Early findings from MONITOR-Breast: ctDNA dynamics during neoadjuvant therapy using an ultrasensitive MRD assay

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Disclosure Information

Julia Foldi, MD, PhD

I have the following relevant financial relationships to disclose:

Employee of UPMC Hillman Cancer Center

Honoraria from BioTheranostics Inc. (a Hologic Company), Daiichi Sankyo, AstraZeneca, Genentech, and Gilead

I have no financial relationships to disclose.

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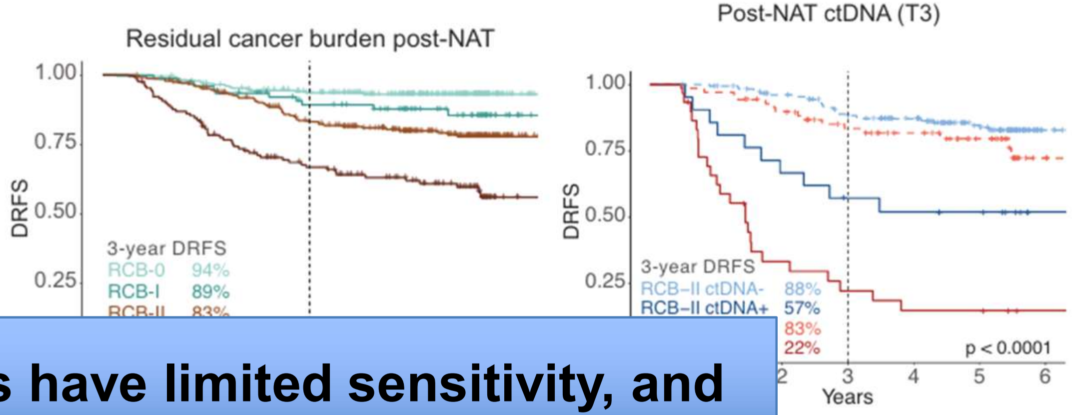
BACKGROUND

- Historically, pathologic response (pCR versus RD and residual cancer burden [RCB]) to neoadjuvant therapy (NAT) has been used for risk stratification, particularly in HER2+ and TN breast cancers
- ctDNA positivity at diagnosis (pre-
  treatment) ar
  surgery) are
  predictors of
  recurrence[1]
- ctDNA clearance/negativity after NAT is associated with favorable long-term outcomes[1,2,3]
- Critically, in patients with RD, ctDNA adds prognostic value independent of pathologic response[1,2,3]

Earlier generation assays have limited sensitivity, and sparse sampling may have missed critical timepoints

I-SPY2



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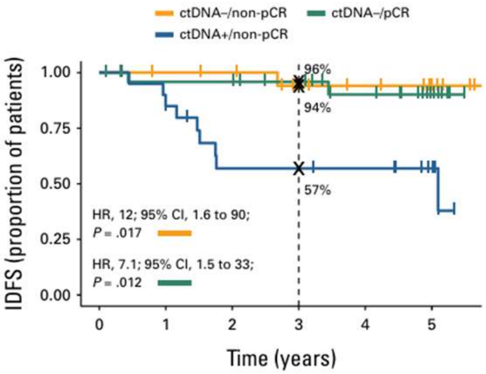
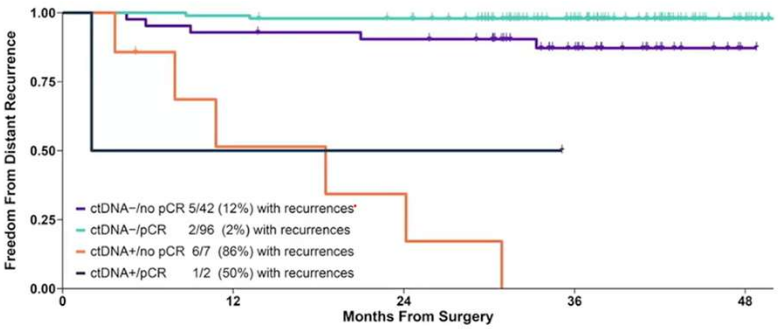
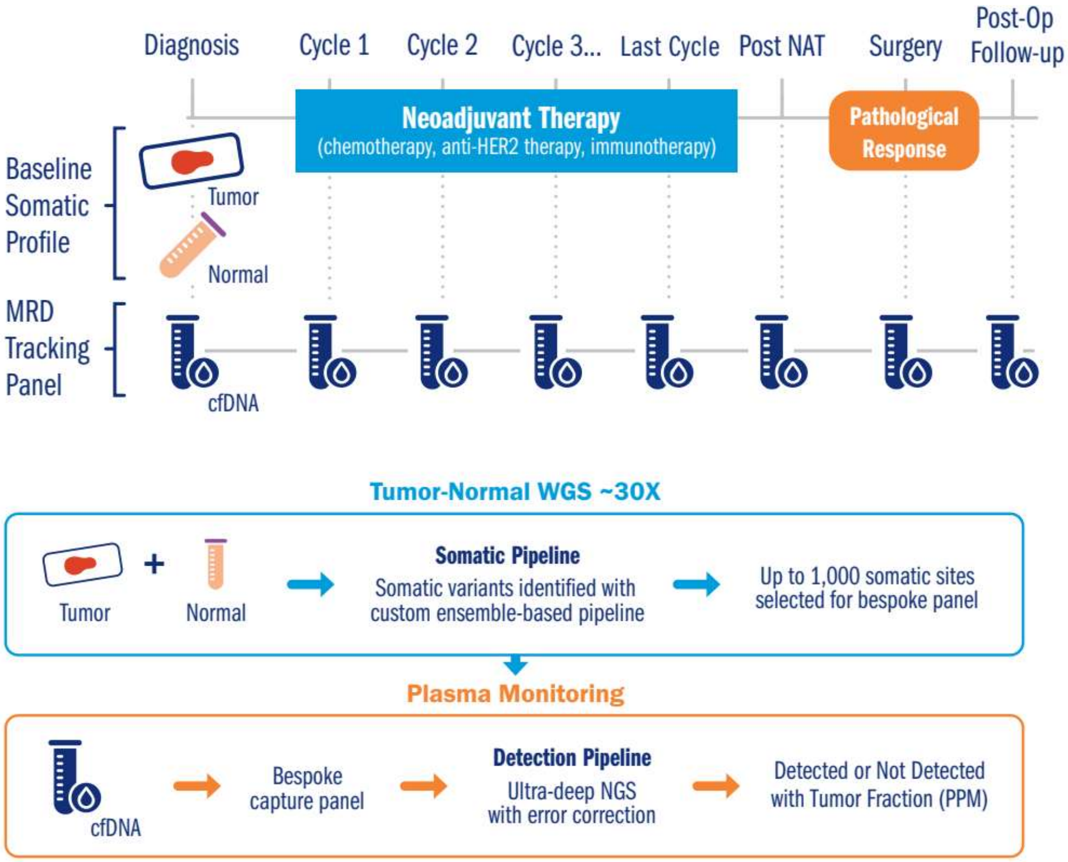


