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

Using the liquid biopsy as an intervention tool to improve outcomes for patients with colorectal cancer.

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4/27/2024

Talk Outline

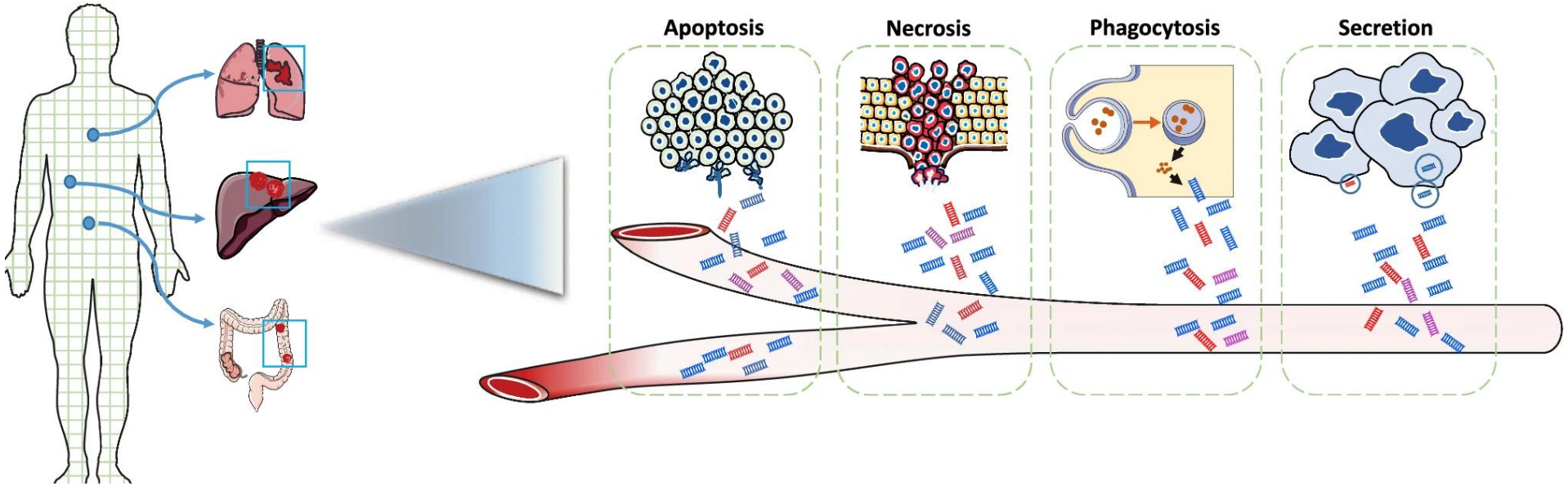
- Use of ctDNA as a tool to inform cancer biology as a liquid biopsy
- ctDNA as a powerful prognosticating tool in management of localized CRC
- INTERCEPT: the MD Anderson GI Medical Oncology experience for incrorporating ctDNA into the clinical management of patients with GI cancers

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

- ctDNA as a powerful prognosticating tool in management of localized CRC

- INTERCEPT: the MD Anderson GI Medical Oncology experience for incrorporating ctDNA into the clinical management of patients with GI cancers

Circulating tumor DNA as a “liquid biopsy”

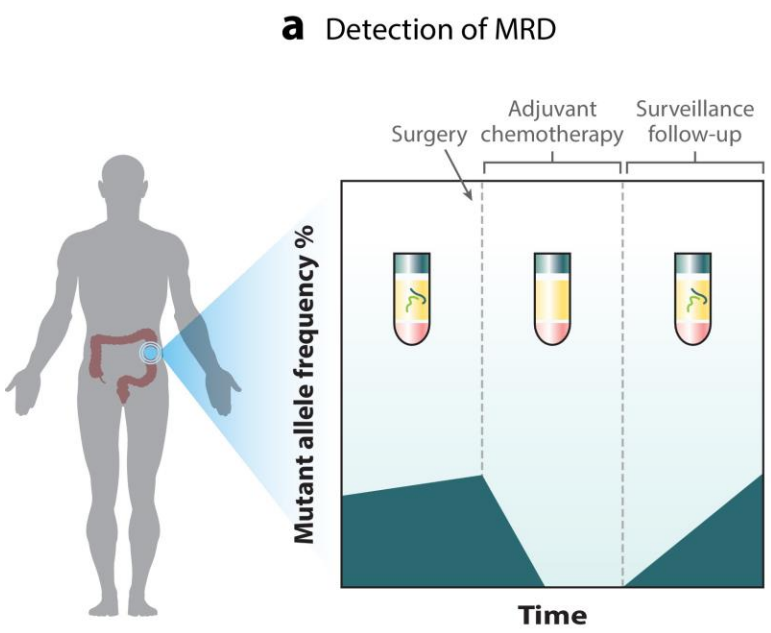


- Circulating tumor DNA (ctDNA) can be detected in blood following release from tumor cells, predominantly via apoptosis.
- Different fragment size for ctDNA: unlike cfDNA fragments [~$(167)_n$ bp in length], ctDNA fragments are ~20-30 bp shorter
- “Real-time” analysis: half-life of ctDNA in plasma ~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

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

Therapeutic applications of ctDNA in management of (colorectal) cancer

CURATIVE SETTING

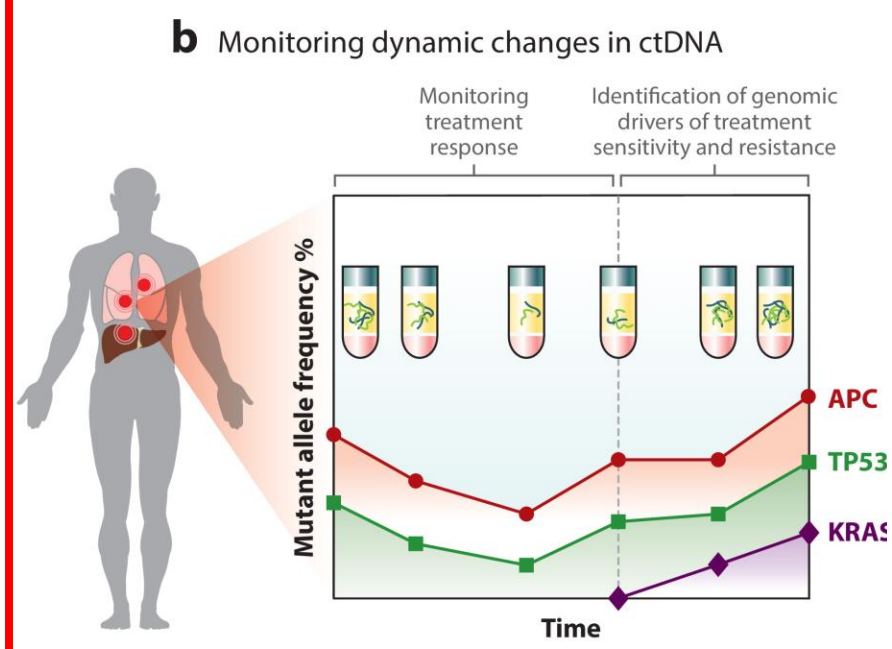


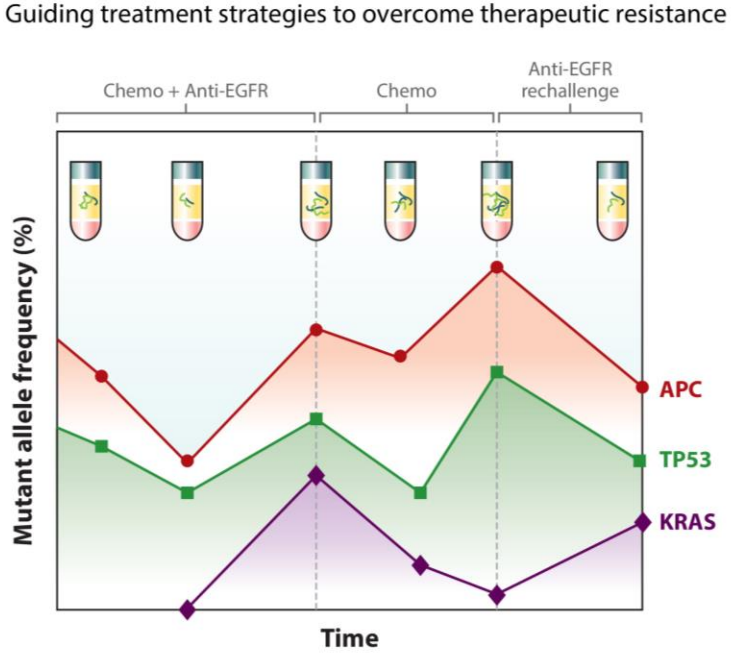
Risk stratifying:
- HIGH RISK patients - in need of (better) curative therapies
- LOW RISK patients needing less toxicity

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

Practical considerations for ctDNA testing

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

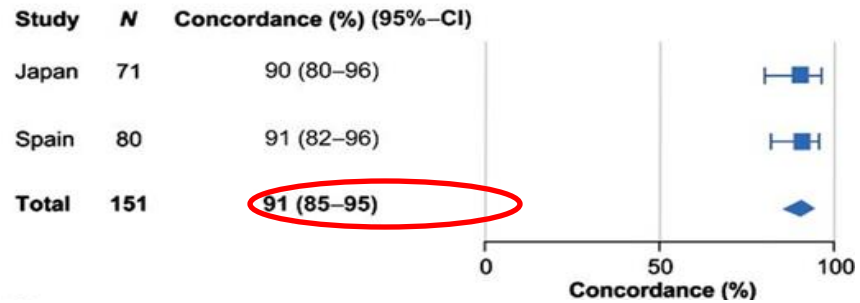
- **WHERE** matters!
- CRC liver mets are more likely to shed ctDNA

