Expert Second Opinion: Optimizing the Use of Immunotherapy, MRD Assessment and Other Novel Approaches for Patients with Localized Colorectal Cancer

A CME Symposium Held Adjunct to the 2026 ASCO® Gastrointestinal Cancers Symposium

Thursday, January 8, 2026

7:15 PM – 8:45 PM PT

Faculty

Stacey A Cohen, MD

Jenny Seligmann, MBChB, PhD

Moderator

Christopher Lieu, MD

RTP RESEARCH TO PRACTICE

Faculty

Stacey A Cohen, MD
Professor
Fred Hutchinson Cancer Center
University of Washington
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Moderator

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RTP
RESEARCH
TO PRACTICE

Dr Cohen — Disclosures
Faculty

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Dr Seligmann — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Dr Lieu — Disclosures
Moderator

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Expert Second Opinion: Current and Future Roles of Immunotherapy and Targeted Therapy in the Management of Advanced Gastroesophageal Cancers

A CME Symposium Held Adjunct to the 2026 ASCO® Gastrointestinal Cancers Symposium

Friday, January 9, 2026

6:00 PM – 8:00 PM PT

Faculty

Jaffer A Ajani, MD

David H Ilson, MD, PhD

Rutika Mehta, MD, MPH

Moderator

Samuel J Klempner, MD

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

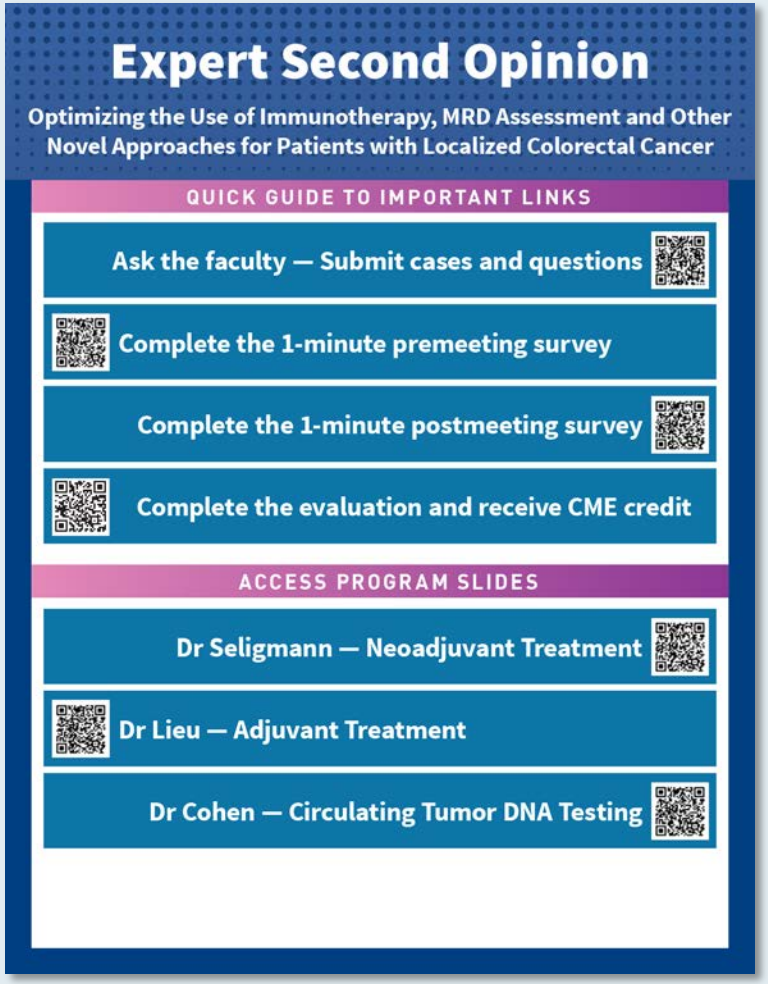
Please refer to the printed handout provided with your meeting syllabus, and scan the corresponding QR code to

Review and Download Program Slides.

Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: We will aim to address as many questions as possible during the program.

Get CME Credit: Complete the course evaluation.



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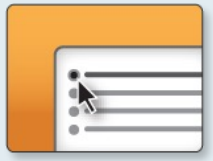
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the pre- and postmeeting surveys.

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

Get CME Credit: A credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Expert Second Opinion: Optimizing the Use of Immunotherapy, MRD Assessment and Other Novel Approaches for Patients with Localized Colorectal Cancer

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Agenda

Module 1: Neoadjuvant Treatment for Localized Colorectal Cancer (CRC) — Dr Seligmann

Module 2: Emerging Novel Approaches to Adjuvant Treatment for Localized CRC — Dr Lieu

Module 3: Role of Circulating Tumor DNA (ctDNA) Testing in Localized CRC — Dr Cohen

Survey of 50 Community-Based General Medical Oncologists

December 22, 2025 – January 7, 2026

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Agenda

Module 1: Neoadjuvant Treatment for Localized Colorectal Cancer (CRC) — Dr Seligmann

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Neoadjuvant treatments for localised CRC: Opportunities for Progress

Jenny Seligmann

Professor of Gastrointestinal Oncology and Honorary Medical Oncologist

University of Leeds, UK

ctru
University of Leeds

FOxTROT
Personalising neo-adjuvant chemotherapy in locally advanced but operable colon cancer

Locally advanced colorectal cancer

A tale of 2 tumor sites.....

Locally advanced rectal cancer		Locally advanced colon cancer
Guideline recommended; RT and/ or chemo	Neoadjuvant treatment	Guideline endorsed (T4); less well established
MRI and CT	Patient selection	CT
cCR, Organ preservation & DFS.	Relevant endpoints	DFS; (pathological response)
Protocolised	Response assessment	No protocols

A tale of 2 biomarker groups.....

MSI-H/ dMMR

- 5% LARC
- 15-20% LACC

MSS/ pMMR

- 95% LARC
- 80-85% LACC

Potential advantages & disadvantages of a neoadjuvant therapy in localised CRC

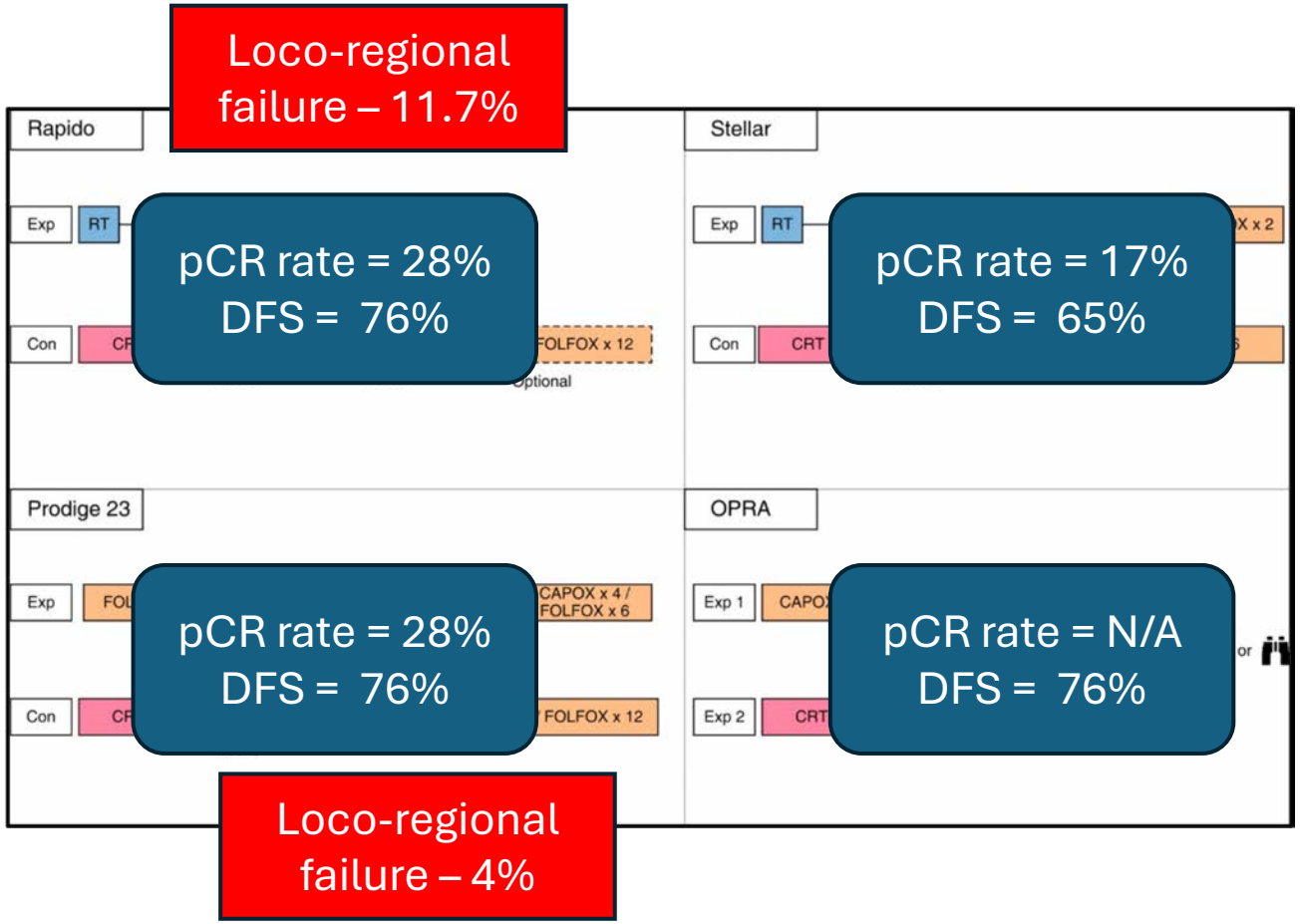
- Positive experience in other cancers
- Early treatment of micro-metastases
- Downstaging for complete surgical resection
- Potential for organ preservation
- Preclinical studies show a stronger and deeper immune response with IO when primary tumor is in situ
  - Tumor microenvironment intact and tumor antigen heterogeneity may be minimal

- Will patients not proceed to surgical resection?
  - PD in neoadjuvant window
  - Toxicity from neoadjuvant treatment
- Will NAC lead to an increase in peri-operative complications?
- Can we select appropriate patients using radiological staging assessment?

Battaglin F. Clin Adv Hematol Oncol. 2018; Sciafani F et al. Cancers (Basel). 2021; Smith HG et al. BJS Open. 2024

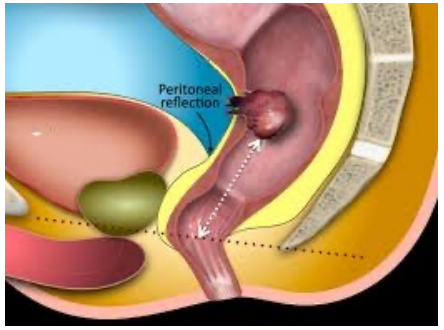
Locally advanced rectal cancer (LARC)

- Total neoadjuvant treatment with chemotherapy and radiotherapy (TNT) is international standard of care to reduce local and distant recurrences
- Multi-modal treatment is life-changing with risk of bladder, sexual, and bowel dysfunction, and risk of permanent stoma
- If complete clinical response (cCR) is achieved, OPRA showed organ preservation is a viable option
    - No detriment in DFS c/w TME
    - Upfront CRT then consolidation chemo led to higher 3 year TME-free rates

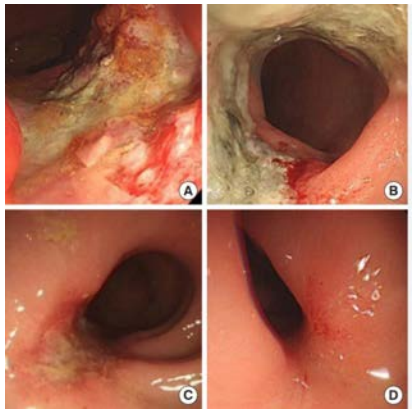


Bahadoer, Lancet Oncol, 2021; Dijkstra, Ann Surg, 2023; Conroy, Lancet Oncol, 2021; Jin, J Clin Oncol, 2022; Garcia-Aguilar et al, JCO 2022

How do you select TNT strategy?

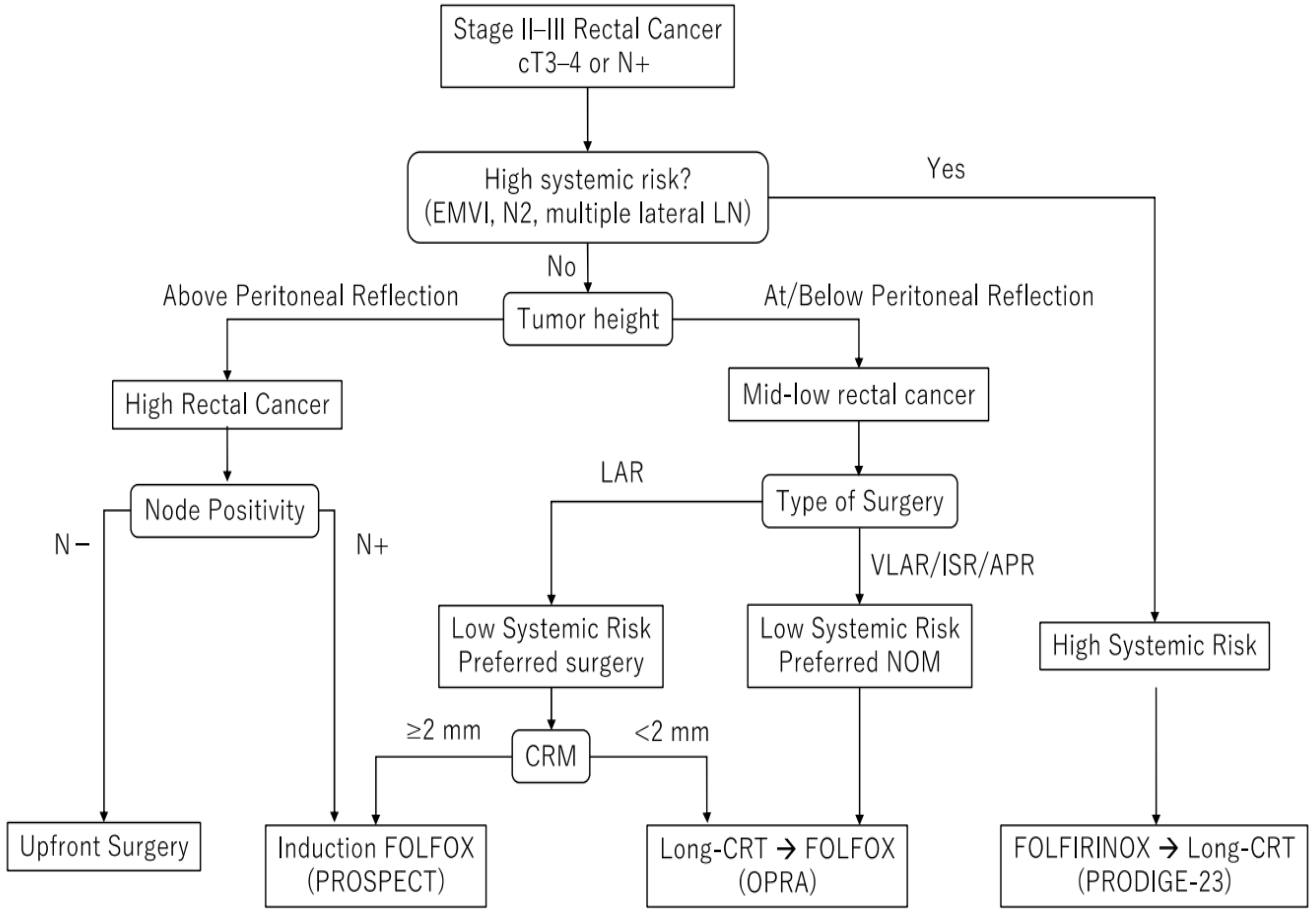


Anatomy



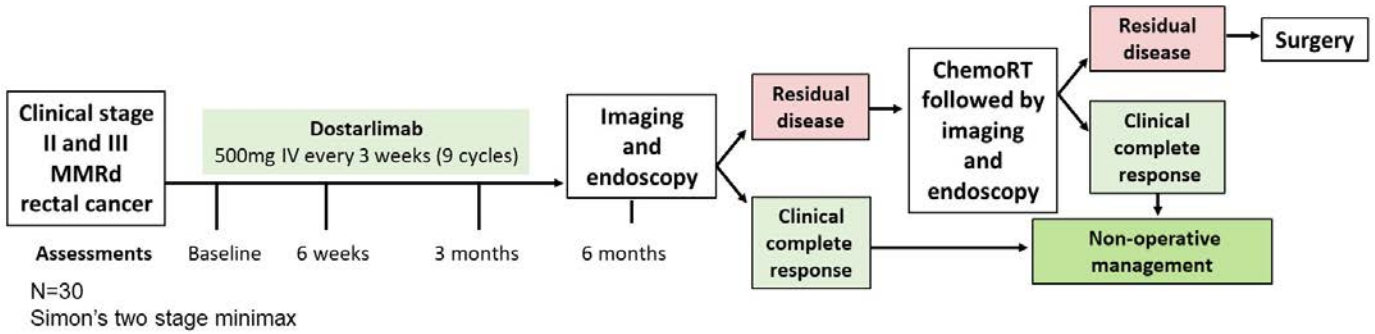
Treatment Intent

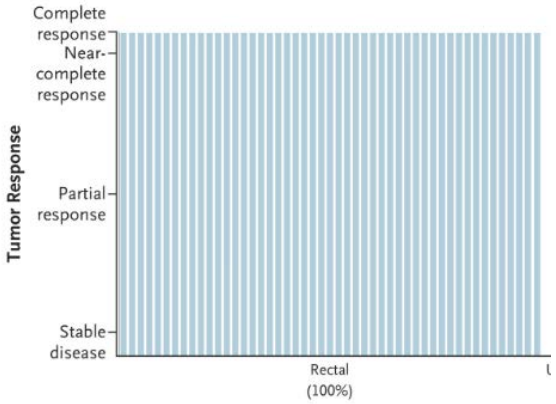
Biology/ local vs systemic risk



Ochiai, Cancers, 2024

MSI-H Locally advanced rectal cancer: dostarlimab definitive treatment



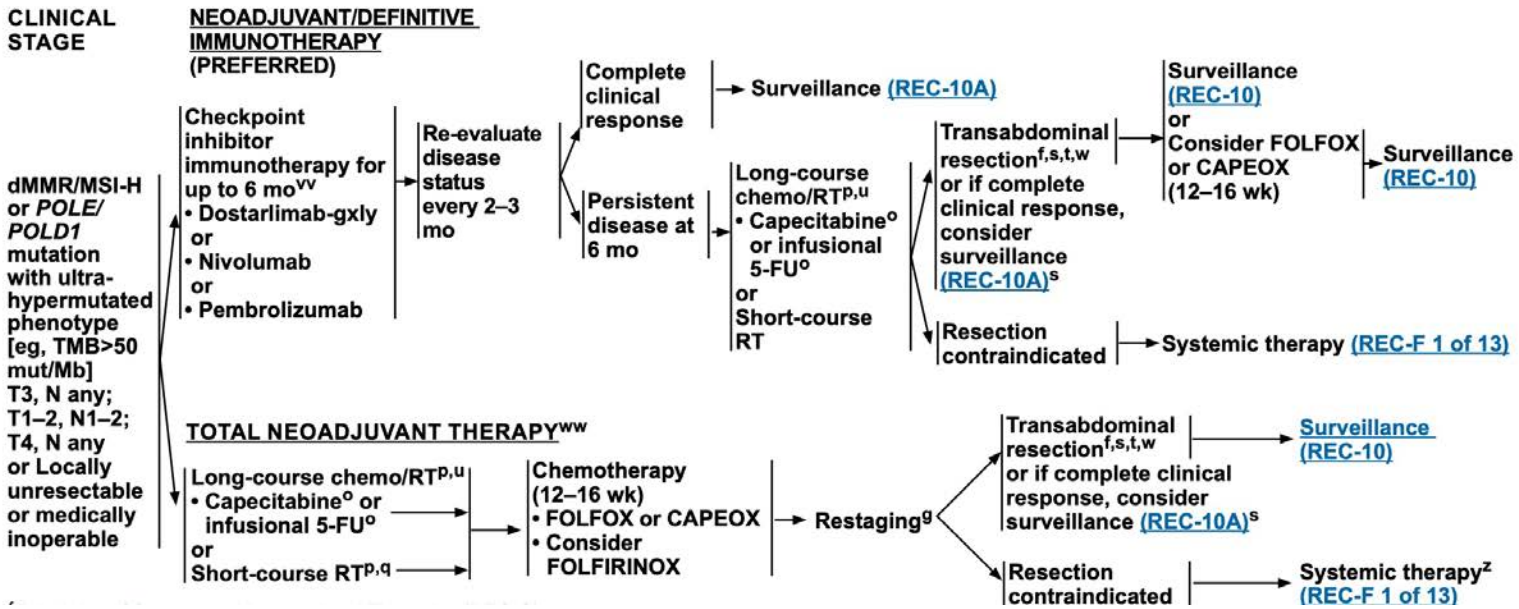


- 49 dMMR rectal cancer
  - 20% T4
- 49 cCR & proceeded to non-operative management
- Median follow up for recurrence 30 months
- RFS 92%
- ctDNA became undetectable during neoadjuvant treatment in complete responders

Cercek et al. NEJM 2022; Cercek, NEJM, 2025

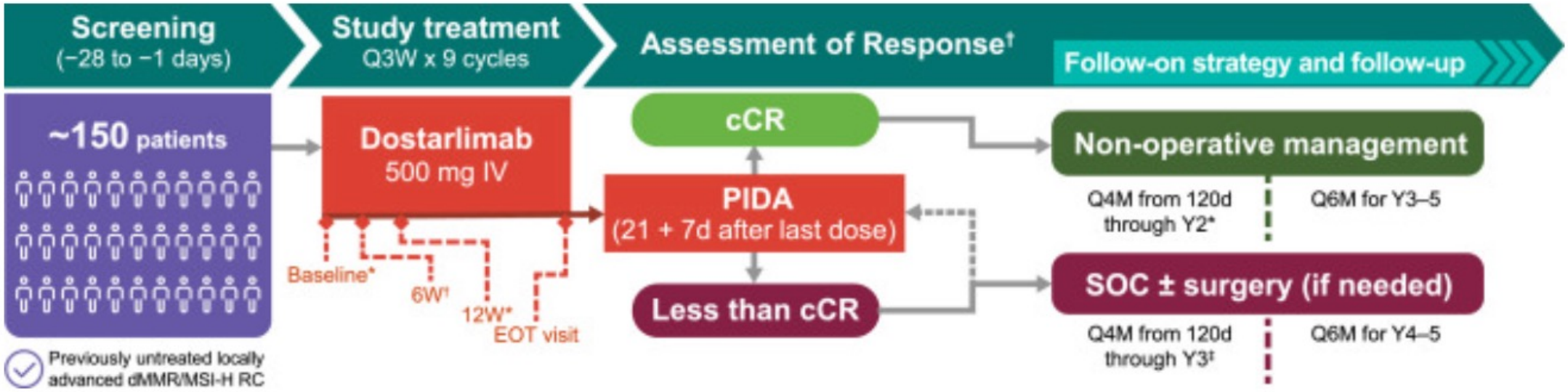
Does this data merit practice change?

- 49 patients
- Single centre with world-leading expertise
- Generalisability of patients?
- BUT – rare population
- Ethics of randomizing to SOC based upon current data



NCCN Rectal Cancer Guidelines, V0.2.2025

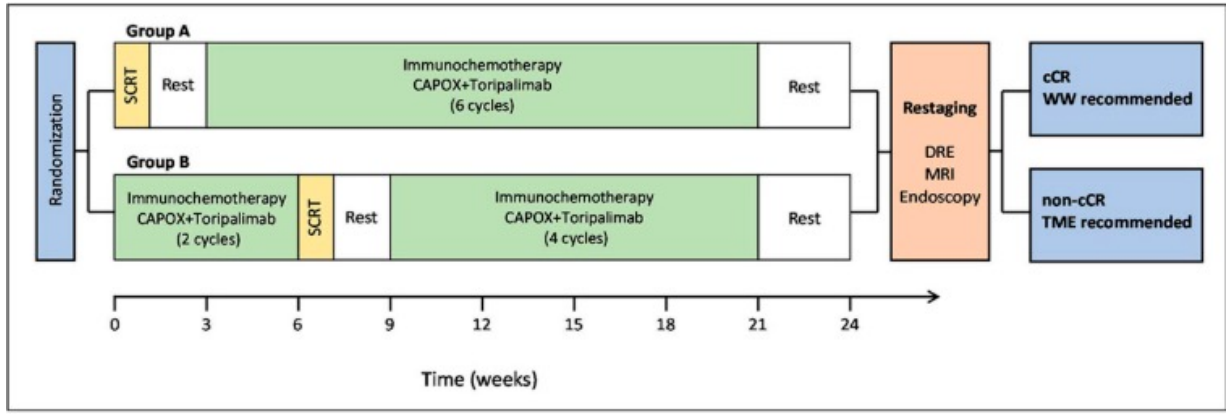
AZUR 1 – Global, single arm phase II registrational study

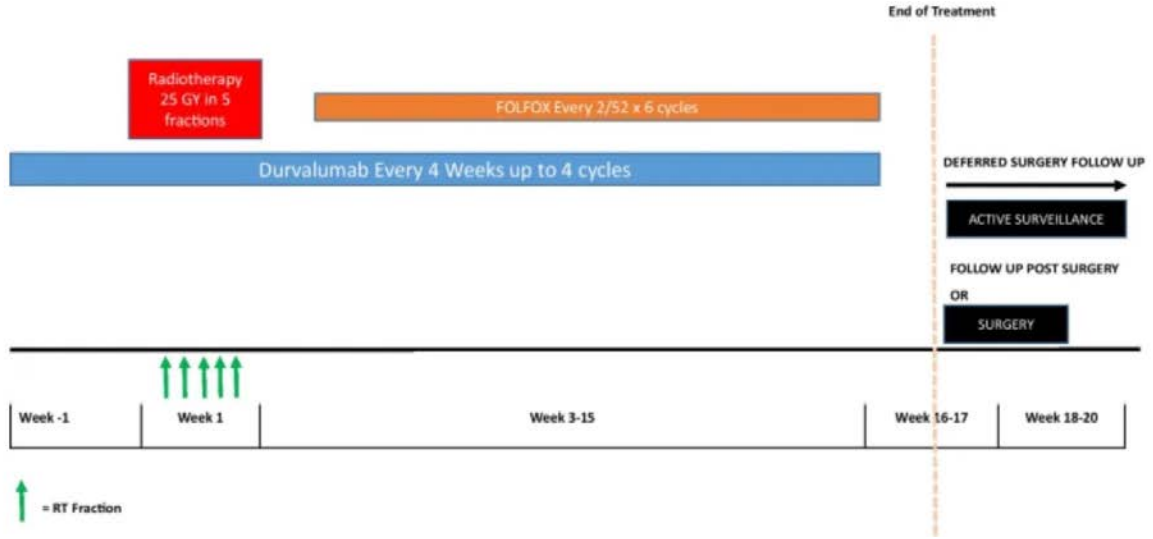


Cercek, Clin Colorectal Cancer, 2025

Neoadjuvant IO in MSS LARC

- Historical control cCR rate of 25%
- TORCH
  - 121 MSS LARC patients
  - CR rate 56.5% in Arm A
  - CR rate 54.2% Arm B
  - 15 pts in each group W & W strategy & remained disease free
- PRIME-RT
  - 46 MSS LARC patients
  - CR rate of 62% with SCRT





Xia, JCO, 2024; Roxburgh, ESTRO Meeting, 2025; Bach, ESTRO Meeting, 2025

Neoadjuvant chemotherapy (NAC) for LACC

Problem:
Cured by surgery
Need:
Improve patient selection for chemotherapy beyond TNM?

