An Update on the role of ctDNA-MRD Assessment in The Management of Breast Cancer

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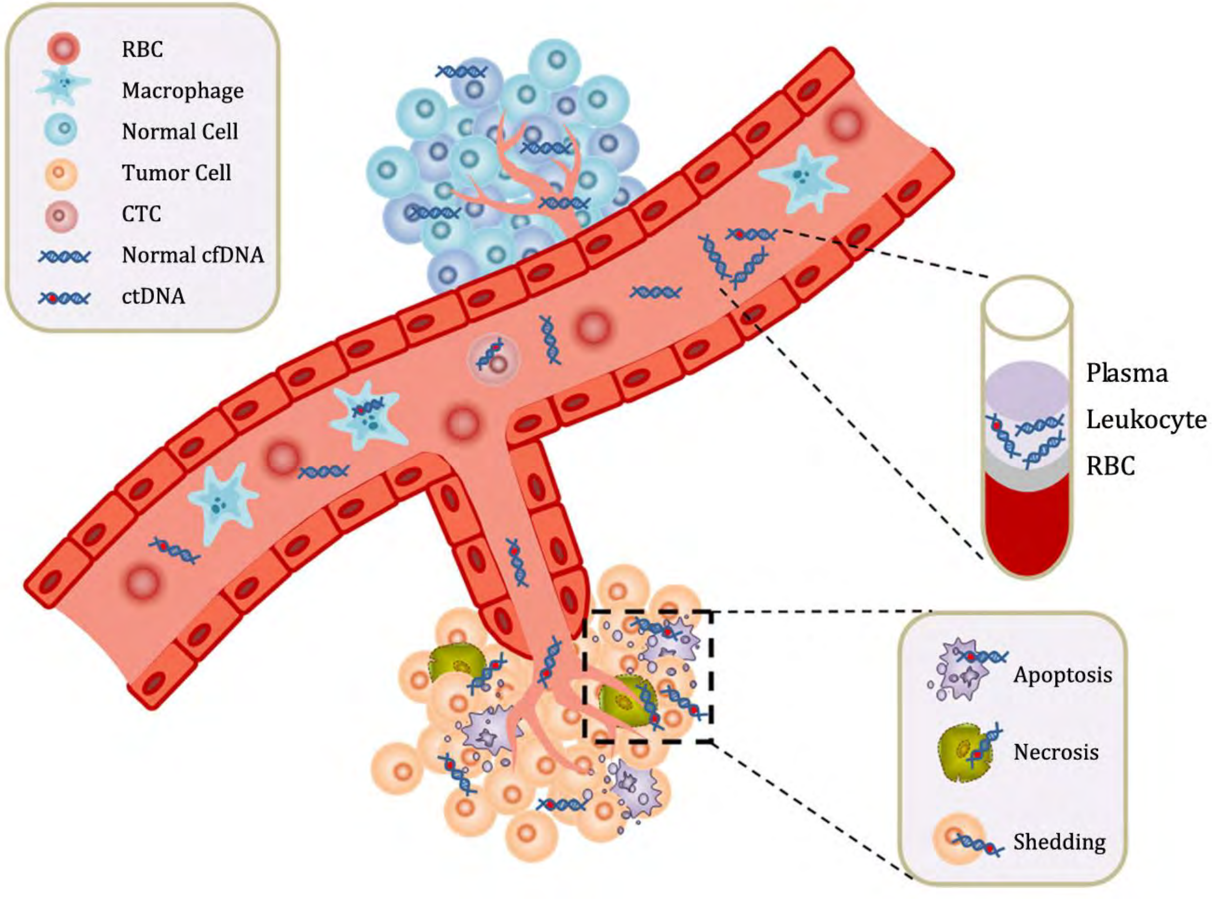
Outline

- Introduction to ctDNA
- Usefulness of ctDNA in early breast cancer
- Usefulness of ctDNA in metastatic breast cancer
- Does ctDNA testing cause Anxiety?
- Practical Guidelines
- Cases

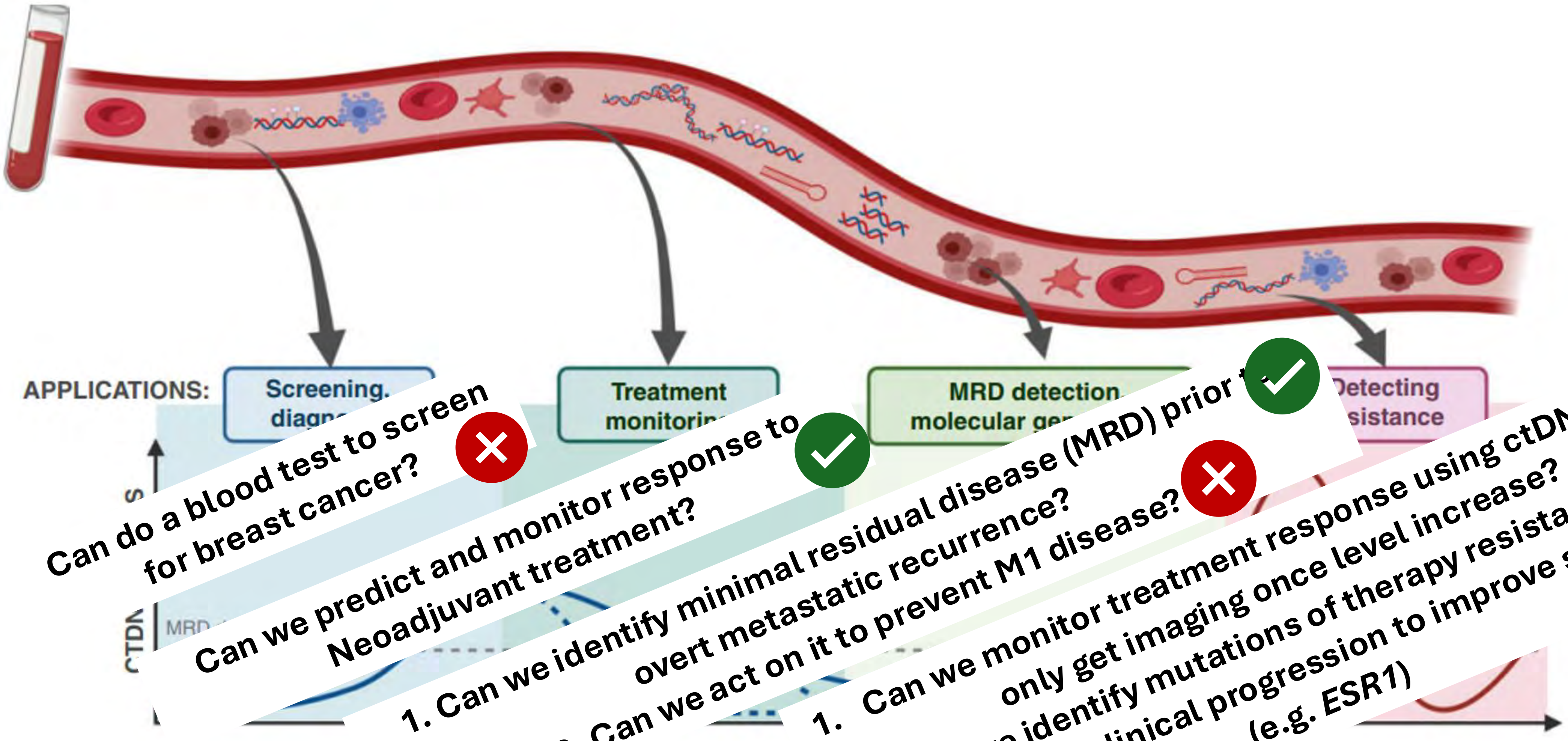
What is circulating tumor DNA (ctDNA) and where does it come from?

- Cell-free DNA (cfDNA)
  - Double strand DNA fragments associated with histones in circulation that have been released by cells
- Circulating tumor DNA (ctDNA)
  - cfDNA released from cancer cells
- Most detected cfDNA are released by normal leukocytes making detecting ctDNA hard



Hahn AW et al., *Kidney Cancer*. 2019

ctDNA is the **future** of Breast Cancer



Can do a blood test to screen for breast cancer? ✗

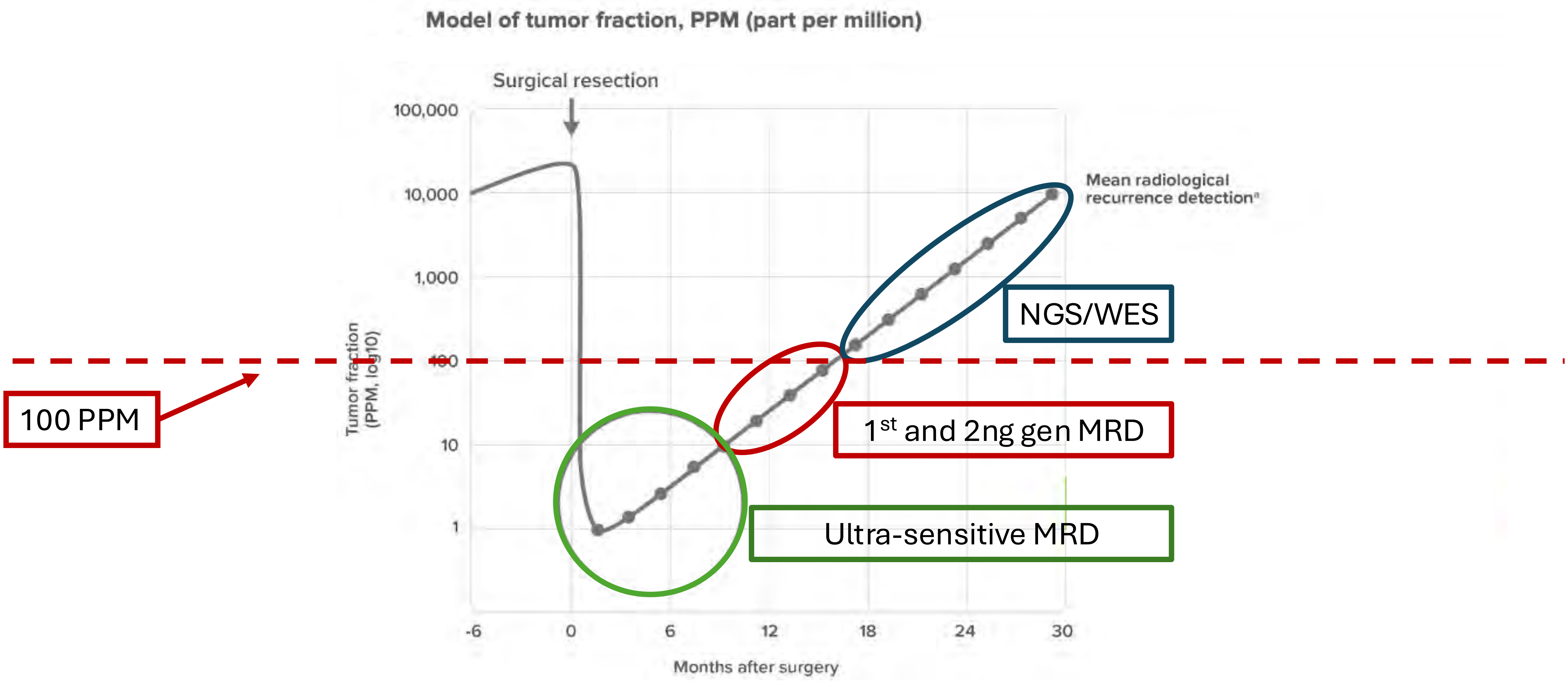
Can we predict and monitor response to Neoadjuvant treatment? ✓

1. Can we identify minimal residual disease (MRD) prior t overt metastatic recurrence? ✓
2. Can we act on it to prevent M1 disease? ✗

1. Can we monitor treatment response using ctDNA and only get imaging once level increase? ✓
2. Can we identify mutations of therapy resistance and act before clinical progression to improve survival? (e.g. *ESR1*) ?

Garcia-Pardo et al., *Br J cancer* 2022

Not all ctDNA tests can give you the same information



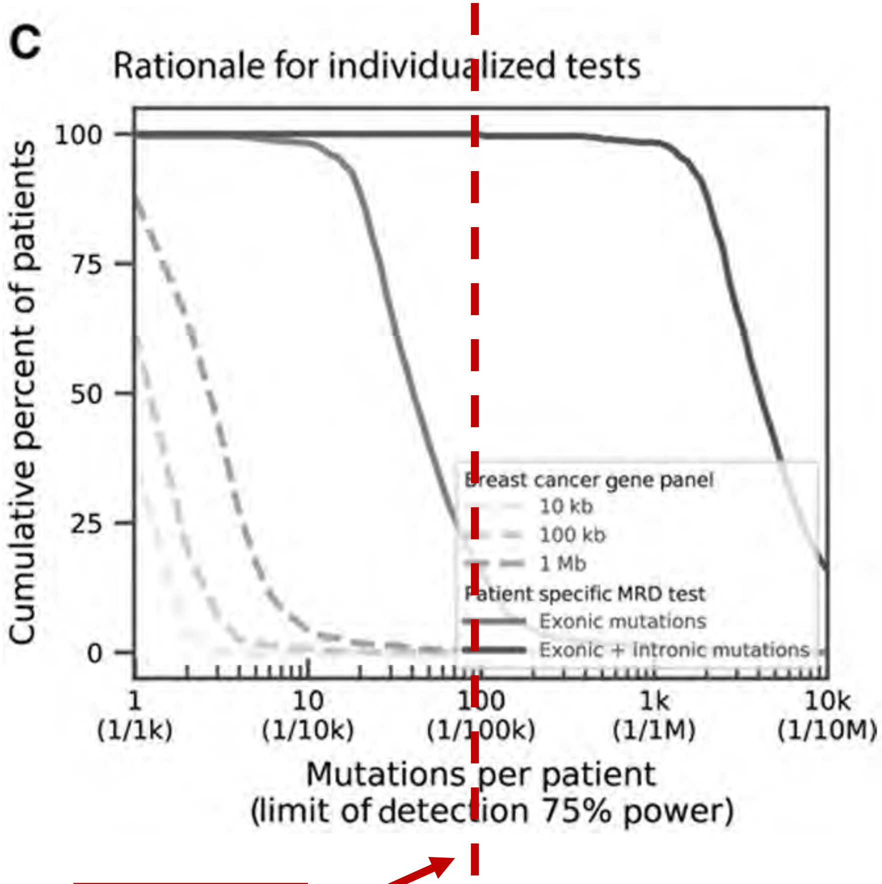
100 PPM

NGS/WES

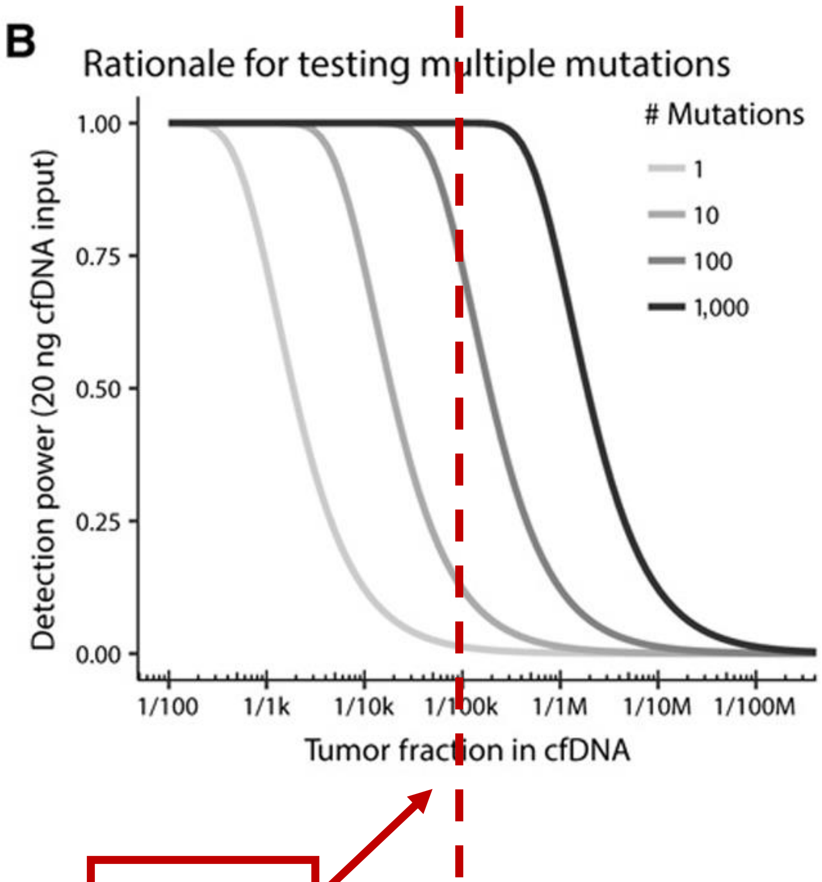
1st and 2ng gen MRD

Ultra-sensitive MRD

Identification of MRD requires highly sensitive tests in Breast Cancer



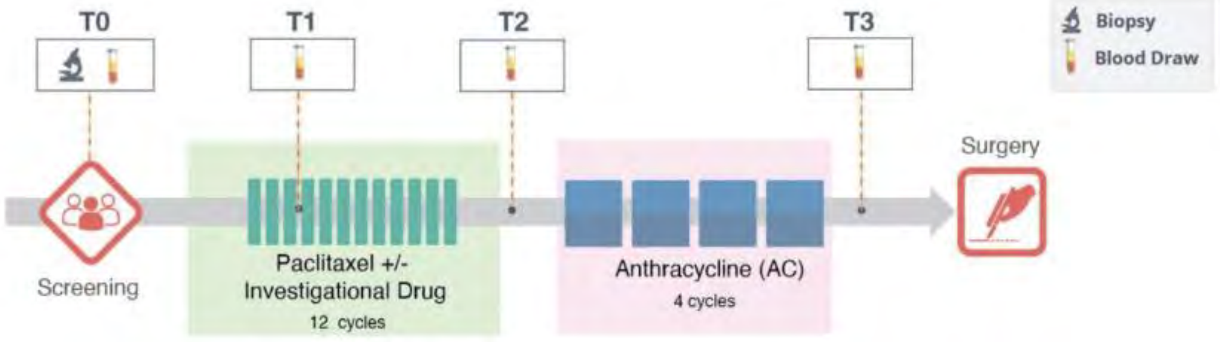
100 PPM

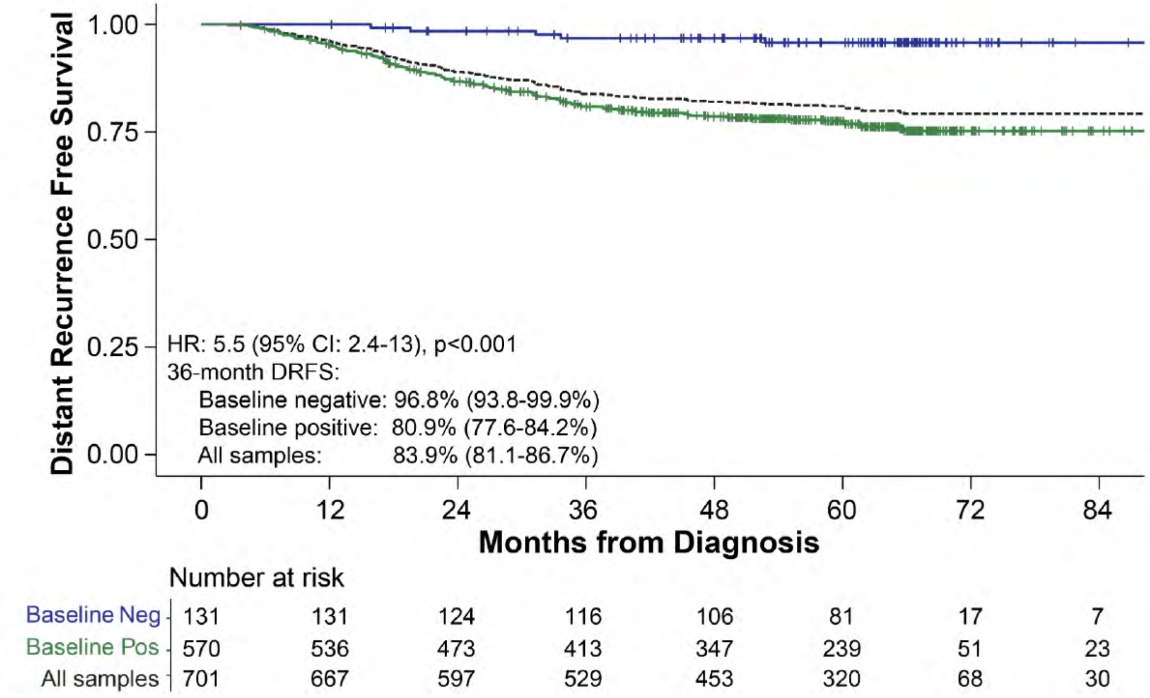


100 PPM

Parsons HA et al., *Clin Cancer Res*.

