Real world applications for ctDNA in colorectal cancer

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Van Morris, M.D.,
Associate Professor,
Dept of Gastrointestinal Medical Oncology

September 30, 2023

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Disclosures

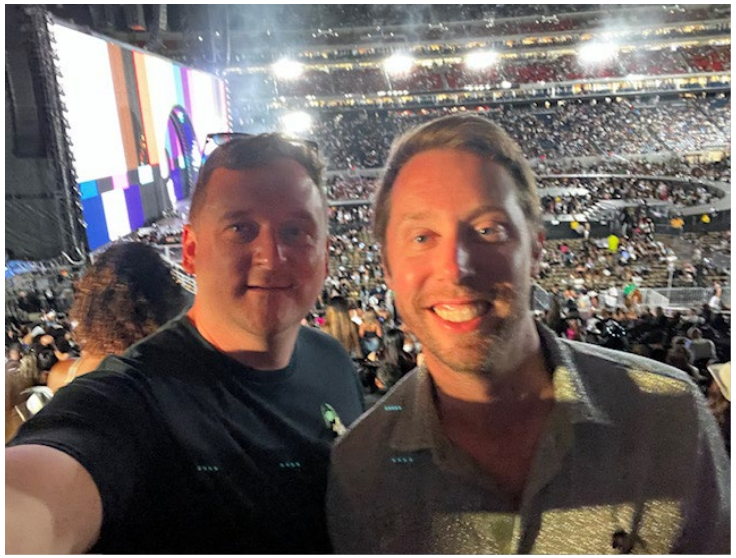
Research Funding (to MD Anderson): Bristol Myers Squibb, Pfizer, EMD Serono, Novartis, BioNTech, Bicara, RedX Pharma

Consulting: Bayer, Regeneron, Novartis

Principal Investigator for ctDNA trials: NRG-GI005 (overall PI), BioNtech (MDACC PI)

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Before a Houstonian, forever a Memphian…



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Overview

- Use of ctDNA as a tool to inform cancer biology as a liquid biopsy
- Informing clinical decision making of CRC using ctDNA technologies
- Recognizing micrometastatic CRC as a unique biologic entity with novel therapeutic opportunities to cure more patients

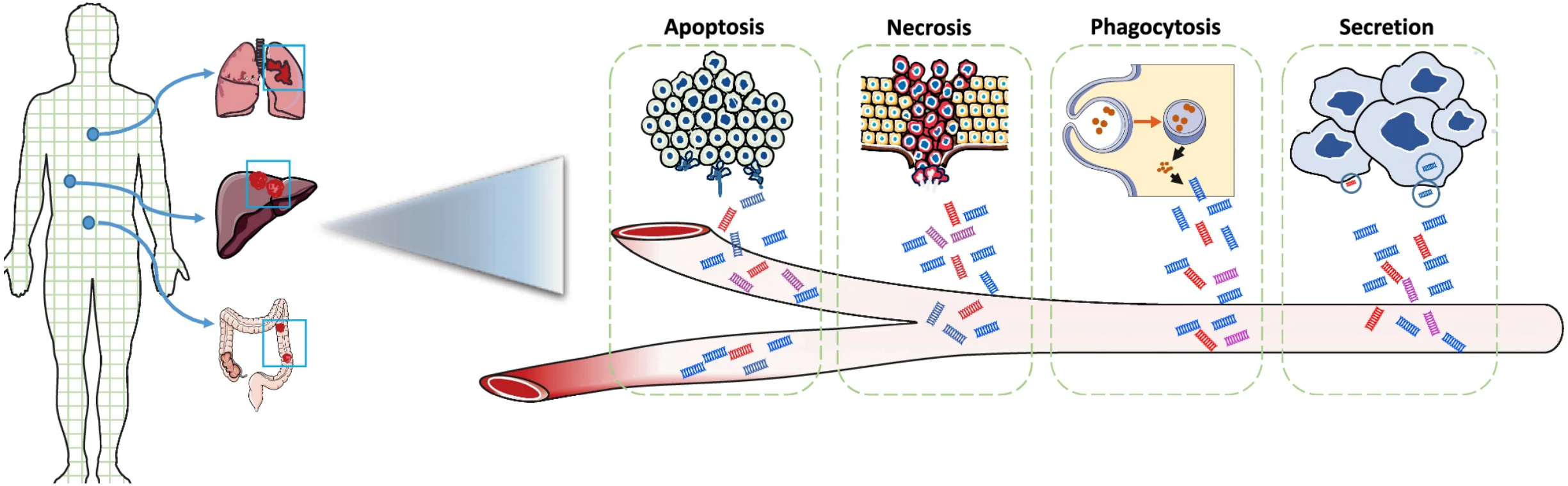
- **Use of ctDNA as a tool to inform cancer biology as a liquid biopsy**

- Informing clinical decision making of CRC using ctDNA technologies

- Recognizing micrometastatic CRC as a unique biologic entity with novel therapeutic opportunities to cure more patients

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Circulating tumor DNA as a “liquid biopsy”



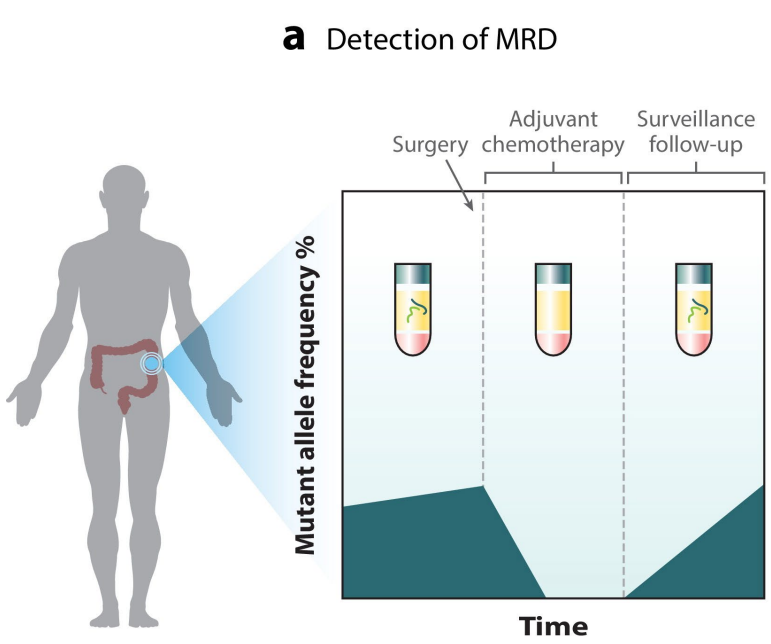
- Circulating tumor DNA (ctDNA) can be detected in blood following release from tumor cells, predominantly via apoptosis.
- Different fragment size for ctDNA: unlike cfDNA fragments [~$(167)_n$ bp in length], ctDNA fragments are ~20-30 bp shorter
- “Real-time” analysis: half-life of ctDNA in plasma ~ 2-3 hours

Underhill H Current Opin 2021; Elazezy M et al Comp Struc Biotech J 2018

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Therapeutic applications of ctDNA in management for (colorectal) cancer

CURATIVE SETTING

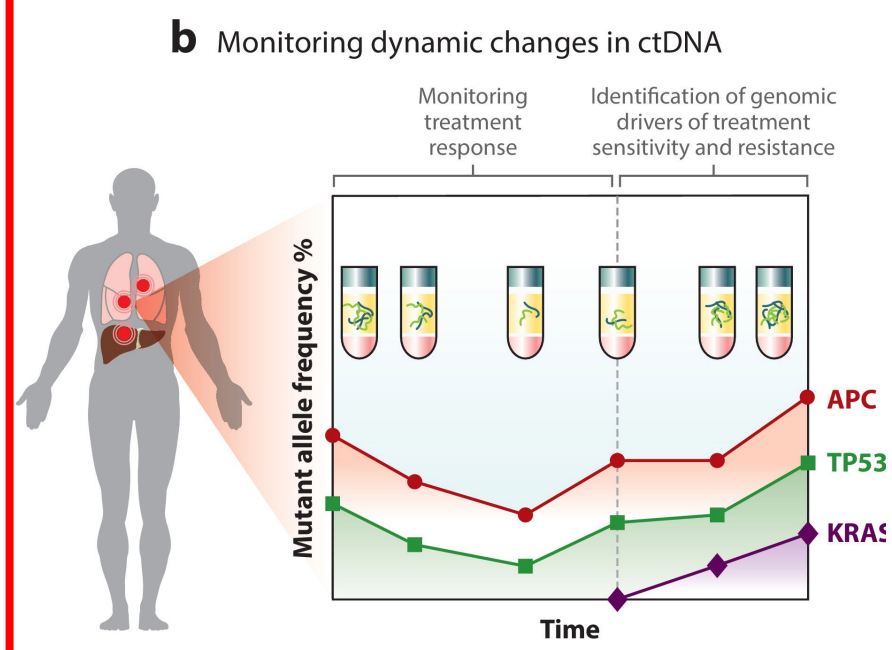


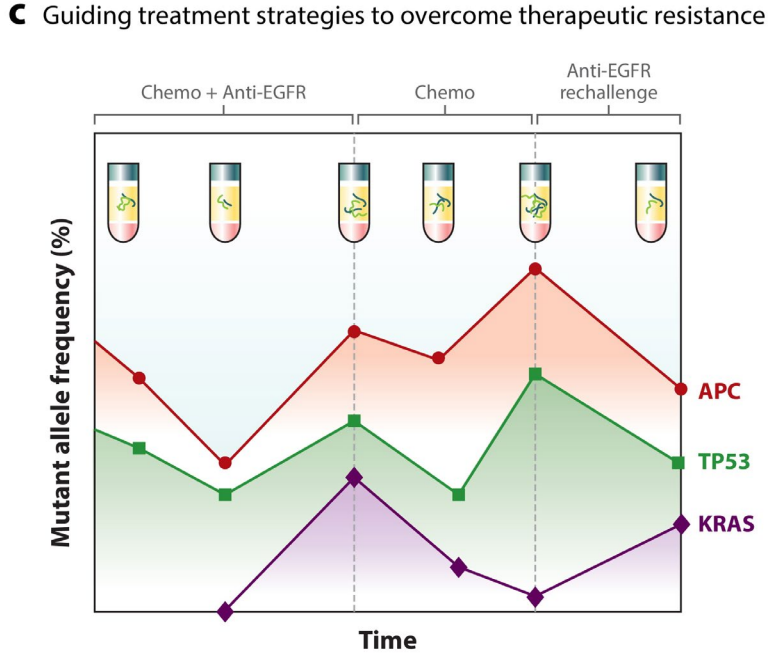
Risk stratifying:
- HIGH RISK patients - in need of (better) curative therapies
- LOW RISK patients needing less toxicity

Better surveillance following curative therapies?

Tumor-agnostic **cancer screening**?

