2026 ESMO BREAST CANCER

Annual Congress

5-year iDFS of the strategy-based, randomized phase II PHERGain trial evaluating chemotherapy de-escalation in HER2+ early breast cancer (EBC) patients

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DECLARATION OF INTERESTS

Consulting/Advisor: *Roche, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Lilly, Merck Sharp&Dohme, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, Expres2ion Biotechnologies, Jazz Pharmaceuticals, Abbvie, BridgeBio, Biontech, Biocon, Circle Pharma, Delcath Systems, Inc., Hexagon Bio, Bliss Biopharmaceutical, Relay Therapeutics*

Honoraria: *Roche, Novartis, Eisai, Pfizer, Lilly, Merck Sharp&Dohme, Daiichi Sankyo, AstraZeneca, Gilead, Steamline Therapeutics, Zuellig Pharma*

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Stock: *MAJ3 Capital, Leuko (relative)*

Travel, accommodation, expenses: *Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead, Merck Sharp&Dhome, Steamline Therapeutics*

Patents: *Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent.Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. ISSUED; 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. LICENSED*

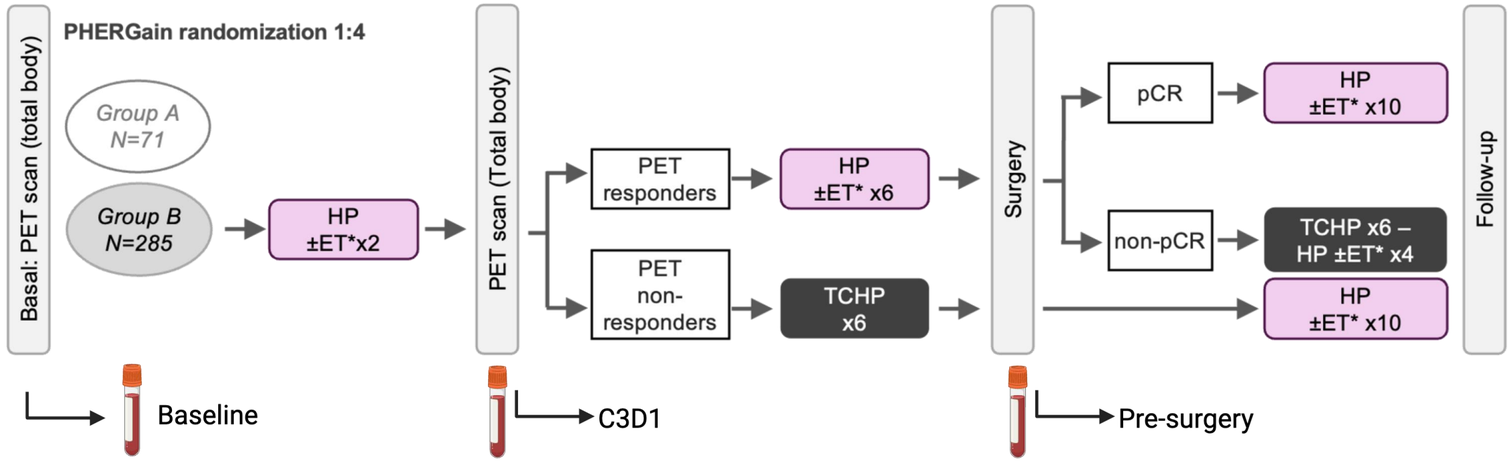
Introduction

- **HER2-directed therapies** have improved the outcome of patients with HER2+ early breast cancer (EBC), leading to de-escalation approaches

- The **PHERGain study** showed the feasibility of a PET–guided, pathological complete response (pCR)-adapted strategy to avoid chemotherapy (CTx) in patients HER2+ EBC undergoing neoadjuvant **dual HER2 blockade with trastuzumab and pertuzumab**.

PHERGain primary endpoints

- **37.9%** of PET-responder patients achieving **pCR**[2]
- **3**-year invasive disease-free survival (**iDFS**) **of 94.3%**[3]