I-SPY 2 Platform





HR: 5.5 (95% CI: 2.4-13), p<0.001
36-month DRFS:
Baseline negative: 96.8% (93.8-99.9%)
Baseline positive: 80.9% (77.6-84.2%)
All samples: 83.9% (81.1-86.7%)

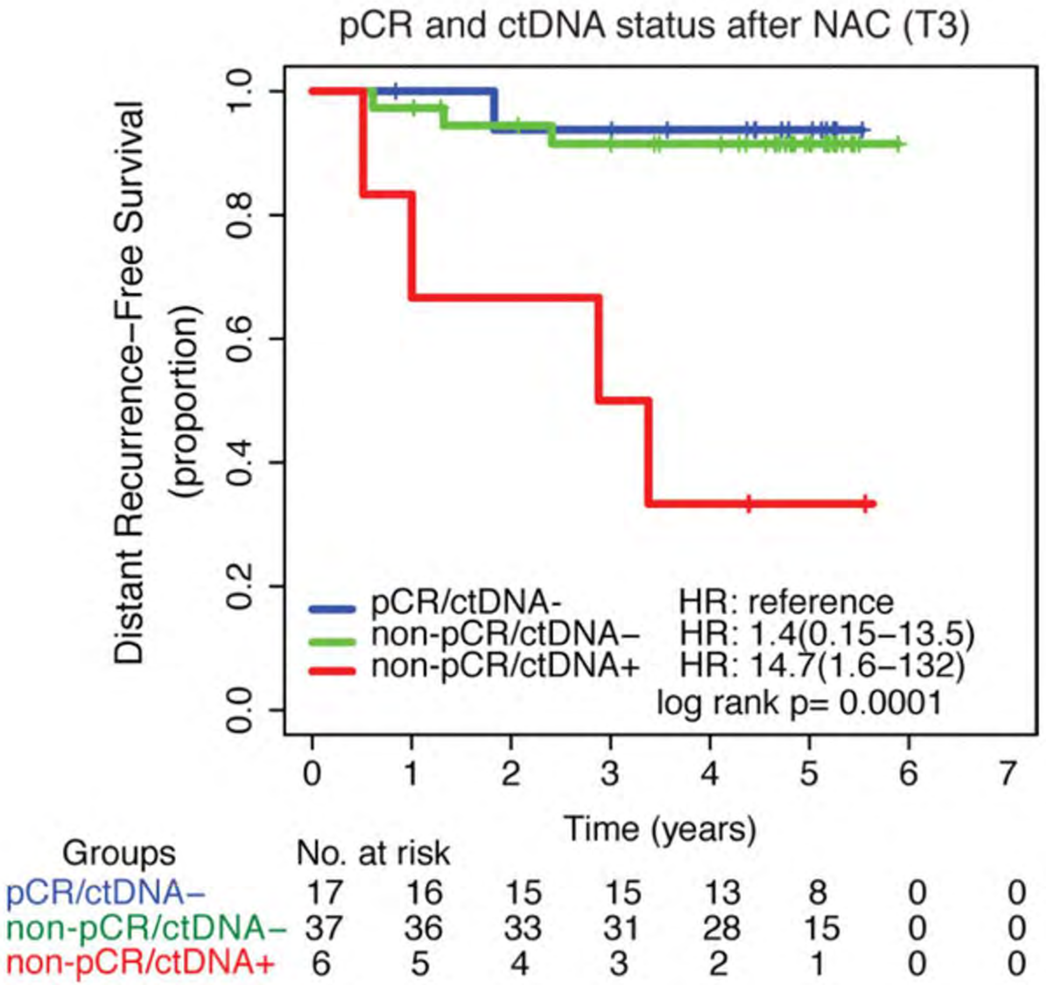
Number at risk

	0	12	24	36	48	60	72	84
Baseline Neg	131	131	124	116	106	81	17	7
Baseline Pos	570	536	473	413	347	239	51	23
All samples	701	667	597	529	453	320	68	30

- At T0 ctDNA was detected in 579/712 (81.3%) pts.
- The 133 (18.7%) who were ctDNA-negative at baseline had extremely good outcomes

Magbanua MJM, ESMO Breast Cancer 2025, Abstract 5MO

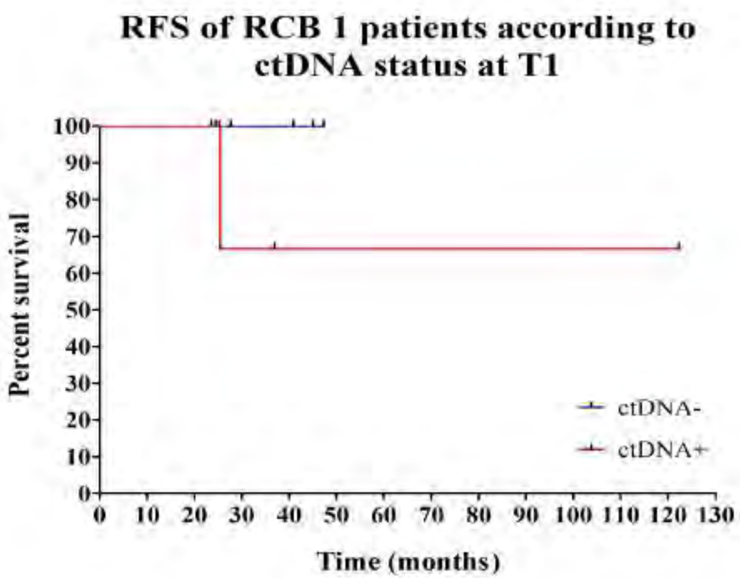
At Surgery: Tumor-informed MRD Detection in Early Breast Cancer is Associated with Distant Recurrence after NAC

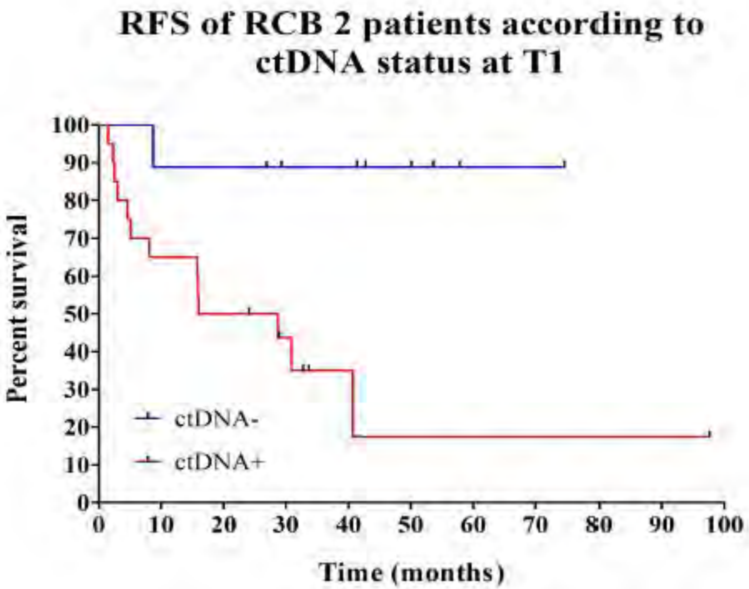


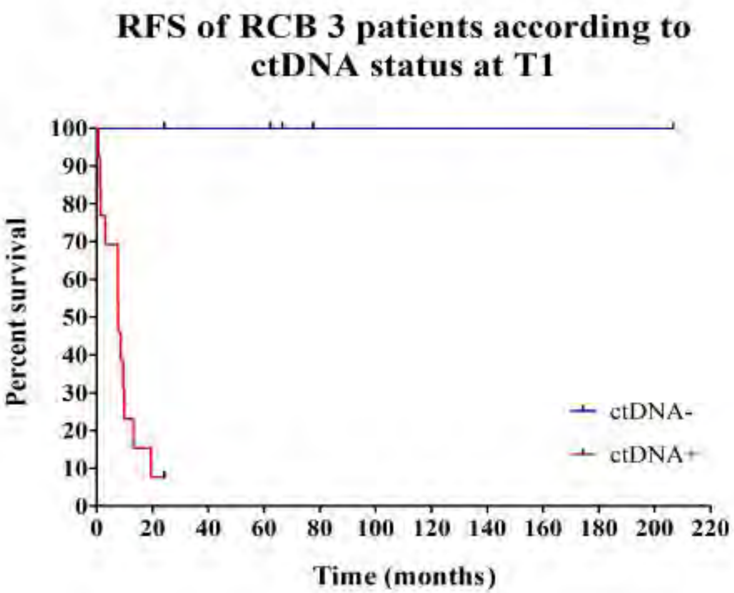
ctDNA-negative better than pathCR at predicting long term outcomes

Magbanua MJM et al., *Ann Oncol*. 2021

At Surgery: Tumor-informed MRD Detection in Early Breast Cancer Better than RCB at Detecting Distant Recurrence in TNBC


RFS of RCB 1 patients according to ctDNA status at T1

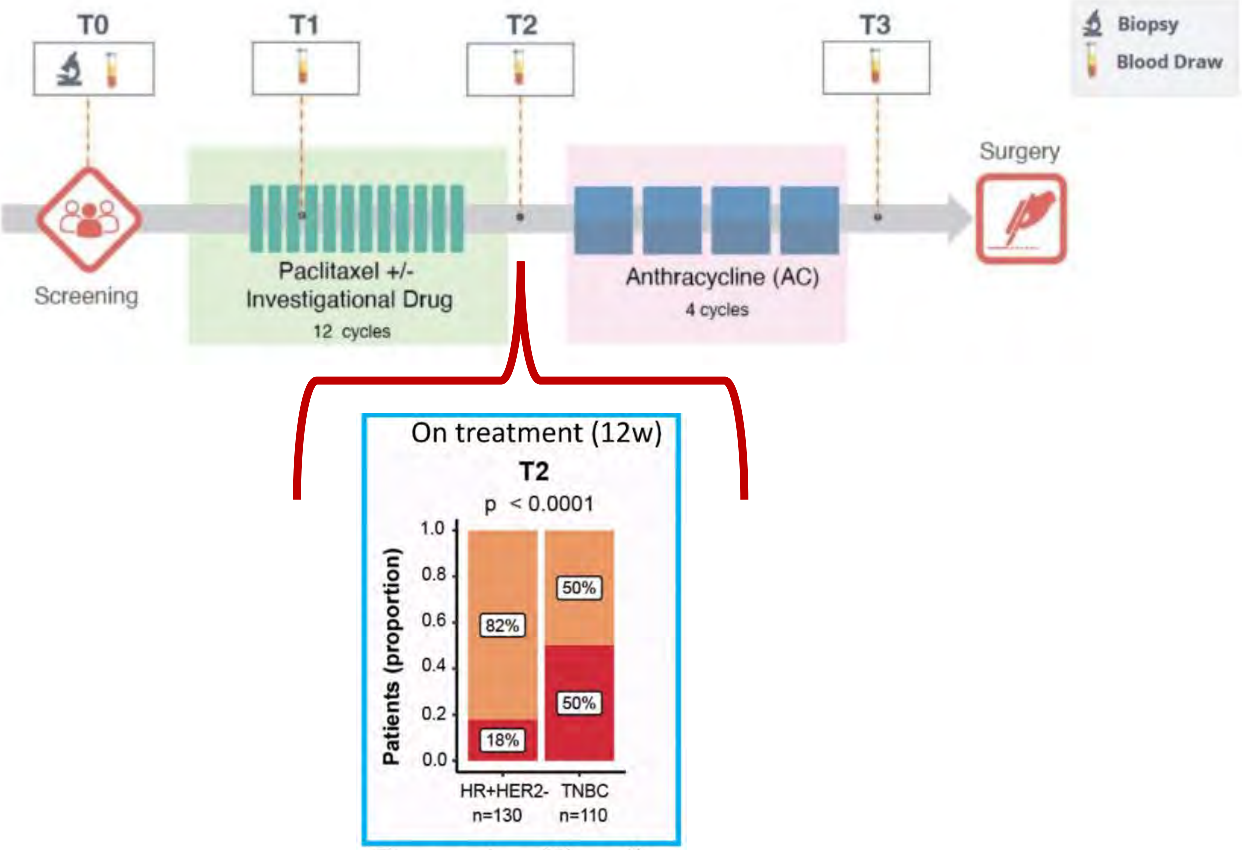

RFS of RCB 2 patients according to ctDNA status at T1


RFS of RCB 3 patients according to ctDNA status at T1

ctDNA-negative better than RCB score at predicting long term outcomes

Roseshter T. et al., SABCS23 P02-14-04

Before Surgery: ctDNA monitoring while on NAC can predict surgical outcomes in early stage breast cancer



Opportunities for De-escalation

Magbanua MJM et al., *Ann Oncol*. 2021

Pre-treatment ctDNA can help facilitate offering primary endocrine therapy and surgical de-escalation in older women (≥ 70) with ER+ breast cancer

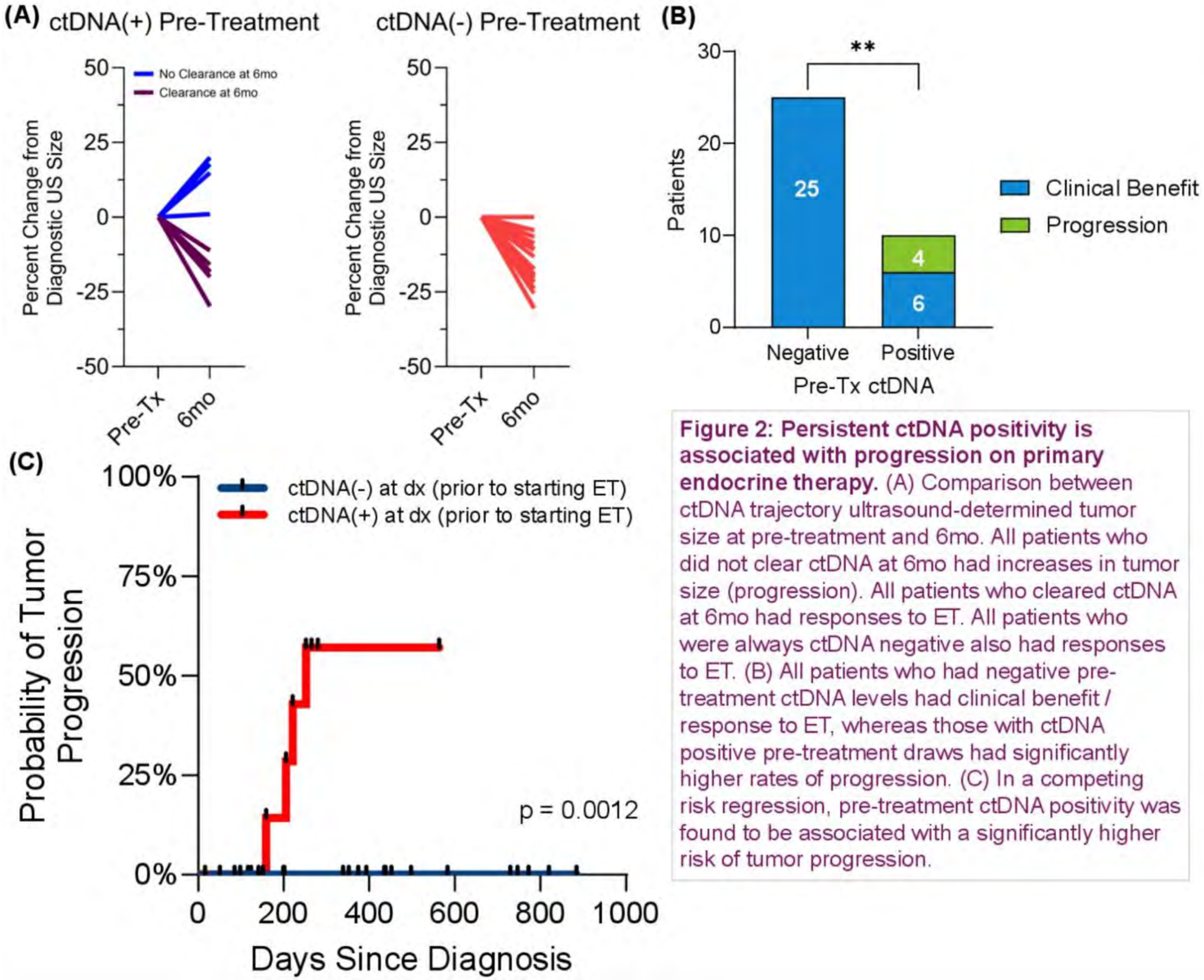


Figure 2: Persistent ctDNA positivity is associated with progression on primary endocrine therapy. (A) Comparison between ctDNA trajectory ultrasound-determined tumor size at pre-treatment and 6mo. All patients who did not clear ctDNA at 6mo had increases in tumor size (progression). All patients who cleared ctDNA at 6mo had responses to ET. All patients who were always ctDNA negative also had responses to ET. (B) All patients who had negative pre-treatment ctDNA levels had clinical benefit / response to ET, whereas those with ctDNA positive pre-treatment draws had significantly higher rates of progression. (C) In a competing risk regression, pre-treatment ctDNA positivity was found to be associated with a significantly higher risk of tumor progression.