Problem
Have disease recurrence despite current SOC

Need:
New treatment strategies beyond current SOC

original reports

Preoperative Chemotherapy for Operable Colon Cancer: Mature Results of an International Randomized Controlled Trial

Dion Morton, MD[1]; Matthew Seymour, MD[2]; Laura Magill, PhD[3]; Kelly Handley, PhD[3]; James Glasbey, MD[3]; Bengt Glimelius, MD[4]; Andy Palmer[5]; Jenny Seligmann, MD[2]; Søren Laurberg, MD[7]; Keigo Murakami, MD[8]; Nick West, MD[9]; Philip Quirke, FMedSci[9]; and Richard Gray, MSc[3]; on behalf of the FOxTROT Collaborative Group

RANDOMIZED CONTROLLED TRIAL

Perioperative FOLFOX 4 Versus FOLFOX 4 Plus Cetuximab Versus Immediate Surgery for High-Risk Stage II and III Colon Cancers

A Phase II Multicenter Randomized Controlled Trial (PRODIGE 22)

*M. Karoui, MD, PhD,[✉] A. Rullier, MD,† G. Piessen, MD, PhD,‡ J. L. Legoux, MD,§ E. Barbier, MD,¶ C. De Chaisemartin, MD,‖ C. Lecaille, MD,** O. Bouche, MD, PhD,†† H. Anmarguellat, MD,‡‡ F. Brunetti, MD,§§ M. Prudhomme, MD, PhD,¶¶ J. M. Regimbeau, MD, PhD,‖‖ O. Glehen, MD, PhD,*** A. Lievre, MD, PhD,††† G. Fortier, MD, PhD,‡‡‡ J. Hartwig, MD,§§§ G. Goujon, MD,¶¶¶ B. Romain, MD, PhD,‖‖‖ C. Lepage, MD, PhD,**** and J. Taieb, MD, PhD††††*

2022 ASCO ANNUAL MEETING

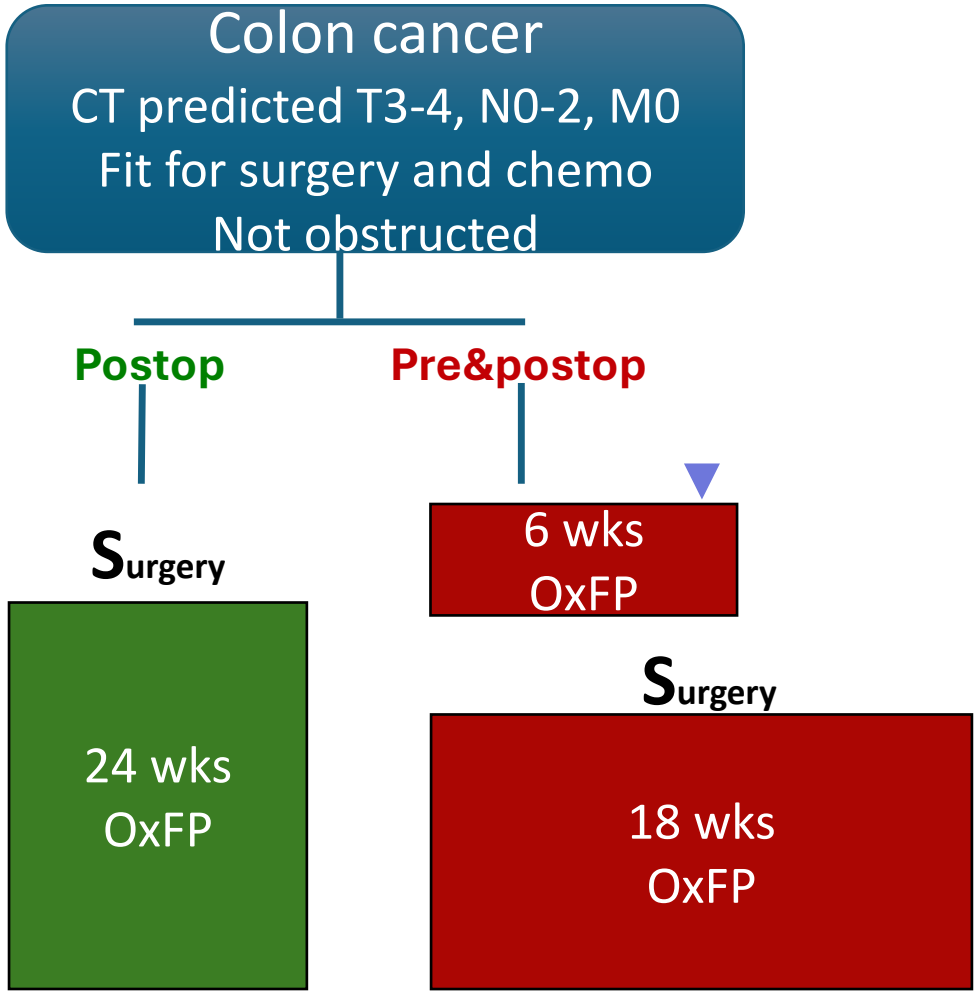
Perioperative Chemotherapy With mFOLFOX6 or CAPOX for Patients With Locally Advanced Colon Cancer (OPTICAL): A Multicenter, Randomized, Phase III Trial

Huabin Hu, Meijin Huang, Yunfeng Li, Ziqiang Wang, Xiaozhong Wang, Ping Liu, Ruyi Zhang, Hao Zhang, Zhongcheng Huang, Haiping Pei, Yongming Zeng, Jiajun Lai, Wenbin Chen, Jiansi Chen, Zhijie Ding, Hongbo Wei, Qingwen Xu, Jigui Chen, Jianping Wang, Yanhong Deng[✉]

2023 ASCO ANNUAL MEETING

Phase III randomized clinical trial comparing the efficacy of neoadjuvant chemotherapy and standard treatment in patients with locally advanced colon cancer

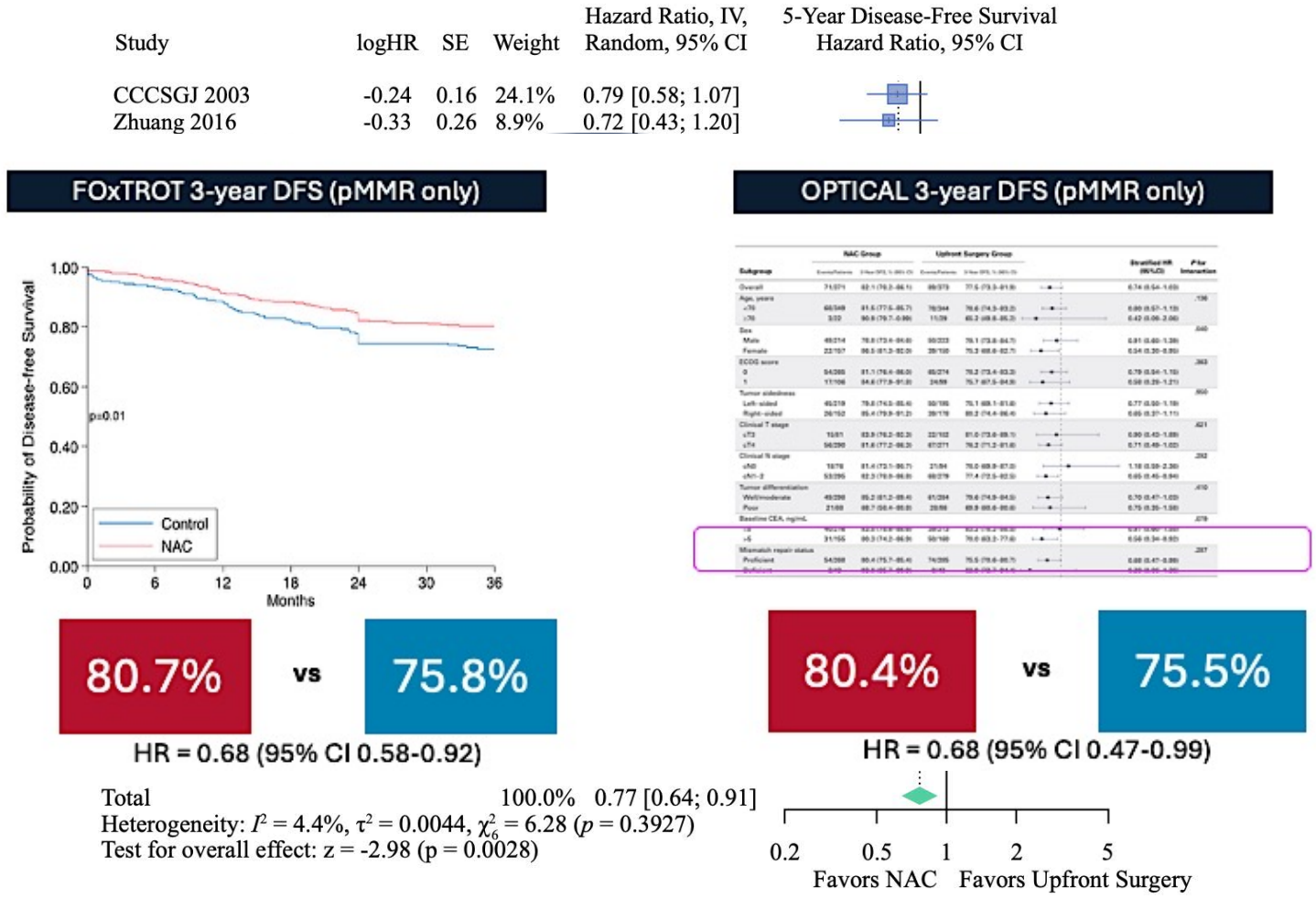
The Scandinavian **NeoCol** trial



Morton, J Clin Oncol, 2023

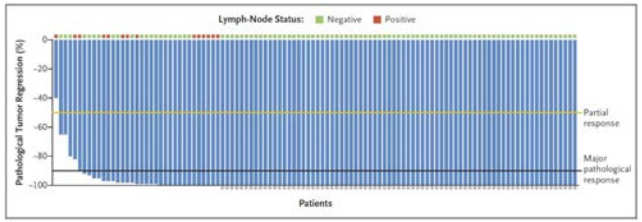
Meta-analysis of NAC in LACC

- 3038 patients included from 8 studies
- Compared with upfront surgery, NAC:
  - Significant improvement in 5-year DFS (HR 0.80) and OS (HR 0.77)
  - Reduction in positive surgical margin (4.1% vs 6.3%, p<0.001)
  - Safety (during NAC & peri-operative) consistent amongst studies
  - Reduction in anastomotic leak (4.4% vs 5.7%, p=0.09)



Sassun, Annals of Surgical Oncology, 2025

Neoadjuvant IO in MSI-H LACC



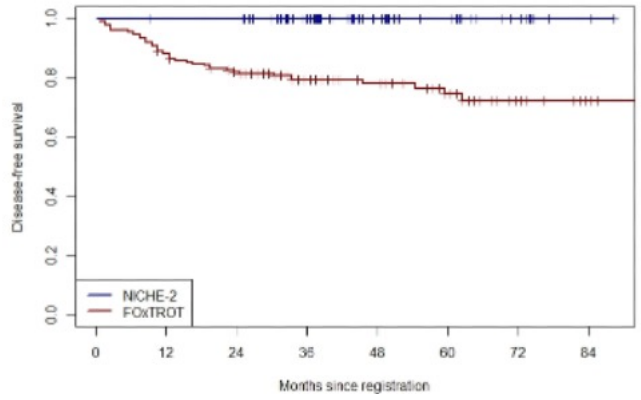
- Safety and deliverability demonstrated
- Consistent impressive efficacy
- Over shorter treatment duration combination appears superior
- Lesser difference in pCR if longer duration of anti-PD1 delivered
- Heterogeneity in study designs limit definitive conclusions on optimal regimen

Study	Design	pCR rate
PICC (34)	Toripalimab +/- celecoxib (12 weeks)	76.5%
Ludford (27)	Pembrolizumab (24 weeks)	79%
NEOPRISM (32)	Pembrolizumab (9 weeks)	53%
IMHOTEP	Pembrolizumab (**6 weeks)**	46.0%
IMHOTEP	Pembrolizumab (**12 weeks)**	68.2%
Xu et al	Sintilimab (4 weeks)	47.7%
NICHE 2 (107)	Nivolimab + ipilimumab (4 weeks)	68.0%
NICHE 3 (59)	Nivolumab +. Retalimab (4 weeks)	68.0%
Xu et al	IBI310 + Sintilimab (4 weeks)	80%
Kasi et al (4)	Botensilimab + balstilimab (4 weeks)	100%

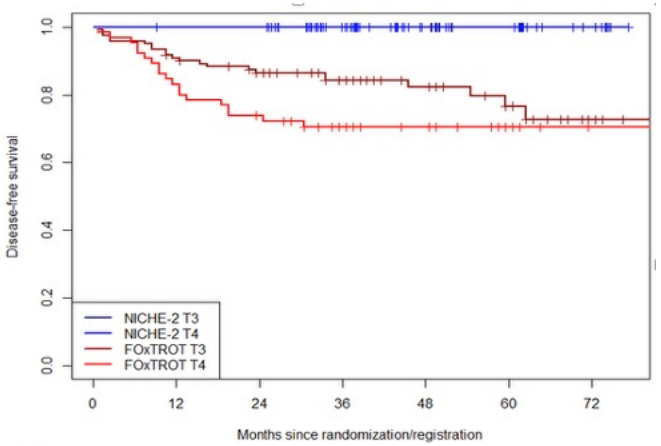
Xu, ASCO Meeting 2024; Shiu, ASCO Meeting 2024; Ludford, JCO, 2023; Hu, Lancet Gastro Hep, 2022; Cercek, ASCO Meeting 2024, Kasi, ASCO GI Meeting, 2024

Do MSI-H LACC patients really need this approach?

Combined DFS analysis of NICHE-2 and FOxTROT dMMR patients

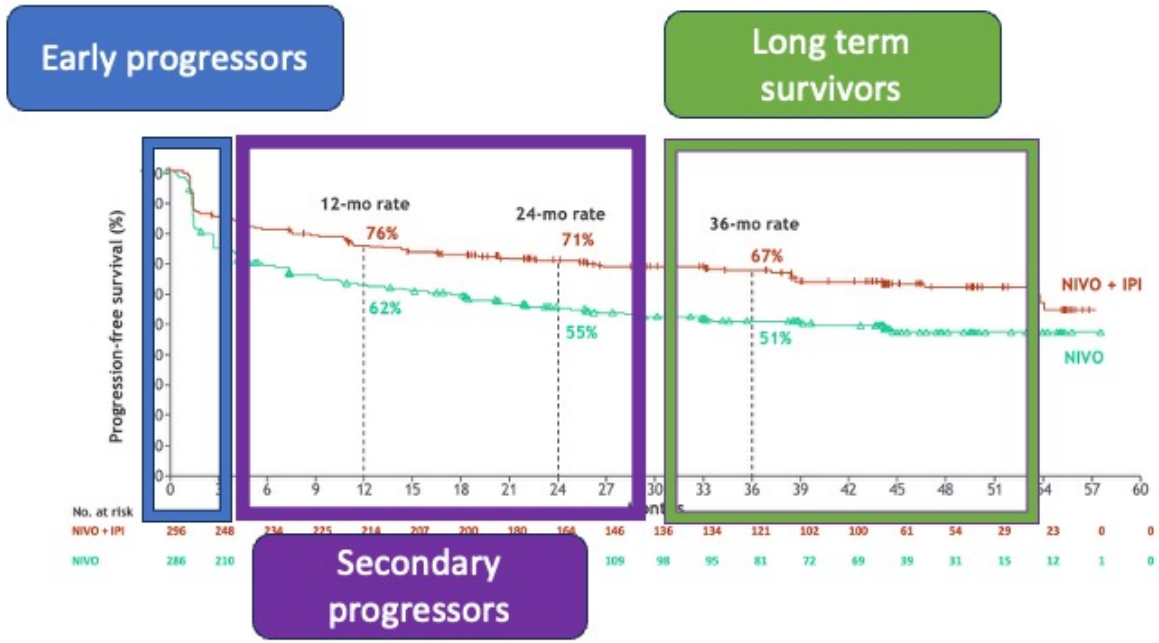


NICHE-2 vs FOxTROT
DFS = 100% vs 80%,
p<0.001%



DFS by T-stage:
T4 DFS = 100% vs 70%,
p<0.001%

Heterogenous outcomes of treatment of metastatic MSI-H CRC



Seligmann, ESMO Congress, 2025; Andre, Lancet, 2025

Has ATOMIC blasted out neoadjuvant IO in MSI-H ?

cT4 tumors

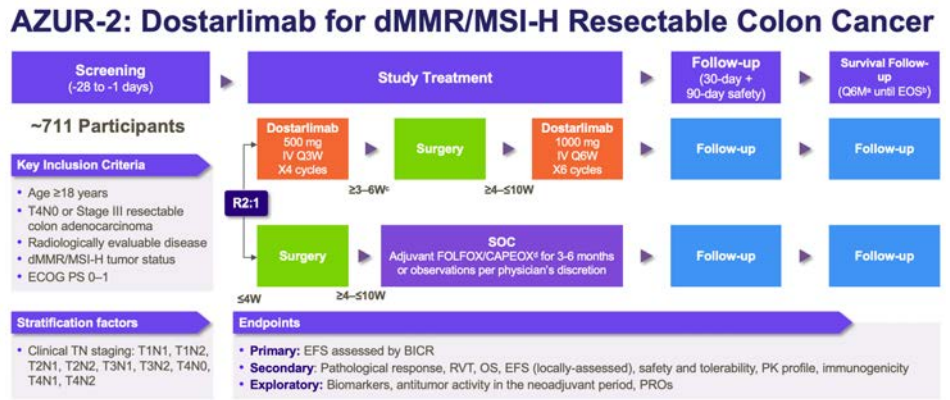
T3/ T4a tumors

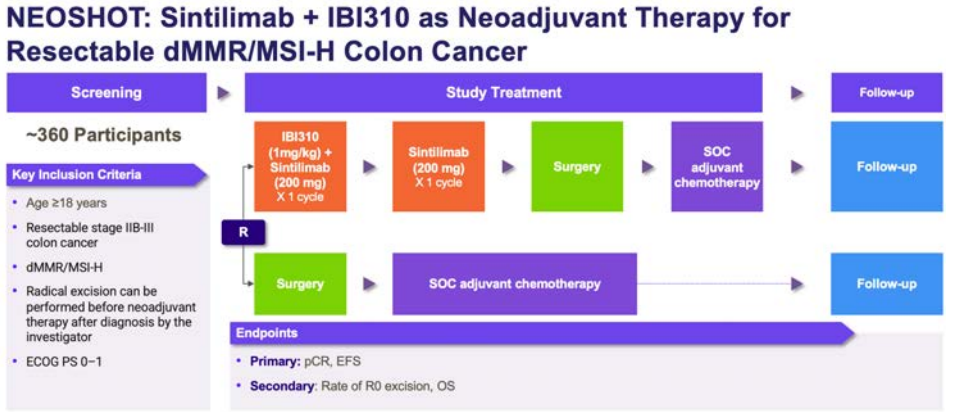
High risk
Difficult to achieve R0 resection without multivisceral resection

What is the benefit compared with ATOMIC or observation?

Should be considered for neoadjuvant IO

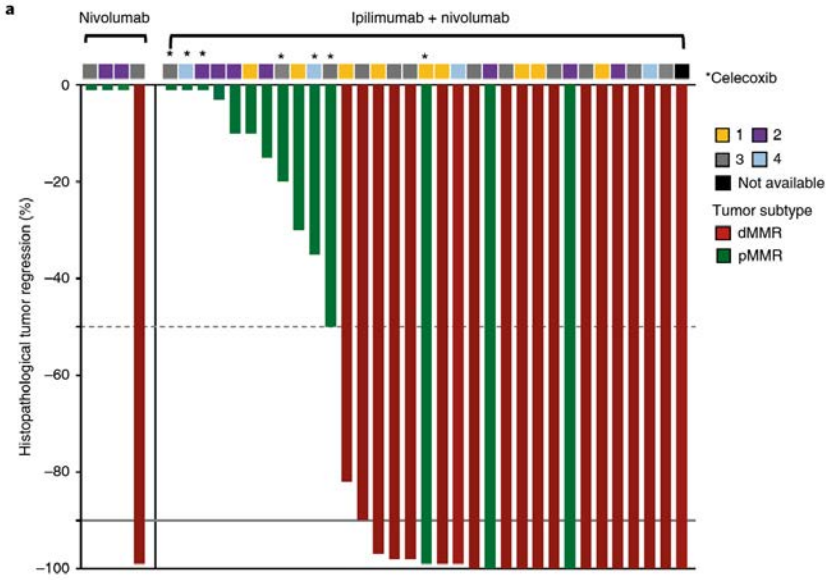
What is needed for regulators?



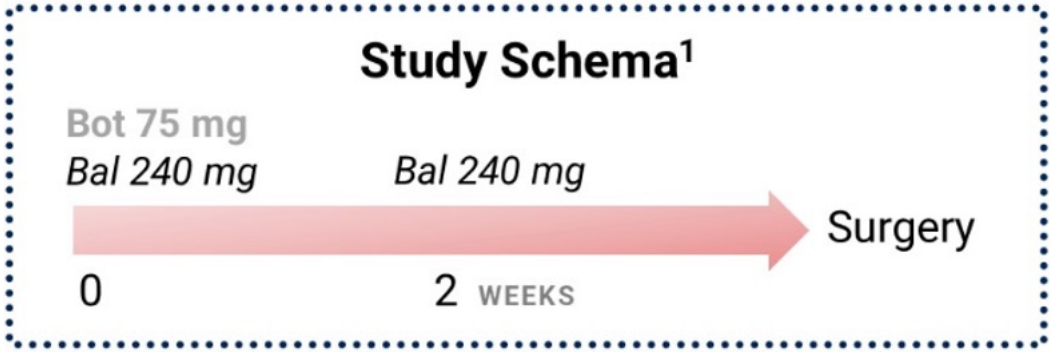


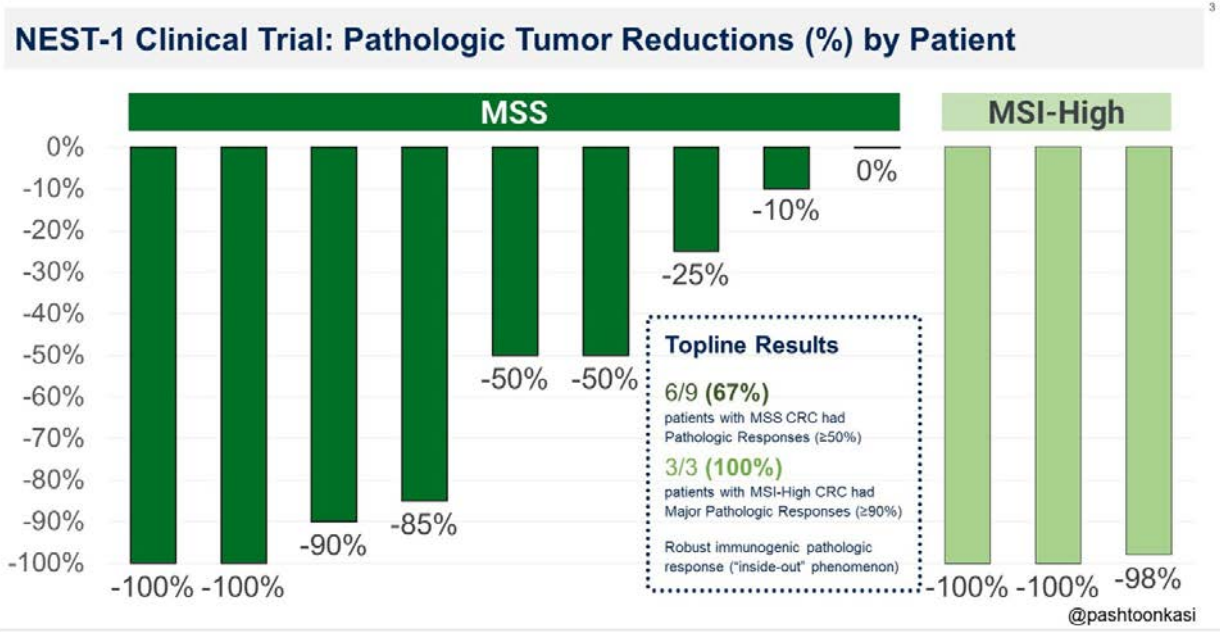
Neoadjuvant immunotherapy in MSS LACC

- Initial data from 20 pMMR tumors in NICHE 1
- 4/15 pMMR tumors (27%) had path responses (3 MPRs, 1 PR, 0 CR)



- NEST-1: Neoadjuvant Botensilimab and Balstilimab in LACC

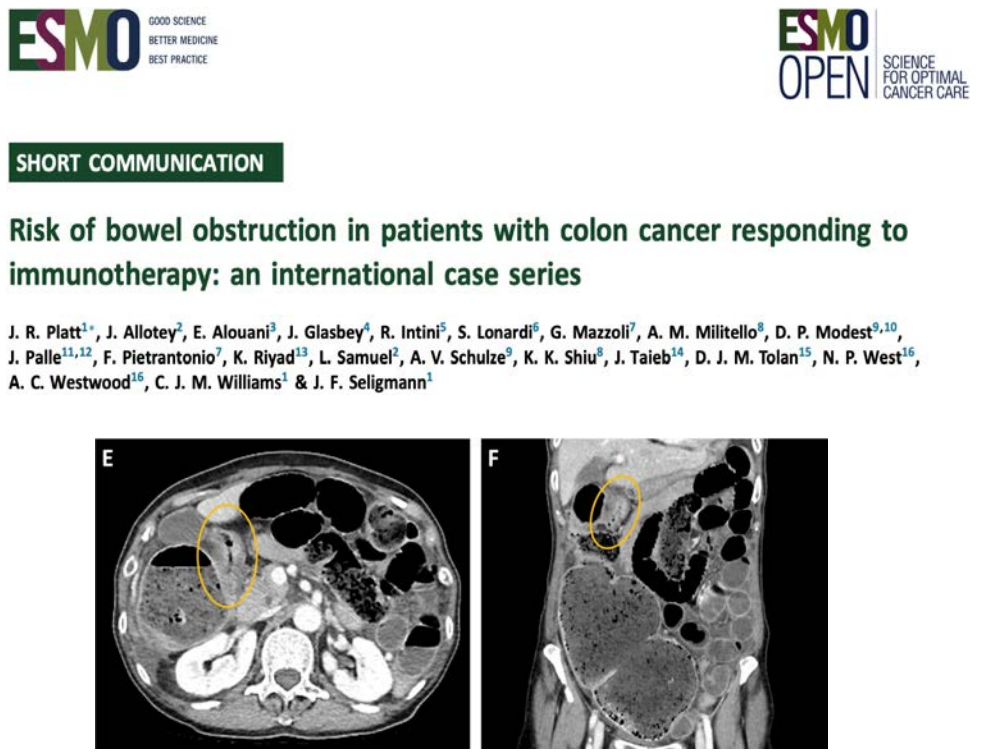




Chalabi et al, Nature Medicine, 2020, Kasi, GI ASCO, 2024

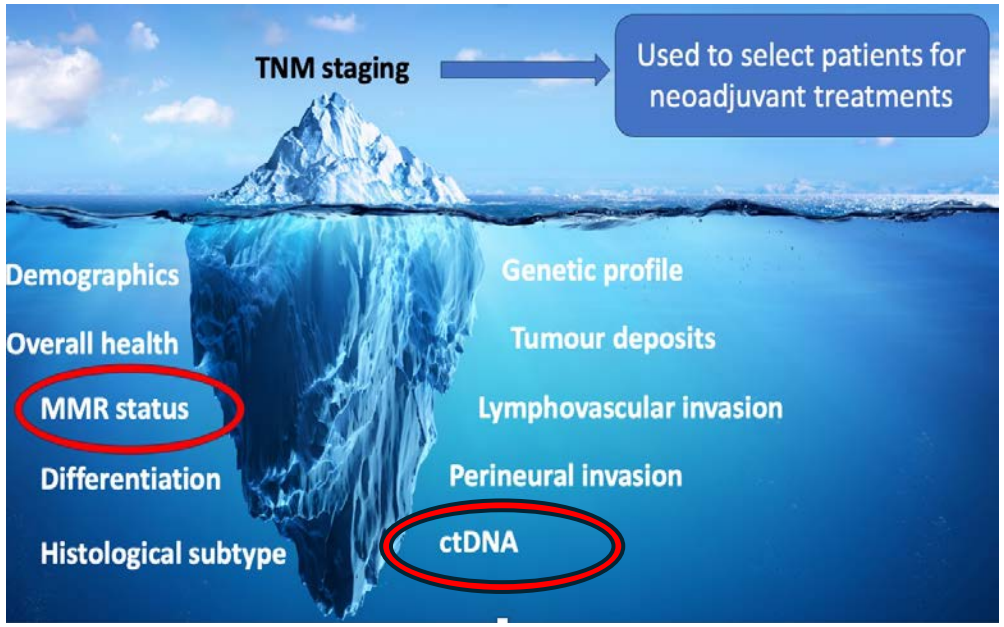
What is the magnitude of risk for emerging safety concerns for IO for locally advanced CRC?