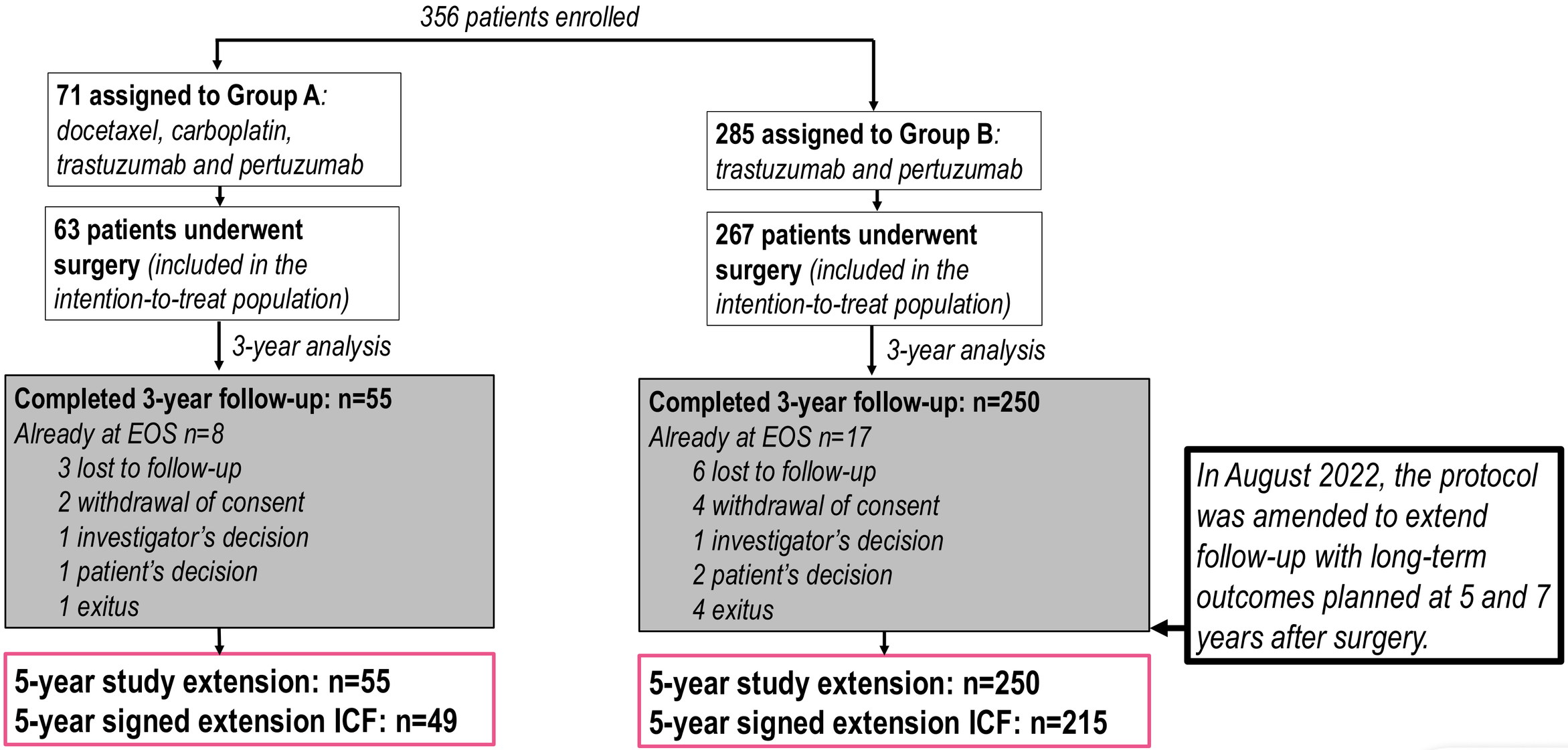


We report the **5-year iDFS** and assess a tumor-uninformed **ctDNA assay** (Guardant Reveal™) to improve the **prediction of pCR and 5-year outcomes**

