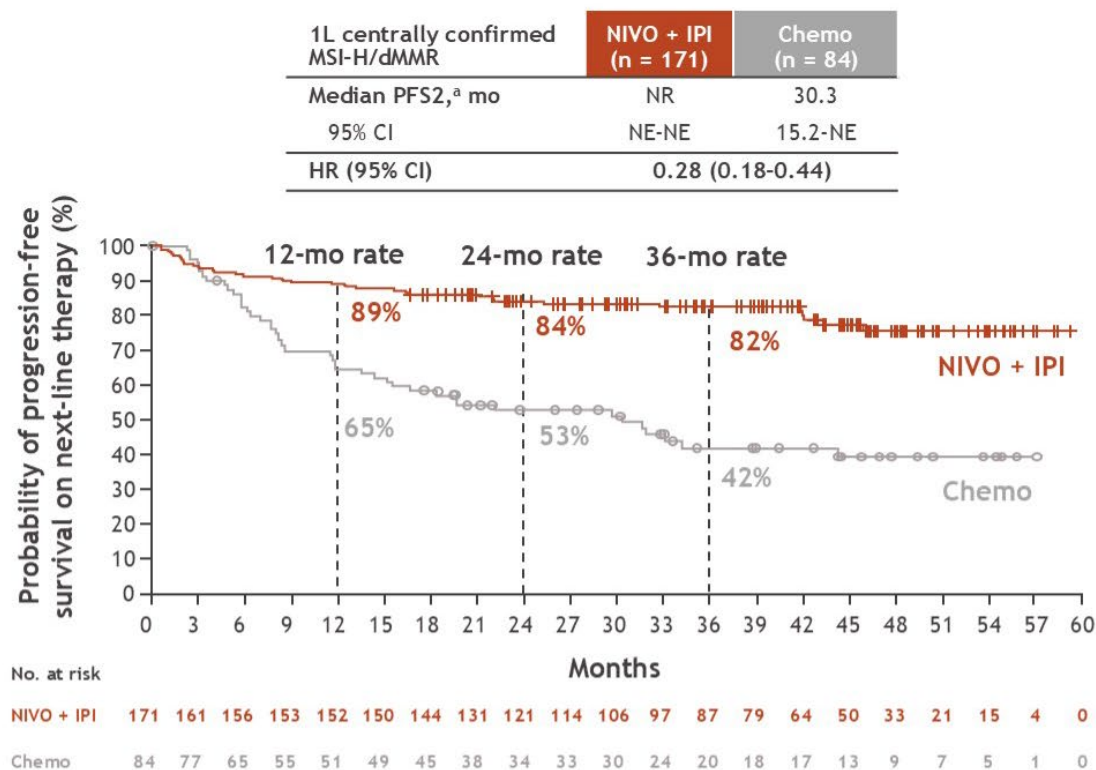
Progression-free survival: NIVO + IPI vs chemo (1L)



Progression-free survival: NIVO + IPI vs NIVO (all lines)



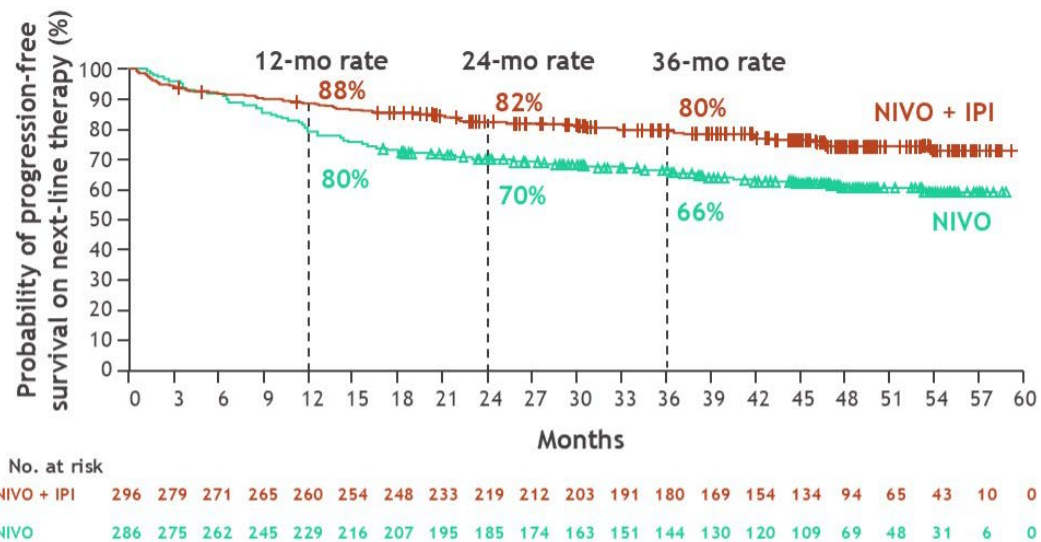
PFS2: NIVO + IPI vs chemo (1L)



