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NEOSPHERE Study Backgrounder

A randomised Phase II study of neoadjuvant pertuzumab and Herceptin in people with locally advanced, inflammatory or early stage HER2-positive breast cancer

Gianni L, et al.

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Background

Pertuzumab is a monoclonal antibody being studied in early stage and advanced HER2-positive breast cancer. It is a novel targeted medicine known as a HER2 dimerisation inhibitor (HDI). Pertuzumab is the first investigational medicine designed to specifically prevent the HER2 receptor from pairing (dimerising) with other HER receptors (HER1, HER3, and HER4).[1] HER receptors , when found in excessive numbers on the surface of some cells, can contribute to abnormal cell behaviours that cause cancer.[1] Pairing of these excess receptors , especially between HER2 and HER3, can lead to a cascade of events inside the cancer cell that cause a tumour to grow and spread. Pertuzumab attaches to a different part of the HER2 receptor than other HER2 targeted medicines, including Herceptin and T-DM1. Combining pertuzumab with other HER2 targeted medicines may create a more comprehensive blockade of cell behaviours that drive tumour growth, without increasing serious side effects.

A previous Phase II study has shown a promising anti-tumour effect of the combination of pertuzumab and Herceptin with chemotherapy in women with metastatic HER2-positive breast cancer that had progressed during previous treatment.[2,3]

NEOSPHERE study

The NEOSPHERE (**NEO**adjuvant **S**tudy of **P**ertuzumab and **H**erceptin in an **E**arly **R**egimen **E**valuation) study evaluated the treatment of early HER2-positive breast cancer with pertuzumab and Herceptin plus chemotherapy (docetaxel) in the neoadjuvant setting. Neoadjuvant treatment is defined as the treatment a patient receives after cancer is diagnosed and before surgery takes place. Results are presented at the 33rd CTRC-AACR San Antonio Breast Cancer Symposium (SABCS).

NEOSPHERE study design

NEOSPHERE is a multicentre, multinational, randomised Phase II study including 417 patients.
Women aged 18 years or over from 78 centres in Australia, Austria, Brazil, Canada, Israel, Italy, Republic of Korea, Mexico, Peru, Poland, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey and the United

Kingdom were enrolled. All had locally advanced, inflammatory or early-stage HER2-positive breast cancer and were scheduled to receive neoadjuvant therapy. Patients were randomised to one of the following four study arms (Figure 1) for the first four cycles (12 weeks) of the study:

- Herceptin and docetaxel
- Herceptin, pertuzumab and docetaxel
- Herceptin and pertuzumab
- Pertuzumab and docetaxel