[2]Hunter, N.B., *et al. J Clin Oncol*, JCO-25-02934.



[3]Balic, M., *et al. SABCS 2025*

MONITOR-Breast Study (Neoadjuvant Cohort)



Diagnosis | Cycle 1 | Cycle 2 | Cycle 3... | Last Cycle | Post NAT | Surgery | Post-Op Follow-up

Neoadjuvant Therapy
(chemotherapy, anti-HER2 therapy, immunotherapy)

Pathological Response

Baseline Somatic Profile: Tumor, Normal

MRD Tracking Panel: cfDNA

Tumor-Normal WGS ~30X

Tumor + Normal → **Somatic Pipeline** Somatic variants identified with custom ensemble-based pipeline → Up to 1,000 somatic sites selected for bespoke panel

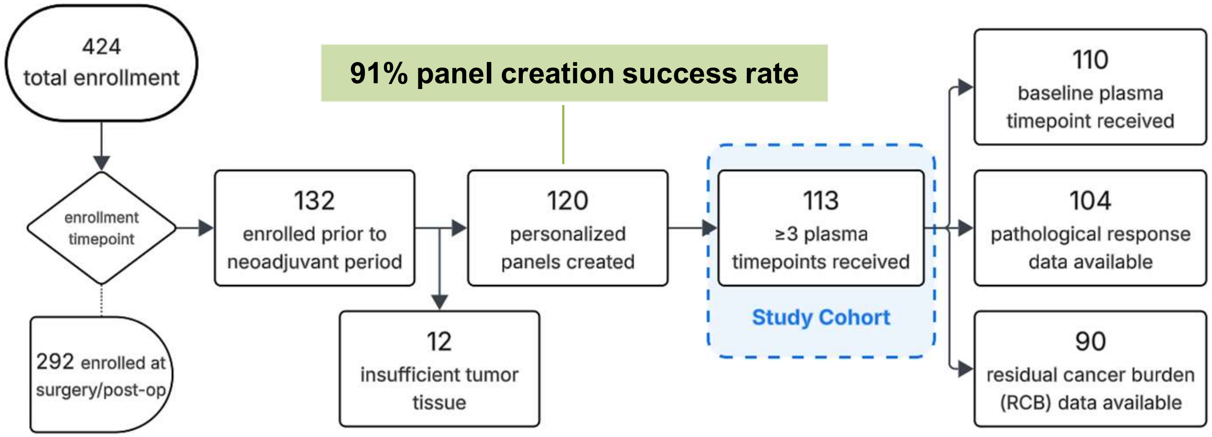
Plasma Monitoring

cfDNA → Bespoke capture panel → **Detection Pipeline** Ultra-deep NGS with error correction → Detected or Not Detected with Tumor Fraction (PPM)

- **Aim:** To prospectively evaluate the association between ctDNA dynamics, measured by an ultrasensitive WGS-based MRD assay throughout NAT, and pathologic response across breast cancer subtypes.

- **Population:** All subtypes, Stages I–III, real-world treatment regimens
- **Ultrasensitive WGS-based assay:** Up to 1,000 individualized variants per patient; detects ctDNA <100 PPM
- **Dense sampling:** Diagnosis, every treatment cycle, post-NAT, surgery, and post-op