Subsequent therapy ^b (1L centrally confirmed MSI-H/dMMR)	NIVO + IPI (n = 171)	Chemo (n = 84)
Radiotherapy, n (%)	3 (2)	1 (1)
Surgery, n (%)	7 (4)	5 (6)
Systemic therapy, ^c n (%)	27 (16)	61 (73)
Immunotherapy	10 (6)	60 (71)
On-study crossover to NIVO + IPI	0	39 (46)
Non-study immunotherapy	10 (6)	21 (25)
EGFR inhibitors	5 (3)	1 (1)
Platinum compounds	11 (6)	3 (4)
VEGFR targeted therapy	8 (5)	4 (5)
MEK, NRAS, and BRAF inhibitors	2 (1)	1 (1)
Other systemic anticancer therapy	17 (10)	5 (6)

PFS2: NIVO + IPI vs NIVO (all lines)

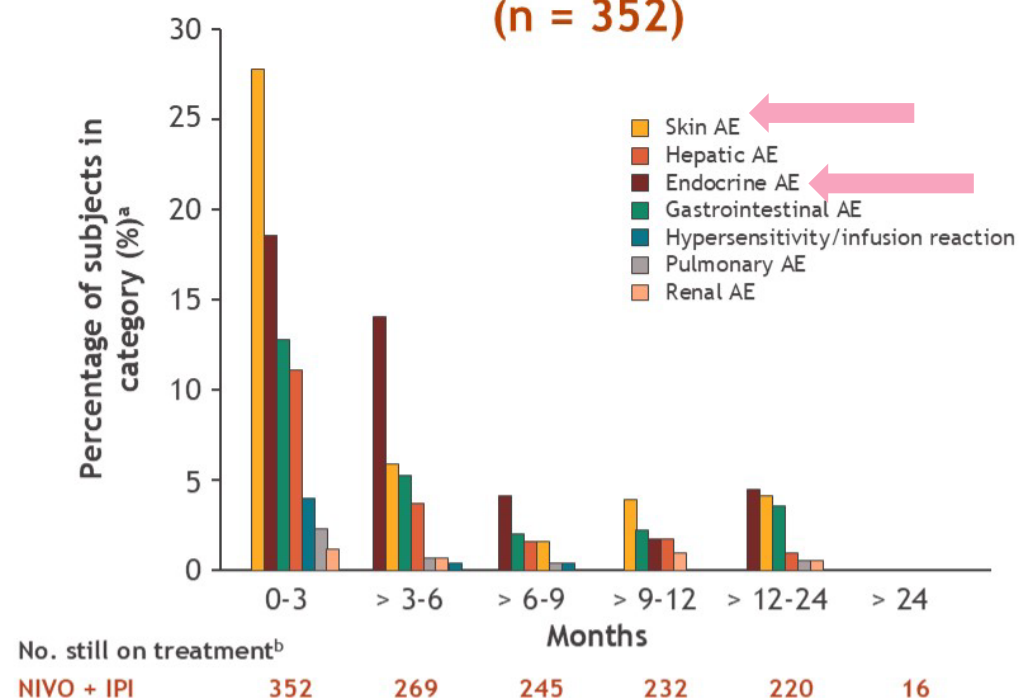
Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS2, ^a mo	NR	NR
95% CI	NE-NE	NE-NE
HR (95% CI)	0.57 (0.42-0.78)	