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

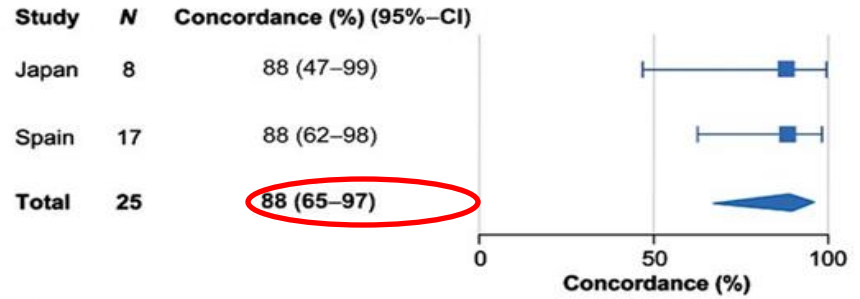
- **WHEN** matters!
- Increased cfDNA/inflammatory milieu after surgical trauma can increase FN likelihood for MRD detection, up to ~4 weeks after surgery

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

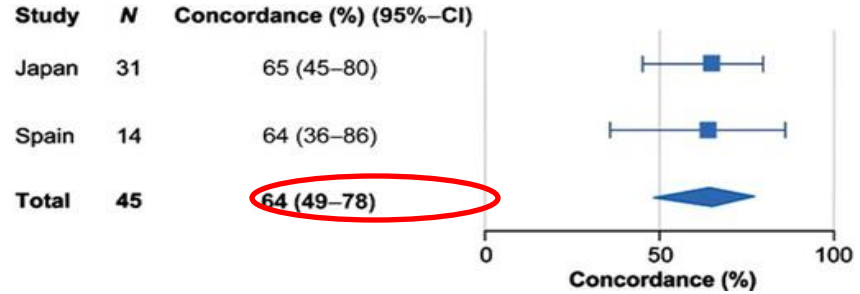
LIVER METASTASES ALONE



PERITONEAL METASTASES ALONE



LUNG METASTASES ALONE



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

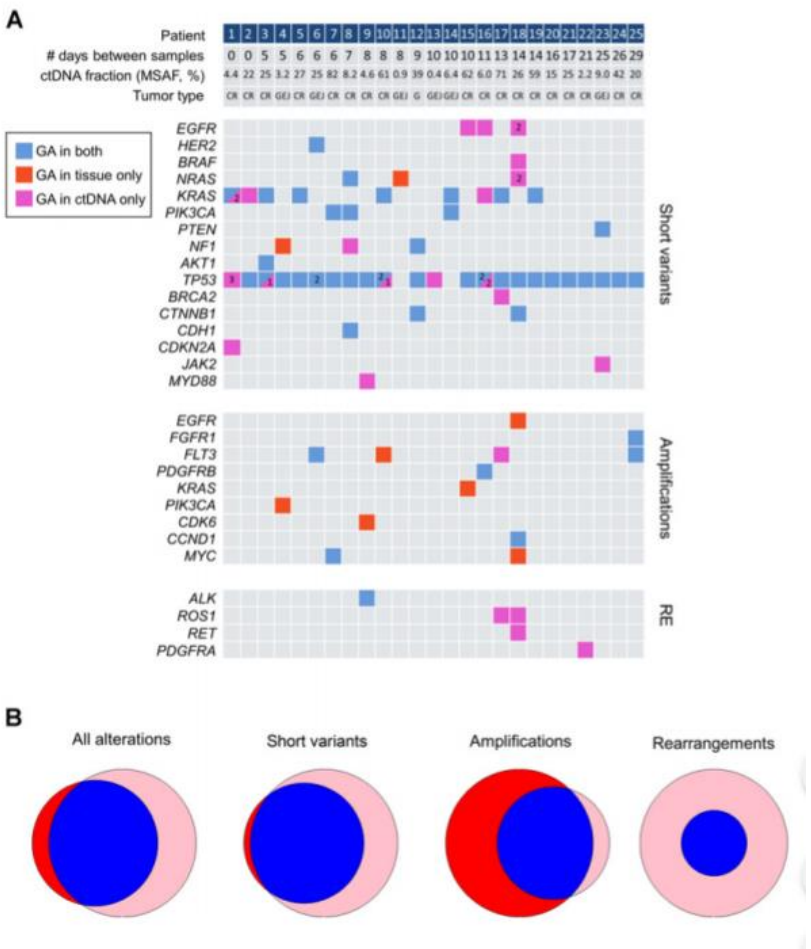
Assessing tumor genome with ctDNA (advanced GI cancers)

- Concordance of genomic alterations between ctDNA and matched tumor tissue is high (~80-90%), especially for driver mutations.
- ctDNA from plasma can detect alterations and integrates the intratumoral (and intertumoral) heterogeneity not captured with a single biopsy.
- Ease for obtaining relevant oncologic information relevant for clinical decision making and low risk of complication are preferable to (patients and) providers.

In general, concordance exists between tissue and ctDNA for calling alteration in CRC…

…. but when should we expect temporal discordance?

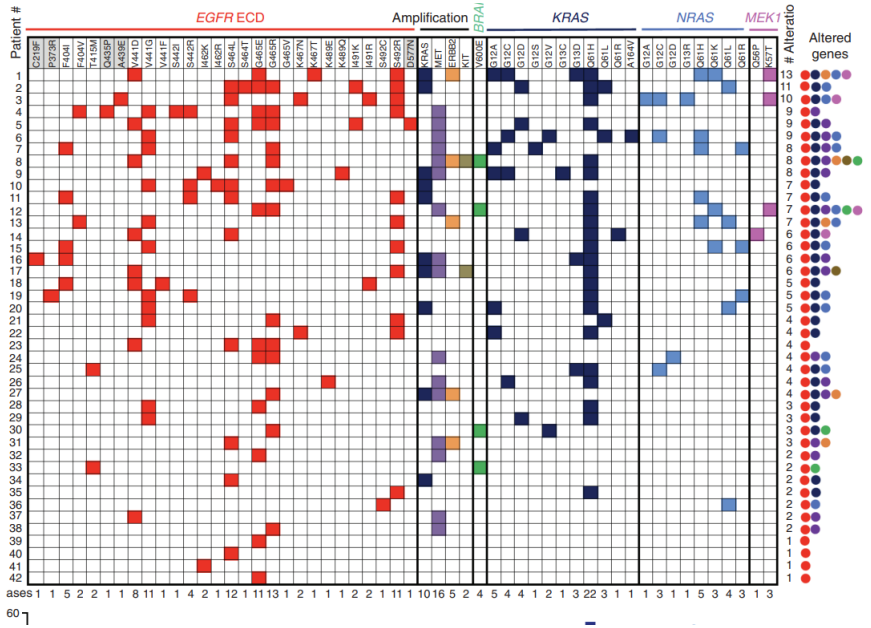
Tissue sequencing vs ctDNA in GI cancers (N=25)

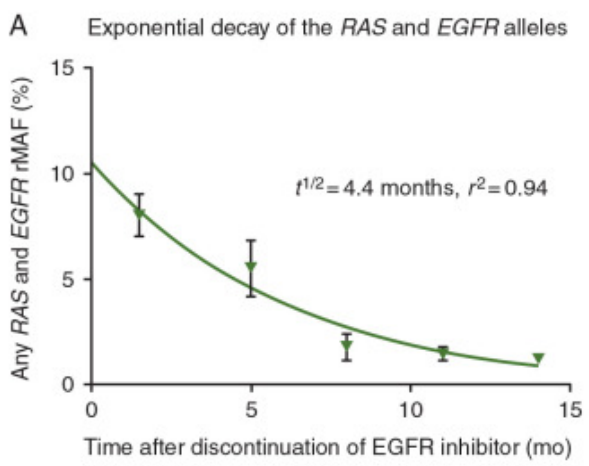


Schrock A et al, CCR 2018; Zill J OA et el, Cancer Disc 2018; Parikh A et al, Nat Med 2019; Perreira A et al, PLOS One 2017

ctDNA to identify “real-time” drivers of therapy resistance/evolution

- Alternative mechanisms for activation of MAPK signaling (e.g., acquired *RAS* mutations, *EGFR* ectodomain mutations) have been implicated in loss of response to targeted therapies against EGFR like cetuximab and panitumumab.
- Resistance profiles differ between patients with the same malignancy who are treated with the same agent.
- ctDNA can identify novel mutations (even unreported variants), which can be annotated in vitro for functional determination.
- Drivers of resistance can decay over time (away from selective pressure) and restore sensitivity to targeted therapies.

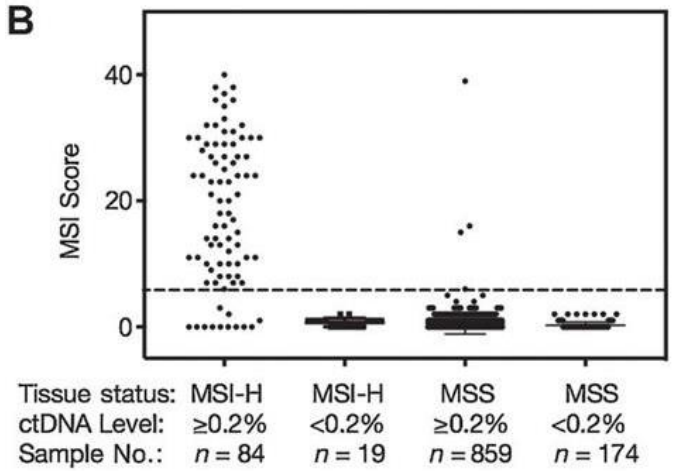


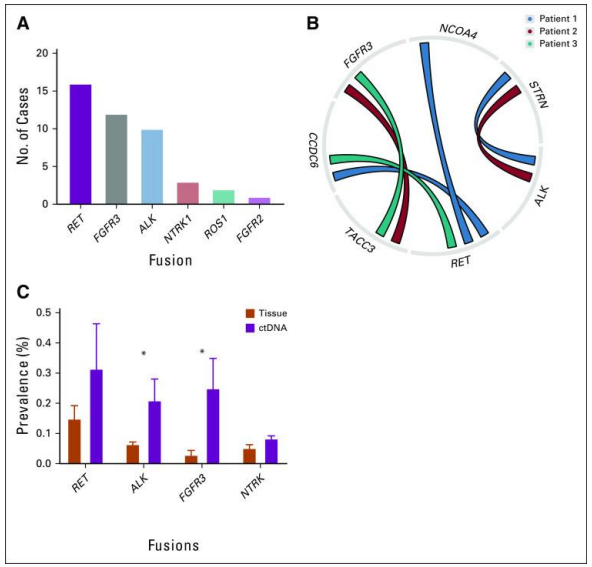


Strickler JH et al, Cancer Discovery 2017; **Parseghian CM et al Ann Oncol 2019**

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!!