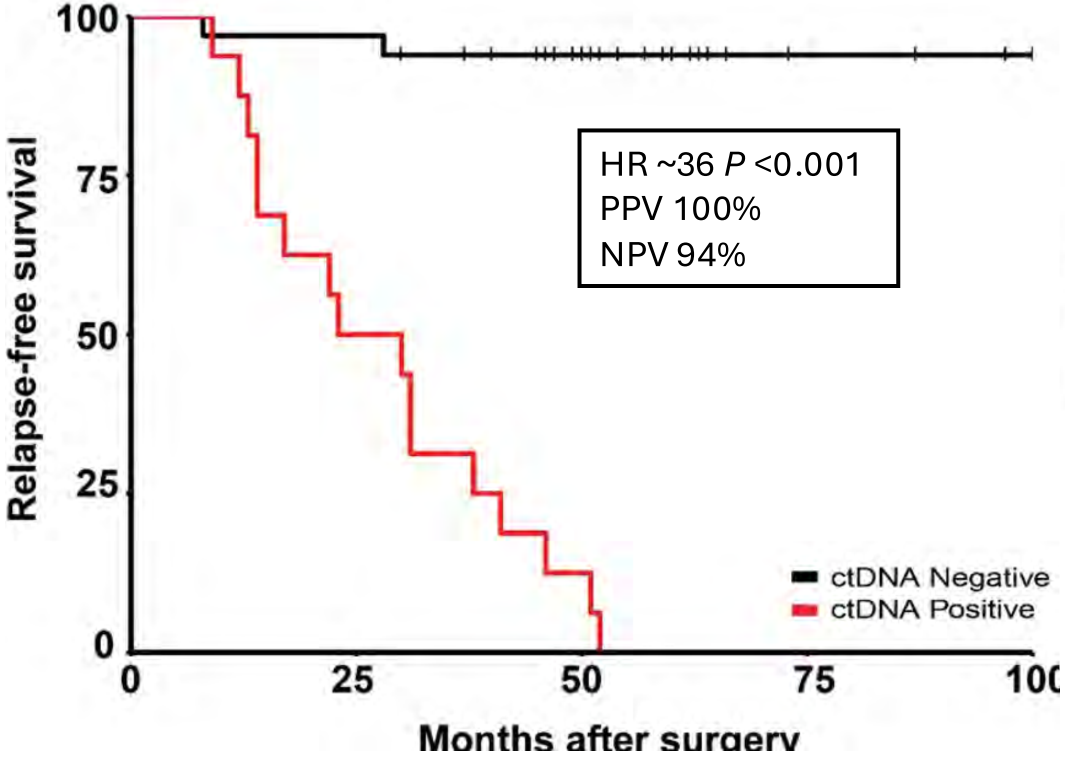
Carleton N.. et al., SABCS 2024, P2-03-21

After Surgery: Tumor-informed MRD Detection in eBC is Associated with Recurrence

Signatera

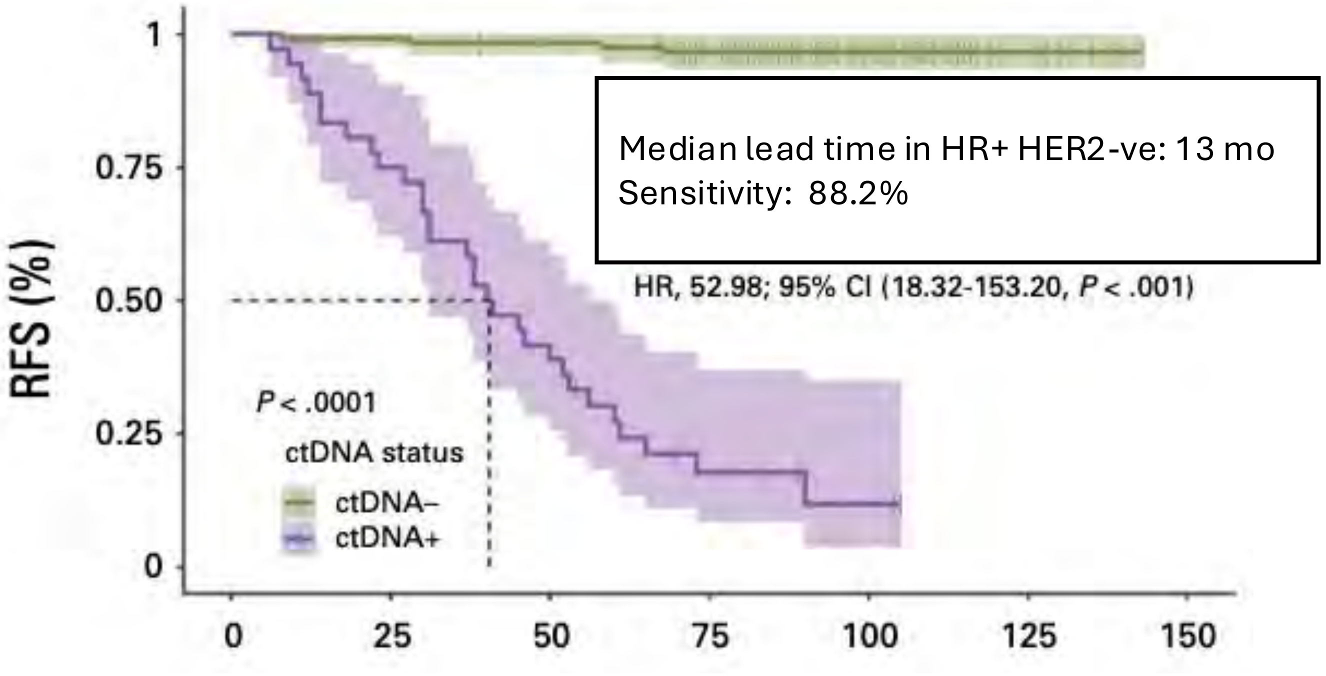
Up to 16 mutations

ctDNA status at any timepoint



HR ~36 *P* <0.001
PPV 100%
NPV 94%

Coombes RC et al., *Clin Cancer Res.* 2019



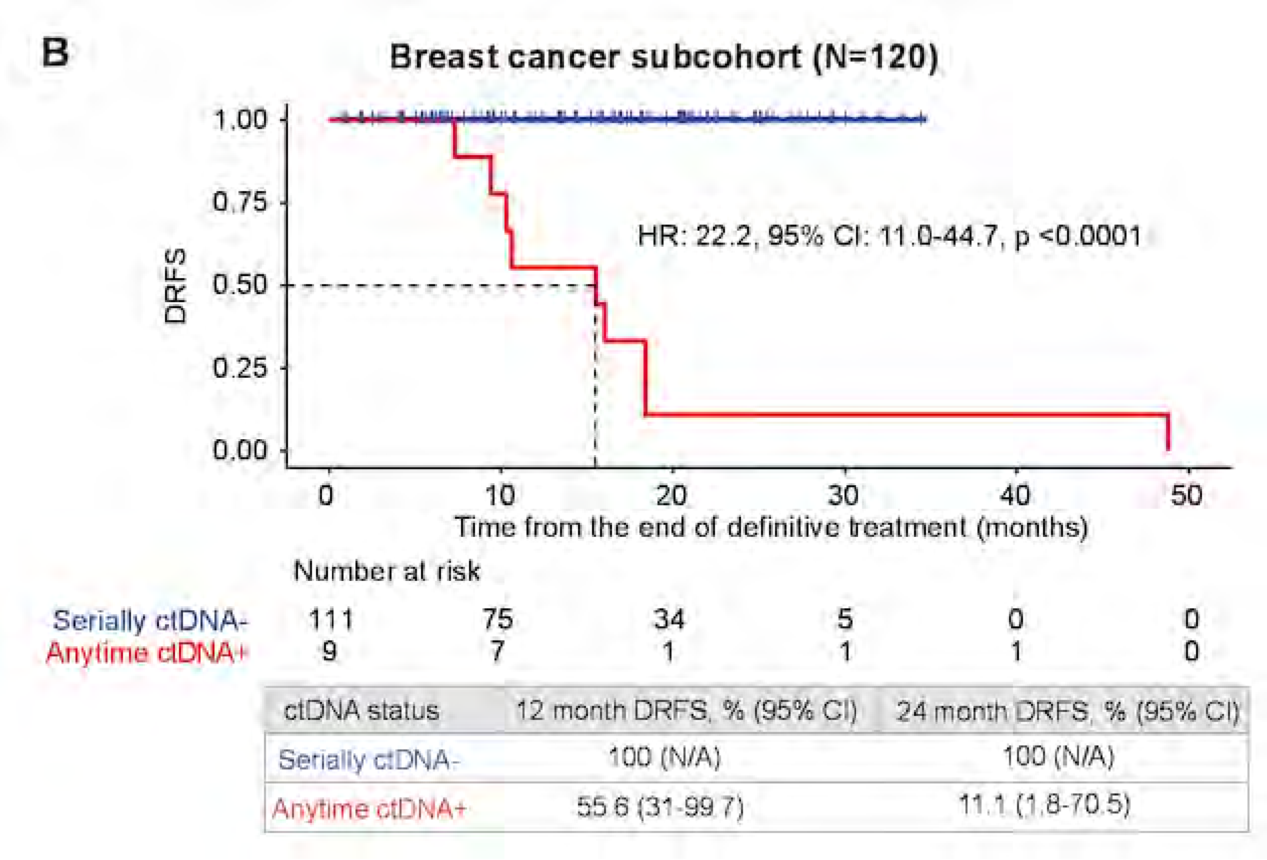
Median lead time in HR+ HER2-ve: 13 mo
Sensitivity: 88.2%

HR, 52.98; 95% CI (18.32-153.20, *P* < .001)

Shaw JA et al., *JCO Pres Onc.* 2024

ctDNA Platform – Signatera Genome (Ultra-sensitive Assay)

- Signatera Genome assay in Breast Cancer (**Up to 64 mutations**)
- LoD95 of 5-9 ppm with a capability to detect down to 1 ppm
  - Sensitivity = 94%
  - Specificity = 100%



Number at risk

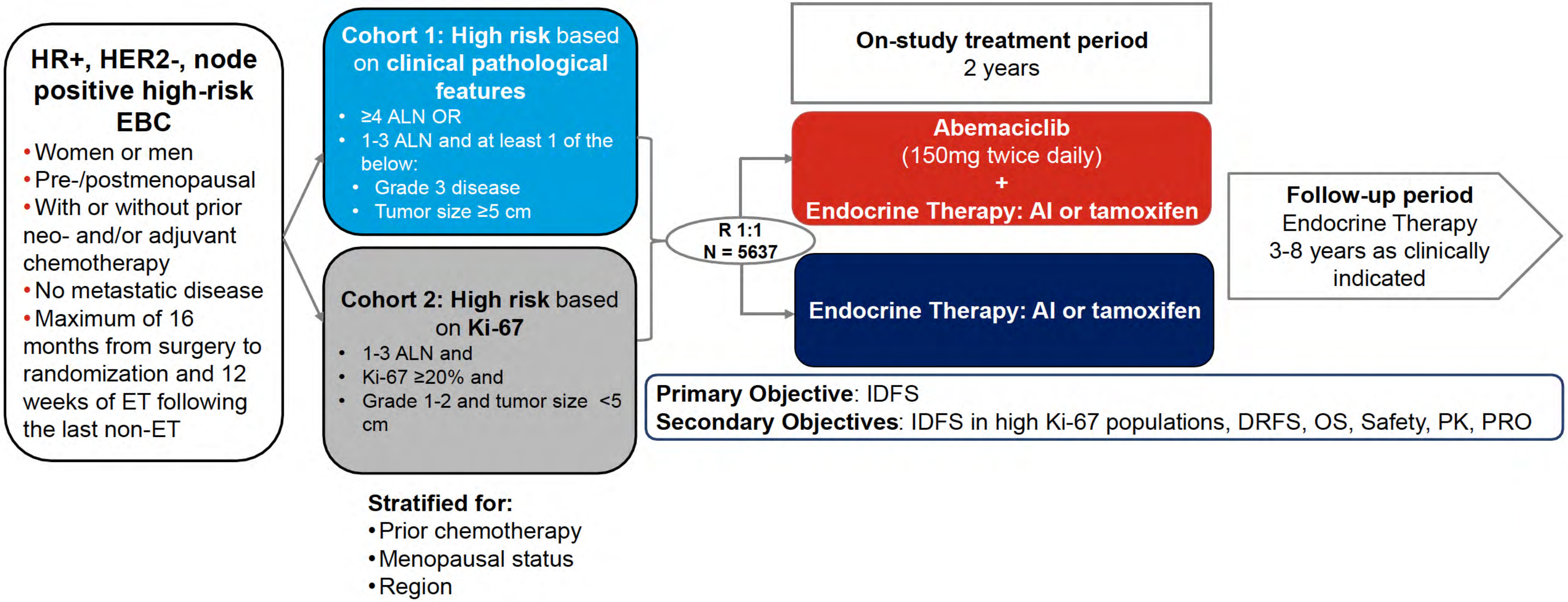
	0	10	20	30	40	50
Serially ctDNA-	111	75	34	5	0	0
Anytime ctDNA+	9	7	1	1	1	0

ctDNA status	12 month DRFS, % (95% CI)	24 month DRFS, % (95% CI)
Serially ctDNA-	100 (N/A)	100 (N/A)
Anytime ctDNA+	55.6 (31-99.7)	11.1 (1.8-70.5)

George M et al., ASCO 2025 Abst 3142

After Surgery: Pilot study from monarchE trial

monarchE Study Design (NCT03155997)



HR+, HER2-, node positive high-risk EBC

- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**

- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**

- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:

- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

On-study treatment period
2 years

Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

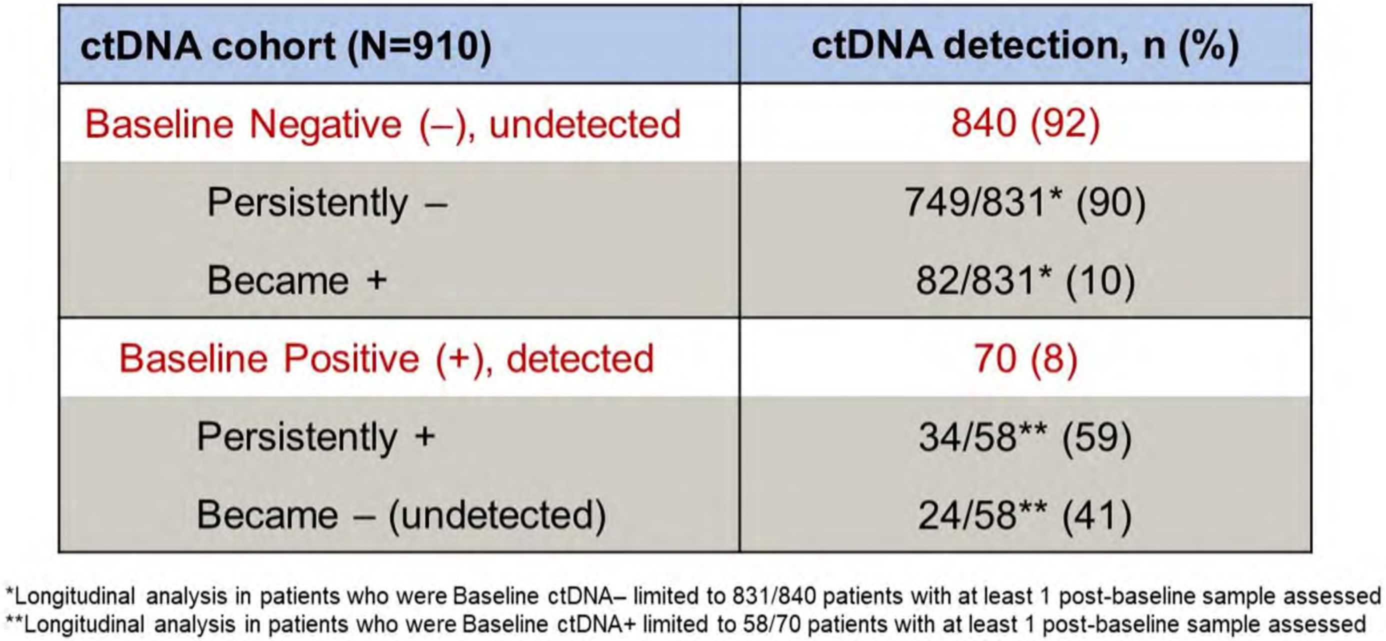
Endocrine Therapy: AI or tamoxifen

Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO

Graff SL, SABCS23, PS06-01

After Surgery: Pilot study from monarchE trial



ctDNA cohort (N=910)	ctDNA detection, n (%)
Baseline Negative (–), undetected	840 (92)
Persistently –	749/831* (90)
Became +	82/831* (10)
Baseline Positive (+), detected	70 (8)
Persistently +	34/58** (59)
Became – (undetected)	24/58** (41)

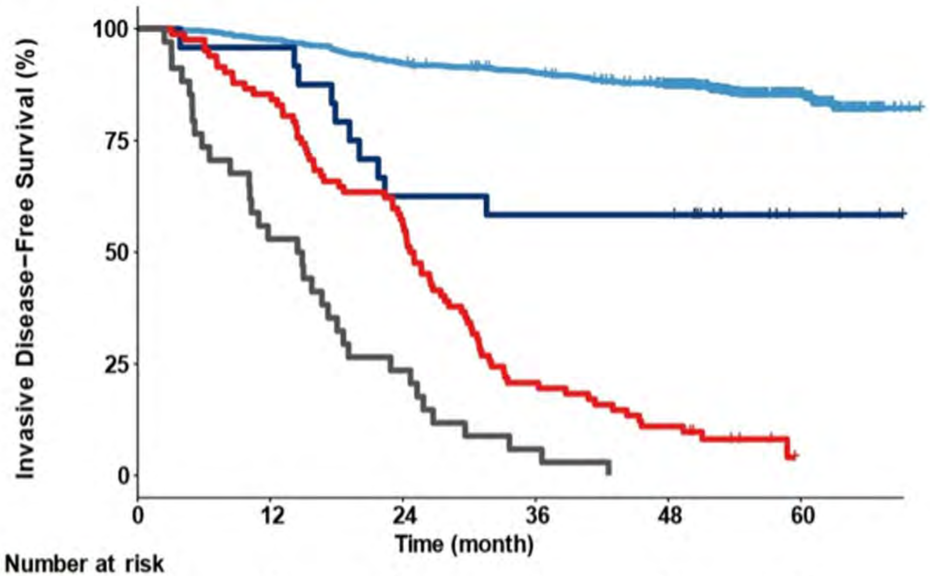
*Longitudinal analysis in patients who were Baseline ctDNA– limited to 831/840 patients with at least 1 post-baseline sample assessed
**Longitudinal analysis in patients who were Baseline ctDNA+ limited to 58/70 patients with at least 1 post-baseline sample assessed

- **ctDNA detection at baseline was 8% (n=70)**
- **Among patients who were Baseline ctDNA–, 82 (10%) Became + on treatment**
- **Among patients who were Baseline ctDNA+, 59% remained Persistently + on treatment**

Loi S, Johnston S, Arteaga C, Graff SL et al. Results from a pilot study exploring ctDNA detection using a tumor-informed assay in the monarchE trial of adjuvant abemaciclib with endocrine therapy in HR+, HER2-, node-positive, high-risk early breast cancer. 2023 San Antonio Breast Cancer Symposium. December 5-8, 2023; San Antonio, TX

Graff SL, SABCS23, PS06-01

After Surgery: Pilot study from monarchE trial



Number at risk

	0	12	24	36	48	60
Persistently –	749	731	691	664	611	162
Became –	24	23	15	14	14	3
Became +	82	70	46	17	9	0
Persistently +	34	18	8	2	0	0

	Longitudinal Analysis (N=889)*			
	Baseline (–), undetected N=831		Baseline (+), detected N=58	
	Persistently –	Became +	Persistently +	Became – (undetected)
N	749 (90)	82 (10)	34 (60)	24 (40)
IDFS event, n (%)	107 (14)	76 (93)	34 (100)	10 (42)
4-year IDFS rate, % (95% CI)	87.5 (85.1-89.9)	11.0 (5.9-20.3)	NA	58.3 (41.6-81.8)

*The ctDNA subset was enriched by patients with IDFS events within 24 months; therefore, the estimated IDFS rates in each subgroup are not reflective of that in the overall population. Robust assessment was limited in 194 patients with <3 post-baseline timepoints and there may be differences in IDFS; total events 227.