Enrollment and Patient Characteristics


424 total enrollment

enrollment timepoint

292 enrolled at surgery/post-op

132 enrolled prior to neoadjuvant period

91% panel creation success rate

120 personalized panels created

12 insufficient tumor tissue

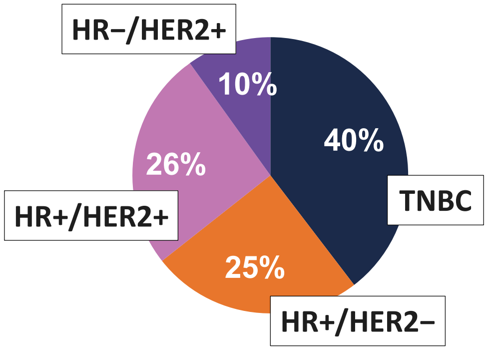
113 ≥3 plasma timepoints received

Study Cohort

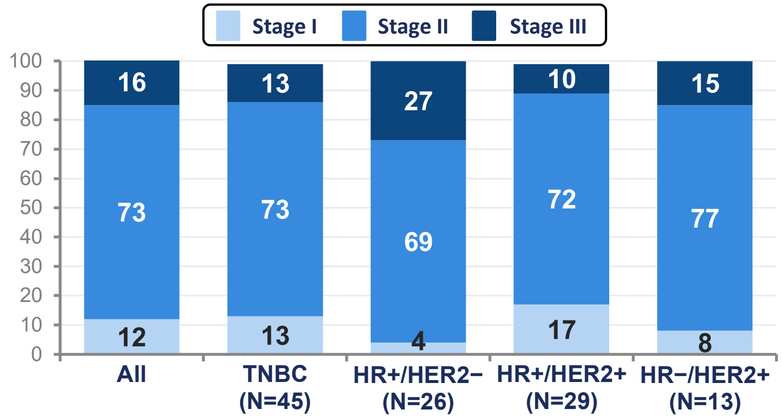
110 baseline plasma timepoint received

104 pathological response data available

90 residual cancer burden (RCB) data available

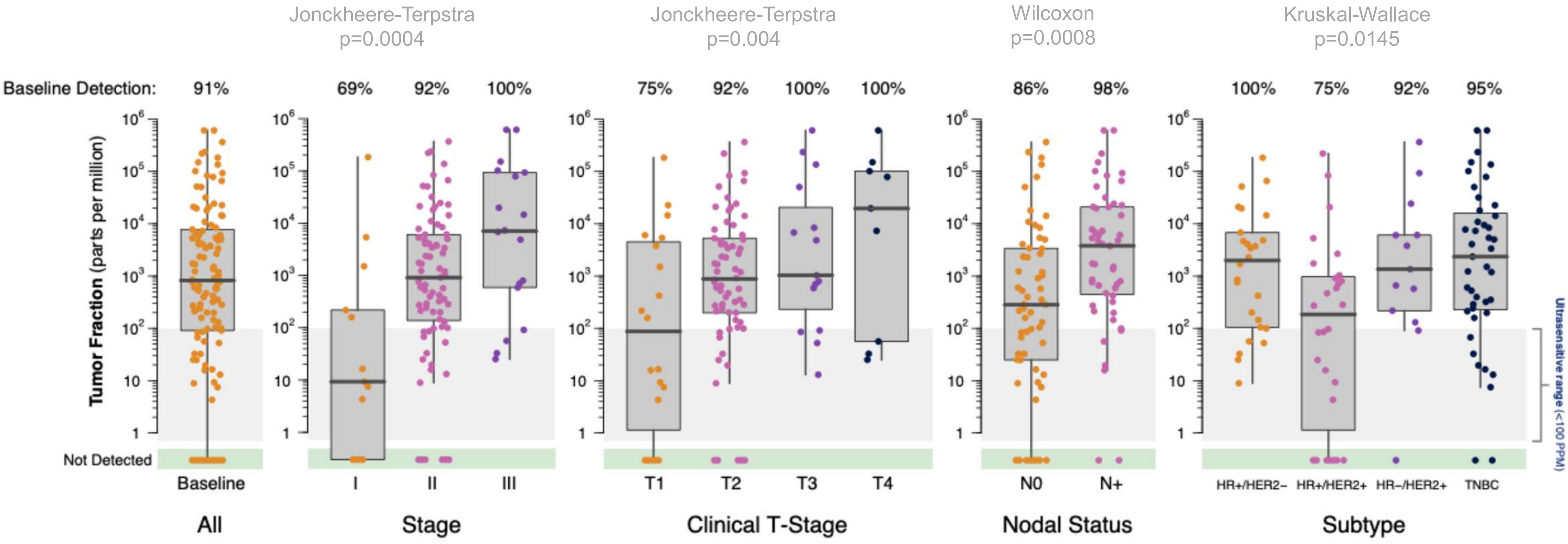


N = 113



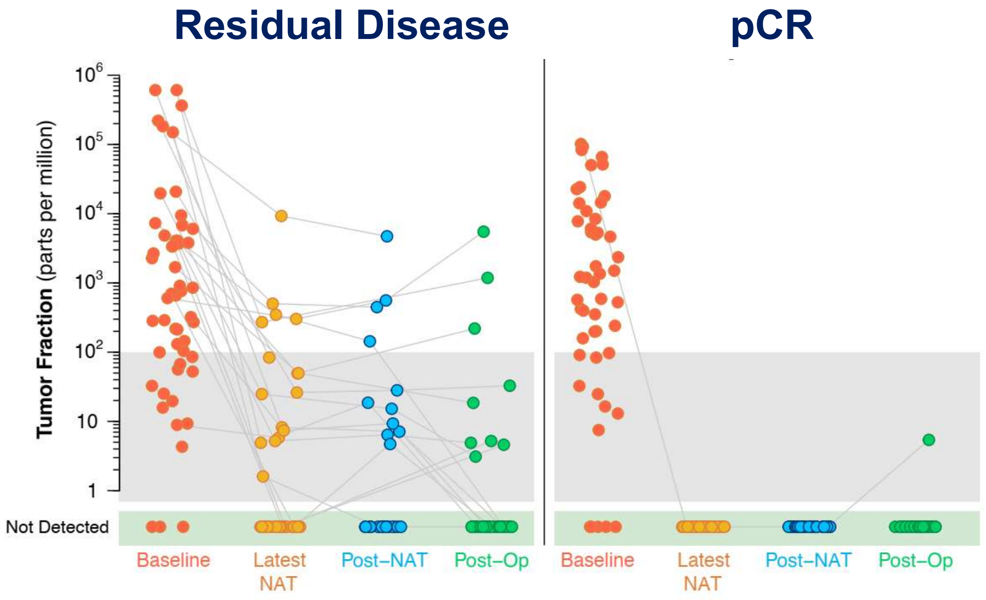
- **Patients:**
  - N=113, female, median age 56
  - All Stages I-III, all subtypes
  - Histology (93% IDC)
  - 95% Single primary disease
  - Nodal status: 53% N0, 45% N+
- **Samples:**
  - 844 total plasma samples analyzed
  - Median 9 timepoints per patient
- **Treatments:**
  - Chemotherapy (100%)
  - Immunotherapy (42%)
  - HER2-targeted therapy (36%)