METASTATIC SETTING





Treatment monitoring:
- EARLY IDENTIFICATION of response to systemic therapies
  - Balance treatment response with associated toxicity
  - Gauging efficacy to neoadjuvant therapies?
- Complement radiographic findings in assessing treatment response
  - Immunotherapy in MSI-H/dMMR GI cancers

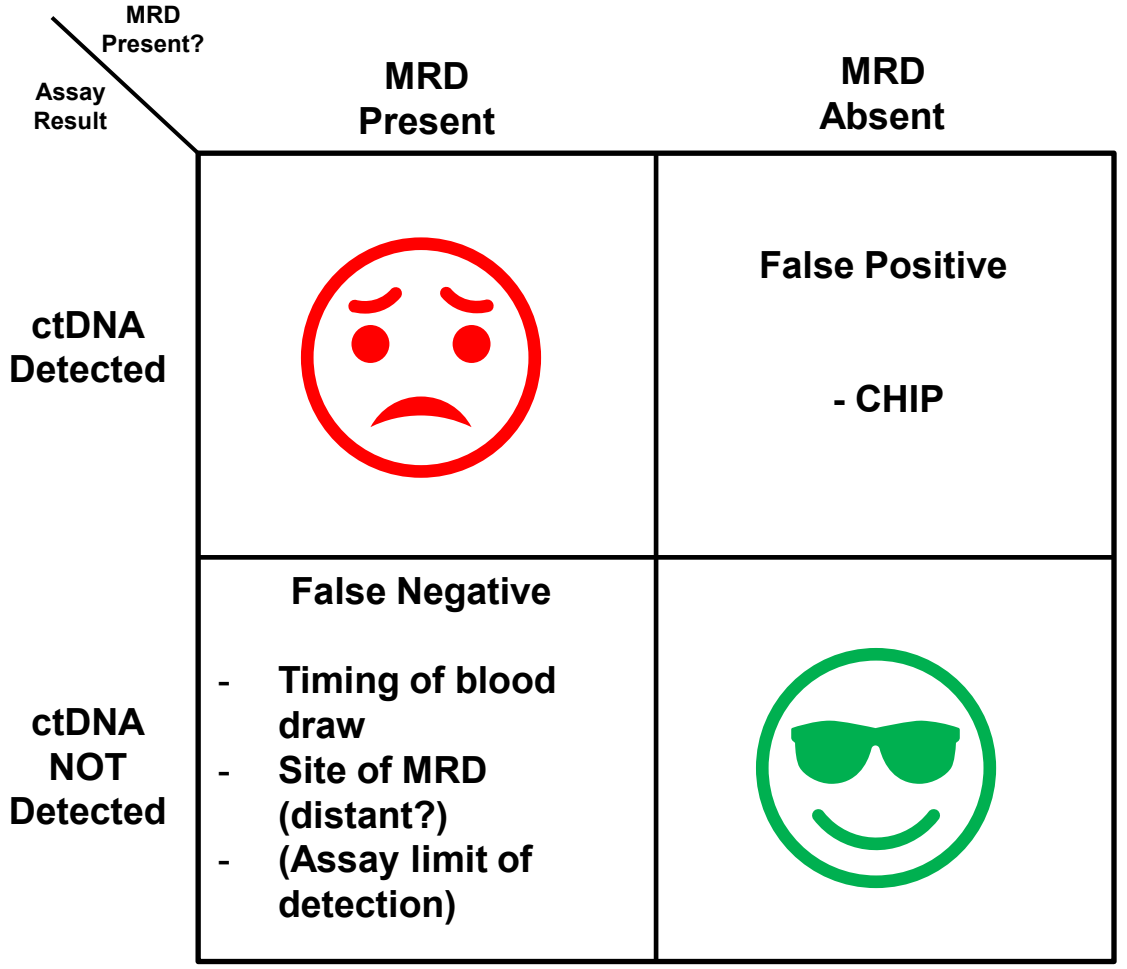
Personalizing further targeted therapies:
- Real-time, less-invasive, more comprehensive characterization of clonal evolution driving treatment resistance
  - Informing on pattern/depth of response?
  - Clinical trial eligibility

Morris VK, Strickler JH Annu Rev Med 2021

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

ctDNA to identify minimal residual disease: practical considerations

- High <u>sensitivity</u> for MRD detection: alterations with VAF < .01% can be detected
- Sensitivity improving with improving cfDNA isolation methods, WES of tumor, and with complementary methylation profiling for cancer-specific aberrations
- High <u>specificity</u>: Detection of ctDNA ~ 100% likelihood for recurrence after resection of CRC



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Different methodologies for ctDNA detection: tumor-informed vs tumor-agnostic

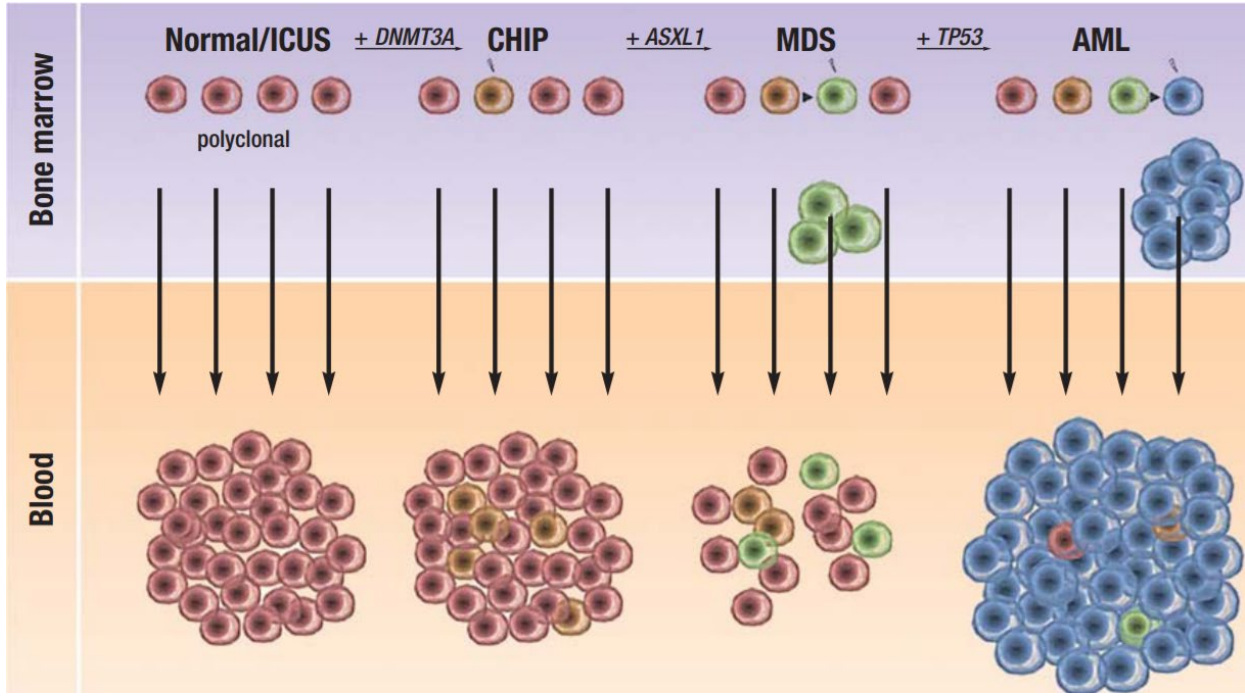
	TUMOR-INFORMED	TUMOR AGNOSTIC
Requires matched tumor tissue?	Yes	No
Turn-around time adequate for adjuvant chemotherapy window?	Longer	Shorter
Gene coverage	Personalized according to deep sequencing of tumor	Extensive panel including most commonly mutated genes
Correction for CHIP confounding?	Yes	Maybe

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

CHIP: blood "contaminant"

Are the ctDNA "positive" results generated reflective of the patient's underlying tumor biology, and how do we account for this in design of clinical trials (especially MRD studies)?

- Clonal hematopoiesis of indeterminate potential (CHIP) refers to the presence of somatic mutations in HSCs detected in the blood, in the absence of an associated hematologic malignancy.
- CHIP occurs more commonly with advancing age and observed especially as mutations in *DNMT3A*, *TET2*, and *AXSL1*.
- CHIP mutations in ctDNA assay have the potential to generate false positives for ctDNA study when assessing for MRD.



Co-sequencing of tumor tissue or isolated PBMCs isolated can distinguish CHIP and germline aberrations from true ctDNA.

Heuser M et al, Dtsch Arztebl 2016; Jaiswal S et al, NEJM 2016

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Practical considerations necessary for ctDNA testing

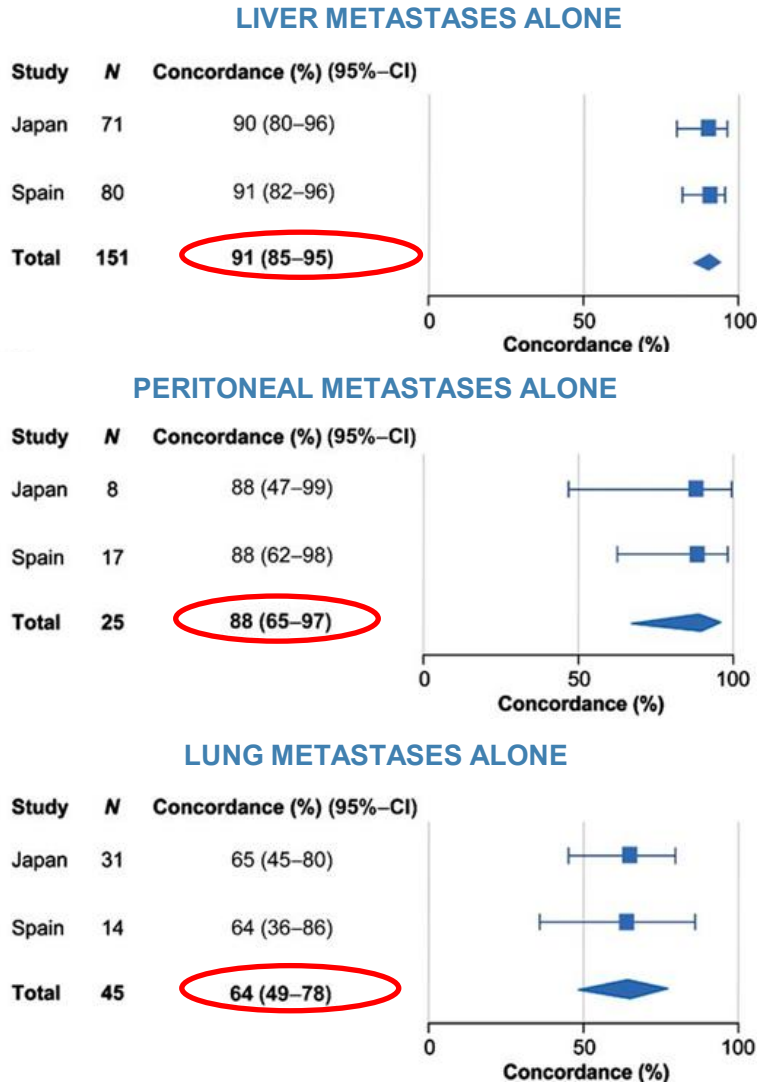
- High concordance of genomic alterations between ctDNA and matched tumor tissue (~80-90%), especially for driver mutations.

- **WHERE** matters!
- CRC liver mets are more likely to shed ctDNA

- **HOW** matters!
- Tumor informed vs tumor-agnostic assay selection: high sensitivity/specificity regardless, shorter turn-around time for tumor-agnostic ctDNA

- **WHEN** matters!
- Increased cfDNA/inflammatory milieu after surgical trauma can increase FN likelihood for MRD detection, up to ~4 weeks after surgery

- **WHAT** matters!
- Knowing what question you are asking when ordering the test guides your management



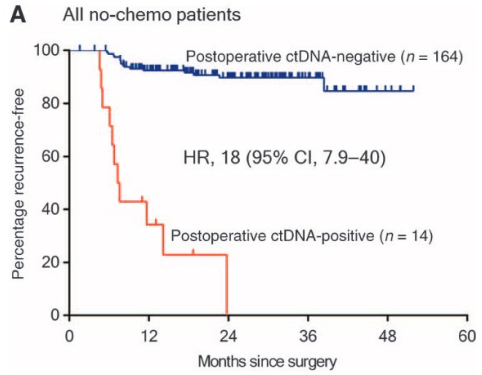
Shrock A et al CCR 2018; Parikh A et al Nat Med 2020; Henriksen T et al Mol Oncol 2020; Kagawa Y et al CCR 2021

- Use of ctDNA as a tool to inform cancer biology as a liquid biopsy
- **Informing clinical decision making of CRC using ctDNA technologies**
- Recognizing micrometastatic CRC as a unique biologic entity with novel therapeutic opportunities to cure more patients