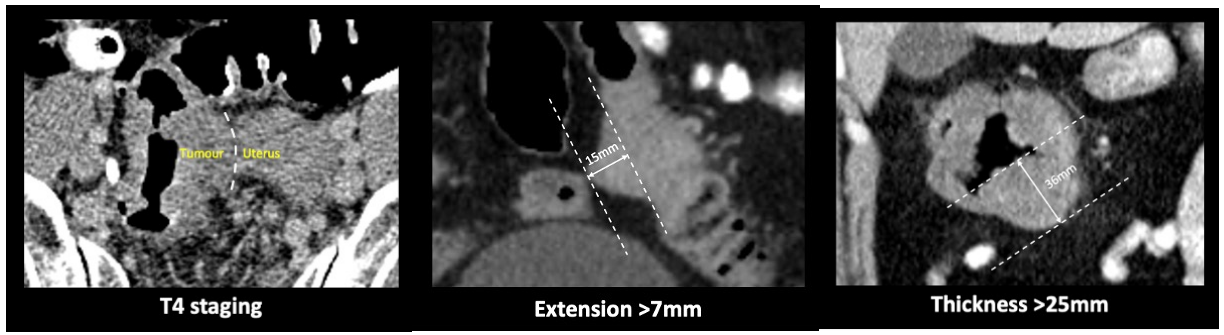
- Risk of grade 5 IO toxicity small but important risk.
- Caution with baseline patient frailty
- Risk of tumor related complications which are associated with good responses
- Low grade endocrinopathies can mean life-long treatment
- However, overall good tolerability & completion rates



De la Fouchardiere, ESMO Meeting 2024; Gooyer, ESMO Meeting 2024; Chalabi, ESMO Meeting 2024, Platt, ESMO Open 2024

Patient selection & changing patient pathways





- Patient selection for neoadjuvant treatments for both LACC and LARC could be improved
- For colon cancer CT staging is possible
  - Radiological/ pathological correlation worse in dMMR than pMMR tumors
  - CT features identify high risk tumors at baseline, regardless of pathology
- MSI/MMR testing pre-surgery is guideline endorsed
- ctDNA may add to identification of the high risk patient at baseline
- Radiology/ surgical engagement critical

Platt, ESMO Congress, 2024

DECISION POINTS IN THE TREATMENT PATHWAY

Pathway coordination

1

MDT rev… of diagnosi… stagin…

PATIENT CHOICE

…gical …tion

2

MDT review of post-operative hist… +/- MSI/MMR status

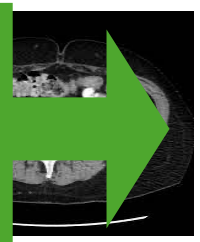
Assessment of post-rx response

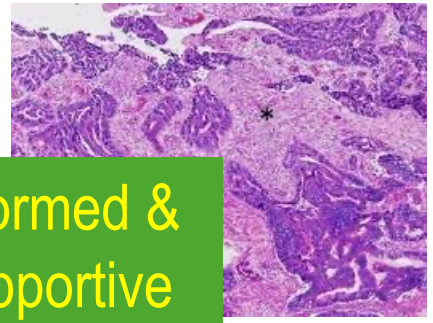
…t

Follow up

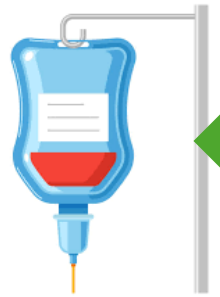
Upfront MMR/MSI

Radiology call on T & N stage





Informed & supportive surgical colleague



Ability to review & treat rapidly

Conclusions

- For locally advanced CRC knowledge of MSI/MMR status at baseline is important
- Use of neoadjuvant IO can be transformative in MSI-H LARC; work on implementation required
- Use of neoadjuvant IO should be recommended in the most advanced MSI-H LACC
  - Further evidence generation shall establish role compared with current SOC; long term data and biology supportive of neoadjuvant approach
- Greatest future opportunity for neoadjuvant IO is with both MSS LARC and LACC
- Neoadjuvant chemotherapy offers well evidenced improvements in long term outcomes compared with current SOC
- Further development urgently required to identify the high risk patient at baseline and response assessment
- The opportunity to cure more LACC patients requires implementation of new patient pathways and MDT collaborative working

Questions from General Medical Oncologists — Neoadjuvant Treatment for Localized Rectal Cancer

54 y/o man, Rectal adenocarcinoma, cT3N1, MSI-high/dMMR

Comorbidities: Obesity, obstructive sleep apnea disease. Surgical team considering total neoadjuvant therapy; oncology considering neoadjuvant PD-1 inhibitor instead of chemoradiation. In locally advanced MSI-high CRC, when should neoadjuvant checkpoint inhibition replace chemotherapy or chemoradiation?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — Neoadjuvant Treatment for Localized Rectal Cancer

A 62-year-old man with rectal bleeding and tenesmus. Colonoscopy reveals a low rectal mass 6 cm from the anal verge. Biopsy confirms adenocarcinoma. MRI pelvis: cT3N1 rectal cancer, threatening the mesorectal fascia. CT chest/abdomen: no distant metastases. Molecular testing: MSI-high/dMMR (loss of MLH1 and PMS2). Multidisciplinary team recommends neoadjuvant immune checkpoint inhibition. Duration of treatment? Dostarlimab administered every 3 weeks for 6 months? Any role for combo IO/IO? Monitoring (MRI and colonoscopy): What is the role of ctDNA and if negative, how frequently should it be reordered?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — Neoadjuvant Treatment for Localized Rectal Cancer

53 y/o M with MSI-H rectal adenocarcinoma, clinical complete response to neoadjuvant dostarlimab. Surgery vs observation, what is the protocol to manage patients without surgery?

55 y/o man with no comorbidities with Stage IIIA rectal cancer, was given 12 weeks of neoadjuvant dostarlimab, achieved clinical CR. Would you recommend additional chemo/RT or only surgery?

Questions from General Medical Oncologists — Neoadjuvant Treatment for Localized Rectal Cancer

36 y/o M with Lynch syndrome and Crohn's disease that is clinically quiescent, newly diagnosed Stage III rectal cancer. Is dostarlimab an option for a patient with Crohn's disease that is not active?

55 y/o M with Stage 3 rectal cancer, found to be MSI-H. Has hx of RA with moderate control on biologic therapy. Would experts consider single-agent IO vs doublet? What are situations where singlet may be preferred?

Questions from General Medical Oncologists — Neoadjuvant Treatment for Localized Colon Cancer

44 yr old male with newly dx clinical Stage II MSI-high colon cancer is curious to see if he can get ICI alone and avoid surgery similar to rectal cancer.
He is open to close monitoring with surveillance scopes, ctDNA and scans.
Any data to show patients with MSI-high colon cancer can avoid chemotherapy? Role of ctDNA?

50 y/o, T4 Nx MSI-high colon cancer. Are CPI ready for prime time for neoadjuvant therapy for MSI-high locally advanced colon cancer?
Role of ctDNA?

RTP
RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Neoadjuvant Treatment for Localized Colon Cancer

24 y/o F with T3N1 distal colon adenocarcinoma, MSI-H, with plan for neoadjuvant therapy followed by surgery. What immunotherapy combination (single vs dual agent) would you recommend?

A 39 y/o male with Stage IIIA, dMMR, RAS- right sided colon cancer, and pt strongly desired neoadjuvant tx approach after being told by surgeon that neoadjuvant tx can help out with surgery later on. Should I give nivo or pembro + FOLFOX, or should I advise dual ICI like nivo + ipi as neoadjuvant tx regimen?

62 y/o female with MSI-high right-sided large colon cancer causing near obstruction. Is neoadjuvant FOLFOX/nivolumab a good option?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — Neoadjuvant Treatment for Localized Colon Cancer

85 y/o M (ECOG 1) with DM w/neuropathy, diabetic retinopathy, HTN, CKD, and T4N0 distal colon adenocarcinoma, MSI-H, with plan for neoadjuvant therapy followed by surgery. What immunotherapy combination (single vs dual agent) would you recommend given patient's age and comorbidities?

85 yr old male with underlying controlled ulcerative colitis diagnosed with low sigmoid colon cancer and borderline surgical candidate. Would you treat a patient like this with IO with curative intent and try avoiding surgery?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — Neoadjuvant Treatment for Localized Colon Cancer

56 yr old male with CRC, Lynch syndrome with 2 isolated liver mets. Any data for ICI such as atezo alone or with chemo prior to resection of oligo met? Any data to suggest chemo/IO is better than IO alone?

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1: Neoadjuvant Treatment for Localized Colorectal Cancer (CRC) — Dr Seligmann

Module 2: Emerging Novel Approaches to Adjuvant Treatment for Localized CRC — Dr Lieu

Module 3: Role of Circulating Tumor DNA (ctDNA) Testing in Localized CRC — Dr Cohen

Cancer Center

NCI-DESIGNATED CONSORTIUM
COMPREHENSIVE CANCER CENTER

Emerging Novel Approaches to Adjuvant Treatment for Localized CRC

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

NCI Designated Comprehensive Cancer Center

Topics for Discussion

- Historical outcomes achieved with standard adjuvant chemotherapy for patients with localized CRC, including for those with MSI-H/dMMR disease
- Addition of atezolizumab to FOLFOX chemotherapy for patients with Stage III CRC and dMMR tumors
- Other ongoing trials evaluating immune checkpoint inhibitors as a component of adjuvant therapy for localized CRC

20+ FDA-Approved Regimens for Metastatic Colorectal Cancer

"Cytotoxics"	Mechanism
1. 5-Fluorouracil (5-FU)	-> pyrimidine analog
2. Capecitabine	-> oral 5-FU pro-drug
3. TAS-102	-> 5-FU drug with metabolism inhibitor
4. Irinotecan	-> topoisomerase I inhibitor
5. Oxaliplatin	-> third-generation platinum

"Biologics/Targeted"	Mechanism
1. Cetuximab	-> antibody against EGFR
2. Panitumumab	-> antibody against EGFR
3. Bevacizumab	-> antibody against VEGF
4. Ziv-aflibercept	-> VEGF trap
5. Ramucirumab	-> antibody against VEGFR2
6. Ipilimumab	-> antibody against CTLA-4 (MSI-high only)
7/8. Regorafenib/fruquintinib	-> multi-tyrosine kinase inhibitors
9/10/11. Pembro/nivo/dostarlimab	-> antibody against PD-1 (MSI-high only)
12. Encorafenib + cetuximab	-> tyrosine kinase inhibitor against BRAF V600E
13. Tucatinib + trastuzumab	-> HER2 tyrosine kinase inhibitor and antibody
14. Trastuzumab deruxtecan	-> HER2 antibody-drug conjugate
15. Adagrasib + cetuximab	-> KRAS G12C inhibitor
16. Sotorasib + cetuximab	-> KRAS G12C inhibitor

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

Only 3 FDA-Approved Drugs for Adjuvant Colorectal Cancer

"Cytotoxics"	Mechanism
1. 5-Fluorouracil (5-FU)	-> pyrimidine analog
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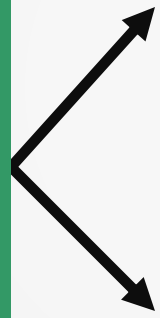
1. ~~cetuximab~~	~~-> antibody against EGFR~~
~~2. panitumumab~~	~~-> antibody against EGFR~~
~~3. bevacizumab~~	~~-> antibody against VEGF~~
~~4. ziv-aflibercept~~	~~-> VEGF trap~~
~~5. ramucirumab~~	~~-> antibody against VEGFR2~~
~~6. regorafenib~~	~~-> multi-tyrosine kinase inhibitor~~
~~7. ramucirumab~~	~~-> antibody against VEGFR2~~
~~8/9. pembrolizumab/nivolumab~~	~~-> antibody against PD-1 (MSI-high only)~~
~~10. ipilimumab~~	~~-> antibody against CTLA-4 (MSI-high only)~~
~~11. encorafenib + cetuximab~~	~~-> tyrosine kinase inhibitor against BRAF V600E~~

Adjuvant Therapy for Resected Primary

"MOSAIC" Trial

n = 2,246
Stage II/III colon CA
Primary endpoint:
3-yr disease free survival (DFS)

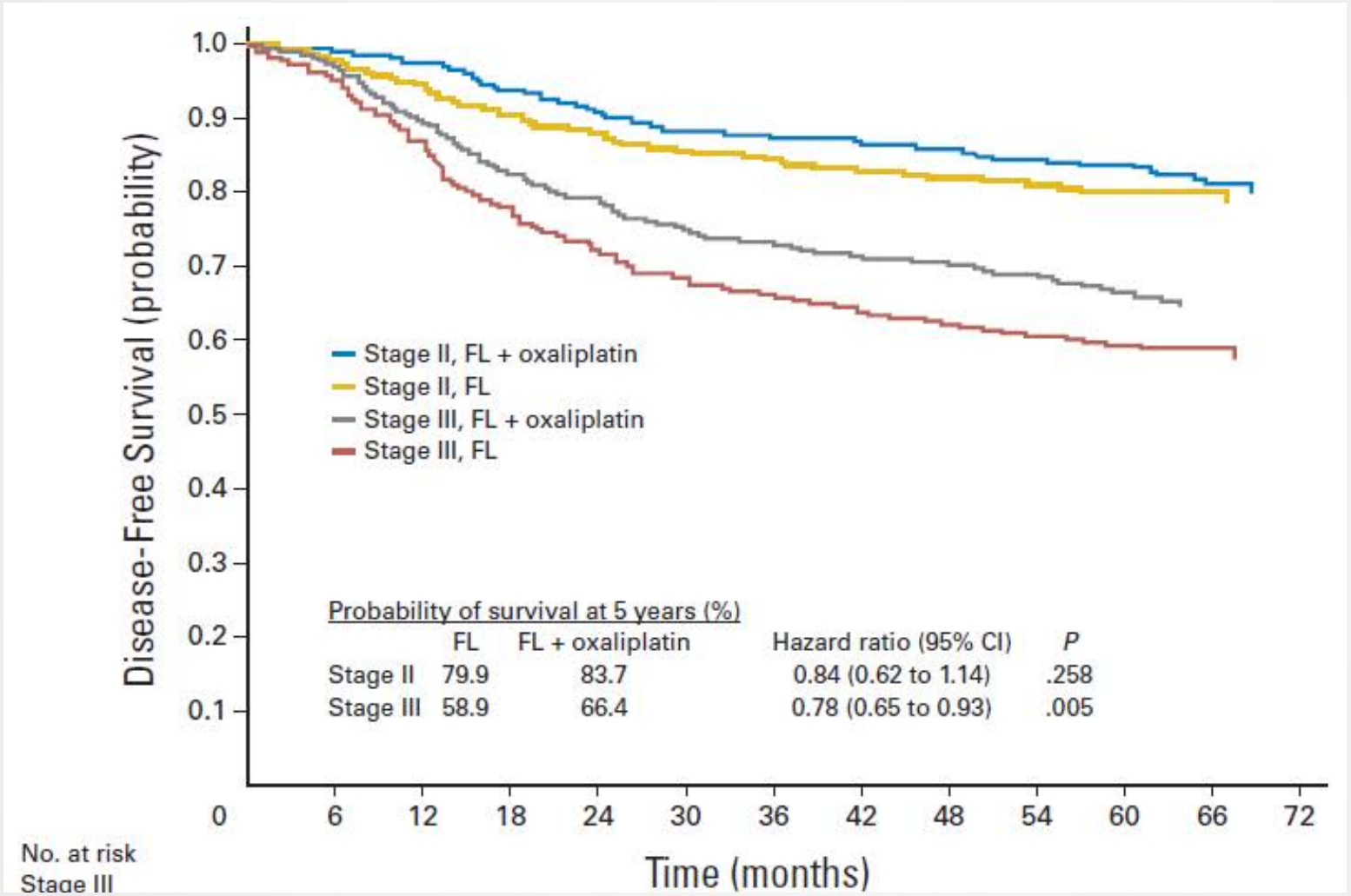


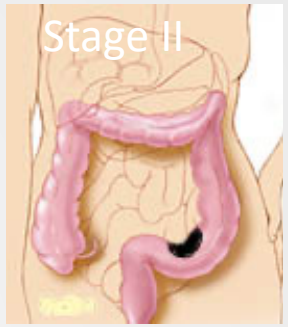
"LV5FU2" x 12
(infusional 5-FU/LV)

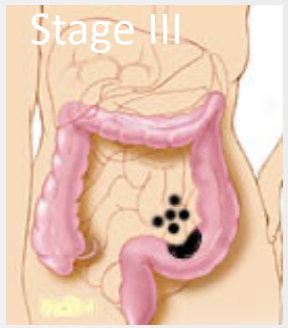
"FOLFOX4" x 12
(infusional 5-FU/LV with oxaliplatin)

Andre, NEJM 2004; Andre, JCO 2009

MOSAIC Trial: Disease-Free Survival







Andre, JCO 2009

MOSAIC:
Stage III Adjuvant FOLFOX

- Study presented with > 5 years follow-up
- 6.6% DFS benefit maintained HR = 0.8, p = 0.003

Overall Survival 6 years	5-FU	FOLFOX	p
Overall	76%	78.6%	0.057
Stage II	86.8%	86.9%	0.996
Stage III	68.6%	73%	0.029

4.4% OS benefit in stage III

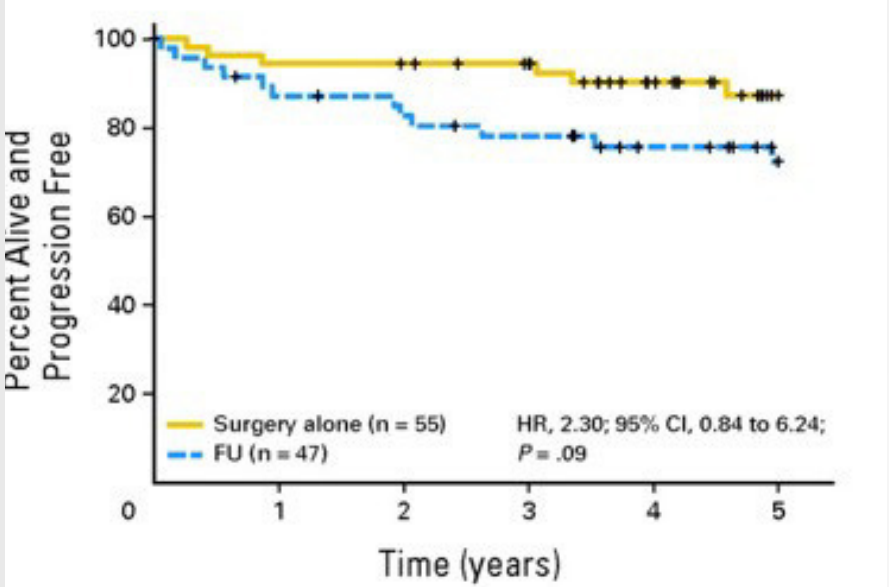
MSI-H in Colon Cancer: Prevalence and Prognosis

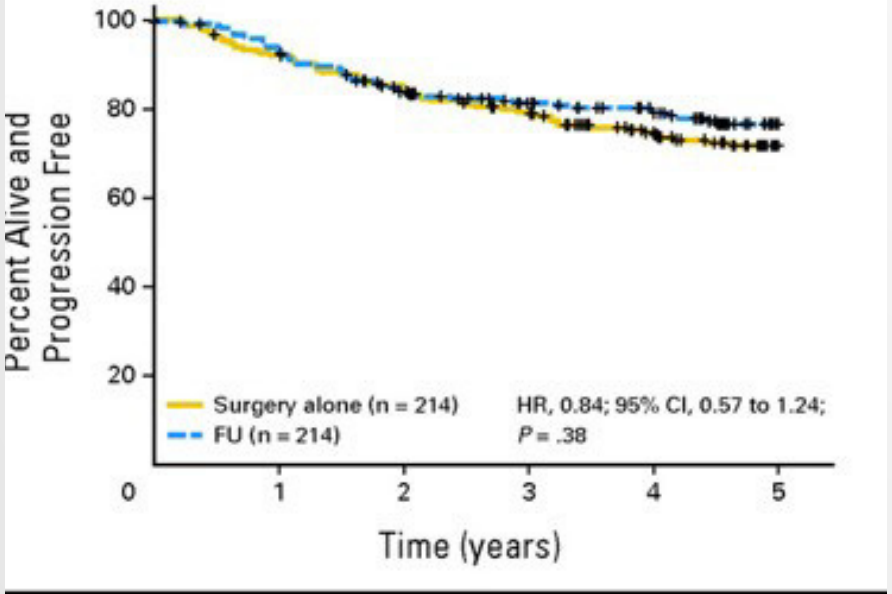
Stage	Prevalence	Prognosis Compared to MSS
II	15%-20%	excellent
III	8%-10%	same
IV	4%-5%	same or worse

- Hypermutated cancers too “deranged” to metastasize
- Immune system can prevent spread
- But once a metastatic clone has been selected, same or worse prognosis than microsatellite stable CRC

MSI-H, high levels of microsatellite instability; MSS, microsatellite stability.
The Cancer Genome Atlas, 2012.

MSI-H (dMMR) and 5-FU in stage II colon cancer

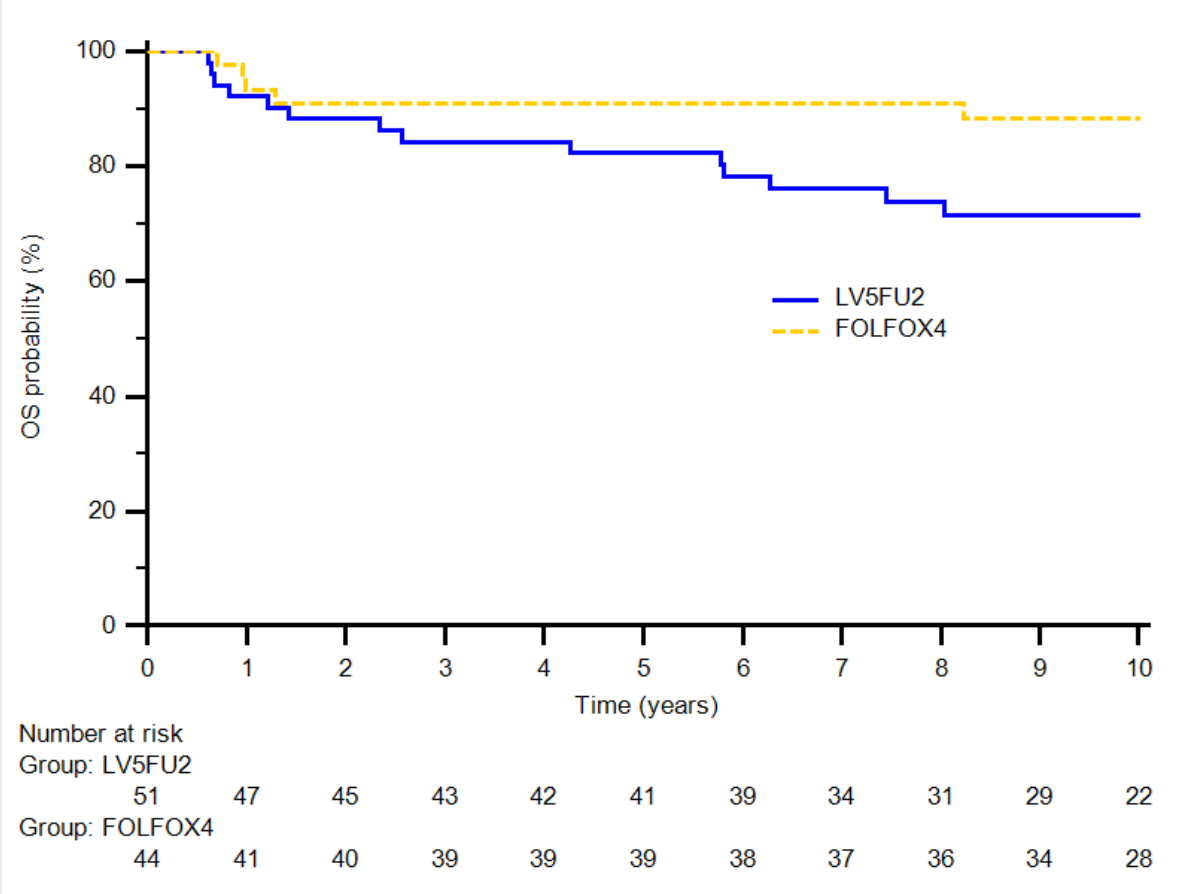




- Disease-free survival in patients with stage II disease and defective DNA mismatch repair (dMMR)
  - Patients did worse with chemo!
- Disease-free survival in patients with stage II disease and proficient mismatch repair (pMMR)
  - No identifiable benefit with chemo and stage II disease

Sargent et al. *J Clin Oncol* 2010;28(20): 3219-3226.

What about dMMR and FOLFOX for stage III CRC?



Although n < 100, data appear reassuring that patients with dMMR/MSI-H stage III derive the same benefit from the addition of oxaliplatin *(HR=0.42, p=.06)*

Endpoint	LV5FU2	FOLFOX	HR	[95% CI]	P value
5-yr OS, % (sd)	82.3 (5.3)	90.9 (4.3)	0.42	0.18-0.98	0.060

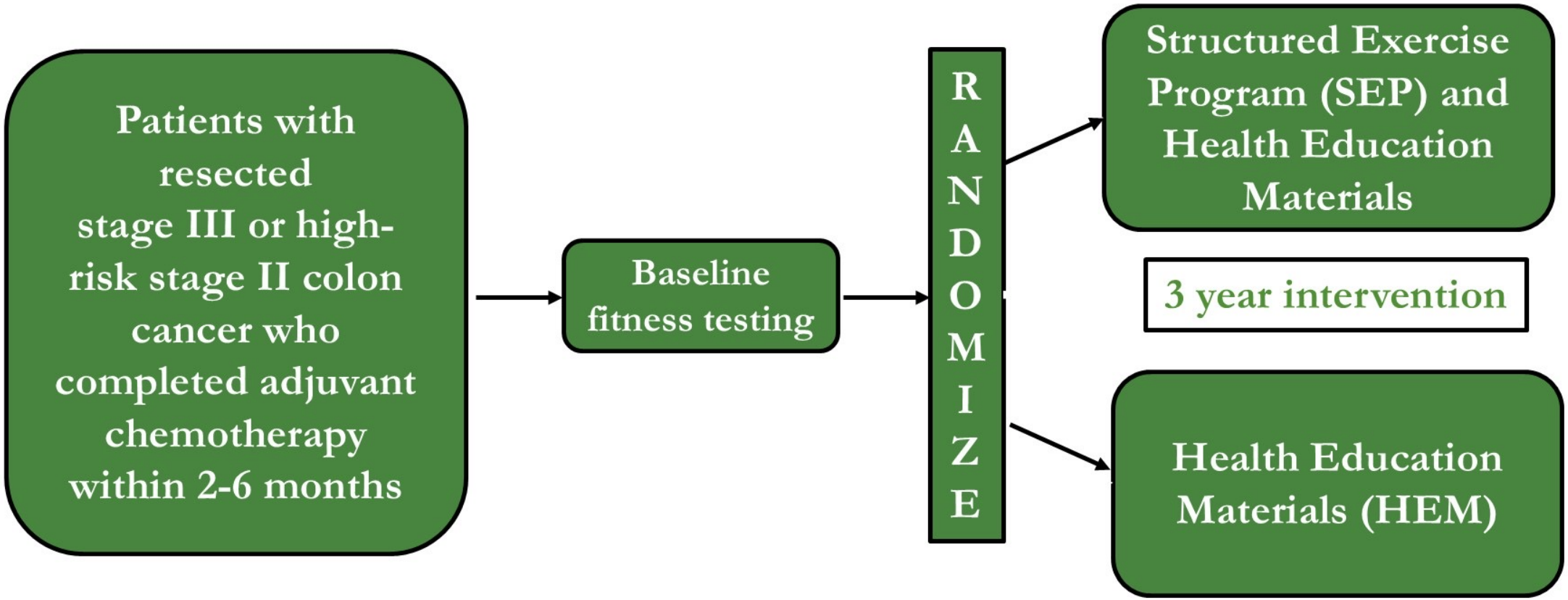
Flejou et al. J Clin Oncol 31, 3524(2013

What's New in Adjuvant Colon Cancer?

Exercise and Aspirin

Making something old – new again!

CO21 Study Schema



Canadian Cancer Trials Group / Groupe canadien des essais sur le cancer

Courneya et al. *N Engl J Med* 2025;393:13-25

What is a MET?

