Best of ASCO 2024

Updates in Neoadjuvant and Adjuvant Treatment of Colon & Rectal Cancers, Anal Cancers

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Disclosure

- I have permission to use slides from Annual Meeting 2024
- Saima Sharif, MD MS reports:
  - Grant/research support - GSK
  - Is a consultant for - none
  - Other - none

Learning Objectives

- Review results from key trials in Neoadjuvant and Adjuvant therapy of Colon and Rectal Cancers, and Anal Cancer presented at ASCO Annual Meeting 2024
- Discuss their relevance to clinical practice

Outline of Presentation

- Neoadjuvant Colon Cancer - Stage II/III, dMMR
  - LBA 3504 – NEOPRISM CRC (Phase II, multicenter, stratified by TMB, open-label trial)
  - Abstract 3505 – IO + CTLA4 (Phase Ib, Randomized, open label trial)
  - Summary and Take-home points
- Adjuvant Colon Cancer - Stage II, pMMR & dMMR
  - Abstract 108 – DYNAMIC TRIAL – (Phase 2, multicenter, randomized trial)
  - Summary and Take-home points
- Neoadjuvant Rectal Cancer – Stage II/III, dMMR
  - LBA 3512 – NAIO in Locally Advanced Rectal Cancer (Phase 2, single arm)
  - Summary and Take-home points
- Anal Cancer – Stage I-III
  - Abstract 3513 – HPV DNA Detection after CCRT as prognostic marker (Single arm)
  - Summary and Take-home points

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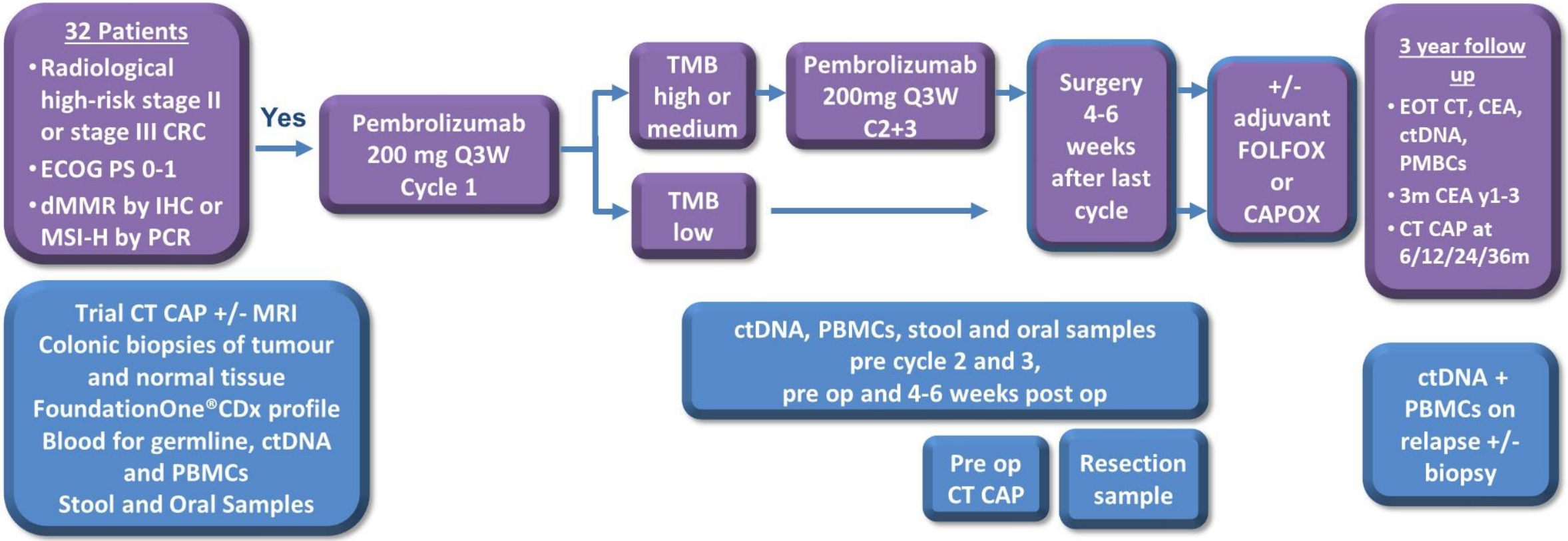
NEOPRISM-CRC Study Design

LBA - 3504



Primary endpoint: Pathological complete response rate

Secondary endpoints: 3-year RFS, OS, Safety, Health-related Quality of Life

Exploratory endpoints: ctDNA response to neoadjuvant therapy, minimal residual disease monitoring, genomic and microbiome biomarker signatures

NCT05197322

PRESENTED BY: Dr Kai-Keen Shiu PhD, FRCP

Patient Characteristics

Characteristic	N=32
Age, median (range)	60 (34-78)
Sex, N (%)	
Male	19 (59)
Female	13 (41)
Race, N (%)	
White	27 (84.4)
Asian	3 (9.4)
Black	2 (6.2)
ECOG PS, N (%)	
0	22 (68.7)
1	10 (31.3)
Lynch Syndrome, N (%)	
Yes	10 (31.3)
No	17 (53.1)
Pending	5 (15.6)
Mutational status, N (%)	**N=34***
BRAF V600E mut	14 (41.2)
KRAS or NRAS mut	9 (26.5)
RAS-RAF wild type	11 (32.3)

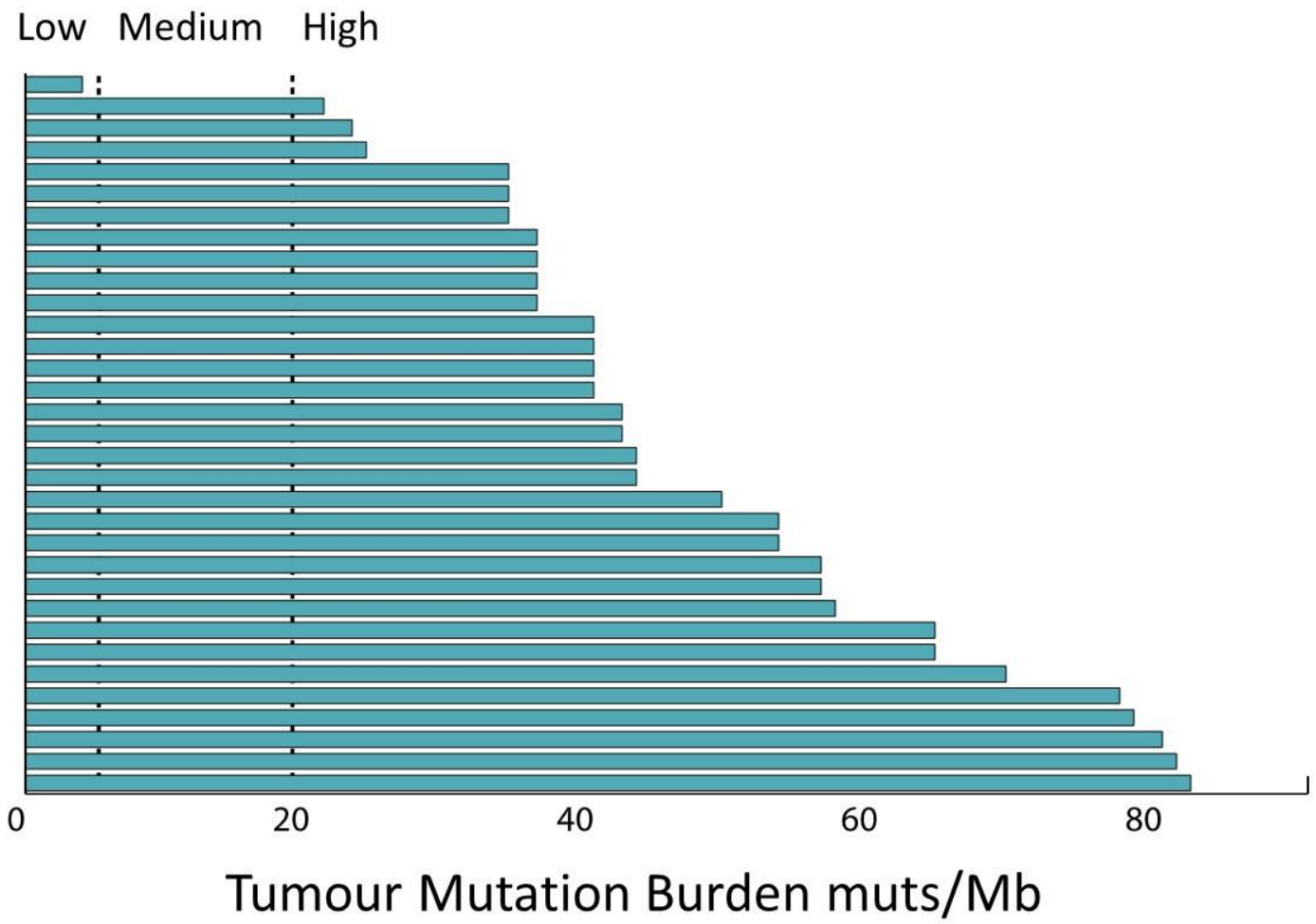
Primary tumour location, N (%)	N=34*
Right side	24 (70.6)
Left side (2 Rectal cancers)	7 (20.6)
Transverse colon	3 (8.8)

Radiological stage, N (%)	N=32
II A	
T3c/d N0 M0	3 (9.4)
II B	
T4a N0 M0	2 (6.2)
II C	
T4b N0 M0	1 (3.1)
IIIB	
T3 -T4 N1 M0	12 (37.5)
T2-T3 N2 M0	4 (12.5)
IIIC	
T4a N2 M0	9 (28.1)
T4b N2 M0	1 (3.1)

Majority had Radiological high risk
21 T4
26 N+

* One patient had 3 synchronous BRAF V600E mutated primary tumours in ascending, transverse and descending colon

Tumour Mutation Burden of 34 Primary Tumours



	Primary Tumours
TMB low (≤4 muts/Mb)	1
TMB medium (5-19 muts/Mb)	0
TMB high (≥ 20 muts/Mb)	**33**
Median TMB (range)	**42 (4-82)**
Total	**34**

Primary endpoint: pCR in TMB high or medium tumours

	All patients N=32	TMB low N=1	TMB high N=31
Intent-to-treat pCR rate (95% CI)	17/32 53% (35-71)	0/1 0% (0-98)	**17/31** **55%** **(36-73)**
Evaluable tumours pCR rate (95% CI)	19/33 58% (39-75)	0/1 0% (0-98)	**19/32** **59%** **(41-76)**

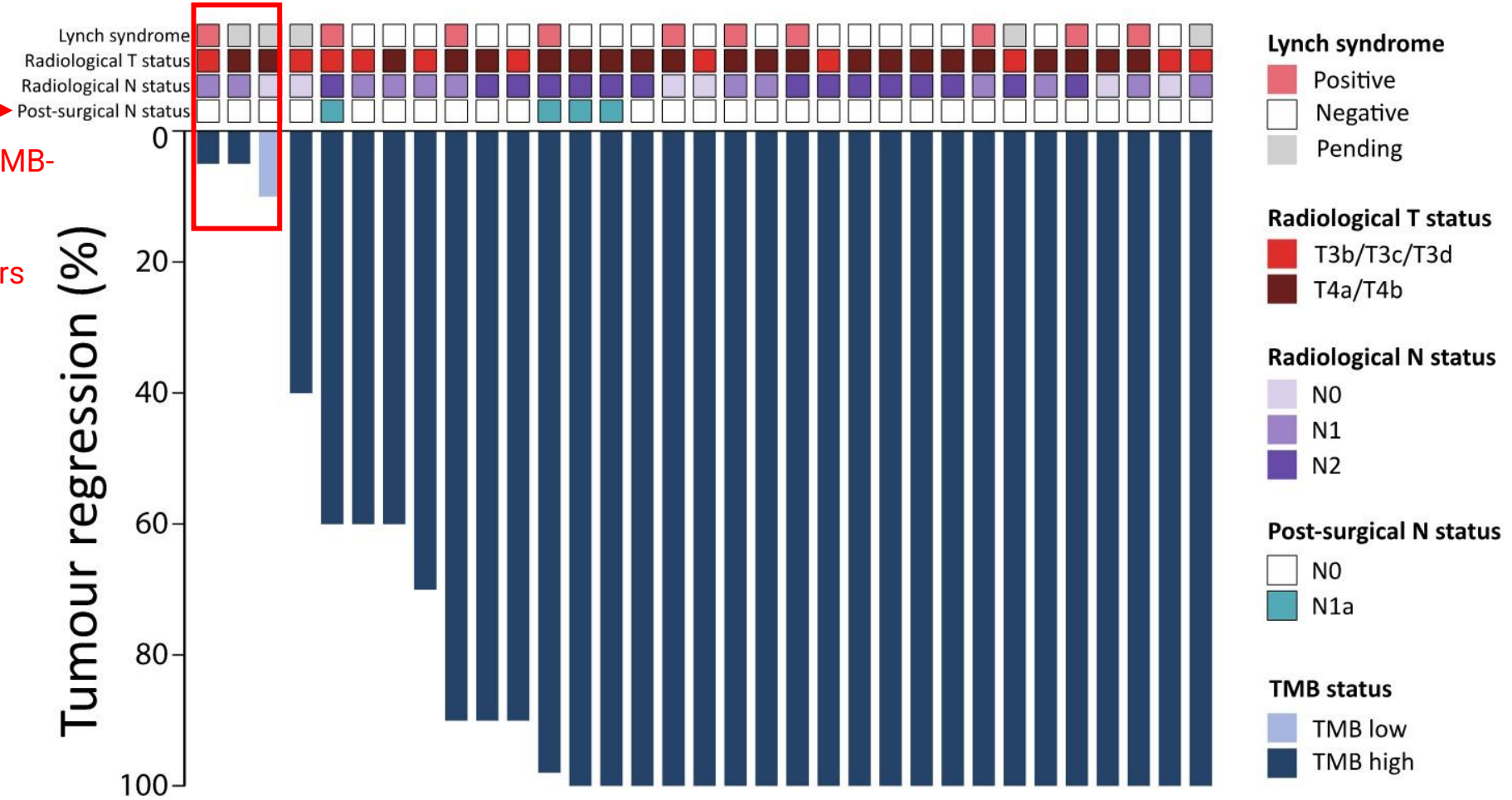
~12 weeks

Median time from cycle 1 pembrolizumab to surgery was 83 days (range 48-109)

This is longer than other reported studies reporting surgery after Neoadjuvant IO (6 weeks)

pCR seen in 59% of 32 TMB-high resected primaries

Why did these TMB-high not respond? Need better biomarkers for response



No disease relapse with median follow up of 9.7 months (range 5.3-19.0) and only 2 patients had adjuvant CAPOX

PRESENTED BY: Dr Kai-Keen Shiu PhD, FRCP

Adverse Events in all treated patients

Event	Any	Grade 3 or 4
	Number of patients (%)	
Any Adverse Event	32 (100)	15 (46.9)
Immune-Related Adverse Events	**20 (62.5)**	**2 (6.2)**

Symptomatic tumors, AEs are not unreasonable

Grade 3 Non-Immune Related Adverse Events included diarrhoea (12.5%), vomiting (6.2%) and pneumonia (6.2%)

No Grade 5 Adverse Events. One patient did not proceed with surgery and died 6 months later from pneumonia

Immune-Related Adverse Events in >5% of patients

Immune-Related AE	Any	Grade 1-2	Grade 3-4
	N° of patients (%)		
Any Immune-Related AE	**20 (62.5)**	**18 (56.3)**	**2[a,b] (6.2)**
Fatigue	9 (28.1)	8 (25.0)	1[a] (3.1)
Hypothyroidism	5 (15.6)	5 (15.6)	0 (0)
Rash	5 (15.6)	5 (15.6)	0 (0)
Hyperthyroidism	4 (12.5)	4 (12.5)	0 (0)
ALT increase	3 (9.4)	2 (6.3)	1[b] (3.1)
Arthralgia	3 (9.4)	3 (9.4)	0(0)
Dry Skin	3 (9.4)	3 (9.4)	0 (0)
Pruritus	3 (9.4)	3 (9.4)	0 (0)
Myalgia	2 (6.3)	1 (3.1)	1[b] (3.1)
Infusion reaction	2 (6.3)	2 (6.3)	0 (0)
ALP increase	2 (6.3)	2 (6.3)	0 (0)
Dry mouth	2 (6.3)	2 (6.3)	0 (0)
Nausea	2 (6.3)	2 (6.3)	0 (0)

Few and manageable surgical complications

Post surgical complications	N° of patients (%)	Clavien Dindo grade
Pneumonia	2 (6.2)	II
Bile leak	1 (3.1)	IIIA
Prolonged Ileus	1 (3.1)	II
Haematoma	1 (3.1)	I

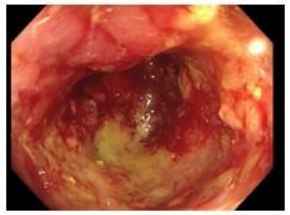
Preoperatively two patients had colonic fistulation, and another two developed bowel obstruction due to treatment response

AE: Adverse Event, ALT: alanine aminotransferase, ALP: alkaline phosphatase
[a] and [b] represent two individual patients with Grade 3 IRAEs

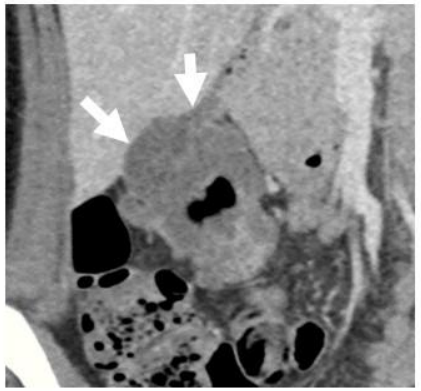
Colonic fistula with pathological complete response

Female, 36 years old
Presented with back pain and anaemia: PS1

Known Lynch Syndrome
MLH1 germline mutation



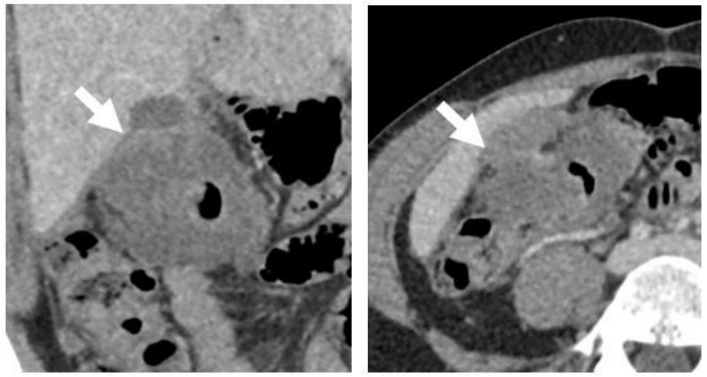
Moderately to poorly differentiated adenocarcinoma
dMMR (MH1 and PMS2 loss)



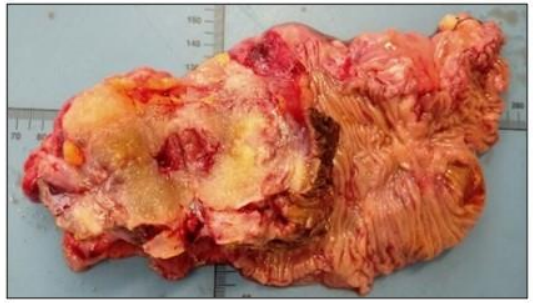
CT CAP rT4bN0M0

Microsatellite status: MSI-H
FoundationOne®CDX:
TMB-High 34 muts/Mb
KRAS A146T and ARID1A Q909* mutation

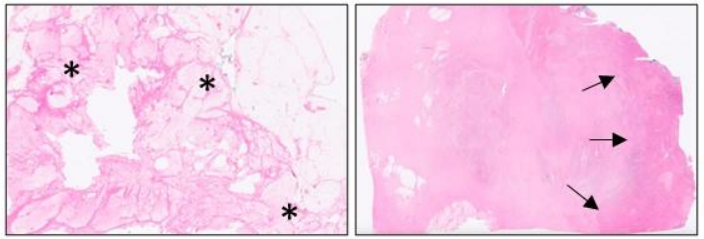
Pembrolizumab 200 mg x 3



Emergency presentation with RUQ pain + fever
Contained gallbladder perforation on CT CAP
Given oral antibiotics and surgery delayed 2 weeks



Open extended right hemicolectomy, *en bloc* partial hepatectomy with cuff of pylorus and subtotal cholecystectomy
Post operative bile leak - stented



TNM 8: ypT0 N0 (0/16) Mx R0 pCR
Large acellular mucin lakes (*) extending into pericolic fat and inflammatory infiltrate extending through bowel wall to the adjacent hepatic parenchyma (arrows). RFS 14 months

