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Circulating tumor DNA (ctDNA) in HER2+ Early Breast Cancer: A translational analysis of PHERGain

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Disclosure Information

Antonio Llombart-Cussac

I have the following relevant financial relationships to disclose:

Consultant for: Lilly, Roche, Pfizer, Novartis

Speaker's Bureau for: Lilly, Astrazeneca, Merck Sharp & Dohme, Pfizer and Novartis

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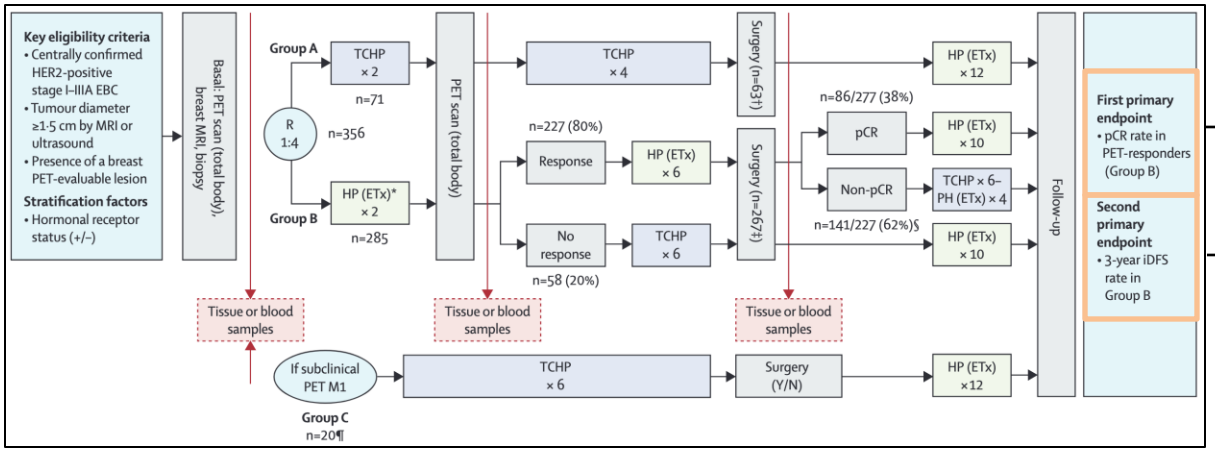
- and -

My additional financial relationship disclosures are:

Patents: HER2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/0338368 A1.

Introduction

- **HER2-directed therapies** have improved the outcome of patients with HER2[+] early breast cancer (EBC), leading to de-escalation approaches[1].
- The **PHERGain study:** PET-guided, pathological complete response (pCR)-adapted strategy to omit chemotherapy (CT) in patients with HER2[+] EBC undergoing neoadjuvant dual HER2 blockade with trastuzumab and pertuzumab (HP)[2,3].



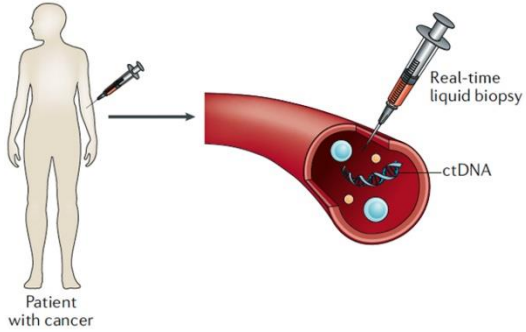
Omission of CT in **37.9% of patients**[1].

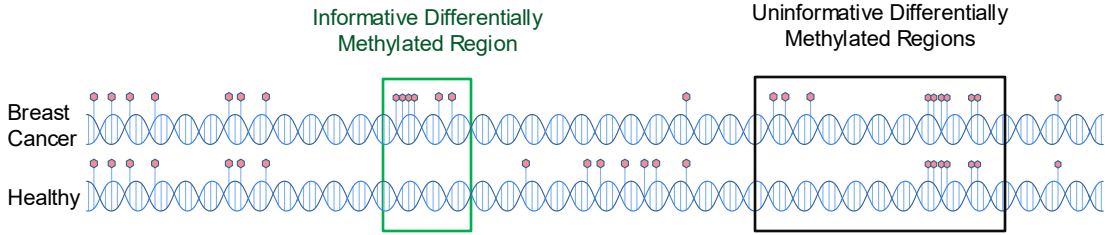
3-year invasive-disease free survival **(iDFS) rate of 94.8%**[2].

1. Lin NU et al., *J Clin Oncol.* 2015
2. Perez-García JM *et al.*, *Lancet Oncol.* 2021
3. Perez-García JM et al., *Lancet.* 2024

Introduction

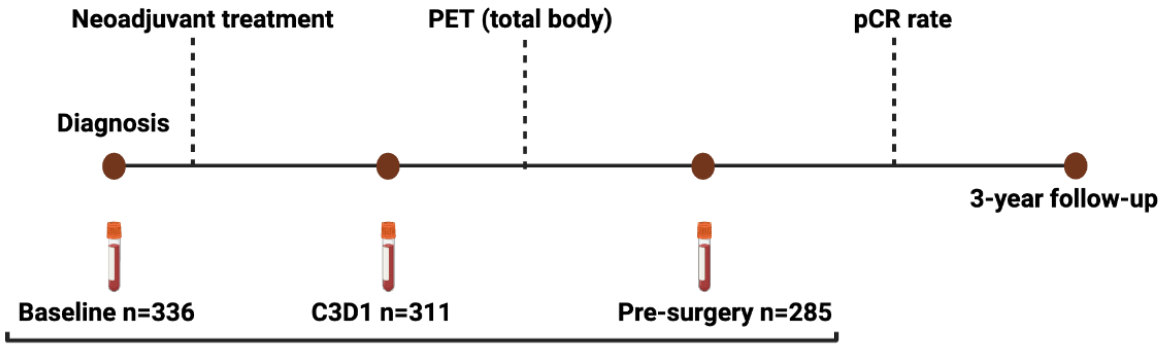
- **ctDNA** is an emerging tool for risk stratification and real-time monitoring in EBC[1].
- For minimal residual disease detection, ctDNA may **improve the prediction** of pCR and long-term outcomes [2,3].
- Best-characterized epigenomic marker in tumors is **DNA methylation**[4].
- ***Guardant Reveal™*** is a tissue-free epigenomic test that evaluates >20,000 methylation regions to maximize sensitivity[5,6].
- Differentially methylated regions are utilized to identify the **presence of ctDNA**[5].