Baseline ctDNA Detection

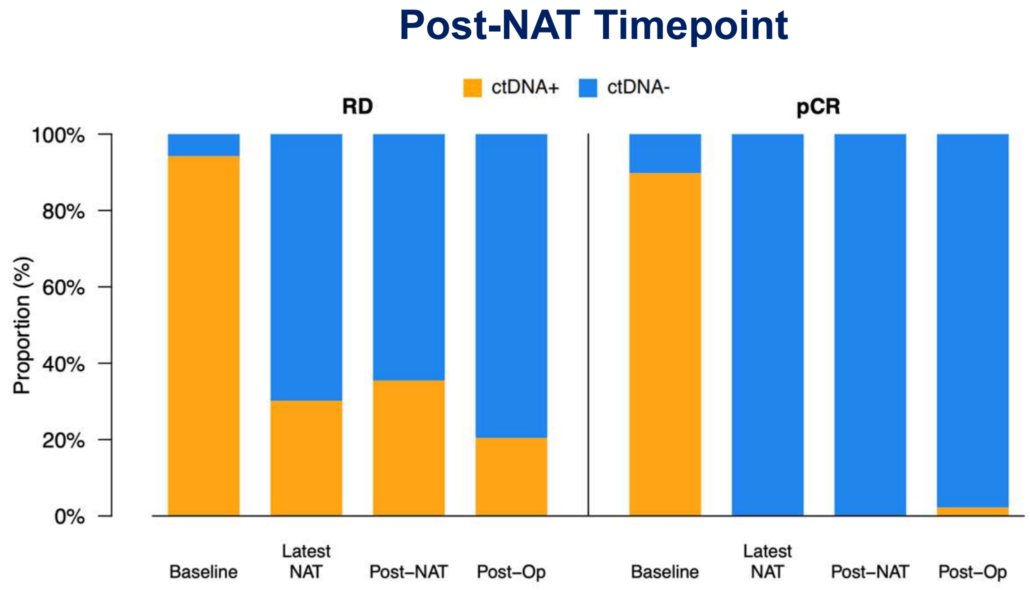


- 20% of samples were detected in the ultrasensitive range (<100 PPM)
- 91% overall detection and increases with disease burden: Stage I: 69% → II: 92% → III: 100%

ctDNA and Pathological Response



Residual Disease **pCR**

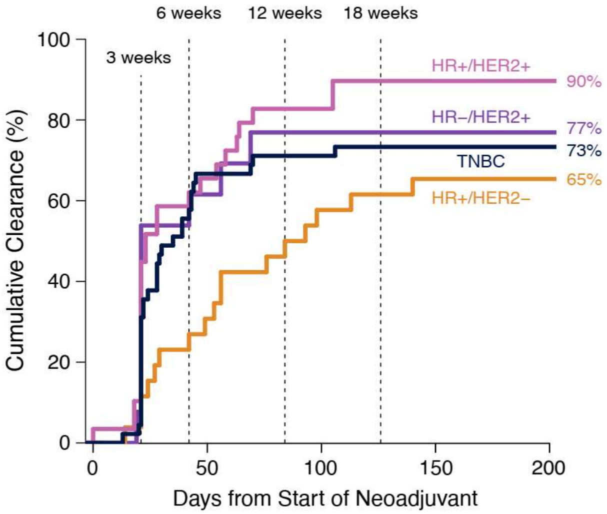


Post-NAT Timepoint

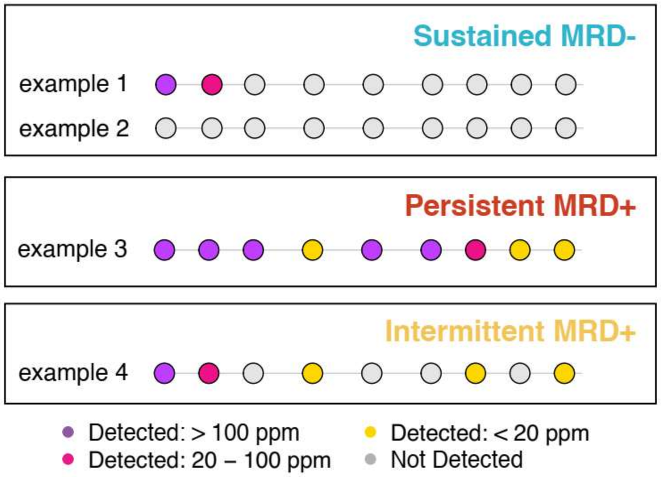
- All 47 pCR patients were ctDNA- at post-NAT (**100% specificity for pCR)**
- 32% of RD patients were ctDNA+ post-NAT vs. 14–20% with earlier assays
- **67%** of samples were in the ultrasensitive range (<100 PPM)
- Post-NAT ctDNA+ → **43x higher odds** of ctDNA+ after surgery (p=6.1×10^{-6})