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

Javier Cortés, *MD, PhD*

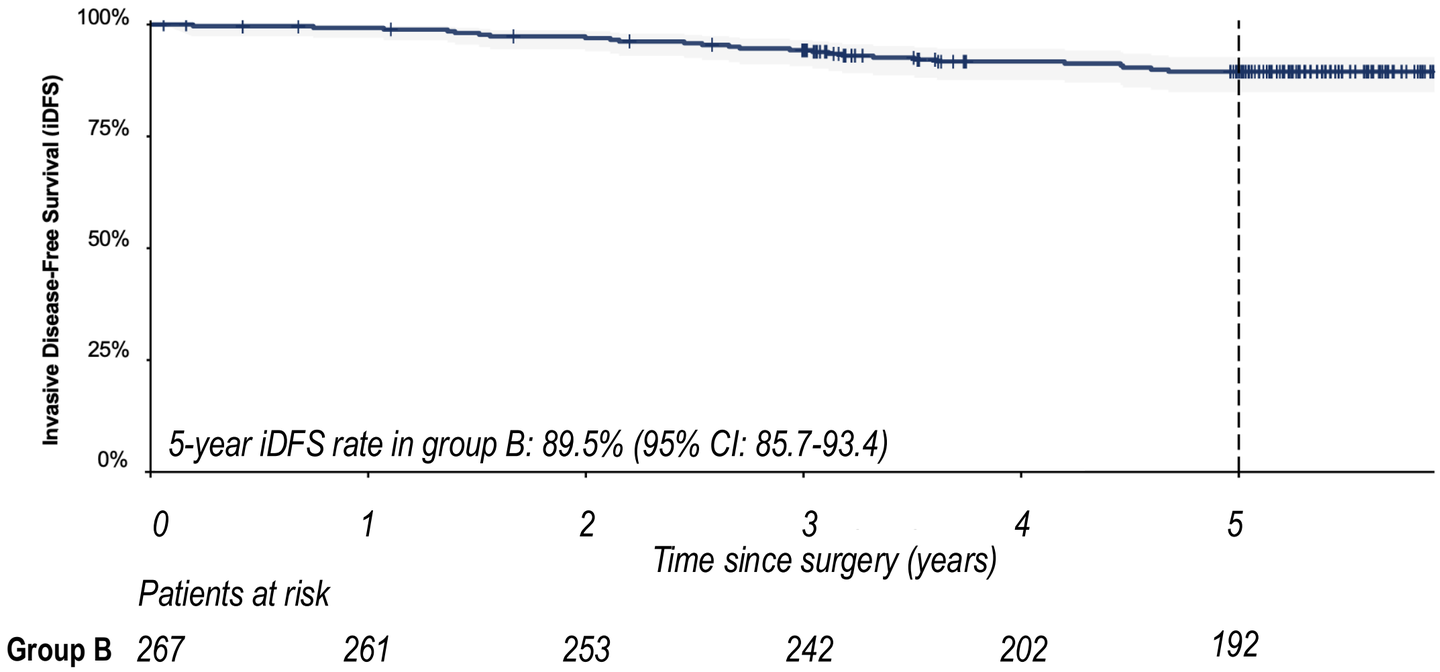
5-year follow up: consort diagram



5-year iDFS rate in the whole group B

3-year iDFS rate

94.3%
(95%CI: 90.9-96.8)



5-year iDFS rate

89.5%
(95%CI: 85.7-93.4)

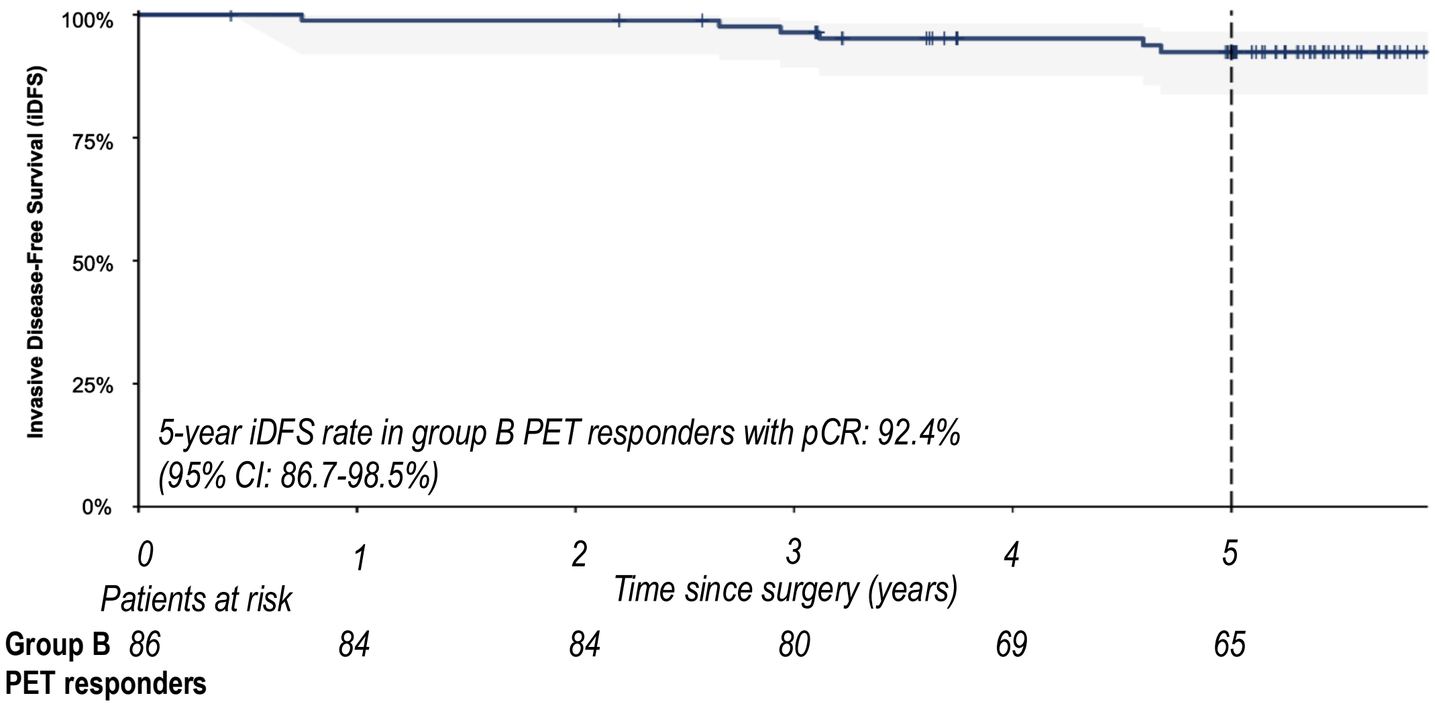
	Group B n (%)
Population who underwent surgery	*n=267*
Invasive disease-free survival events	*26 (9.7)*
Ipsilateral invasive breast cancer recurrence	*3 (1.1)*
Regional invasive breast cancer recurrence	*3 (1.1)*
Contralateral invasive breast cancer	*1 (0.4)*
Distant recurrence	*14 (5.2)*
Second primary non-breast cancer	*4 (1.5)*
Death	*1 (0.4)*