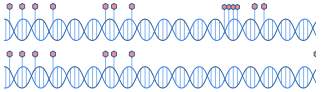


1. Lin NU et al., *J Clin Oncol*. 2015. 2. Nakamura Y et al., *Nat Med*. 2025. 3. Ademuyiwa FO et al., *Clin Cancer Res*. 2025.
4. Esteller M. *N Engl J Med*. 2008. 5. Pantel K, Alix-Panabières C. *Nat Rev Clin Oncol*. 2019. 6. Quinn et al., *AACR* 2025.

PHERGuide: methodology and objectives



ctDNA isolation and analysis

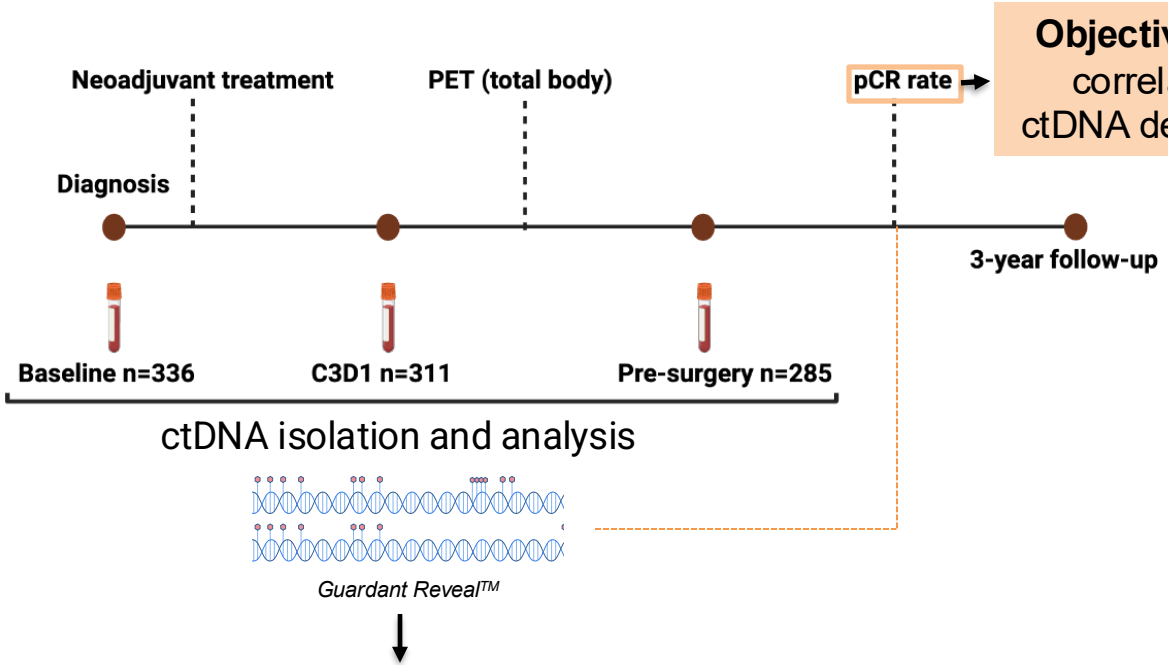


Guardant Reveal™

Tissue-free epigenomic assay:

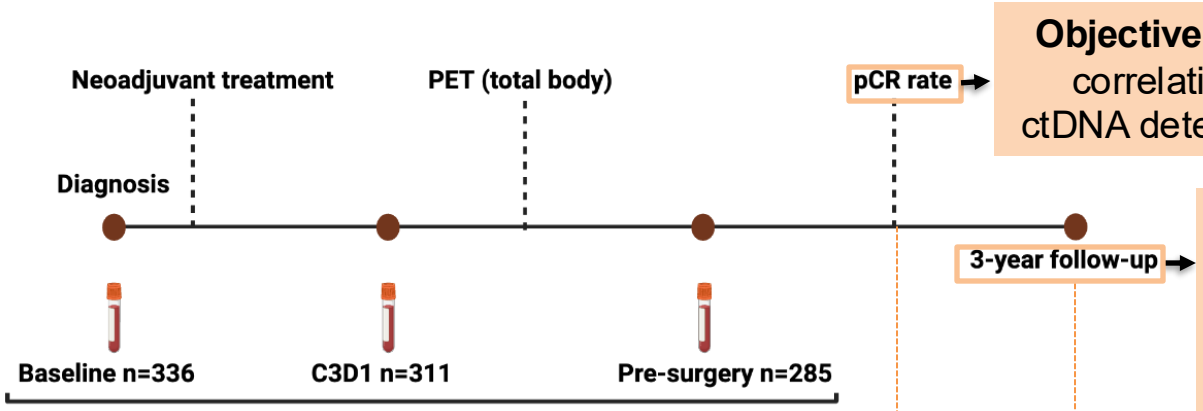
ctDNA detection+estimated tumor fraction