ctDNA Dynamics yield Distinct Patterns

Subtype Differences



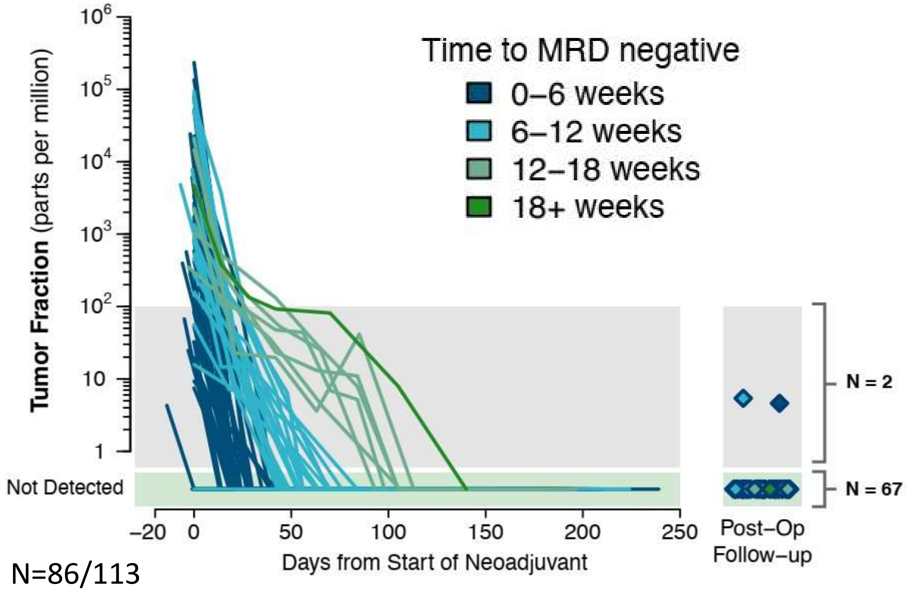
Clearance Patterns



N (%)	PCR Rate
76% (86/113)	63%
12% (13/113)	0%
12% (14/113)	7%

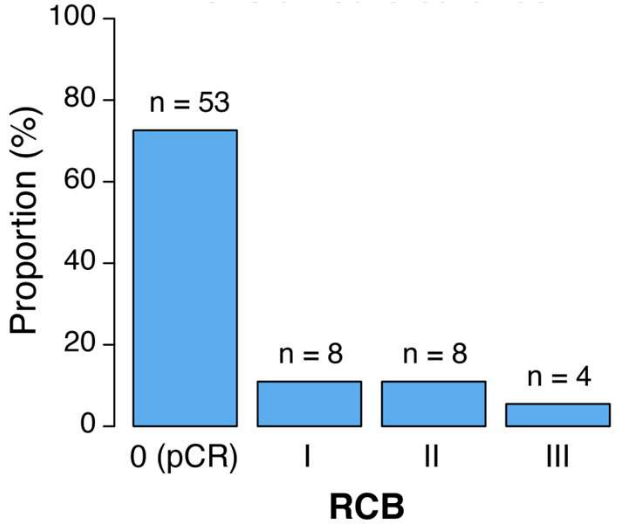
- Clearance timing by subtype:
  - TNBC: 90% cleared within **45 days**
  - HR+/HER2−: required **16 weeks** to capture 90% of clearers
- **Timing of clearance alone did not predict pCR but sustained negativity did**

Sustained ctDNA Clearance



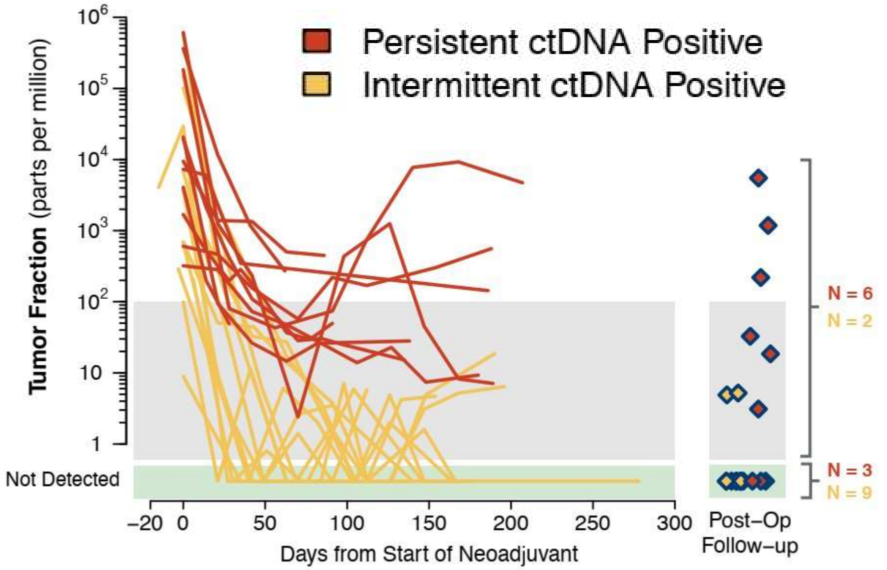
N=86/113

Post-Op ctDNA+
<3% (2/69)

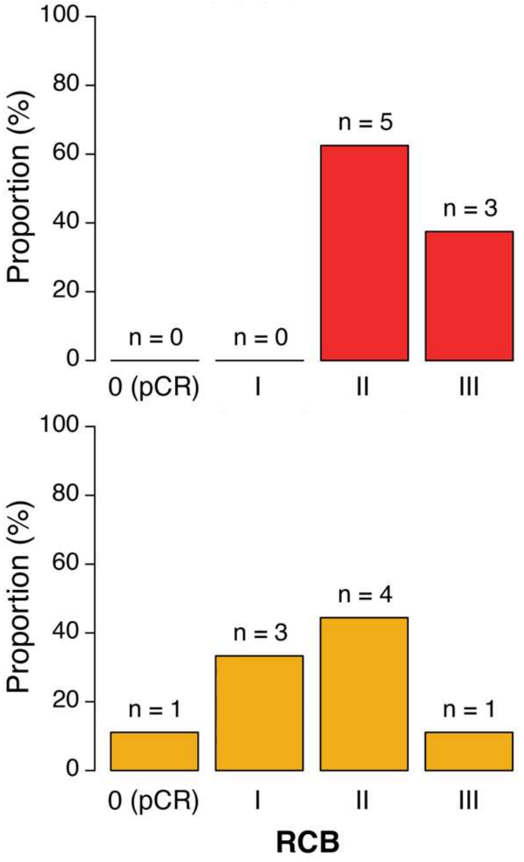


- 76% of all patients achieved sustained clearance
- Sustained clearers continued NAT for **avg 119 days** (IQR 92–155) with undetectable ctDNA
- **63%** achieved pCR vs. **4%** in persistent/intermittent groups ($p=1.74\times10^{-7}$)