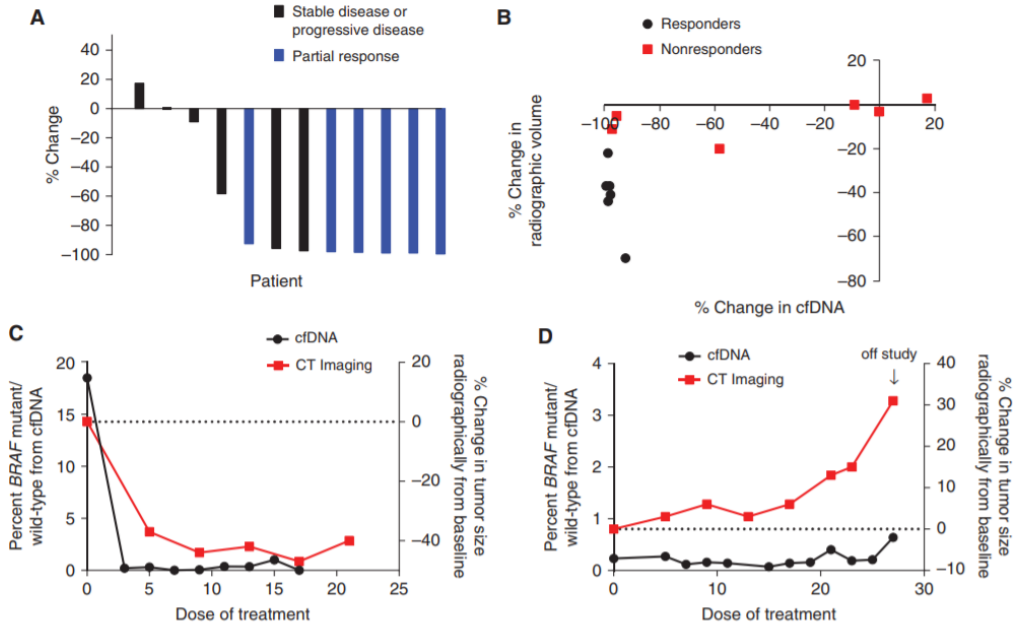




Drusbosky L et al ASCO 2021; **Willis J et al CCR 2019**; **Clifton K et al JCO PO 2019**; Parikh A et al CCR 2021

ctDNA: early monitoring for treatment response in metastatic CRC

- Since CEA is a non-specific marker (and not all patients with metastatic CRC have high CEA), can we use a more-specific assay for real-time analysis?



Phase I trial at MDACC of vemurafenib + irinotecan + cetuximab for *BRAF*^{V600E} metastatic CRC

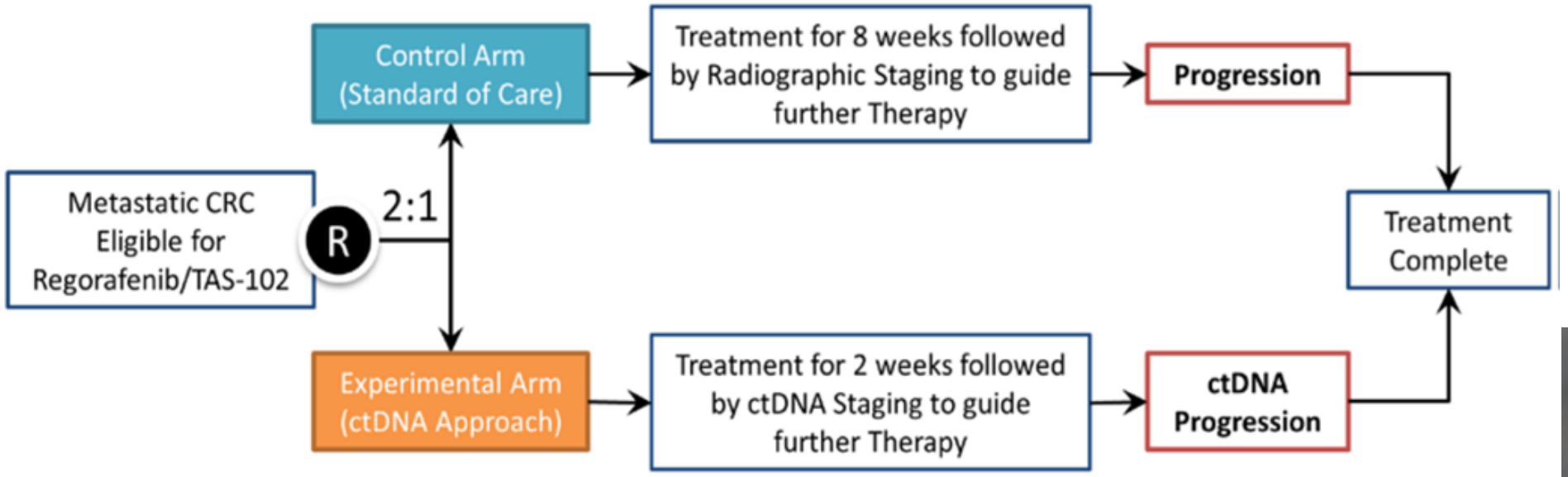
- Predictions in radiographic responses could be detected after a single dose of treatment with vemurafenib + irinotecan + cetuximab.

We can use ctDNA to identify early a clinical response (or lack thereof) of systemic agents.

Hong DS*, Morris VK* et al, Cancer Discovery 2016

Using ctDNA to evaluate early treatment response in metastatic CRC: a first-in-kind clinical trial (TACT-D)

A Randomized Study Evaluating Tailoring of Advanced/Metastatic Colorectal Cancer (mCRC) Therapy using Circulating Cell-free Tumor DNA (ctDNA) (TACT-D)



Endpoints:

- **Improved QOL**, reduced AE with maintained efficacy
- Confirmation of ctDNA prediction of radiographic lack of benefit

PI: K. Raghav (MDACC)

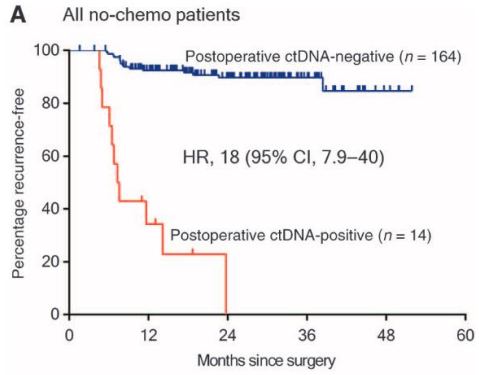
- Use of ctDNA as a tool to inform cancer biology as a liquid biopsy

- **ctDNA as a powerful prognosticating tool in management of localized CRC**

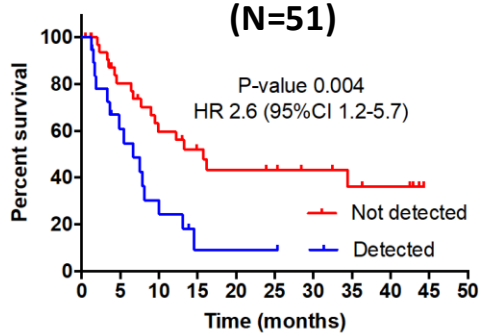
- INTERCEPT: the MD Anderson GI Medical Oncology experience for incorporating ctDNA into the clinical management of patients with GI cancers

ctDNA detection as a prognostic biomarker in CRC

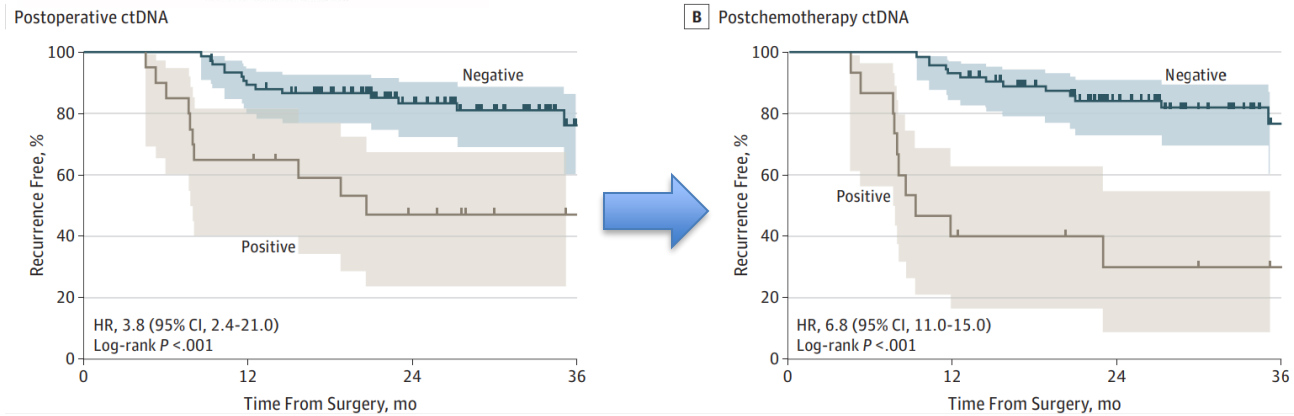
Stage II CC (N=178)



Stage IV CC (N=51)



Stage III CC (N=96)



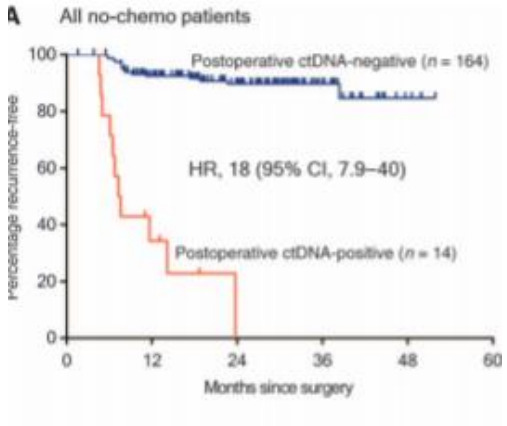
Detection of ctDNA is a biomarker for poor prognosis across all stages of colorectal cancer.