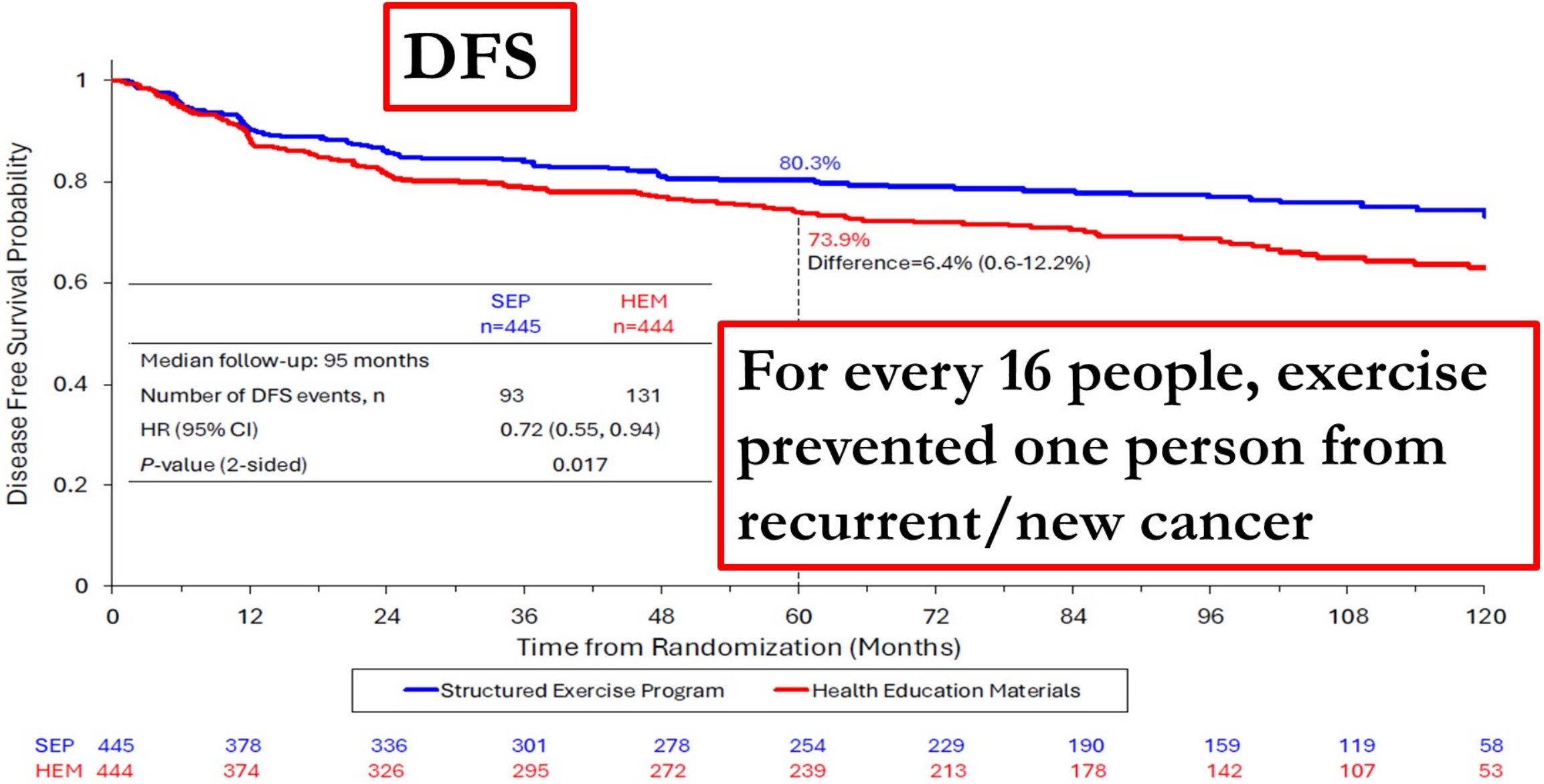
- CO.21 target was to increase physical activity by 10 MET/hrs/week above baseline

- 1 MET = unit of energy expended by sitting for one hour
- 1 hour of brisk walking = 4 MET-hours

- 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

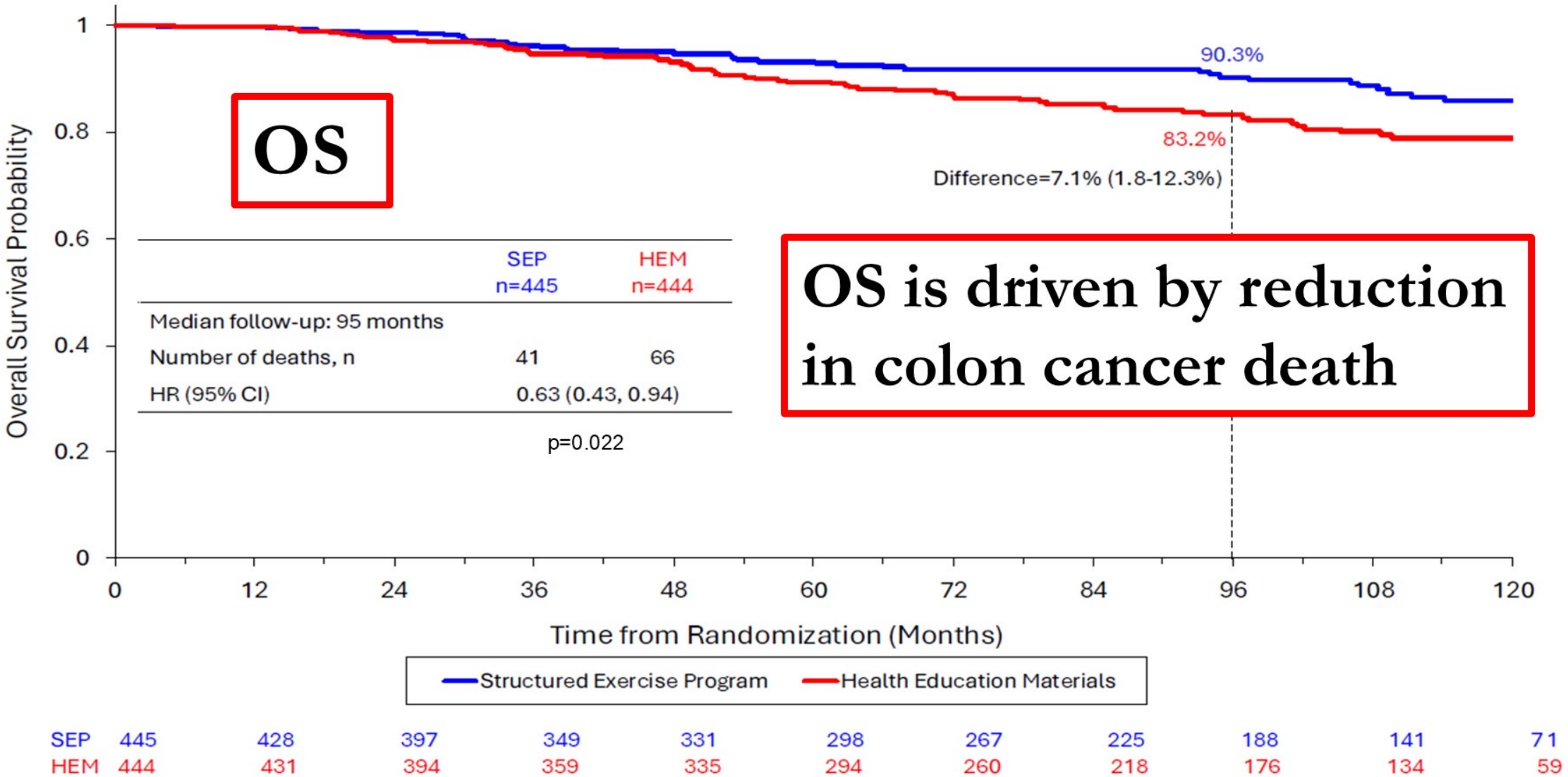
Courneya et al. *N Engl J Med* 2025;393:13-25

DFS



For every 16 people, exercise prevented one person from recurrent/new cancer

Courneya et al. *N Engl J Med* 2025;393:13-25



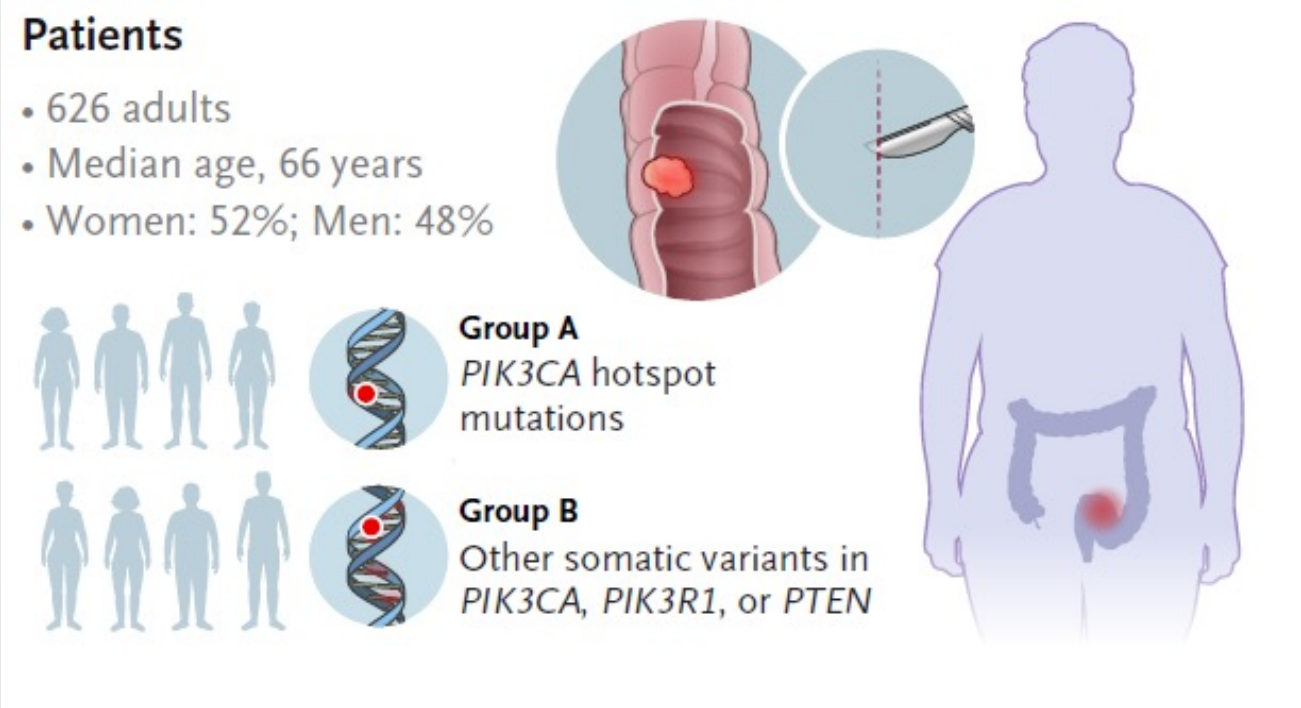
Courneya et al. *N Engl J Med* 2025;393:13-25

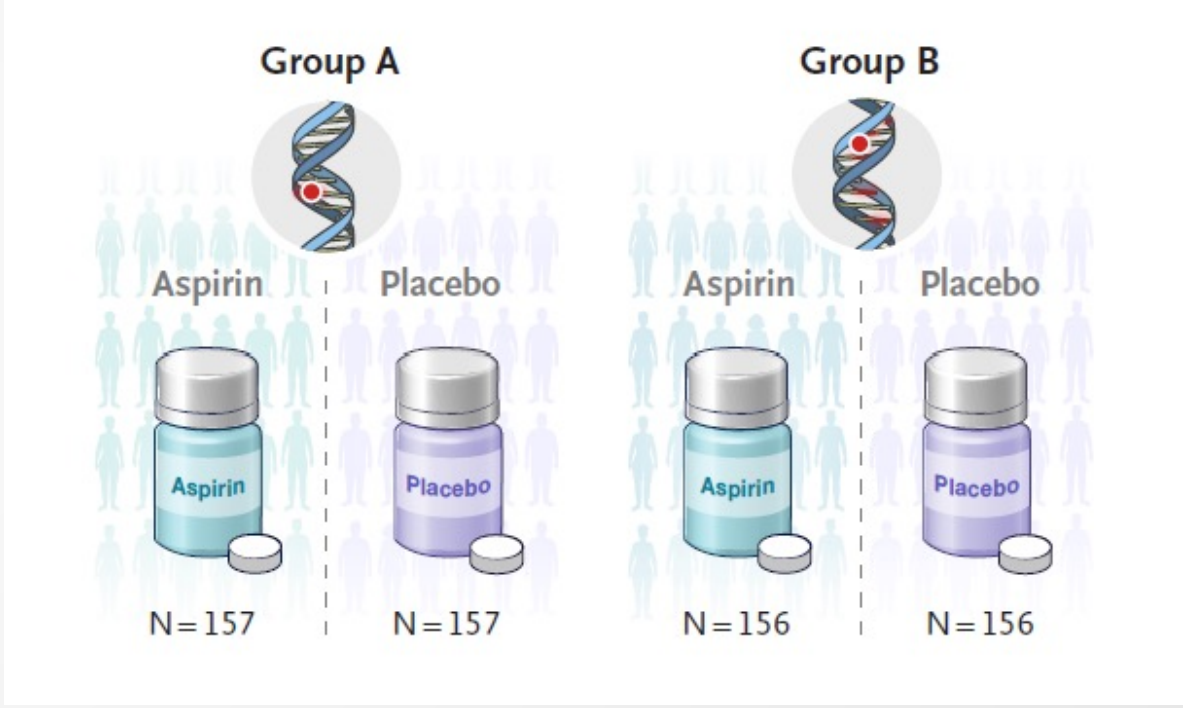
Putting CO.21 Effect Size in Context

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	Breast	1.8% at 10 years

Courneya et al. *N Engl J Med* 2025;393:13-25

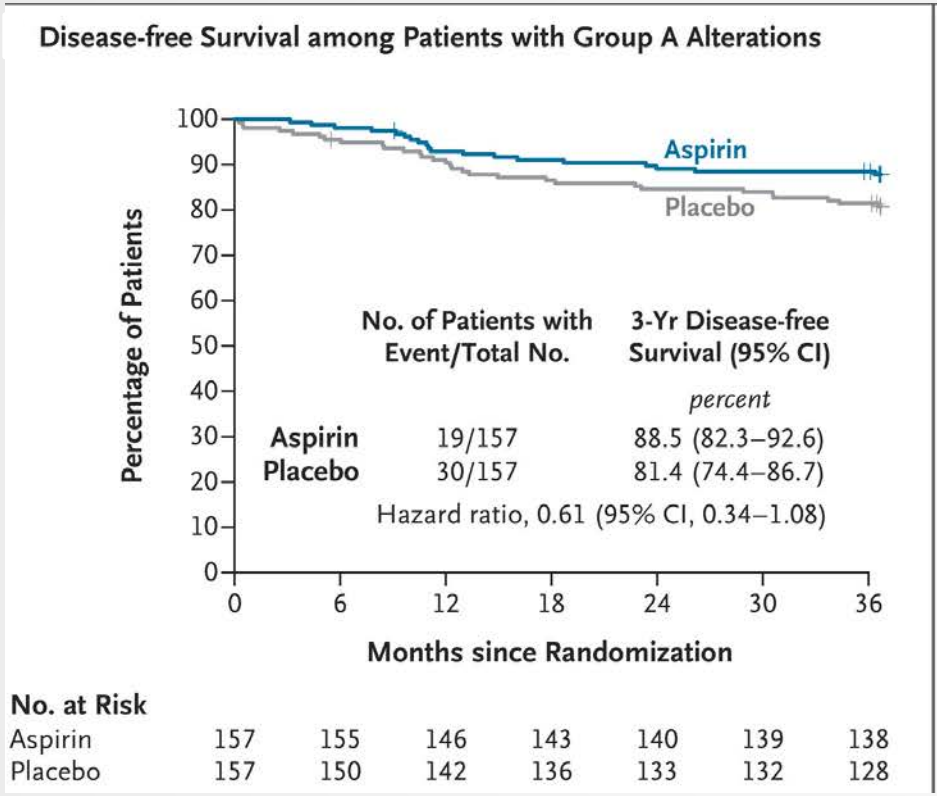
Aspirin and Colon Cancer Recurrence
ALASSCA Study

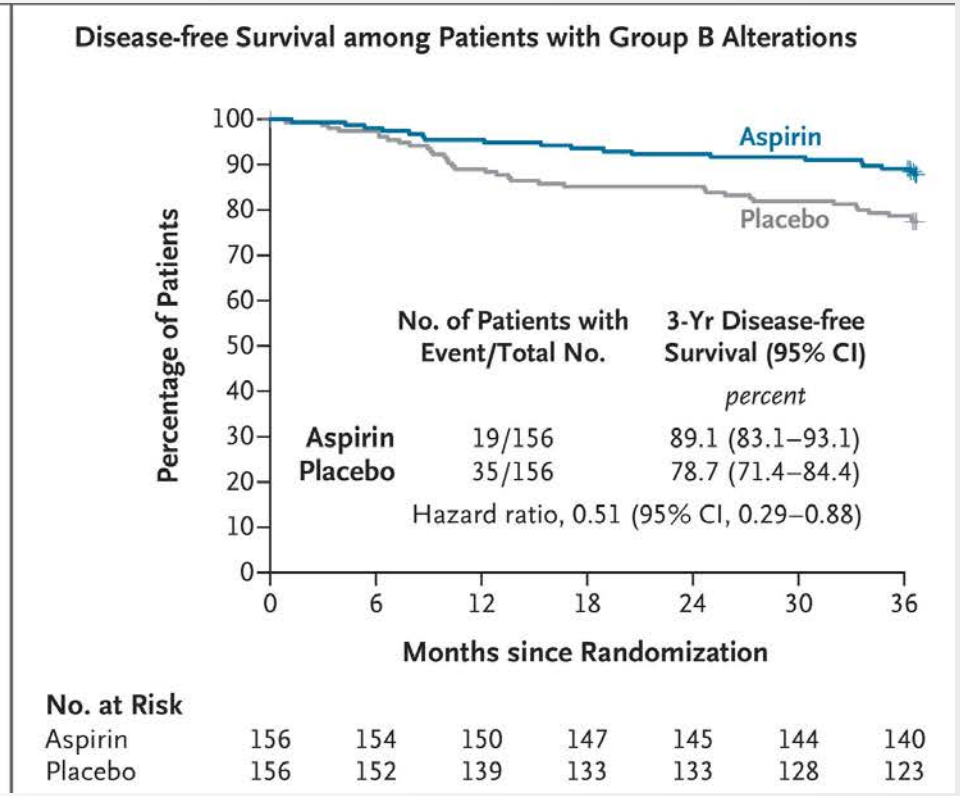


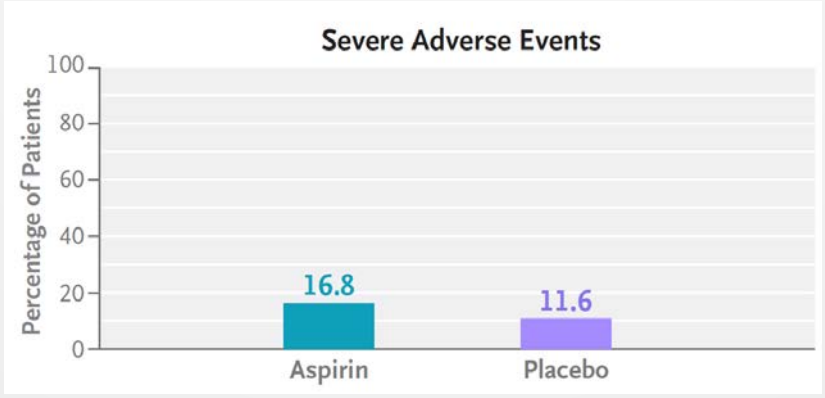


Martling et al. *N Engl J Med* 2025;393:1051-1064

ALASSCA Study





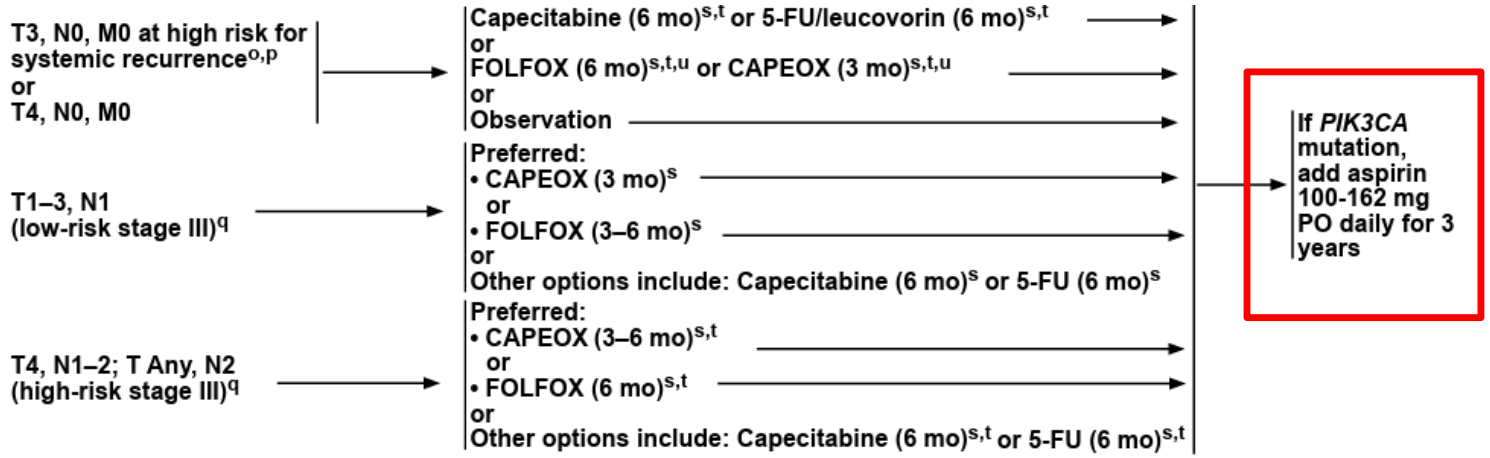


Martling et al. *N Engl J Med* 2025;393:1051-1064

Take Home Points:

Exercise!

Aspirin should be given to patients with a PIK3CA mutation



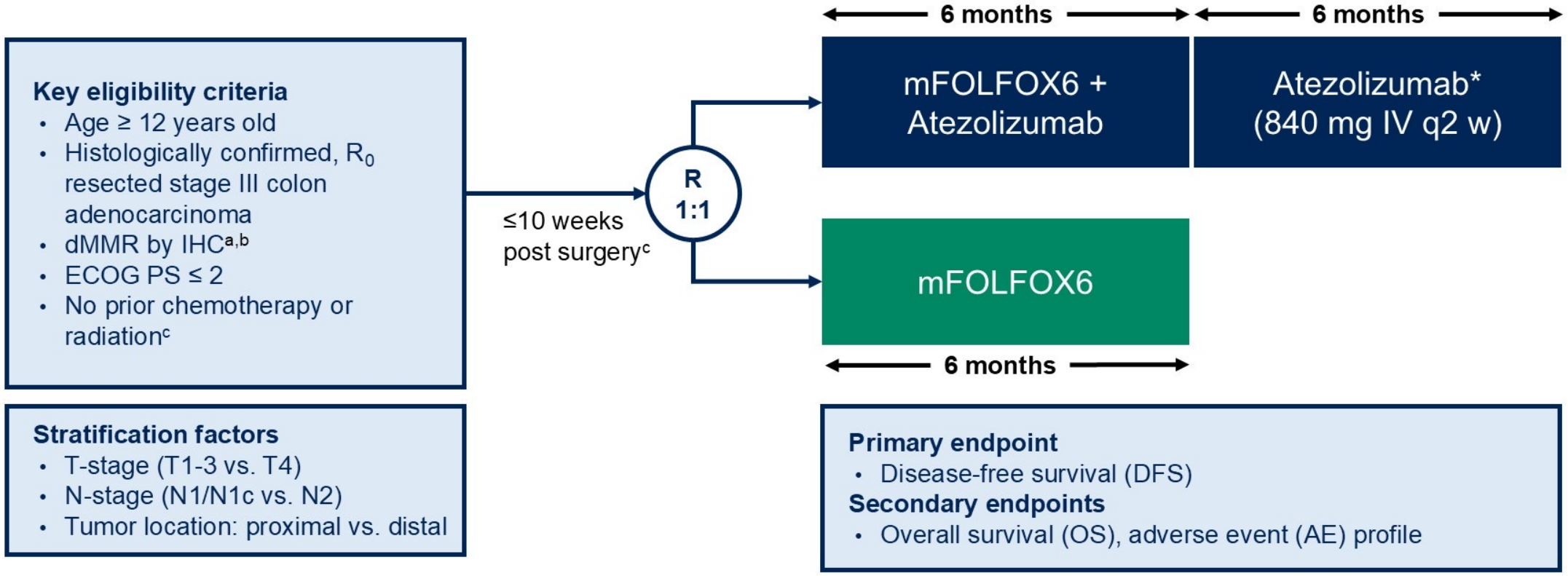
QUESTIONS:

- Should we be hiring more personal trainers and giving less oxaliplatin?
- How many providers are testing for PIK3CA in early-stage CRC?
- What is the optimal dose and duration of aspirin?

What's New in Adjuvant Colon Cancer?

Adjuvant Atezolizumab for dMMR/MSI-H

ATOMIC: addition of atezolizumab to standard chemotherapy for dMMR/MSI-H colon cancer



[a] **dMMR by immunohistochemistry (IHC) locally or at site-selected reference laboratory. Retrospective central confirmation of dMMR also performed.**
[b] Lynch syndrome included.
[c] One cycle of mFOLFOX6 prior to randomization permitted.