Persistent and Intermittent ctDNA Positive



Post-Op ctDNA+
67% (6/9)
18% (2/11)



- **Persistently Positive:**
  - 12/12 (100%) had residual disease — all RCB-II or RCB-III
  - 6/9 remained ctDNA+ at first post-operative visit
- **Intermittently Positive:**
  - 13/14 (93%) had residual disease at surgery
  - Re-emergence at <20 PPM only visible with frequent sampling
  - **Additional sampling identifies more patients at risk for residual disease**

Summary

- Frequent, ultrasensitive MRD testing reveals response patterns not visible with sparse sampling
- Patterns and opportunities for treatment optimization:
  - **76%** sustained clearance, often early in NAT → opportunity for **de-escalation**
  - **24%** persistent or intermittent positivity and 96% had RD → opportunity for **escalation**
  - Frequent testing identified **64% more patients at risk of RD** vs. post-NAT testing alone
- Post-NAT ctDNA was significantly associated with pathological response and post-operative ctDNA positivity
- Long-term survival outcomes are not yet available. MONITOR-Breast follow-up is ongoing
- Future MRD-guided prospective trials should determine whether acting on these response patterns have utility to meaningfully change outcomes beyond standard approaches

Acknowledgements

- The authors thank the patients who participated in this trial, their families, and their clinicians for their participation in the study

Participating Sites

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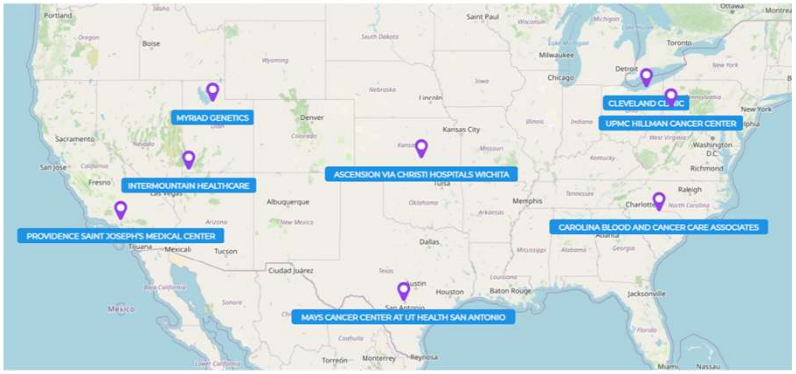
- Intermountain Healthcare, Saint George, UT
- Mays Cancer Center at UT Health San Antonio, San Antonio, TX
- Cleveland Clinic, Department of Hematology and Oncology, Cleveland, OH
- Ascension Via Christi Hospitals Wichita, Inc., Wichita, KS
- Carolina Blood and Cancer Care Associates, Lancaster, SC
- National Cancer Center Hospital East, Kashiwa, Japan
- Providence Saint Joseph’s Medical Center, Burbank, CA



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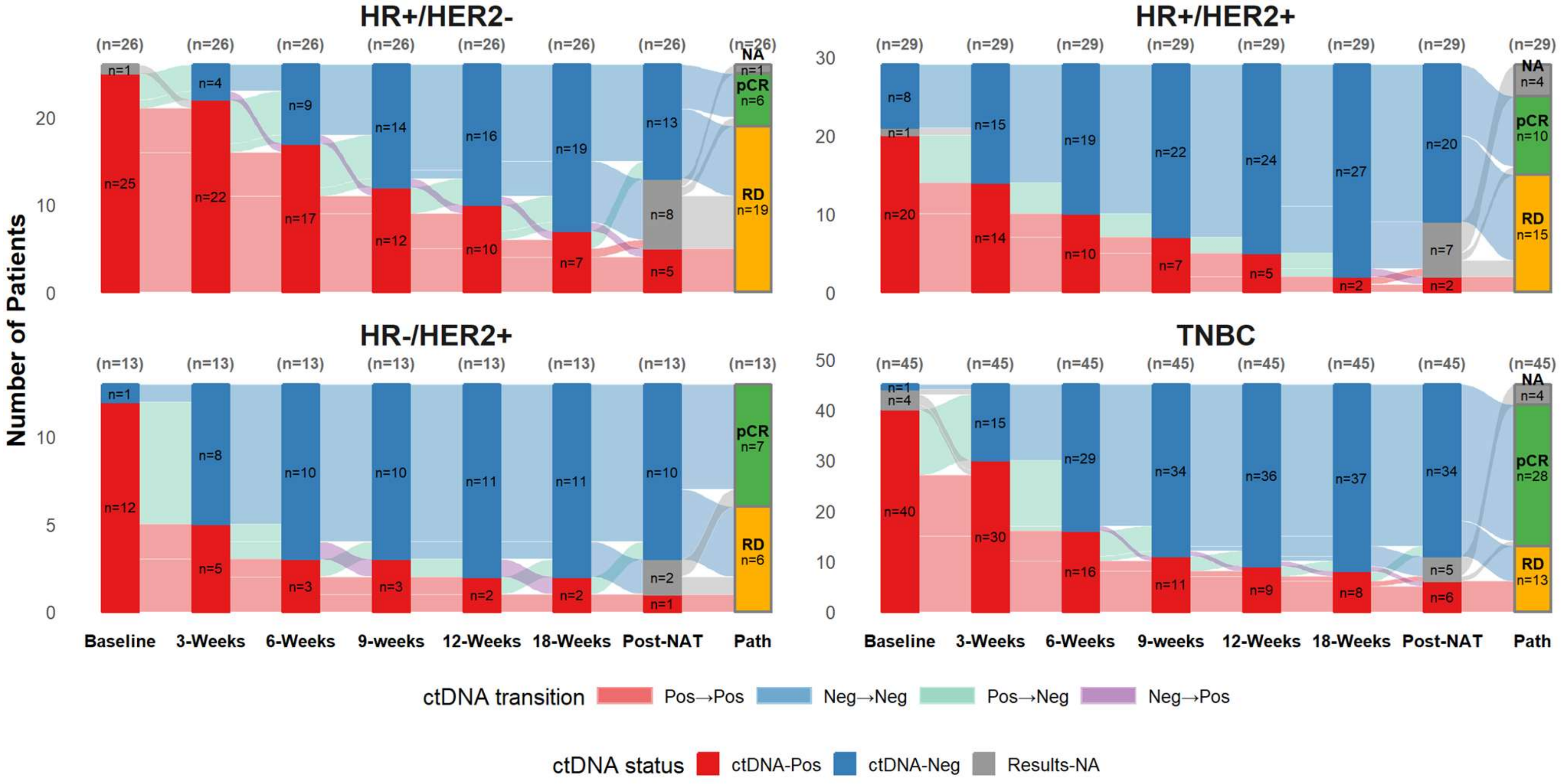
Supplementary Slides