Patients who remained Persistently + or Became + on treatment were more likely to experience an IDFS event compared to those who Became – (undetected) or remained Persistently – on treatment

Loi S, Johnston S, Arteaga C, Graff SL et al. Results from a pilot study exploring ctDNA detection using a tumor-informed assay in the monarchE trial of adjuvant abemaciclib with endocrine therapy in HR+, HER2-, node-positive, high-risk early breast cancer. 2023 San Antonio Breast Cancer Symposium. December 5-8, 2023; San Antonio, TX.

Graff SL, SABCS23, PS06-01

Circulating tumor (ct)DNA monitoring of ER+/HER2- high-risk breast cancer during adjuvant endocrine therapy

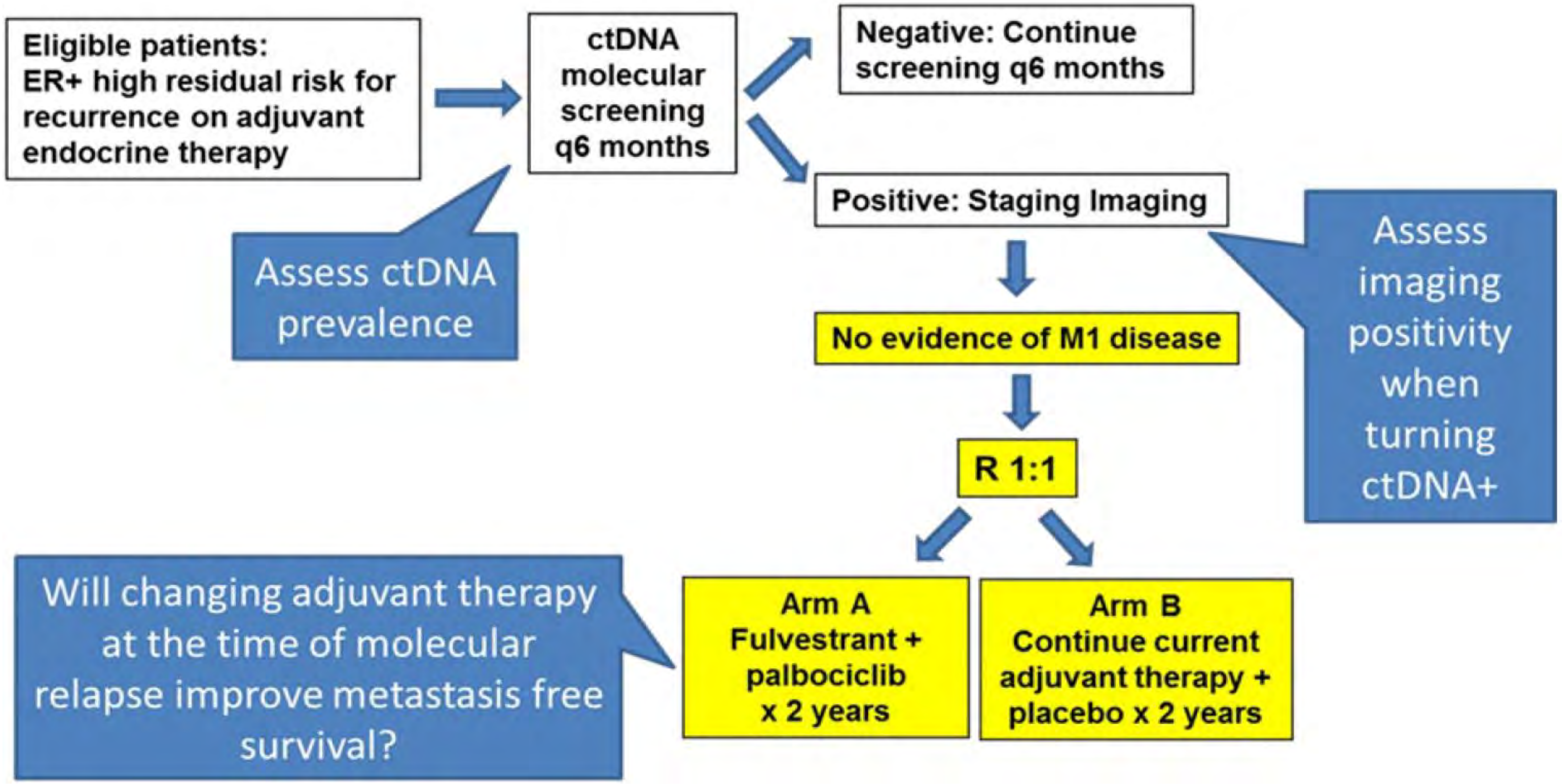
Preliminary results from a prospective, multicenter, randomized, ctDNA interventional trial, DARE (NCT04567420)

Presenting author: **Lajos Pusztai**[1]

Coauthors: Carly Bess Scalise,[2] Ekaterina Kalashnikova,[2] Ursa Glaberman,[3] Sima Ehsani,[4] Alison Stopeck,[5] Manali Bhave,[6] Alexandra Zimmer,[7] Evanthia Roussos Torres,[8] Paula Klein,[9] Sagar Sardesai,[10] Fengting Yan,[11] Marina Sharifi,[12] Peter Kabos,[13] Wajeeha Razaq,[14] Michelle Loch,[15] Angel Rodriguez,[2] Minetta Liu[2]

[1]Yale Cancer Center, Yale School of Medicine, New Haven, CT; [2]Natera, Inc., Austin, TX; [3]UNM Comprehensive Cancer Center, Albuquerque, NM; [4]Cancer Center, University of Arizona, Tucson, AZ; [5]Stony Brook University Cancer Center, Stony Brook, NY; [6]Department of Hematology/Oncology, Emory University, Atlanta, GA; [7]Oregon Health & Science University, Portland, OR; [8]Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; [9]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [10]Ohio State University, Columbus, OH; [11]Swedish Cancer Institute, First Hill-True Family Women's Cancer Center, Seattle, WA; [12]University of Wisconsin, Madison, WI; [13]University of Colorado, Aurora, CO; [14]University of Okahoma Health Sciences Center, Oklahoma City, OK; [15]Louisiana State University Health Sciences Center, New Orleans, LA

DARE Trial: ctDNA monitoring of ER+/HER2- high risk breast cancer during adjuvant endocrine therapy



Eligible patients:
ER+ high residual risk for recurrence on adjuvant endocrine therapy

ctDNA molecular screening q6 months

Negative: Continue screening q6 months

Positive: Staging Imaging

No evidence of M1 disease

R 1:1

Arm A
Fulvestrant + palbociclib x 2 years

Arm B
Continue current adjuvant therapy + placebo x 2 years

Assess ctDNA prevalence

Assess imaging positivity when turning ctDNA+

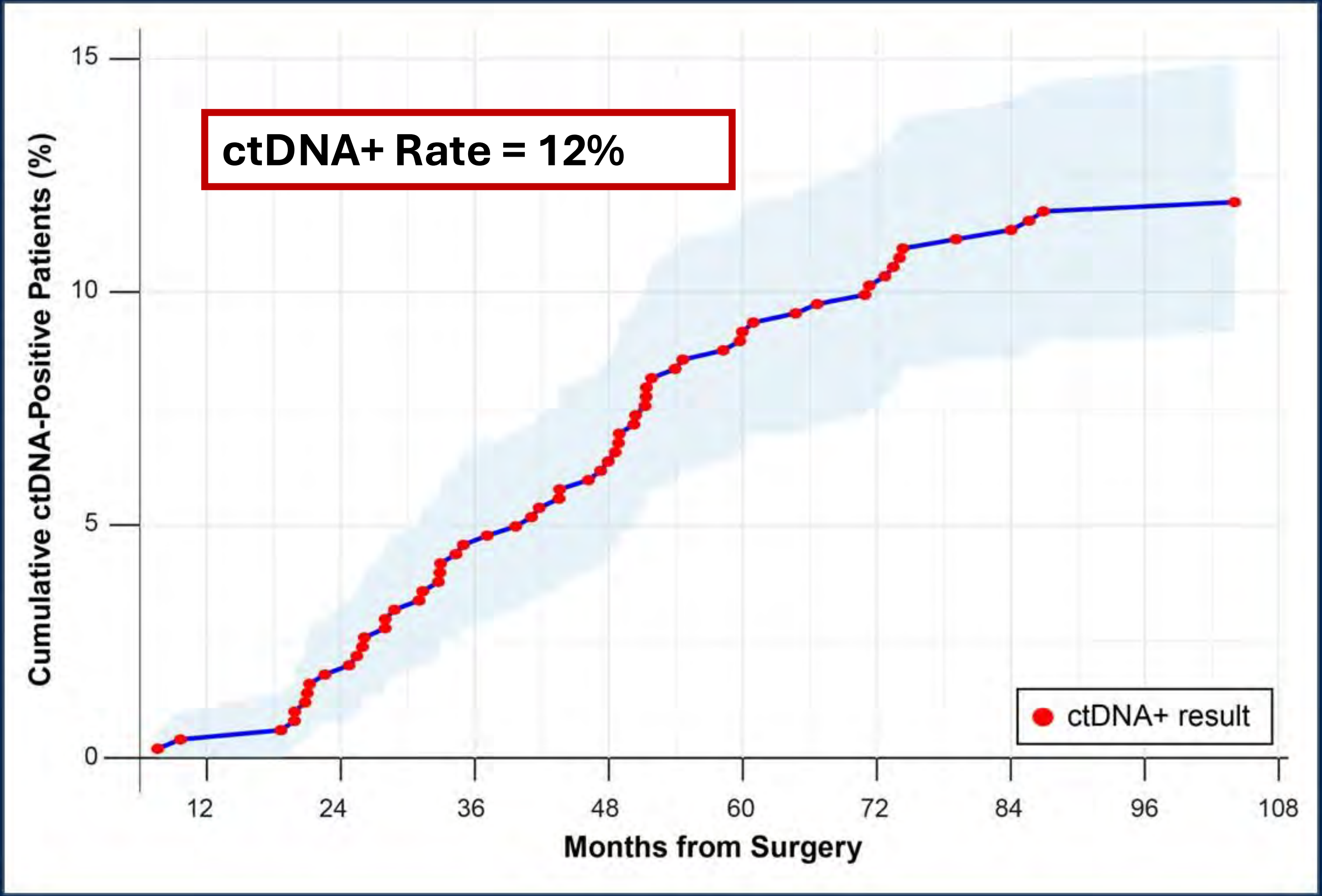
Will changing adjuvant therapy at the time of molecular relapse improve metastasis free survival?

Eligibility:

- Adjuvant ET >6mo to <7yrs
- Risk of recurrence > 15% calculated by PREDICT, RSPC, or CTS5, or
  - > 4 +LN
  - or T > 5 cm
  - or 1-3 +LN/G3
  - or > 3 cm tumor with RS > 26, MP high, EndoPredict > 4, Prosigna score > 60

Pusztai L. et al., SABCS23, PS06-02

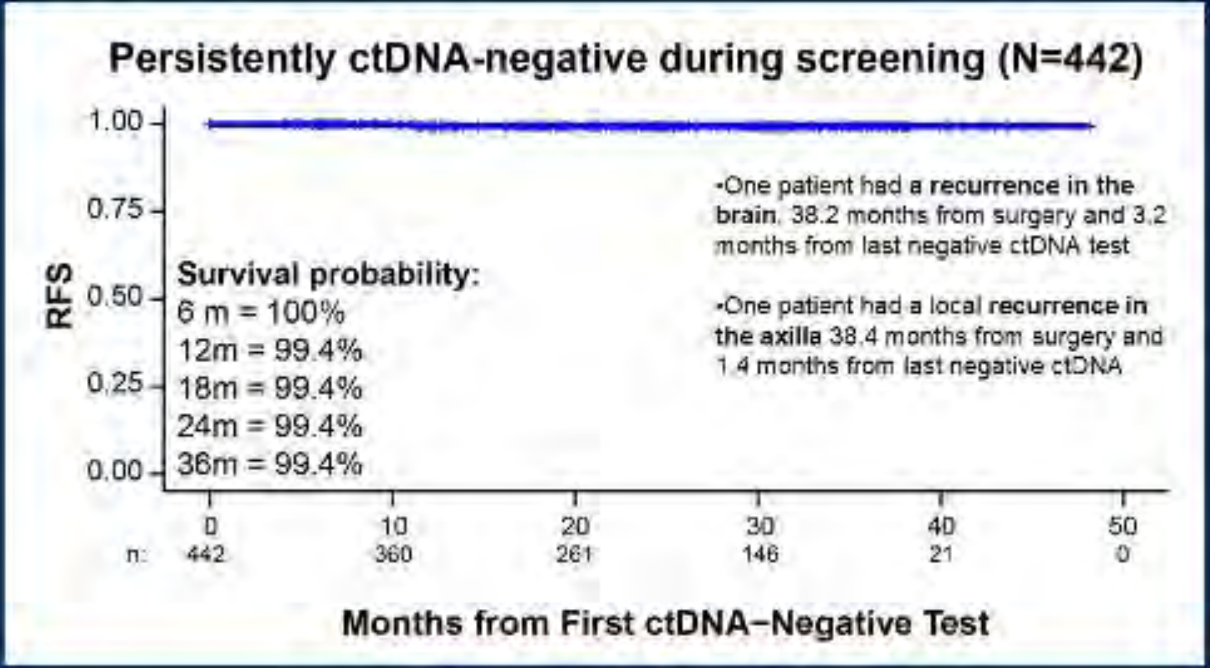
Longitudinal molecular relapse detection post-surgery (N=507)



- Median # ctDNA tests/patient = 5 (range: 1-9)
- Median follow-up = 29 months (range: 0-48.1)

N=37 tested ctDNA+ at the first screen and N=23 turned positive after one or more initially negative ctDNA result

Molecular and clinical relapse among patients with serial screening



Persistently ctDNA-negative during screening (N=442)

Survival probability:
6 m = 100%
12m = 99.4%
18m = 99.4%
24m = 99.4%
36m = 99.4%

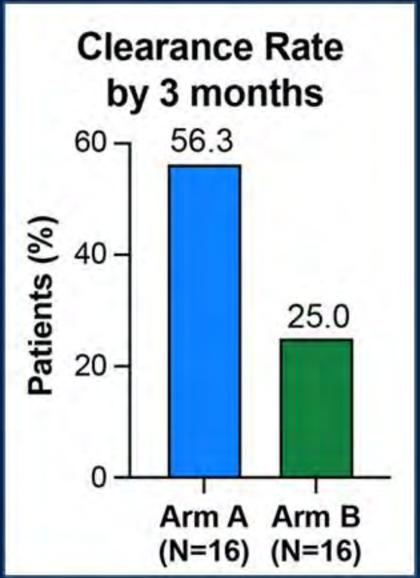
- One patient had a **recurrence in the brain**, 38.2 months from surgery and 3.2 months from last negative ctDNA test
- One patient had a local **recurrence in the axilla** 38.4 months from surgery and 1.4 months from last negative ctDNA