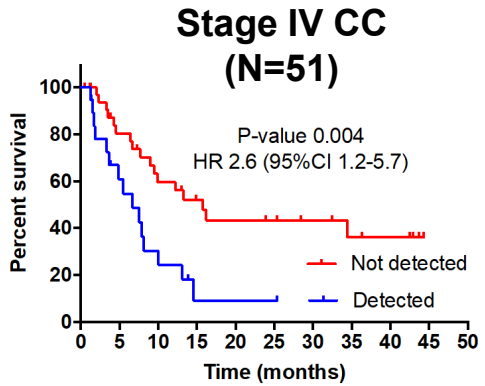
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

ctDNA detection as a prognostic biomarker in CRC

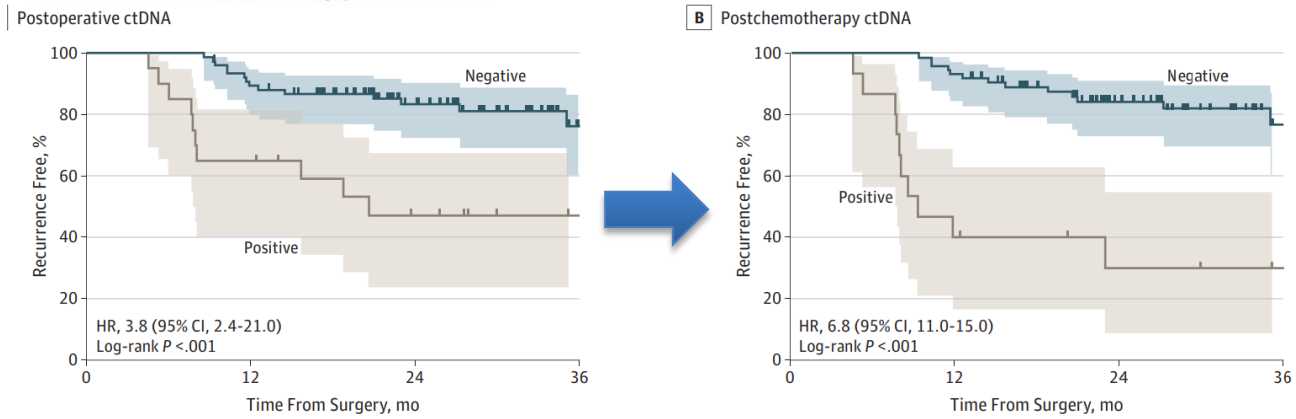
Stage II CC (N=178)



Stage IV CC (N=51)



Stage III CC (N=96)



Detection of ctDNA is a biomarker for poor prognosis across all stages of colorectal cancer.

Detection of ctDNA precedes clinical/radiographic recurrence by median ~5-6 months in CRC.

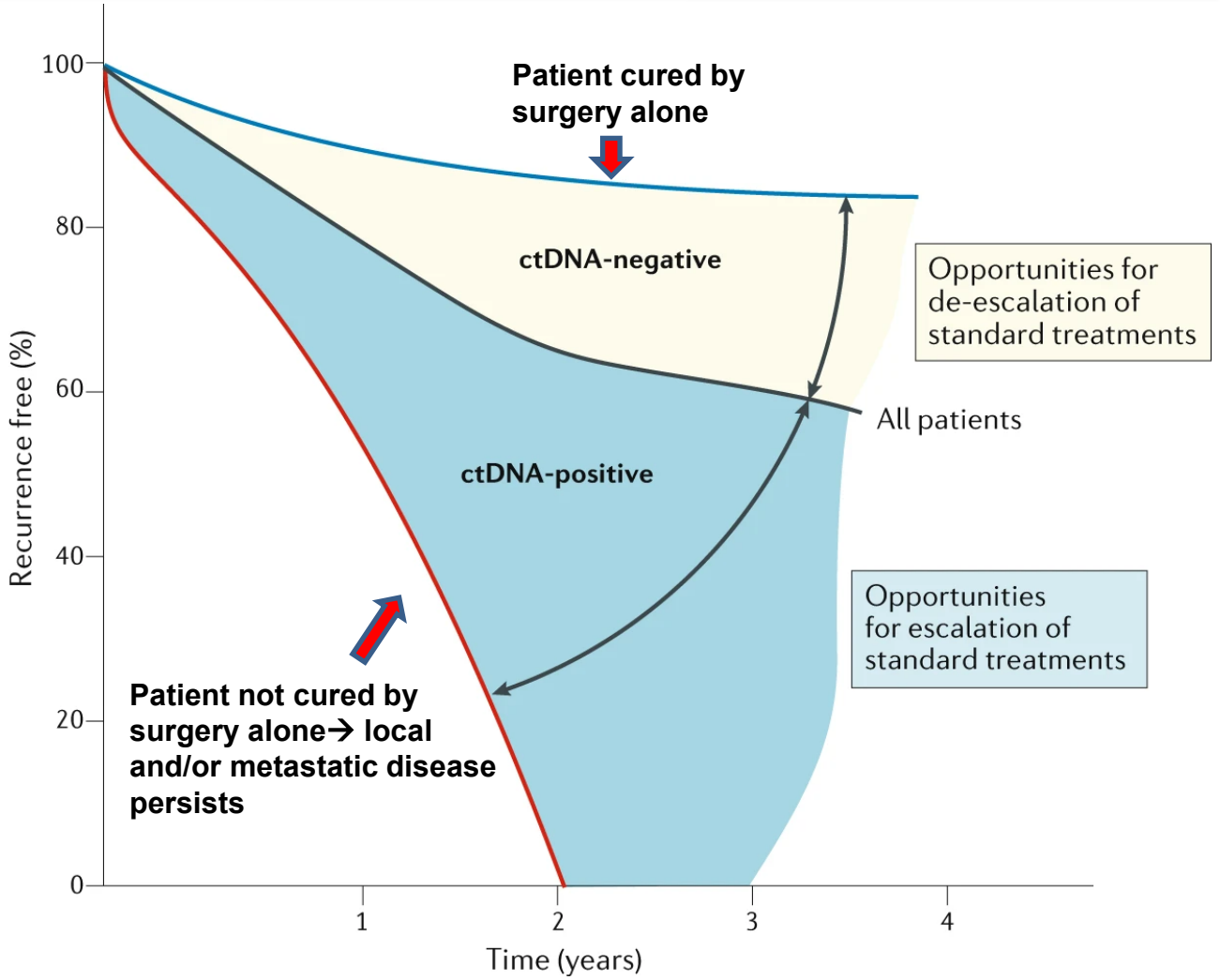
Tie J et al, Sci Transl Med 2015; Tie J et al JAMA Oncol 2019; Overman M et al ASCO 2017

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Application of ctDNA towards treatment of MRD in colon cancer

- ctDNA(-) patients: UNLIKELY to recur
  - Opportunities for **de-escalation**?
  - Minimizing (unnecessary?) toxicity of treatment without affecting survival outcome?

- ctDNA(+) patients: LIKELY to recur
  - Opportunities for **escalation**?
  - Accepting toxicity of (additional?) treatment to improve likelihood of favorable outcome

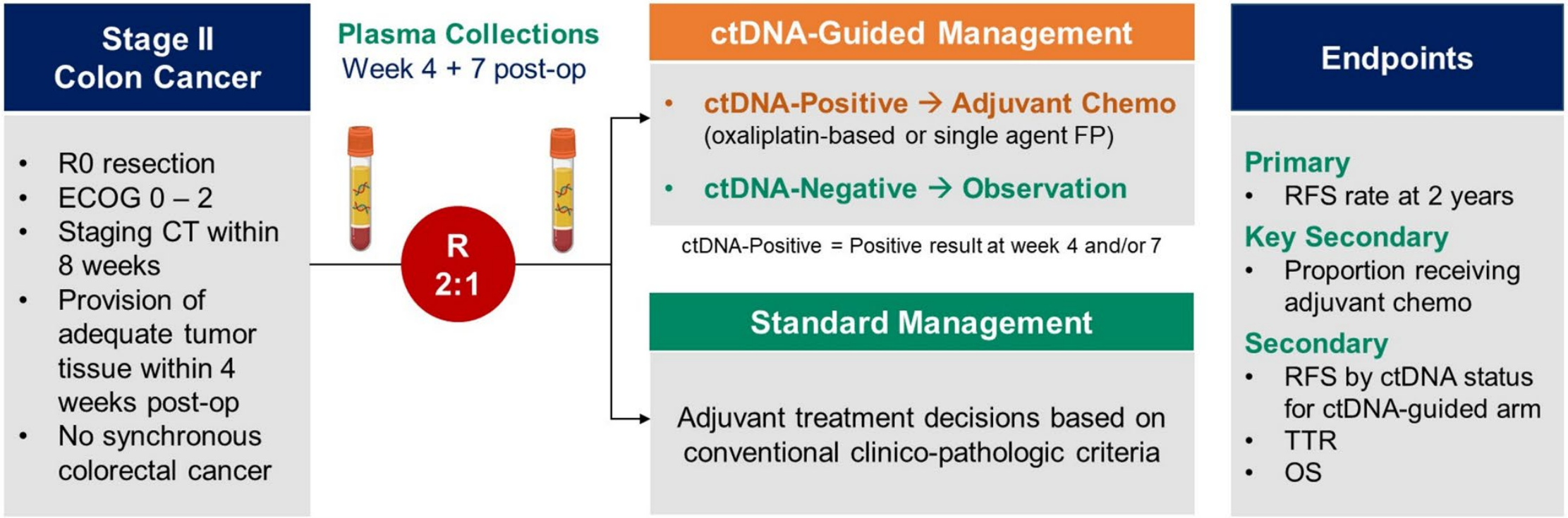


Is ctDNA ready for routine use in adjuvant treatment decision making following resection of stage II/III colon cancer?

Dasari A, Morris VK et al, Nat Rev Clin Oncol 2020

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

DYNAMIC schema



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

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

Study was designed to investigate whether a **ctDNA-guided approach vs standard approach** could reduce the use of adjuvant chemotherapy without compromising the recurrence risk for patients with stage II colon cancer.

Tie J et al, NEJM 2022

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Chemotherapy selection according to treatment approach (DYNAMIC)

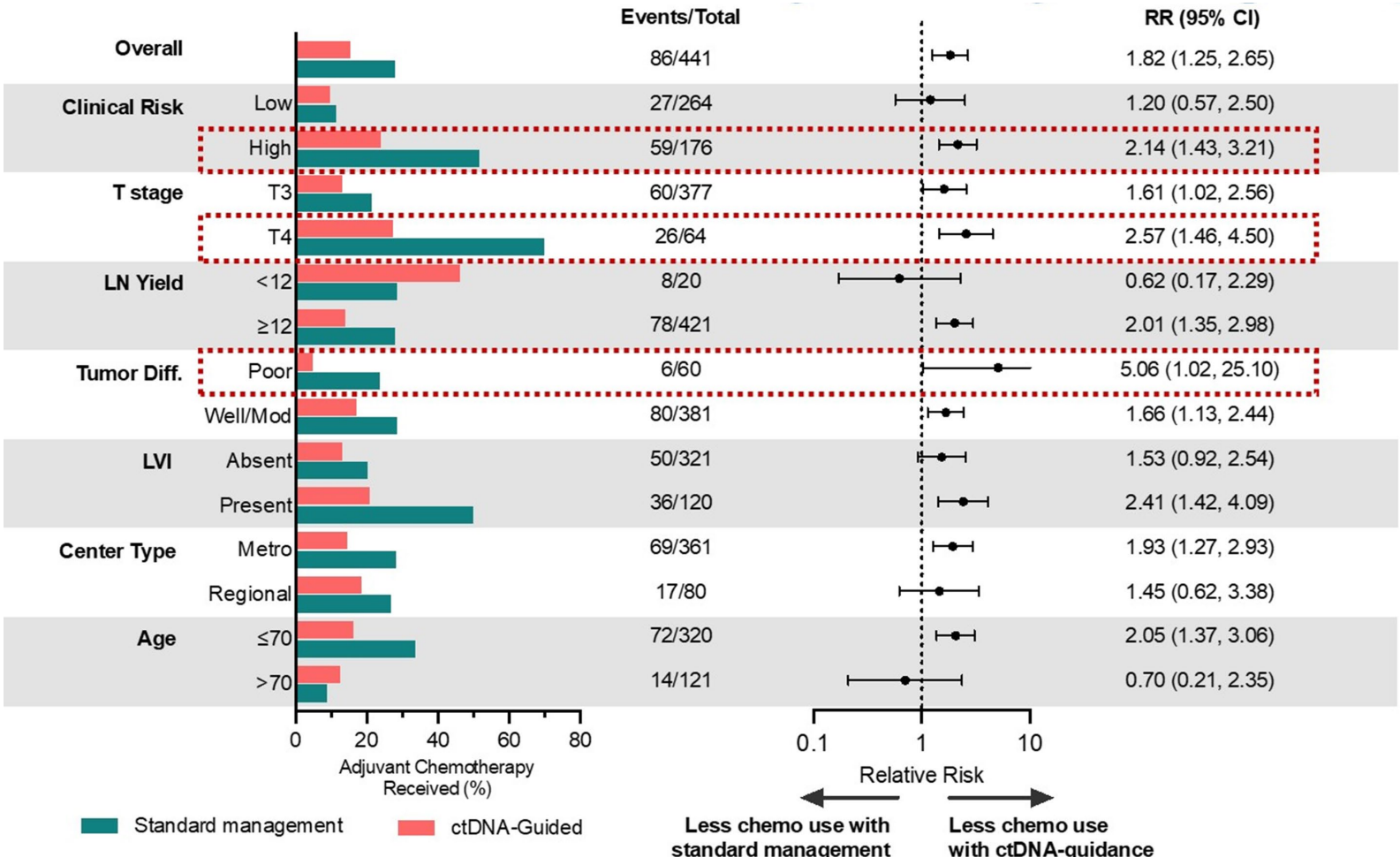
Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent fluoropyrimidine	17/45 **(38%)**	37/41 **(90%)**	<.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
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