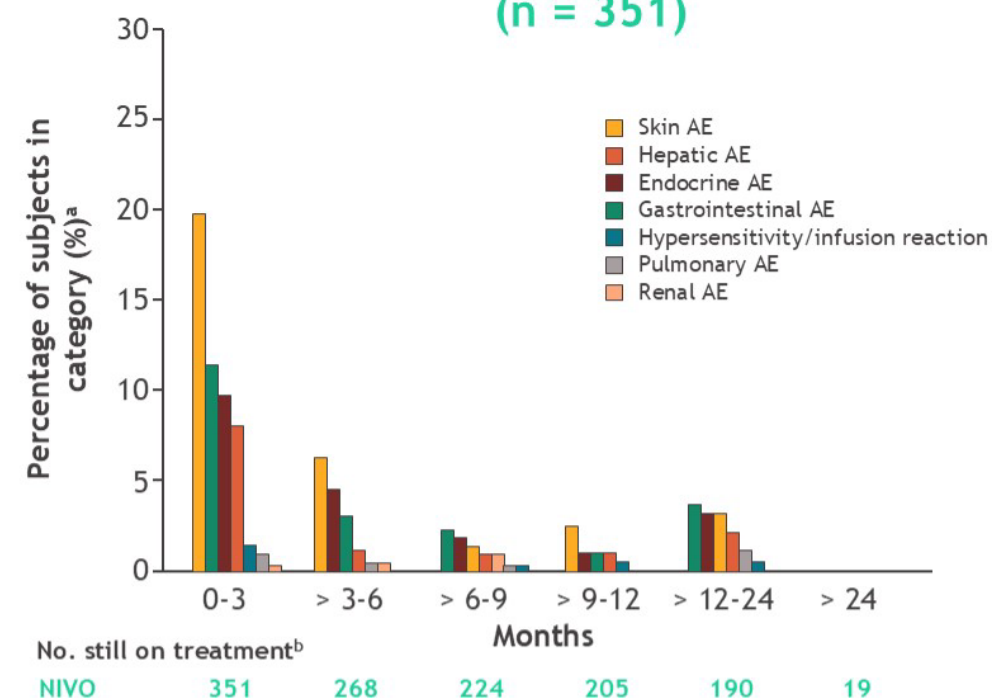
Subsequent therapy ^b (centrally confirmed MSI-H/dMMR)	NIVO + IPI (n = 296)	NIVO (n = 286)
Radiotherapy, n (%)	4 (1)	4 (1)
Surgery, n (%)	15 (5)	18 (6)
Systemic therapy, ^c n (%)	54 (18)	83 (29)
Immunotherapy	25 (8)	40 (14)
EGFR inhibitors	15 (5)	14 (5)
Platinum compounds	15 (5)	29 (10)
VEGFR targeted therapy	16 (5)	25 (9)
MEK, NRAS, and BRAF inhibitors	6 (2)	7 (2)
Other systemic anticancer therapy	31 (11)	49 (17)

Is it safe?

**NIVO + IPI
(n = 352)**



**NIVO
(n = 351)**



How will this change our practice?

CHECKMATE 8HW showed that doublet immunotherapy with nivo+ipi significantly improved PFS and PFS2 in MSI-H unresectable or metastatic colon cancer patients when compared to standard chemotherapy or single-agent nivolumab.

There was significant survival benefit along with durable responses as fewer patients needed subsequent treatment after receiving nivo+ipi in the first-line setting.

While the safety data shows increased toxicity with the doublet immunotherapy, the frequencies were similar with the nivolumab arm.

For the right patient population (ex. young) this can become the new first-line SOC for MSI-H/dMMR metastatic CRC

DYNAMIC III

CTDNA-GUIDED ESCALATION FOR STAGE III COLON CANCER

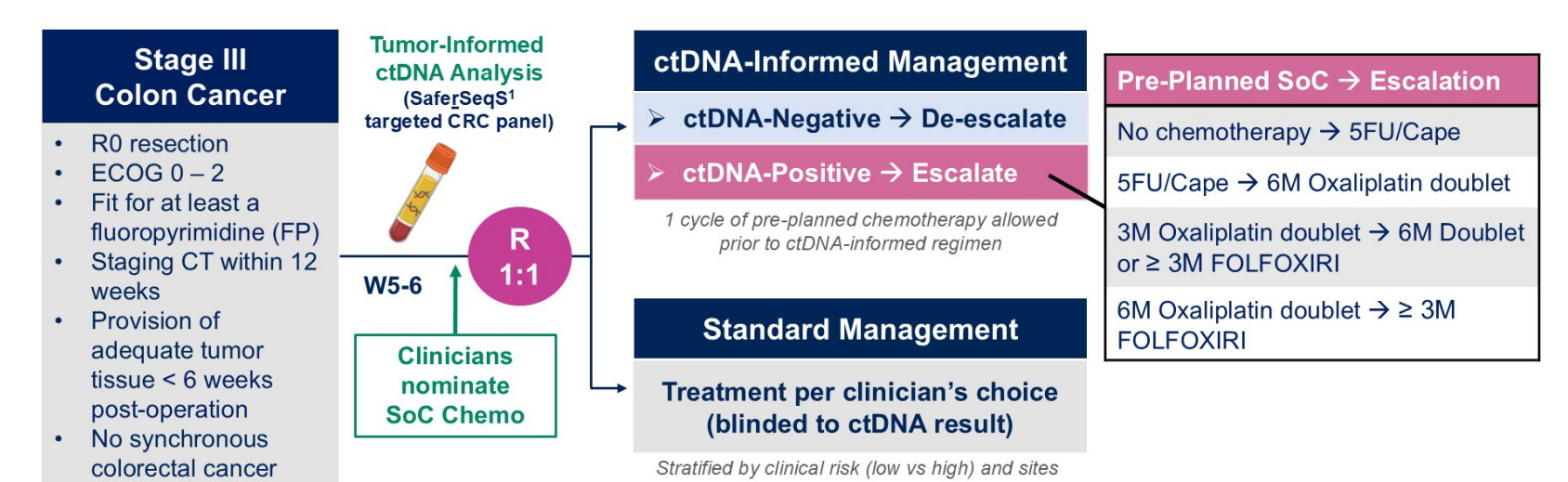
A large number of patients with resected stage III colon cancer still develop recurrence despite SOC adjuvant chemotherapy

