**TRIAL SUMMARY:** Benefits of adding pertuzumab to trastuzumab and docetaxel in first-line treatment of HER2+ metastatic breast cancer


In this double-blind Phase III study, 808 patients with centrally confirmed human epidermal growth factor receptor 2-positive (HER2+) metastatic or locally recurrent, unresectable breast cancer were randomized to receive either placebo + trastuzumab (H) + docetaxel (T) or pertuzumab (P) + H + T. Patients could have received one prior hormonal treatment for metastatic breast cancer (MBC) and/or prior systemic neoadjuvant or adjuvant therapy including H and T. Patients had to have a baseline left ventricular ejection fraction ≥50% and no history of declines to <50% during or after prior H therapy.

Study medication was as follows: P 840 mg loading dose followed by 420 mg q3w; H 8 mg/kg loading dose followed by 6 mg/kg q3w; T 75 mg/m² q3w (with subsequent dose escalation to 100 mg/m² if 75 mg/m² was well tolerated). Patients were recommended to receive at least 6 cycles of T. In the case of chemotherapy discontinuation due to cumulative toxicity, antibody therapy was continued until disease progression, unacceptable toxicity or withdrawal of consent. Patients were stratified according to region and prior treatment status (adjuvant therapy or de novo MBC).

The primary endpoint for the study was independently-assessed PFS. Secondary endpoints were OS, investigator-determined PFS, objective response rate (ORR) and safety.

Results showed the median PFS was 12.4 months in the control group vs 18.5 months in the P group (HR for progression or death, 0.62; 95% CI 0.51 to 0.75; p<0.001). OS interim analysis showed a strong trend in favour of P + H + T. The safety profile was generally similar in the 2 groups, with no increase in left ventricular systolic dysfunction; the rates of febrile neutropenia and diarrhoea of ≥grade 3 were higher in the P group vs the control group.

**COMMENTARY:** HER2 is overexpressed in 20% to 30% of invasive breast cancers and is associated with increased cell proliferation and motility, tumour invasiveness, enhanced angiogenesis and decreased apoptosis. Trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain of the HER2 receptor and inhibits cell proliferation. The pivotal Phase III trial of trastuzumab combined with chemotherapy as first-line treatment for women with HER2+ MBC showed significant benefits with the combination compared to chemotherapy alone in terms of tumour ORR, time to tumour progression (TTP) and OS. These results led to the widespread use of trastuzumab combined with primarily taxane-based chemotherapy as first-line treatment in HER2+ MBC. However, resistance to trastuzumab eventually occurs and it is unclear if these tumours are insensitive to the HER2 signalling pathway altogether in this situation.

Pertuzumab is a fully humanized monoclonal antibody that also targets the HER2 receptor but at a different epitope than trastuzumab. This drug inhibits HER2 dimerization with the other receptors of the HER family, resulting in decreased downstream signalling. Preclinical studies with pertuzumab demonstrated antitumour activity as a single agent and in combination with trastuzumab. In a Phase II study in HER2+ MBC and after tumour progression on trastuzumab, pertuzumab + trastuzumab conferred a 50% clinical benefit rate (objective tumour response plus stable disease for >6 months) and a 24% tumour ORR. NEOSPHERE (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation) is a randomized Phase II study in women with locally advanced, inflammatory or early HER2+ breast cancer. Women treated with pertuzumab, trastuzumab + docetaxel chemotherapy had a significantly improved tumour pathology complete response rate (pCR) of 46% vs 29% in the trastuzumab + docetaxel-treated patients.

This CLEOPATRA study is a Phase III randomized, double-blind, placebo-controlled trial of trastuzumab and docetaxel with pertuzumab or placebo as first-line therapy for 808 women with HER2+ MBC. HER2 status was centrally confirmed and the primary endpoint was independently-assessed PFS with secondary endpoints of ORR, OS and safety. There was a significant improvement in median PFS with the combination of trastuzumab + docetaxel + pertuzumab, with HR of 0.62 (95% CI 0.51–0.75; p≤0.001) and a 6.1-month absolute improvement in PFS from 12.4 months (trastuzumab + docetaxel) to 18.5 months (trastuzumab + docetaxel + pertuzumab). The benefit was noted in all subgroups of patients except those without visceral disease. Similarly, the combination including pertuzumab improved tumour response rates from 69.3% to 80%. There was also a trend toward an OS benefit with HR of 0.64 (but not statistically significant), and the number of events required to evaluate OS in this interim analysis has not been reached at this time. In terms of...
safety, toxicities were primarily grade 1 and 2 and manageable. Of note, there was no increased cardiac dysfunction with the addition of pertuzumab. Diarrhea, rash, mucosal inflammation, dry skin and febrile neutropenia were higher in the pertuzumab-treated group. The authors concluded that the combination of trastuzumab + docetaxel + pertuzumab may be practice-changing in the setting of HER2+ MBC.

For women meeting the eligibility criteria for this trial, the combination may indeed set a new standard. However, only approximately 10% of women had received prior trastuzumab in the CLEOPATRA study. Therefore, with the widespread use of adjuvant trastuzumab in early HER2+ breast cancer, it is unclear how the results of this study will apply to patients today. One might speculate that the significant benefits seen with the addition of pertuzumab in this trial may not be as robust in women previously treated with adjuvant trastuzumab. Nevertheless, the results from this landmark study are convincing and further outcomes from adjuvant trials of the combination are highly anticipated. The APHINITY adjuvant study in HER2+ early breast cancer (BIG 4-11/NCIC MA.54) is one such trial and will open for accrual in Canadian centres in March 2012.

However, pertuzumab is not the only emerging agent targeting the HER pathway. There are a number of other drugs including lapatinib, the small molecule inhibitor of the epidermal growth factor receptor (EGFR/HER1) and HER2 receptor approved by Health Canada for HER2+ MBC in combination with capecitabine after disease progression on trastuzumab. Also showing great promise are the T-DM1 novel agent containing trastuzumab conjugated with the anti-microtubule agent emtansine and demonstrating significant antitumour activity;4,7 neratinib, the irreversible tyrosine kinase inhibitor of EGFR, HER2 and HER4; and afatinib, another small molecule inhibitor of EGFR, HER2 and HER4.2

This is an exciting era in successful targeting of the HER family of receptors. With a plethora of emerging agents, the challenge is how best to incorporate these drugs in clinical practice, taking cost into consideration. At present, only trastuzumab and lapatinib are available in Canada outside of clinical trials, but the other HER2-targeting agents are in rapid clinical development and will likely become available in the foreseeable future. Thus, outcomes for women with HER2 positive breast cancer continue to strengthen.

References

Disclosure
Dr. Grenier reports no conflicts of interest relevant to this article.