For stage II colon cancer, ctDNA-informed decision making resulted in
- LESS overall use of chemotherapy (more DE-ESCALATION)
- When used, MORE use of (escalated) chemotherapy

Tie J et al, NEJM 2022

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

DYNAMIC: association of ctDNA status with chemotherapy use



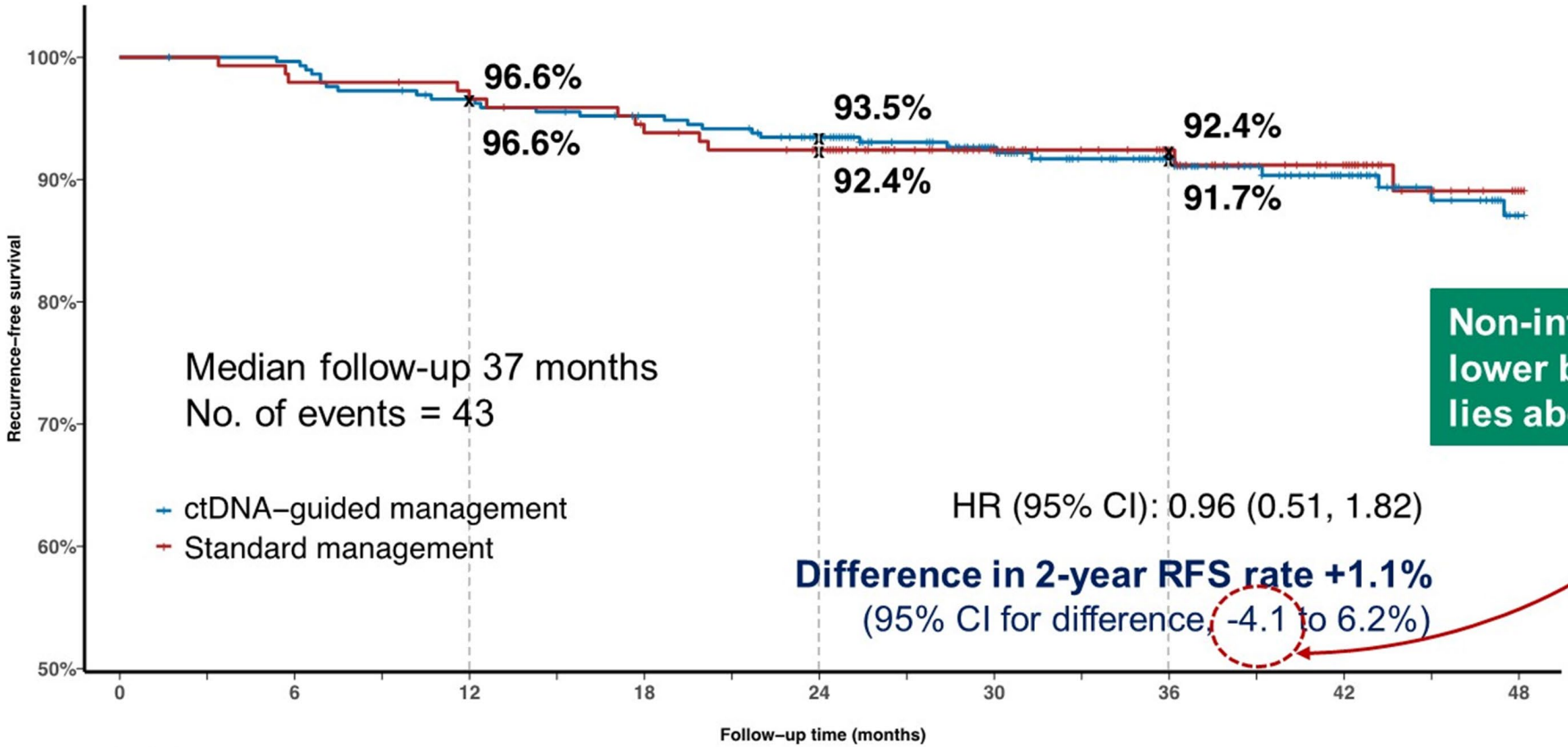
For stage II colon cancer, ctDNA results directed less chemotherapy for:

- clinically “high risk” stage II colon cancers
- T4 primary tumors
- poorly differentiated tumors

Tie J et al, NEJM 2022

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

DYNAMIC: recurrence-free survival outcomes



Non-inferiority confirmed: lower bound of 95% CI lies above -8.5%

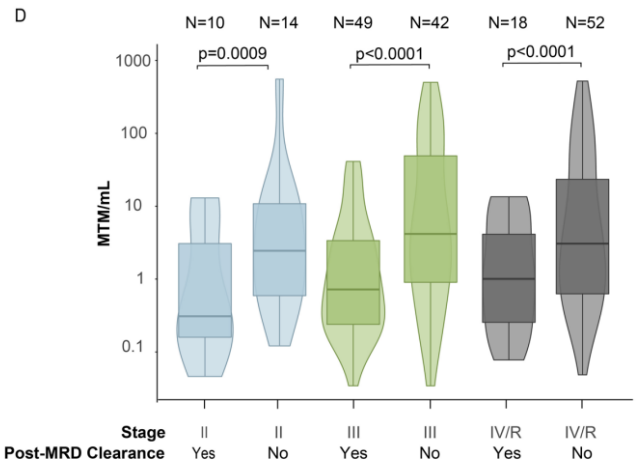
Numbers at risk

ctDNA-guided	294	292	281	273	259	207	155	109	64
Standard	147	144	142	136	128	97	78	57	33

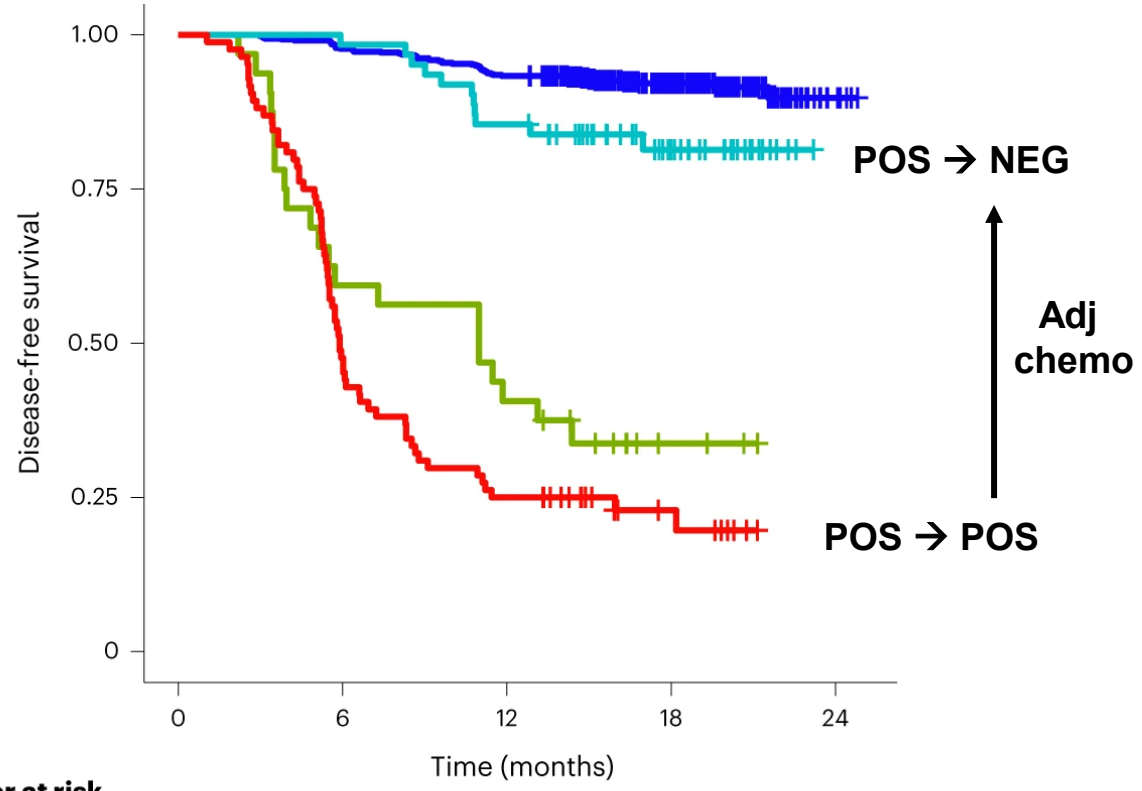
Tie J et al, NEJM 2022

Evaluating ctDNA kinetics qualitatively in treatment of MRD (GALAXY)

- Observational study evaluating changes in ctDNA from weeks 4 → 12 post-op (N=838) in patients with resected colon cancer.
- Clearance of ctDNA with adjuvant chemo was associated with improved 18-month DFS (81% vs 22%).
- Clearance of ctDNA was linked to lower total ctDNA burden at time of MRD detection:



next page for caption.

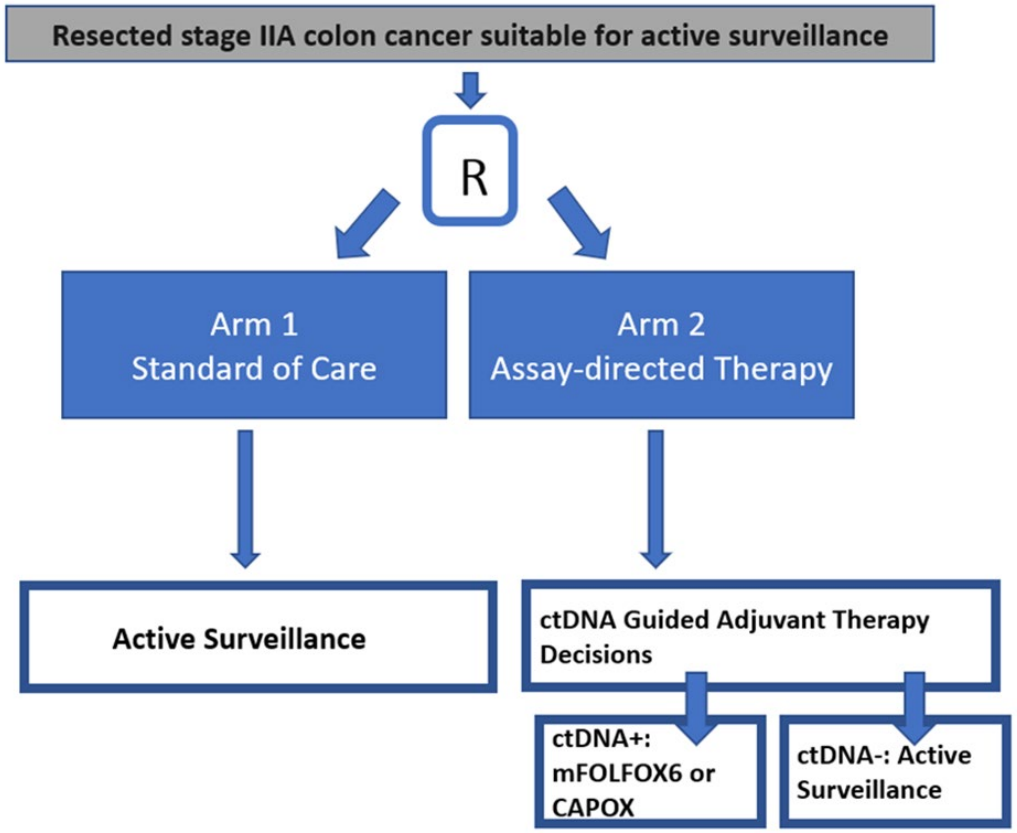


Number at risk					
Persistently negative	660	645	616	271	5
Converted positive	32	19	13	3	0
Converted negative	62	61	53	28	0
Persistently positive	84	40	21	7	0

Kotani D et al Nat Med 2023

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Does chemotherapy clear ctDNA in stage II colon cancer?