Cumulative clinical relapse

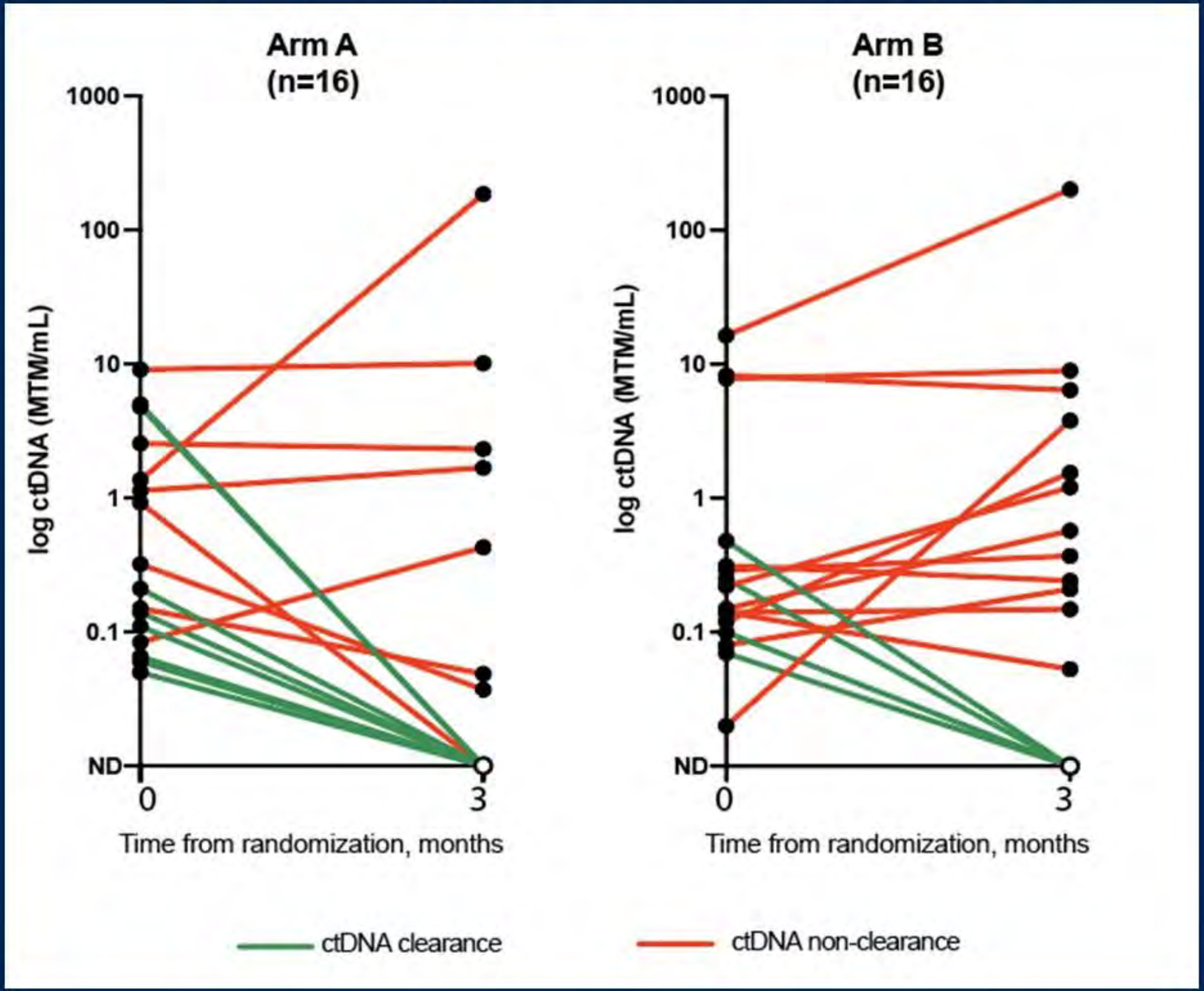
	Time from first negative test		
	< 6 mos	<12 mos	>12 mos
Total screened, N	200	396	442
Cumulative Clinical relapse, N	0	1	2 (0.5%)
NPV (Clinical relapse)	100	99.7	99.5
NPV (Clinical distant extracranial relapse)	100	100	100

ctDNA dynamics in the randomized cohort

Randomization Rate*	
Overall	**70.4% (38/54)**
Initially ctDNA positive	**59% (19/32)**
ctDNA positive after a negative result	**86% (19/22)**


Clearance Rate by 3 months

N=32 of 38 patients had post-randomization ctDNA available


Arm A (n=16)

Arm B (n=16)

*excluding ineligible patients due to reasons other than metastatic disease on imaging

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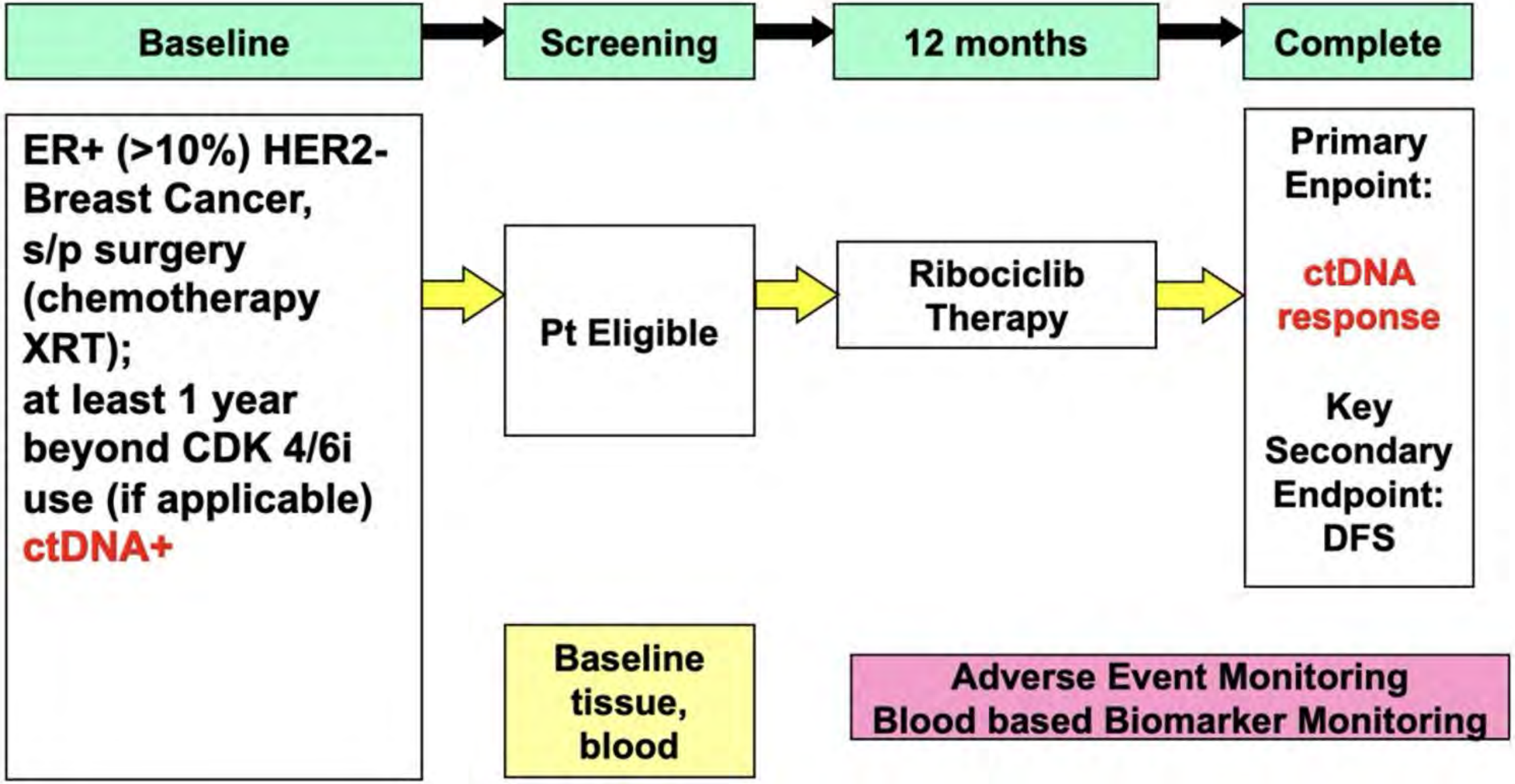
Personalized circulating tumor DNA (ctDNA) testing, intervention, and temporal dynamics in ER+/HER2- early-stage breast cancer (LEADER)

Arielle J Medford, MD
Mass General Brigham Cancer Institute/Harvard Medical School
Boston, MA

LEADER Study Schema



Baseline → **Screening** → **12 months** → **Complete**

ER+ (>10%) HER2- Breast Cancer, s/p surgery (chemotherapy XRT); at least 1 year beyond CDK 4/6i use (if applicable) ctDNA+

Pt Eligible

Ribociclib Therapy

Primary Enpoint:

ctDNA response

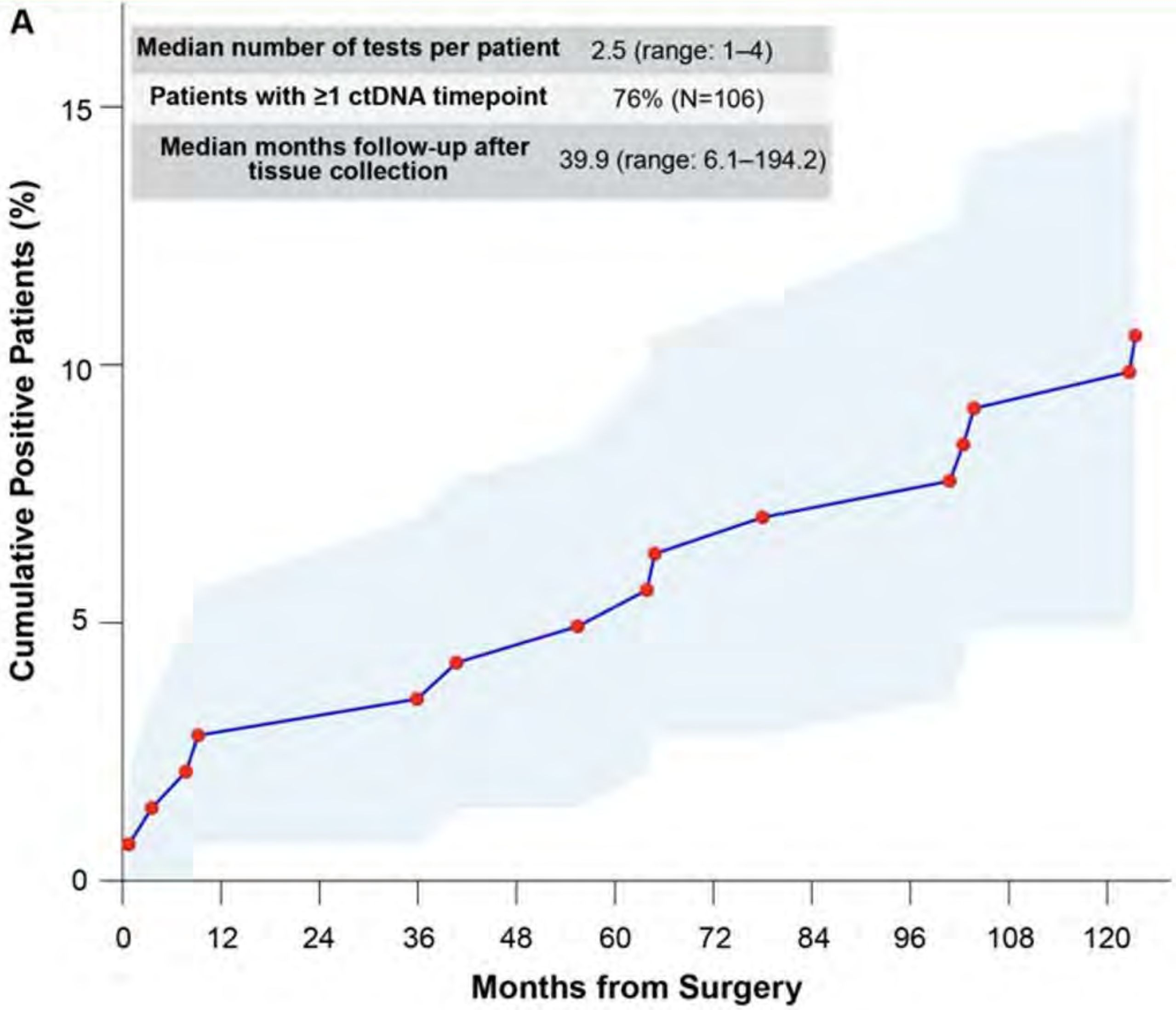
Key Secondary Endpoint: DFS

Baseline tissue, blood

Adverse Event Monitoring
Blood based Biomarker Monitoring

Medford A.; SABCS 2025 PD5-01

Results

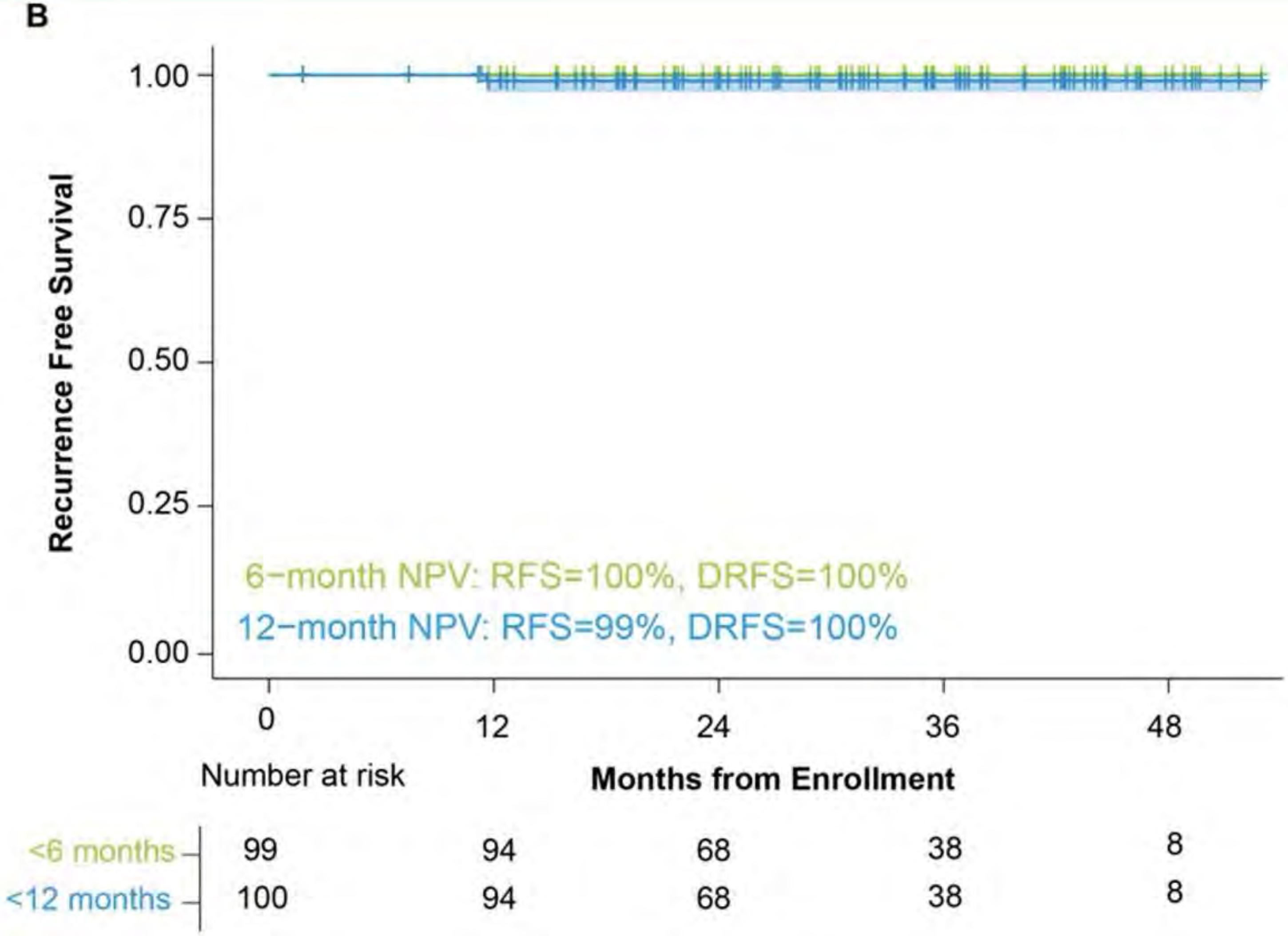


Median number of tests per patient	2.5 (range: 1–4)
Patients with ≥1 ctDNA timepoint	76% (N=106)
Median months follow-up after tissue collection	39.9 (range: 6.1–194.2)

- ctDNA positivity rate of 11% (15/140)
- 87% (13/15) +ctDNA at 1st time point
  - 27% (4/15) withdrew due to radiographic recurrence
  - 7% (1/15) lost to follow-up.