PHERGuide: methodology and objectives



Objective 1: assess the correlation between ctDNA detection and pCR

PHERGuide: methodology and objectives



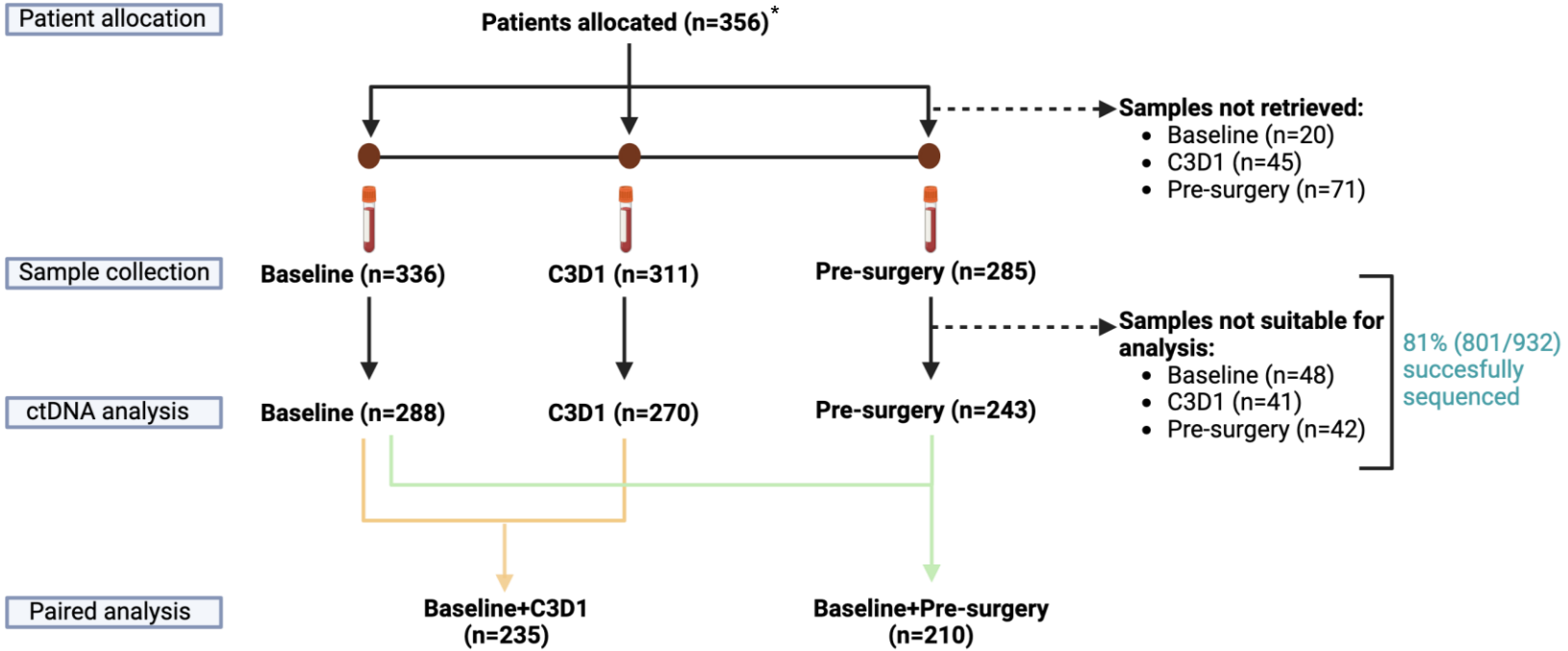
Objective 1: assess the correlation between ctDNA detection and pCR

Objective 2: evaluate the association between ctDNA detection and/or clearance with patient outcomes

Tissue-free epigenomic assay:

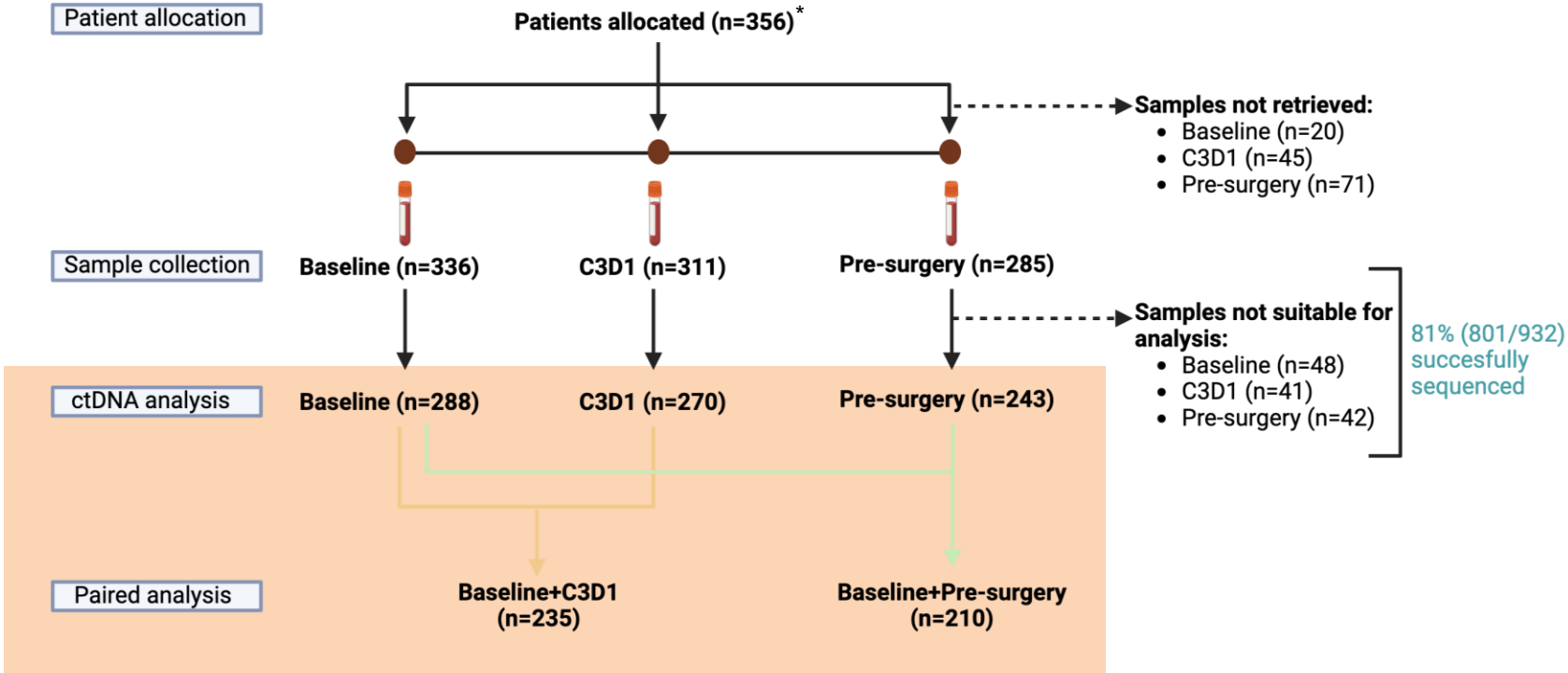
ctDNA detection+estimated tumor fraction

PHERGuide: eligible samples



*including group A and group B

PHERGuide: eligible samples



*including group A and group B

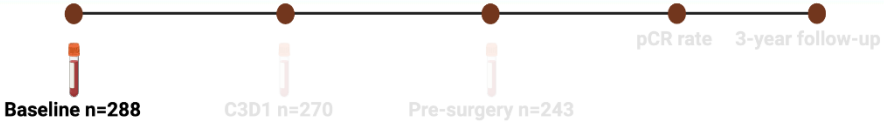
Patient and tumor characteristics

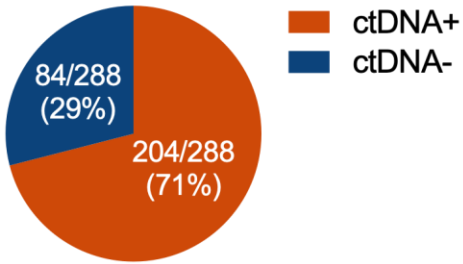
	PHERGain (n=356)*	PHERGuide (n=288)
Age median (min-max)	50.0 (20.0-82.0)	51.0 (20.0-77.0)
Postmenopausal		
No	183 (51.4%)	151 (52.4%)
Yes	173 (48.6%)	137 (47.6%)
ER status		
Negative	128 (36.0%)	109 (37.8%)
Positive	228 (64.0%)	179 (62.2%)
HER2 IHC		
2+ / FISH-positive	77 (21.6%)	61 (21.2%)
3+	279 (78.4%)	227 (78.8%)
TNM Stage		
I	33 (9.3%)	27 (9.4%)
II	269 (75.6%)	217 (75.3%)
III	54 (15.2%)	44 (15.3%)
Nodal status		
N0	184 (51.7%)	149 (51.7%)
N+	172 (48.3%)	139 (48.3%)

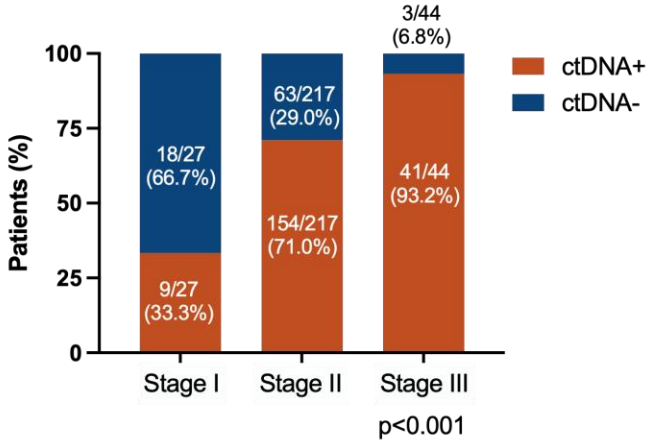
	PHERGain (n=356)*	PHERGuide (n=288)
pCR rate (95% CI)	39.9% (34.8; 45.2)	40.6% (34.9; 46.5)
3-year iDFS rate % (95% CI)	95.6% (93.4-97.8)	94.7% (92.0-97.4)