In group B, **26 (9.7%)** of 267 patients **had an invasive disease event or death** within 5 years after surgery and the **5-year iDFS** rate was **89.5% besides one third never received CTx**

5-year iDFS rate in group B patients with pCR and no CTx

3-year iDFS rate with pCR and no CTx
96.4%
(95%CI: 89.3-98.8)

5-year iDFS rate with pCR and no CTx
92.4%
(95%CI: 86.7-98.5)



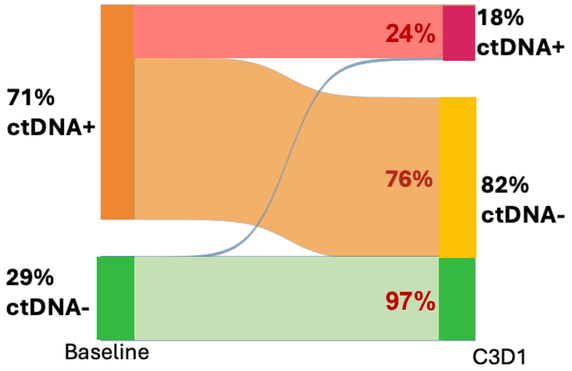
	Group B with pCR and no CTx n (%)
Population who underwent surgery	*n=86*
Invasive disease-free survival events	*6 (7.0)*
Ipsilateral invasive breast cancer recurrence	*2 (2.0)*
Regional invasive breast cancer recurrence	*0*
Contralateral invasive breast cancer	*1 (1.0)*
Distant recurrence	*1 (1.0)*
Second primary non-breast cancer	*2 (2.0)*
Death	*0*

The **5-year iDFS** rate in patients that had a pCR and never received CTx was **92.4%**, with only one distant recurrence.

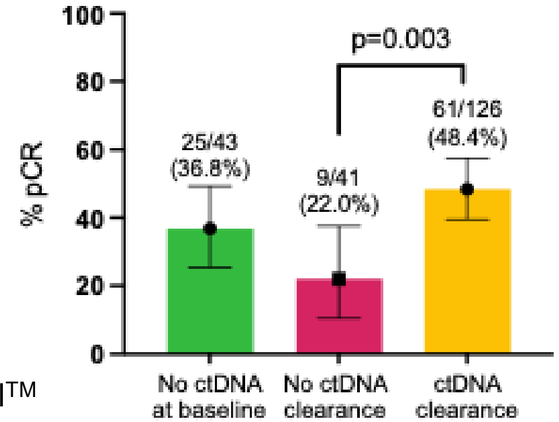
Early ctDNA clearance (C3D1) association with outcomes