Primary Endpoints:
ctDNA clearnance (phase II)
Recurrence-free survival (phase III)

ctDNA assay: LUNAR-1 (blood-only)

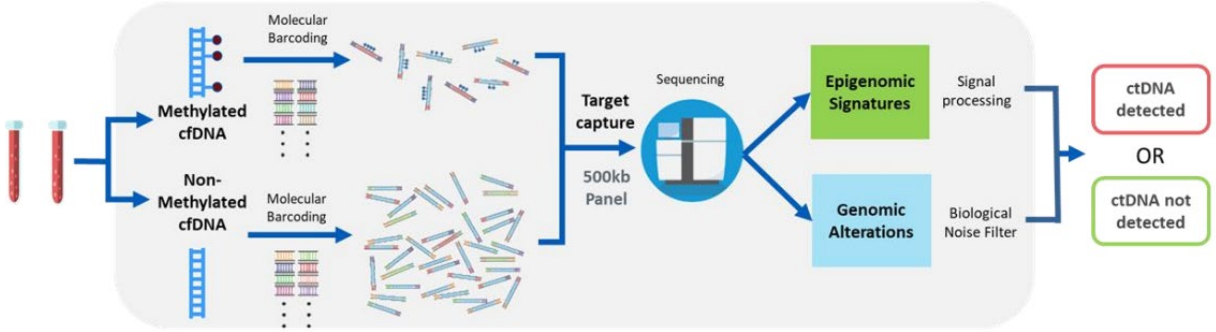
PI: Van Morris (MD Anderson)

NCT04068103

First NCI-supported trial for any solid tumor type to incorporate ctDNA as an intergal biomarker : Developed here at MD Anderson!!

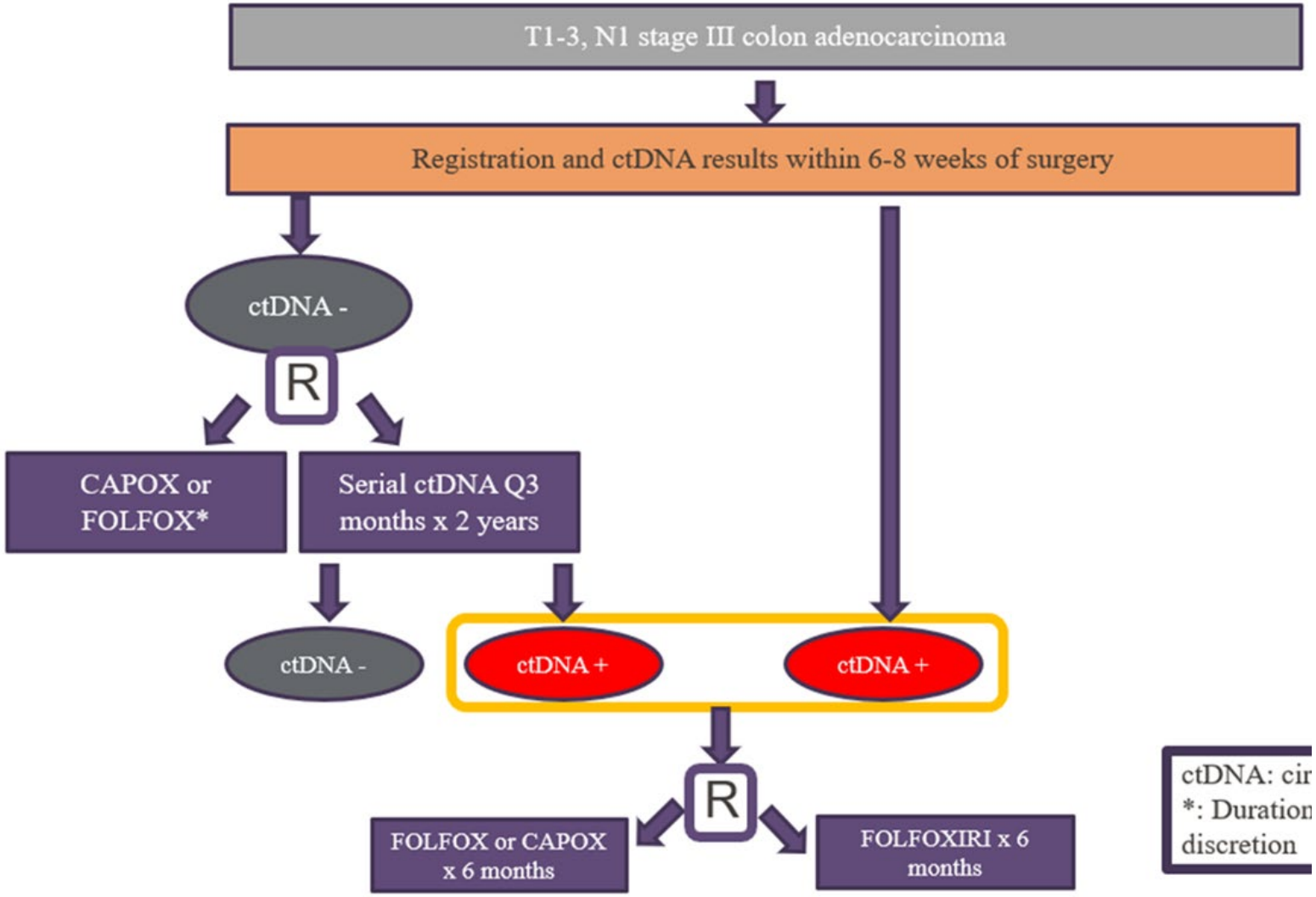
NRG GI005
COBRA
(Low-risk stage IIA)

CLOSED TO ENROLLMENT 7/2023



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

ctDNA for escalation/de-escalation of chemotherapy in stage III colon cancer



CIRCULATE-US
(High-risk stage II/stage III)

ctDNA assay: Signatera (tumor-informed)

Principal Investigators:
Arvind Dasari (MD Anderson)
Christopher Lieu (Colorado)

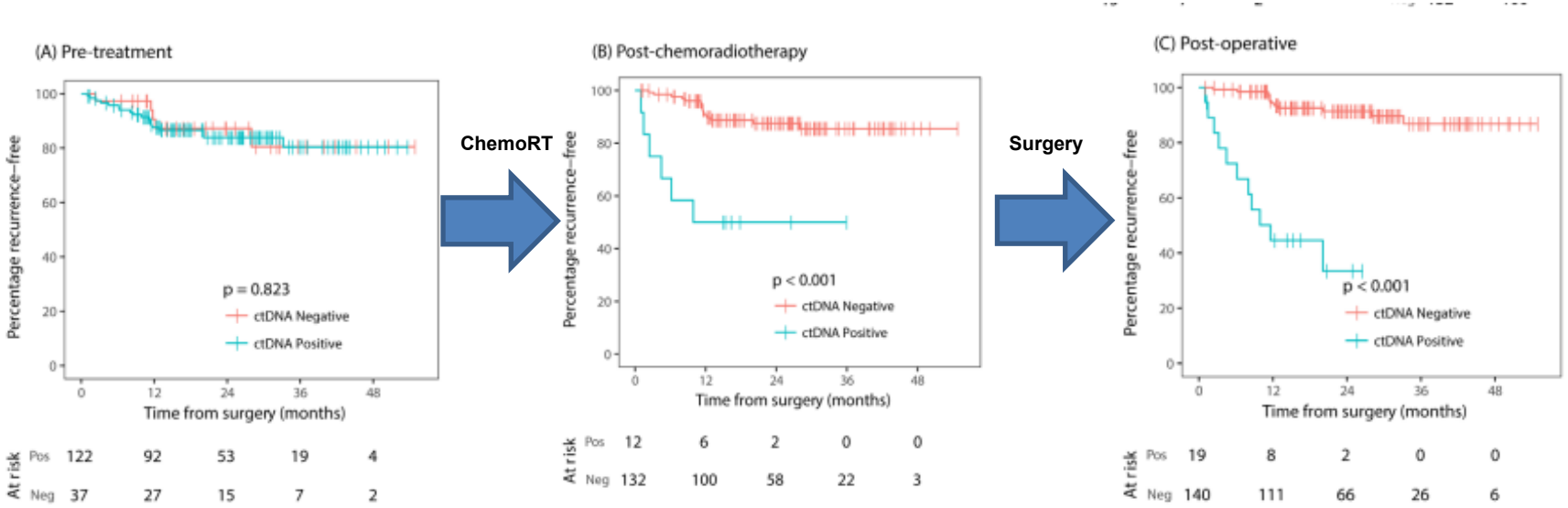
NCT04089631

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

ctDNA for evaluating treatment response for rectal cancer

- Management of localized rectal cancer has shifted to total neoadjuvant therapy (scRT → FP/oxaliplatin), with a goal of non-operative, “watch and wait” approach for patients with complete endoscopic and radiographic response…

- Can we identify patients cured by TNT approach?



N	**159**	**144**	**159**
ctDNA(+)	**77%**	**8%**	**12%**

Does this identify patients experiencing pCR?

Tie J et al, Gut 2019

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Association between post chemoRT ctDNA status and pCR

Table 1 Clinicopathological characteristics and recurrence, according to ctDNA status

	Pretreatment ctDNA (n=159)			Postchemoradiotherapy ctDNA (n=144)			Postoperative ctDNA (n=159)		
Variable	Positive (n=122)	Negative (n=37)	P	Positive (n=12)	Negative (n=132)	P	Positive (n=19)	Negative (n=140)	P
Age, years									
Median	63	59	0.69	61	62	0.97	59	63	0.97
Range	28–85	31–86		41–86	28–86		41–86	28–86	
Sex, n (%)									
Female	40 (33)	12 (32)	1.00	4 (33)	43 (33)	1.00	6 (32)	46 (33)	1.00
Male	82 (67)	25 (68)		8 (67)	89 (67)		13 (68)	94 (67)	
Distance from anal verge (cm), n (%)									
0–5	44 (36)	13 (35)	0.77	4 (33)	48 (36)	0.79	6 (32)	51 (37)	0.01
> 5–10	55 (45)	19 (51)		5 (42)	62 (47)		5 (26)	69 (49)	
> 10	23 (19)	5 (14)		3 (25)	22 (17)		8 (42)	20 (14)	
Clinical disease stage, n (%)									
Stage II	23 (19)	12 (32)	0.11	2 (17)	29 (22)	1.00	2 (11)	33 (24)	0.25
Stage III	99 (81)	25 (68)		10 (83)	103 (78)		17 (89)	107 (76)	
Pathological T stage, n (%)									
ypT0-2	65 (53)	23 (62)	0.36	5 (42)	73 (55)	0.38	5 (26)	83 (59)	0.01
ypT3-4	57 (47)	14 (38)		7 (58)	59 (45)		14 (74)	57 (41)	
Pathological N stage, n (%)									
ypN0	91 (75)	25 (68)	0.40	6 (50)	97 (73)	0.10	10 (53)	106 (76)	0.05
ypN1-2	31 (25)	12 (32)		6 (50)	35 (27)		9 (47)	34 (24)	
Pathological complete response, n (%)									
Yes	24 (20)	10 (27)	0.36	1 (9)	28 (21)	0.46	2 (11)	32 (23)	0.37
No	98 (80)	27 (73)		11 (89)	104 (79)		17 (89)	108 (77)	
Adjuvant chemotherapy, n (%)									
Yes	40 (33)	17 (46)	0.17	4 (33)	43 (33)	1.00	11 (58)	91 (65)	0.61
No	82 (67)	20 (54)		8 (67)	89 (67)		8 (42)	49 (35)	
Recurrence at any site, n (%)									
Yes	18 (15)	5 (14)	1.00	6 (50)	15 (11)	0.003	11 (58)	12 (9)	< 0.001
No	104 (85)	32 (86)		6 (50)	117 (89)		8 (42)	128 (91)	
Site of recurrence, n (%)									
Locoregional only	3/18 (17)	0/5 (0)	1.00	0/6 (0)	3/15 (20)	0.53	1/11 (9)	2/12 (17)	1.00
Distant±locoregional	15/18 (83)	5/5 (100)		6/6 (100)	12/15 (80)		10/11 (91)	10/12 (83)	

ctDNA, circulating tumour DNA.