Treatment Heterogeneity

Chemotherapy regimen	N
Platinum–Taxane → AC	35
Platinum–Taxane	33
AC → Taxane-only	17
Taxane-only	6
Taxane-only → AC	6
Platinum–Taxane → Taxane-only → AC	5
Platinum–Taxane → Taxane-only	3
AC → Platinum–Taxane	2
CT	2
Platinum–Taxane → C	1
Platinum–Taxane → CT	1
Platinum–Taxane → TA → AC	1
AC → Platinum–Taxane → Taxane-only	1

⟶: Transition to next regimen
AC: cyclophosphamide + doxorubicin
Taxane: paclitaxel or docetaxel
Platinum-taxane: carboplatin + paclitaxel or docetaxel
C: carboplatin
CT: cyclophosphamide + paclitaxel or docetaxel
TA: paclitaxel or docetaxel + doxorubicin

Characteristic	n	Baseline detection rate, %, 95% CI (n)	Baseline tumor fraction (ppm), median (range)[1]	Difference in tumor fraction
Clinical Stage (n=100)				
I	29	72, 54-85 (21)	218 (4–183,391)	Jonckheere-Terpstra $p=8.0\times10^{-7}$
II	58	97, 88-99 (56)	1,291 (13–364,920)	
III	23	100, 86-100 (23)	14,525 (25–610,111)	
T stage (n=100)				
T1	20	75, 53-89 (15)	422 (4–183,391)	Jonckheere-Terpstra p=0.004
T2	66	92, 84-97 (61)	1,227 (9–364,920)	
T3	15	100, 80-100 (15)	1,034 (13–609,925)	
T4	9	100, 70-100 (9)	19,671 (25–610,111)	
Nodal status (n=100)				
N0 (53)	59	86, 76-93 (51)	525 (4-364,920)	Wilcoxon p=0.0008
N+ (43)	49	98, 89-100 (48)	4367 (16-610,111)	
NX (2)	2	50, 10-91 (1)	660 (660-660)	
Subtype (n=100)				
TNBC	43	95, 85-99 (41)	3,357 (8–610,111)	Kruskal-Wallace p=0.0145
HR+/ HER2+	28	75, 57-87 (21)	589 (4–220,304)	
HR-/ HER2+	13	92, 67-99 (12)	2,576 (91–364,920)	
HR+/ HER2-	26	100, 87-100 (26)	1,983 (9–183,391)	



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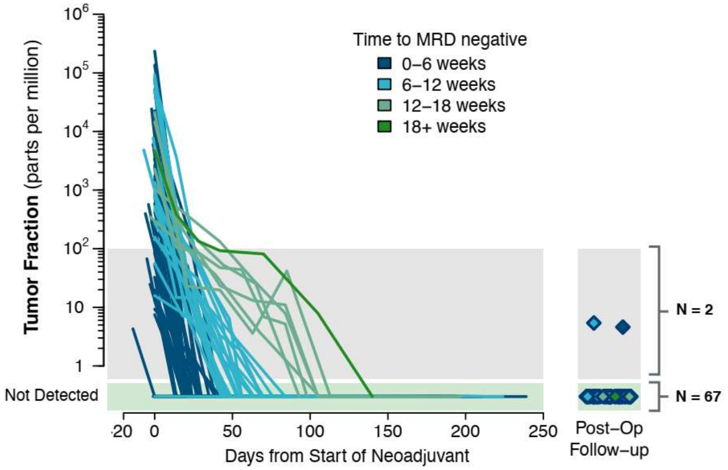
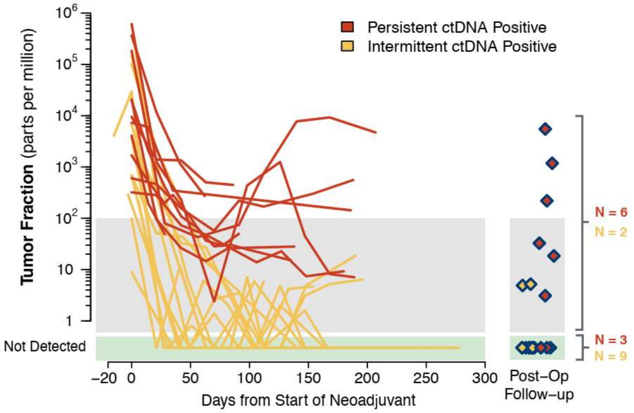
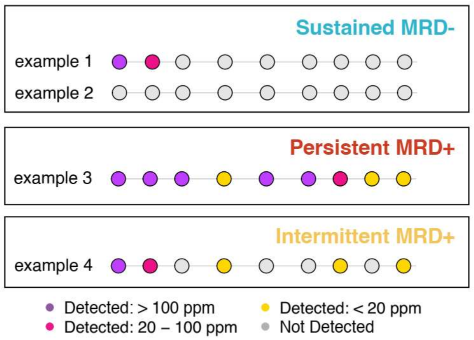
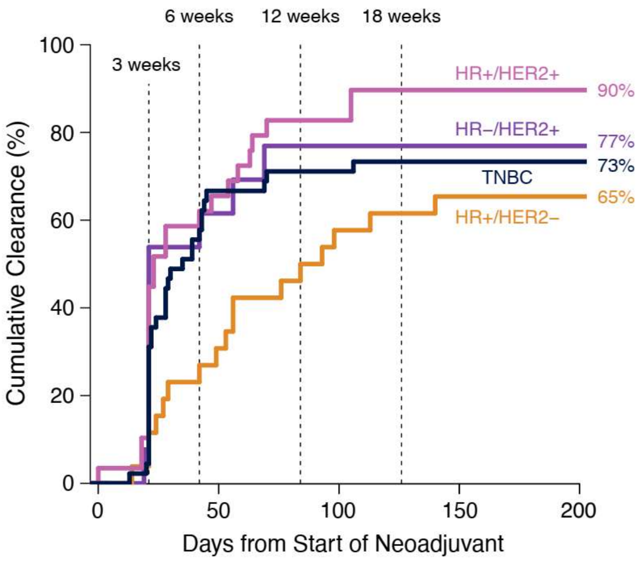
ctDNA Dynamics yields Distinct Patterns