All patients: Group A + Group B

Baseline n=288
C3D1 n=270

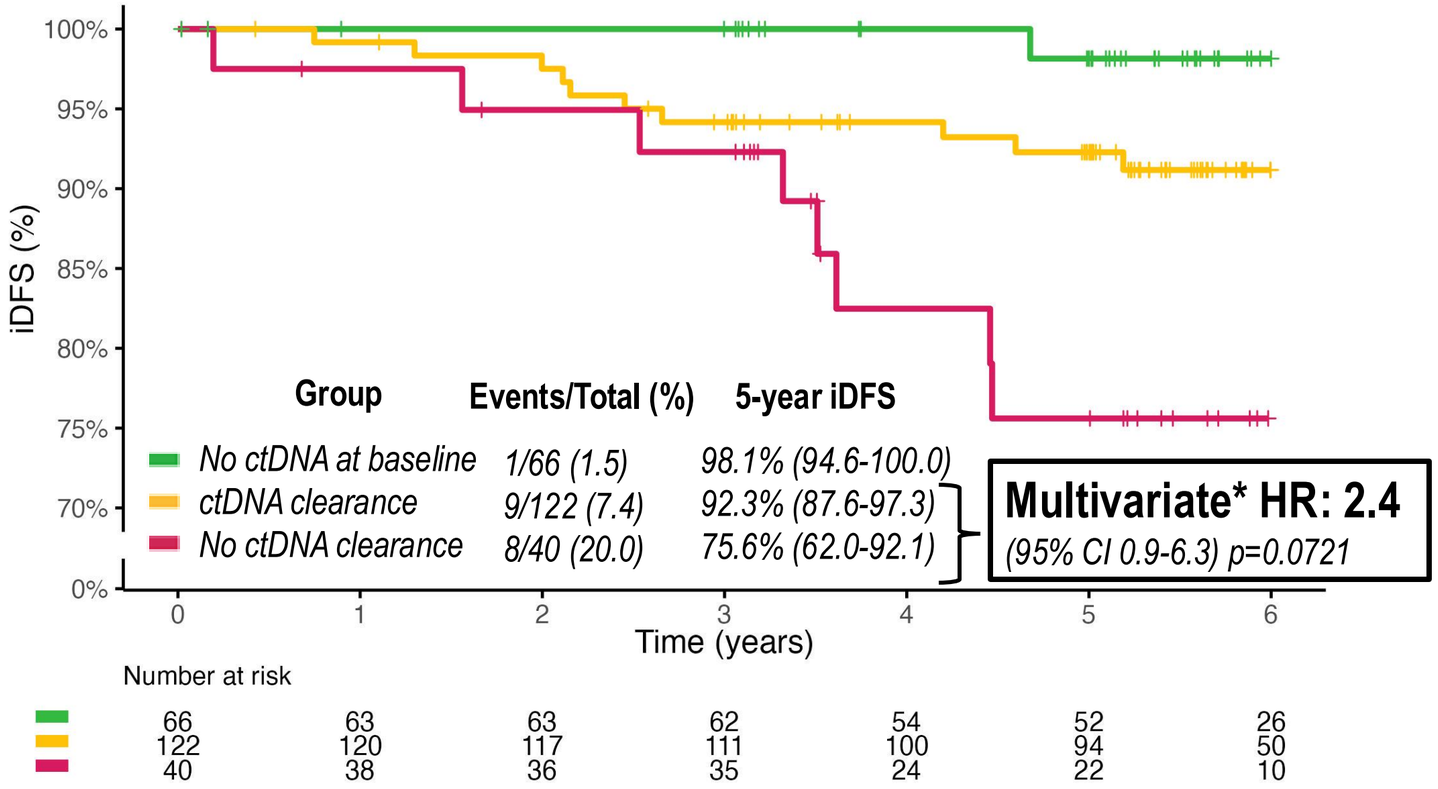


pCR rate



Guardant Reveal™

5-year iDFS



A **76% relative reduction in ctDNA** positivity is found at C3D1 and **ctDNA clearance correlated with pCR** and improved **5-year iDFS** in all patients

*Multivariate model adjusted to breast cancer staging and nodal status. Analysis performed comparing ctDNA clearance (ref) vs no ctDNA clearance.

Conclusion

- At **5 years** post-surgery, patients in group B achieved an **iDFS of 89.5%** (95% CI, 85.7 to 93.4), despite nearly one-third did not receive CTx **and no one received adjuvant T-DM1**.

- **Early ctDNA clearance after two treatment cycles** was associated with achieving a pCR and an **improved 5-year iDFS** in all patients.

- **ctDNA** represents a **promising tool for response assessment and treatment individualization** in HER2+ EBC and potentially for guiding the design of future therapeutic escalation and de-escalation trials.

Within 5 years of follow-up, PHERGain continues to demonstrate that a PET-based, pCR-adapted strategy **can identify a subset of HER2+ EBC patients who may safely omit CTx** and be treated exclusively with dual HER2 blockade.

ACKNOWDLEGMENTS

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