NEOPRISM-CRC is a translationally enriched clinical trial

FM1®CDx Profile

TMB
Molecular Subgroups

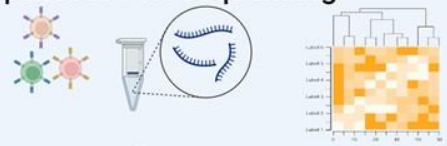
Pre-Rx biopsy

TCR diversity in blood

PBMCs TCR seq

Tumour Immune Microenvironment

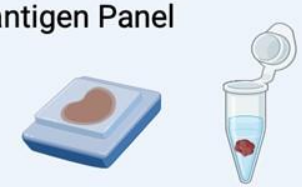
Pre- and post-Rx TCR sequencing



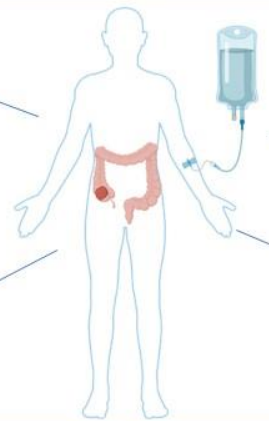
Multiplex Immunofluorescence

DNA and RNA sequencing

WES
Targeted Neoantigen Panel
Bulk RNA seq



Pre- and post-Rx tumour



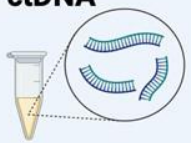
Organoid and immune cell co-culture

Functional analysis of tumour immune interaction

- Signalling networks and T cell surface markers
- WES and Targeted Neoantigen Panel
- TCR diversity

Circulating Tumour DNA

Temporal monitoring of **ctDNA** presence and quantity



Microbiome

Analysis of changes to microbiome in response to IO

Created with BioRender.com

Thanks to Yanrong Jiang, Monika Madrova *Ramos-Zapatero,Tong *et al*. 2023 Cell

Conclusions / Key Takeaways

- Nine weeks of neoadjuvant pembrolizumab is effective in downstaging high risk stage 2 or stage 3 dMMR/MSI-High CRC with a pathological complete response rate of 59%
- No patients have relapsed disease with median follow-up of 9.7 months (range 5.3 - 19.0)
- Extensive genomic, microbiome and other translational work in progress
- Trial is being expanded to a 3-year Relapse Free Survival Endpoint
- The importance of the multidisciplinary team in caring for our patients

Summary - NEOPRISM – LBA 3504

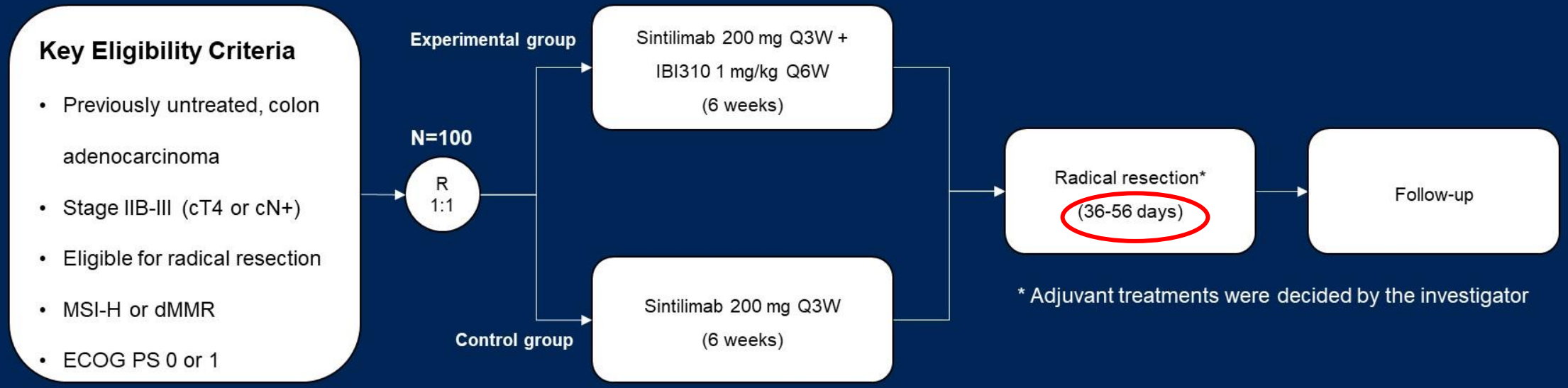
Strengths:

- **Gives us pCR data with single agent IO of 59%**
- **Translationally enriched clinical trial may help with answering why some TMB high did not respond**
- **AE data was acceptable given the symptomatic patients with bulky tumors**

Limitations:

- **Small sample size of 32, plan to expand to 70 patients**
- **Short follow up of 9.7 mo (plan is for 3-year RFS)**

Abstract 3505 – Neoadjuvant IBI310 (CTLA4 antibody) plus Sintilimab anti-PD-1 antibody) in dMMR colon cancer – Randomized, open-labeled, Phase 1b Study



Stratification Factors:
Age: < 55 years vs ≥ 55 years
Baseline imaging: high-risk (T4 or N2) vs low-risk (T1-3 and N1)

Primary endpoint: pCR rate
Secondary endpoints: EFS, OS, R0 resection rate, Safety

■ The statistical hypotheses:

H0: pCR rate of experimental group ≤ pCR rate of control group

H1: pCR rate of experimental group > pCR rate of control group

■ Sample size assumption:

pCR rate in experimental group=60%; pCR rate in control group= 30%; dropout rate =10%; two-sided alpha=0.05; power=82.8%.

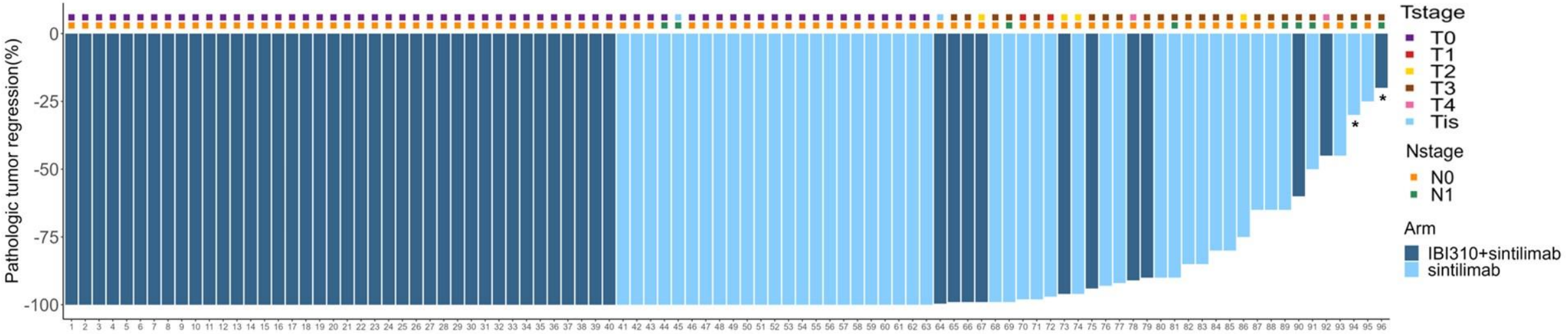
Baseline characteristics

Data cutoff date: 2024-2-24

		IBI310+sintilimab (N=52)	sintilimab (N=49)	Total (N=101)
Gender, n (%)	Male	29 (55.8)	27 (55.1)	56 (55.4)
	Female	23 (44.2)	22 (44.9)	45 (44.6)
Age, years	Median (range)	56.0 (30-77)	56.0 (23-75)	56.0 (23-77)
ECOG PS, n (%)	0	22 (42.3)	24 (49.0)	46 (45.5)
	1	30 (57.7)	25 (51.0)	55 (54.5)
Tumor location, n (%)	Left	13 (25.0)	17 (34.7)	30 (29.7)
	Right	39 (75.0)	32 (65.3)	71 (70.3)
T stage, n (%)	T2	1 (1.9)	0	1 (1.0)
	T3	17 (32.7)	14 (28.6)	31 (30.7)
	T4	34 (65.4)	35 (71.4)	69 (68.3)
N stage, n (%)	N0	12 (23.1)	9 (18.4)	21 (20.8)
	N1	26 (50.0)	24 (49.0)	50 (49.5)
	N2	14 (26.9)	16 (32.7)	30 (29.7)
Risk, n (%) T4, N+	**High**	**39 (75.0)**	**38 (77.6)**	**77 (76.2)**
	Low	13 (25.0)	11 (22.4)	24 (23.8)
Lynch syndrome*, n (%)	**Suspected pathogenic mutations**	**3 (5.8)**	**4 (8.3)**	**7 (7.0)**
	Pathogenic mutations	**14 (26.9)**	**10 (20.8)**	**24 (24.0)**

*All patients were quired to have genetic screening for Lynch syndrome.

Primary endpoint: pCR rate (mITT set)



- In mITT set, pCR was observed in patients with neoadjuvant IBI310 plus sintilimab (40/51) and sintilimab alone (21/45) with significant improved pCR rates (78.4% versus 46.7%, p=0.0015).

* Patient 96 in experimental arm and patient 94 in control arm were found to be pMMR according to postoperative evaluation, and were considered as major protocol deviation.

Postoperative pathological evaluation

- All patients in both treatment groups had R0 resection. According to postoperative pathological evaluation, 2 patients (3.9%) with IBI310 plus sintilimab and 7 patients (15.9%) with sintilimab alone were stage N+.

	IBI310+sintilimab (N=51)	sintilimab (N=45)
Residual tumor classification, n (%)		
Complete resection (R0)	51 (100)	45 (100)
Postoperative pathological evaluation, n (%)		
T0N0	40 (78.4)	21 (46.7)
TisN0	1 (2.0)	0
T1-T3N0	6 (11.8)	17(37.8)
T4N0	2 (3.9)	0
TisN1/T0-T3N1	2 (3.9)	7 (15.6)
T4N1-N2/TanyN2	0	0

Overview of adverse events

- IBI310 plus sintilimab did not increase safety risk compared to sintilimab alone.

	IBI310+sintilimab (n=52)		Sintilimab (n=49)	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Treatment-emergent adverse event (TEAE)	48 (92.3)	14 (26.9)	40 (81.6)	9 (18.4)
Treatment-related adverse event (TRAE)	35 (67.3)	3 (5.8)	23 (46.9)	5 (10.2)
Treatment-related serious adverse event (TRSAE)	4 (7.7)	3 (5.8)	3 (6.1)	2 (4.1)
TRAE leading to treatment interruption	1 (1.9)	0	2 (4.1)	2 (4.1)
TRAE leading to treatment discontinuation**	0	0	1 (2.0)	1 (2.0)
TRAE leading to death**	0	0	1 (2.0)	1 (2.0)
TRAE leading to surgery delay*	2 (3.8)	0	0	0
TRAE leading to surgery cancellation**	0	0	1 (2.0)	1 (2.0)
irAE	25 (48.1)	3 (5.8)	19 (38.8)	4 (8.2)

* 2 patients with IBI310 plus sintilimab had TRAE leading to delayed surgery due to hypothyroidism (grade 2, delayed 2 days) and thyroiditis (grade 1, delayed 13 days).

** 1 patient with sintilimab alone had immune-mediated myocarditis (grade 5).

Adjuvant treatments

- After surgery, 19 (37.3%) patients in IBI310 plus sintilimab group and 20 (44.4%) patients in sintilimab group (mITT set) had adjuvant treatments.

- With median follow-up of 5.65 months, no patient had disease recurrence.

■ **Table 1. Use of adjuvant treatments by postoperative pathological evaluation**

mITT set	**IBI310+sintilimab (N=51)**	**sintilimab (N=45)**
pT0N0	12/40 (15%)	8/21 (38%)
pTis-T3N0	3/7 (43%)	7/17 (41%)
pT4N0	2/2 (100%)	0
pT0-T4N+	2/2 (100%)	5/7 (71%)*

*1 patient refused adjuvant treatment due to economic reason. 1 patient was pT0N1a.

■ **Table 2. Adjuvant treatments in different groups**

mITT set	PD-1 inhibitors	PD-1 inhibitors + chemotherapy	chemotherapy	Unknown	Total
IBI310+sintilimab (N=51)	14	1	4	0	19 (37.3%)
sintilimab (N=45)	17	0	2	1	20 (44.4%)

Conclusions

- The first randomized study report unprecedented efficacy of neoadjuvant dual inhibition of PD-1 and CTLA-4 in MSI-H/dMMR colon cancer:
  - ***pCR 80.0% with IBI310+sintilimab versus 47.7% with sintilimab alone, p=0.0007 (PP set).***
  - ***Among patients underwent surgery, all patients had R0 resection and no patient had disease recurrence as of the cutoff date.***
- Safety profiles were comparable and manageable in both treatment groups.
  - ***Compared to sintilimab alone, no risk of surgery delay or cancellation was observed with IBI310 plus sintilimab.***
- A randomized, controlled, phase 3 study (Neoshot, NCT05890742) of neoadjuvant IBI310 plus sintilimab for resectable MSI-H/dMMR colon cancer is ongoing in China.

Summary - Neoadjuvant IO + CTLA4 – Abstract 3505

Strengths:

- **Randomized study on IO +/- CTLA4 antibody**
- **Met Primary endpoint**
- **Able to compare pCR rates prospectively w/CTLA4 antibody + IO 74% vs 49% w/IO alone**

Limitations:

- **Small sample size (plan to expand to 70 patients)**
- **Short follow up of 9.7 mo (plan is for 3-year RFS)**
- **No correlatives described in the presentation**

Take-home points LBA 3504 & Abstract 3505…..

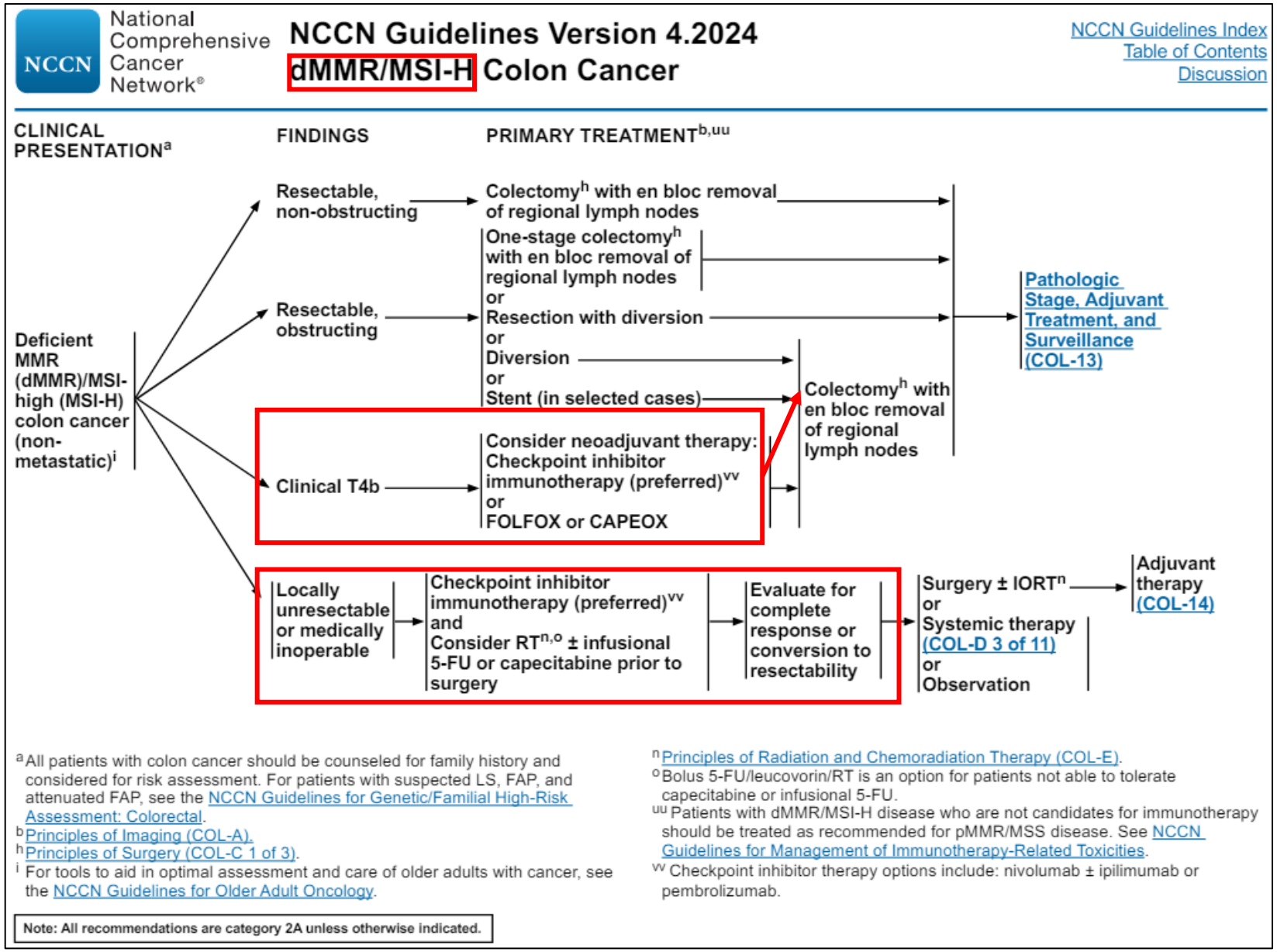
Clinically Relevant? YES, gives us more data on NAIO

Immediately Practice Changing? Currently in NCCN Guidelines

Unanswered questions?
- Is pCR a surrogate for long term cure?
- Is adjuvant treatment necessary if pCR?

Impact on value/cost of care, benefit for patients?
- None, presently
- This does not change standard of care in US to give adjuvant chemo to resected node-positive colon cancers
- Await results of ATOMIC trial for benefit of adjuvant IO

NCCN Guidelines v 4.2024



NCCN Guidelines v 4.2024

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
dMMR/MSI-H Colon Cancer

NCCN Guidelines Index
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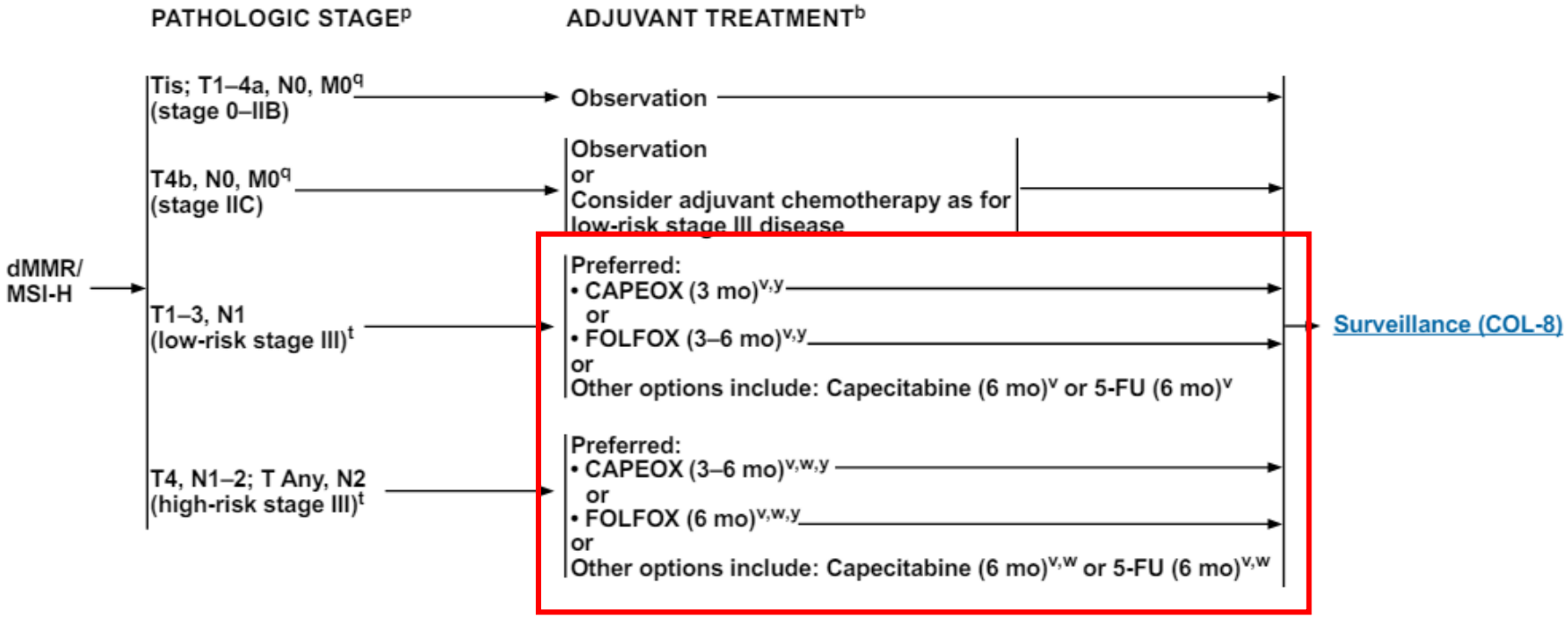
Discussion



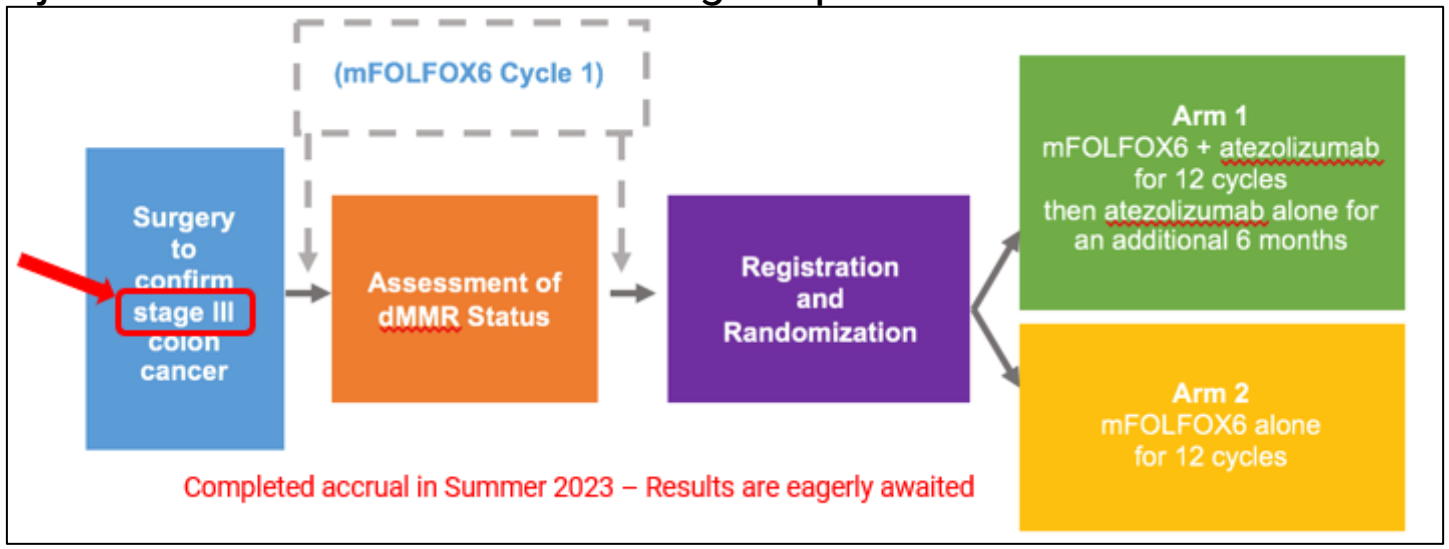
[b] Principles of Imaging (COL-A).
[p] Principles of Pathologic Review (COL-B).
[q] Principles of Risk Assessment for Stage II Disease (COL-F).
[t] While non-inferiority of 3 mo vs. 6 mo of CAPEOX has not been proven, 3 mo of CAPEOX numerically appeared similar to 6 mo of CAPEOX for 5-year overall survival (82.1% vs. 81.2%; HR, 0.96), with considerably less toxicity (Andre T, et al. Lancet Oncol 2020;21:1620-1629). These results support the use of 3 mo of adjuvant CAPEOX over 6 mo in the vast majority of patients with stage III colon cancer. In patients with colon cancer, staged as T1–3, N1 (low-risk stage III), 3 mo of CAPEOX is non-inferior to 6 mo for DFS; non-inferiority of 3 mo vs. 6 mo of FOLFOX has not been proven. In patients with colon cancer staged as T4, N1–2 or T any, N2 (high-risk stage III), 3 mo of FOLFOX is inferior to 6 mo for DFS, whereas non-inferiority of 3 mo vs. 6 mo of CAPEOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 mo vs. 6 mo of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CAPEOX). Grothey A, et al. N Engl J Med 2018;378:1177-1188.