The current SOC is 3-6 months of oxaliplatin-based chemotherapy, with high risk patients benefitting more from 6 months of therapy

Post-operative circulating tumor DNA (ctDNA) has been used as a prognostic tool in order to de-escalate treatment for stage II colon cancer based on the DYNAMIC trial

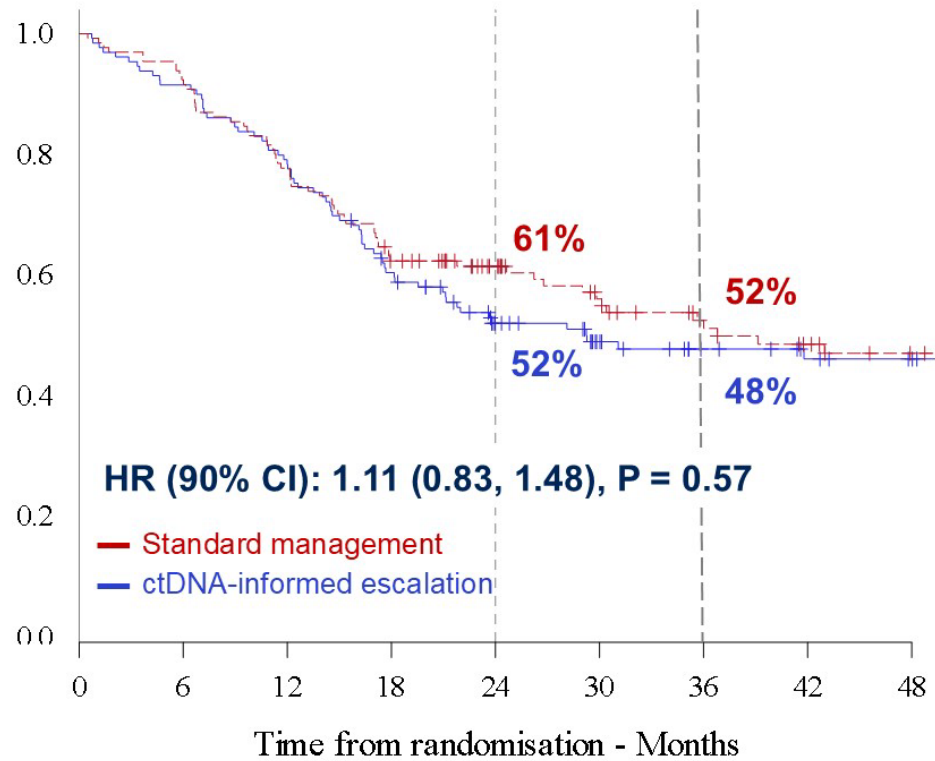
Will ctDNA also help in guiding escalation of adjuvant treatment for stage III colon cancer?