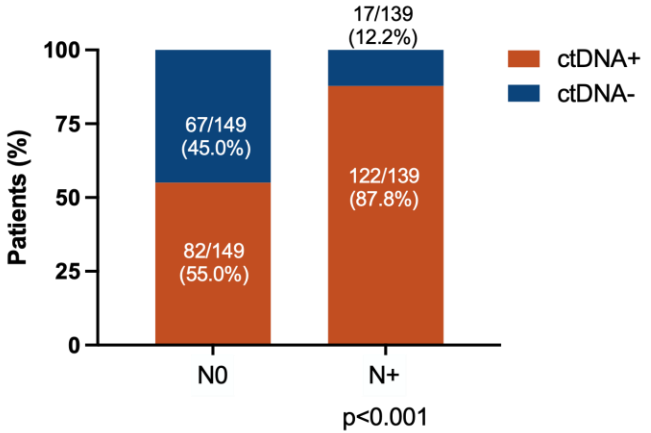
*including group A and group B

ctDNA detection at baseline



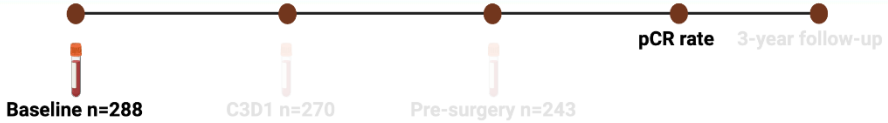


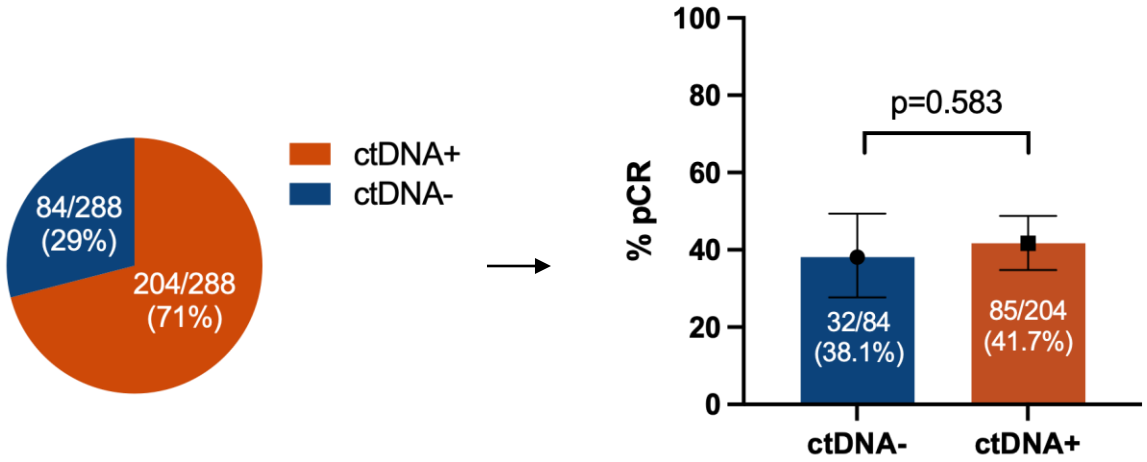




- ctDNA was detected in 204 of 288 (71%) baseline samples.
- Detection rates were significantly correlated with disease stage (p<0.001) and nodal status (p<0.001).

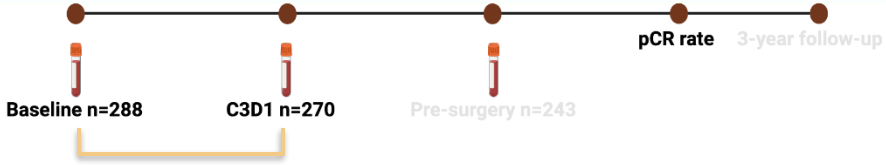
ctDNA detection at baseline and pCR

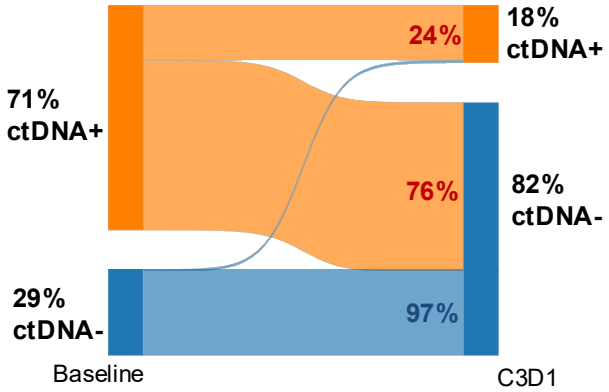


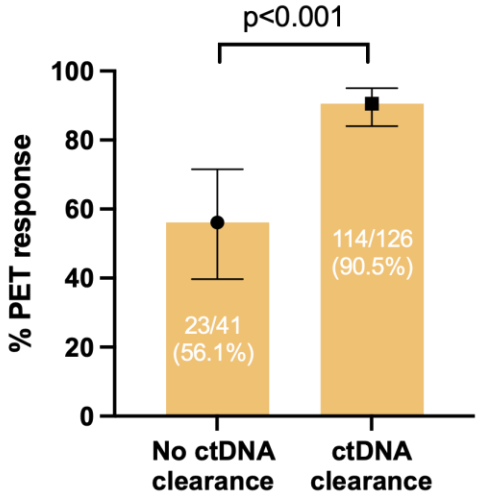


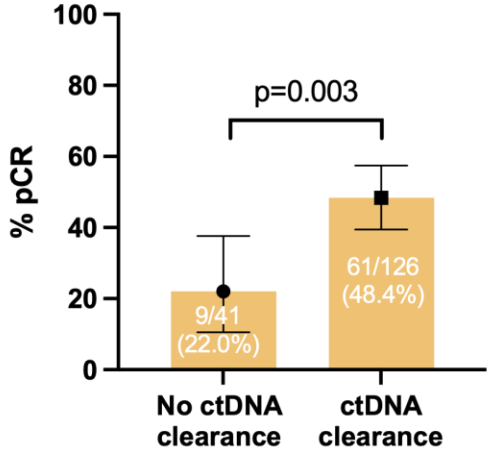
No significant correlation was observed between baseline ctDNA status and pCR (p=0.583).