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

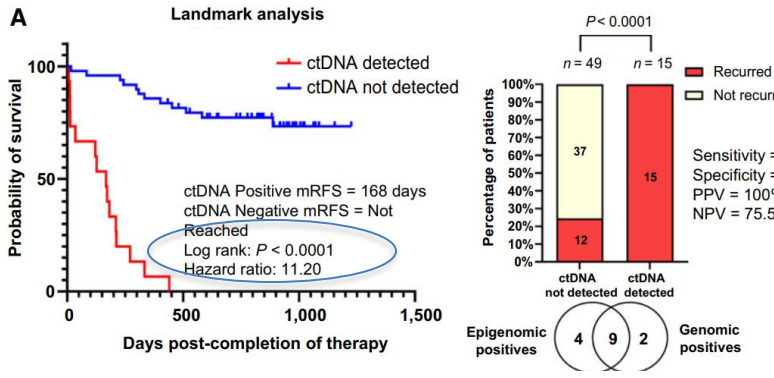
ctDNA outperforms “traditional” prognostic factors in CRC

Stage II CRC (N=178)



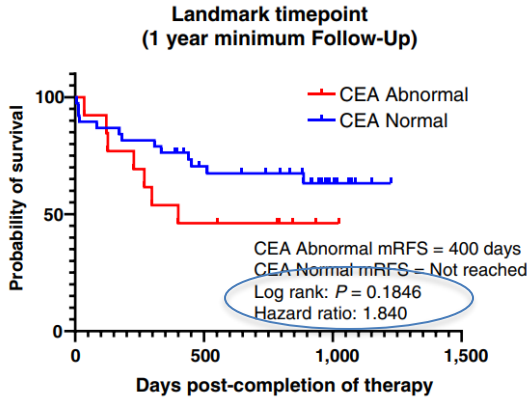
Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Patients not treated with chemotherapy (*n* = 178)						
Age, <70 versus ≥70	0.92	0.43–2.0	0.8			
Sex, male versus female	1.3	0.62–2.8	0.5			
Tumor site, right versus left	1.5	0.69–3.3	0.3			
Tumor differentiation, well/moderate versus poor	0.39	0.09–1.7	0.2			
T stage, T3 versus T4	4.0	1.7–9.5	0.002	8.1	3.1–21	<0.001
Lymph node yield, ≥12 versus <12	3.1	1.3–7.4	0.009			
Lymphovascular invasion, no versus yes	2.4	1.1–5.4	0.03			
MMR status, deficient versus proficient	3.6	0.86–15	0.08			
Clinicopathologic risk group, low versus high	3.2	1.5–6.9	0.002			
Postoperative CEA, normal versus elevated	1.6	0.37–6.8	0.5			
Postoperative ctDNA status, negative versus positive	18	7.9–40	<0.001	28	11–68	<0.001

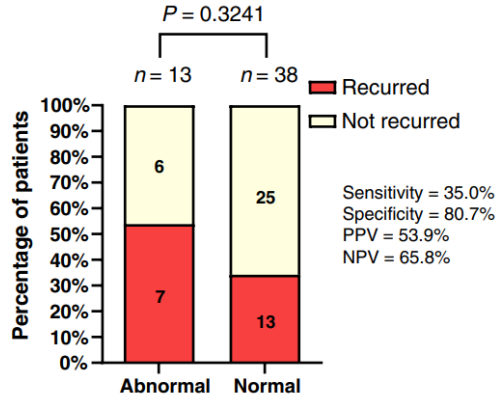
ctDNA as prognostic biomarker



Stages I-IV CRC (N=103)

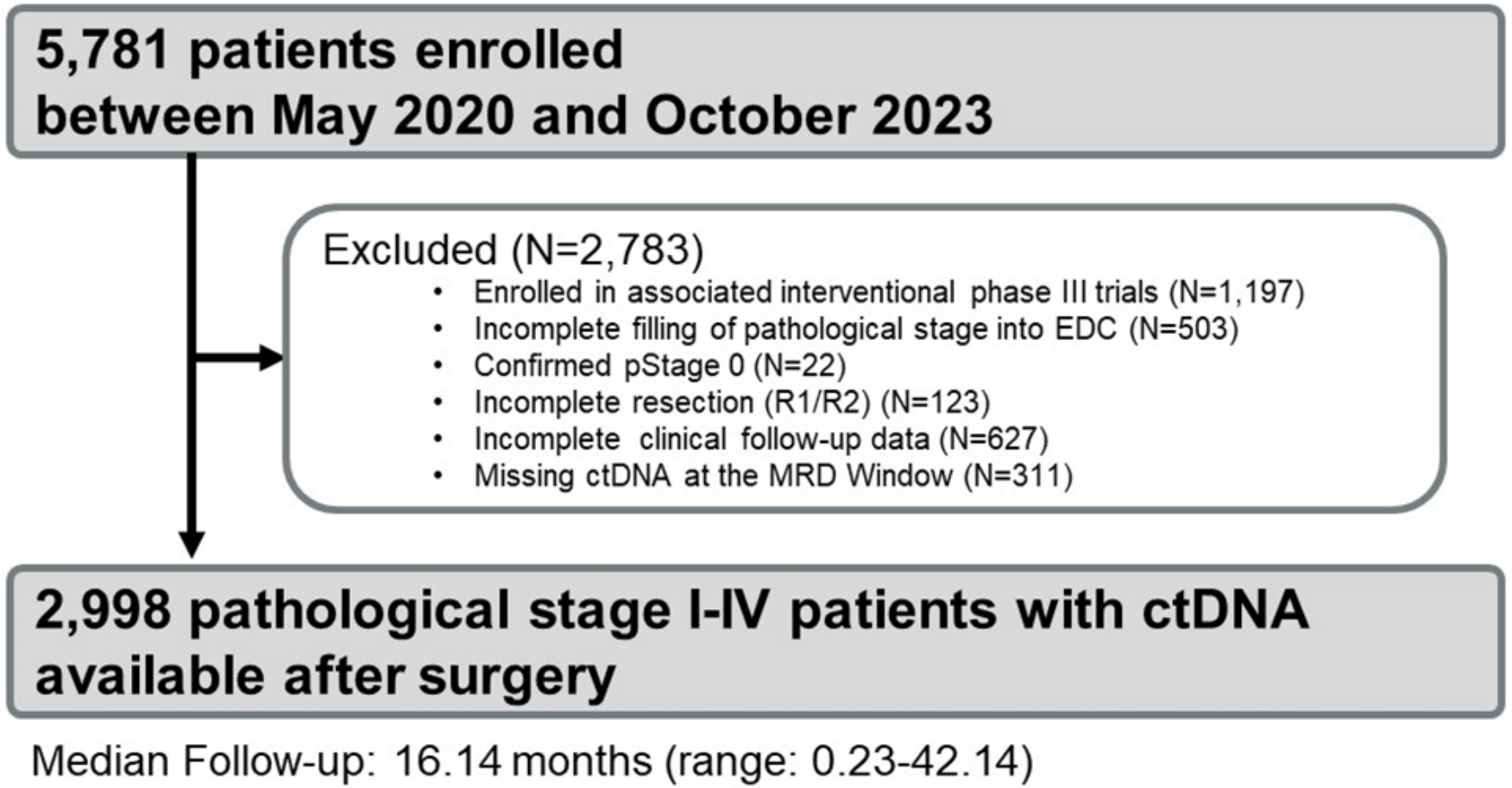
CEA as prognostic biomarker





Tie J et al, Sci Transl Med 2015; Parikh A et al CCR 2021

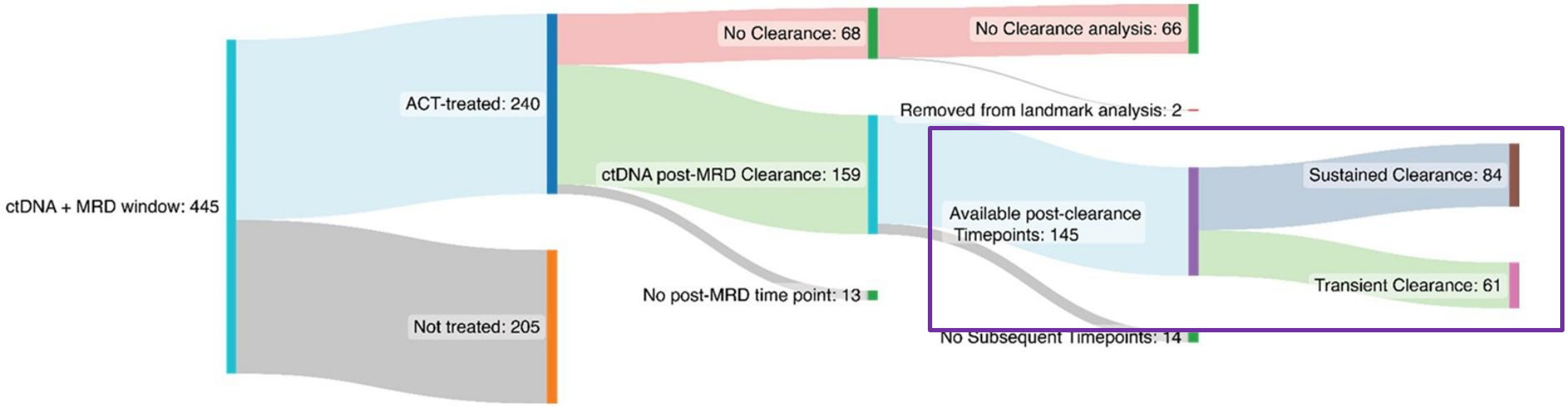
GALAXY Schema:
Japanese observational study for stages I-IV CRC