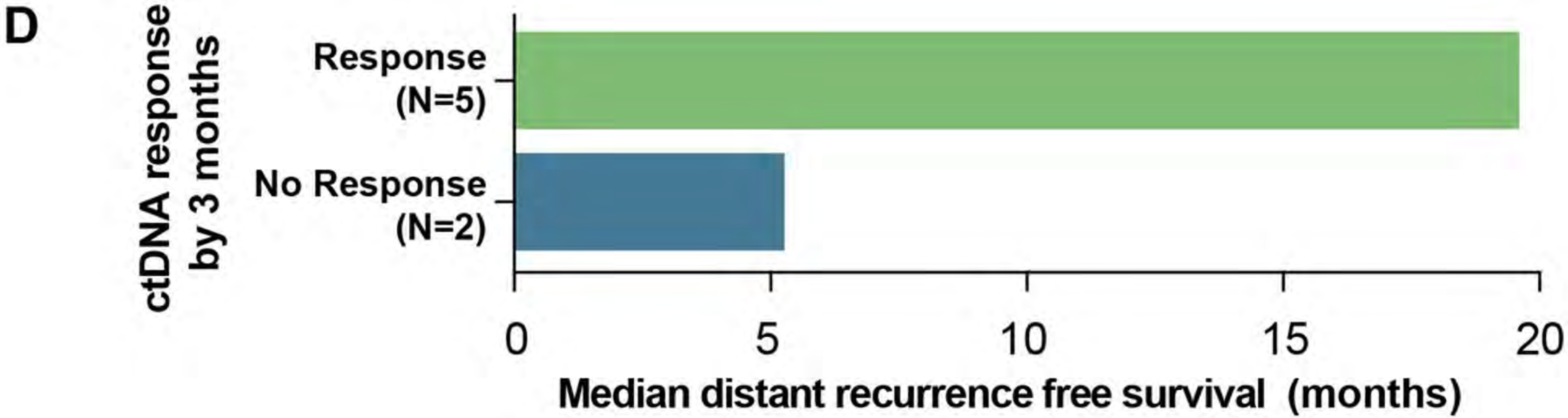
Medford A.; SABCS 2025 PD5-01

Results



- 89% (125/140) ctDNA-
- 80% (100/125) w/ clinical follow-up (median 31.1 months (range 0-52.9)
  - NPV at 6 & 12 months - 100% and 99% for RFS
  - NPV at 6 & 12 months - 100% and 100% for DRFS

Results



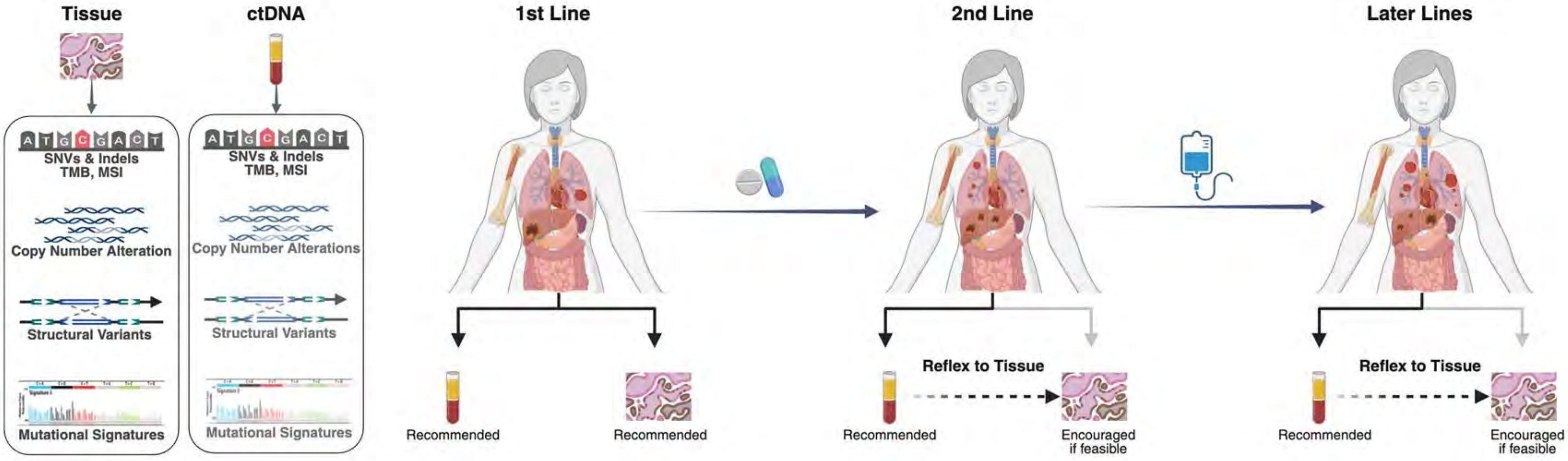
Medford A.; SABCS 2025 PD5-01

ctDNA monitoring in Metastatic Breast Cancer and Metastatic ILC

Circulating tumor DNA (ctDNA) dynamics as a predictor of treatment response in metastatic breast cancer (mBC)

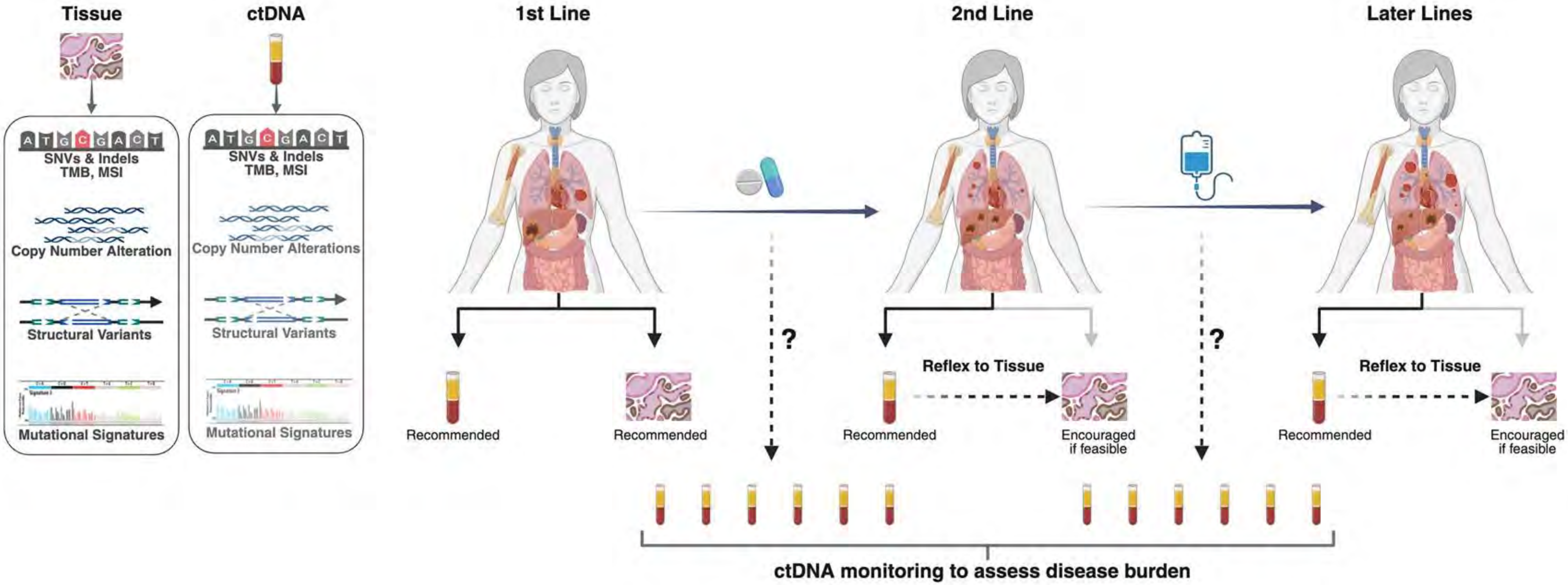
Pedram Razavi, Luc Cabel, Jimmitti Teysir, Julia A. An, Samuel Rivero-Hinojosa, Sandro Satta, Sara L. Bristow, Ekaterina Kalashnikova, Angel A. Rodriguez, Minetta C. Liu, Mark E. Robson, Sarat Chandarlapaty

ctDNA is routinely utilized in mBC to identify actionable alterations



- ctDNA constantly released through apoptosis and necrosis, active secretion.
- **ctDNA levels are highly correlated with disease burden.**
- Rapidly cleared by liver macrophages (Kupffer cells), kidneys, and circulating nucleases
- **Short half life**: Few hours → **highly dynamic and accurate biomarker for disease burden**

Can we utilize serial ctDNA to monitor disease burden?



Tissue

SNVs & Indels
TMB, MSI

Copy Number Alteration

Structural Variants

Mutational Signatures

ctDNA

SNVs & Indels
TMB, MSI

Copy Number Alterations

Structural Variants

Mutational Signatures

1st Line

Recommended

Recommended

?

2nd Line

Recommended

Reflex to Tissue

Encouraged
if feasible

?

Later Lines

Recommended

Reflex to Tissue

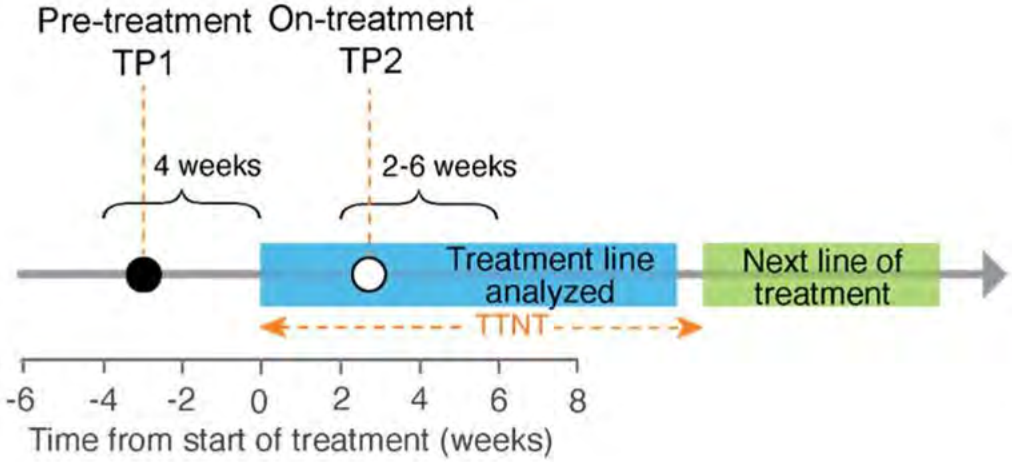
Encouraged
if feasible

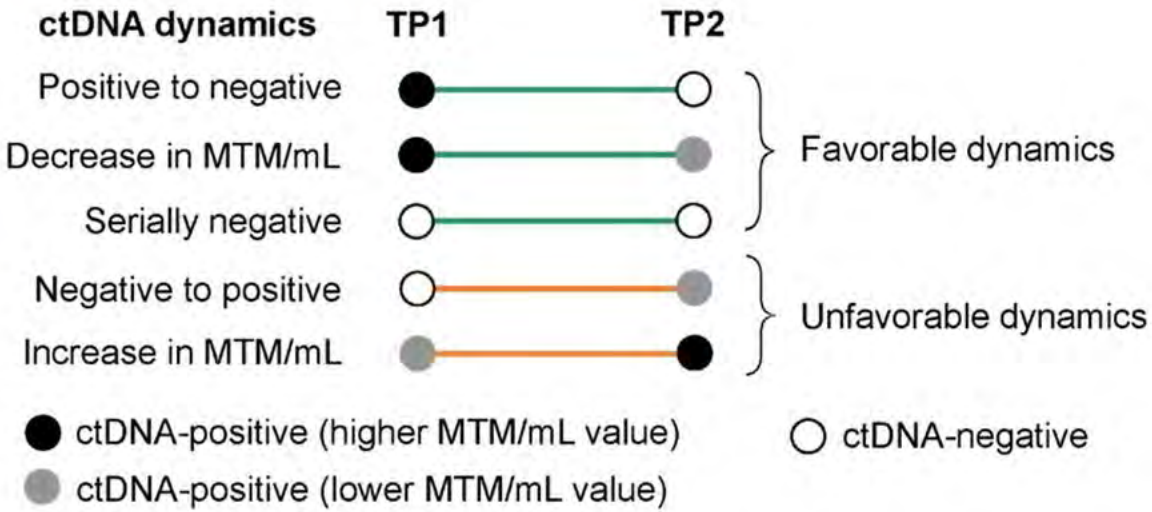
ctDNA monitoring to assess disease burden

Methods

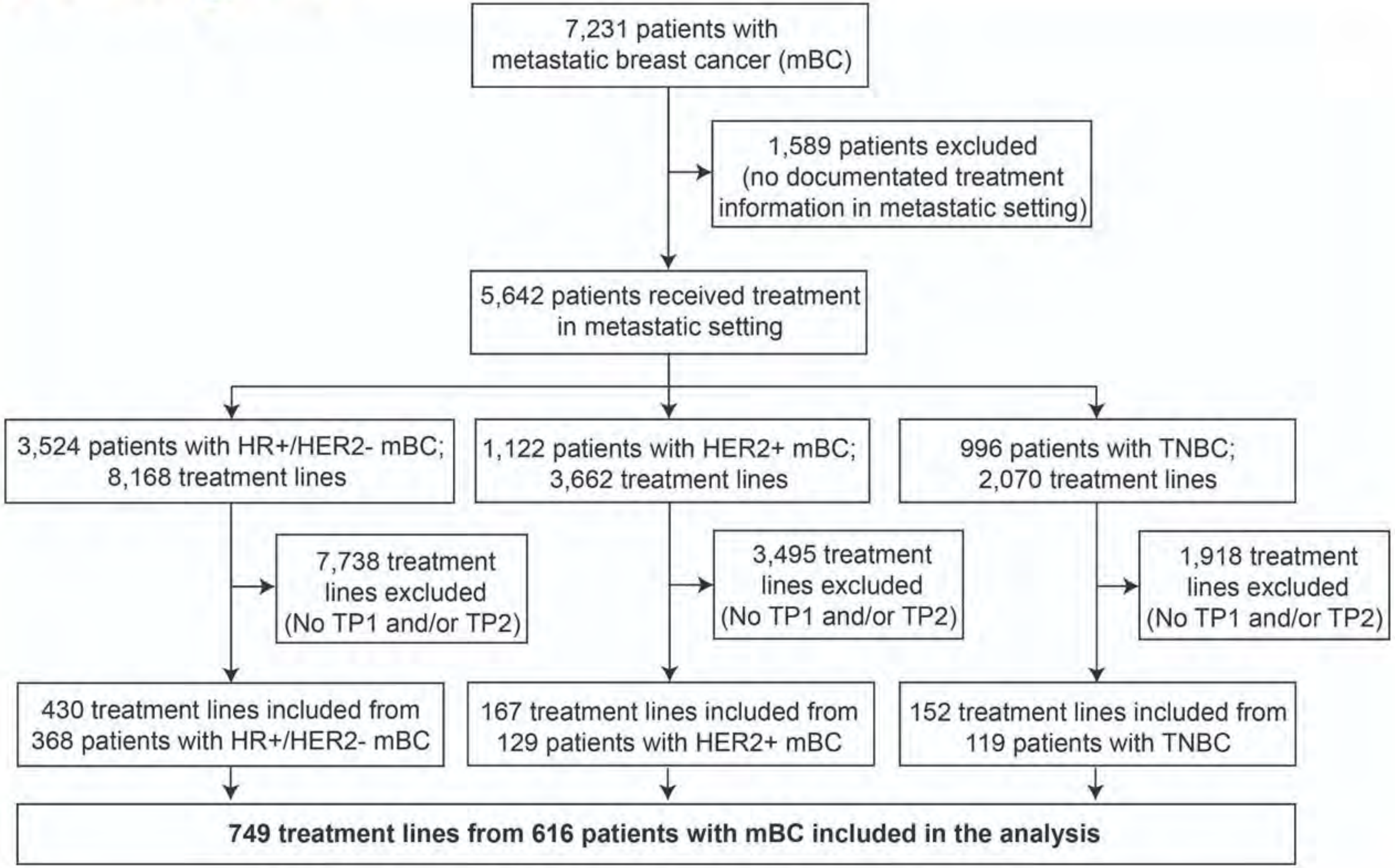
Treatment line inclusion criteria:

- Treatment after metastatic recurrence
- Pre-treatment ctDNA time point (Tp1): up to 4 weeks before the start of treatment
- On-treatment time point (Tp2): between 2-6 weeks after the start of treatment





CONSORT diagram



7,231 patients with metastatic breast cancer (mBC)

1,589 patients excluded (no documentated treatment information in metastatic setting)

5,642 patients received treatment in metastatic setting

3,524 patients with HR+/HER2- mBC; 8,168 treatment lines

1,122 patients with HER2+ mBC; 3,662 treatment lines

996 patients with TNBC; 2,070 treatment lines

7,738 treatment lines excluded (No TP1 and/or TP2)

3,495 treatment lines excluded (No TP1 and/or TP2)

1,918 treatment lines excluded (No TP1 and/or TP2)

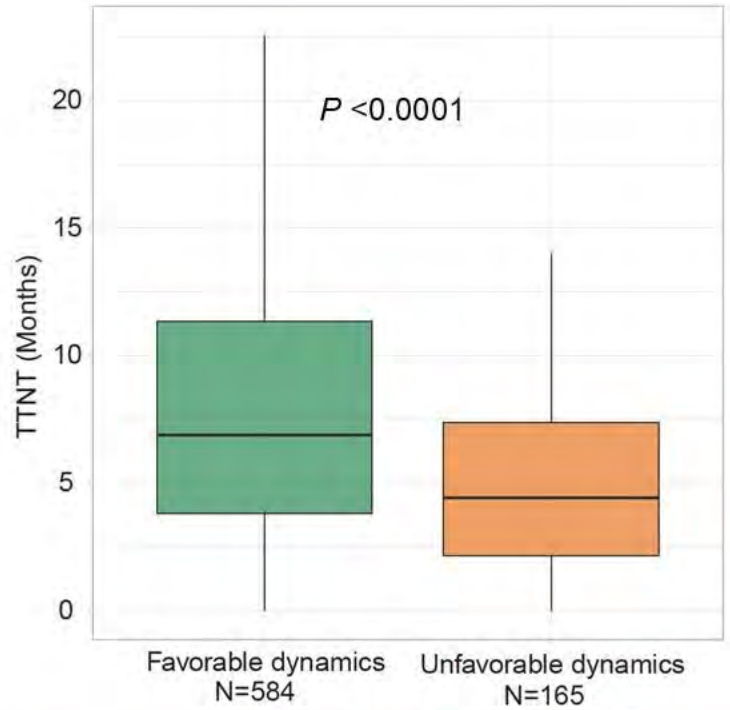
430 treatment lines included from 368 patients with HR+/HER2- mBC

167 treatment lines included from 129 patients with HER2+ mBC

152 treatment lines included from 119 patients with TNBC

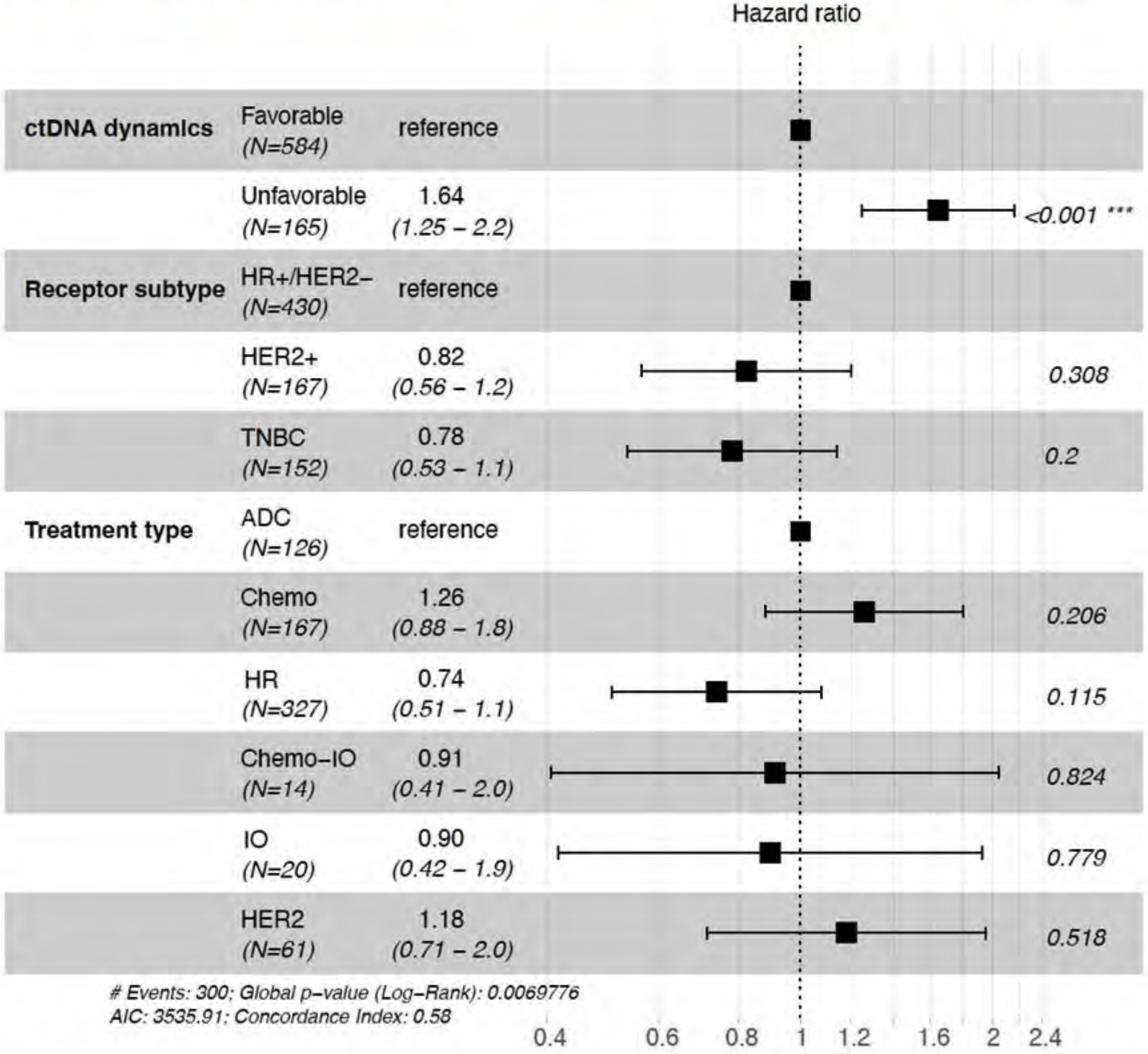
749 treatment lines from 616 patients with mBC included in the analysis