Early ctDNA dynamics and pCR



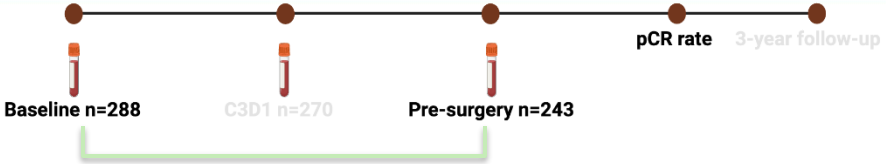


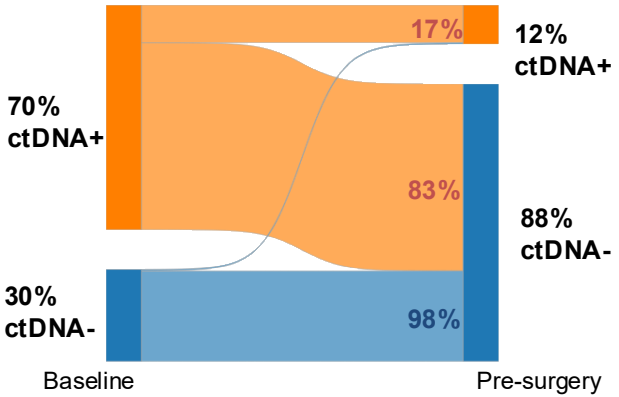


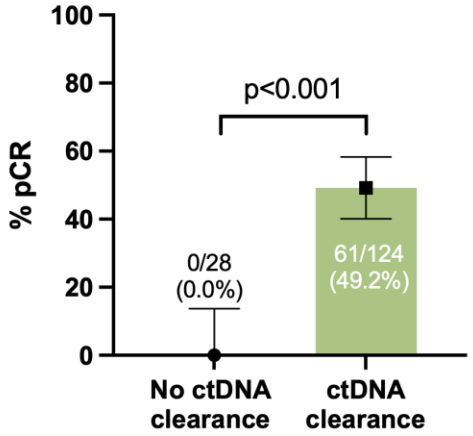


- A 76% relative reduction in ctDNA positivity was achieved after 2 treatment cycles.
- ctDNA clearance after two cycles strongly correlated with PET response (p<0.001) and pCR (p=0.003).

Late ctDNA dynamics and pCR

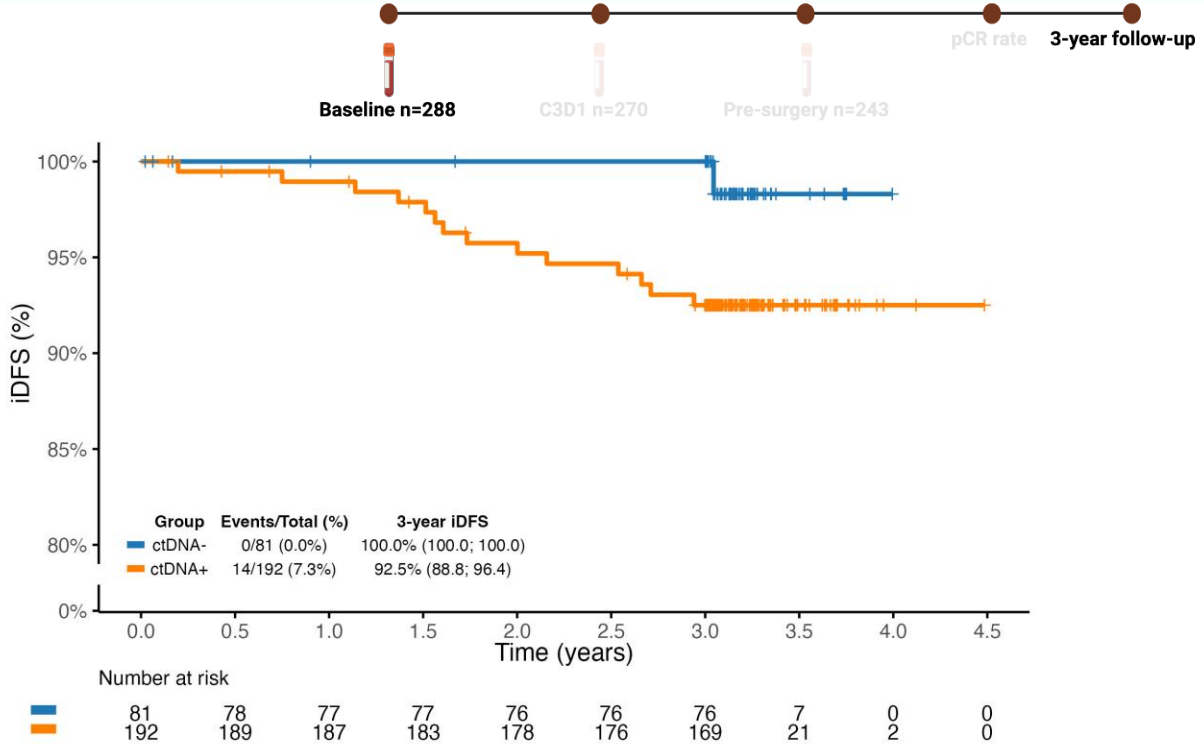






- A 83% relative reduction in ctDNA positivity was achieved prior to surgery.
- ctDNA clearance at the presurgical time point (p<0.001) was significantly associated with achieving a pCR.
- No patient with detectable ctDNA prior to surgery (n=28) achieved a pCR.