Median Follow-up: 16.14 months (range: 0.23-42.14)

Yukami H et al, ASCO GI 2024

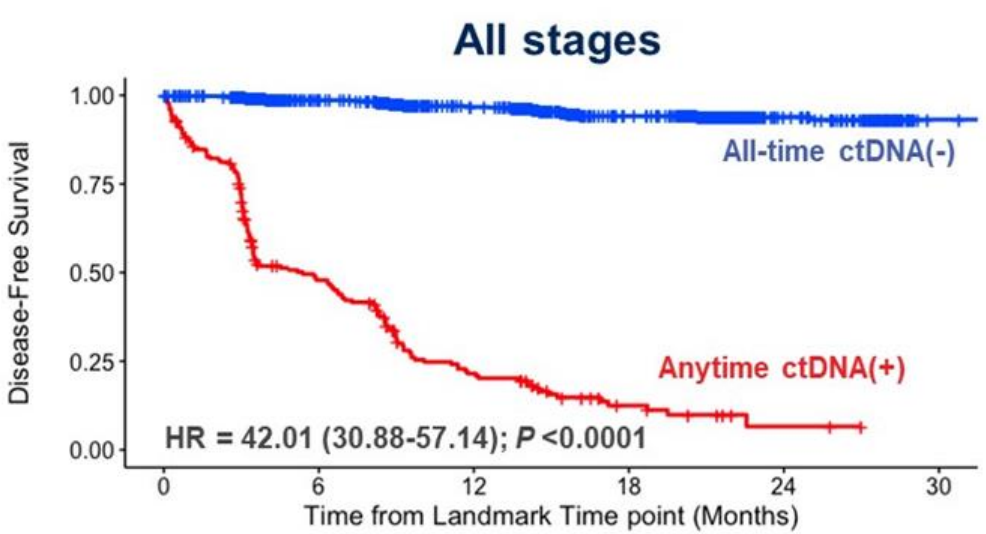
ctDNA clearance with adjuvant chemotherapy for treatment of CRC (GALAXY)



Should we be using ctDNA clearance as a primary endpoint for current clinical trials?

Yukami H et al, ASCO GI 2024

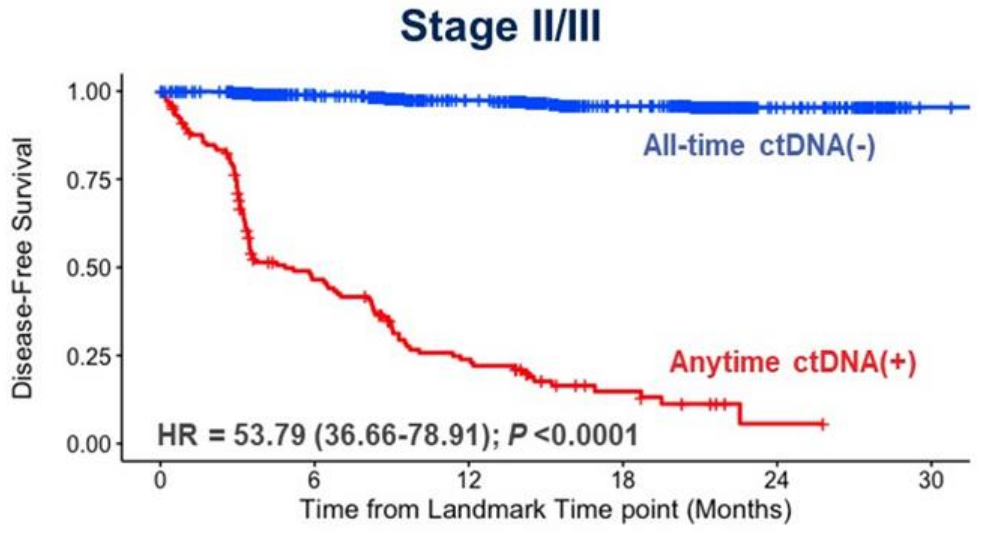
DFS during surveillance according to ctDNA status (GALAXY)



Number at risk

ctDNA Negative	1582	1211	885	432	125	8
ctDNA Positive	204	84	33	10	2	0

ctDNA status	All-time Negative	Anytime Positive
Events %	3.7 (58/1582)	77.5 (158/204)
24M-DFS % (95% CI)*	93.9 (92–95.4)	6.6 (2–14.9)



Number at risk

ctDNA Negative	1326	1022	737	355	97	5
ctDNA Positive	146	57	26	9	1	0

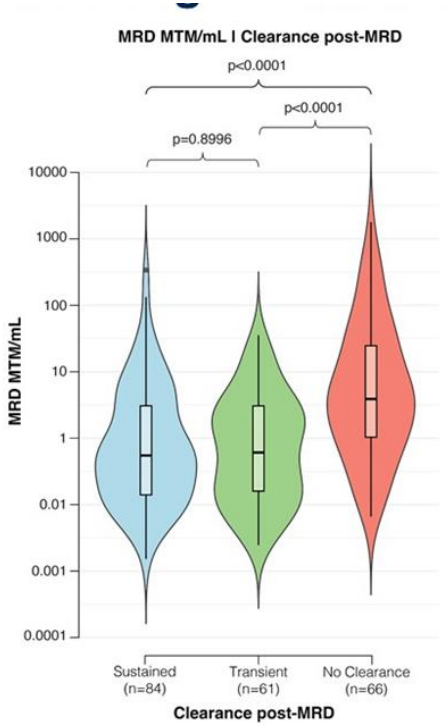
ctDNA status	All-time Negative	Anytime Positive
Events %	2.7 (36/1326)	75.3 (110/146)
24M-DFS % (95% CI)*	95.4 (93.5–96.8)	5.6 (0.8–18.3)

**DFS % from landmark time point*

ctDNA(+) status after completion of all planned curative-intent therapy is predictive of inferior DFS.

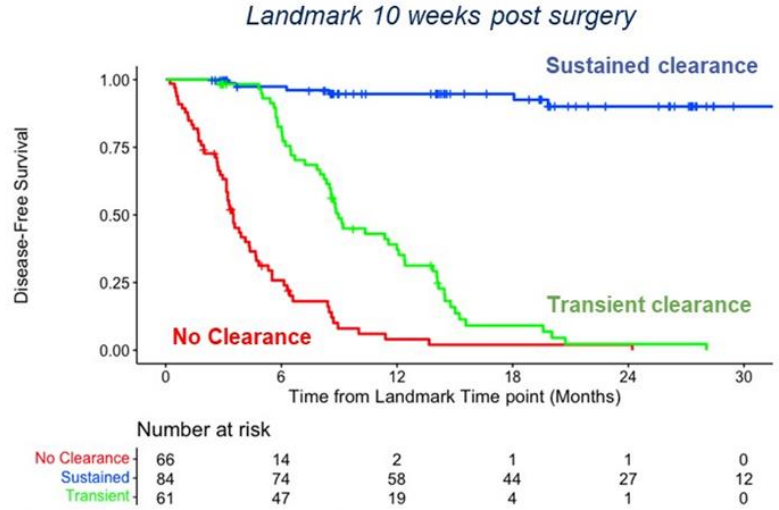
Yukami H et al, ASCO GI 2024

DFS according to ctDNA clearance in ctDNA(+) patients (GALAXY)



Group	Median MRD MTM/mL
Sustained	0.61
Transient	0.53
No Clearance	3.89

**P values from Wilcoxon rank-sum test*



ctDNA Clearance	Sustained Clearance	Transient Clearance	No Clearance
Events %	7.1 (6/84)	85.2 (52/61)	89.4 (59/66)
Median DFS months (95% CI)	NR	9 (8.5–12.4)	3.5 (3.2–4.7)
24M-DFS % (95% CI)*	90.1 (78.6–95.6)	2.3 (0.02–10.3)	2 (0.02–9.2)
HR	**Reference**	**25.13**	**87.08**
95% CI	Not applicable	10.57–59.73	36.14–209.84
P	Not applicable	<0.0001	<0.0001

**DFS % from landmark time point*

Sustained ctDNA clearance is associated with far superior DFS relative to "transient clearance" or "no clearance" patients