[v] Principles of Adjuvant Therapy (COL-G).
[w] Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation and Chemoradiation Therapy (COL-E).
[y] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged ≥70 years has not been proven.

Note: All recommendations are category 2A unless otherwise indicated.

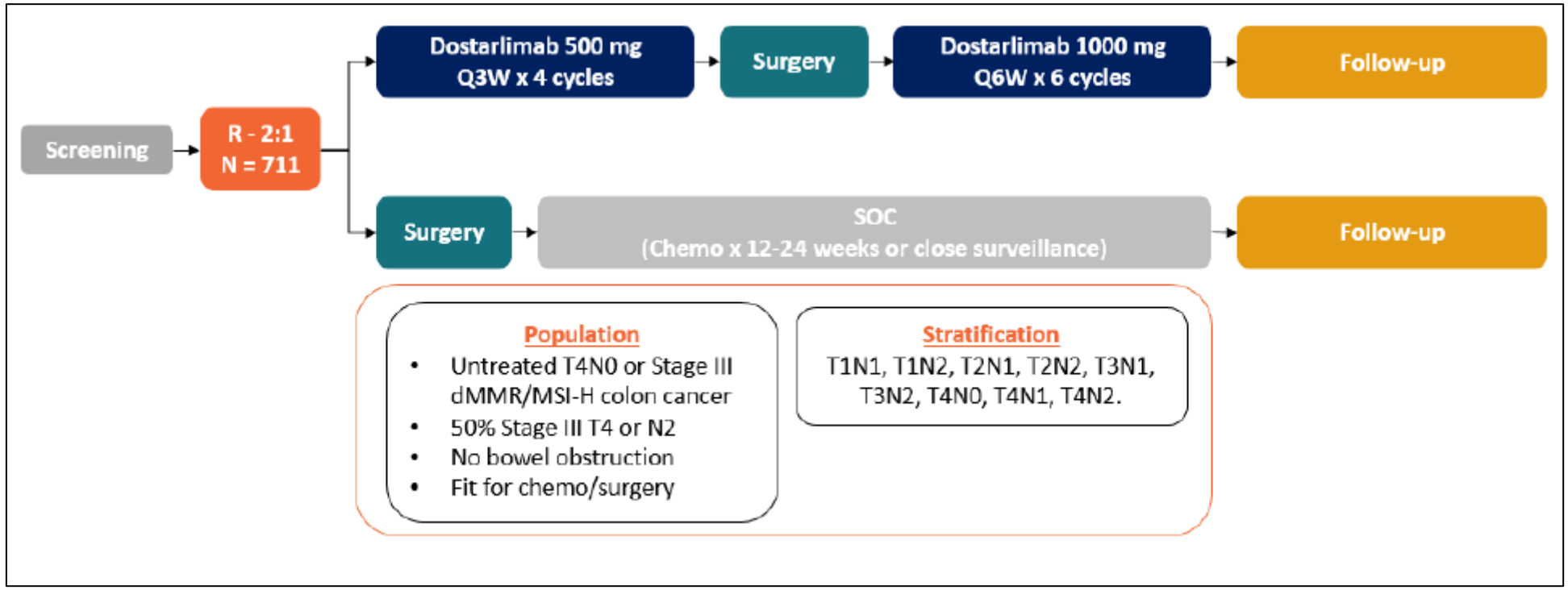
Questions to ask in neoadjuvant treatment of dMMR Colon Cancers...

- IO vs. IO + CTLA4 antibody? Toxicity vs. efficacy vs. long term benefit for cure?
- Do patients with Lynch Syndrome respond better or worse?
- Is adjuvant therapy necessary especially if pCR?
- Is pCR a good surrogate for long term cure?
- What is the optimal length of Neoadjuvant IO therapy?
- Is addition of adjuvant chemo +/- IO benefit Stage III patients? ATOMIC Trial



Is perioperative IO alone better than standard of care?

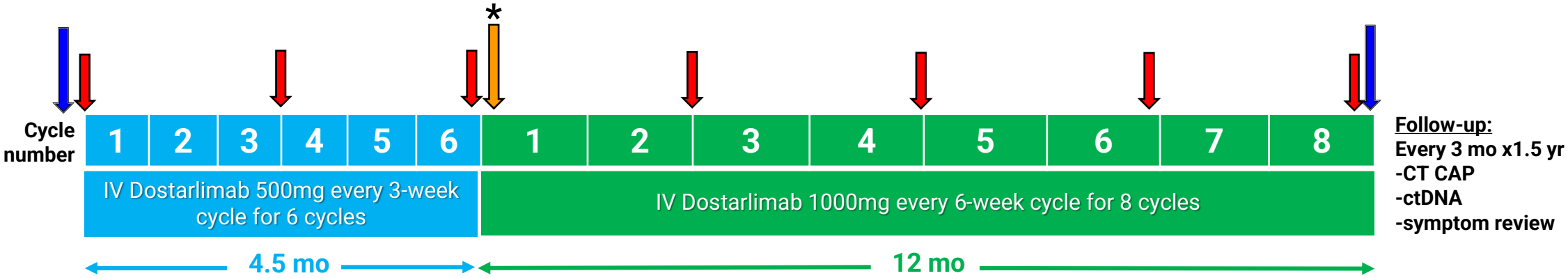
AZUR-2 Trial (all patients get surgery) :A Phase 3, Open-Label, Randomized Study of Perioperative Dostarlimab Monotherapy versus Standard of Care in Participants with Untreated T4N0 or Stage III dMMR/MSI-H Resectable Colon Cancer



https://clinicaltrials.gov/study/NCT05855200

Can some patients avoid surgery after neoadjuvant IO?

Phase II, Single arm study of Neoadjuvant Dostarlimab (IO) in Stage II/III dMMR Colon Ca with <u>non-operative management in responders</u> after 6 cycles* of IO



ctDNA and CT CAP

Colonoscopy – Research*

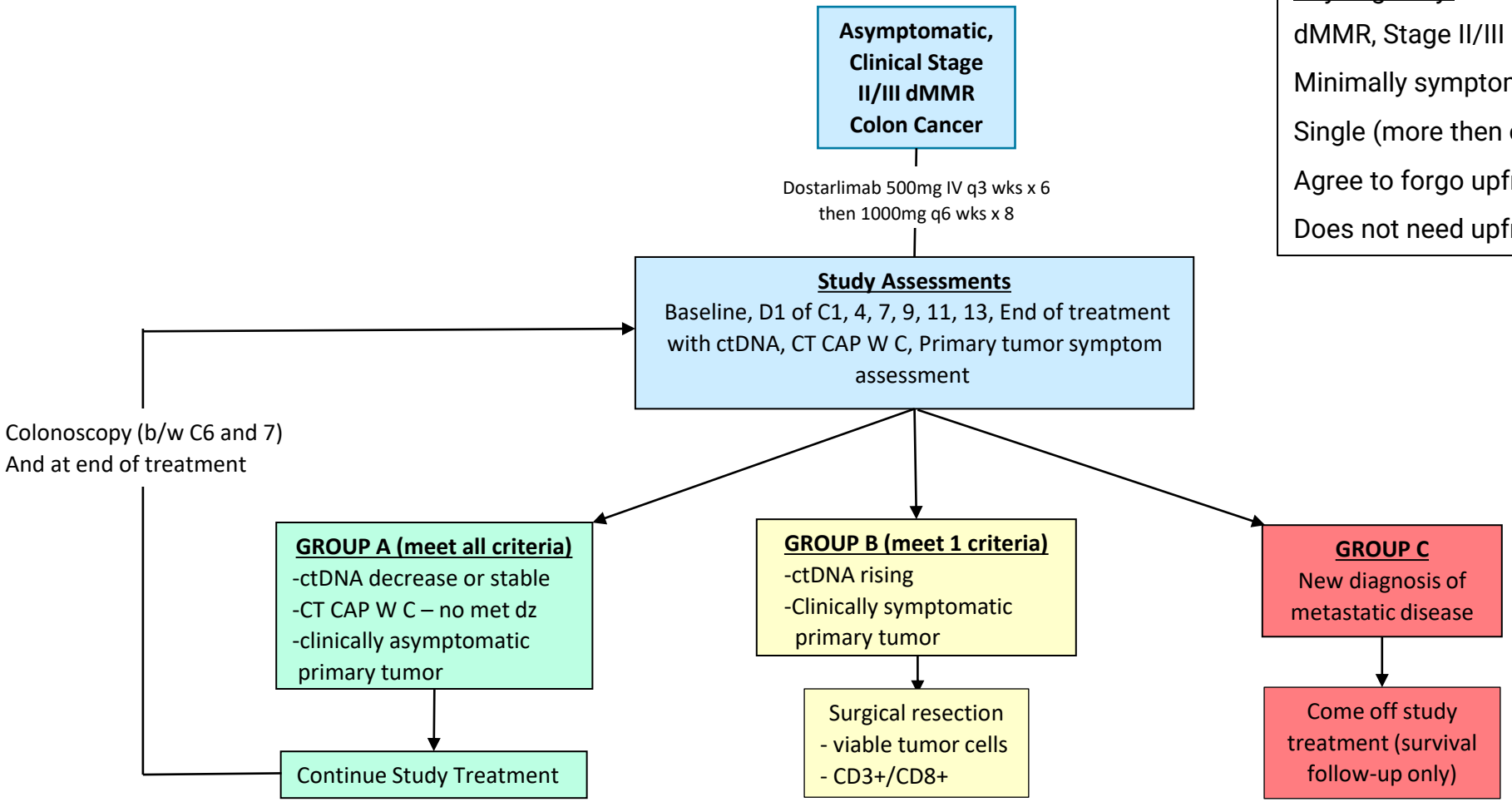
Colonoscopy – Standard of care (SOC)

<u>Key Eligibility:</u>

- Stage II/III dMMR Colon Cancer
- Minimal symptoms
- Fit for surgery per colorectal surgeon
- Single primary
- Agreeable to forgo upfront surgery
- <u>NO</u> cT4 tumors

University of Iowa Holden Comprehensive Cancer Center
https://classic.clinicaltrials.gov/ct2/show/NCT05239546
PI – Saima Sharif, MD MS
Sample size - 25

Phase II, Single Arm Study of Neoadjuvant Dostarlimab (TSR-042) in Stage II/III Deficient Mismatch Repair (dMMR) Colon Cancers



Key Eligibility:

dMMR, Stage II/III Colon Adenocarcinoma

Minimally symptomatic

Single (more then one primary not allowed)

Agree to forgo upfront surgery

Does not need upfront surgery per colorectal surgeon

Outline of Presentation

- Neoadjuvant Colon Cancer - Stage II/III, dMMR
  - LBA 3504 – NEOPRISM CRC (Phase II, multicenter, stratified by TMB, open-label trial)
  - Abstract 3505 – IO + CTLA4 (Phase Ib, Randomized, open label trial)
  - Summary and Take-home points
- Adjuvant Colon Cancer - Stage II, pMMR & dMMR
  - Abstract 108 – DYNAMIC TRIAL – (Phase 2, multicenter, randomized trial)
  - Summary and Take-home points
- Neoadjuvant Rectal Cancer – Stage II/III, dMMR
  - LBA 3512 – NAIO in Locally Advanced Rectal Cancer (Phase 2, single arm)
  - Summary and Take-home points
- Anal Cancer – Stage I-III
  - Abstract 3513 – HPV DNA Detection after CCRT as prognostic marker (Single arm)
  - Summary and Take-home points

2024 ASCO ANNUAL MEETING

Abstract 108

Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

Overall Survival and Updated 5-Year Results from the Randomized DYNAMIC Trial

Jeanne Tie

Peter MacCallum Cancer Centre and Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia

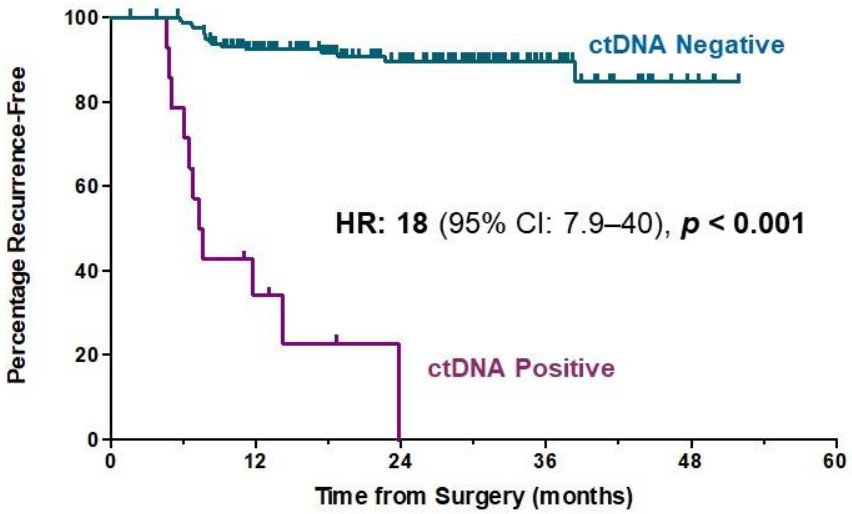
On behalf of the DYNAMIC Investigators

Yuxuan Wang, Serigne Lo, Kamel Lahouel, Joshua Cohen, Rachel Wong, Jeremy Shapiro, Samuel Harris, Adnan Khattak, Matthew Burge, Margaret Lee, Marion Harris, Sue-Anne McLachlan, Sumitra Ananda, Craig Underhill, Nickolas Papadopoulos, Cristian Tomasetti, Kenneth Kinzler, Bert Vogelstein, Peter Gibbs

Recurrence Risk Prediction for Stage II CC Needs Improvement

- **Optimal management of stage II CC continues to be debated**
  - Surgery alone cures > 80%
  - No clear overall survival benefit in adjuvant trials, even with oxaliplatin doublet in high-risk patients[1-5]
  - More precise recurrence risk prediction is required to better inform treatment selection
- **Post-op ctDNA MRD detection → highly prognostic**

Stage II: Not Treated with Adjuvant Chemo[6]



Could a ctDNA-informed approach to adjuvant therapy selection in stage II colon cancer reduce chemotherapy use without compromising survival outcomes?

1. Figueredo et al. Cochrane Database Syst Rev 2008:Cd005390 2. Andre et al. J Clin Oncol 2015;33:4176-87, 3. Bockelman et al. Acta Oncol 2015;54:5-16, 4.Tournigand et al. J Clin Oncol 30:3353-3360, 5. Yothers et al. J Clin Oncol 29:3768-3774, 6. Tie et al. Sci Transl Med. 2016 Jul 6;8(346):346ra92

DYNAMIC Study Design

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

Tumor-Informed ctDNA Analysis

(Targeted CRC panel)

(N = 455)

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

Follow-Up

Until recurrence

- CEA: 3-monthly for 24M, then 6-monthly to 5 years
- CT C/A/P: 6-monthly for 24M, then at 36M

Post-recurrence

- Survival: 6-monthly to 5 years

2022

Endpoints

Primary: RFS at 2 years (non-inferiority margin 8.5%)	**Secondary:** RFS by ctDNA status, EoT ctDNA clearance
Key secondary: Proportion receiving adjuvant chemo, OS	**Exploratory:** Post-op ctDNA levels

2024

PRESENTED BY: Jeanne Tie, MBChB FRACP MD

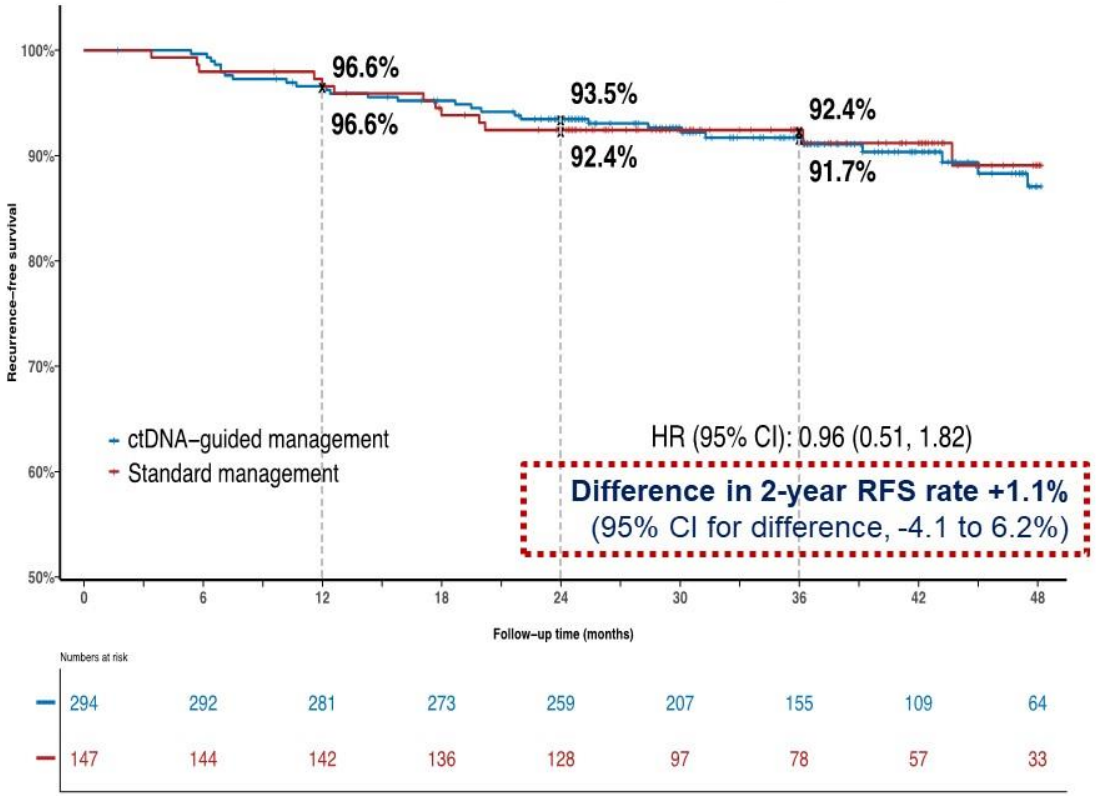
ctDNA-Guided Adjuvant Treatment in Stage II Colon Cancer