DYNAMIC III Study Design

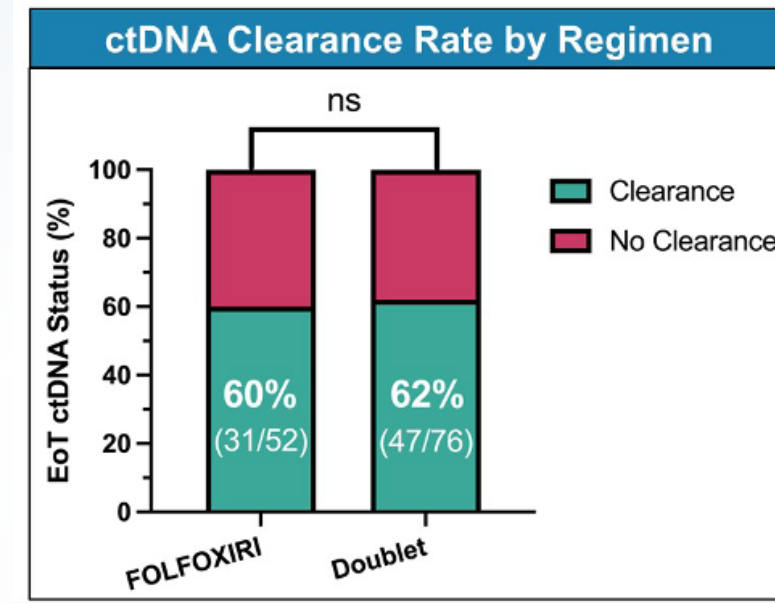


Treatment Information		ctDNA-Informed Escalation N = 129, N (%)	Standard Management N = 130, N (%)
Commenced protocol treatment escalation		115 (89)	--
Chemotherapy received	No Chemotherapy	4 (3)	4 (3)
	Single agent FP	3 (2)	14 (11)
	3M Oxaliplatin doublet	1 (1)	59 (45)
	6M Oxaliplatin doublet	56 (44)	53 (41)
	≥ 3M FOLFOXIRI	65 (50)	0 (0)

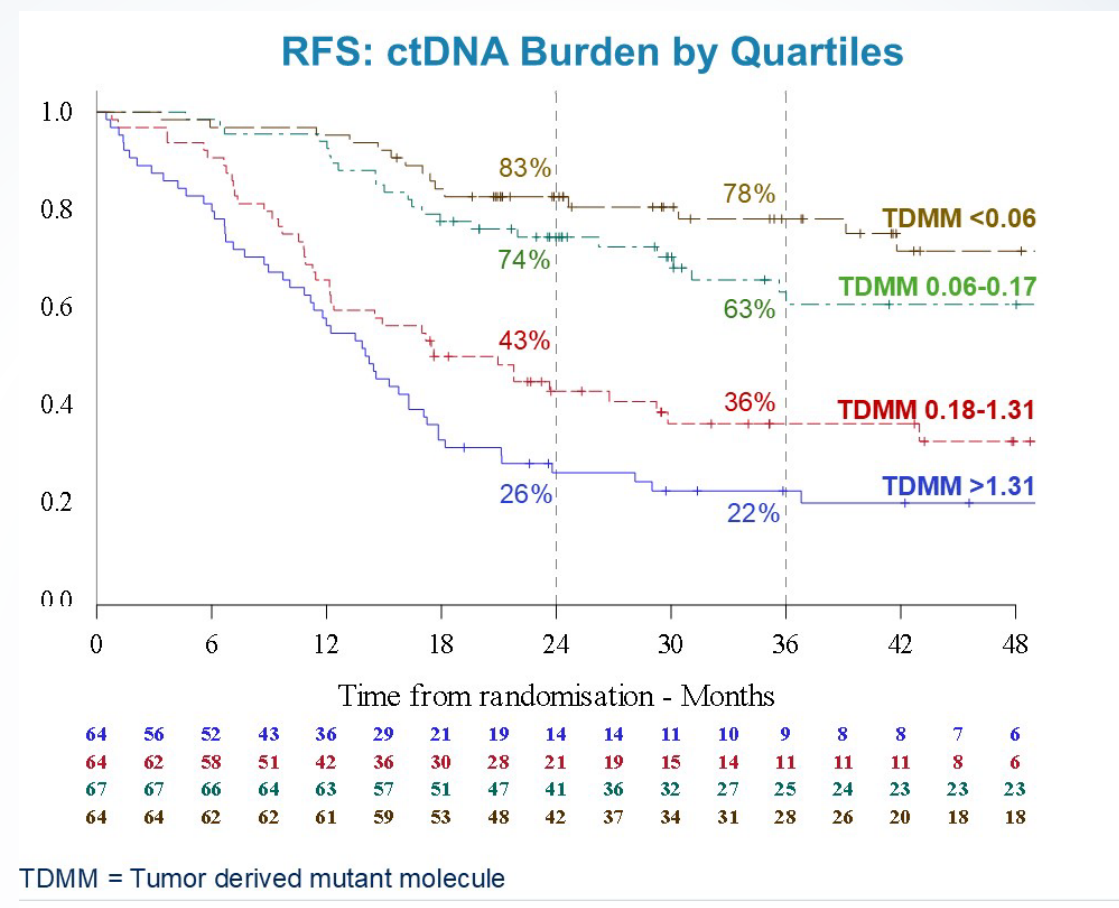
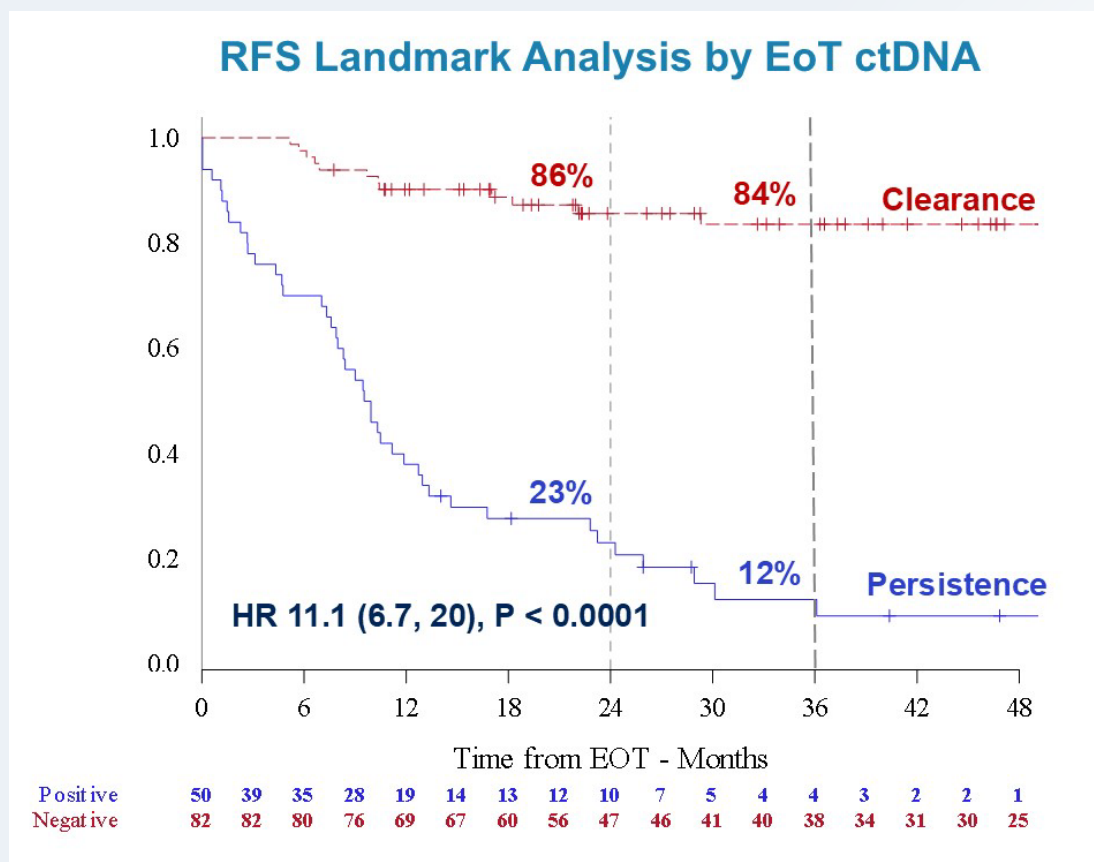
Recurrence-Free Survival