Basal ctDNA status and 3-year iDFS rate



Hazard ratio

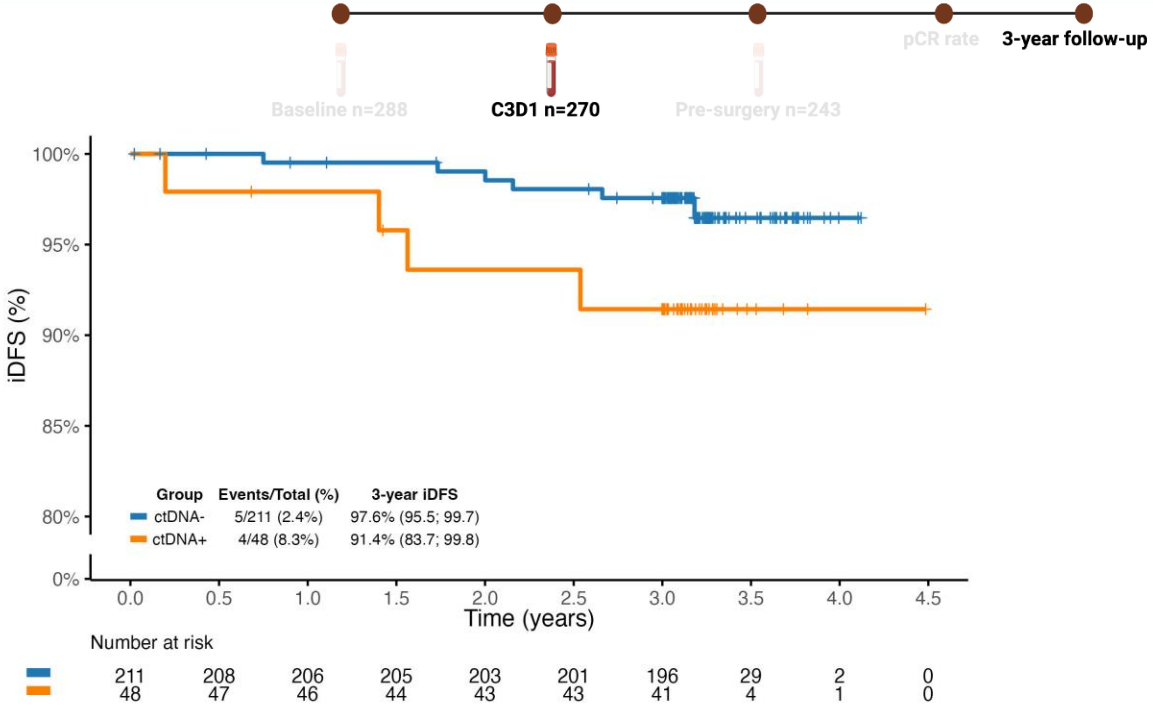
4.1

(95% CI 0.7; 23.5)

p=0.046

ctDNA positivity at baseline was associated with a worse 3-year iDFS.

C3D1 ctDNA status and 3-year iDFS rate



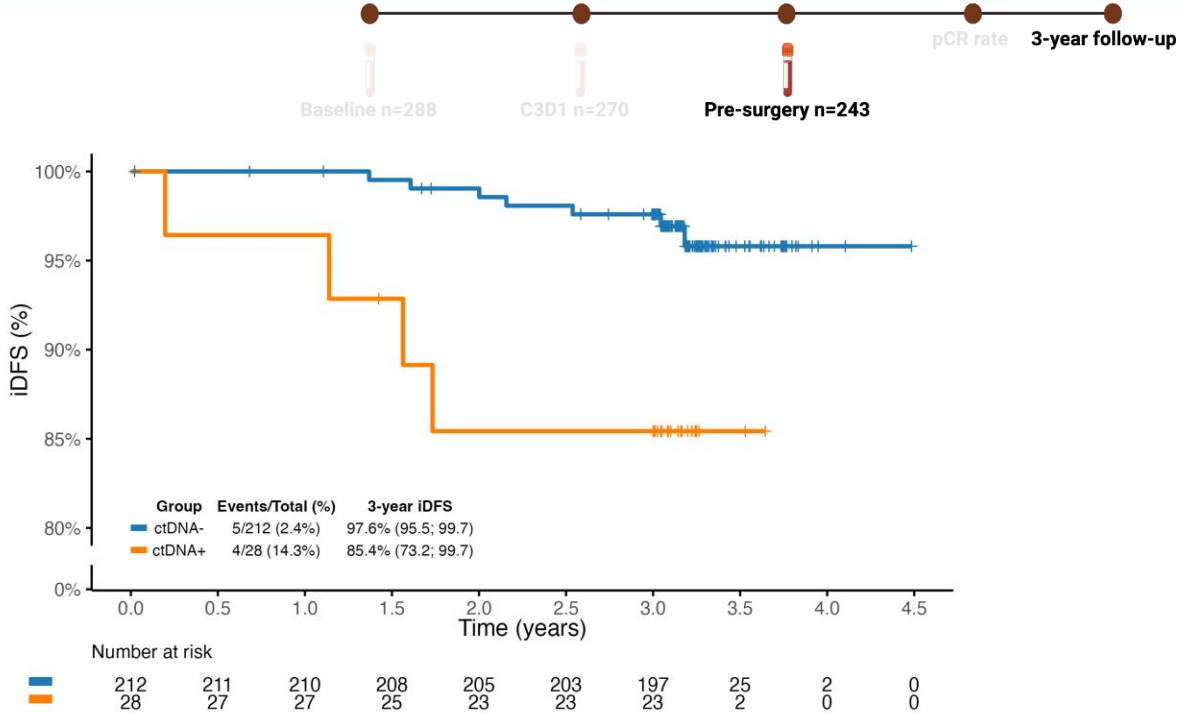
Hazard ratio

3.2

(95% CI 0.9; 11.4)
p=0.072

ctDNA positivity at C3D1 was not significantly associated with a worse 3-year iDFS. However, the design of the study included treatment changes (chemotherapy) for non PET-responders.