NEJM, June 2022

Treatment delivery: ctDNA-guided approach significantly reduced chemotherapy use

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent FP	17/45 **(38%)**	37/41 **(90%)**	<.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318

Primary RFS analysis: ctDNA-guided approach non-inferior to standard management



PRESENTED BY: Jeanne Tie, MBChB FRACP MD

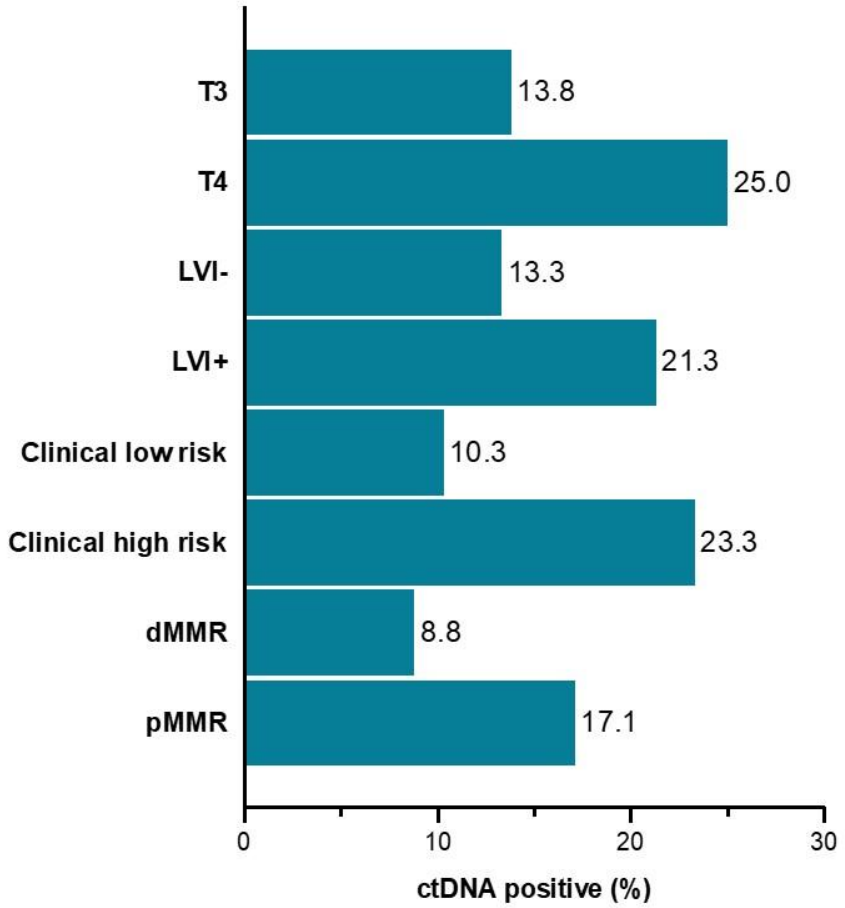
Baseline Characteristics

Characteristics	ctDNA-Guided Management N = 294, N (%)	Standard Management N = 147, N (%)
Age, median (range), yrs	65 (30 , 94)	62 (28 , 84)
Sex, Male	154 (52)	81 (55)
ECOG, 0	226 (77)	124 (84)
Tumor stage, T3	250 (85)	127 (86)
Lymph node yield, < 12	13 (4)	7 (5)
Lymphovascular invasion, present	82 (28)	38 (26)
MMR, deficient	59 (20)	27 (18)
Clinical risk group, high*	116 (40)	60 (41)

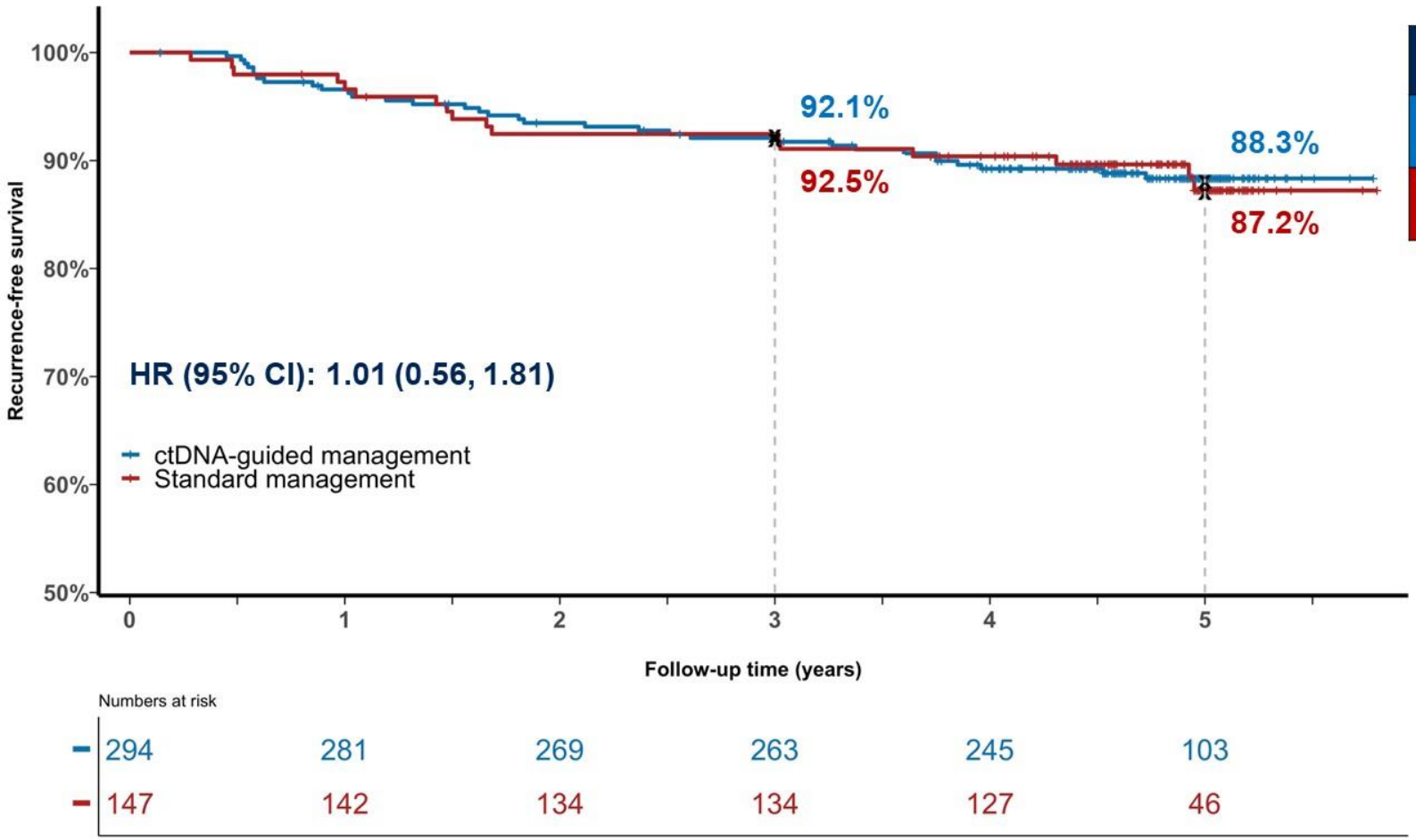
*High clinical risk = proficient MMR + ≥1 high-risk feature (T4, poor tumor differentiation, <12 lymph node yield, LVI, tumor perforation and/or bowel obstruction)

Post-op ctDNA Detection

(ctDNA-Guided Arm)



Updated 5-Year RFS Analysis



5-Year RFS Rate, %	
ctDNA	88.3
SoC	87.2

Difference in 5-year RFS rate +1.1%
(95% CI for difference, -5.8 to 8.0%)

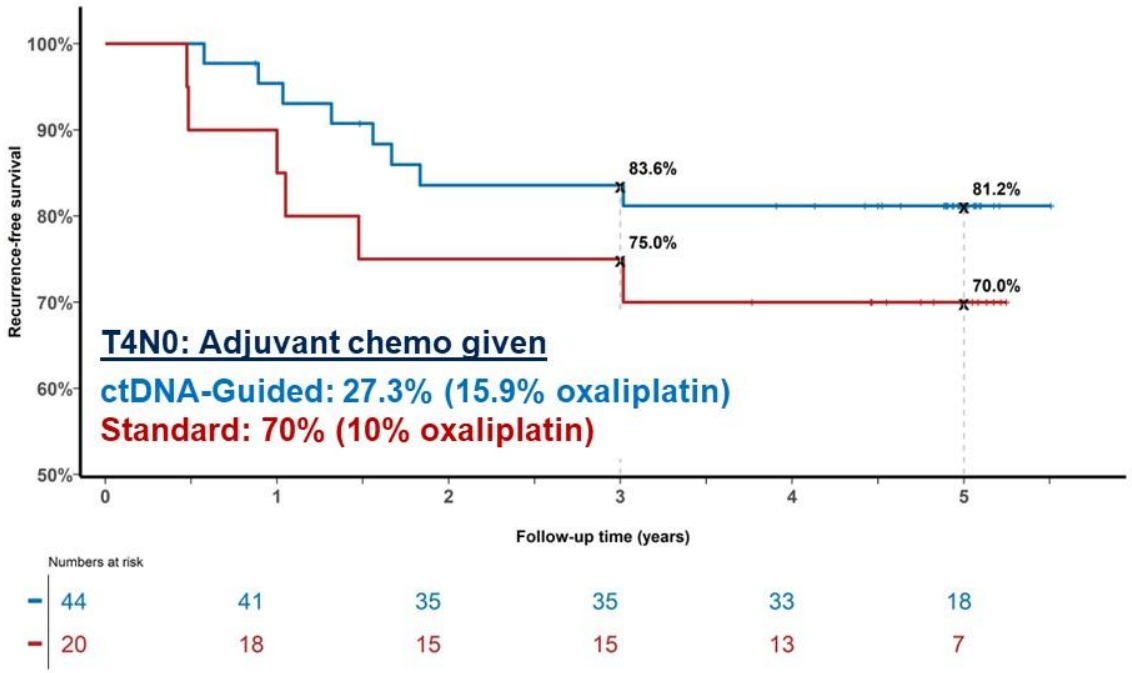
Median Follow-Up
ctDNA-Guided 59.7 months
SoC 59.7 months
(IQR 55.0 – 61.5)

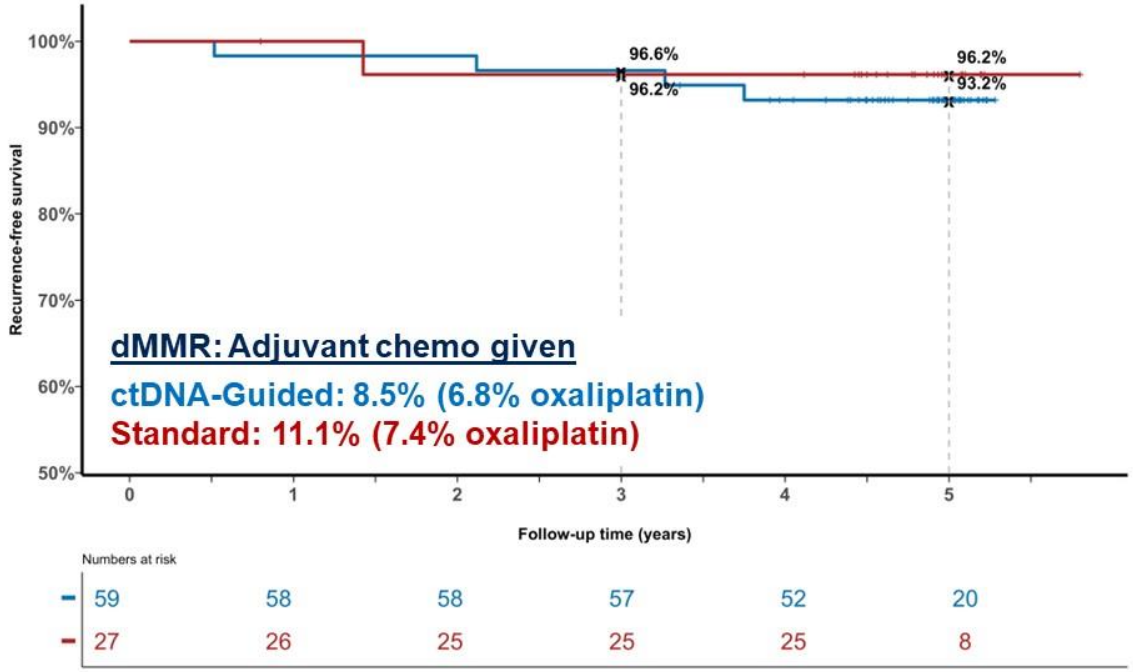
Data cut-off: 17 Jan 2024

RFS by Subgroup: T4N0 and dMMR

T4N0 5-Year RFS Rate, %		Recurrence, N (%)	Death w/o recur, N (%)
ctDNA (N = 44)	**81.2**	7 (15.9)	1 (2.3)
SoC (N = 20)	**70.0**	6 (30.0)	0 (0)
HR (95% CI): 1.79 (0.62, 5.15), p = 0.275			

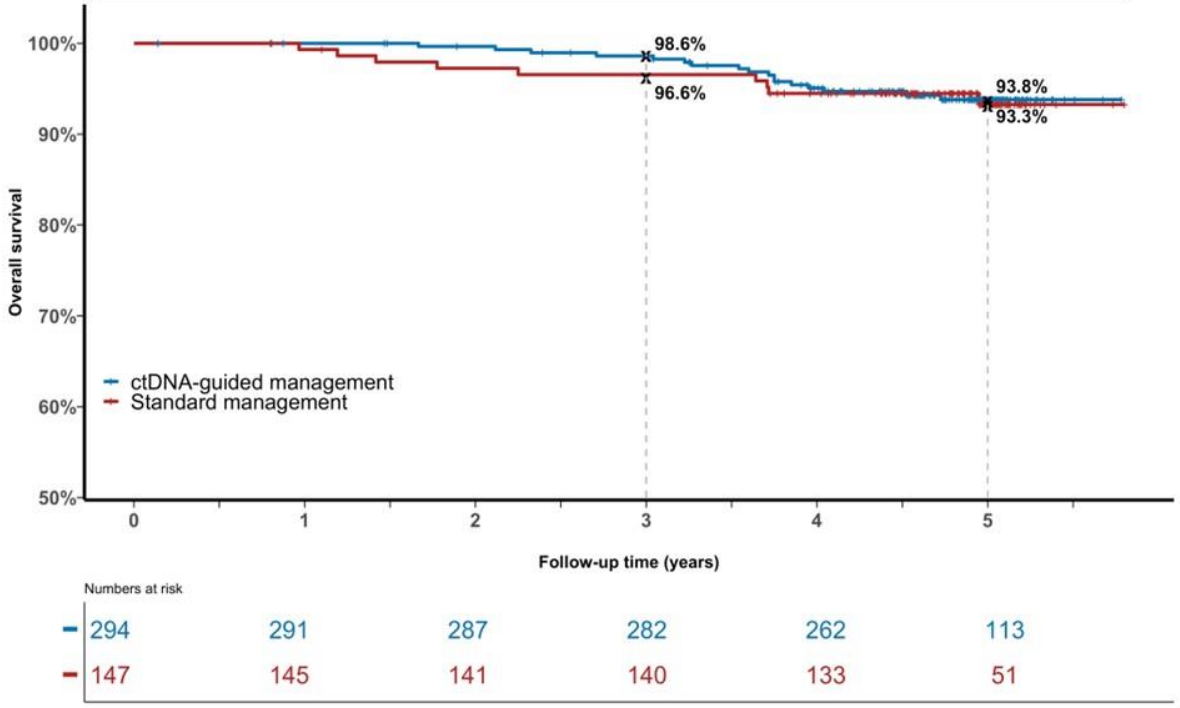
dMMR 5-Year RFS Rate, %		Recurrence, N (%)	Death w/o recur, N (%)
ctDNA (N = 59)	**93.2**	1 (1.7)	3 (5.1)
SoC (N = 27)	**96.2**	1 (3.7)	0 (0)
HR (95% CI): 0.48 (0.05, 4.27), p = 0.512			



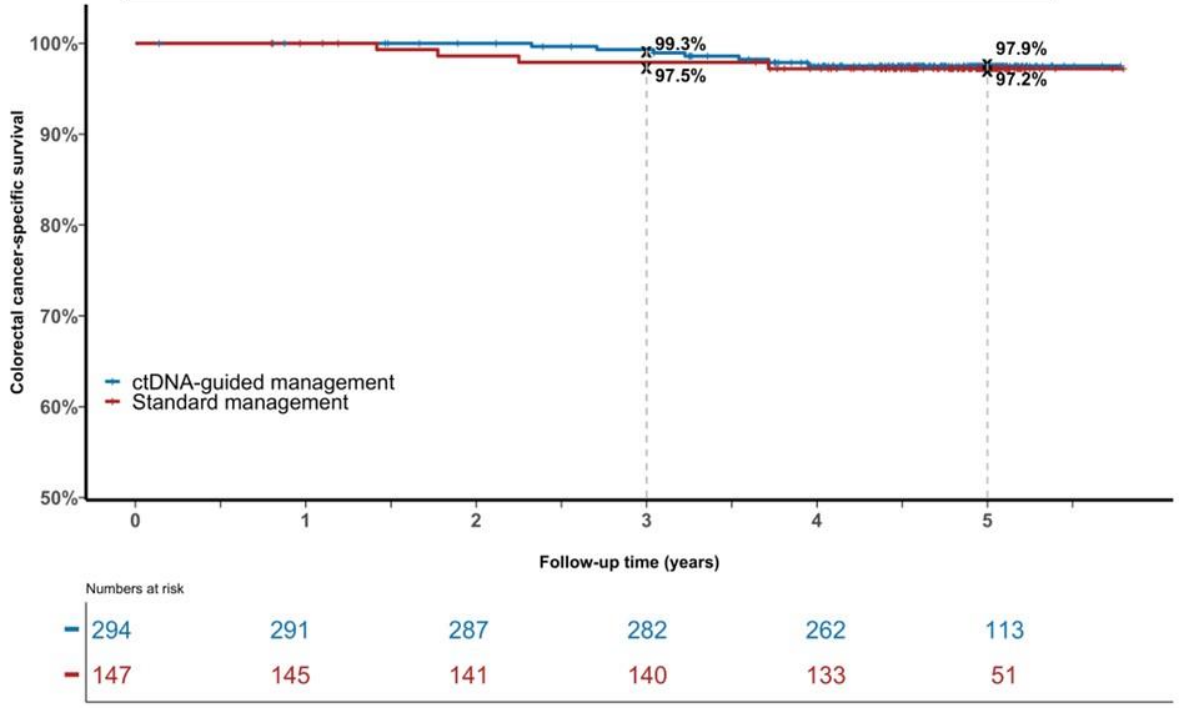


Overall Survival

5-Year OS Rate, %		CRC deaths, N	Non-CRC deaths, N
ctDNA (N = 294)	**93.8**	7	10
SoC (N = 147)	**93.3**	4	5
HR (95% CI): 1.05 (0.47, 2.37), p = 0.887			

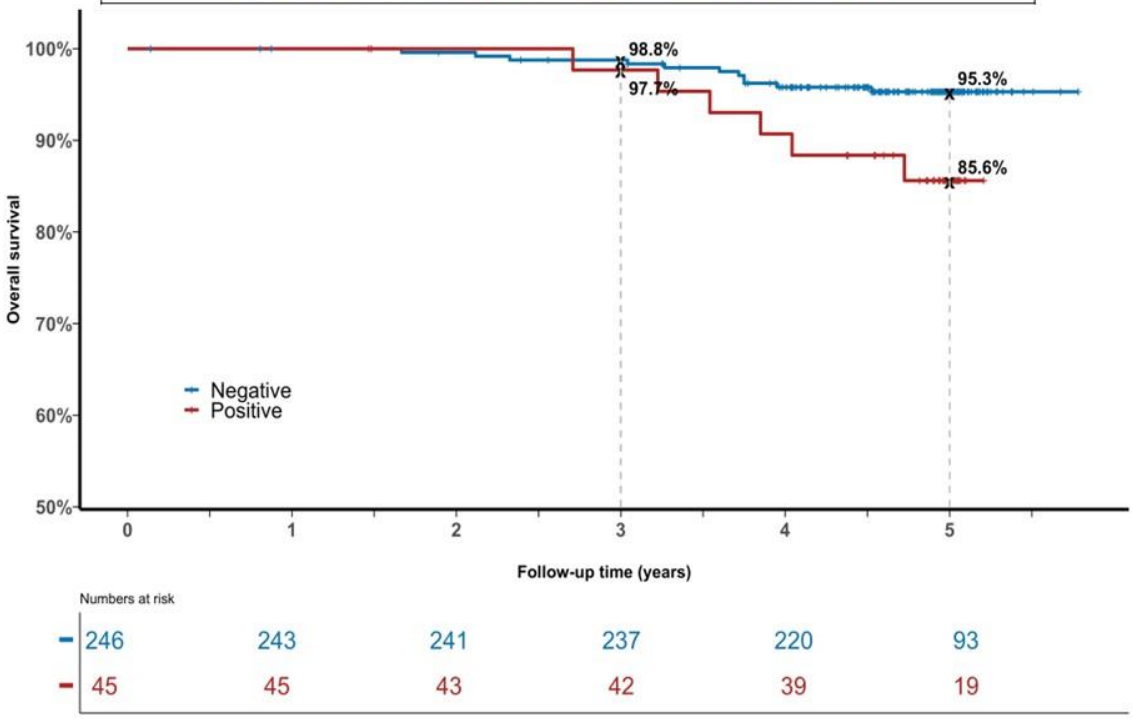


5-Year Disease-Specific Survival Rate, %	
ctDNA (N = 294)	**97.9**
SoC (N = 147)	**97.2**
HR (95% CI): 1.19 (0.35, 4.09), p = 0.792	