Tie J et al, Gut 2019

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Adding context for assessing response to immunotherapy?

- Anti-PD(L)1 based combinations are very effective (and curative) in patients with advanced MSI-H solid tumors like CRC.

- However, radiographic findings may "overcall" true pathologic response:

14 patients with MSI-H CRC treated with anti-PD1 +/- anti-CLTA-4 antibodies
13/14 with radiographically persistent disease
13/14 with pathologic CR at resection; 1/14 with near-pCR

Patient number	Location of primary tumor in the colon	Stage of colon cancer	Age at diagnosis, y	Sex	Deficient mismatch repair protein (by IHC)	Etiology (Lynch or s poradic)	Immuno-therapy	No. of cycles before surgery	Surgery	Intent of surgery	Pathology postresection	Best overall radiographic response
1	Transverse	IV	33	M	MSH2	Lynch	Pembro	3	Right hemicolectomy	Curative	Near pCR	SD
2	Right	IV	48	F	MLH1/PMS2	Lynch	Pembro	4	Right hemicolectomy	Palliative	pCR	SD
3	Right	III	70	F	MLH1/PMS2	Sporadic	Nivo	8	Right hemicolectomy	Curative	pCR	SD
4	Left	IV	45	M	MSH2/MSH6	Lynch-like	Nivo	14	Rectal stump resection and hepatic metastasectomy	Curative and palliative	pCR	PR
5	Right	IV	30	M	MSH2/MSH6	Lynch	Nivo	56	Peritoneal metastasectomy	Curative	pCR	PR
6	Left	IV	55	M	MSH6	Lynch	Nivo + Ipi	27	Pelvic mass metastasectomy	Palliative	pCR	PR
7	Right	IV	67	F	MLH1	Sporadic	Pembro	35	Peritoneal metastasectomy	Curative	pCR	PR
8	Left	IV	45	F	MLH1	Lynch	Pembro	16	Hepatic metastasectomy	Curative	pCR	PR
9	Right	IV	38	M	MSH2	Lynch	Nivo + Ipi	54	Right hemicolectomy	Curative	pCR	CR
10	Right	IV	37	M	MSH2/MSH6	Lynch	Nivo + Ipi	24	Ileocolectomy and peritoneal metastasectomy	Curative	pCR	SD
11	Left	IV	37	M	MLH1/PMS2	Lynch	Nivo+ Ipil	12	Laparoscopic jejunostomy	Palliative	pCR	SD
12	Left	IV	39	M	MLH1	Lynch-like	Nivo + Ipi	24	Liver metastasectomy	Curative	pCR	PR
13	Right	IV	31	M	MLH1	Lynch-like	Pembro	15	Liver metastasectomy	Curative	pCR	PR
14	Left	IV	59	M	MSH2/MSH6	Sporadic	Nivo + Ipi	24	Sigmoidectomy	Curative	pCR	PR

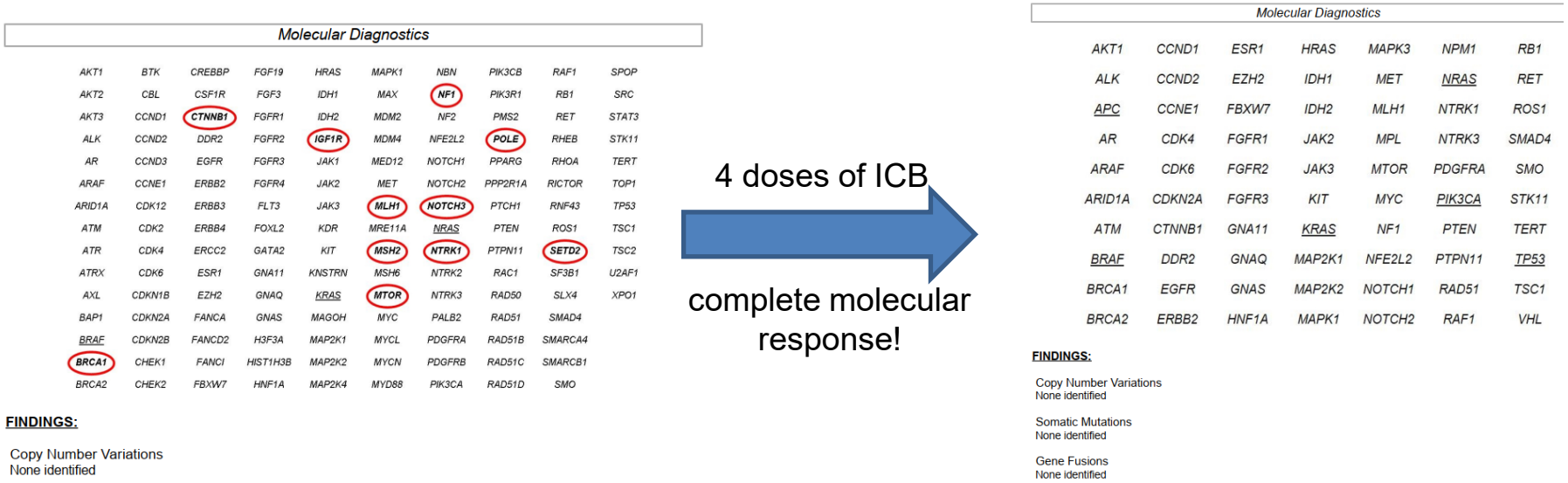
Ludford K et al JNCI 2019

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Adding context for assessing response to immunotherapy?

- Patient with newly diagnosed stage IV rectal cancer with oligometastatic disease to the liver presented to MDACC for further treatment.

- Molecular profiling notable for *POLE* mutation/ hypermutated status.



4 doses of ICB

complete molecular response!

- Liver “metastasis” remains “stable” though patient remains without evidence of clinical, biochemical, or radiographic recurrence off treatment for > 2 years.

Are we ready to replace standard imaging for use of ctDNA to gauge curative response?

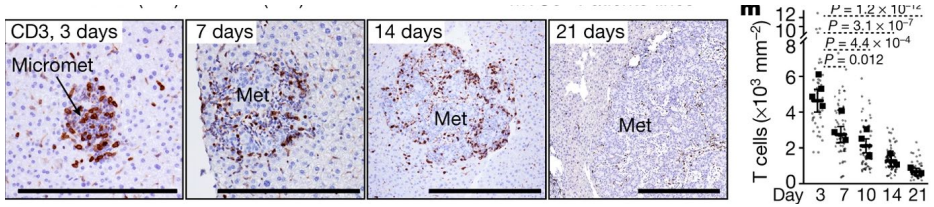
- Use of ctDNA as a tool to inform cancer biology as a liquid biopsy
- Informing clinical decision making of CRC using ctDNA technologies
- **Recognizing micrometastatic CRC as a unique biologic entity with novel therapeutic opportunities to cure more patients**

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

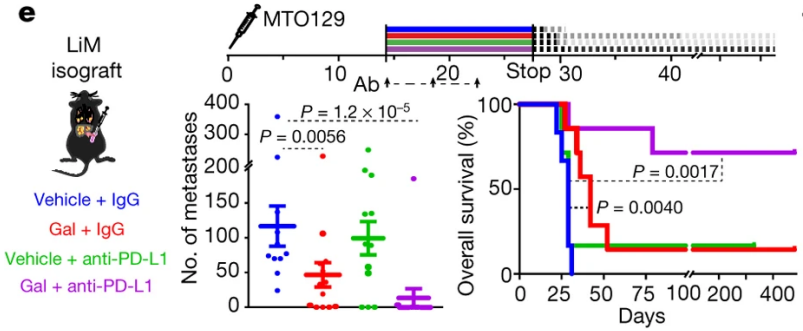
Immune cell inclusion: specific to CRC micromets?

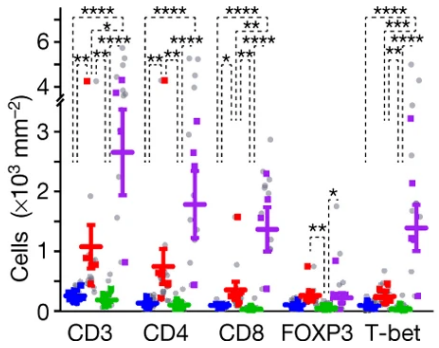
- **CRC is characterized transcriptomically by ↓ CD8 T cell signature and low immune activation (desert/exclusion) phenotype.**
- ***In vivo*, CRC micrometastases may harbor ↑ T cells than macrometasases.**
- **Increased TGF-β signature has been linked with immune exclusion and worse survival following atezolizumab[7].**
- **As tumors grow, TGF-β drives exclusion of immune cells from tumor microenvironment in CRC preclinical models.**
- **Concomitant targeting of TGF-β overcomes de novo anti-PD-1 resistance.**

Exclusion of T cells in TME with time



Anti-tumor activity in LiM CRC model with dual TGFβ/PD1 targeting





Restoration of CTLs in TME

Can clearance of TGF-β systemically prime CRC micrometastases for response to immune checkpoint blockade?

Can we utilize ctDNA technologies to identify such patients?

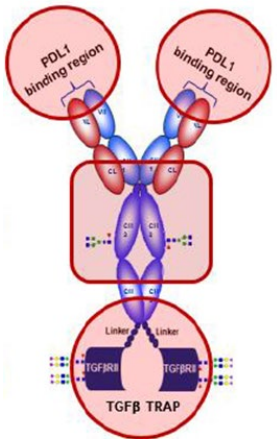
[1]Angelova M et al Genome Biol 2015; [2]Tauriello D et al Nature 2018

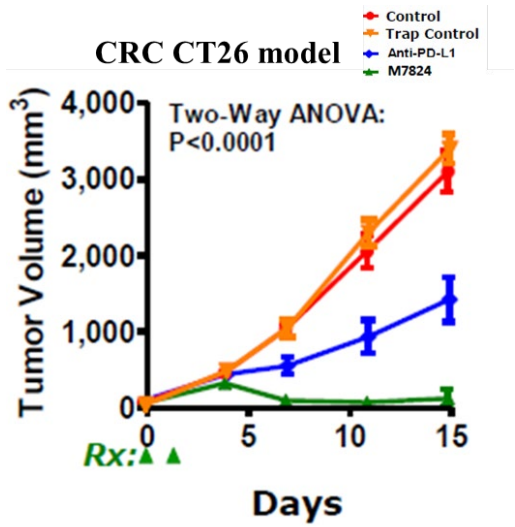
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Targeting TGF-β and PD-L1 in patients w/ ctDNA(+) liver-limited resected met CRC

- **Bintrafusp alfa is a dual TGF-β trap: anti-PD-L1 molecule safe and well tolerated in patients with advanced cancers.**

- **Addition of a TGF-β trap has been shown to augment sensitivity to anti-PD-1 therapies in preclinical models of CRC and melanoma[2].**





Patients with liver-limited metastatic colorectal cancer with detectable ctDNA following resection and completion of all standard therapy → Bintrafusp alfa (1200 mg IV) x 6 doses every 2 weeks → Test for ctDNA clearance

N=15

- **Eligibility criteria:**
  - **MSS/pMMR CRC s/p complete resection of primary tumor and all liver mets**
  - **Completion of all standard of care adjuvant therapy**
  - **No radiographic evidence of disease**
  - **ctDNA+ using CLIA-compliant Guardant assay collected > 14 days after treatment completion**
- **Primary endpoint**
  - **Clearance of ctDNA in >30% of patients at 12 weeks**

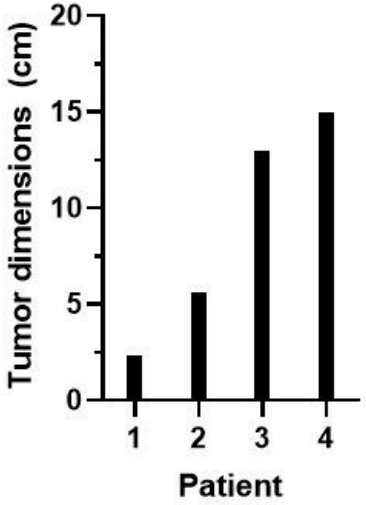
To our knowledge, the first trial (for CRC) to use (1) ctDNA as an integral biomarker and (2) use ctDNA clearance for response evaluation.

