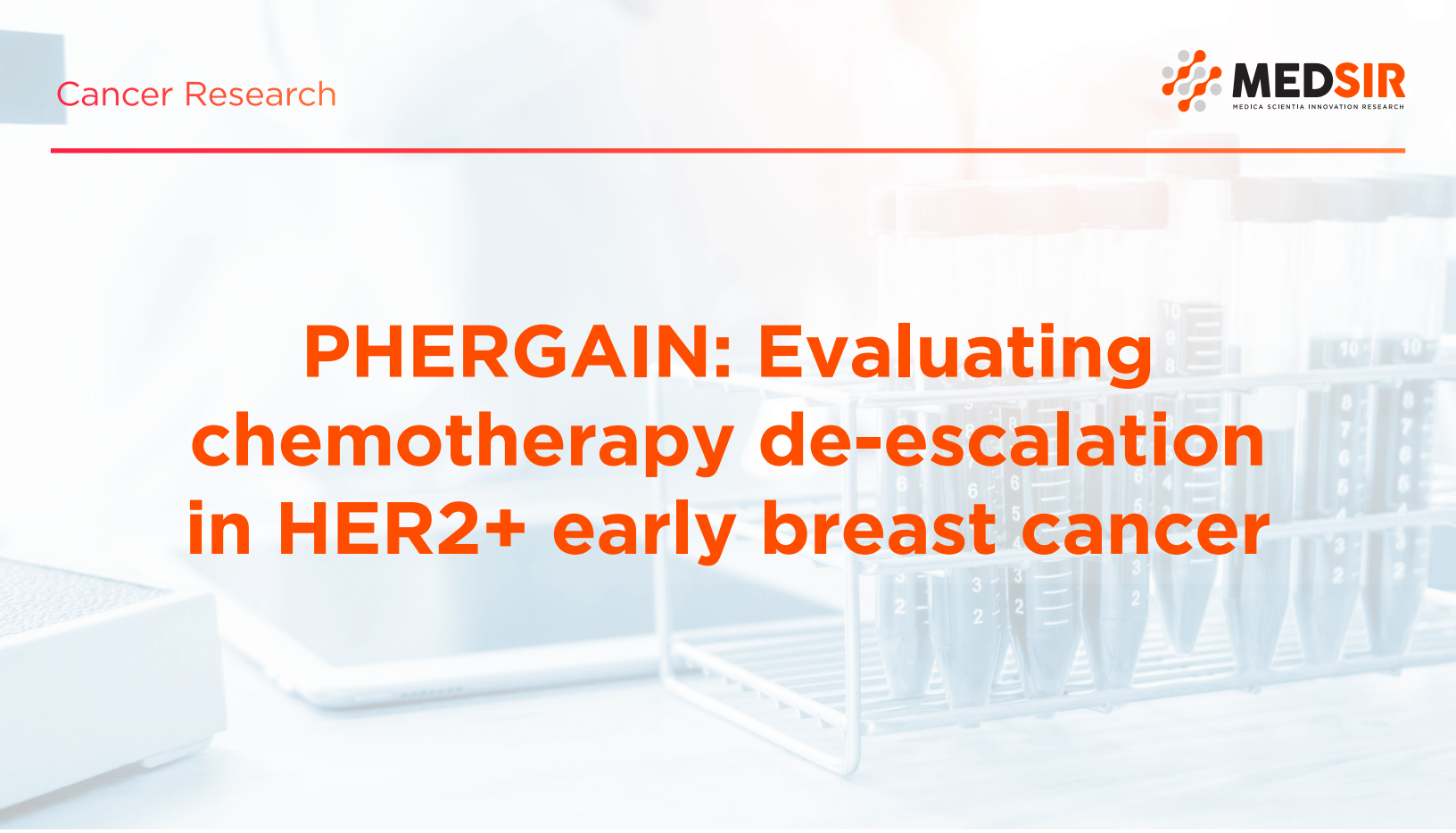


PHERGAIN: Evaluating chemotherapy de-escalation in HER2+ early breast cancer

Why was this trial needed?

The human epidermal growth factor receptor (HER) family plays an important role in cancer proliferation and progression and the *HER2 gene* has been found to be amplified in approximately 15-20% of all breast cancer cases.[1] The standard treatment in these HER2-positive patients is chemotherapy plus dual HER2 blockade but is associated with chemotherapy-related side effects.

Dual anti-HER2 blockade with trastuzumab and pertuzumab have dramatically improved outcomes in patients with HER2+ early breast cancer and has furthered the question of whether chemotherapy could be eliminated for a subset of these patients. Therefore, there is a need for treatment strategies that provide a cure without the toxic effects of chemotherapy and a way to identify patients who could have a clinical benefit from these approaches.

What was the design of the trial?

The study involved 356 patients and had two arms where Group A received a combination of trastuzumab, pertuzumab and chemotherapy (with docetaxel, and carboplatin) throughout the course of the study.

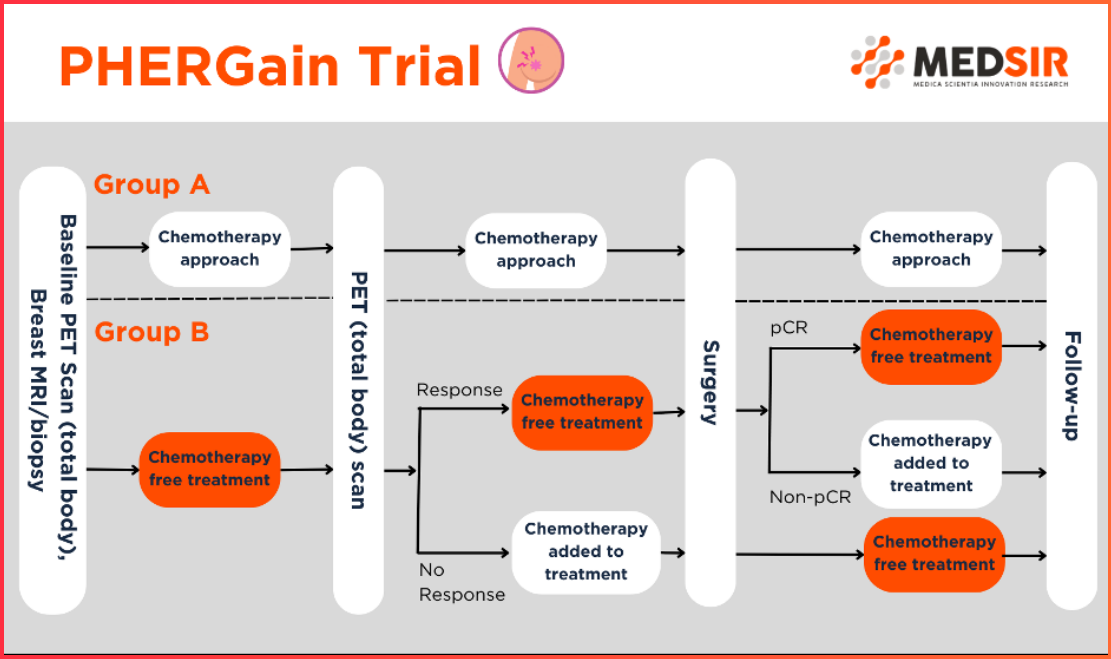
Group B patients were part of an adaptative treatment plan with the intent to treat without chemotherapy by evaluating each treatment course and changing it if there was no response. Specifically, all patients in Group B started with two cycles of pertuzumab, trastuzumab ± endocrine therapy which were followed by a PET (total body) scan. If the PET scan demonstrated a response to treatment (PET responder), patients continued with six additional cycles of the chemotherapy-free approach (trastuzumab, pertuzumab ± endocrine therapy). Patients with no response as indicated by the PET scan (PET non-responders) were switched to receive six cycles of chemotherapy (docetaxel and carboplatin) in combination with trastuzumab and pertuzumab. Patients received surgery after 6 treatment cycles (Group A) or 8 treatment cycles (Group B).

As an exploratory objective the study will assess efficacy of nal-IRI in patients with stable brain metastases.

Following surgery, PET responders were evaluated to determine if there were no signs of cancer, known as a pathological complete response (pCR). PET responders with a pCR continued with the chemotherapy-free treatment whereas PET responders with no pCR had chemotherapy added to their treatment. All patients from groups A and B completed up to 18 cycles of treatment with trastuzumab and pertuzumab. The goals of the study were (i) to assess the pCR rate in the breast and axilla at the time of surgery in PET-responders (first primary endpoint) and (ii) the 3-year invasive disease-free survival (iDFS) in Group B (second primary endpoint).

What were the results?

Results of the first primary endpoint of PHERGain were previously reported, showing that 37.9% of the Group B PET responders achieved a pCR.[2] At ASCO 2023 we reported the second primary endpoint: the 3-year iDFS in Group B patients, which showed that 255 (95.4%) of patients remained relapse-free. Among the group of patients that were treated without chemotherapy throughout the trial, the iDFS was 99%. The one patient with disease relapse had a localized recurrence, which can be treated with curative intent. The Group B had less toxicity as compared with the group A, and the toxicity was even lower in the patients of group B who did not receive chemotherapy.



Why is this trial important?

This is the first study to gradually adjust each patient's treatment based on how they are responding to therapy, moving therapy towards a more personalized medicine approach. Instead of comparing two treatment arms, which is the standard for clinical trials, PHERGain was designed to determine how each patient was responding to treatment and adapt their care based on their needs.

- For those patients who received trastuzumab and pertuzumab ± endocrine therapy and achieved a response by PET, about 40% of them have a pathological complete remission.
- 95.4% of patients who were part of the adaptive treatment strategy remained cancer-free after 3-years of follow up. For those patients who never received chemotherapy, the 3-year invasive disease-free survival was about 99%.
- The 3-year disease free survival results provide further support that pathologic complete responses are associated with excellent long-term prognoses.
- The study was a large undertaking involving investigators for 45 centers in seven countries across Europe with a total of 356 patients with HER2+ early breast cancer.
- This trial will allow for further studies to develop prognostic tools that can better identify patients with localized HER2+ breast cancer that can safely omit chemotherapy.
- The positive results not only show that some patients can be treated safely and effectively without chemotherapy, but it also shows that adaptive trial designs are beneficial and should be implemented when possible.

ABOUT MEDSIR

Founded in 2012, MEDSIR works closely with its partners to drive innovation in oncology research. Based in Spain and the United States, the company manages all aspects of clinical trials, from study design to publication, utilizing a global network of experts and integrated technology to streamline the process. The company offers proof-of-concept support and a strategic approach that helps research partners experience the best of both worlds from industry-based clinical research and investigator-driven trials. To promote independent cancer research worldwide, MEDSIR has a strategic alliance with Oncoclínicas, the leading oncology group in Brazil with the greatest research potential in South America. Learn how MEDSIR brings ideas to life: www.medsir.org

References

1. Waks AG, et al. Breast cancer treatment: A review. JAMA. 2019; DOI:10.1001/jama.2018.19323.
2. Pérez-García, JM. Et al. Chemotherapy de-escalation using an 18F-FDG-PET-based pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain): a multicentre, randomised, open-label, non-comparative, phase 2 trial. The Lancet Oncology 2021; DOI:10.1016/S1470-2045(21)00122-4