Yukami H et al, ASCO GI 2024

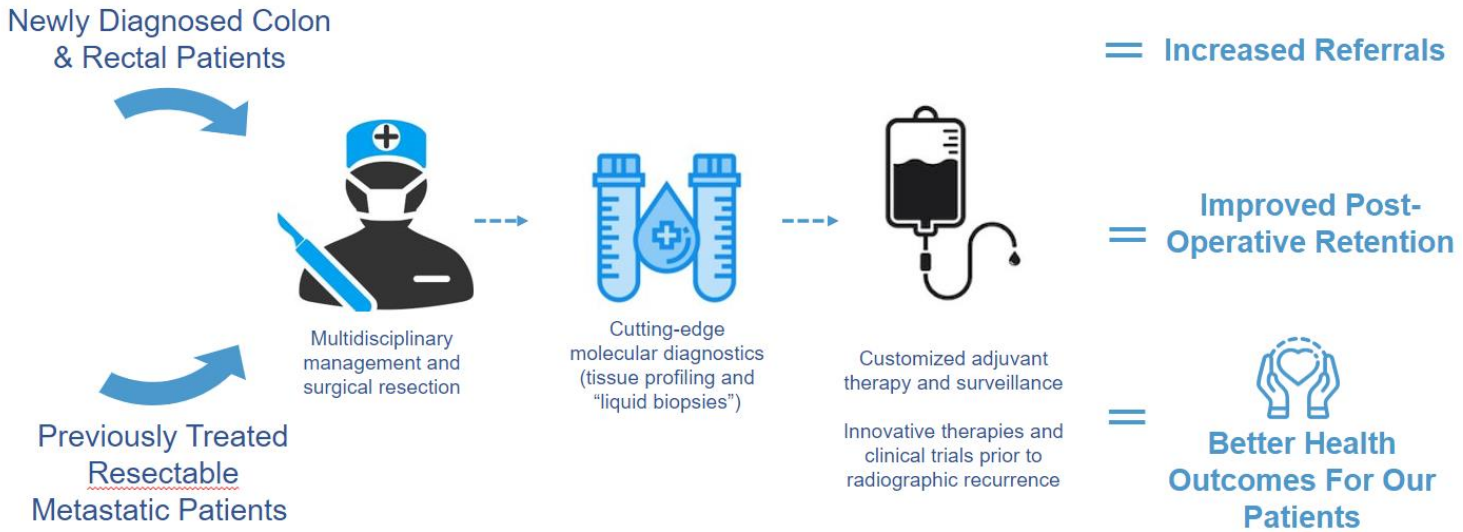
- Use of ctDNA as a tool to inform cancer biology as a liquid biopsy

- ctDNA as a powerful prognosticating tool in management of localized CRC

- **INTERCEPT: the MD Anderson GI Medical Oncology experience for incrorporating ctDNA into the clinical management of patients with GI cancers**

MD Anderson INTERCEPT: Intervening early on ctDNA

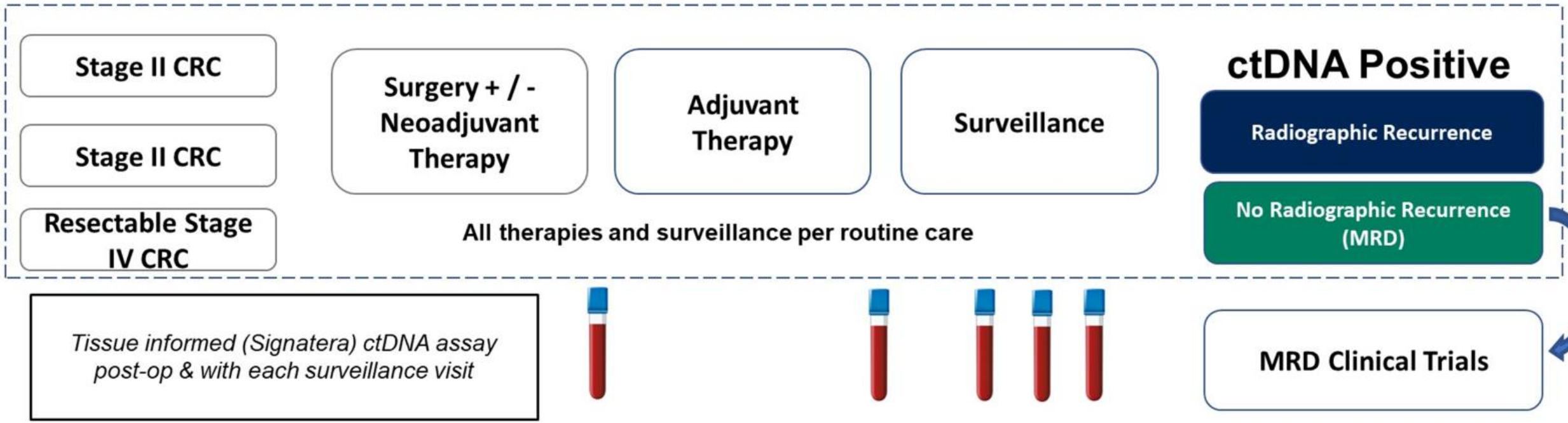
Integrated Post-surgical Surveillance, MRD Monitoring, and Intervention



MD Anderson INTERCEPT Program

- ctDNA for MRD Monitoring: When and How to order ctDNA
- Risk Based Surveillance: When and How
- Intervention: Clinical Trials

INTERCEPT Schema

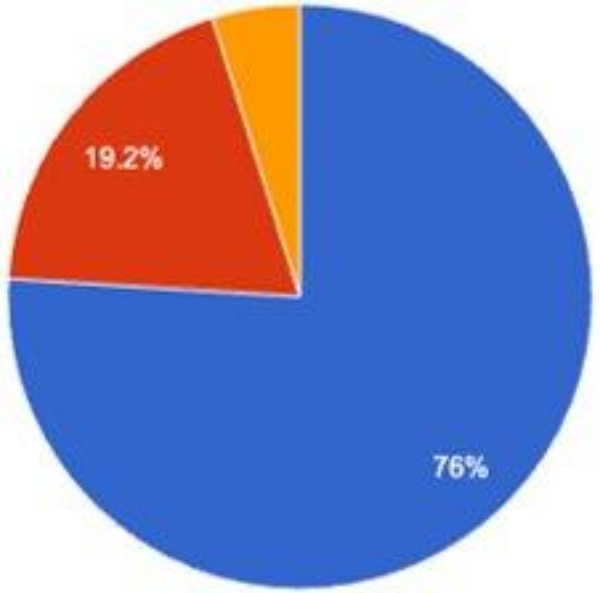


Dasari A et al, ASCO 2023

INTERCEPT Metrics (as of 11/2023)

Unique Count of MRNs with an Order placed: 2,323
Unique Count of Blood Draws: 4,517

Unique Count of MRNs with Completed Orders: 2,044
Unique Count of Completed Draws: 3,578



Draw Managed By:
Counts/frequency:
Clinic (76.0%),
Mobile (19.2%),
Unknown (4.9%)

Patient demographics (INTERCEPT)

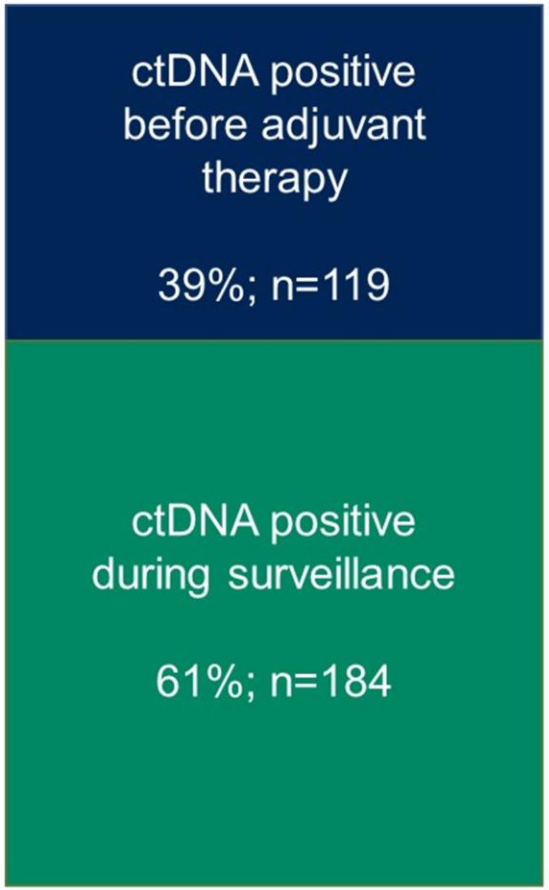
Characteristic	Category	N (%)
Age (years)	Median	58
	Range	21-93
Gender	Male	611 (55)
	Female	504 (45)
Primary Location	Colon	680 (61)
	Rectum	389 (35)
	Not Specified	46 (4)
Pathologic Stage	0-II	260 (24)
	III	294 (26)
	IV/Recurrent	561 (50)
# of ctDNA Assays	Median	3
	Range	1-11