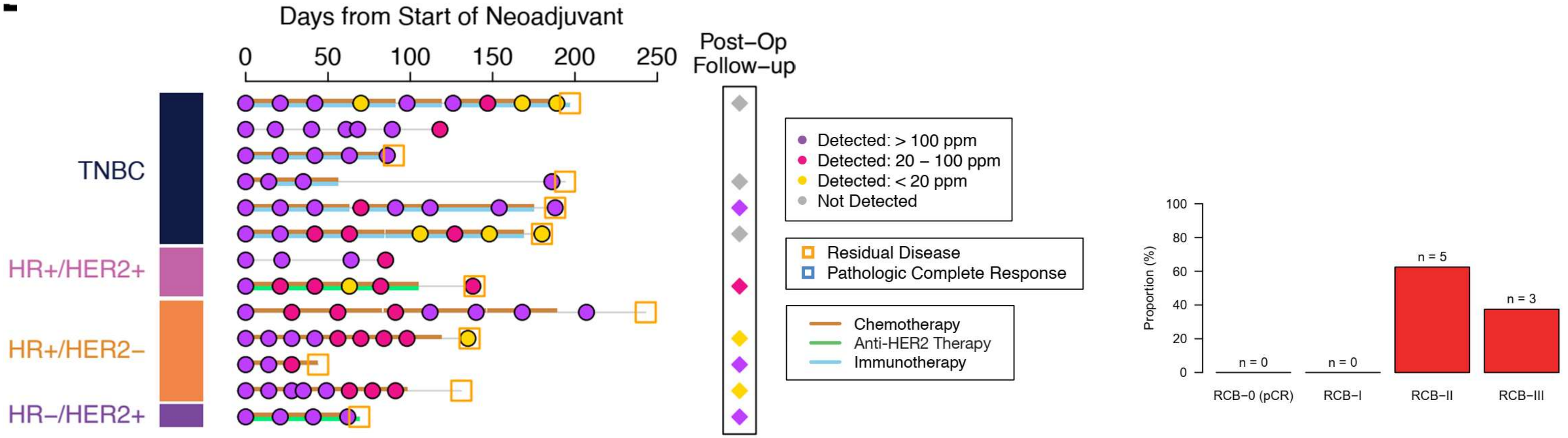








Persistently Positive



- 12/12 (100%) had residual disease
- All had RCB-II or RCB-III
- 6/9 were ctDNA+ at first post-operative visit
- **Frequent monitoring identifies non-responders before surgery**

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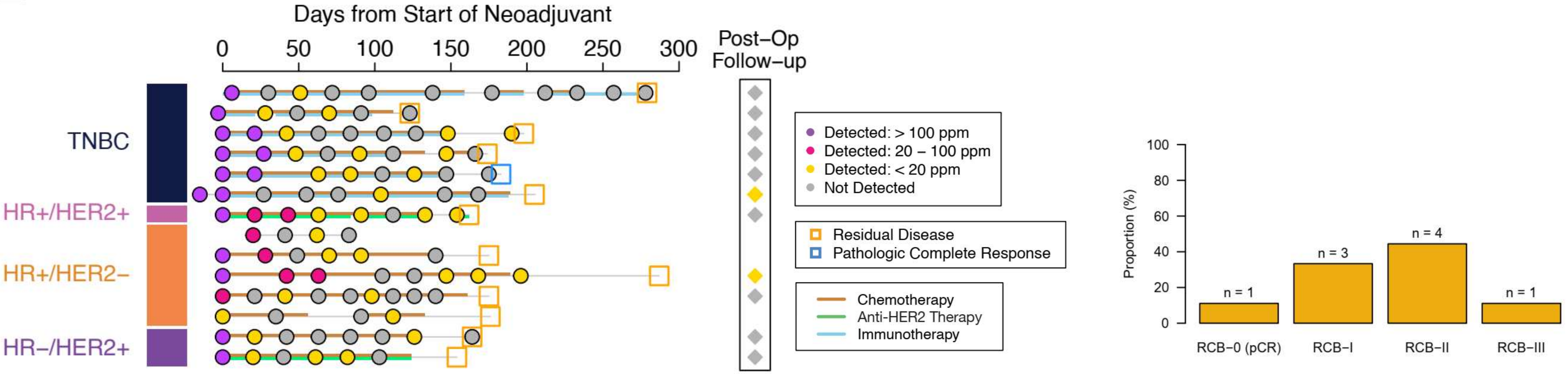
Intermittently Positive



- •13/14 (93%) had residual disease
- •Re-emergence at <20 PPM was only visible with frequent sampling
- **•A single negative result mid-NAT was not sufficient to confirm clearance**

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Pathological Response by Subtype