*Atezolizumab (anti-PD-L1)

NCT02912559

Sinicrope et al. J Clin Oncol 43, 2025 (suppl 17; abstr LBA1)

Baseline Characteristics

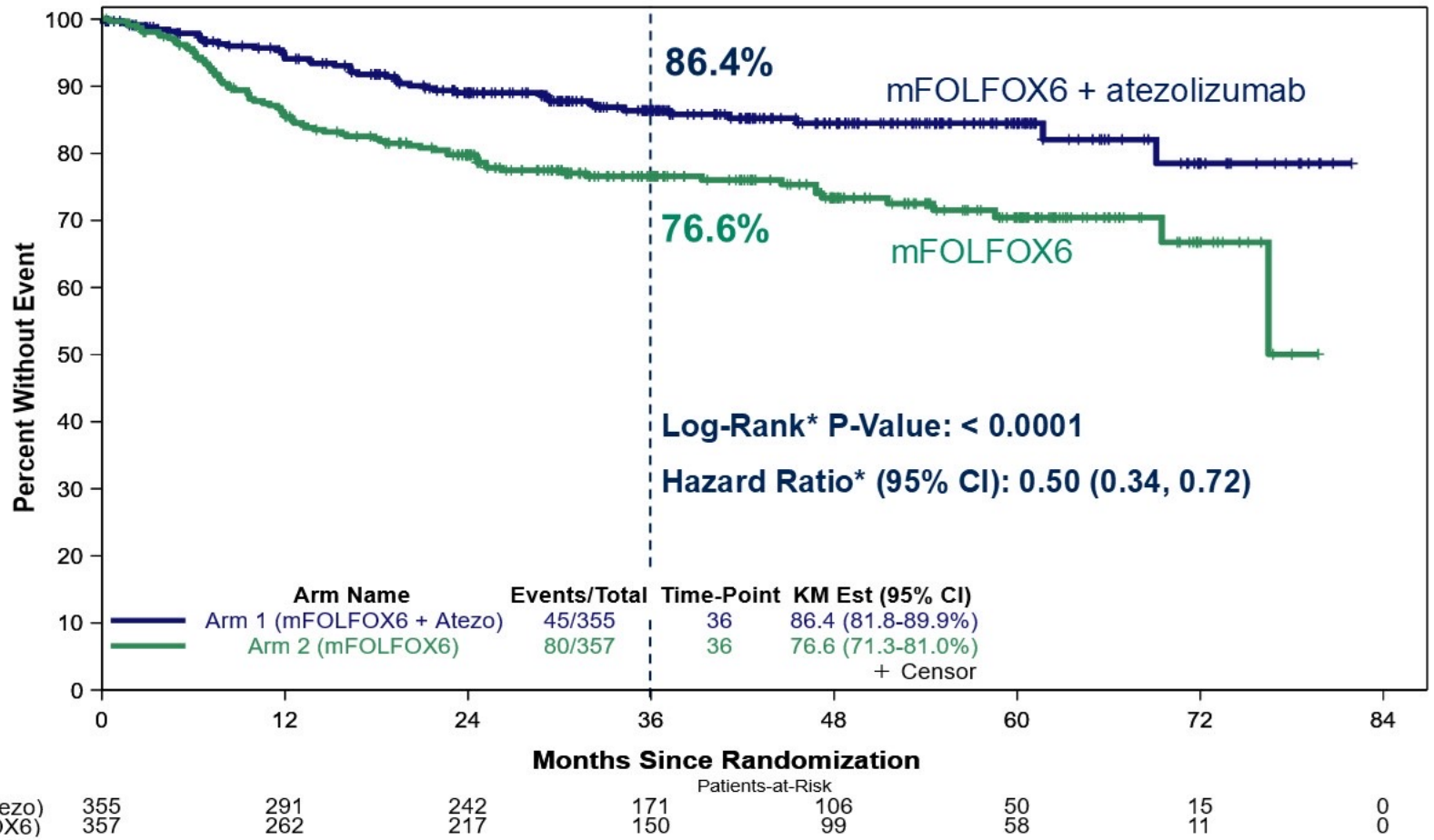
	mFOLFOX6 + Atezo (N=355)	mFOLFOX6 (N=357)
Age (years)		
Median	65	63
Q1, Q3	51.0, 73.0	48.0, 73.0
Sex, n (%)		
Female	186 (52.4%)	206 (57.7%)
Male	169 (47.6%)	151 (42.3%)
Race, n (%)		
White	302 (85.1%)	305 (85.4%)
Black	28 (7.9%)	22 (6.2%)
Other	25 (6.0%)	30 (8.4%)
Primary Tumor Site, n (%)		
Proximal	301 (84.8%)	296 (82.9%)
Distal	53 (14.9%)	57 (16.0%)
Multiple	1 (0.3%)	4 (1.1%)

	mFOLFOX6 + Atezo (N=355)	mFOLFOX6 (N=357)
T-Stage, n (%)		
Tx	0	1 (0.3%)
T1	11 (3.1%)	4 (1.1%)
T2	30 (8.5%)	22 (6.2%)
T3	202 (56.9%)	216 (60.5%)
T4	112 (31.5%)	114 (31.9%)
N-Stage, n (%)		
N1/N1c	226 (63.7%)	225 (63.0%)
N2	129 (36.3%)	132 (37.0%)
Risk Group, n (%)		
Low (Tx-T3 and N1/N1c)	164 (46.2%)	164 (45.9%)
High (T4 and/or N2)	191 (53.8%)	193 (54.1%)
ECOG, n (%)		
0	238 (67.0%)	225 (63.0%)
1	111 (31.3%)	127 (35.6%)
2	6 (1.7%)	5 (1.4%)

Baseline patient characteristics were well balanced between study arms

Sinicrope et al. J Clin Oncol 43, 2025 (suppl 17; abstr LBA1)

Primary Endpoint: DFS



Patients-at-Risk

Arm 1 (mFOLFOX6 + Atezo)	355	291	242	171	106	50	15	0
Arm 2 (mFOLFOX6)	357	262	217	150	99	58	11	0

Confirmed dMMR by central reference laboratory: Log-Rank P-Value: 0.0007, Hazard Ratio (95% CI): 0.53 (0.36, 0.79)

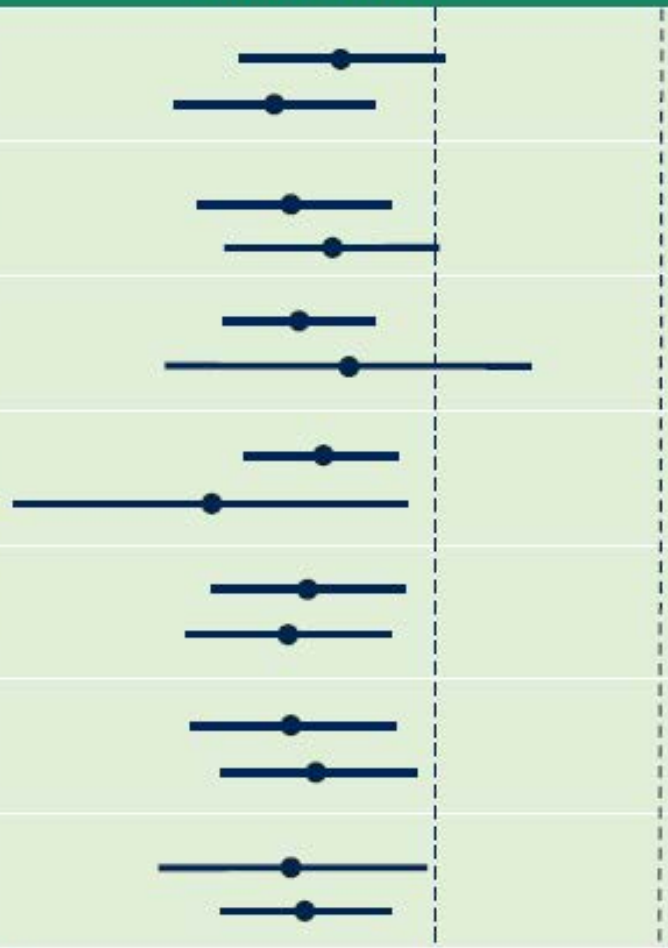
*Stratified by randomization factors

Median follow-up = 37.2 mos

Sinicrope et al. J Clin Oncol 43, 2025 (suppl 17; abstr LBA1)

DFS by Subgroups

		mFOLFOX6 + Atezo	mFOLFOX6	HR (95% CI)
Age	< 65 year	22/173	36/187	0.61 (0.36, 1.04)
	≥ 65 year	23/182	44/170	0.43 (0.26, 0.72)
Sex	Female	24/186	50/206	0.48 (0.29, 0.77)
	Male	21/169	30/151	0.58 (0.33, 1.01)
Race	White	38/302	69/305	0.50 (0.33, 0.74)
	Other	7/53	11/52	0.63 (0.25, 1.63)
Tumor Location	Proximal	40/301	65/296	0.56 (0.38, 0.83)
	Distal	5/53	14/57	0.31 (0.11, 0.87)
T-Stage	Tx/T1-T3	23/243	44/243	0.51 (0.31, 0.85)
	T4	22/112	36/114	0.46 (0.27, 0.79)
N-Stage	$N1/N1_c$	21/226	41/225	0.48 (0.28, 0.81)
	N2	24/129	39/132	0.54 (0.33, 0.90)
Risk Group	Low*	12/164	25/164	0.47 (0.24, 0.94)
	High*	33/191	55/193	0.51 (0.33, 0.78)
		Events/Patients	Events/Patients	



*Low (Tx-T3 and N1/N1c); High (T4 or N2)

Sinicrope et al. J Clin Oncol 43, 2025 (suppl 17; abstr LBA1)

Safety Summary

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

Investigator attribution of treatment-related adverse events (AE)

Received at least one dose of treatment

*1 sudden death NOS (possibly related); 1 sepsis (possibly related)

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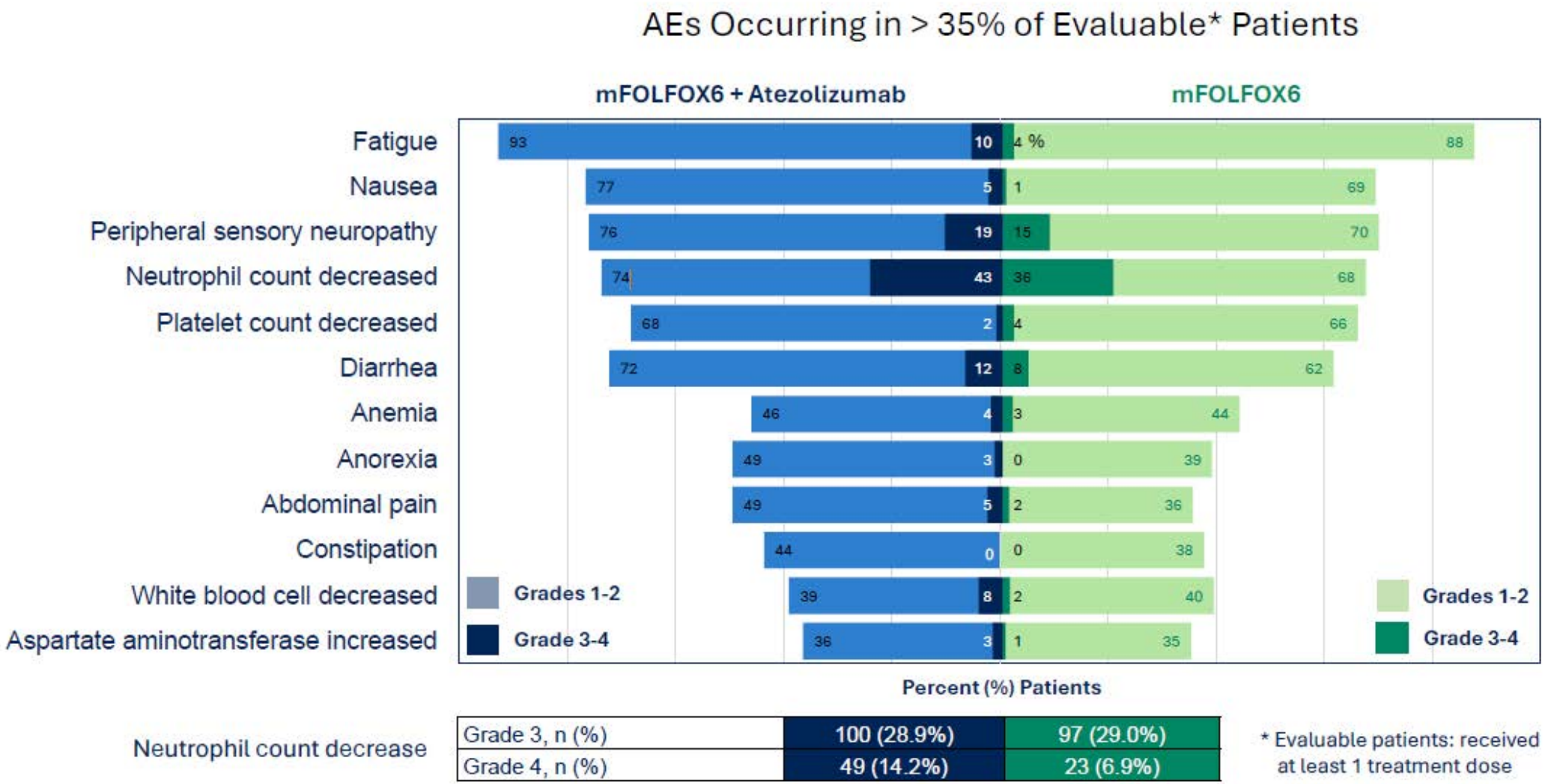
Patient Safety



Neutrophil count decrease	mFOLFOX6 + Atezolizumab	mFOLFOX6
Grade 3, n (%)	100 (28.9%)	97 (29.0%)
Grade 4, n (%)	49 (14.2%)	23 (6.9%)

* Evaluable patients: received at least 1 treatment dose

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Immune-Related AEs

No clinically significant differences in grade 3-4 immune-related AEs

		mFOLFOX6 + Atezo (N=346, %)#		mFOLFOX6 (N=334, %)#	
		Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Endocrinopathies	Adrenal insufficiency	0.3	0.9	0	0
	Hyperglycemia	17.9	2.6	9.0	1.2
	Hypothyroidism	20.5	0	3.6	0
Colitis	Colitis	5.5	1.2	0.6	0
	Diarrhea	60.1	12.1	53.3	8.4
Myositis	Generalized muscle weakness	7.8	0.9	3.3	0
Dermatitis	Rash maculo-papular	13.3	0.9	6.0	0

	Grade 3-4	
Hepatitis, n (%)		
ALT or AST increase	5.2%	1.8%
Alk phos or bilirubin increase	1.8%	0%
Pneumonitis, n (%)	2%	0.9%

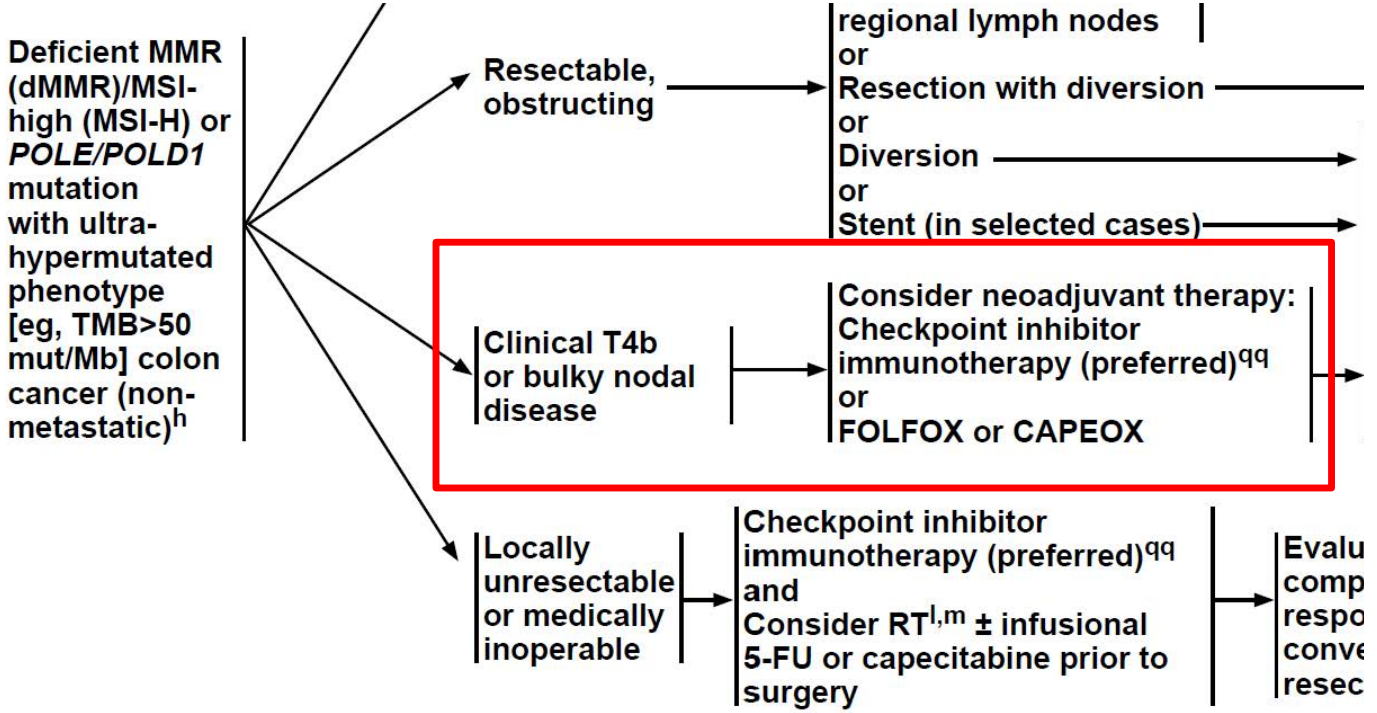
Received at least one dose of treatment
AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Alk phos: Alkaline phosphatase

Sinicrope et al. J Clin Oncol 43, 2025 (suppl 17; abstr LBA1)

Take Home Points:

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

FOLFOX/atezolizumab is the new standard in patients not receiving neoadjuvant therapy



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 after resection?
- Is there a role for immunotherapy in pMMR/MSS colon cancer?

What’s New in Adjuvant Colon Cancer?

Ongoing immunotherapy trials

AZUR-4: randomized study of neoadjuvant dostarlimab plus CAPEOX vs CAPEOX in untreated T4N0 or stage III in pMMR/MSS colon cancer

[a]Dostarlimab solution for infusion will be administered as a dose of 500 mg Q3W beginning on day 1 of each 21-day cycle for 4 cycles. [b]Oxaliplatin will be administered as an infusion with dose of 130 mg/m² Q3W on day 1 of each 21-day cycle for 4 cycles. Capecitabine will be administered as an oral agent for 14 days of a 21-day cycle with a dose of 1000 mg/m² BID for 4 cycles. [c]At least 3 and no more than 6 (+2) weeks after last dose of neoadjuvant chemotherapy.

Primary Endpoints:

- **Major pathological response (≤ 10% residual viable tumor)**
- **Safety**

Secondary Endpoints:

- **Primary tumor resection exclusion**
- **Pathological response**

Rasschaert et al. *2025 ASCO Annual Meeting*

A Phase II Clinical Trial Comparing the Efficacy of RO7198457 Versus Watchful Waiting in Patients With ctDNA-positive, Resected Stage II (High Risk) and Stage III Colorectal Cancer

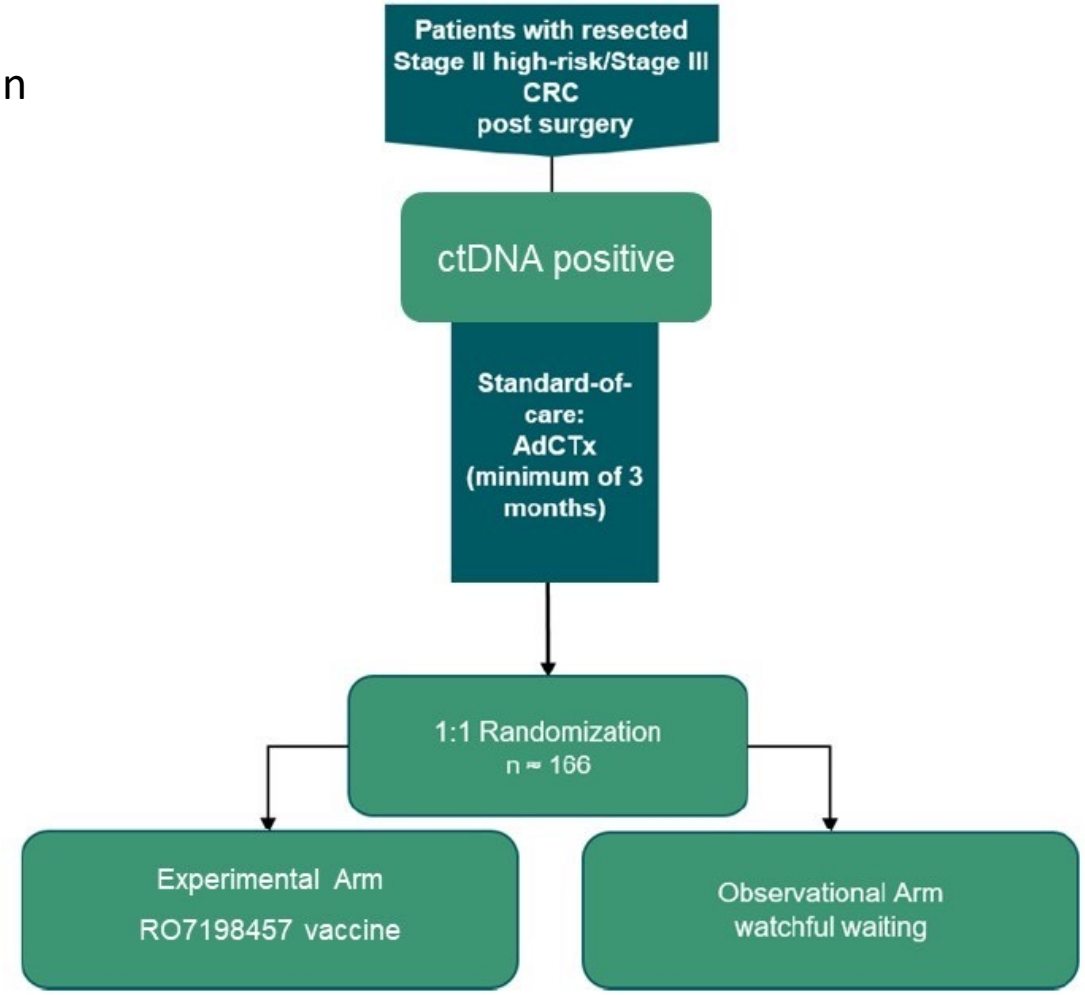
RO7198457 (BNT122) = *Personalized mRNA Cancer Vaccine*

Key Eligibility Criteria:

- Stage II/Stage III rectal cancer or Stage II (high risk)/Stage III colon cancer
- Patients must have detectable ctDNA prior to start of adjuvant chemotherapy

Primary Endpoint: Disease Free Survival

Estimated enrollment = 327



CRC MRD
Colorectal Cancer
Minimal Residual Disease

CRCMRD.COM

https://crcmrd.com/?avada_portfolio=biontech

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

58-year-old male. Resected colon adenocarcinoma, Stage IIIA. MSI-H, BRAFV600E. Type 2 DM, peripheral neuropathy. Given CAPEOX and atezo. Which clinicopathologic features (ex: T stage, nodal burden, LVI, BRAF status) most strongly influence your recommendation for adjuvant treatment in MSI-high disease?

66 y/o M with Stage IIIb colon ca, MSI-high, ctDNA negative. What is the optimal adjuvant chemo? FOLFOX + nivolumab? Role of ctDNA?

RTP
RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

71 yr old female with uncontrolled diabetes mellitus and grade 2 neuropathy at baseline has Stage III sigmoid cancer with 6 positive nodes. Tumor is MSI-H. One month post-op ctDNA is negative. Are there any situations where you would completely skip adjuvant chemotherapy and give only immunotherapy? If ctDNA is positive in this patient but tumor is MSI-high, would you still feel comfortable in proceeding with immunotherapy only?

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

82 y/o with DM, CAD, asthma with Stage III MSI-H colon cancer. Post op ctDNA negative. I do not offer patients with Stage III MSI-H colon cancer adjuvant therapy if ctDNA is negative, especially if older than 70. I do not think it is beneficial. I wait for them to have metastatic disease and treat with ICI. Curiously, in the 6 years since I've been doing this, none has had disease progression. Is this a reasonable practice?

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

Has any other ICI other than atezo been studied in combination with chemotherapy in colon cancer in adjuvant setting?

Management of 55 yo man with POLE mutation and oligometastatic disease to the lung, s/p resection? Management of localized and metastatic POLE mutant disease?

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

92 yr old female with Stage IIIc colon cancer status post surgery with 15 positive LN and positive ctDNA. Would you treat with single agent IO due to advanced age and if so for how long?

83 yo female stage 3 MSI-high CRC. Would you offer CPI to an 83-year-old?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

55 yr old male with end stage renal disease in dialysis diagnosed with Stage IIIb colon cancer and baseline grade 2 peripheral neuropathy. Would you treat this patient with 5-FU and IO without oxaliplatin?

77 y/o with COPD, oxygen-dependent, diagnosed with Stage III colon cancer, post-op ctDNA negative. Is there a rationale for treating MSI-H colon cancer with adjuvant fluoropyrimidines (since it is inherently resistant)?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

37 yr old male with newly diagnosed Stage III colon cancer, wants to be aggressive with treatment and is interested in considering immunotherapy. He asks if we can skip chemotherapy if his ctDNA remains negative. He does want benefit of immunotherapy maintenance. Based on the ATOMIC trial, for a young patient who wants to be aggressive would you give atezo with chemo? If ctDNA remains negative in the post op period at 1 mo and 3 mo, would you skip additional chemotherapy and continue only with immunotherapy?

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

Age/Sex: 62/M Diagnosis/stage: Colon adenocarcinoma, Stage III (pT3N2a), dMMR/MSI-H, BRAF WT. Comorbidities: Rheumatoid arthritis on low-dose prednisone + methotrexate (immune-toxicity risk), obesity. Post-op discussion: standard FOLFOX/CAPOX recommended; patient is very hesitant about neuropathy and asks about "immunotherapy instead." For MSI-H Stage III, what is the current best practice: standard adjuvant oxaliplatin-based chemo, clinical trials of PD-1, or ctDNA-guided escalation/ de-escalation — how do you counsel?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

53 yr old man with Stage II T4N0, contemplating adjuvant therapy. Any role for IO therapy in Stage II high-risk? ctDNA role here?

A 43 y/o female with Stage IIc, dMMR and positive liquid Bx, ctDNA+ after surgery; pt desired no chemo regimen be given adjuvantly. In this unique case, can I give nivo or pembro alone as adjuvant tx regimen? If so, for how long?

I have a 51 yo man with comorbidities of HTN and Stage IIA MSI-H colon cancer, s/p hemicolectomy, ctDNA negative. Would you offer adjuvant immunotherapy?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Adjuvant Treatment for Localized CRC

72 yo F, resected colon adenocarcinoma Stage II (T4aN0). MSI-H, BRAF wt, CAD. CKD stage 3. Observation. If adjuvant chemotherapy is chosen, do you modify regimen selection or duration (ex: 3 vs 6 months) specifically for MSI-high tumors?

56 yo F with right side pT4N0 colon cancer, MSI-high, ctDNA positive. What would be a good adjuvant regimen? Adjuvant therapy is usually not indicated for right-sided MSI-high Stage II colon cancer, but pT4 carries higher risks of occult peritoneal disease, and ctDNA is positive.

RTP
RESEARCH TO PRACTICE

Agenda

Module 1: Neoadjuvant Treatment for Localized Colorectal Cancer (CRC) — Dr Seligmann

Module 2: Emerging Novel Approaches to Adjuvant Treatment for Localized CRC — Dr Lieu

Module 3: Role of Circulating Tumor DNA (ctDNA) Testing in Localized CRC — Dr Cohen

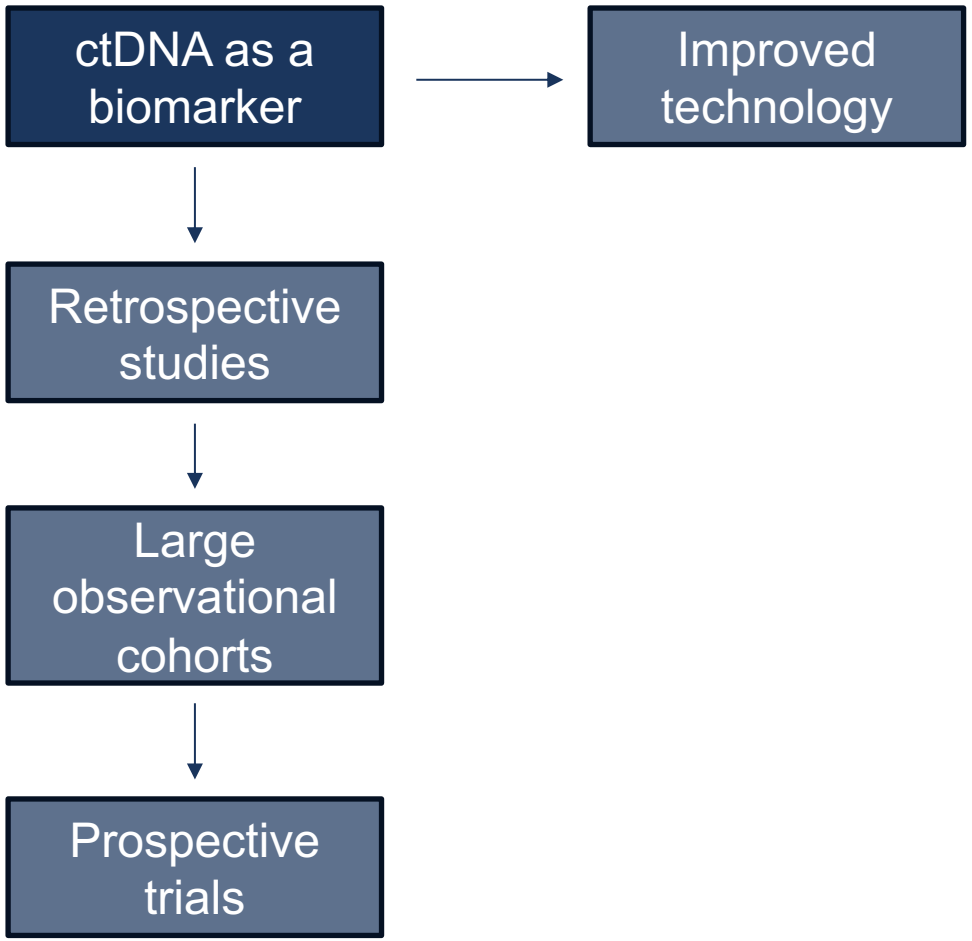
Fred Hutch
Cancer Center

MODULE 3:
Role of Circulating Tumor DNA (ctDNA) Testing in Localized CRC

Stacey A. Cohen, MD
Professor, Fred Hutchinson Cancer Center &
University of Washington

UW Medicine

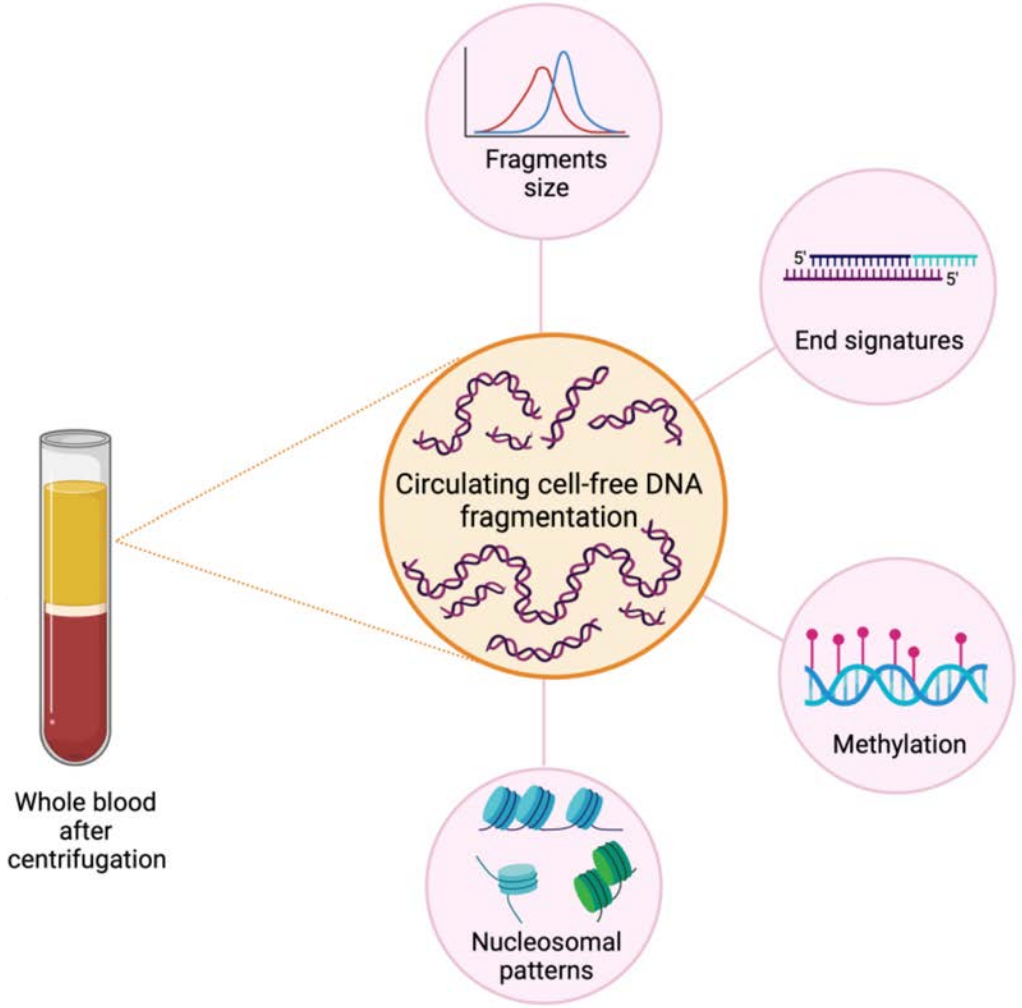
State of the data on ctDNA in colorectal cancer