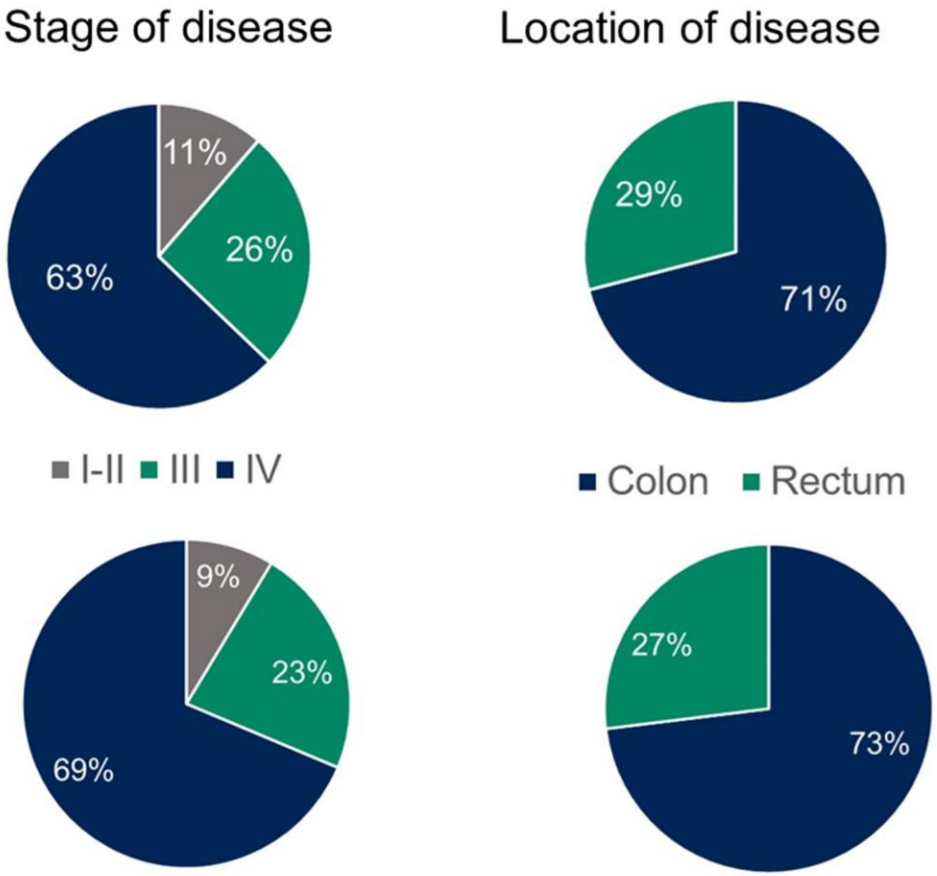
N = 1115

Enrollment: 12/2021-3/2023

Dasari A et al, ASCO 2023

Distribution by stage and tumor location (INTERCEPT)





Dasari A et al, ASCO 2023

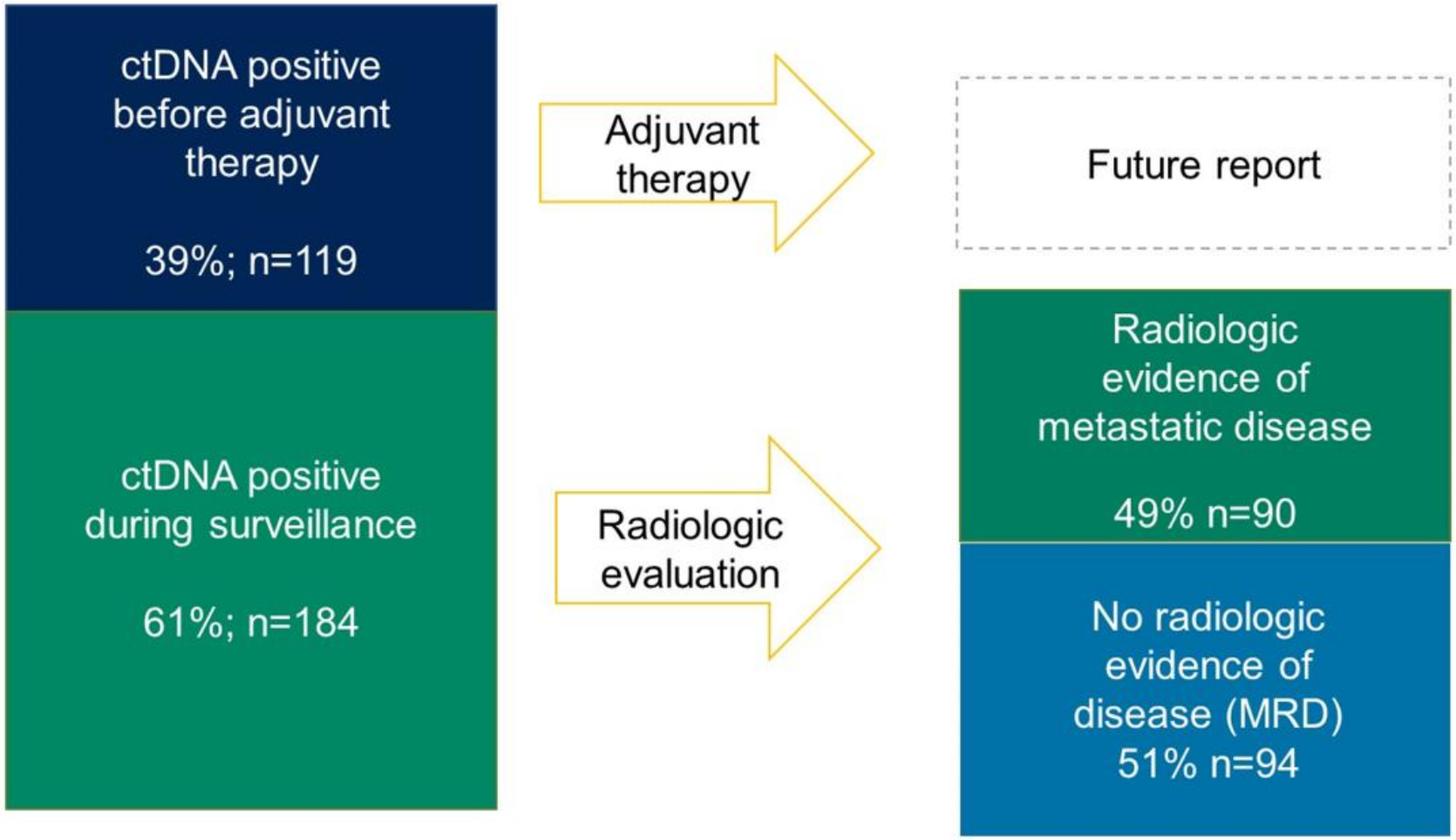
Clinical utility: radiographic evidence of ctDNA(+) patients during surveillance (INTERCEPT)

# 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

Clinical utility: radiographic findings of ctDNA(+) patients during surveillance (INTERCEPT)

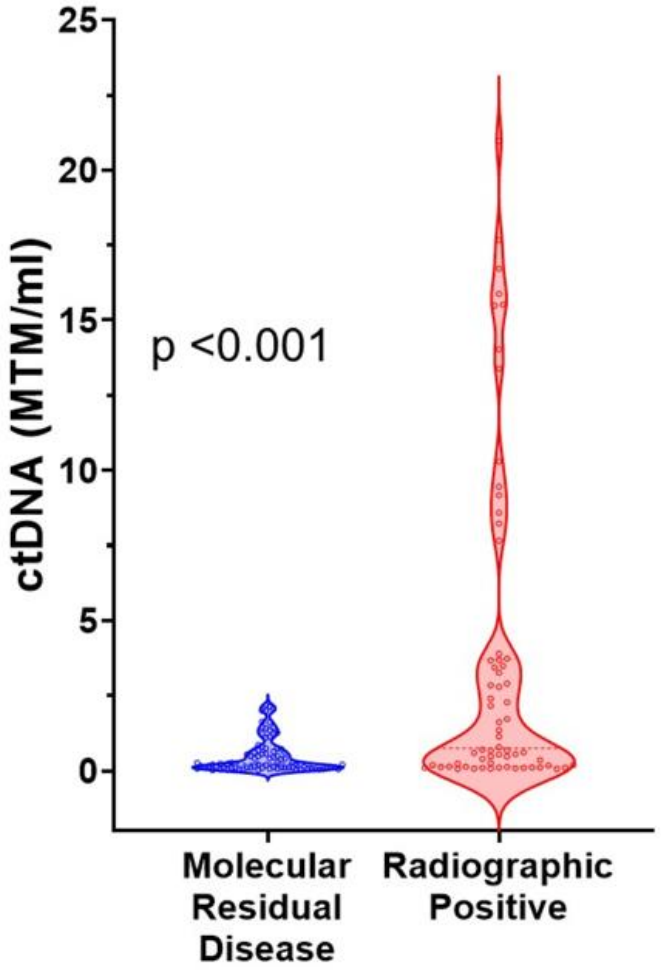


Dasari A et al, ASCO 2023

Quantitative interpretation: ctDNA level vs radiographic status (INTERCEPT)