ctDNA-Informed	129	123	118	109	101	90	76	68	55	52	42	38	33	32	28	26	25
Standard	130	126	120	111	101	91	79	74	63	54	50	44	40	37	34	30	28



How does ctDNA clearance affect RFS?



Patients who had a persistently positive ctDNA had poorer outcomes than those who cleared the ctDNA during treatment

DYNAMIC III Takeaways

This is what we know from the trial:

- There is compelling evidence in using ctDNA as a prognostic marker for stage III colon cancer
- Recurrence risk increases with high ctDNA burden and the inability to clear ctDNA
- Escalating adjuvant treatment did not impact ctDNA clearance or survival

While it was a negative trial, it showed that we have very limited effective treatments for this high risk population, and we may need to focus on novel agents.

DESTINY-GASTRIC04

TRASTUZUMAB DERUXTECAN FOR 2ND HER2+ GASTRIC/GEJ ADENOCARCINOMA

DESTINY-GASTRIC 04

Trastuzumab deruxtecan is currently approved for 2nd + line treatment of HER2+ gastric/GEJ adenocarcinoma after progression on trastuzumab-based therapy

Approval was given based on the phase II DESTINY-GASTRIC 02

ORR 38%, mPFS 5.5 months, OS 8 months

DESTINY-GASTRIC 04 is the first phase III trial comparing TDXd in the 2nd line setting, head to head with the current SOC, ramucirumab + paclitaxel

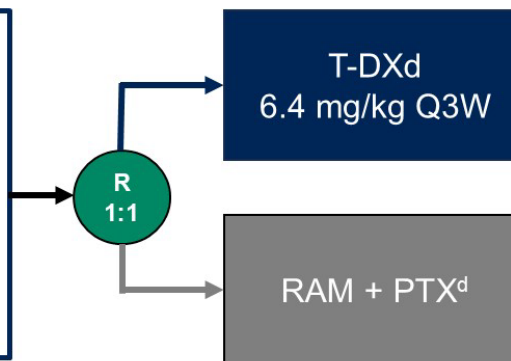
DESTINY-GASTRIC 04 Study Design

Patient Population

- HER2+ (IHC 3+ or IHC 2+/ISH+)^a GC/GEJA
- HER2 status confirmed locally or centrally^b on a recent biopsy obtained after progression on trastuzumab
- ECOG PS 0 or 1
- No clinically active CNS metastases^c