Defining circulating tumor DNA (ctDNA)

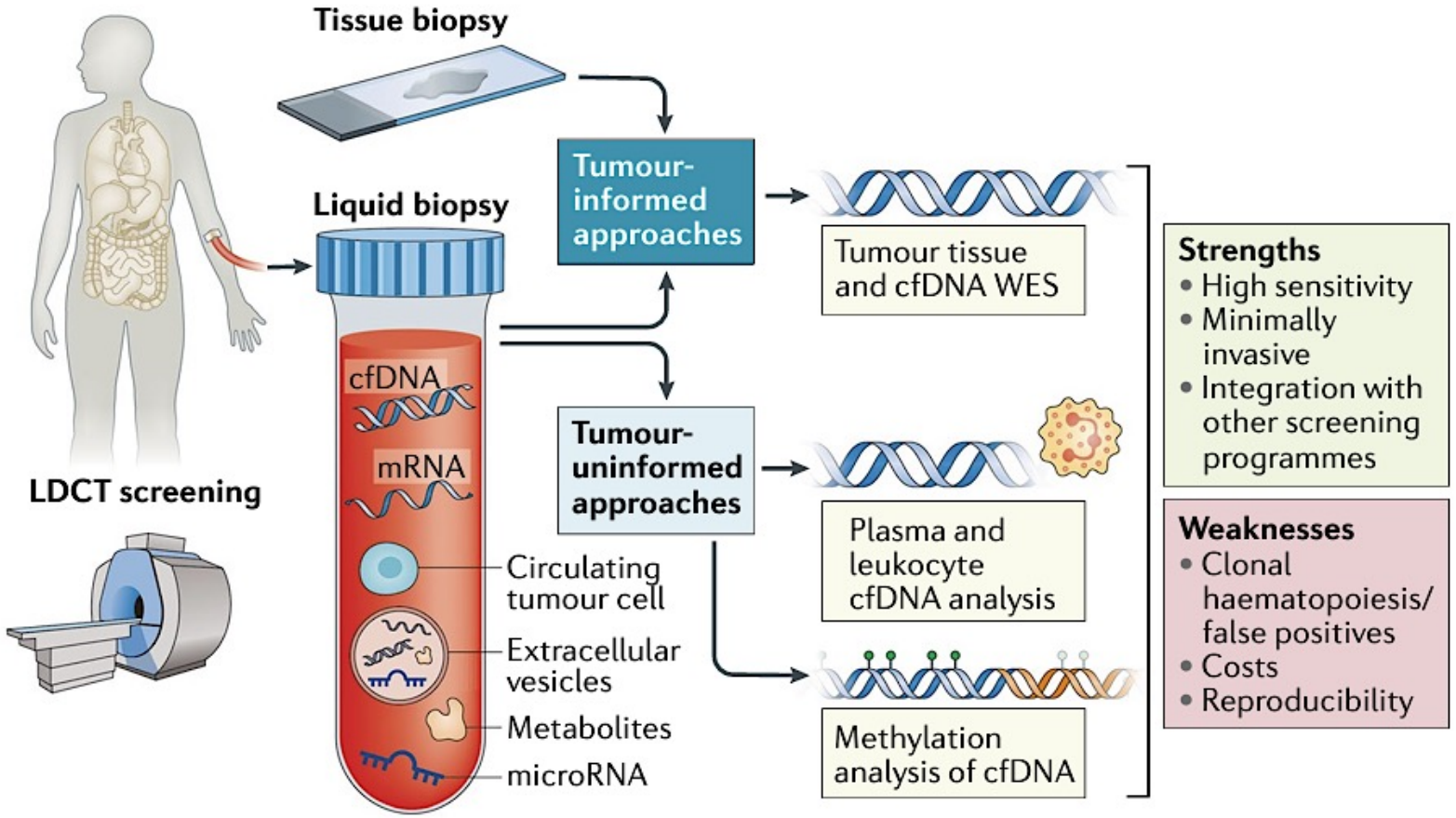
ctDNA is a putative biomarker for disease activity

- Low levels of cell-free DNA (cfDNA) can be detected even in the plasma of healthy individuals (1-10 ng/ml)
- ctDNA = detecting mutations in cfDNA that are highly specific for cancer
  - Differences in genetic, epigenetic alterations
  - Different fragment sizes
- Half-life: <2 hours
  - May fluctuate after trauma (surgery), chemotherapy



Gianni, *Int J Mol Sci* 2022

Tumor-informed vs tumor agnostic

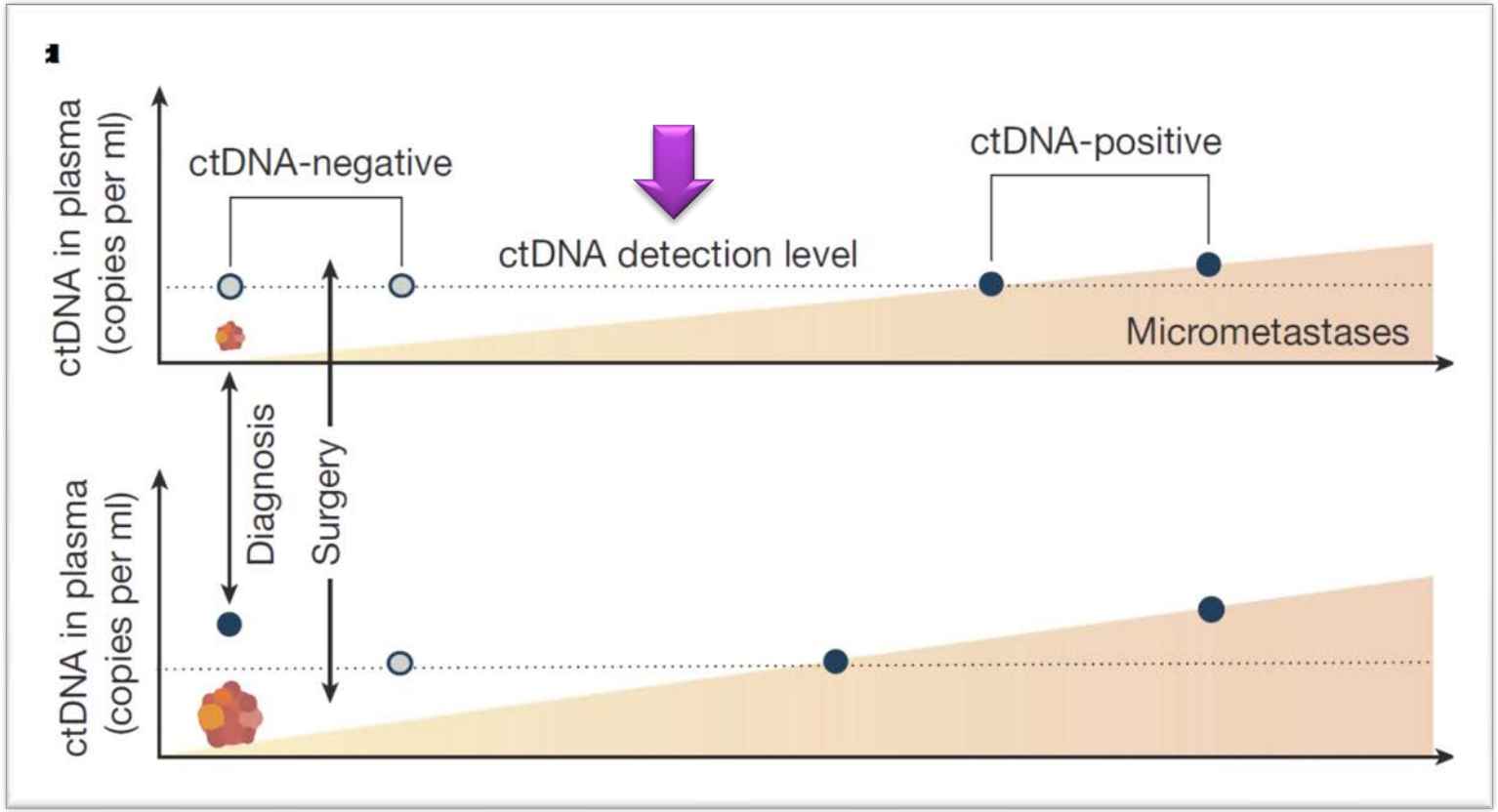


- Tumor-informed vs. tumor-uninformed (a.k.a. tumor-naïve, plasma only)
  - Blood results typically return in 7-14 days
- Tumor-informed approaches may be more sensitive for MRD
  - Longer turnaround time for initial test result (~4-6 weeks)

Rolfo, *Nat Rev Clin Oncol* 2020

Longitudinal collection may overcome assay limitations

Repeat testing can increase sensitivity



- Detection is cancer tumor burden dependent
- Longitudinal testing can overcome extremely low-level disease
- Rate of increase (*e.g.*, doubling time) can be informative

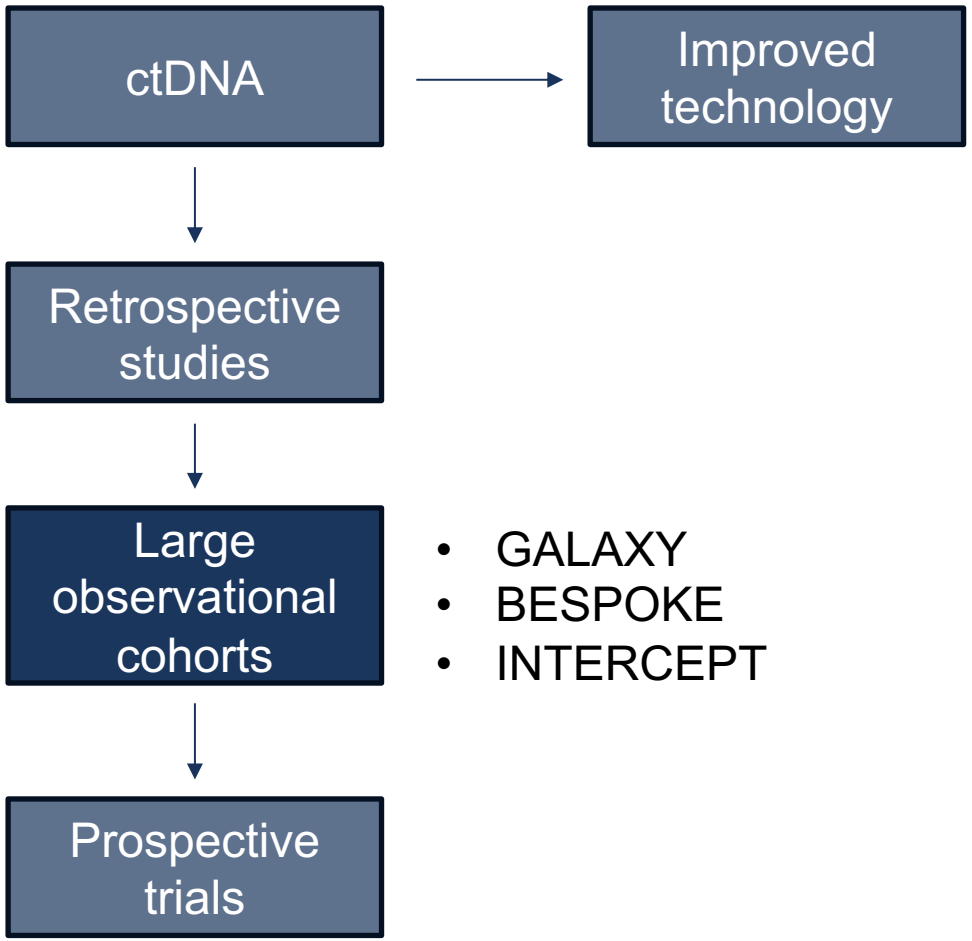
Cohen, *Nature* 2023

Minimal/molecular residual disease (MRD)

MRD = small volume disease not appreciated radiographically or with other clinical measures

- Hypothesis: ctDNA can pick up recurrences faster than would be detected radiographically or by other blood-based assays (ex. CEA)
- Analyses have largely been retrospective and observational, but with emerging prospective data

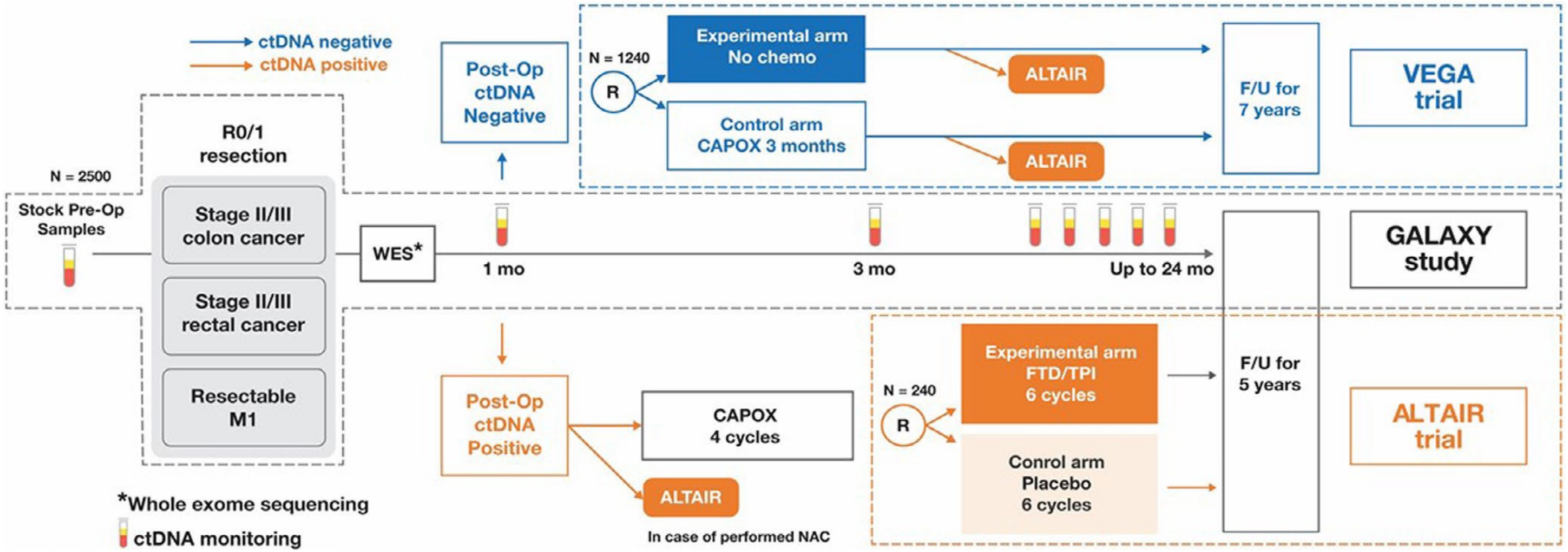
State of the data on ctDNA in colorectal cancer



- GALAXY
- BESPOKE
- INTERCEPT

CIRCULATE-Japan: GALAXY sub-study

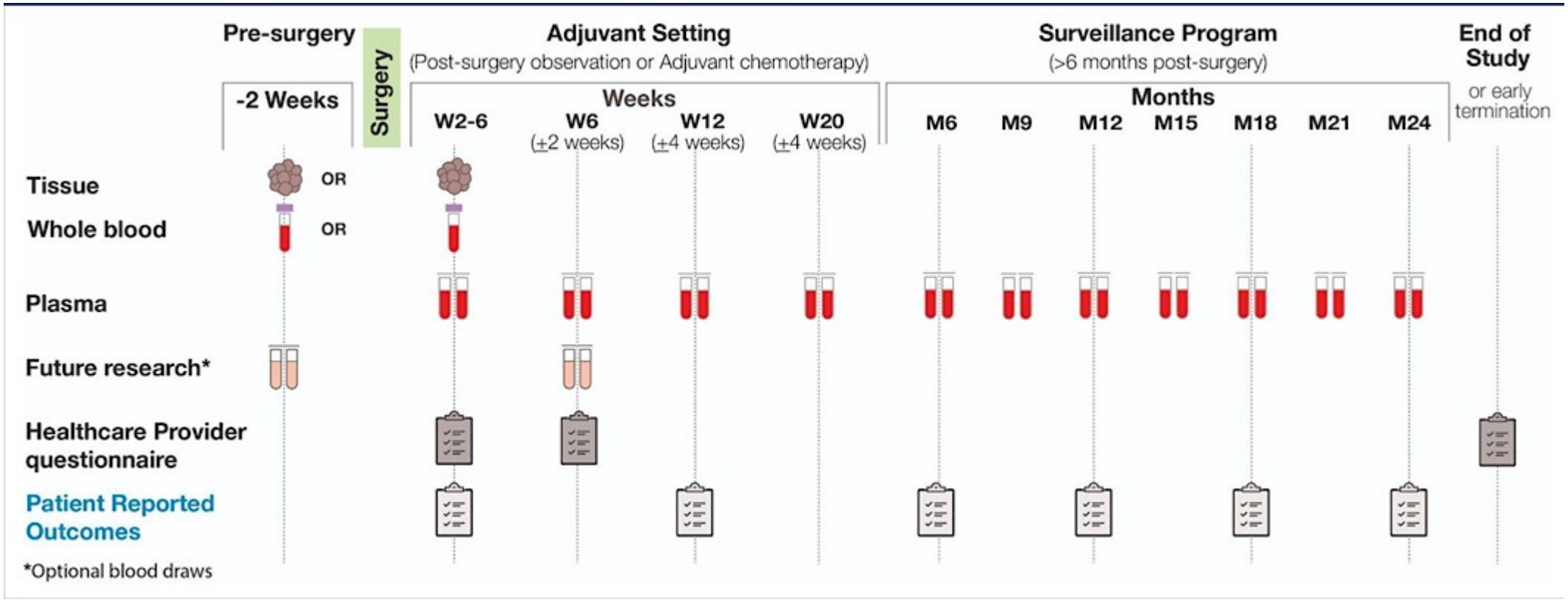
n=6061 → 2240 with stage 2/3



Kotani, *GI ASCO* 2022; Nakamura *Nat Med* 2024

BESPOKE

n=1780 → 1166 with stage 2/3

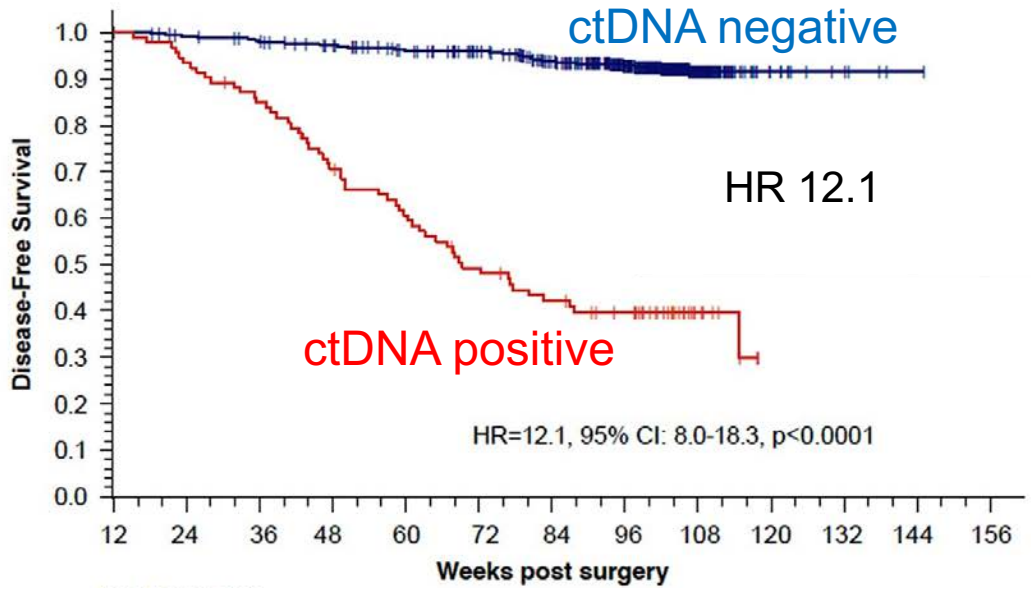


Shah, *ASCO GI* 2025

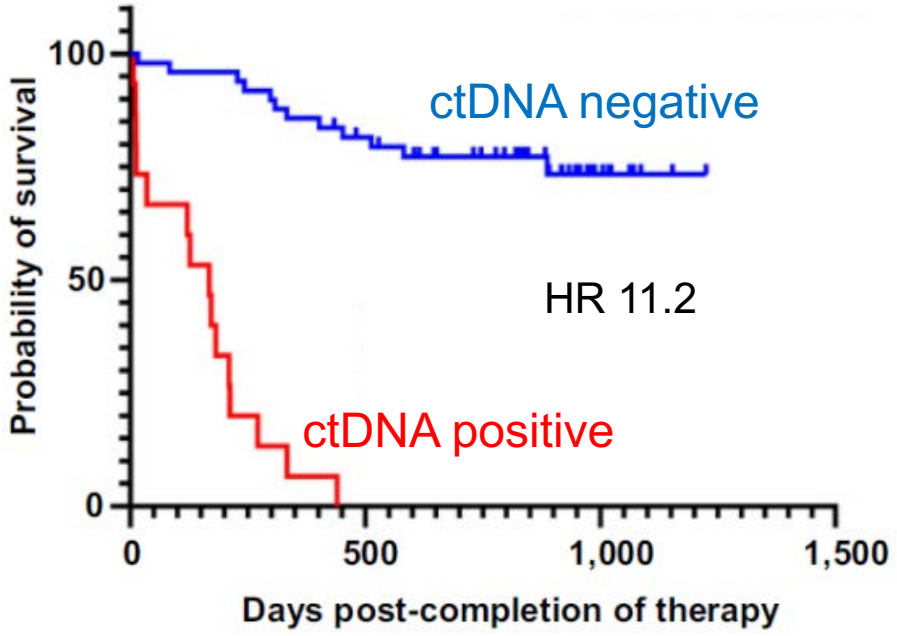
ctDNA is a strong prognostic risk factor

Emerging data with both tumor-informed (LEFT) and tumor-agnostic (RIGHT) platforms

RFS by ctDNA status after surgery



15% ctDNA+; recurrence 60 vs. 7%

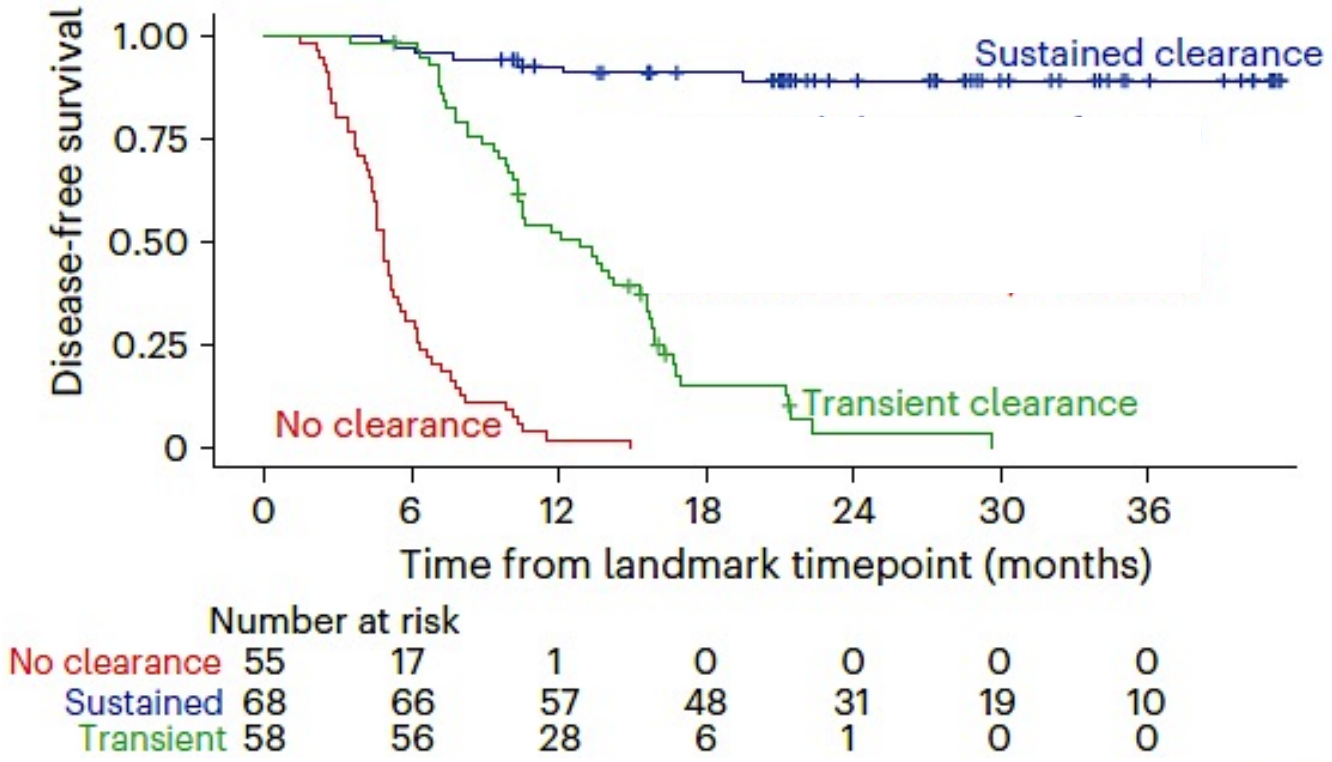


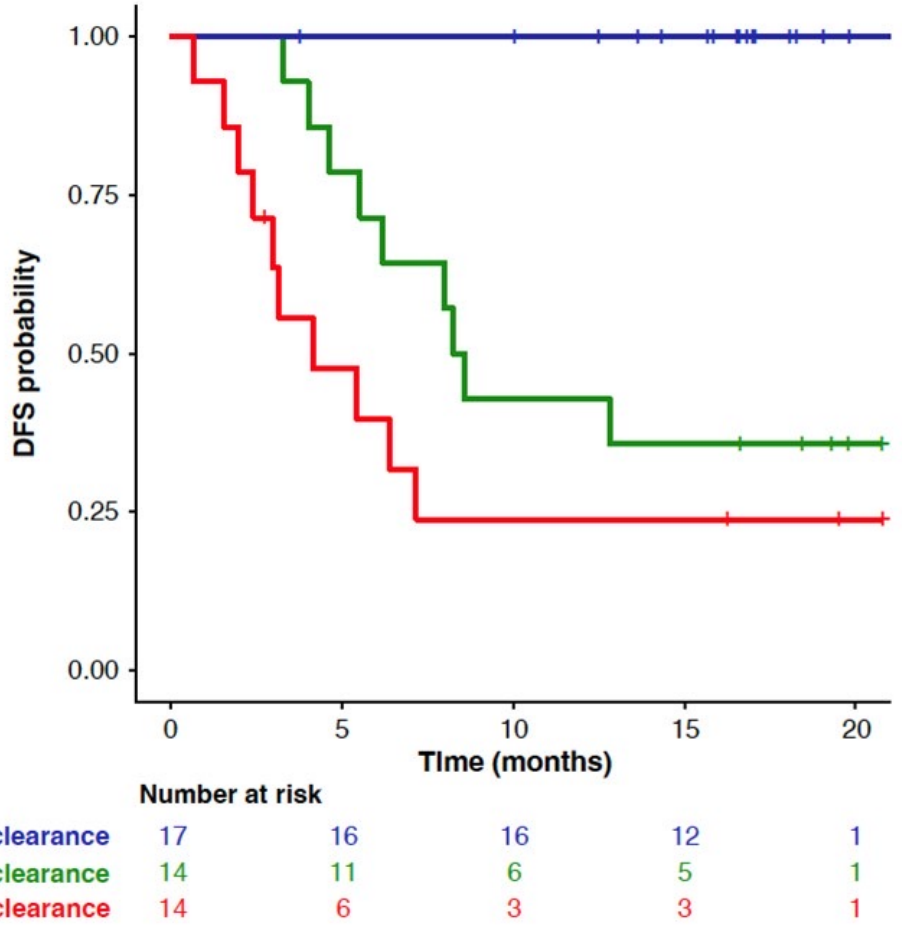
18% ctDNA+; recurrence 100 vs. 24%

Kasi, *GI ASCO* 2024; Parikh, *Clin Can Res* 2021

Longitudinal ctDNA clearance patterns are prognostic

GALAXY (Japan) and BESPOKE (USA) studies





Nakamura, *Nat Med* 2024; Kasi, *GI ASCO* 2024

ctDNA+ as a real-time predictor of metastasis

MDACC INTERCEPT study: n=1115 stage 2-4 with ctDNA evaluation after surgery

- 184 ctDNA+ during surveillance

# of Reflex Investigations	# of Patients
1	48
2	18
> 2	7

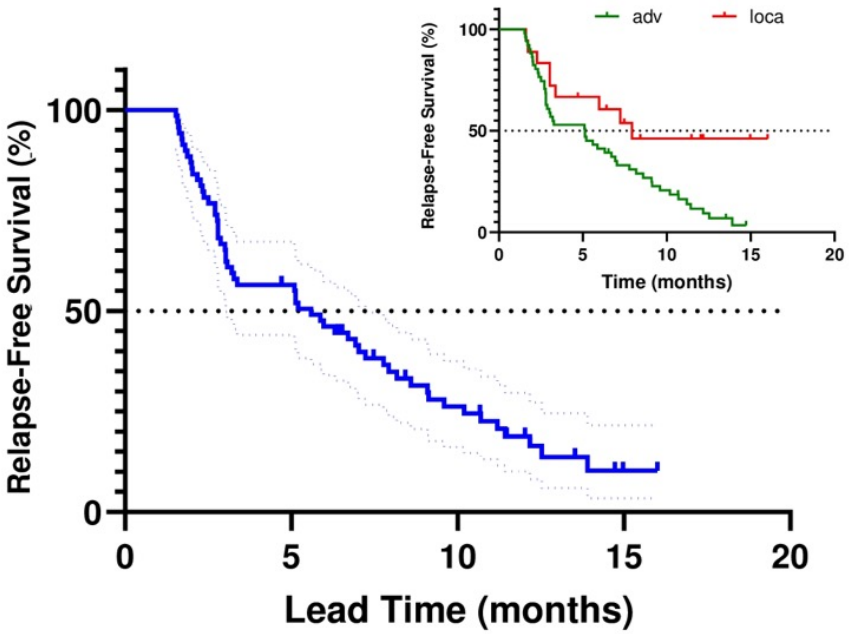
Type of Reflex Investigation	# of Patients
Additional CT	25
MRI	21
PET, PET/CT	37
Biopsy	13
Ultrasound	1