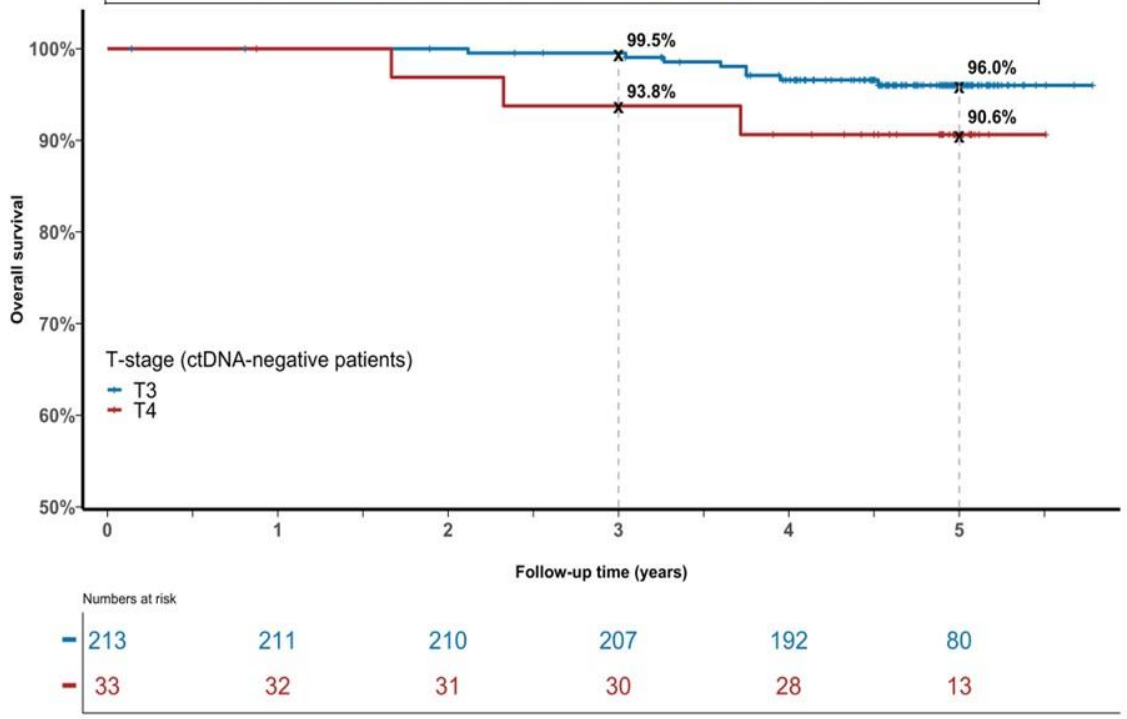


Overall Survival in ctDNA-Guided Arm

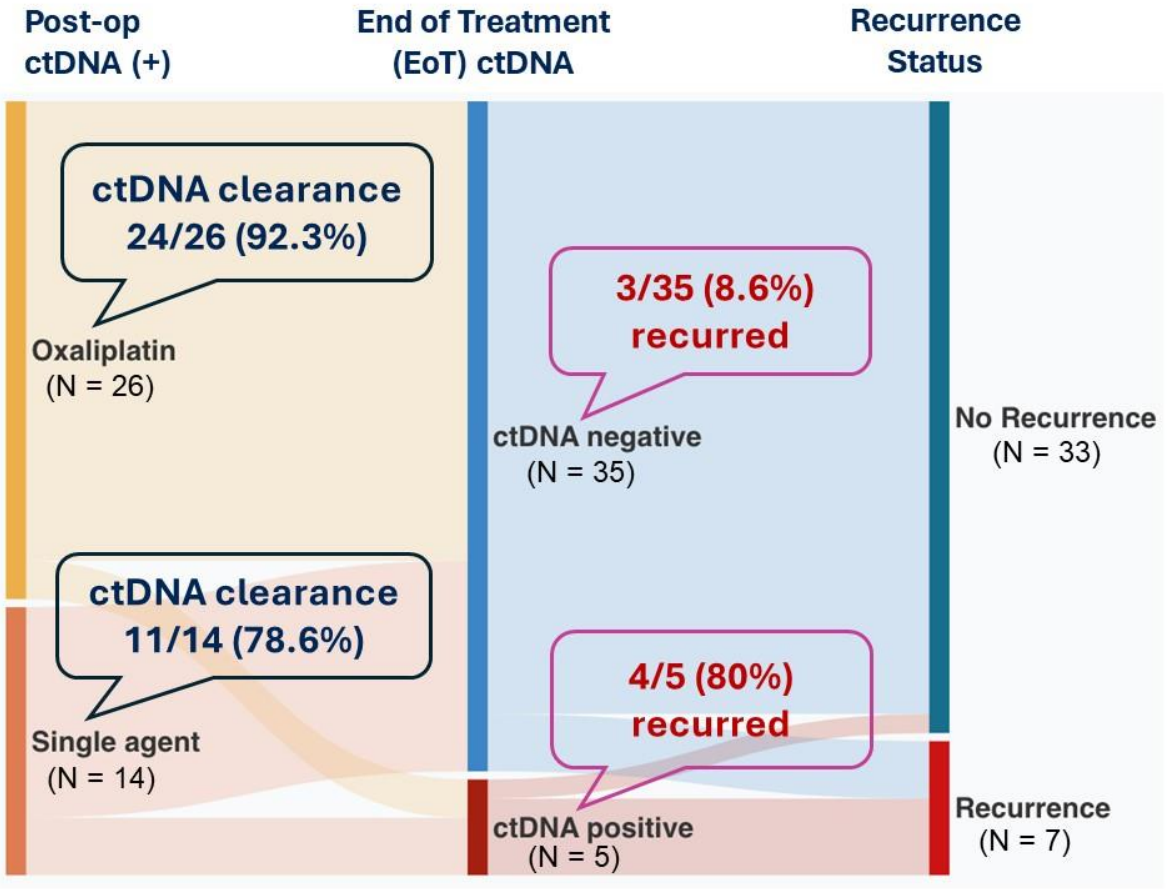
5-Year OS Rate, %	
ctDNA-Neg (N = 246)	95.3
ctDNA-Pos (N = 45)	85.6
HR (95% CI): 3.30 (1.20, 9.05), p = 0.014	

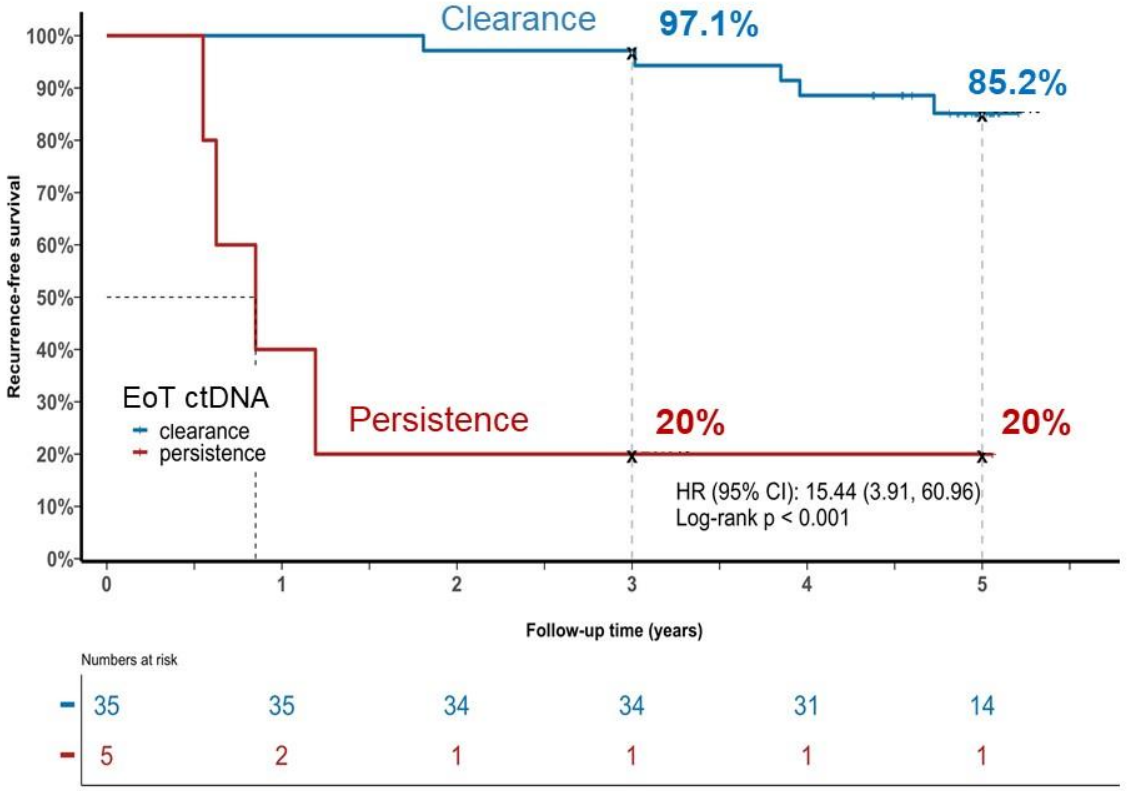


5-Year OS Rate, %	
T3 ctDNA-Neg (N = 213)	96.0
T4 ctDNA-Neg (N = 33)	90.6
HR (95% CI): 2.45 (0.58, 9.25), p = 0.171	



Post-op ctDNA Positive: EoT ctDNA Clearance and RFS

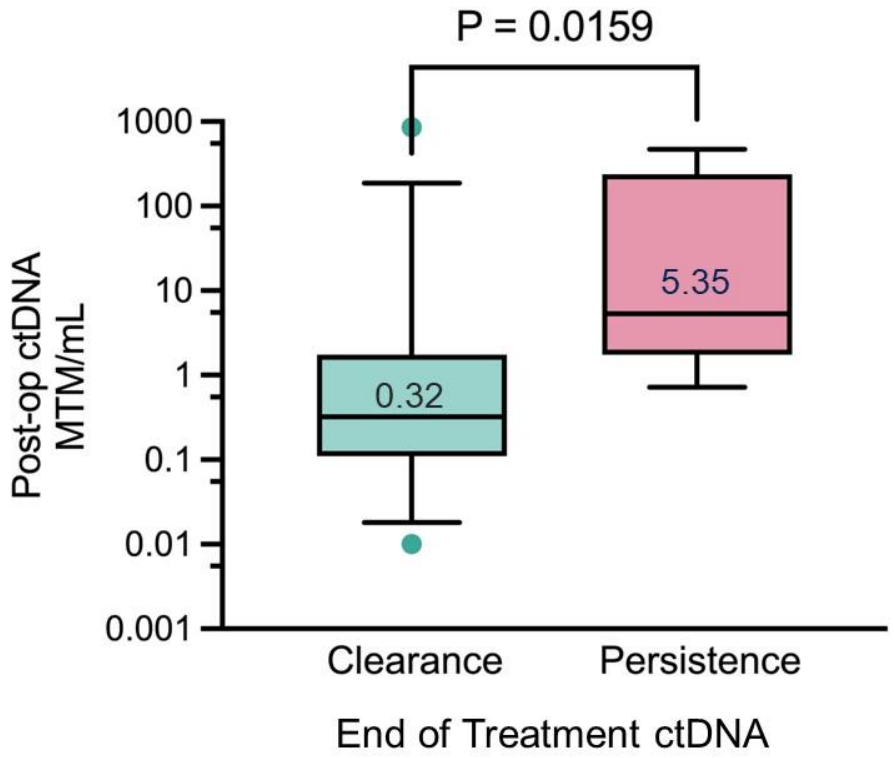


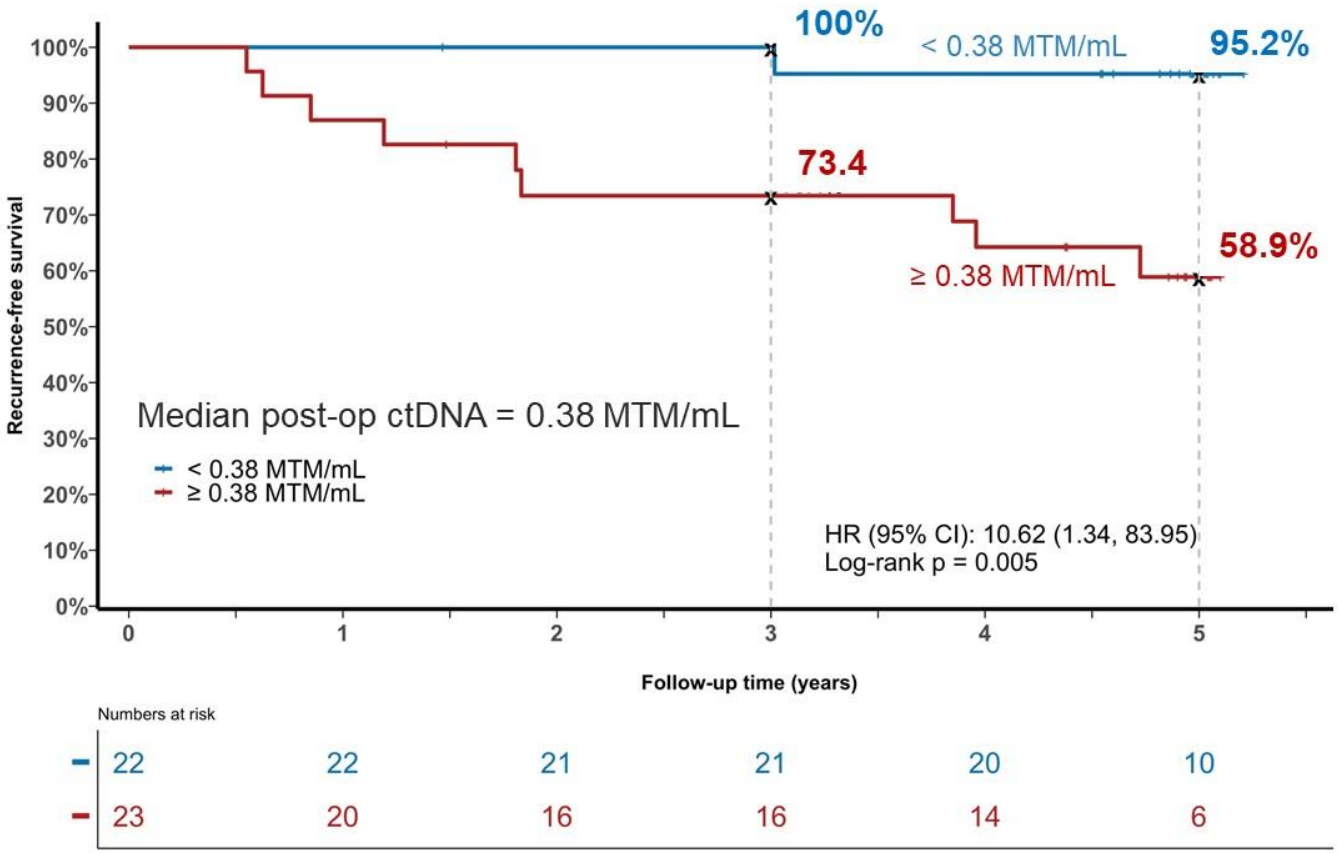


EoT = 4 weeks post chemo

PRESENTED BY: Jeanne Tie, MBChB FRACP MD

Post-op ctDNA Molecular Burden, Clearance and RFS

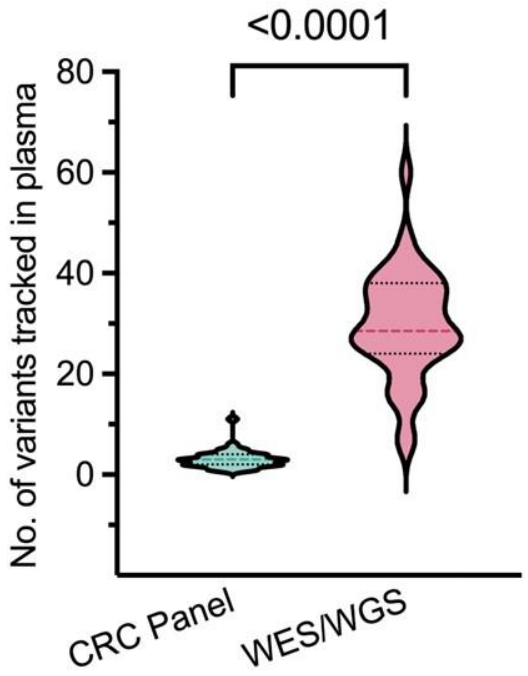




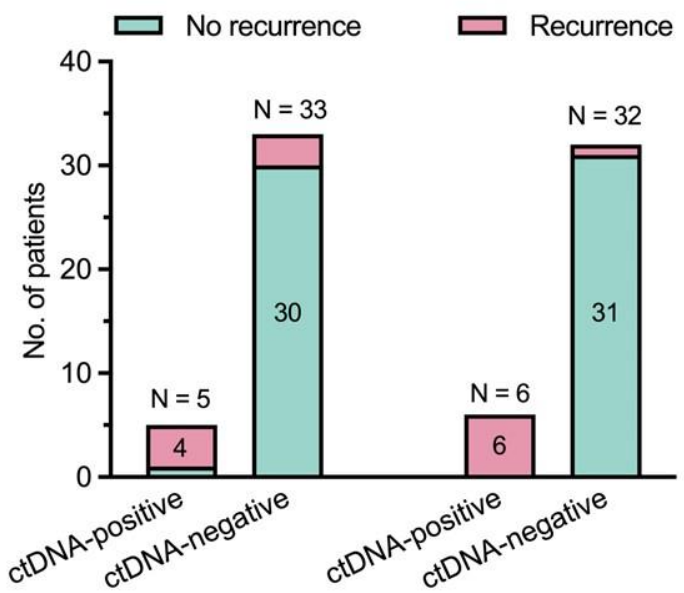
MTM = mean tumor molecule

Tracking More Variants Identified in Tumor Improves Testing for MRD

EoT plasma samples (N = 38 with residual samples)

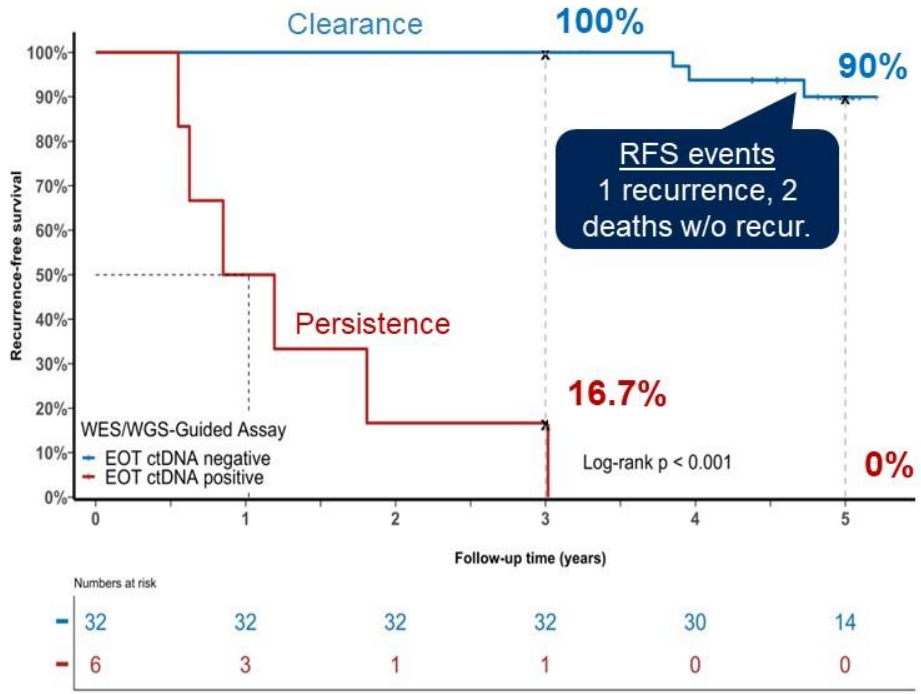


# Variants	CRC panel	WES*
Median (IQR)	**3** (2, 4)	**29** (24, 38)



CRC Panel	WES-Informed
Sensitivity 57.1% **Specificity 96.8%** **PPV 80.0%** **NPV 90.9%**	**Sensitivity 85.7%** **Specificity 100%** **PPV 100%** **NPV 96.9%**

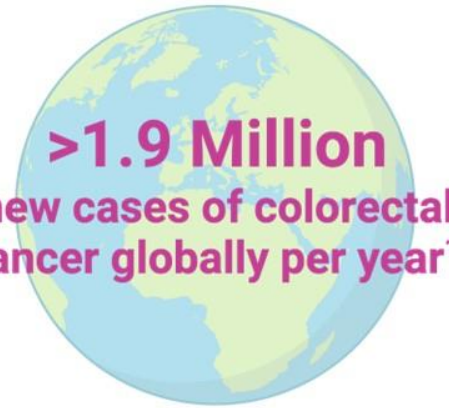
RFS by EoT ctDNA (WES-Informed assay)



**WGS (whole genome sequencing) in 3 patients due to low no. of suitable variants by WES (whole exome sequencing)*

DYNAMIC Trial 5-year Update: Summary and Impact

In stage II CC, post-op ctDNA analysis informs patient selection for adjuvant treatment



>1.9 Million
new cases of colorectal cancer globally per year[1]

~ 25% of patients have stage II disease[2,3]

~ 500,000 patients with stage II colon cancer (CC)

- A ctDNA-guided approach (treating only patients with a positive ctDNA after surgery) compared to standard-of-care treatment selection reduced the use of adjuvant chemotherapy without compromising 5-year RFS
- Excellent survival rates were achieved with a ctDNA-informed approach, including a 5-year OS rate of 90.6% in untreated, ctDNA-negative T4 tumors
- ctDNA clearance was achieved with adjuvant chemotherapy in a very high proportion of ctDNA-positive patients (87.5%), and was associated with a favorable outcome (5-year RFS 85% vs 20% in patients without ctDNA clearance)

1. Globocan 2022, available at https://gco.iarc.who.int/en, 2. National Cancer Control Indicators 2018, available at https://ncci.canceraustralia.gov.au/diagnosis/distribution-cancer-stage/distribution-cancer-stage,
3. The Lancet Oncology. 2021 Jul 1;22(7):1002-13.