Pre-surgery ctDNA status and 3-year iDFS rate



Hazard ratio

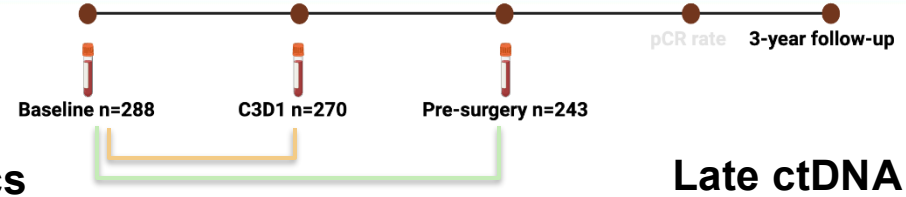
5.1

(95% CI 1.5; 17.3)

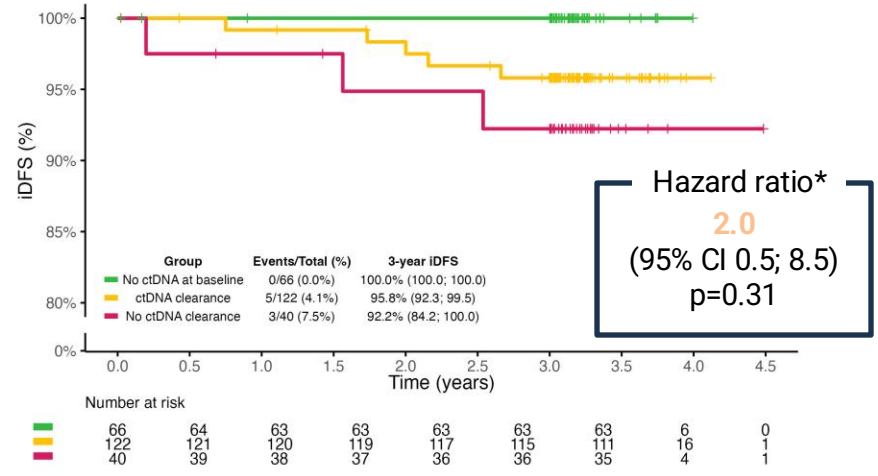
p=0.014

ctDNA positivity at pre-surgery was associated with a worse 3-year iDFS rate.

ctDNA dynamics and 3-year iDFS

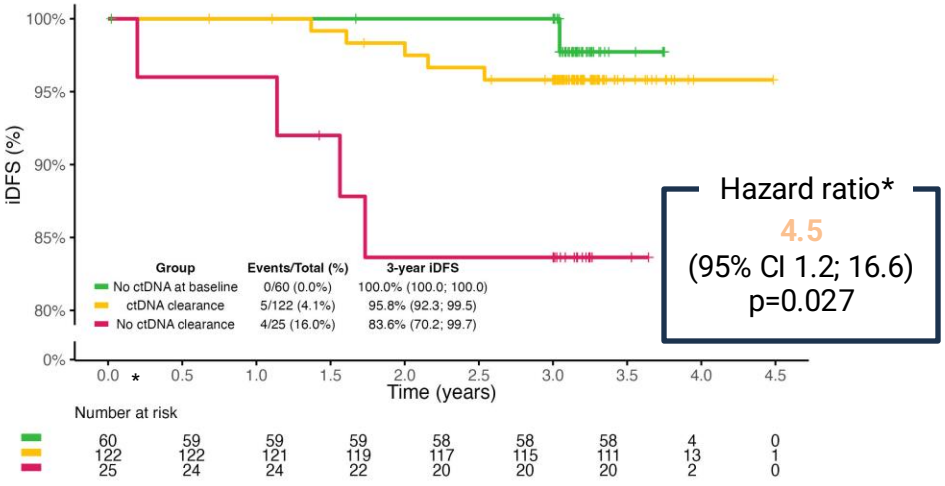


Early ctDNA Dynamics



Hazard ratio*
2.0
(95% CI 0.5; 8.5)
p=0.31

Late ctDNA Dynamics



Hazard ratio*
4.5
(95% CI 1.2; 16.6)
p=0.027

ctDNA clearance at C3D1 and pre-surgery was associated with a lower iDFS event risk.

*Analysis perfomed comparing ctDNA clearance (ref) vs no ctDNA clearance

Conclusions

- In the PHERGain study, **baseline ctDNA presence correlated with clinical stage and nodal involvement** but did not predict pCR in early HER2-positive breast cancer.
- **Early ctDNA clearance (C3D1) was strongly associated with pCR** ($p = 0.003$); notably, all patients who remained ctDNA-positive prior to surgery presented residual infiltrating disease.
- **ctDNA clearance at pre-surgery occurred in 83% of patients** with ctDNA detected at baseline.
- Both **absence of detectable baseline ctDNA and ctDNA clearance** during neoadjuvant therapy **predicted improved iDFS** at 3 years.
- **ctDNA assessment** using Guardant Reveal™ shows **promise for refining tumor staging and informing treatment decisions** in early HER2-positive breast cancer.

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Presentation

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