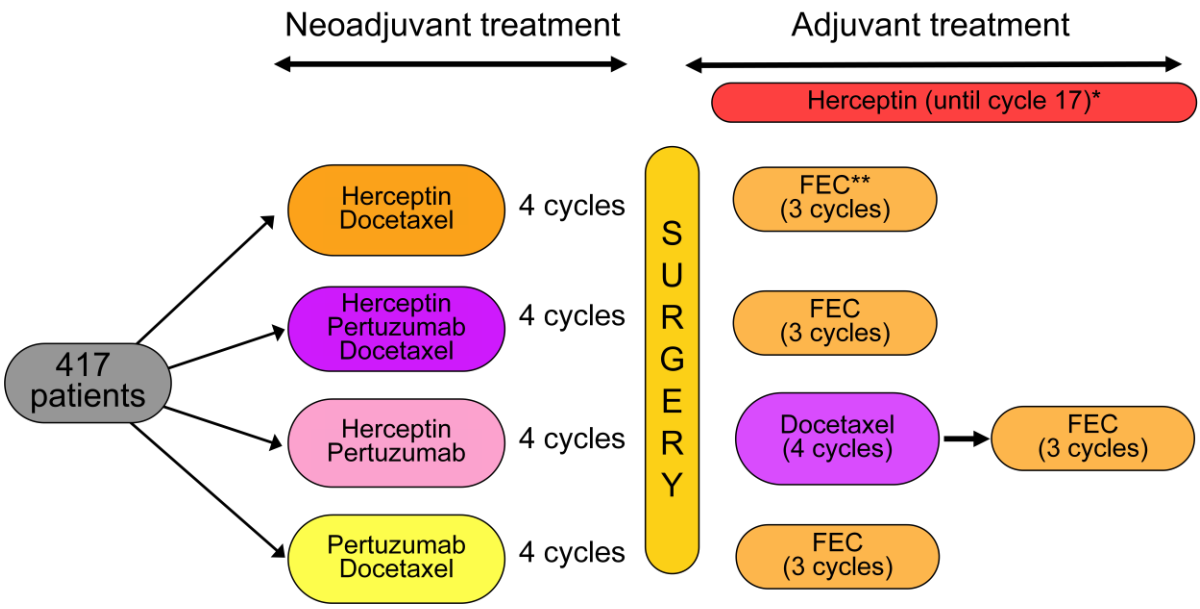

Figure 1 NEOSPHERE study design

* All patients received Herceptin for a total of 52 weeks

** FEC = 5-fluorouracil, epirubicin and cyclophosphamide

The results of the following treatment regimens were compared:

- Herceptin and docetaxel vs Herceptin, pertuzumab and docetaxel
- Herceptin and docetaxel vs Herceptin and pertuzumab
- Herceptin, pertuzumab and docetaxel vs pertuzumab and docetaxel

Study endpoints

The primary endpoint of the NEOSPHERE study was pathological complete response (pCR) after four cycles (12 weeks) of therapy. This means the disappearance of all clinical evidence of disease in the breast.

Secondary endpoints were:

- Clinical response
- Time to clinical response
- Safety profile
- Disease-free survival
- Breast conserving surgery rate
- Biomarker response assessment

Study results

NEOSPHERE study results showed that there was a significantly higher rate of complete tumour disappearance in the breast (pathological complete response, pCR) when the combination of pertuzumab and Herceptin with docetaxel was used in women with early-stage HER2-positive breast cancer in the neoadjuvant setting compared to the current standard of care Herceptin plus docetaxel.

The Herceptin pertuzumab plus docetaxel regimen showed a 45.8 percent pCR vs 29.0 percent pCR for Herceptin plus docetaxel regimen (p= 0.014)[4]

pCR results for each regimen were as follows:

- Herceptin plus docetaxel regimen showed a pCR of 29.0 percent
- Herceptin pertuzumab plus docetaxel regimen showed a pCR of 45.8 percent
- Herceptin pertuzumab regimen showed a pCR of 16.8 percent
- Pertuzumab plus docetaxel regimen showed a pCR of 24.0 percent[4]

The pertuzumab and Herceptin plus docetaxel regimen was not associated with any new safety signals and no substantial increase in cardiac risk was observed. NEOSPHERE also showed that combined use of pertuzumab plus Herceptin without chemotherapy (docetaxel) was associated with promising anti-tumour activity (pCR = 16.8 percent) and an encouraging risk-benefit profile.

Study implications

The NEOSPHERE study showed that both pertuzumab and Herceptin are active against early-stage HER2-positive breast cancer when used in combination with docetaxel, but that the combination of the two antibodies together plus docetaxel is more active than either antibody alone plus docetaxel.[4] This suggests that pertuzumab and Herceptin may have a complementary effect on the cancer cells and perform a more comprehensive blockade on the HER2 receptor than either agent used alone.

These findings need to be confirmed in Phase III trials. A Phase III study (CLEOPATRA) evaluating the efficacy and safety of a pertuzumab and Herceptin plus docetaxel regimen in previously untreated HER2-positive metastatic breast cancer is ongoing. In addition, a Phase III study in early-stage HER2-positive breast cancer is being planned.

References

[1] Franklin MC et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell* 2004;5:317–328.
[2] Baselga J et al. Phase II Trial of Pertuzumab and Trastuzumab in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer That Progressed During Prior Trastuzumab Therapy. *Journal of Clinical Oncology* 2010;28:1138–1134.
[3] Cortes J, Baselga J, Petrella T, Gelmon K, Fumoleau P, Verma S. Pertuzumab based monotherapy following trastuzumab-based treatment: activity and tolerability in patients with advance HER-2 positive breast cancer *J Clin Oncol* 2009 27 (May 20 Supplement), 1022.
[4] Gianni L, et al. A Phase II study of neoadjuvant pertuzumab and Herceptin in people with locally advanced, inflammatory or early stage HER2-positive breast cancer. San Antonio Breast Cancer Symposium; 2010 Dec 8 -12; San Antonio, Texas, USA Abstract 851293