Stratification factors

- HER2 status (IHC 3+ vs IHC 2+/ISH+)
- Geography (Asia [excluding mainland China] vs Western Europe vs mainland China/rest of world)
- Time to progression on 1L therapy (<6 months vs ≥6 months)



Primary Endpoint

- OS

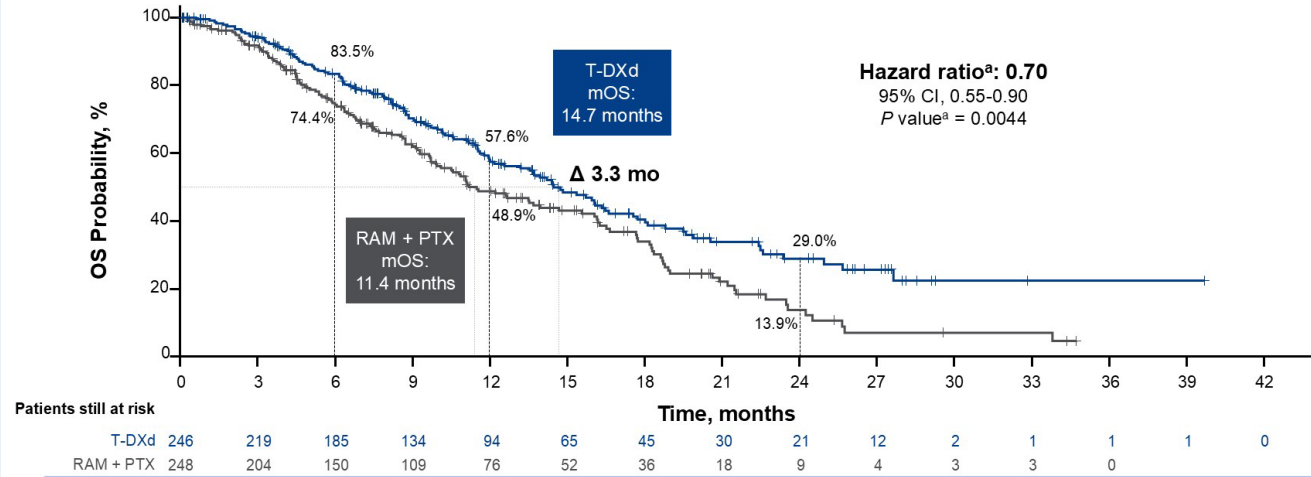
Secondary Endpoints

- PFS (INV)^e
- Confirmed ORR (INV)^e
- DCR (INV)^e
- DOR (INV)^e
- Safety

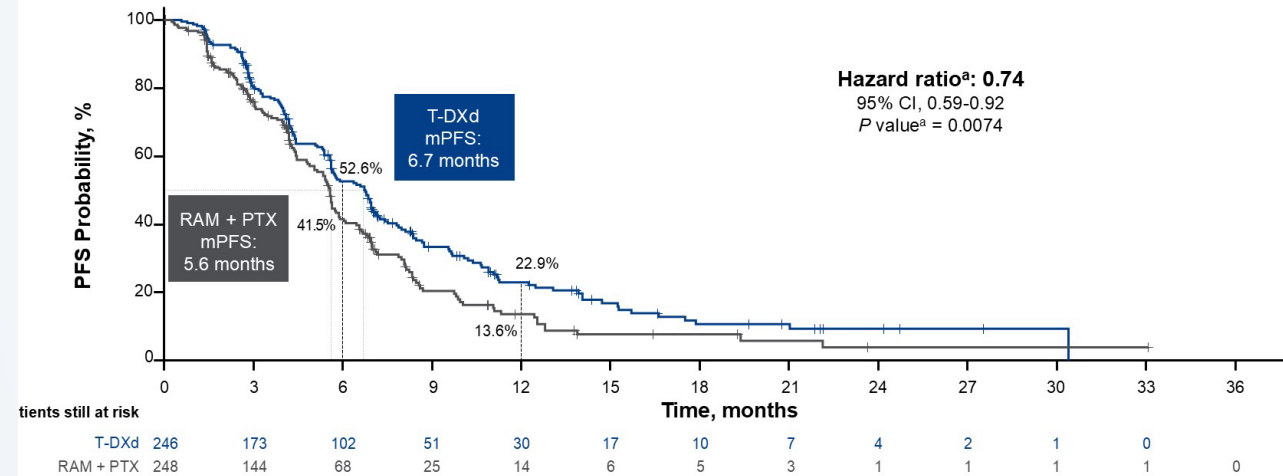
Exploratory Endpoints

- PROs^f

OS: Primary Endpoint

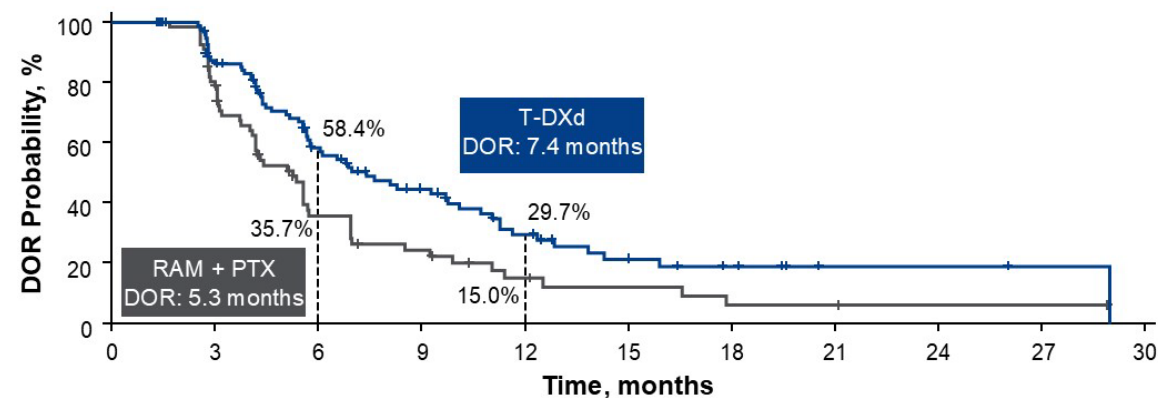


PFS by Investigator: Key Secondary Endpoint



ORR and DOR

	T-DXd n = 246	RAM + PTX n = 248
Confirmed ORR (95% CI),^c %	44.3 (37.8-50.9)	29.1 (23.4-35.3)
<i>P</i> value ^d	0.0006	
Difference (95% CI), ^e %	15.1 (6.1-24.2)	
DOR, median (95% CI), mo	7.4 (5.7-10.1)	5.3 (4.1-5.7)
DCR (95% CI), %	91.9 (87.7-95.1)	75.9 (70.0-81.2)
Confirmed BOR, n (%)		
CR ^f	7 (3.0)	3 (1.3)
PR	97 (41.3)	66 (27.8)
SD ^g	112 (47.7)	111 (46.8)
PD	13 (5.5)	22 (9.3)
NE	6 (2.6)	35 (14.8)



Patients still at risk

T-DXd	104	81	45	29	17	10	6	2	2	1	0
RAM + PTX	69	50	19	12	6	4	2	2	1	1	0

Safety Profile

	Safety analysis set N = 477	
	T-DXd n = 244	RAM + PTX n = 233