Patients with favorable ctDNA dynamics had longer TTNT



ctDNA Dynamics	Median TTNT (months)	95% CI
Favorable	6.9	6.5 - 7.6
Unfavorable	4.4	3.5 - 5.3

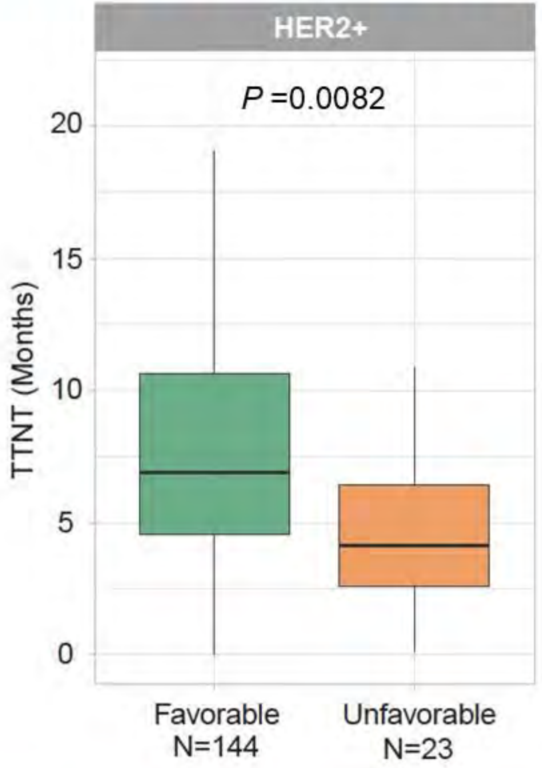
TTNT: Time to next treatment



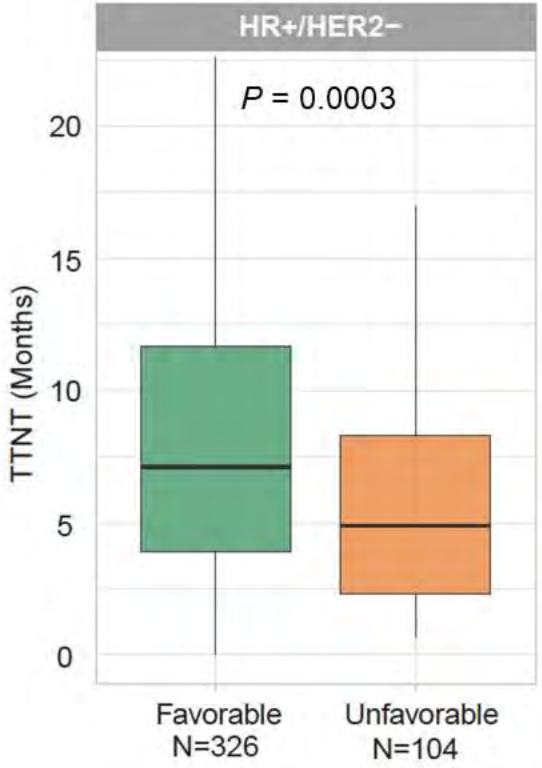
ctDNA dynamics	Favorable *(N=584)*	reference	
	Unfavorable *(N=165)*	1.64 *(1.25 – 2.2)*	*<0.001 ****
Receptor subtype	HR+/HER2– *(N=430)*	reference	
	HER2+ *(N=167)*	0.82 *(0.56 – 1.2)*	*0.308*
	TNBC *(N=152)*	0.78 *(0.53 – 1.1)*	*0.2*
Treatment type	ADC *(N=126)*	reference	
	Chemo *(N=167)*	1.26 *(0.88 – 1.8)*	*0.206*
	HR *(N=327)*	0.74 *(0.51 – 1.1)*	*0.115*
	Chemo–IO *(N=14)*	0.91 *(0.41 – 2.0)*	*0.824*
	IO *(N=20)*	0.90 *(0.42 – 1.9)*	*0.779*
	HER2 *(N=61)*	1.18 *(0.71 – 2.0)*	*0.518*

 # Events: 300; Global p–value (Log–Rank): 0.0069776
AIC: 3535.91; Concordance Index: 0.58

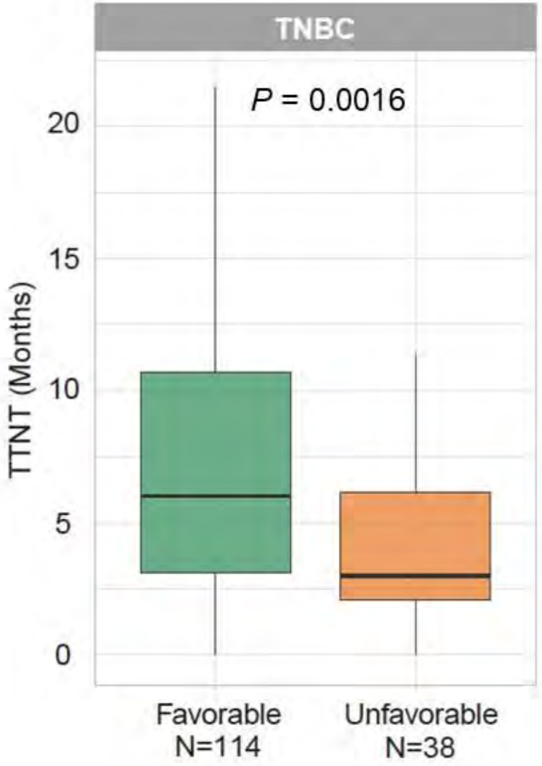
Patients with favorable ctDNA dynamics had longer TTNT across all subtypes



ctDNA Dynamics	Median TTNT (months)	95% CI
Favorable	6.9	6.3 - 8.3
Unfavorable	4.1	3.0 - 5.8



Median TTNT (months)	95% CI
7.1	6.4 - 8.2
4.9	3.7 - 5.8



Median TTNT (months)	95% CI
6.0	4.8 - 7.7
3.0	2.2 - 4.4

scientific reports

OPEN Longitudinal dynamics of circulating tumor DNA for treatment monitoring in patients with breast cancer recurrence

…eon Jeon[2,3],

Tae-Kyung Robyn Yoo[1,7], Ji-Your
Ha Ra Jun[2,3], Sae Byul Lee[1], Il Y
Jong Won Lee[1], Byung Ho Son
Jin-Hee Ahn[5], Kyung Hae Jung
Jisun Kim[1] & Sung-Min Chu

The prevalence and dynamics
recurrence or de novo metast
observational cohort. Twenty
distant metastasis) were en
were selected from the targ
in-house developed assay
treatment and follow-up.
for ctDNA detection. ctD
18 (78.5%, 18/23) cases
significantly related to
enriched variant allele
progressive disease re
ctDNA eVAF prior to
ctDNA dynamics me
recurrence.

Keywords Breast

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npj | breast cancer

Published in partnership with the Breast Cancer Research Foundation

https

Personalized ctDNA monitorin
metastatic HR+/HER2− breas
patients during endocrine and
inhibitor therapy

Jesús Fuentes-Antrás[1,2,10], Mitchell J. Elliott[1,10], Sasha C. Main[3,4,10], Philippe Echelard[5],
Philippe L. Bedard[1], Eitan Amir[1], Michelle B. Nadler[1], Nicholas Meti[6], Nancy Gregorio[1], El
Emily Van de Laar[1], Celeste Yu[1], Yangqing Deng[7], Lisa Gates[8], Clodagh Murray[8], Christo
Amber Chevalier[8], Scott V. Bratman[3,4,9], Lillian L. Siu[1], Hal K. Berman[5] & David W. Cescor

Improved methods to monitor treatment response may enhance patient managemer
outcomes. This study assessed the feasibility and performance of a tumor-informed c
DNA (ctDNA) assay in metastatic HR+/HER2− breast cancer patients receiving endo
6 inhibitor therapy. By conducting whole exome sequencing on archival tumors, hig
personalized ctDNA panels were designed for blood monitoring. The assay showed
sensitivity (91% baseline, 70% all timepoints) and associations between higher bas
variant allele fractions, liver metastases, and shorter time to treatment failure (TTF) ar
(OS). Complete molecular response, defined as ctDNA clearance, was observed in
and correlated with improved TTF (HR 0.07) and OS (HR 0.07). The last cleared tim
treatment failure by a median 14.3 months. ctDNA rises or limited decreases prece
progression. Molecular metrics may facilitate plasma-first monitoring and innovativ
clinical practice and trial design.

JAMA Network | Open

Original Investigation | Oncology

Circulating Tumor DNA and Survival in Metastatic Breast Cancer
A Systematic Review and Meta-Analysis

Kyle Dickinson, PhD; Archi Sharma, MSc; Ramana-Kumar Venkata Agnihotram, PhD; Selin Altuntur, MISt; Morag Park, PhD; Sarkis Meterissian, MD; Julia V. Burnier, PhD

Abstract

IMPORTANCE Metastatic breast cancer (MBC) poses a substantial clinical challenge despite advancements in diagnosis and treatment. While tissue biopsies offer a static snapshot of disease, liquid biopsy—through detection of circulating tumor DNA (ctDNA)—provides minimally invasive, real-time insight into tumor biology.

OBJECTIVE To determine the association between ctDNA and survival outcomes in patients with MBC.

DATA SOURCES An electronic search was performed in 5 databases (CINAHL, Cochrane Library, Embase, Medline, and Web of Science) and included all articles published from inception until October 23, 2023.

STUDY SELECTION To be included in the meta-analysis, studies had to (1) include women diagnosed with MBC; (2) report baseline plasma ctDNA data; and (3) report overall survival, progression-free survival, or disease-free survival with associated hazards ratios.

DATA EXTRACTION AND SYNTHESIS Titles and abstracts were screened independently by 2 authors. Data were pooled using a random-effects model. This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline, and quality was assessed using the Newcastle-Ottawa Scale.

MAIN OUTCOMES AND MEASURES The primary study outcome was the association between detection of specific genomic alterations in ctDNA with survival outcomes. Secondary objectives were associations of study methodology with survival.

RESULTS Of 3162 articles reviewed, 37 met the inclusion criteria and reported data from 4264 female patients aged 20 to 94 years. Aggregated analysis revealed a significant association between ctDNA detection and worse survival (hazard ratio, 1.40; 95% CI, 1.22-1.58). Subgroup analysis identified significant associations of *TP53* and *ESR1* alterations with worse survival (hazard ratios, 1.58 [95% CI, 1.34-1.81] and 1.28 [95% CI, 0.96-1.60], respectively), while *PIK3CA* alterations were not associated with survival outcomes. Stratifying by detection method, ctDNA detection through next-generation sequencing and digital polymerase chain reaction was associated with worse survival (hazard ratios, 1.48 [95% CI, 1.22-1.74] and 1.28 [95% CI, 1.05-1.50], respectively).

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, detection of specific genomic alterations in ctDNA was associated with worse overall, progression-free, and disease-free survival, suggesting its potential as a prognostic biomarker in MBC. These results may help guide the design of future studies to determine the actionability of ctDNA findings.

Key Points

Question What is the association between detection of specific alterations in circulating tumor DNA (ctDNA) and survival in patients with metastatic breast cancer?

Findings In this systematic review and meta-analysis reporting data from 4264 patients in 37 studies, detection of ctDNA was associated with worse overall, progression-free, and disease-free survival in patients with metastatic breast cancer. This association remained significant irrespective of differences in study design, including ctDNA detection method and type of blood collection tubes.

Meaning These findings suggest the potential of ctDNA detection as a prognostic biomarker in patients with metastatic breast cancer and may help guide the design of future clinical studies.

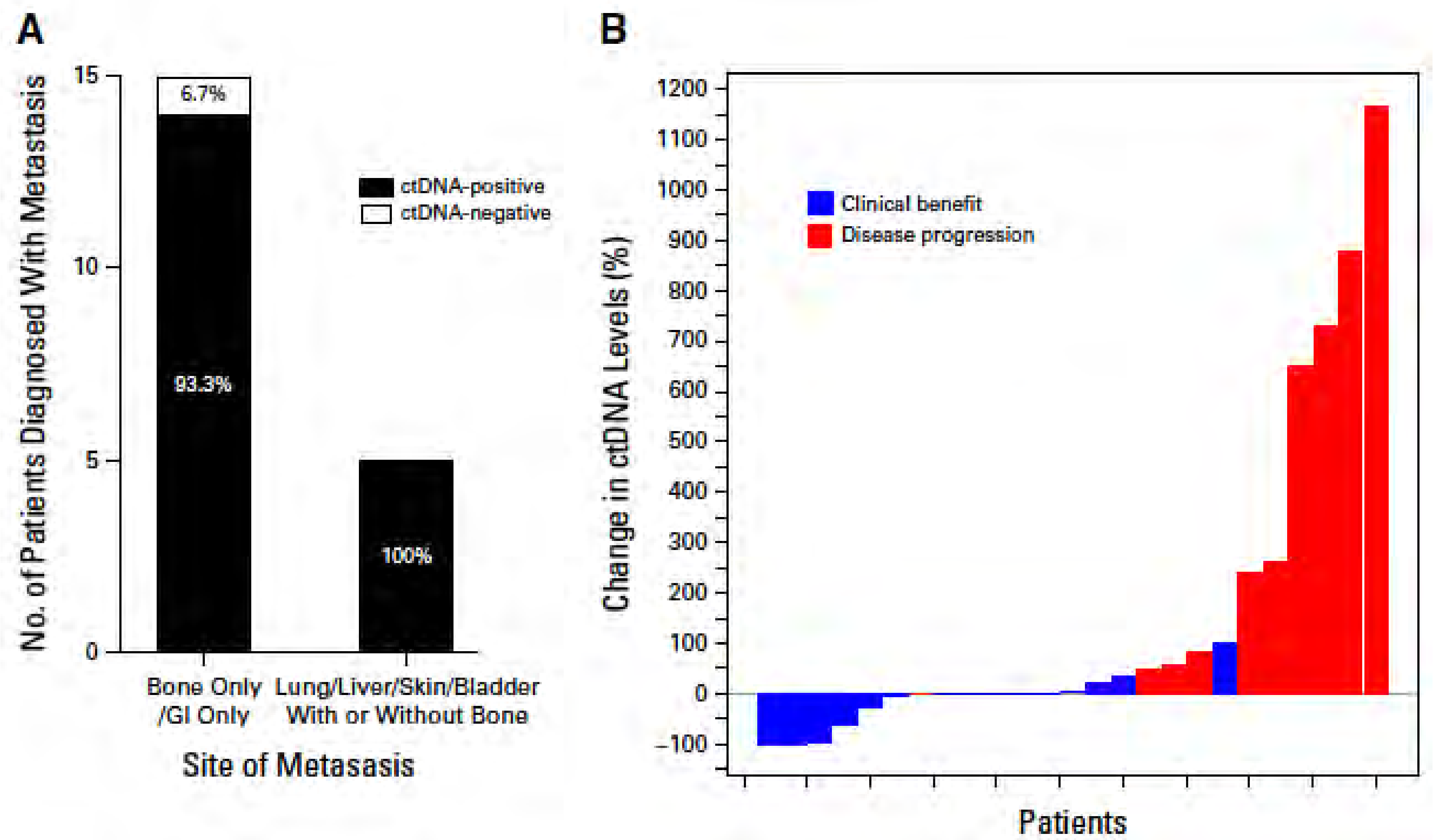
+ Supplemental content

Author affiliations and article information are listed at the end of this article.