[1]Strauss J et al Clin Cancer Res 2018; [2]Ravi R et al Nature Comm 2018; [3]Morris VK et al Cancer Res Commun 2022

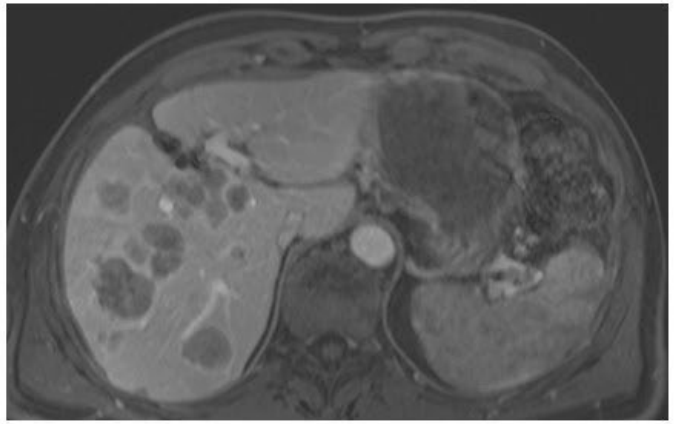
Bintrafusp alfa for ctDNA(+) liver-limited resected met CRC: clinical outcomes

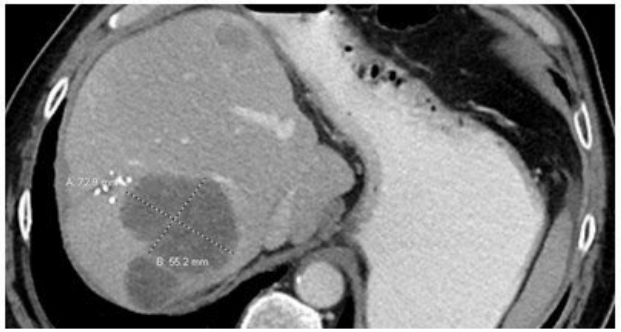
4 participants treated with bintrafusp alfa:

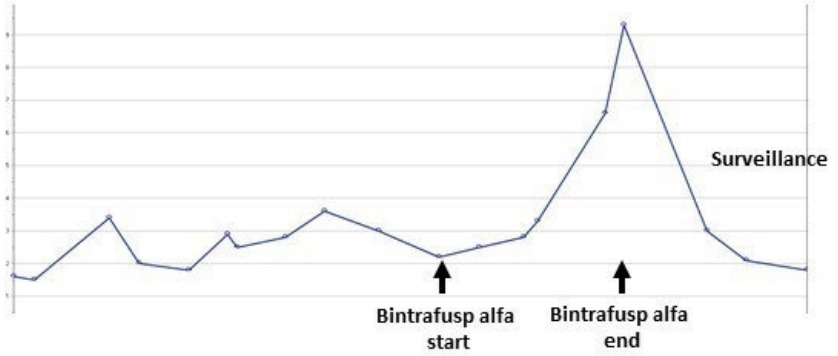
(A)



(B)







Trial stopped early due to concern for loss of equipoise.

Morris VK et al Cancer Res Commun 2022

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Biochemical progression following bintrafusp alfa: a ctDNA analysis

Patient	Mutation	Pretreatment VAF (%)	Post-recurrence VAF (%)
1	APC^{A703fs}	0.5	0.4
	$TP53^{P278fs}$	< 0.3	0.3
	$TP53^{C277G}$	0.4	---
2	$TP53^{R196*}$	0.5	65.7
	APC^{R876*}	< 0.3	64.7
	$KRAS^{G12D}$	< 0.3	60.8
	MET^{N786fs}	0.3	< 0.3
	$MTOR^{R206H}$	< 0.3	---
	$BRCA2^{D1360Y}$	---	0.3
3	$TP53^{C238Y}$	0.3	< 0.2
	$SMAD4^{D335G}$	---	31.5
	APC^{R1450*}	---	23.3
	APC^{R216*}	---	23.0
	$KRAS^{G12D}$	---	21.0
	$MAPK1^{Q97K}$	---	1.2
	$STK11^{D330E}$	---	0.4
	KIT^{R804W}	---	< 0.2
4	$ERBB2^{R288W}$	< 0.2	(not tested)

Morris VK et al Cancer Res Commun 2022

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Integrating post-surgical surveillance, MRD monitoring and intervention (INTERCEPT)

Stage II CRC

Stage II CRC

Resectable Stage IV CRC

Surgery + / - Neoadjuvant Therapy

Adjuvant Therapy

Surveillance

All therapies and surveillance per routine care

ctDNA Positive

Radiographic Recurrence

No Radiographic Recurrence (MRD)

MRD Clinical Trials

Tissue informed (Signatera) ctDNA assay post-op & with each surveillance visit

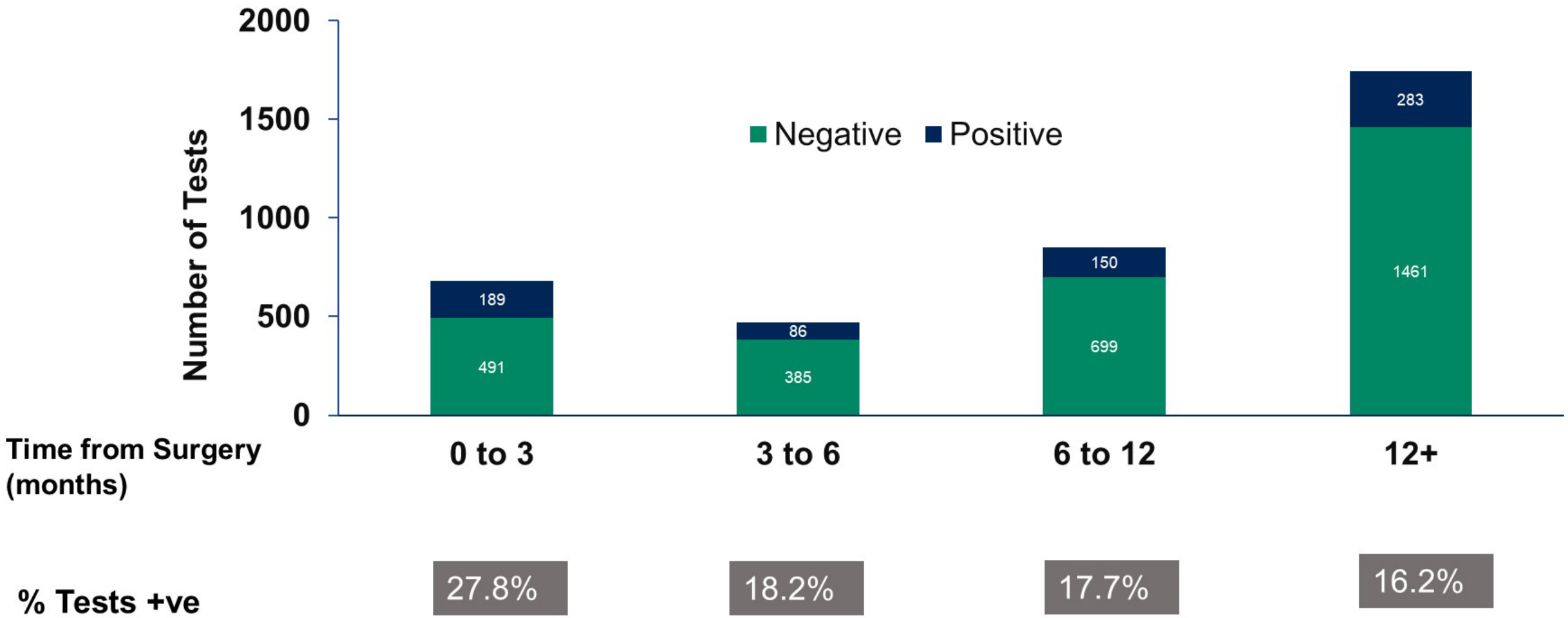
Characteristic	Category	N (%)
Age (years)	Median	58
	Range	21-93
Gender	Male	611 (55)
	Female	504 (45)
Primary Location	Colon	680 (61)
	Rectum	389 (35)
	Not Specified	46 (4)
Pathologic Stage	0-II	260 (24)
	III	294 (26)
	IV/Recurrent	561 (50)
# of ctDNA Assays	Median	3
	Range	1-11

1115 patients with CRC evaluated at MD Anderson between 12/2021 - 3/2023.

Dasari A et al, ASCO 2023

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

ctDNA results according to time from surgery for CRC (INTERCEPT)



Dasari A et al, ASCO 2023

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Distribution of ctDNA(+) status by stage and location of CRC (INTERCEPT)

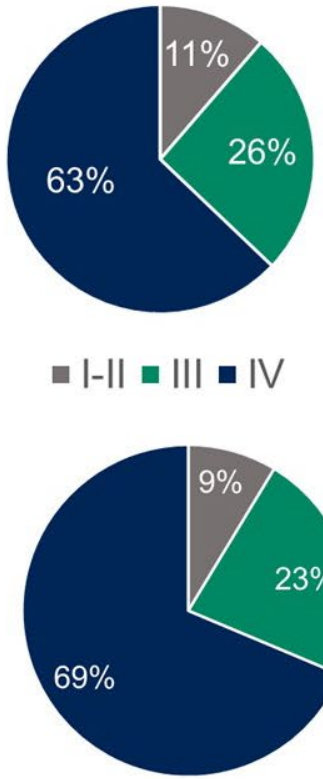
ctDNA positive before adjuvant therapy

39%; n=119

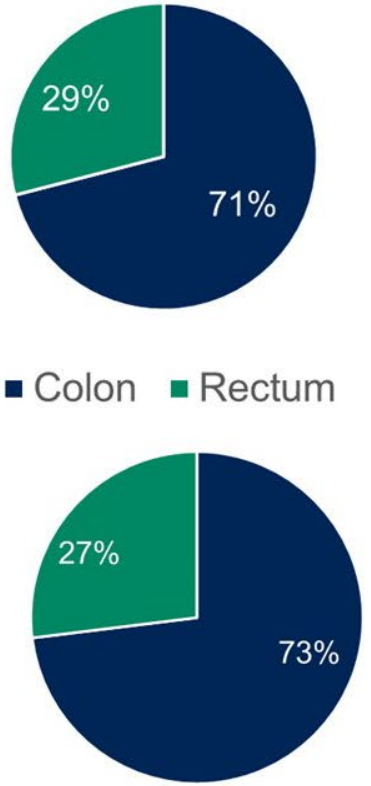
ctDNA positive during surveillance

61%; n=184

Stage of disease



Location of disease



Dasari A et al, ASCO 2023

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Evaluations driven by ctDNA(+) status during surveillance for CRC (INTERCEPT)