Radiologic evidence of metastatic disease

49% n=90

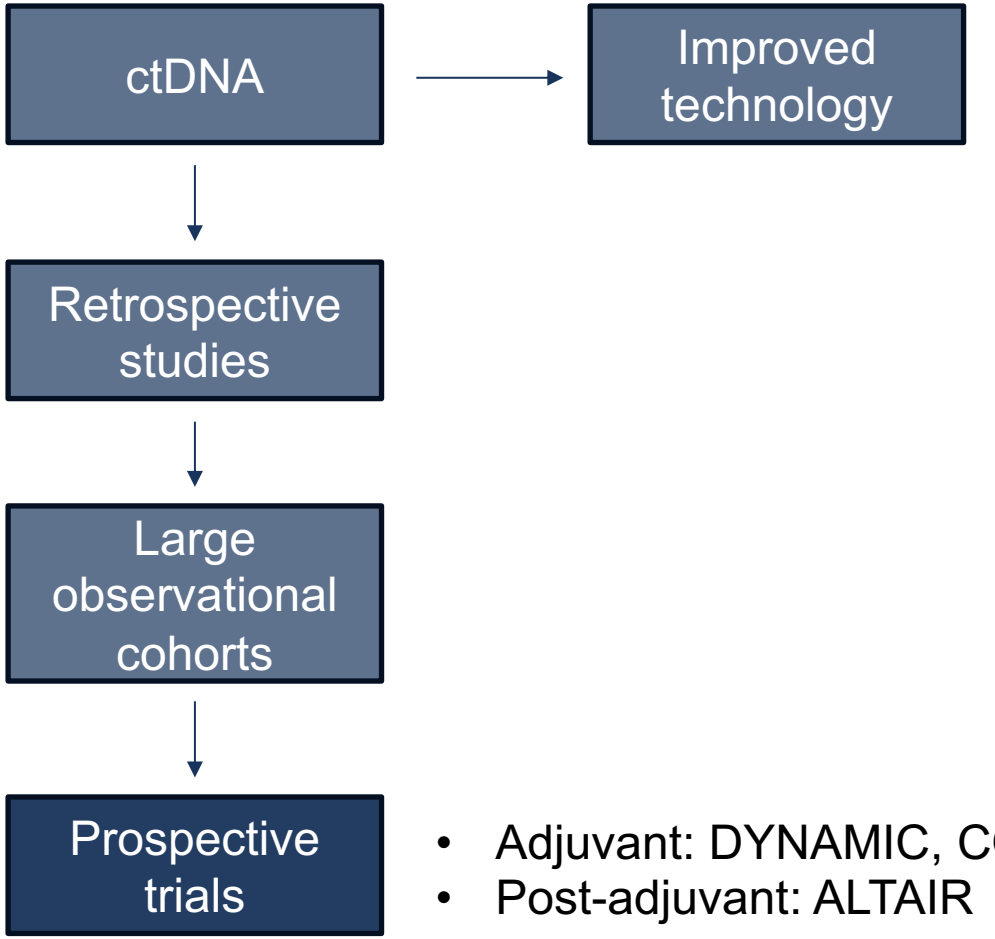
No radiologic evidence of disease (MRD)
51% n=94

- Median lead time: 3 mo
  - Excluding concomitant relapse: 5.6 mo



Dasari, *ASCO* 2023; Maddalena, *GI ASCO* 2024

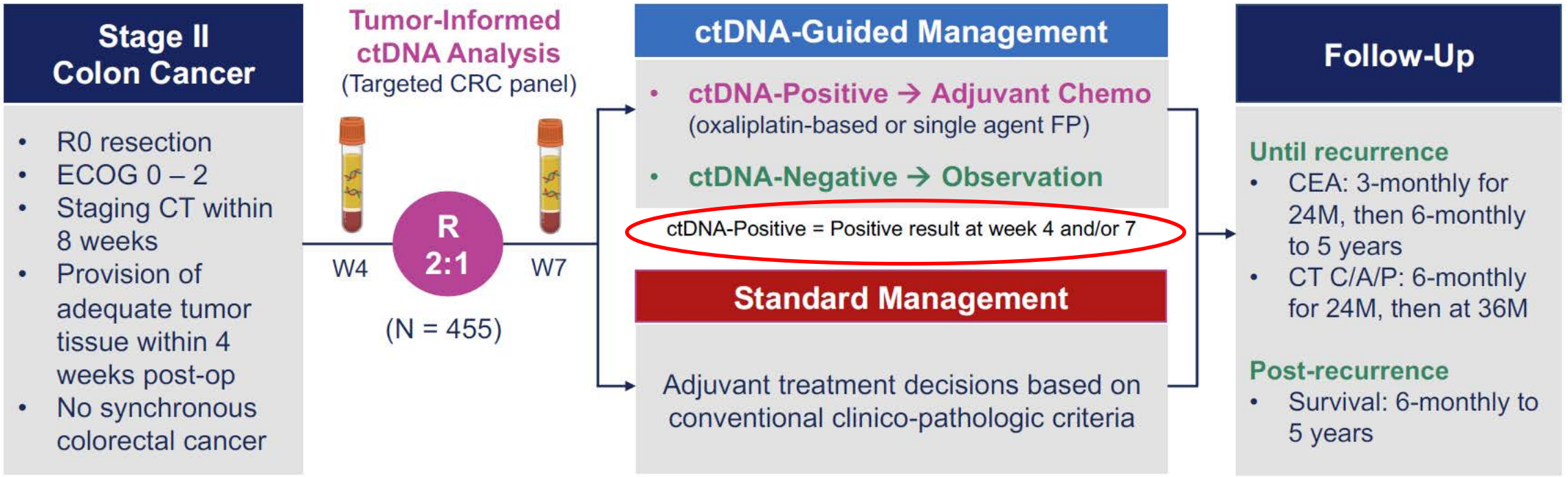
State of the data on ctDNA in colorectal cancer



- Adjuvant: DYNAMIC, COBRA, DYNAMIC-III
- Post-adjuvant: ALTAIR

DYNAMIC study

Prospective study randomizing resected stage **II** colon cancer 2:1 to ctDNA-guided management



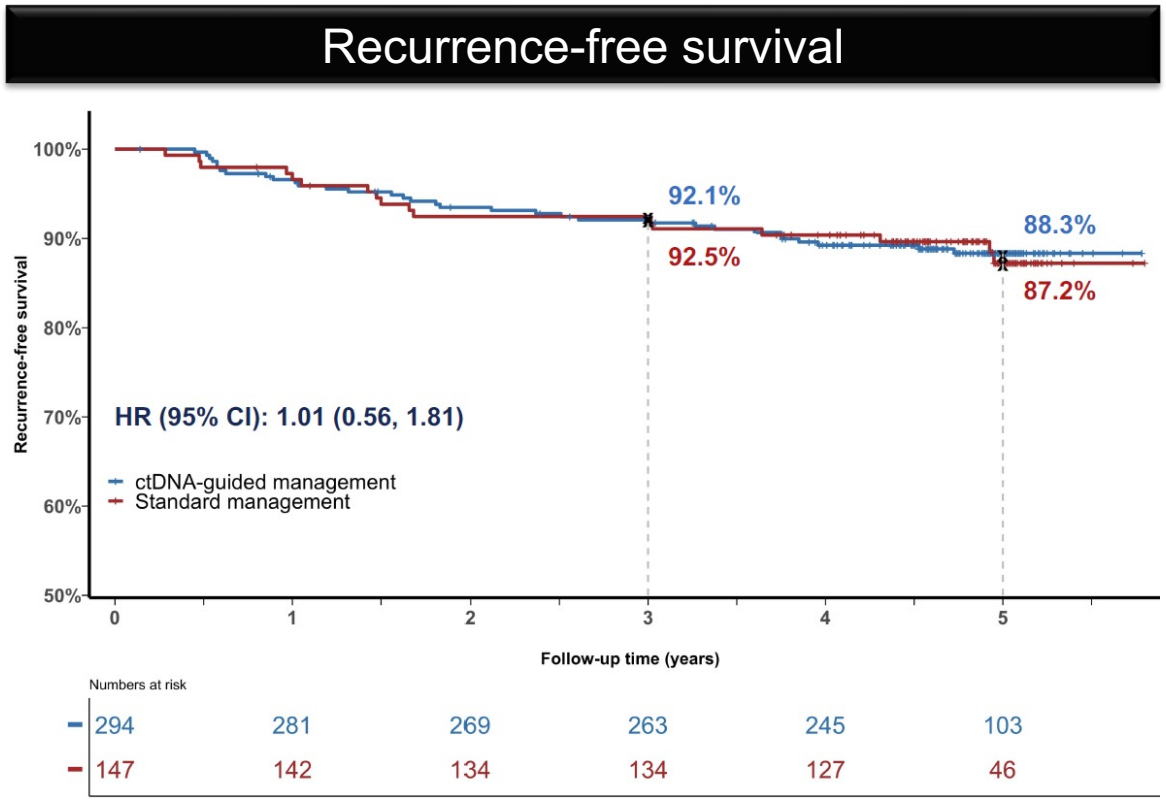
40% were clinical high risk
20% were MSI-H

Primary endpoint: 2-year RFS

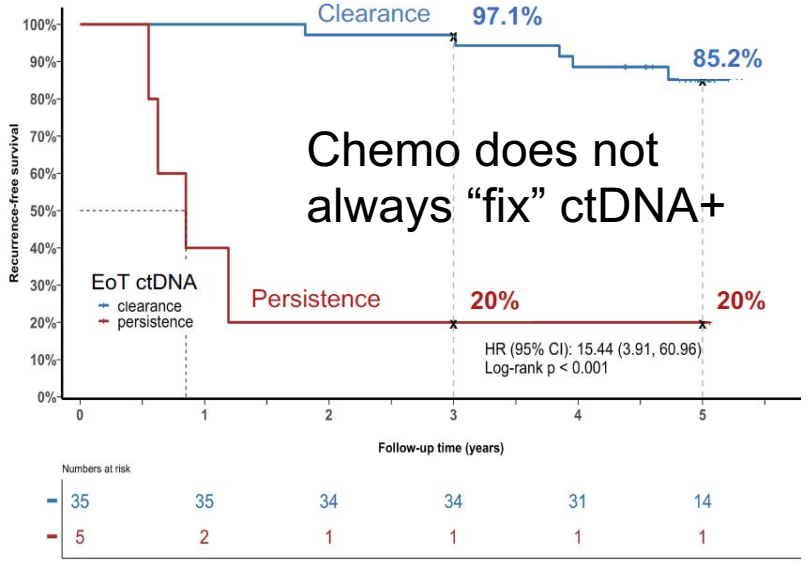
Tie, *ASCO* 2024; Tie, *New Engl J Med* 2022

DYNAMIC: recurrence-free survival

Non-inferior outcomes, despite differences in chemotherapy receipt



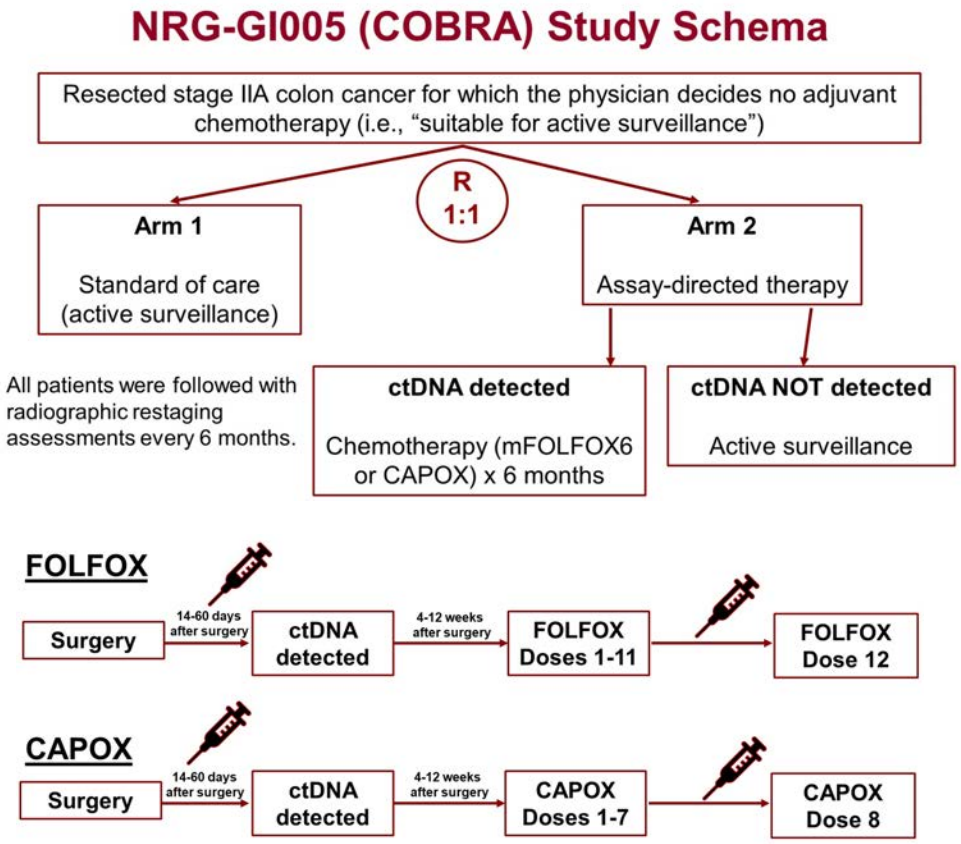
Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent FP	17/45 **(38%)**	37/41 **(90%)**	<.0001



Tie, *ASCO* 2024; *New Engl J Med* 2022

COBRA

Stage IIA (T3N0) colon cancer

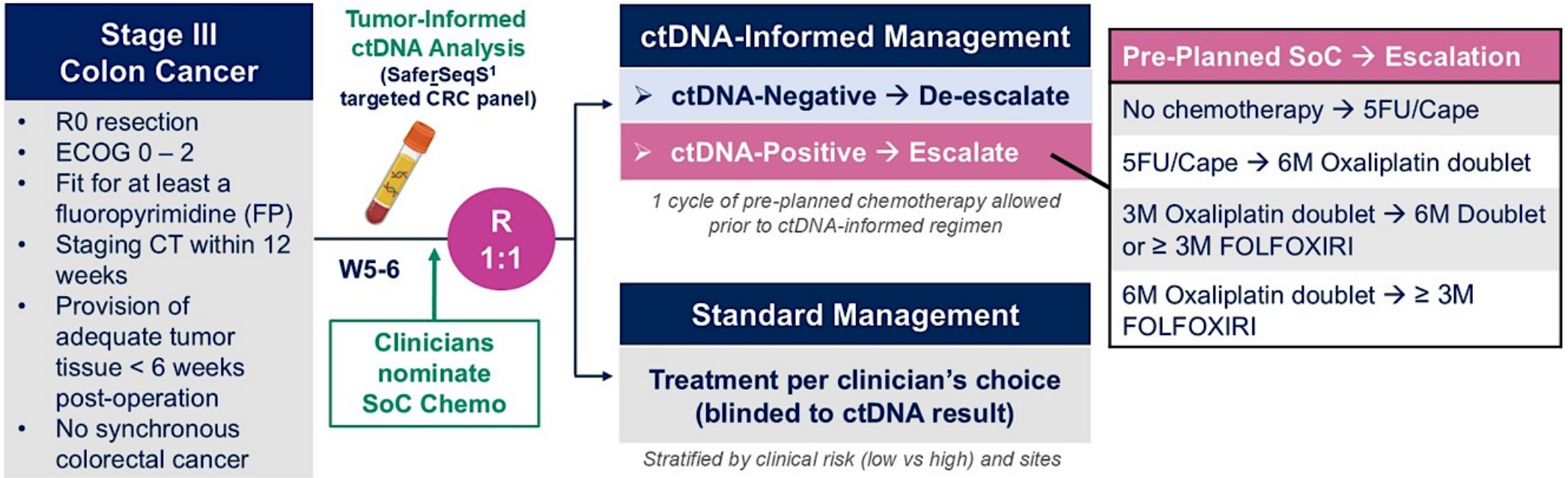


- Using a (now older) tumor-naïve assay
- 6% ctDNA positive
  - 43% spontaneously cleared in the observation arm (perhaps below the limit of the assay??)
  - 11% cleared in the chemotherapy arm
- Trial stopped early for futility (due to assay issues??)

Morris, *GI ASCO* 2024

DYNAMIC-III study

Prospective study randomizing resected stage **III** colon cancer 2:1 to ctDNA-guided management



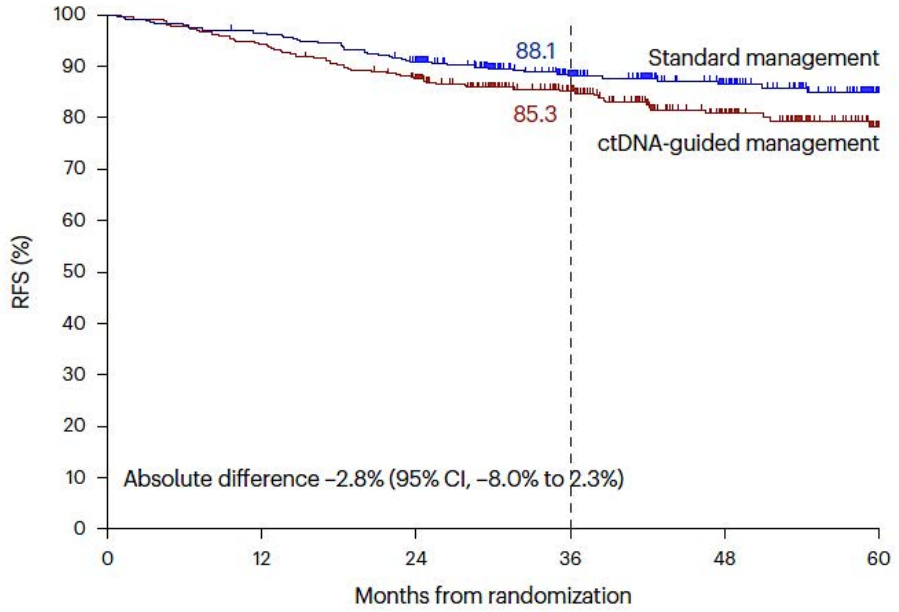
Primary Analysis of ctDNA-Positive Cohort: Endpoints to be Presented	
Primary: 2 years RFS	**Secondary:** safety, end-of-treatment (EoT) ctDNA clearance
	Exploratory: post-operative ctDNA levels

Tie, *ASCO* 2025; Tie, *Nat Med* 2025

DYNAMIC-III: Recurrence-free survival

Improved outcomes with standard management

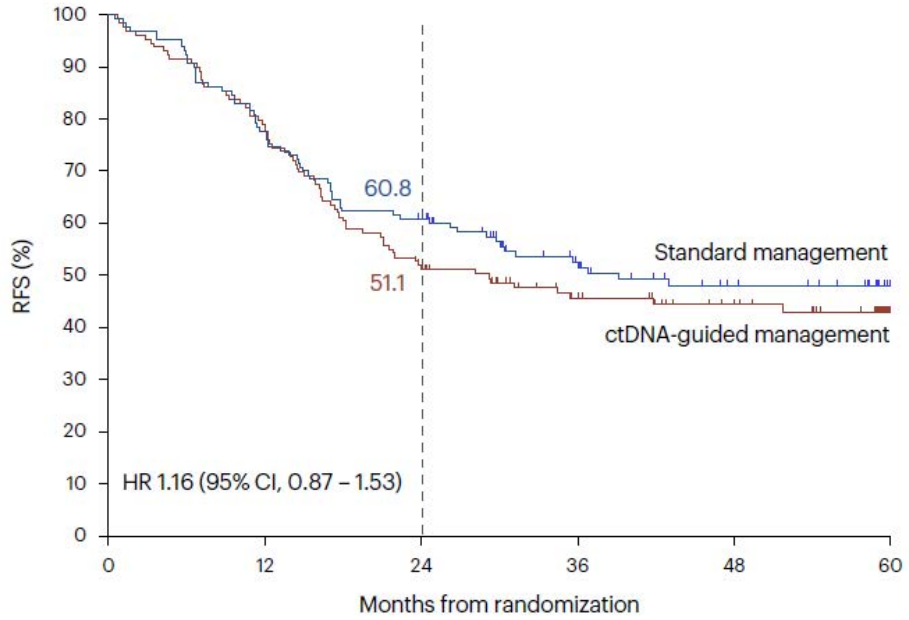
RFS: ctDNA-negative



Number at risk

ctDNA-guided management	353	333	303	214	124	51
Standard management	349	336	310	223	143	46

RFS: ctDNA-positive



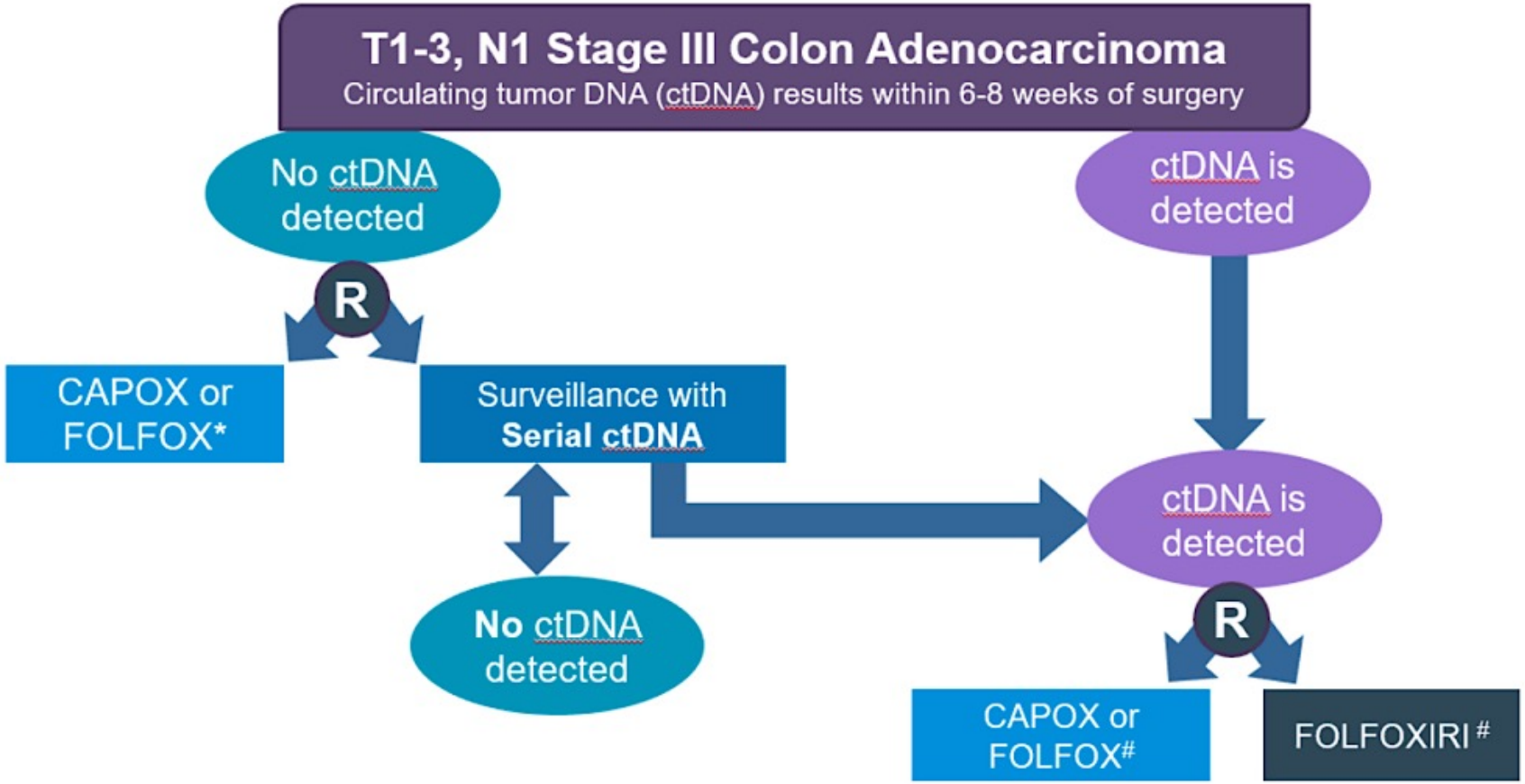
Number at risk

ctDNA-guided management	129	101	64	45	31	7
Standard management	130	101	78	49	33	15

….Is it the assay? Cohort heterogeneity? Specific regimen?

Tie, *Nat Med* 2025

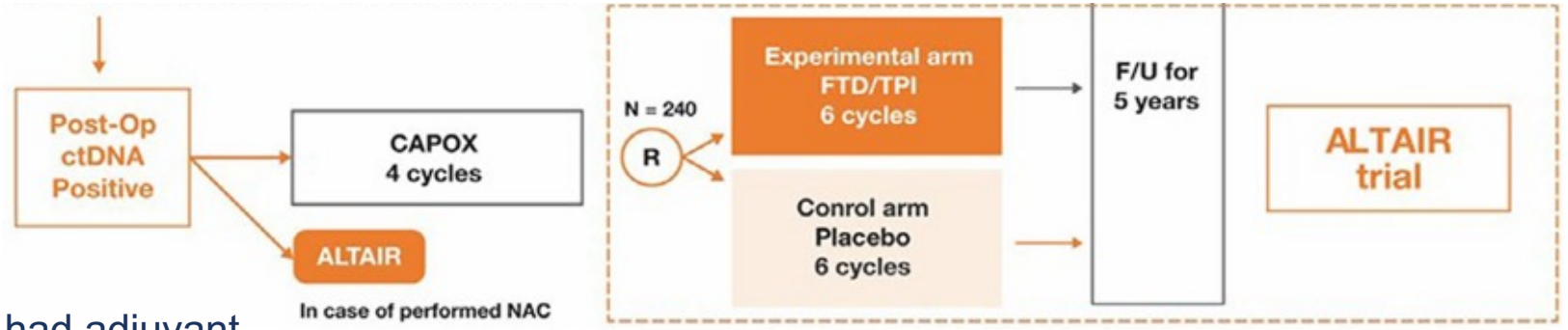
CIRCULATE-North America



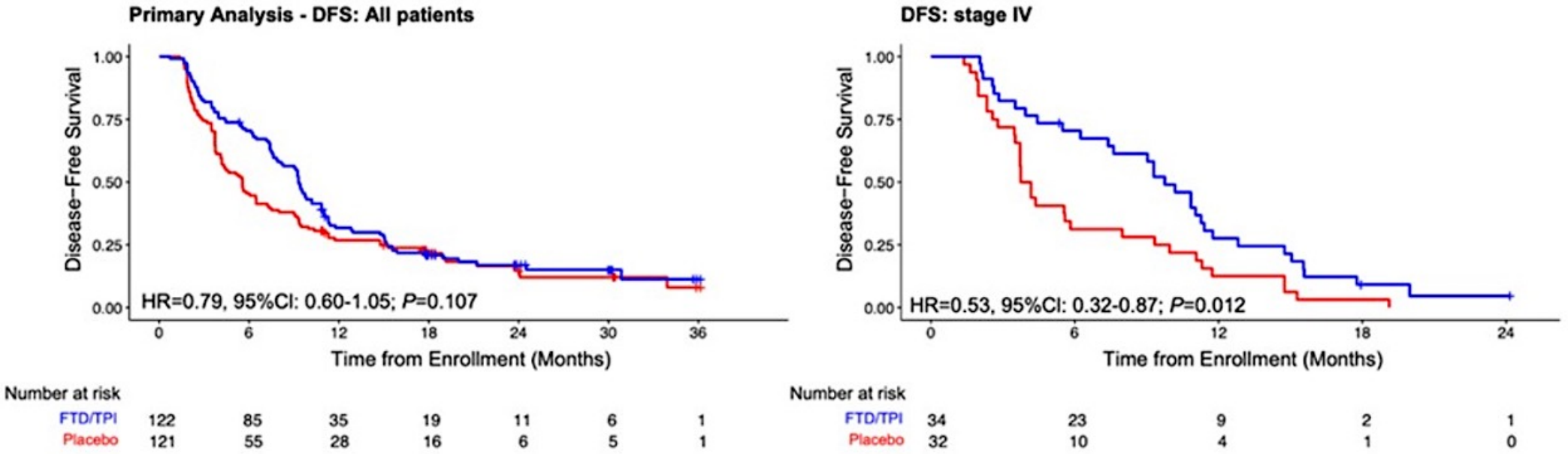
Dasari et al. ASCO 2025;Abstract TPS3644.

ALTAIR

Post-adjuvant study

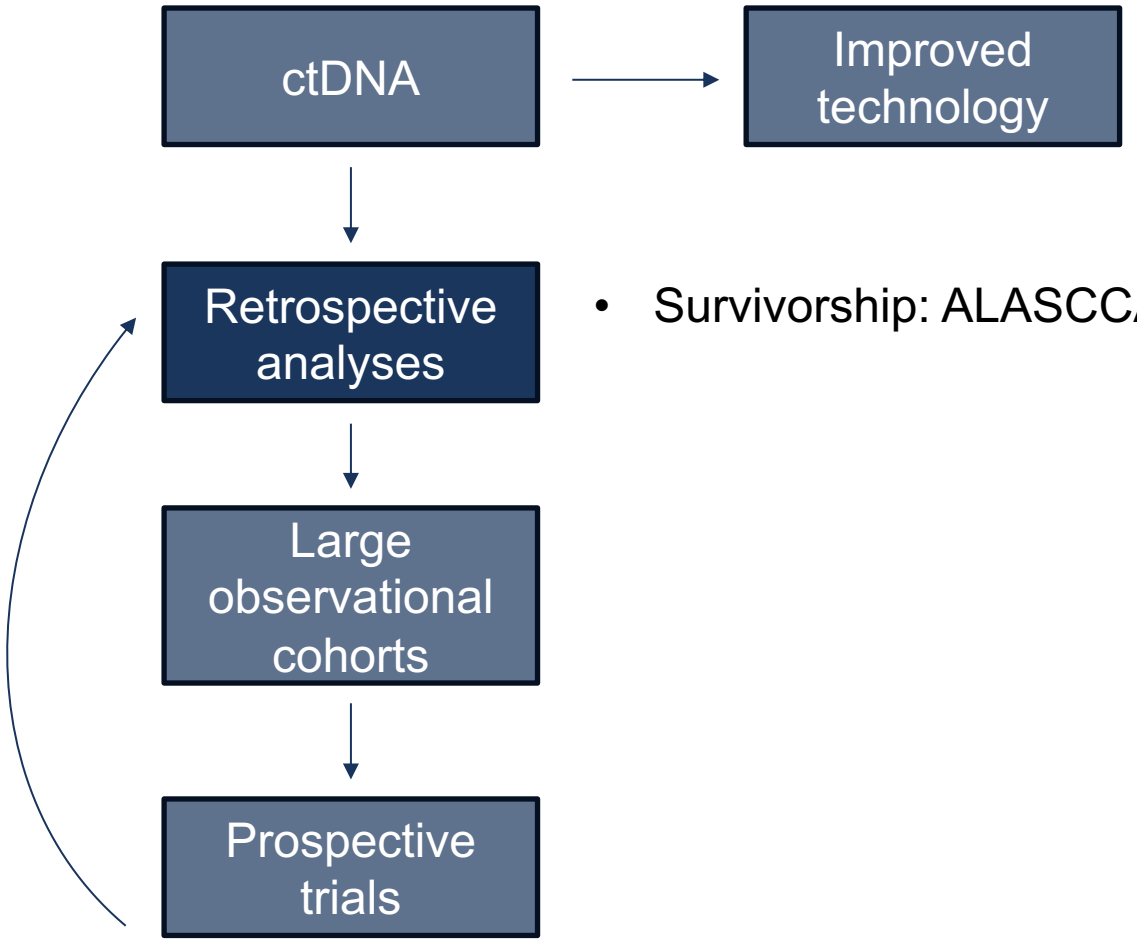


- N=243, stage 2-4
- 36% had neoadjuvant chemo, 46% had adjuvant
- Early data suggests a negative study



Bando, *GI ASCO* 2025

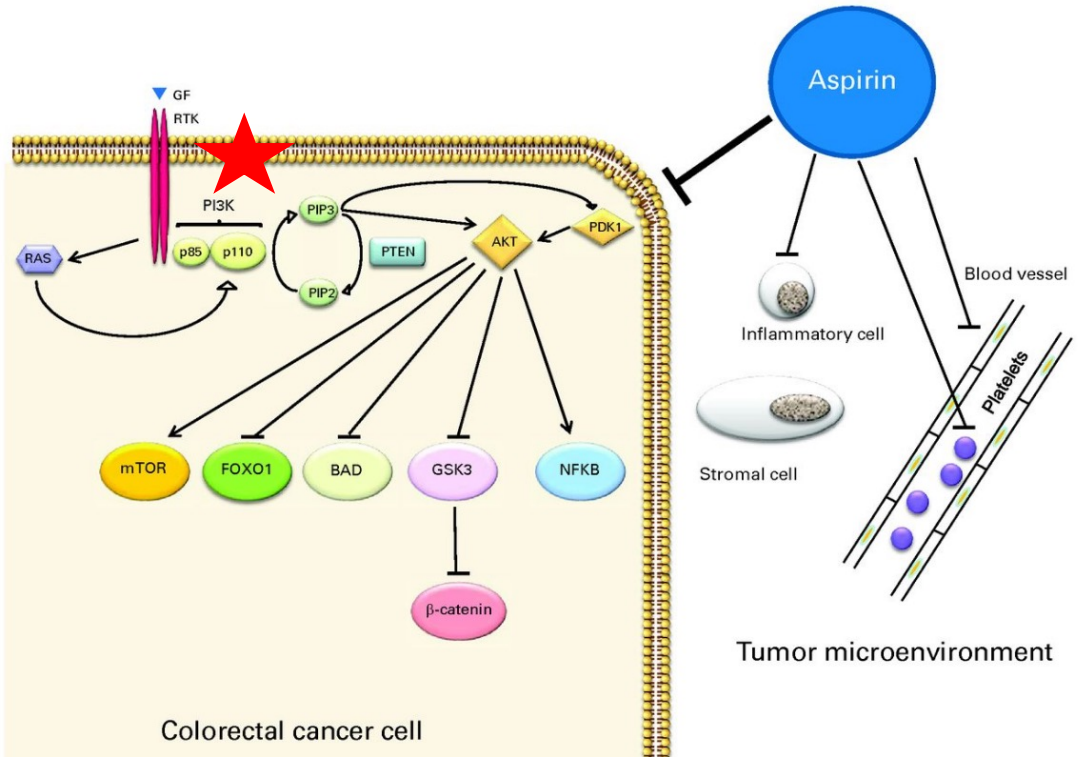
State of the data on ctDNA in colorectal cancer

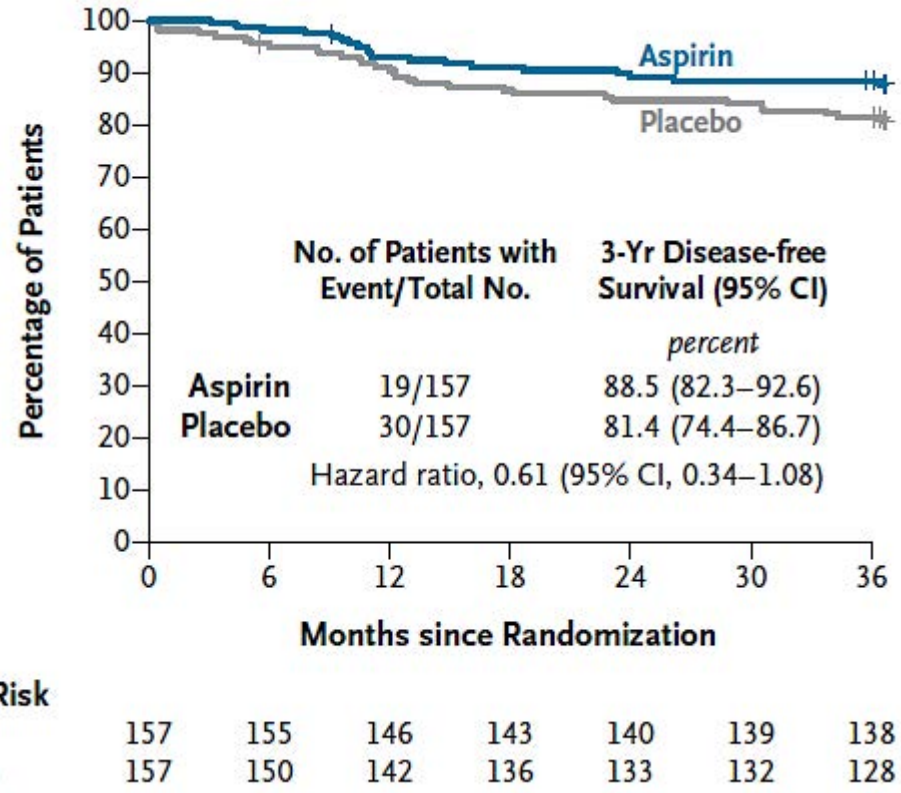


- Survivorship: ALASCCA, 80702

ALASCCA

Prospective study of adjuvant 160mg aspirin vs placebo x 3 years for localized PI3Kmut CRC

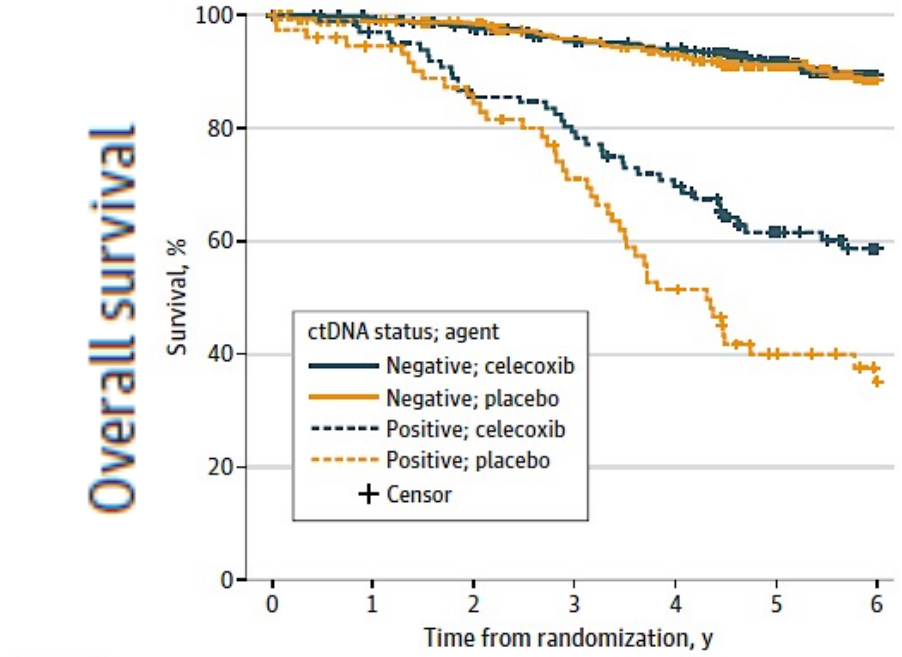




Fuchs, *J Clin Oncol* 2013; Martling, *New Engl J Med* 2025

CALGB/SWOG 80702

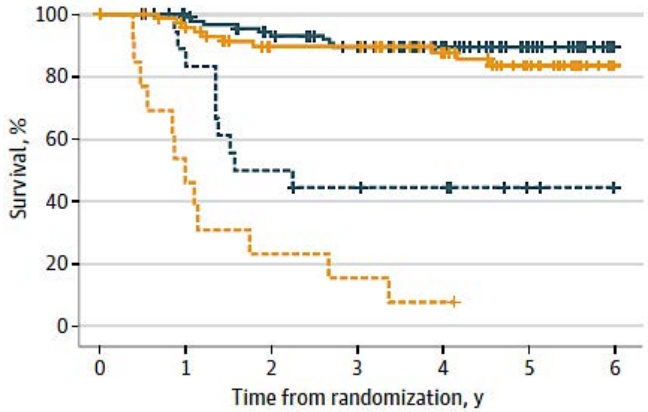
Post-hoc analysis of this stage 3 adjuvant 3 vs 6 mo chemotherapy trial



No. at risk

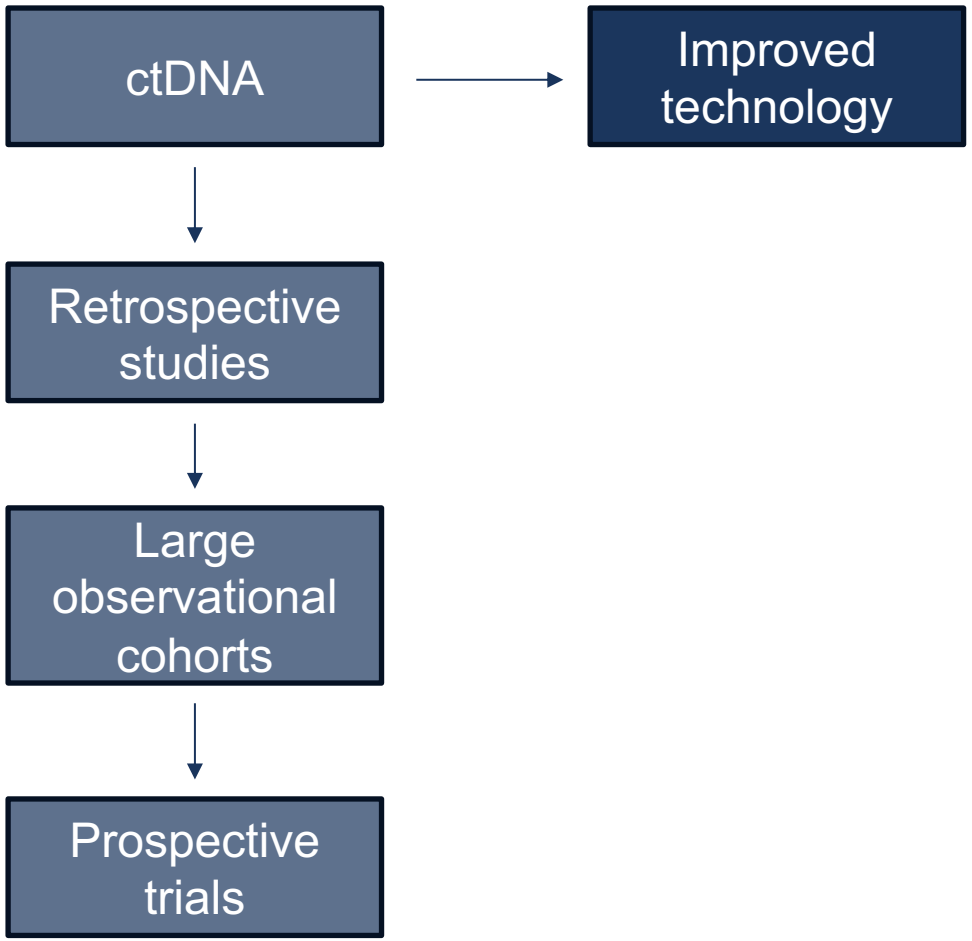
Negative, celecoxib	375	361	344	327	317	266	168
Negative, placebo	392	372	359	340	323	269	155
Positive, celecoxib	99	94	82	75	65	47	32
Positive, placebo	74	67	59	47	34	21	14

- Patients were additionally randomized to 3 years of celecoxib or placebo
- ctDNA remains associated with poor prognosis
- Benefit of celecoxib seems to be in the ctDNA+ patients, even when restricting to PIK3CA-mut (22%)



Nowak, *GI ASCO* 2025; Zhang, *JAMA Oncol* 2025

State of the data on ctDNA in colorectal cancer



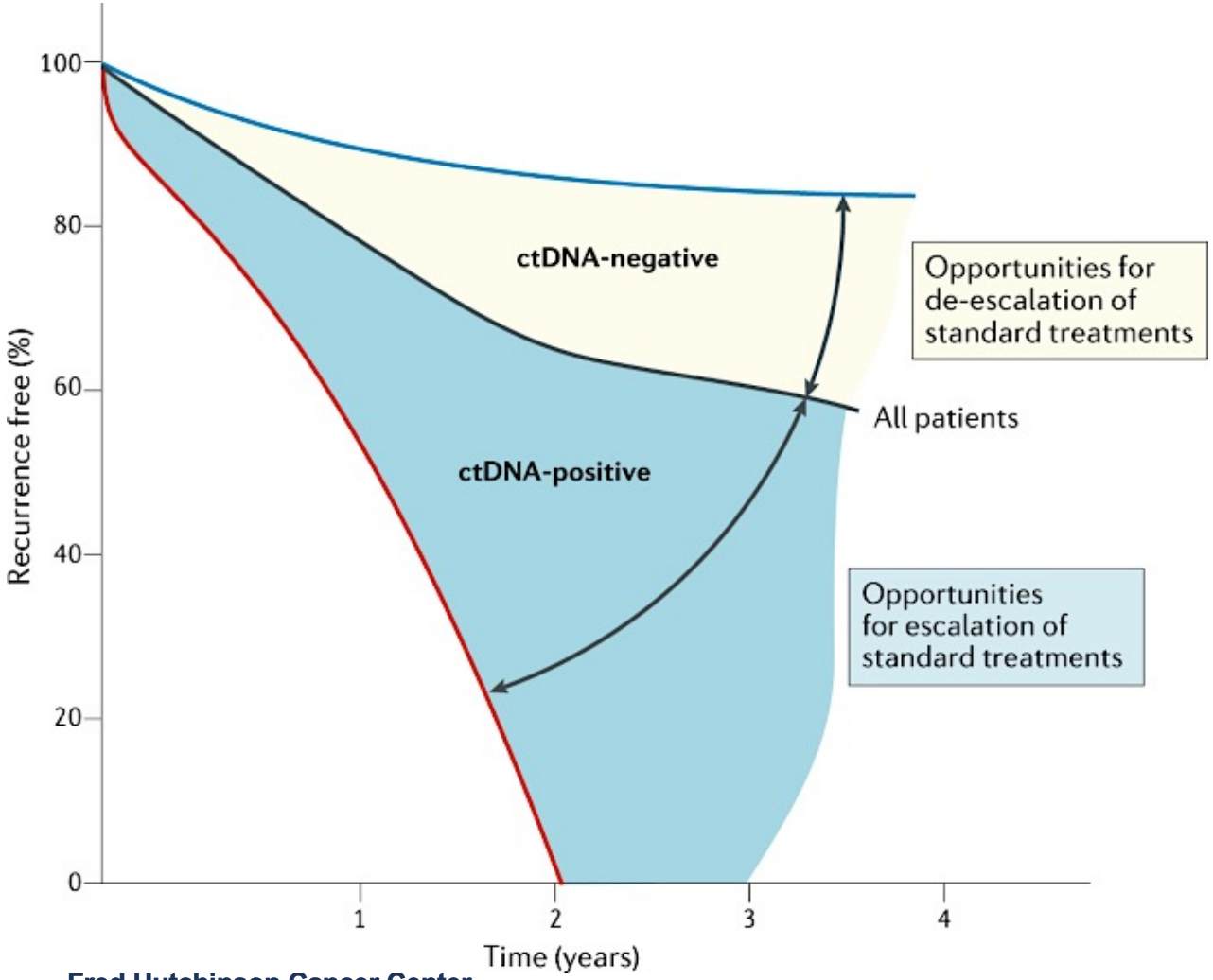
- Genetic changes
- Epigenetics
- Fragmentomics

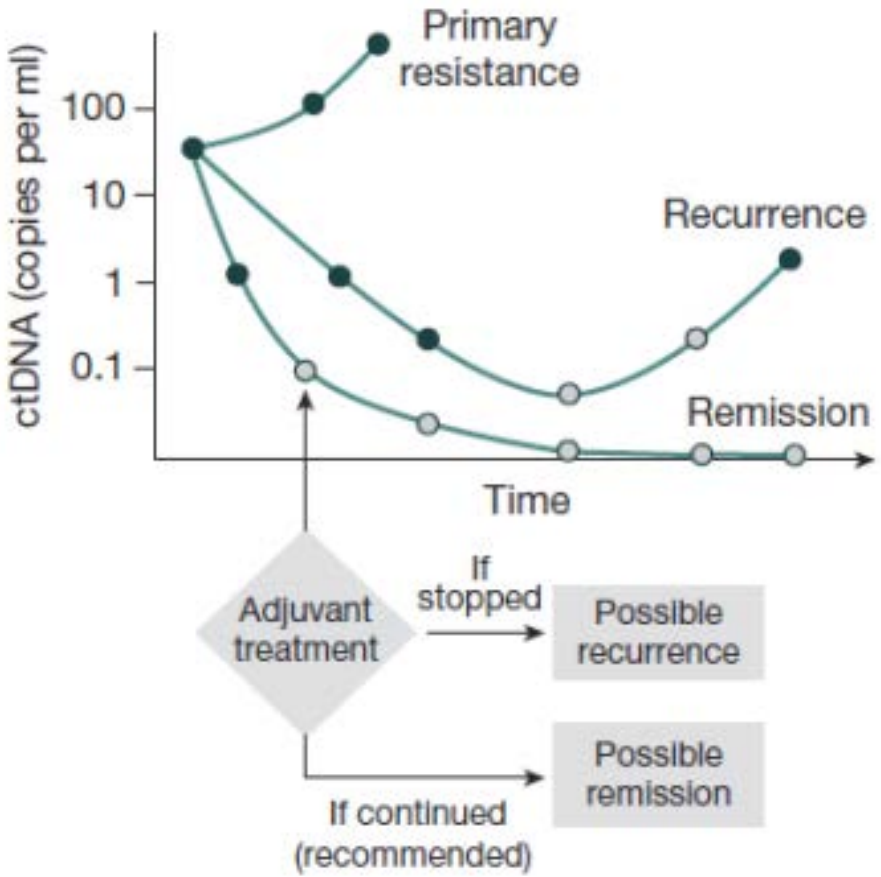
ctDNA is not static, it is a technology

Ongoing and future developments

- Discrete number of variants per patient (*e.g.*, 16) → increased panel sizes
- Depth and breadth of sequencing (Whole exome → whole genome)
- Inclusion/improvement of epigenetics
  – Especially relevant for tumor-agnostic assays
- Better cancellation of background “noise” (*e.g.*, CHiP)
- Binary reporting (positive/negative) → quantitative trending → evaluations of fold differences as a biomarker

Is ctDNA the future? Most likely in some capacity





Dasari, *Nat Rev Clin Oncol* 2020; Cohen, *Nature* 2023

Questions from General Medical Oncologists — Role of ctDNA Testing in Localized CRC

65 y/o with Stage II colon cancer – how comfortable are we in recommending chemo for Stage II colon cancer if MRD positive?

Stage IIb CRC adjuvant: preferred choice between available ctDNA testing platforms? Practicality of waiting for testing results?

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Questions from General Medical Oncologists — Role of ctDNA Testing in Localized CRC

A 58-year-old man undergoes right hemicolectomy for colon cancer. Pathology: pT3N0 (Stage II) adenocarcinoma, moderately differentiated, no LVI. Adequate nodal sampling (18 nodes). MMR proficient (MSS). Traditional risk assessment: Clinically low–intermediate risk. Adjuvant chemotherapy would typically be optional or omitted. ctDNA performed 4 weeks post-op and was MRD-positive. Clinical dilemma: Standard clinicopathologic features suggest observation, MRD positivity implies high risk of recurrence. How do you approach low clinical risk patients, do you check ctDNA on everyone?

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Questions from General Medical Oncologists — Role of ctDNA Testing in Localized CRC

72 yr old female with standard risk Stage IIIb colon cancer and ctDNA negative. If a patient would prefer not to receive chemotherapy do you think it's a reasonable option to omit chemo if MRD tests are negative?

55 y/o female pt with Stage IIIA left-sided colon cancer, with only 1/16 LNs +, pt strongly wants MRD testing to decide adjuvant chemotherapy. Is it okay to go by ctDNA test result to guide FOLFOX adjuvant chemo in this pt's case?

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Questions from General Medical Oncologists — Role of ctDNA Testing in Localized CRC

58 y/o F with DM neuropathy and Stage II colon cancer with high Onco*type* DX® Recurrence Score®, ctDNA for MRD is negative. Is it safe to omit adjuvant therapy in this pt?

68 y/o M with L-sided colon cancer s/p hemicolectomy, about to start adjuvant FOLFOX and initial ctDNA testing positive. Should positive ctDNA test at initiation of adjuvant therapy affect aggressiveness or duration of therapy?

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Questions from General Medical Oncologists — Role of ctDNA Testing in Localized CRC

82F with hypothyroidism, DM, HTN, CAD, and T3N2 colon cancer s/p surgery, recommendation is for adjuvant chemotherapy. Patient is worried about chemo toxicities and functional decline. Would MRD assay results help you with treatment duration decision-making?

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Questions from General Medical Oncologists — Role of ctDNA Testing in Localized CRC

68 y/o with Stage III MSI-H rectal cancer treated with 6 months of dostarlimab and achieves clinical CR on images and sigmoidoscopy but ctDNA positive. How many negative ctDNA tests are sufficient to stop testing? How often do you test?

66 y/o man with osteoarthritis Stage IIIA rectal cancer s/p TNT and surgery, had pCR, but ctDNA+. Would you recommend additional therapy?

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Questions from General Medical Oncologists — Role of ctDNA Testing in Localized CRC

48-year-old man with Stage IIIB colorectal cancer s/p hemicolectomy s/p FOLFOX x 12C with +ctDNA. What to do with patients who have completed a full course of adjuvant therapy who have +ctDNA?

65 y/o F with L-sided colon ca s/p hemicolectomy and adjuvant FOLFOX. ctDNA testing negative for 1 year then returns low positive. Would experts start systemic therapy for a new positive ctDNA test after previous negativity?

Questions from General Medical Oncologists — Role of ctDNA Testing in Localized CRC

52 y/o female. Stage III colon cancer. ctDNA was positive. After 3 months of adjuvant FOLFOX, ctDNA was zero. But it turned positive at 6 months. Now CT showed upper abdominal LN. FOLFIRI and Bev started. When imaging shows evidence of recurrence, and ctDNA is positive, is a biopsy still needed to confirm the recurrence?

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Expert Second Opinion: Current and Future Roles of Immunotherapy and Targeted Therapy in the Management of Advanced Gastroesophageal Cancers

A CME Symposium Held Adjunct to the 2026 ASCO® Gastrointestinal Cancers Symposium

Friday, January 9, 2026

6:00 PM – 8:00 PM PT

Faculty

Jaffer A Ajani, MD

David H Ilson, MD, PhD

Rutika Mehta, MD, MPH

Moderator

Samuel J Klempner, MD

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