Any TEAE, n (%)	244 (100)	228 (97.9)
Drug-related	227 (93.0)	213 (91.4)
Grade ≥3 TEAEs, n (%)	166 (68.0)	172 (73.8)
Drug-related	122 (50.0)	126 (54.1)
Serious TEAEs, n (%)	100 (41.0)	101 (43.3)
Drug-related	45 (18.4)	41 (17.6)
TEAEs associated with dose discontinuation, n (%)	35 (14.3)	40 (17.2)
Drug-related	28 (11.5)	31 (13.3)
TEAEs associated with dose interruption, n (%)	137 (56.1)	141 (60.5)
Drug-related	94 (38.5)	119 (51.1)
TEAEs associated with dose reduction, n (%)	77 (31.6)	87 (37.3)
Drug-related	76 (31.1)	84 (36.1)
TEAEs associated with death, n (%)	22 (9.0)	35 (15.0)
Drug-related ^a	4 (1.6)	2 (0.9)

Adjudicated drug-related ILD/pneumonitis

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 244)	7 (2.9)	26 (10.7)	1 (0.4)	0	0	34 (13.9)
RAM + PTX (n = 233)	0	0	2 (0.9)	0	1 (0.4)	3 (1.3)

Left ventricular dysfunction^a

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 244)	0	3 (1.2)	3 (1.2)	0	0	6 (2.5)
RAM + PTX (n = 233)	2 (0.9)	2 (0.9)	0	0	0	4 (1.7)

DESTINY-GASTRIC 04

DESTINY-GASTRIC 04 confirmed that TDXd is the 2nd line treatment for metastatic HER2+ gastric/GEJ adenocarcinoma

There was significant improvement in PFS in this highly aggressive cancer