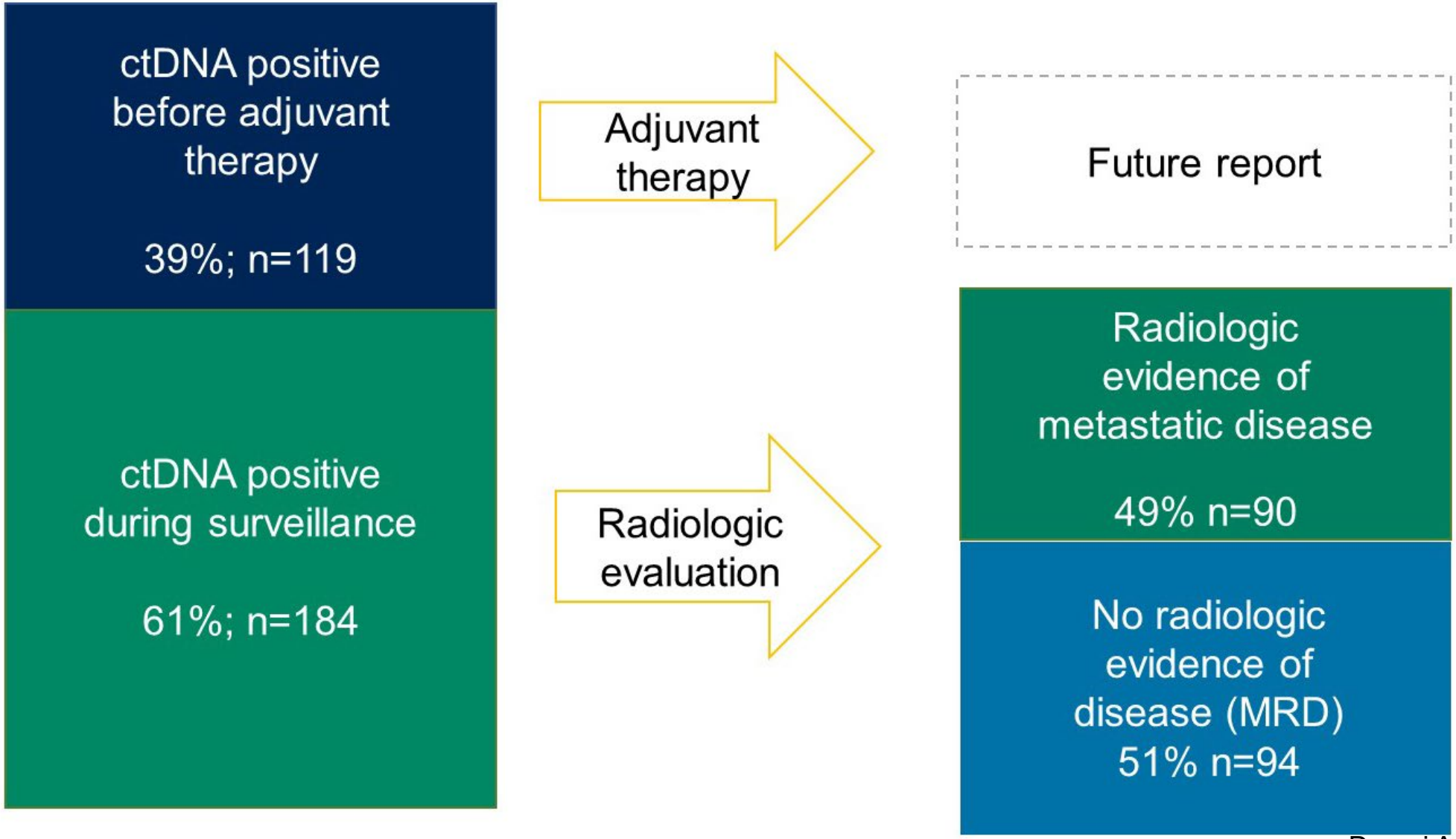
# of Reflex Investigations	# of Patients
1	48
2	18
> 2	7

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

Dasari A et al, ASCO 2023

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

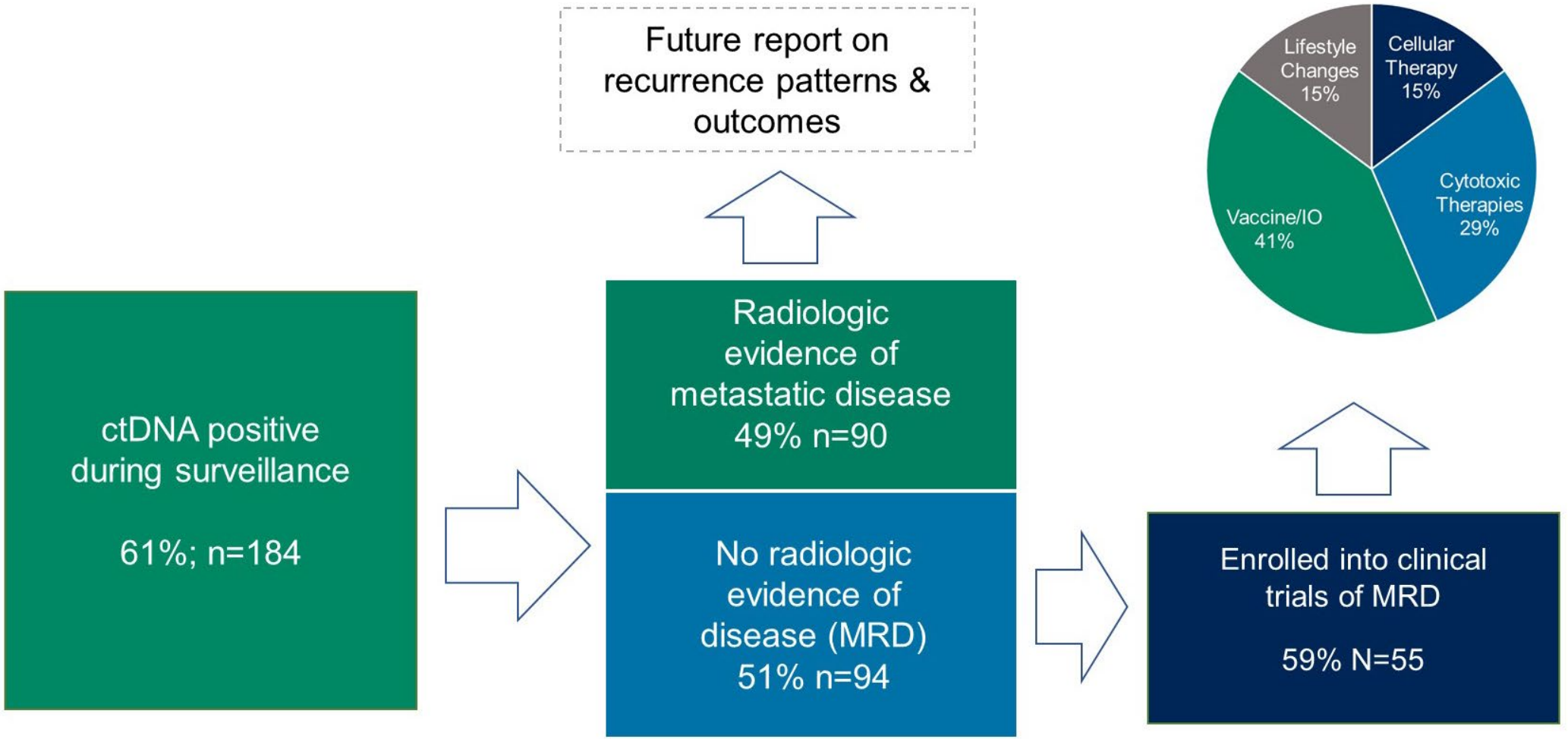
Radiographic findings of CRC patients with ctDNA(+) status during surveillance (INTERCEPT)



Dasari A et al, ASCO 2023

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

ctDNA treatment trials for intervention on MRD at MDACC (INTERCEPT)

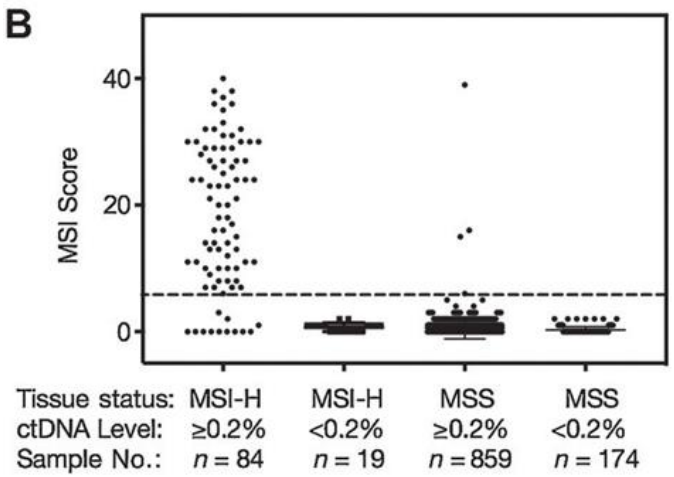


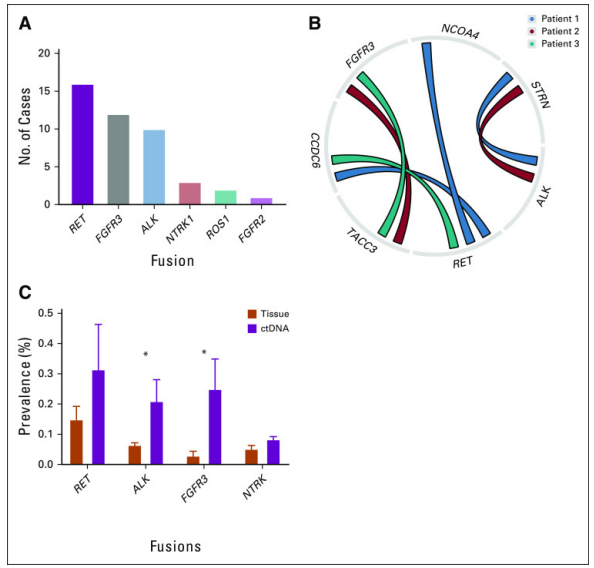
Dasari A et al, ASCO 2023

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

More than a somatic mutation test….

- **Tumor mutation burden**
  - higher TMB reported for ctDNA > tissue
  - clinical context matters: can targeted therapy resistance signature overcall true TMB?
- **MSI status**
  - correlates w/ “gold-standard” tissue specimens - improved sensitivity at higher total ctDNA level
- **Fusion detection**
  - Rare in patients with colorectal cancer
  - Low VAF fusion detection possible
- **Methylation**
  - Unique CRC methylation markers identifiable and distinguish from other cancers
  - Improved sensitivity for MRD detection in CRC
- **Viral (HPV) integration**
  - The power of great collaboration at MD Anderson!!





Drusbosky L et al ASCO 2021; **Willis J et al CCR 2019**; **Clifton K et al JCO PO 2019**; Parikh A et al CCR 2021

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Summary

- Use of ctDNA as a tool to inform cancer biology as a liquid biopsy
  - High-performance test for detection of somatic mutations, TMB, MSI status, fusions, ….
- Complementing current management of CRC using ctDNA
  - Very sensitive method for reliably identifying MRD and prognosticating recurrence risk
  - Informative tool to complement standard approaches to assessing response
- Defining ctDNA as the gold standard for guiding adjuvant therapy decisions
  - De-escalation:
  - Escalation: ongoing clinical trials will inform on predictive utility
- Recognizing micrometastatic CRC as a unique biologic entity
  - Bench discoveries may translate to novel treatment approaches to cure more patients
  - INTERCEPT program for CRC: proof-of-concept for intervening on ctDNA(+) identification of MRD with novel therapeutic approaches

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Acknowledgements

Dept of GI Medical Oncology

- Dr. James Yao
- **Dr. Scott Kopetz**
- **Dr. Arvind Dasari**
- Dr. Kanwal Raghav
- Dr. Christine Parseghian
- Dr. Alisha Bent
- Dr. Benny Johnson
- Dr. Pia Morelli
- Dr. Shubham Pant
- **Kristin Alfaro**
- Trish Jensen-Loewe
- **Robert Kell**
- **GITT team**
- Jamie Faber
- Shaelynn Riley
- Kathryn Aziz

Division of Surgical Oncology

- **Dr. Tsuyoshi Konishi**
- Dr. Nancy You
- Dr. Abhineet Uppal
- Dr. Timothy Newhook
- Dr. George Chang

Division of Cancer Medicine

- Dr. Chris Flowers
- Dr. Robert Wolff
- Dr. Waun Ki Hong

Division of Pathology

- Dr. Dipen Maru
- Dr. Ignacio Wistuba
- Dr. Neus Bota Rabassedas

NIH

NRG ONCOLOGY

SWOG
Leading cancer research. Together.

ANDREW SABIN FAMILY FOUNDATION

CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS