PHERGain trial:

3-year invasive disease-free survival (iDFS) of the strategy-based, randomized phase II PHERGain trial evaluating chemotherapy (CT) de-escalation in human epidermal growth factor receptor 2-positive (HER2[+]) early breast cancer (EBC)

HER2-positive breast cancer is characterized by the overexpression of a protein called human epidermal growth factor receptor 2 (HER2), which contributes to aggressive tumor growth. Currently, HER2-positive patients with early breast cancer (EBC), which means that the tumor has not spread beyond the breast, are treated with a combination of chemotherapy and targeted therapy against HER2. Chemotherapy is very effective in killing cancer cells but is associated with high toxicity and side effects, since it also harms other healthy cells. Chemotherapy-free approaches, such as HER2 targeted therapies which specifically block HER2 positive cells (i.e. trastuzumab and pertuzumab) can stop, prevent, or slow down the cancer cell growth with less side effects. Thus, trastuzumab and pertuzumab combined with chemotherapy is already approved for use in HER2-positive breast cancer patients.

Here we present the PHERGain study which was designed to investigate the feasibility of a chemotherapy-free treatment approach for patients with HER2-positive EBC. To reduce the toxicity of chemotherapy and to maintain the high treatment efficacy, the treatment that patients received was adapted depending on the imaging results of PET CT scans (which measure the metabolic activity of tumors) and the evaluation of the pathological complete response (the absence of any residual cancer cells after treatment). By monitoring the metabolic response of cancer cells, the treatment could be tailored and the patients who may not need chemotherapy could be identified.

In a previously reported analysis of this study, it was shown that a significant number of patients responded well to the chemotherapy-free treatment (receiving just trastuzumab and pertuzumab) and achieved a pathological complete response.
In the present analysis, we evaluated the 3-year invasive disease-free survival (iDFS) rate, which is the proportion of patients who remain cancer-free for 3 years after surgery.

METHODS:
Participants of PHERGain study needed to have a tumor which could be removed by surgery after previous treatment (called neaoadjuvant treatment). Patients were divided into either group A, where they received chemotherapy plus concurrent trastuzumab and pertuzumab, or group B, where they initially received trastuzumab and pertuzumab. The response of tumor cells was closely monitored in all patients to ensure the treatment efficacy. PET CT scans were performed before starting treatment and after two treatment cycles. Patients from group A that received standard treatment of the already approved chemotherapy plus targeted treatment, completed an additional six cycles regardless of PET CT results. Patients assigned to group B (that initially received only targeted therapy with trastuzumab and pertuzumab) continued treatment for six further cycles only if the

reduction of the tumor was clearly confirmed by PET CT scan after 2 initial cycles (PET CT responders). If there was no clear reduction of the tumor (PET CT non responders), patients switched to standard treatment with six cycles of chemotherapy plus concurrent trastuzumab and pertuzumab. Patients received surgery after 6 treatment cycles (Group A) or 8 treatment cycles (Group B). 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.

RESULTS:
Between June 2017 and April 2019, a total of 356 patients were randomly assigned to either group A (chemotherapy group, 71 patients) or group B (adaptive strategy group, 285 patients). After eight cycles of treatment, 37.9% of participants assigned to group B who had an early response to the chemotherapy-free treatment of trastuzumab and pertuzumab experienced complete disappearance of all cancer cells (pCR) in the breast and axillary nodes. In long term, after three years from surgery, a highly significant proportion of patients (95.4%) who followed the adaptive strategy (group B) remained cancer-free, achieving one of the main objectives of the study.

Furthermore, among patients treated without chemotherapy throughout the whole study, almost all (98.8%) were cancer-free three years after the surgery. This finding suggests that patients with an early response to trastuzumab and pertuzumab detected by PET CT scan may have an excellent outcome without the need for additional chemotherapy. Additionally, as expected, the treatment-related side effects were lower in patients treated without chemotherapy.

CONCLUSION:
A treatment strategy that is based on evaluating an early response to HER2 dual blockade may be able to detect patients with HER2-positive early breast cancer who could benefit from chemotherapy-free treatment.
This highlights the potential benefit of avoiding chemotherapy in selected patients as it can help minimize treatment-related complications while still maintaining high treatment efficacy.