Conclusions

- More mature follow-up data confirms the initial findings of the DYNAMIC study → a ctDNA-guided approach to adjuvant treatment in stage II colon cancer reduces use of chemotherapy compared to standard-of-care without compromising survival outcomes
- A ctDNA-guided approach achieves excellent survival outcomes, including in patients with T4 disease
- ctDNA clearance can be achieved with adjuvant chemotherapy in a high proportion of post-op ctDNA-positive patients and is associated with favorable outcomes
- There is potential for improved precision of the ctDNA-informed approach (by increasing variant number and incorporating ctDNA molecular burden), but further validation of these preliminary findings is required

Summary - ctDNA-guided Rx in Stage II CC-Abstract 108

Strengths:

- Prospective, Randomized study
- Addresses questions of high clinical need like T4 and clinicopathological high and low risk patients
- RFS met 5-yr non-inferiority endpoint
- No difference in 5-yr OS in ctDNA guided arm vs SoC arm
- ctDNA numerical value cut-off is important for clearance and relapse risk

Limitations:

- Variation in chemotherapy given can add bias
- Only 20% dMMR and only 40% clinical high risk
- ctDNA platform used is not commercially available in the US

Take-home points….

Clinically Relevant? YES

Immediately Practice Changing? YES

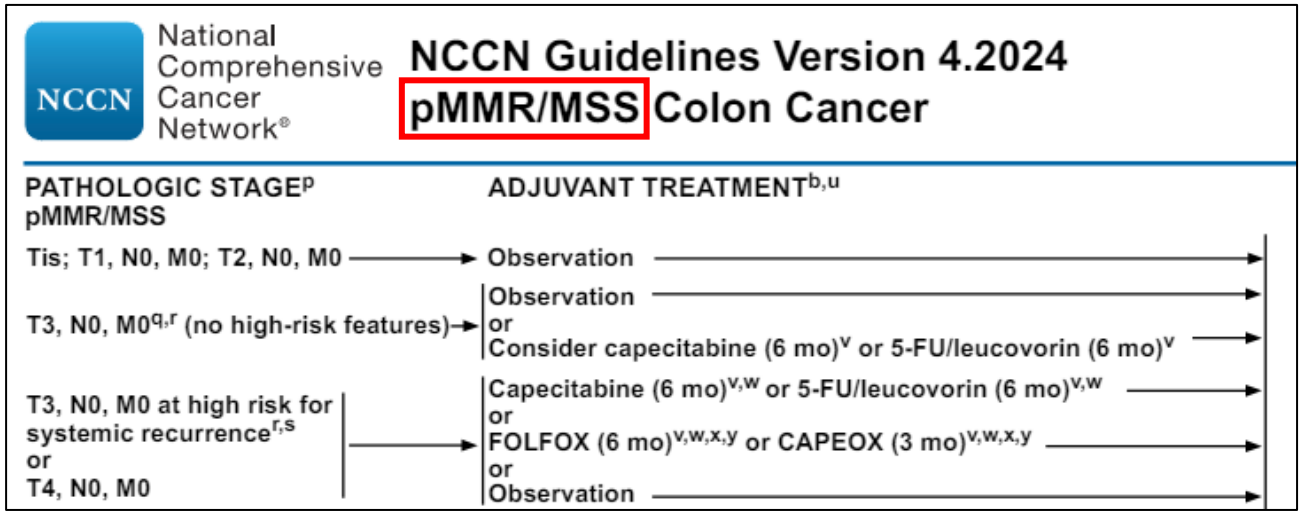
Unanswered questions? Can WES contribute to increasing sensitivity of tumor informed ctDNA Assays

Impact on value/cost of care, benefit for patients?

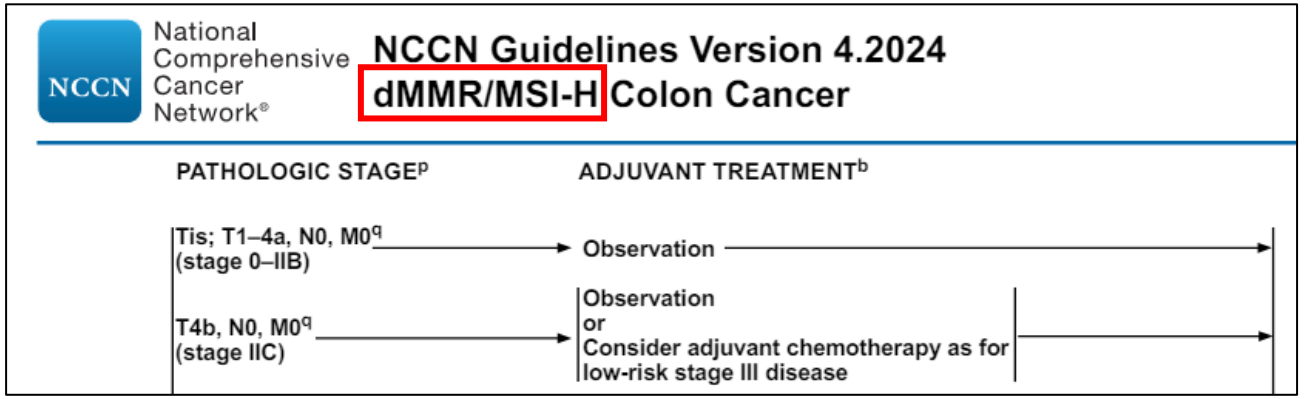
- Value is in selecting only those that will benefit from chemo without compromising RFS and OS in those who will not benefit
- Decrease morbidity to the patient
- Decrease cost to the health care system

Stage II Colon Cancers

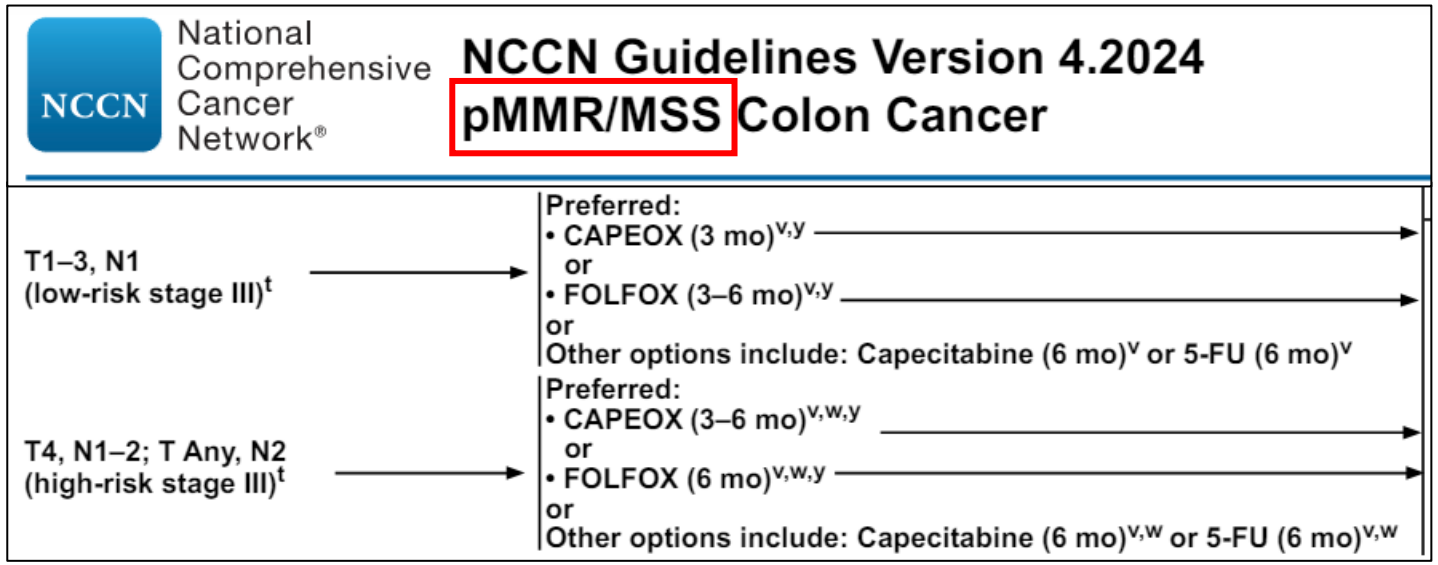
pMMR – Equipoise whether they get chemo or not, a discussion needs to be had with the patient



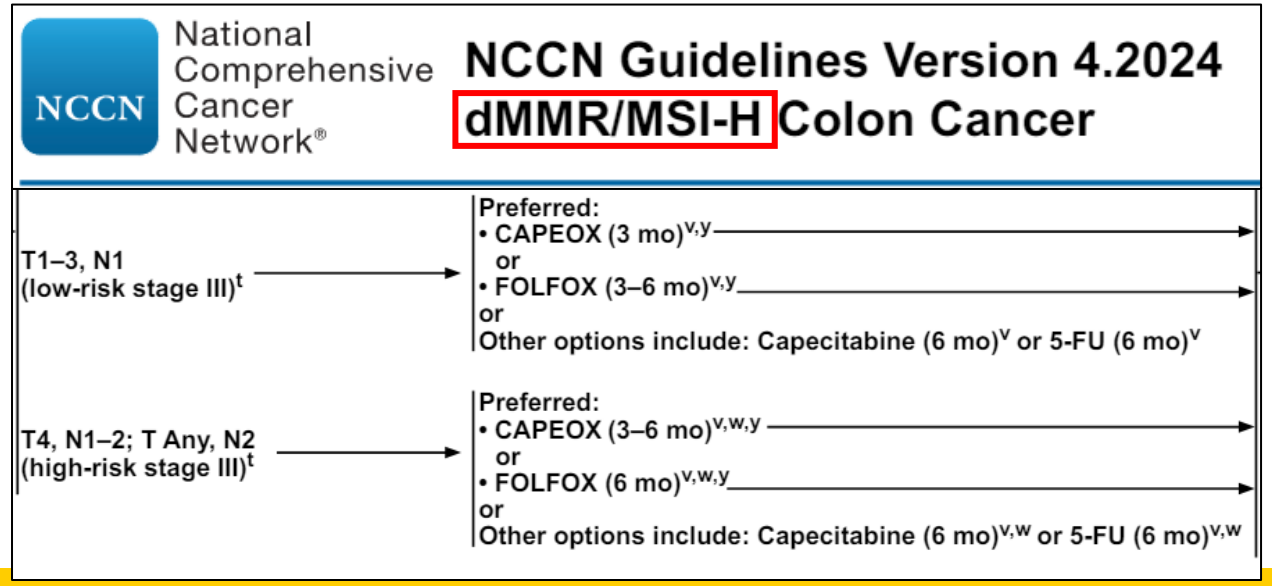
dMMR – Usually do not get chemotherapy unless maybe T4



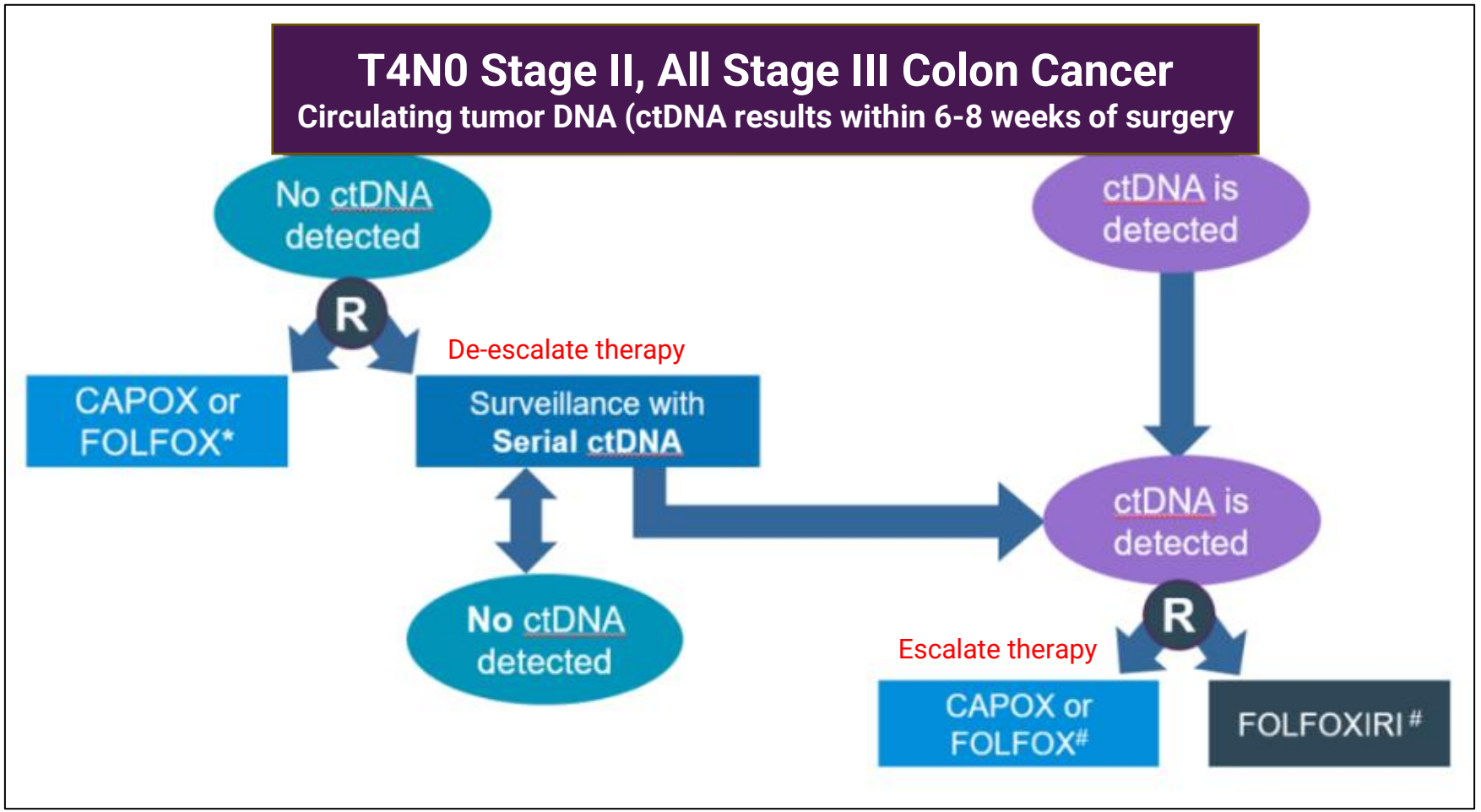
What about Stage III Colon Cancers?



Both pMMR and dMMR are recommended adjuvant chemotherapy



CIRCULATE – USA (Currently enrolling)



Outline of Presentation

- Neoadjuvant Colon Cancer - Stage II/III, dMMR
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  - Abstract 3505 – IO + CTLA4 (Phase Ib, Randomized, open label trial)
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  - Abstract 108 – DYNAMIC TRIAL – (Phase 2, multicenter, randomized trial)
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  - LBA 3512 – NAIO in Locally Advanced Rectal Cancer (Phase 2, single arm)
  - Summary and Take-home points
- Anal Cancer – Stage I-III
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  - Summary and Take-home points

2024 ASCO ANNUAL MEETING

LBA 3512

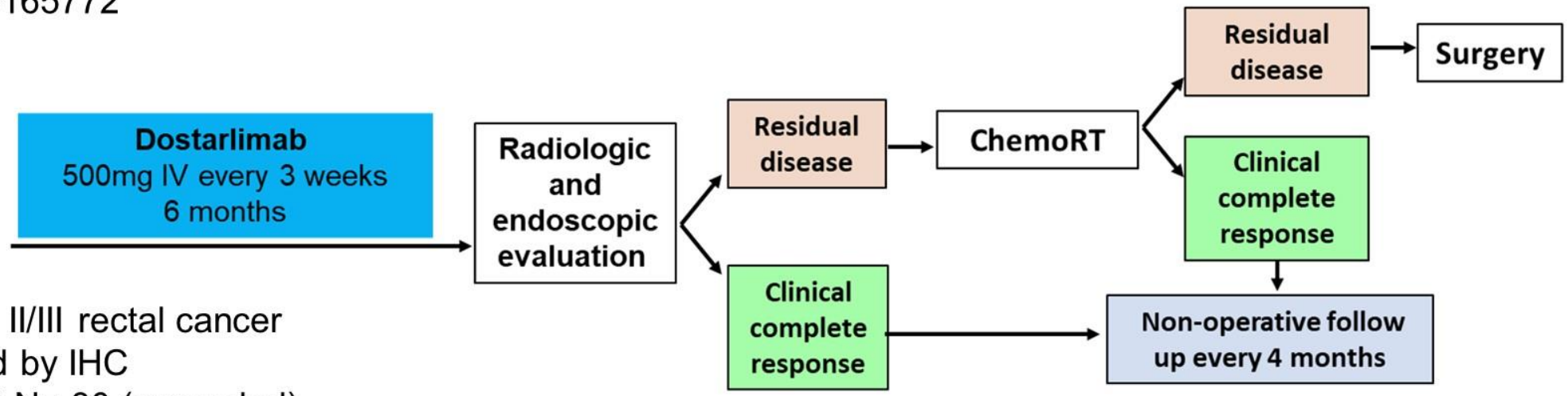
Durable complete responses to PD-1 blockade alone in dMMR locally advanced rectal cancer

Andrea Cercek, M.D. , J. Joshua Smith, M.D., Ph.D. , Jinru Shia, M.D., Michael B. Foote, M.D., Jenna Sinoploi, N.P. Jill Weiss, B.A., Lindsay Temple, B.A., Henry Walch, M.S. , Miteshkumar Patel, M.S., Callahan Wilde, B.S., Leonard B. Saltz, M.D., Melissa Lumish, M.D., Benoit Rousseau, M.D., Ph.D., Guillem Argiles, M.D. , Zsofia Stadler, M.D. , Rona Yaeger, M.D. , Neil Segal, M.D., Philip Paty M.D., Marina Shcherba, M.D., Ryan Sugarman, M.D., Christopher Crane, M.D., Paul B. Romesser, M.D., Avni Desai, M.D., Imane El Dika, M.D., Maria Widmar, M.D., Iris Wei, M.D., Emmanouil Pappou, M.D., Ph.D., Gerard Fumo, M.D., Santiago Aparo, M.D., Mithat Gonen, M.D., Marc Gollub, M.D., Vetri S. Jayaprakasham, M.B.B.S., F.R.C.R., Tae-Hyung Kim, M.D., Julio Garcia Aguilar, M.D., Ph.D., Martin Weiser, M.D., and Luis A. Diaz, Jr., M.D.