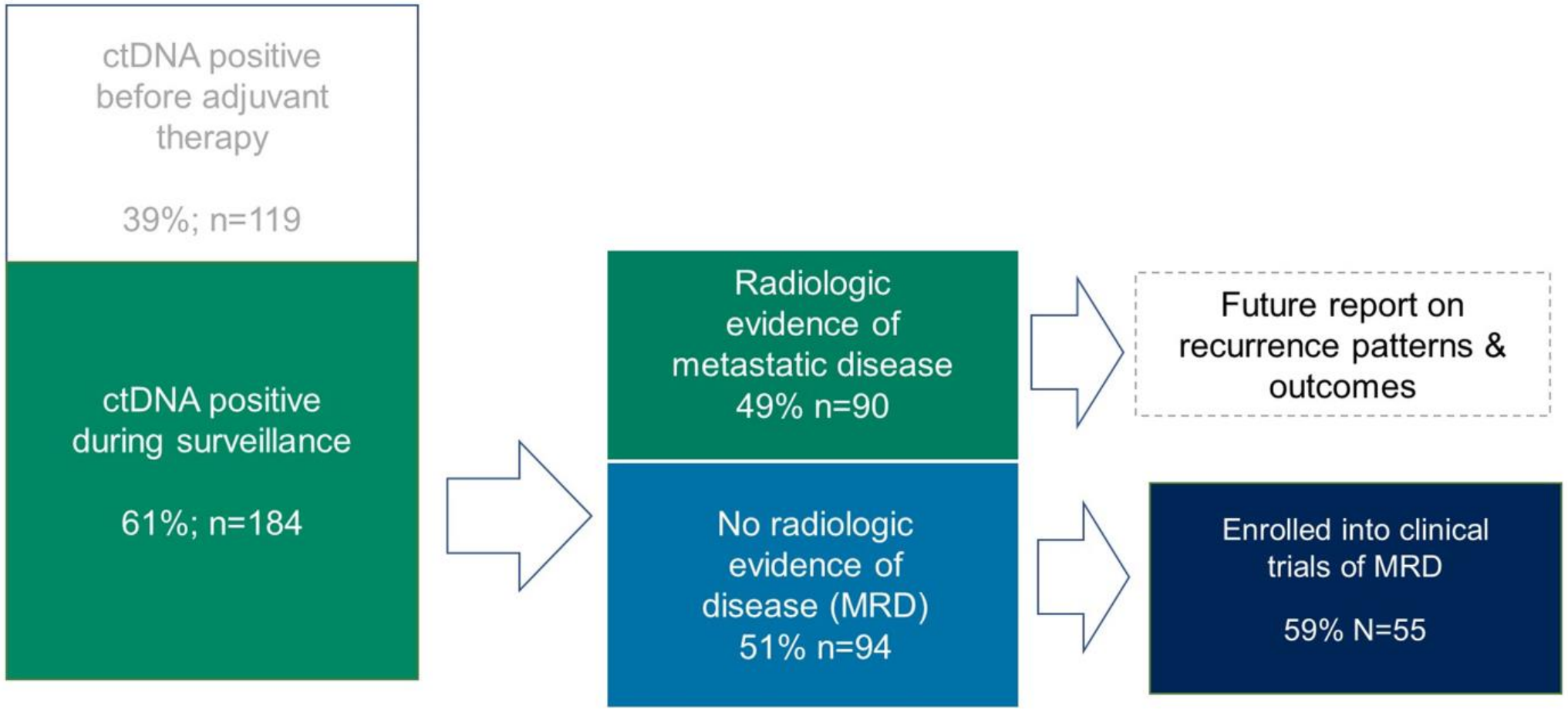
- Patients with no evidence of radiologic disease are more likely to have lower ctDNA levels (MTM/mL)

	Median	Interquartile Range
Minimal residual disease	0.49	0.11 – 2.05
Radiologic disease detected	2.22	0.20 – 13.87



Dasari A et al, ASCO 2023

Clinical utility: enrollment of ctDNA(+) CRC patients on clinical trials at MD Anderson (INTERCEPT)



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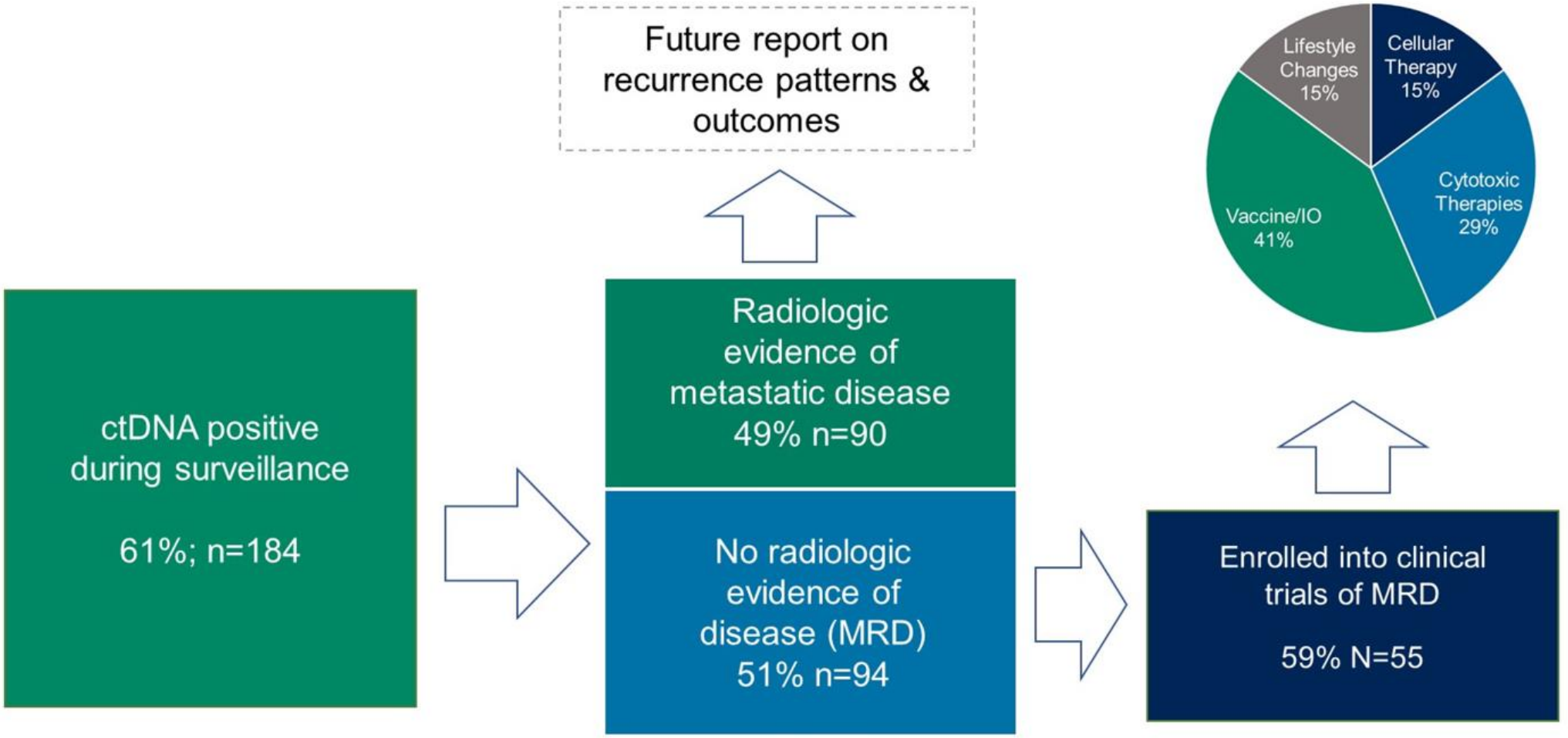
Clinical utility: enrollment of ctDNA(+) CRC patients on clinical trials at MD Anderson (INTERCEPT)



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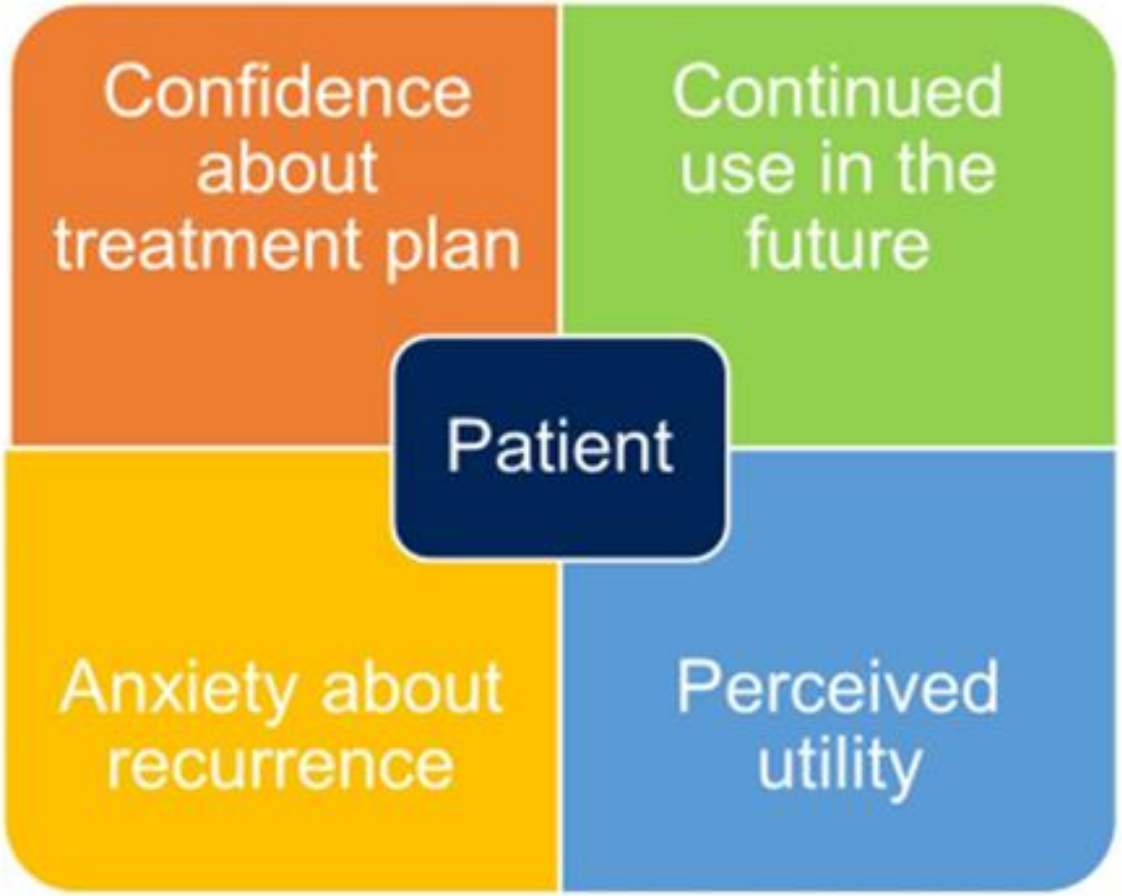
Patient experience with ctDNA collection: Are we afraid with what to do next?



73% reported ctDNA results reduced anxiety about cancer recurrence

87% felt they were receiving the right treatment after receiving their results

92% would continue using the ctDNA test to monitor cancer

96% valued the additional information received from ctDNA results

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