JAMA Network Open. 2024;7(9):e2431722. doi:10.1001/jamanetworkopen.2024.31722

ctDNA response monitoring in mILC

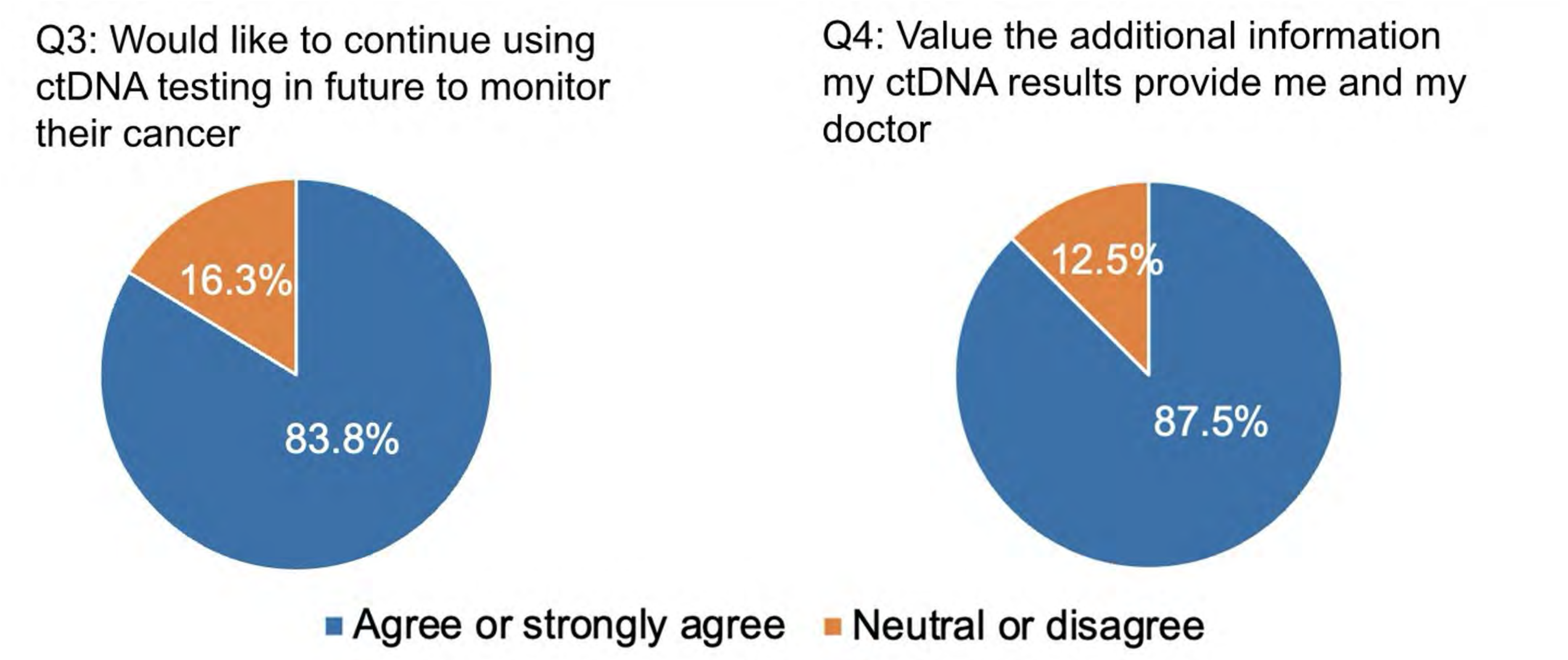
Retrospective study of 66 patients mILC with serial ctDNA collections (Signatera) show promise for ctDNA-based response monitoring



Foldi J et al, JCO Precis Oncol 9:e2400577

Does ctDNA testing increase anxiety?

I-SURV Study – Impact of ctDNA surveillance on QoL



Q3: Would like to continue using ctDNA testing in future to monitor their cancer

Q4: Value the additional information my ctDNA results provide me and my doctor

Cheng C. et al., SABCS 2025 PD5-05

Should we offer MRD testing?

- Individualize testing instead of universal testing
- Have an honest and balanced discussion about the clinical utility
  - "This test gives us excellent prognostic information, but MRD-guided treatment intensification is not yet standard of care"

Implication of a positive test

- Higher risk for recurrence
- Reflex imaging should be done for every positive test
- Closer surveillance
- Consideration for clinical trials if available
- Treatment outside of clinical trial? (consider changing ET backbone, adding CDK4/6i etc)

Implication of a negative result

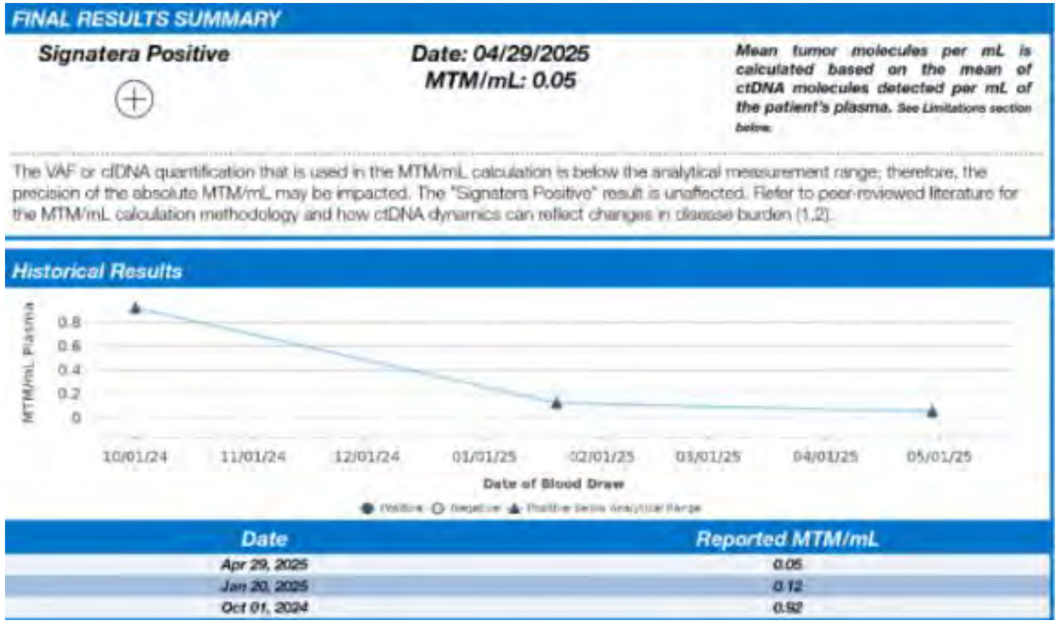
- Patients may need help understanding that ctDNA-negative does not equal cure and that a negative ctDNA does not negate the need for adjuvant therapy
- False-negative results are still a problem
- There is a need for longitudinal monitoring (serial negative increase NPV)

Case 1 – B.F.

- 67 years old female
  - (6/2020) Diagnosed with Left sided T1c N1 Invasive Lobular Carcinoma G3 ER 98% PR 98% HER2 0 Ki67 66%
  - Staging PET/CT negative for M1 disease
  - Underwent lumpectomy with SLNB = 1.4 cm; 2+/2 LN
  - ODX 19 -> No chemotherapy
  - Adjuvant XRT
  - Adjuvant endocrine therapy with Letrozole

Case 1 – B.F.

- Patient worried about recurrence and want to be aggressive in preventing it
- Signatera ordered (4/2024) that came back positive (0.91)
- Staging PET/CT showed NED
- Started promptly on Abemaciclib (continued Letrozole)



FINAL RESULTS SUMMARY

Signatera Positive

⊕

Date: 04/29/2025
MTM/mL: 0.05

Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma. See Limitations section below.

The VAF or ctDNA quantification that is used in the MTM/mL calculation is below the analytical measurement range; therefore, the precision of the absolute MTM/mL may be impacted. The "Signatera Positive" result is unaffected. Refer to peer-reviewed literature for the MTM/mL calculation methodology and how ctDNA dynamics can reflect changes in disease burden (1,2).

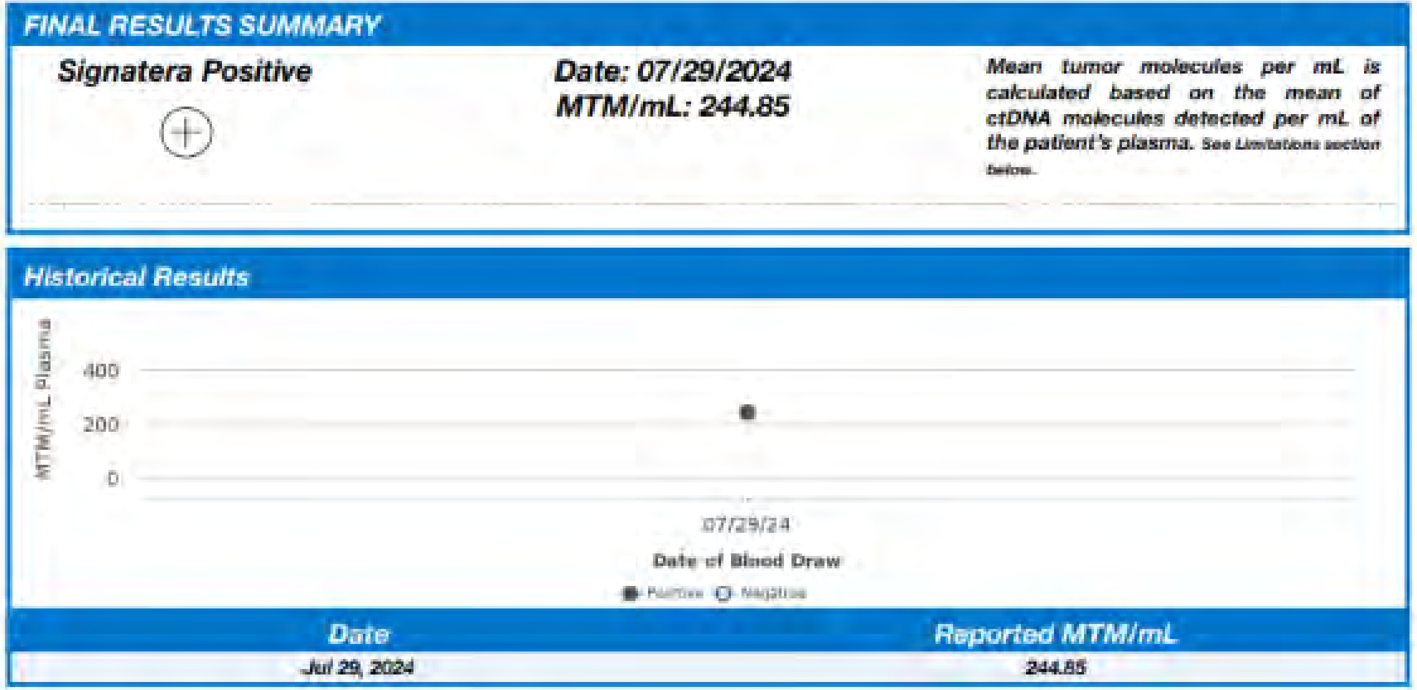
Historical Results

Date	Reported MTM/mL
Apr 29, 2025	0.05
Jan 20, 2025	0.12
Oct 01, 2024	0.92

Case 2 L.L.

65 yo F:

- (2/2021) De novo mILC ER/PR+ HER2-low
- 1L therapy with anastrozole and palbociclib (27 cycles)
- NGS = ESR1 mutation
- 2L Elacestrant and got a baseline Signatera (given cancer poorly visualized on imaging)



FINAL RESULTS SUMMARY

Signatera Positive

⊕

Date: 07/29/2024
MTM/mL: 244.85

Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma. See Limitations section below.

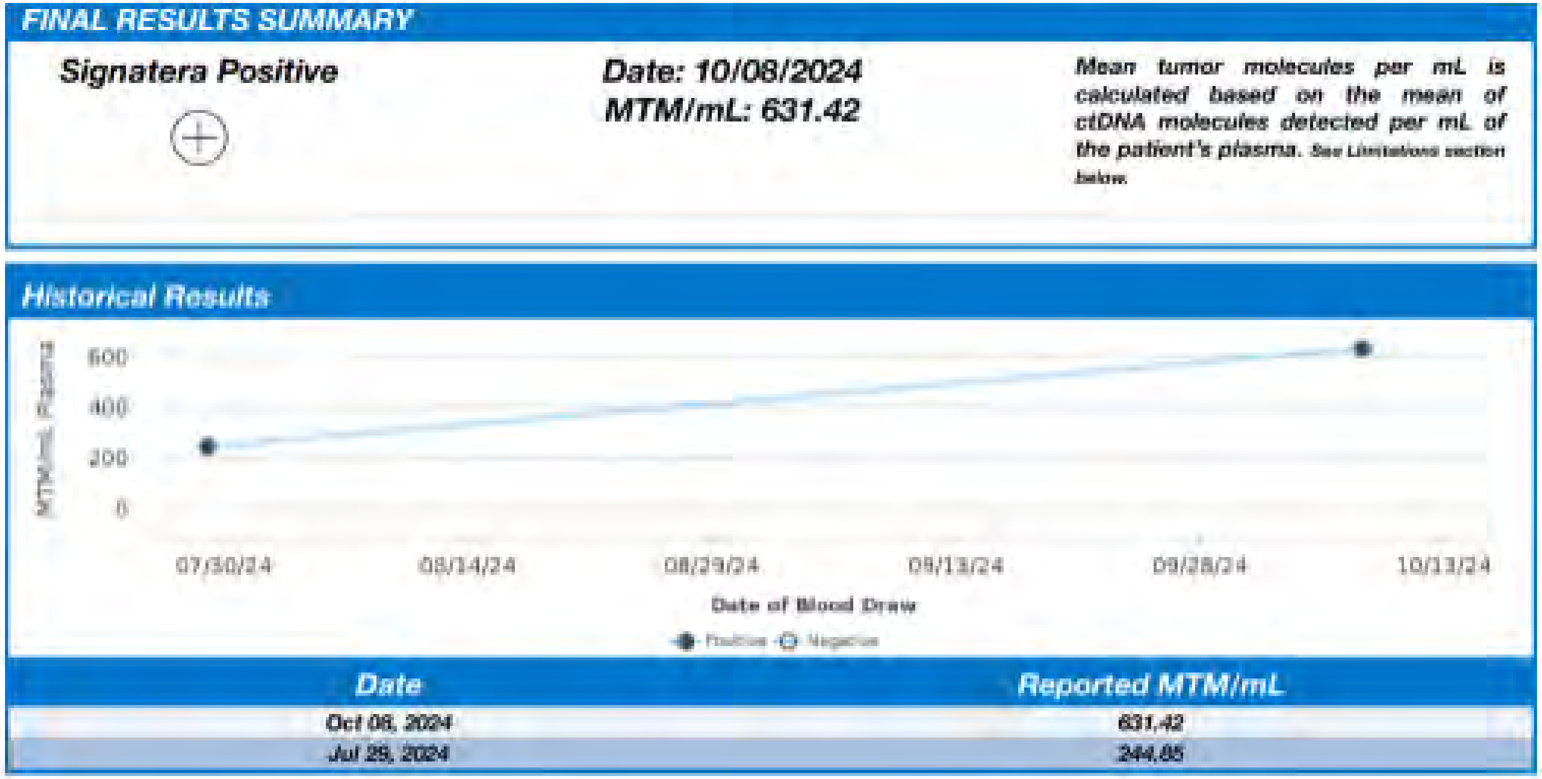
Historical Results

Date	Reported MTM/mL
Jul 29, 2024	244.85

Case 3 L.L.

3 months later, patients feeling worst and developed pancytopenia.

- Bone marrow biopsy showing infiltrative disease to the marrow.



FINAL RESULTS SUMMARY

Signatera Positive

⊕

Date: 10/08/2024
MTM/mL: 631.42

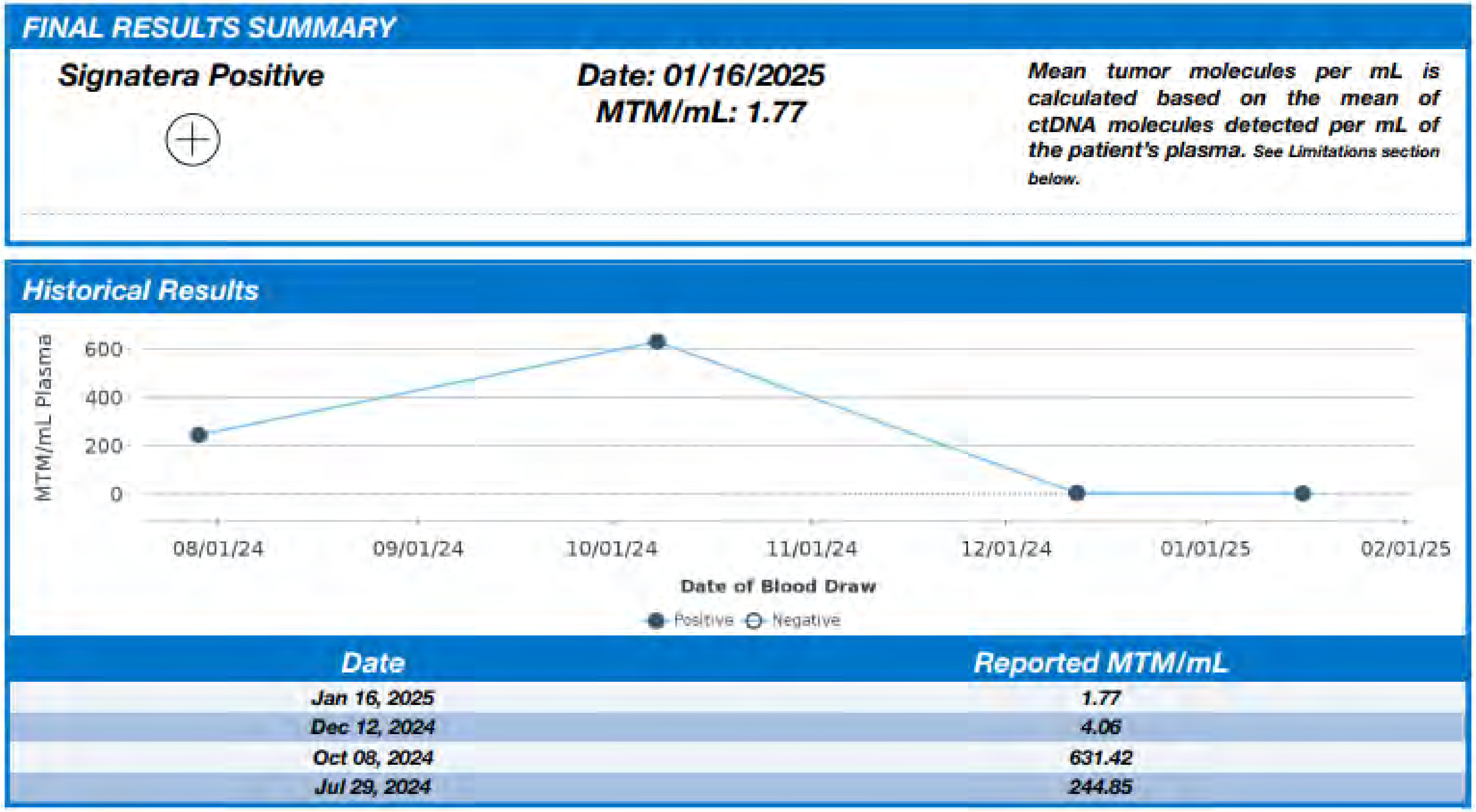
Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma. See Limitations section below.

Historical Results

Date	Reported MTM/mL
Oct 08, 2024	631.42
Jul 25, 2024	244.85

Case 3 L.L.

- Given HER2-low started T-DXd



FINAL RESULTS SUMMARY

Signatera Positive ⊕

Date: 01/16/2025
MTM/mL: 1.77

Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma. See Limitations section below.

Historical Results

Date	Reported MTM/mL
Jan 16, 2025	1.77
Dec 12, 2024	4.06
Oct 08, 2024	631.42
Jul 29, 2024	244.85

Q&A