Memorial Sloan Kettering Cancer Center
New York, NY

Neoadjuvant PD1 blockade in dMMR locally advanced rectal cancer

NCT04165772



Stage II/III rectal cancer
MMRd by IHC
Target N= 30 (expanded)

Primary Endpoints:

- ORR after completion of PD-1 alone or in combination with chemoRT
- pCR or sustained cCR for 12 mo after completion of PD1 alone or in combination with chemoRT

Sample Collection: ctDNA, biopsy, imaging

Baseline, 6 weeks, 3 mo, 6 mo and q4 mo during NOM

Cercek, et al. NEJM 2022

Initial Results

Primary Objectives

- Overall response rate of PD-1 blockade

Presented initial data June 2022
14 consecutive patients with clinical complete response (cCR) to dostarlimab alone

Clinical trial is ongoing (NCT04165772)

PD-1 blockade incorporated into NCCN guidelines for locally advanced dMMR rectal cancer May 2023

Cercek et al, NEJM 2022; Cercek ASCO 2022; NCCN guidelines 2024

Study Objectives

Primary Objectives

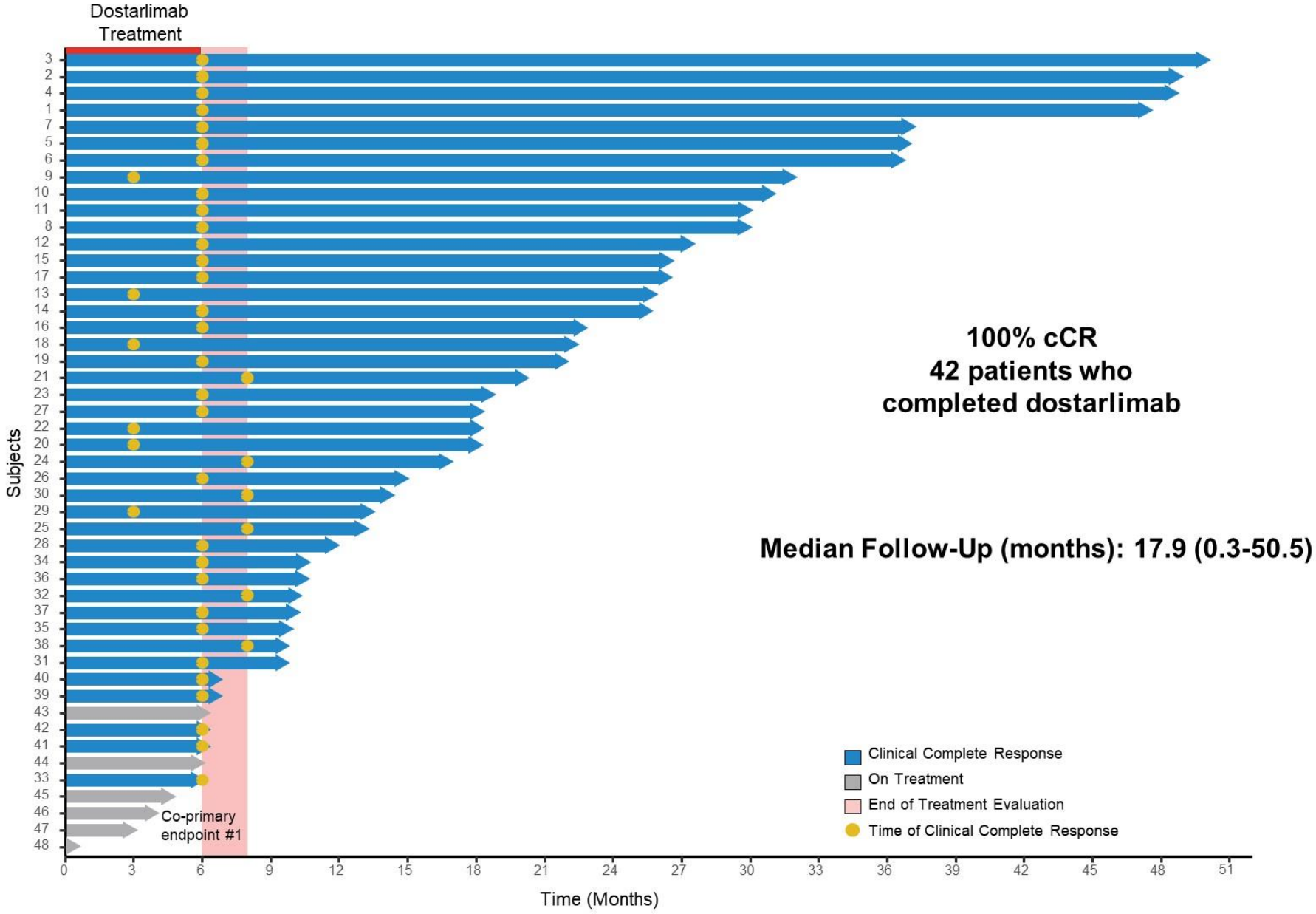
- Overall response rate of PD-1 blockade with or without chemoradiation
- Clinical complete response (cCR) rate at 12 months after PD-1 blockade

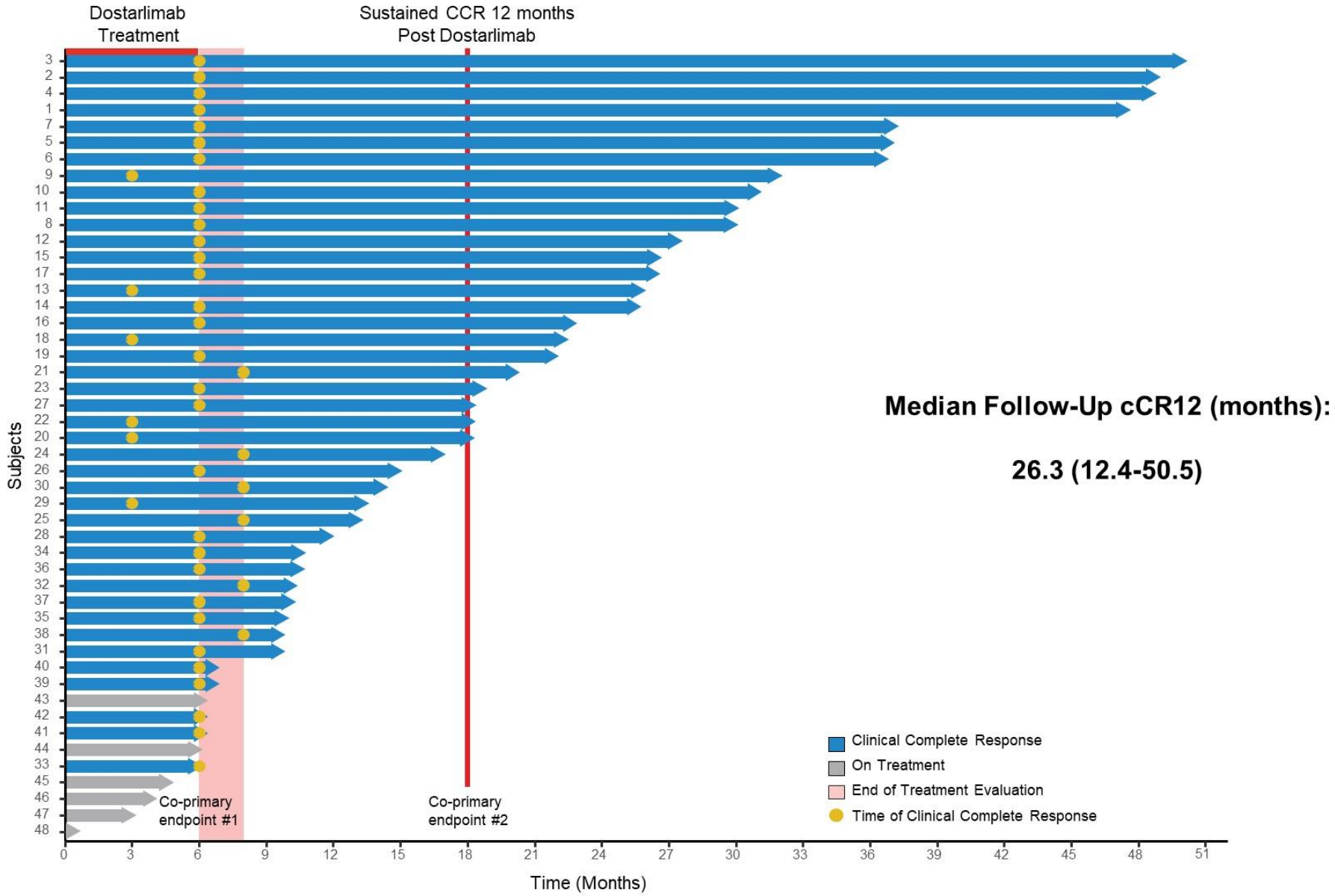
Secondary Objective

- Safety and tolerability

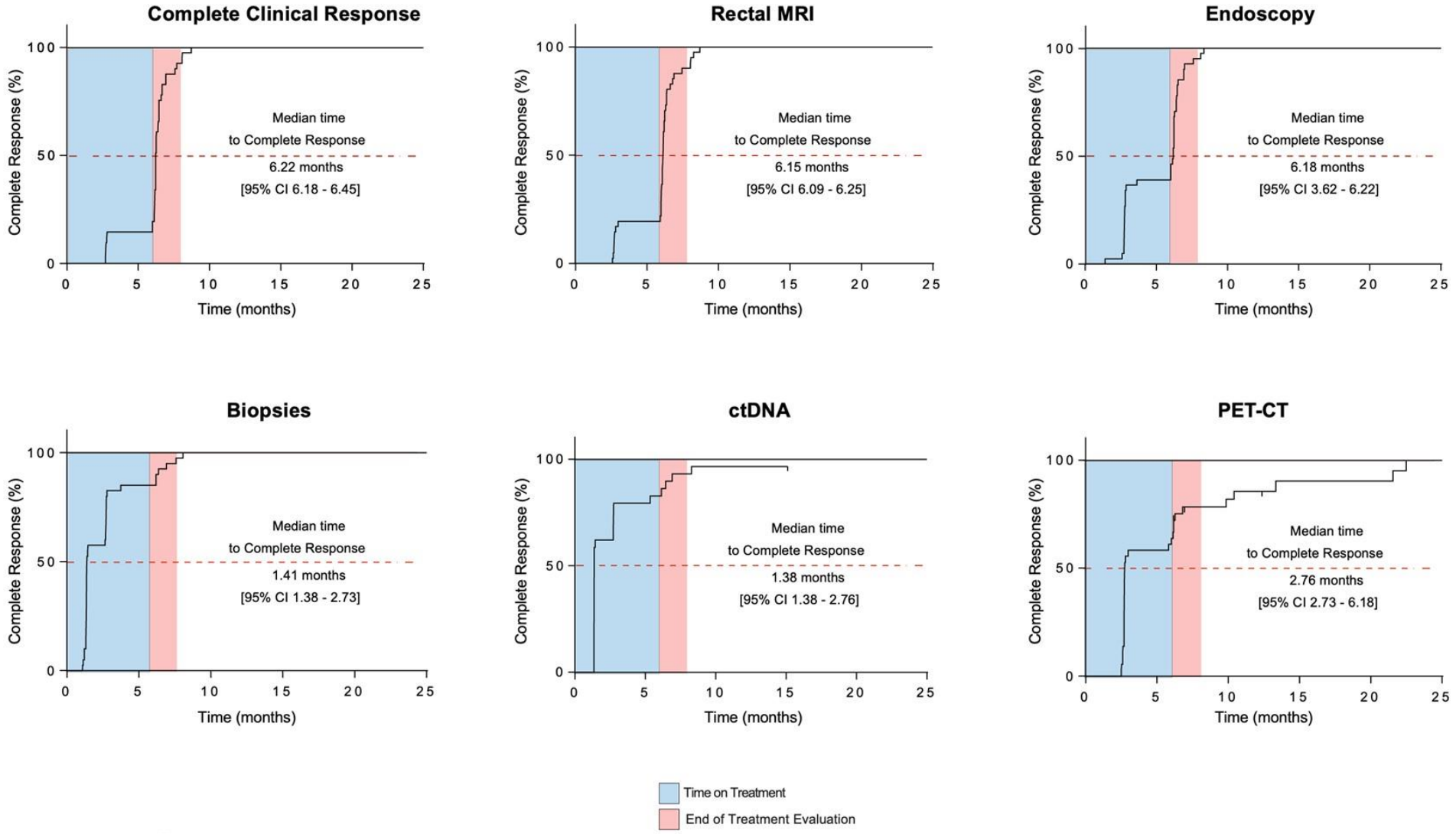
Patient Demographics N= 48	N (%)
Female Sex	**28 (58)**
Median Age (range)	**51 (26,78)**
Race	
White	**37 (77)**
Asian	**5(10)**
Black	**6 (13)**
Non Hispanic/Latino	**42 (85)**
Hispanic/Latino	**6 (13)**
Tumor Stage	
T 0/1/2	**10 (21)**
T 3	**23 (48)**
T 4	**15 (31)**
N +	**41 (85)**
Median Distance from anal verge (cm)	**5.1 (0, 14.8)**

Patient Demographics N= 48		N (%)
ECOG	0	**40 (83)**
	1	**8 (17)**
Pathogenic Germline Mutations Associated with Lynch syndrome (N=41)		**21 (51)**
	MSH2	**8 (19)**
	MSH6	**4 (10)**
	PMS2	**4 (10)**
	MLH1	**4 (10)**
Mismatch Repair Deficiency by IHC		
	MSH2 alone	**3 (6)**
	MSH6 alone	**5 (10)**
	PMS2 alone	**5 (10)**
	MSH2 and MSH6	**15 (31)**
	MLH1 and PMS2	**20 (42)**
Tumor Mutation Burden (range)		**53.6 (27.2-106.3)**
BRAF V600E mutated		**1 (2)**





Time to cCR



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)

Conclusions

- 100% clinical complete response in all 42 patients who completed dostarlimab
- Clinical complete responses are durable over 2 years
- No patients have required chemotherapy, radiation or surgery
- AZUR1 Global confirmatory study of dostarlimab in dMMR rectal cancer is ongoing

Summary - NAIO In LARC – LBA 3512

Strengths:

- Addresses an unmet need in rectal cancer patients to avoid surgery
- Median follow-up of 20 months with ongoing cCR
- ctDNA turns negative within 3 weeks of NAIO initiation as a surrogate for response to IO

Limitations:

- Predominance of Lynch Syndrome patients
- Need longer f/u to be sure 6 mo of IO is enough in this patient population

Take-home points…..

Clinically Relevant? YES

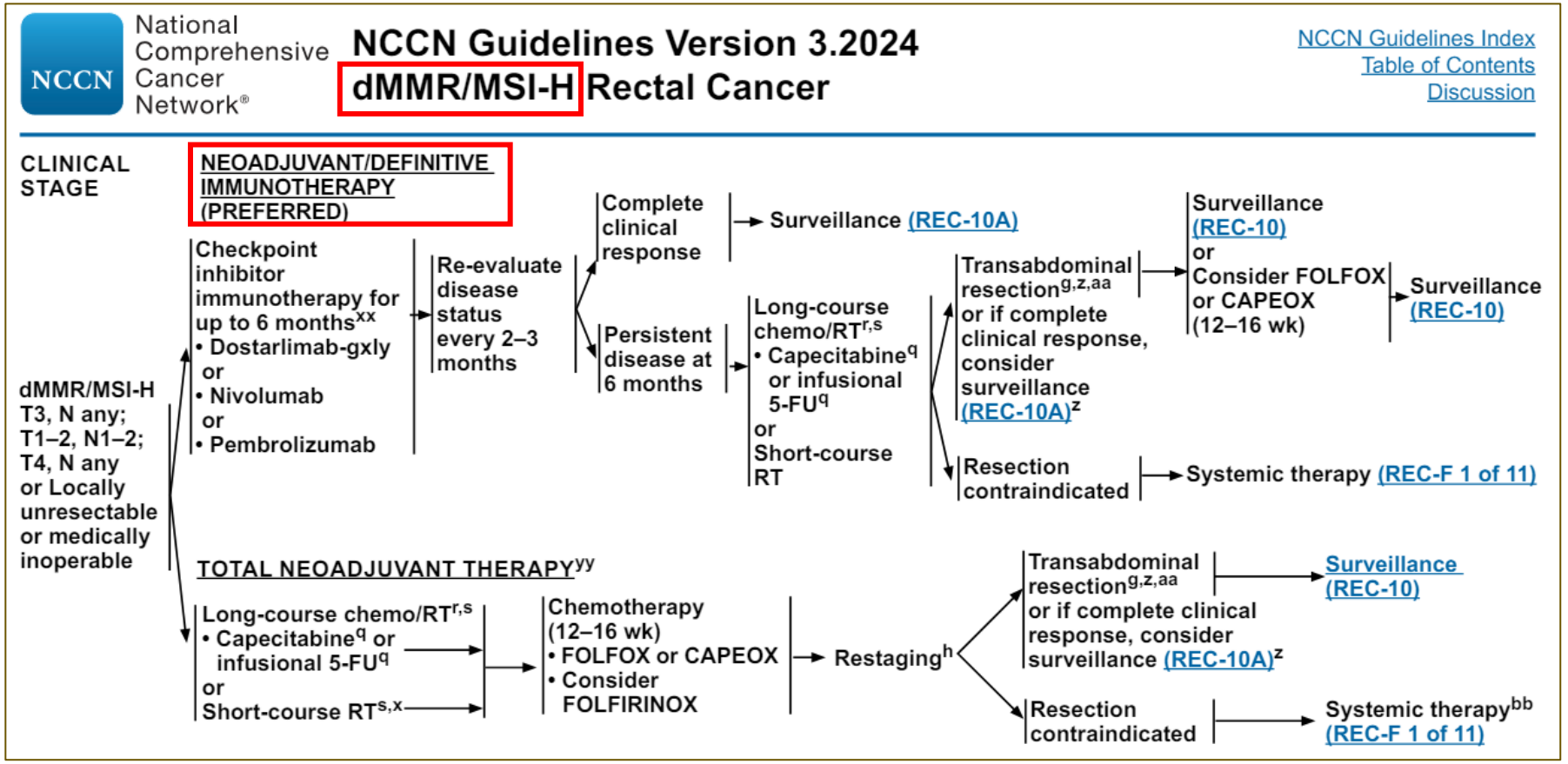
Immediately Practice Changing? Already part of NCCN Guidelines

Unanswered questions? Is 6 months NAIO enough for best RFS and OS outcomes in these patients? Need longer follow-up

Impact on value/cost of care, benefit for patients?

- Non-operative management brings value to the patients' QOL
- Decrease morbidity to patient!
- Decrease cost to the health system

Guidelines of dMMR locally advanced Rectal Cancer



Outline of Presentation

- Neoadjuvant Colon Cancer - Stage II/III, dMMR
  - LBA 3504 – NEOPRISM CRC (Phase II, multicenter, stratified by TMB, open-label trial)
  - Abstract 3505 – IO + CTLA4 (Phase Ib, Randomized, open label trial)
  - Summary and Take-home points
- Adjuvant Colon Cancer - Stage II, pMMR & dMMR
  - Abstract 108 – DYNAMIC TRIAL – (Phase 2, multicenter, randomized trial)
  - Summary and Take-home points
- Neoadjuvant Rectal Cancer – Stage II/III, dMMR
  - LBA 3512 – NAIO in Locally Advanced Rectal Cancer (Phase 2, single arm)
  - Summary and Take-home points
- Anal Cancer – Stage I-III
  - Abstract 3513 – HPV DNA Detection after CCRT as prognostic marker (Single arm)
  - Summary and Take-home points

2024 ASCO ANNUAL MEETING

Abstract - 3513

Time dependency for HPV ctDNA detection as a prognostic biomarker for anal cancer

Van K. Morris[1], Weihong Xiao[2], Emma B. Holliday[3], Kangyu Lin[1], Ryan W. Huey[1], Sonal S. Noticewala[3], Ethan B. Ludmir[3], Alisha H. Bent[1], Victoria Higbie[1], Eugene J. Koay[3], Albert C. Koong[3], Prajnan Das[3], Maura L. Gillison[2]

Departments of [1]Gastrointestinal Medical Oncology, [2]Thoracic/Head & Neck Medical Oncology, and [3]Gastrointestinal Radiation Oncology, The University of Texas- MD Anderson Cancer Center, Houston, TX

Key Takeaways

- HPV ctDNA using a highly-sensitive ddPCR assay is prognostic for recurrence after chemoradiation for anal cancer and outperforms other clinical/pathologic factors in determining risk for recurrence.
- 3 months after completion of chemoradiation appears to be first time point for assessing recurrence risk with HPV ctDNA in patients with localized anal cancer.
- Baseline detection of HPV ctDNA is associated with more advanced clinical stage → not all patients have detectable HPV ctDNA at initial presentation.
- Clinical trials incorporating HPV ctDNA as an eligibility criteria for MRD presence in HPV+ cancers like anal cancer are forthcoming.

Background

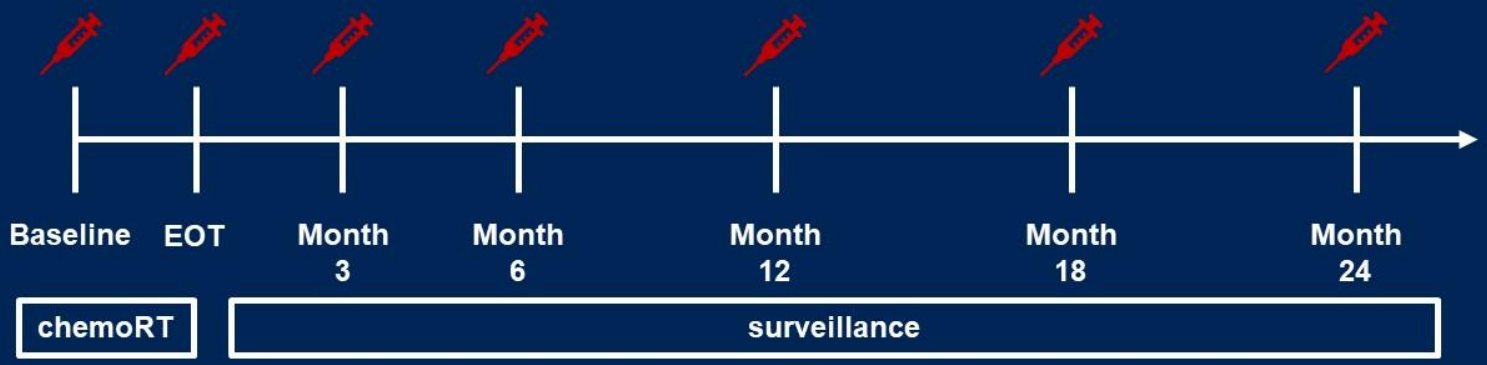
- Anal cancer incidence is increasing in the United States, with a trend towards more advanced staging at initial presentation[1].
- In contrast to surgery for most other solid tumors, chemoradiation (chemoRT) is the standard treatment for localized anal cancer[2].
- Identification of ctDNA as a surrogate for minimal residual disease (MRD) after curative-intent treatment is highly prognostic for recurrence, often informed by mutation calling[3] → is this the best strategy for risk assessment for anal cancer (low TMB[4])?
- >90% anal cancers are caused by HPV[5]. HPV ctDNA assays have demonstrated clinical utility in prognosticating recurrence across HPV-associated cancers[6, 7].
- Anti-tumor effects of chemoRT can last up to 6 months after treatment completion in anal cancer[8].

When is the best time to test for risk recurrence using HPV ctDNA?

[1]Deshmukh AA et al JNCI 2020; [2]James RD et al Lancet 2013; [3]Dasari A et al Nat Rev Oncol 2020; [4]Morris VK et al Mol Cancer Res 2017; [5]Daling JR et al Cancer 2004; [6]Chera B et al Clin Cancer Res 2019; [7]Bernard-Tessier A et al Clin Cancer Res 2019; [8]Glynne Jones R et al Lancet Oncol 2017

Methods

Patients at MDACC with stages I-III anal cancer treated with chemoRT



- All patients completed planned curative-intent chemoradiation with a fluoropyrimidine/platinum combination[1]:
  - 50-58 Gy to primary tumor and 43-47 Gy to elective nodes over 25-29 fractions.
  - 5-fluorouracil 300 mg/m^2/day IV on days of radiation + cisplatin 20 mg/m^2 IV weekly.
- HPV ddPCR ctDNA assay covering 13 oncogenic HPV types previously validated in HPV+ head/neck cancer[2]
  - Same assay used in CLIA environment for ongoing MDACC trial of balstilimab for treatment of HPV ctDNA(+) head/neck cancers after curative-intent treatment (NCT05363709).
- Threshold for **≥16 copies/mL** validated for "detectable" HPV ctDNA status.
- Associations between HPV ctDNA status & clinicopathologic factors done by X^2 test; median survival estimated via Kaplan-Meier method, with survival comparisons by log-rank test.

[1]Hollliday EB et al The Oncologist 2022; [2]Wotman M et al ASCO 2024

Baseline detection of HPV ctDNA prior to treatment

66 patients with stages I-III anal cancer

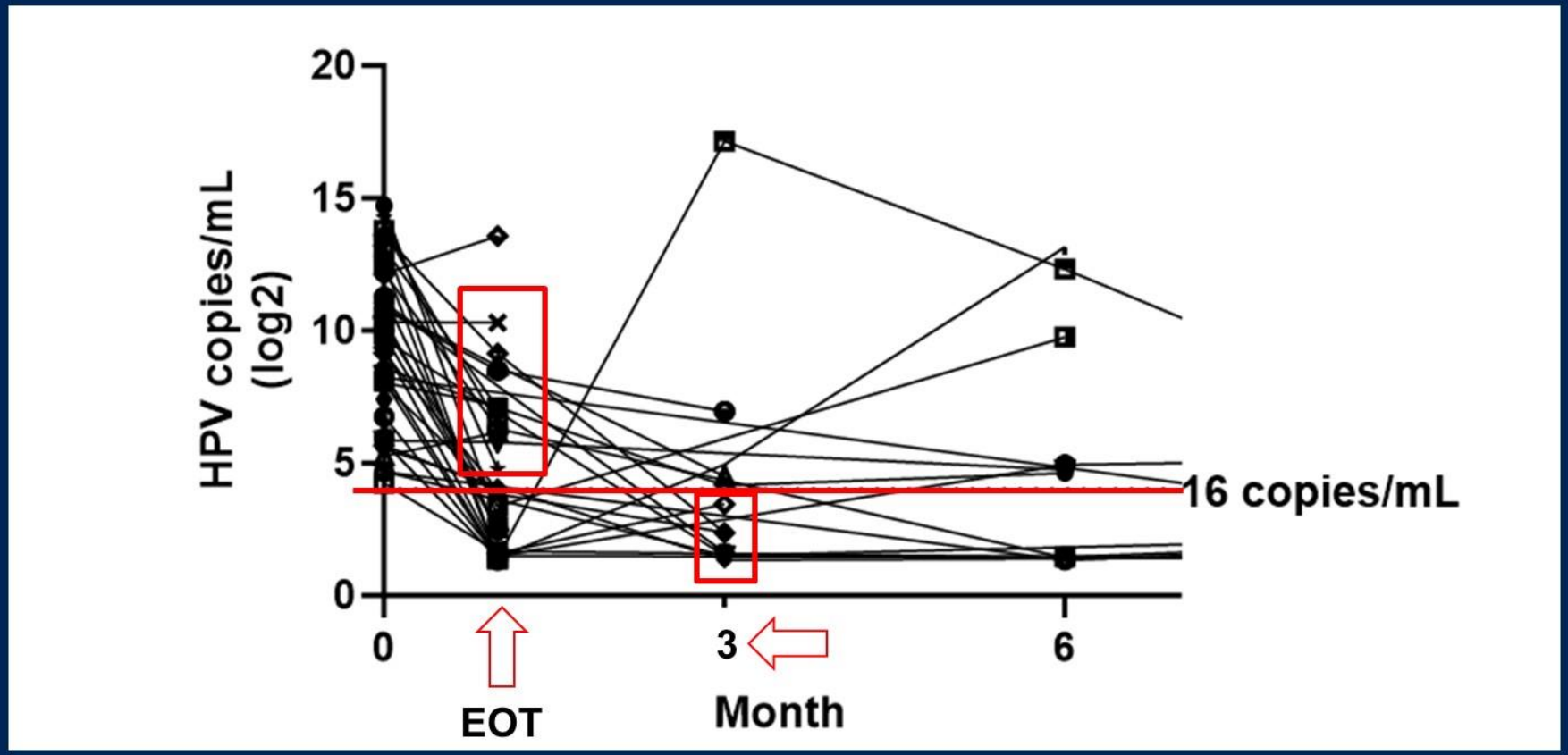
22 participants (33%) w/ undetected HPV ctDNA (HPV ctDNA < 16 copies/mL)

44 participants (67%) with detected HPV ctDNA at baseline (HPV ctDNA ≥ 16 copies/mL)

HPV-16 (N=43)
HPV-33 (N=1)

Baseline HPV ctDNA status (N=66)			
	NOT DETECTED (< 16 copies/mL) N=22	DETECTED (≥ 16 copies/mL) N=44	P-value
Age (years, SD)	62.4 (11.2)	61.0 (9.2)	.682
Gender (%)			
Female	17 (77)	33 (75)	1
Male	5 (23)	11 (25)	
T stage (%)			.01
1-2	18 (82)	20 (45)	
3-4	4 (18)	24 (55)	
N stage (%)			.01
0	15 (68)	14 (32)	
1	7 (32)	30 (68)	
Clinical stage (%)			.009
1-2	17 (81)	19 (43)	
3	4 (19)	25 (57)	

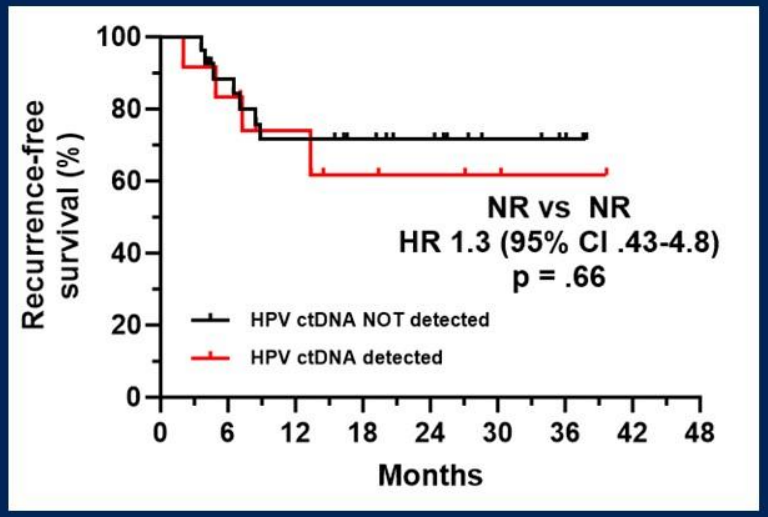
Serial HPV ctDNA kinetics over time with chemoradiation



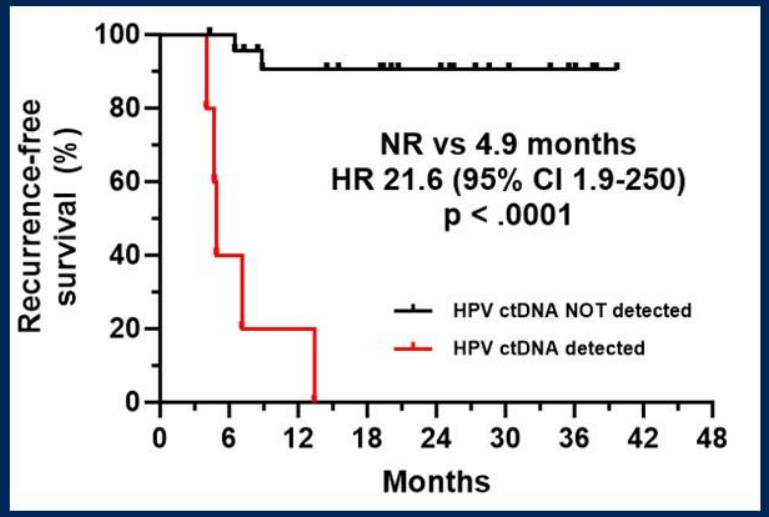
Many patients have detectable HPV ctDNA at EOT, but not at 3 months.

HPV ctDNA as a time-dependent prognostic biomarker

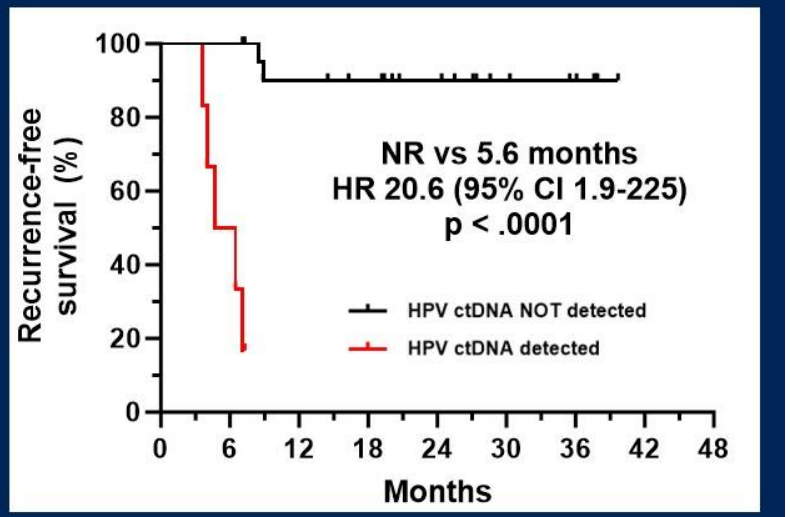
End of treatment



Month 3 after treatment

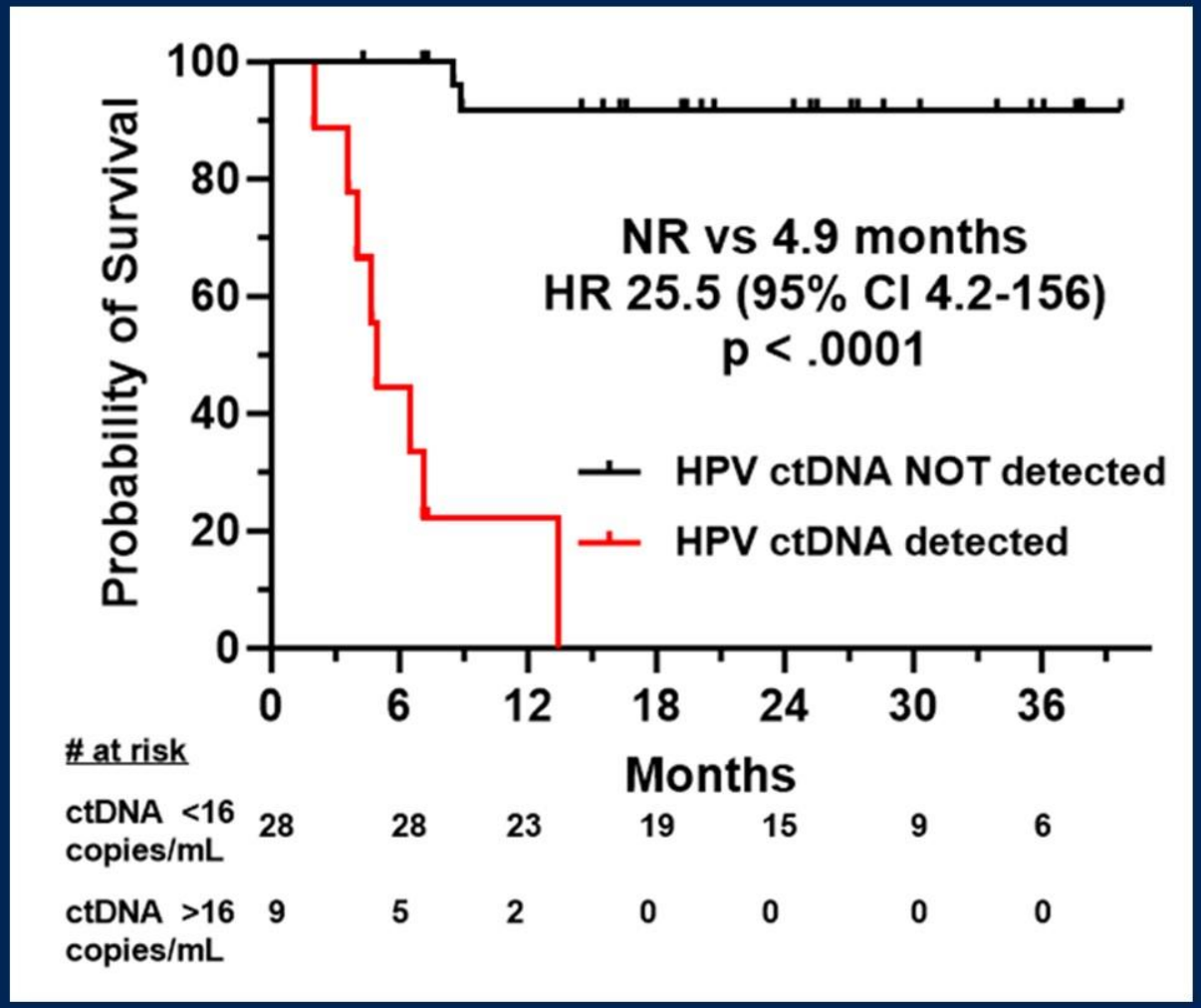


Month 6 after treatment



3 months after completion of chemoRT was earliest time point for which HPV ctDNA status is prognostic for recurrence.

HPV ctDNA > 3 months after chemoradiation as prognostic biomarker

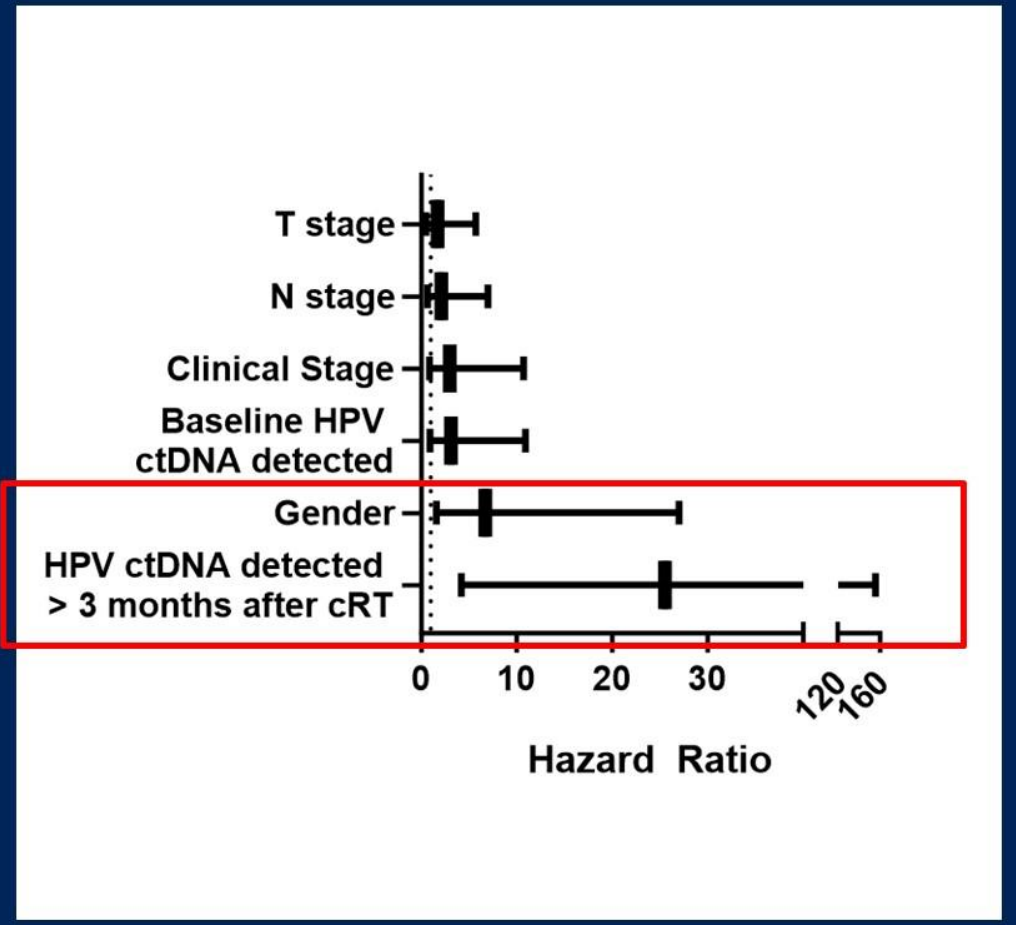


Performance of using HPV ctDNA 3 months after chemoradiation completion:

- Sensitivity 80%
- Specificity 96%
- PPV 89%
- NPV 93%

Clinicopathologic features associated with recurrence after chemoradiation

	Hazard ratio	P-value
T stage	1.7 (.52 – 5.7)	.38
N stage	2.1 (.65 – 7.0)	.21
Clinical stage	3.0 (.87 – 10.7)	.08
Baseline HPV ctDNA >16 copies/mL	3.1 (.91 – 10.9)	.07
Male gender	6.7 (1.6 – 27)	.01
HPV ctDNA > 16 copies/mL >3 months after cRT	25.5 (4.2 – 156)	< .001



Phase II trial targeting PD-L1 + TIGIT for treatment of HPV MRD[10] after curative-intent therapies

- Patients with stages I-III HPV+ SCCs of head/neck, cervix, anus/rectum, vagina/vulva, or penis
- HPV ctDNA ≥ 16 copies mL >3 months after curative treatment
- No evidence of clinical or radiographic disease

→ Atezolizumab 1200 mg IV + Tiragolumab 600 mg IV every 3 weeks x 8 doses

→ Evaluate for clinical and HPV ctDNA endpoints

N= 48 participants
Activation by Q4 2024

PI: Holliday (GI Radiation Oncology)

Conclusions

- HPV ctDNA using a highly-sensitive ddPCR assay is prognostic for recurrence after chemoradiation for anal cancer and outperforms other clinical/pathologic factors in determining risk for recurrence.
- 3 months after completion of chemoradiation appears to be first time point for assessing recurrence risk with HPV ctDNA in patients with localized anal cancer.
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- Clinical trials incorporating HPV ctDNA as an eligibility criteria for MRD presence in HPV+ cancers like anal cancer are forthcoming.

Summary - ctDNA in Anal Cancer - Abstract 3513

Strengths:

- **Clinically relevant**
- **Fills unmet need to prognosticate patient early after completing potentially curative treatment**

Limitations:

- **Small sample size**
- **Single institution**
- **Does not provide information if local or distant recurrences**

Take-home points…..

Clinically Relevant? YES

Immediately Practice Changing? YES

Unanswered questions? Pattern of recurrence, local vs distant?

Impact on value/cost of care, benefit for patients? In a cancer with a high cure rate with CCRT, knowing this information is a valuable adjunct to clinical exam by colorectal surgeon to detect early recurrences when the disease may still be resectable for cure

Thank you for your attention

Questions?