Research Review
PRODUCT REVIEW

Pertuzumab combination therapy for the neoadjuvant treatment of HER2-positive early breast cancer

About the Reviewers

Dr Sheridan Wilson
MB ChB FRACP

Dr Sheridan Wilson is a Medical Oncologist specialising in the treatment of breast cancer. Sheridan graduated from the Auckland University School of Medicine in 2003 and became a Fellow of the Royal Australasian College of Physicians in 2012. Between 2013 and 2014, Sheridan completed a clinical research fellowship in breast cancer at The British Columbia Cancer Agency, Vancouver, Canada. Since her return to New Zealand, Sheridan has maintained an interest in translational research and is an active participant in the Breast Cancer Special Interest Group of New Zealand. Sheridan works at ADHB where she currently holds the position of Clinical Lead for the breast team in Medical Oncology.

Associate Professor Ian Campbell

Associate Professor Ian Campbell is a general and breast cancer surgeon at the Waikato District Health Board, but in addition to this participates in numerous other breast cancer-related groups and activities.

These include:

- Working as an Associate Professor in Surgery at the University of Auckland School of Medicine.
- Conducting research into breast cancer. Of note are the clinical trials currently underway looking at the sentinel node-based management of lymph nodes in those with breast cancer.
- Participating as the New Zealand director on the board of the Australia New Zealand Clinical Trials Group (ANZBCTG).
- Contributing to the Breast Special Interest Group associated with the New Zealand Association of Cancer Specialists.
- Being a founding member and driving force of the Waikato Breast Cancer Research Trust.

Pertuzumab is the first in a new class of targeted cancer treatments termed HER2 dimerization inhibitors. In New Zealand, pertuzumab is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with inflammatory or locally advanced HER2-positive breast cancer as part of a complete treatment regimen AND in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease. In the metastatic setting, pertuzumab is fully funded by Pharmac for patients who meet pre-defined criteria. Pertuzumab is not Pharmac-funded in the neoadjuvant early breast cancer setting. Roche New Zealand has a Cost Share Programme for pertuzumab in the neoadjuvant setting. The programme provides a number of doses of the medicine at no charge (the cost of the Roche medicine only). There are criteria for enrolling into the Cost Share Programme. Please contact Roche for more details. The NeoSphere trial demonstrated that the addition of pertuzumab to trastuzumab and docetaxel for the neoadjuvant treatment of HER2-positive early breast cancer resulted in a significant improvement in pathological complete response. Furthermore, the TRYPHAENA trial supported the benefit of neoadjuvant dual anti-HER2 therapy. Long-term survival data from NeoSphere demonstrated a correlation between pathological complete response and improved survival in this patient population. Expert commentary on the use of pertuzumab from a clinical practice perspective is provided by Dr Sheridan Wilson from Auckland District Health Board and Associate Professor Ian Campbell from Waikato Disrict Health Board. This review is sponsored by Roche (NZ) Ltd.

Introduction

Breast cancer is the most common cancer in women worldwide, with an estimated 1.7 million new cases annually.[1] In 2012, breast cancer was estimated to have caused the death of approximately half a million women globally.[1] Breast cancer is New Zealand's third most common cancer and accounts for more than 600 deaths every year.[2]

Approximately 20% of breast cancers are human epidermal growth factor receptor 2 (HER2)-positive.[3-5] Normally, the HER2 protein functions as a receptor on the surface of healthy breast cells and controls how such cells grow, divide and repair. HER2-positive breast cancer is characterised by chromosomal mutation leading to amplification of protein-coding exons of the HER2 gene, driving proliferation and survival of breast cancer cells.[3-5] Historically, HER2-positive breast cancer was considered to be among the most aggressive female cancers. However, with the recent introduction of HER2-directed therapies, this breast cancer subtype has become treatable in the neoadjuvant and adjuvant clinical settings.[6-8] Indeed, the anti-HER2 monoclonal antibody, trastuzumab, combined with chemotherapy showed significantly improved overall survival in patients with metastatic HER2-positive breast cancer.[9] Furthermore, administering trastuzumab to patients with early stage, locally advanced HER2-positive breast cancer demonstrated similar survival benefits,[7,8,10,11] thereby transforming the management of this breast cancer subtype in the adjuvant and neoadjuvant settings.

Pertuzumab

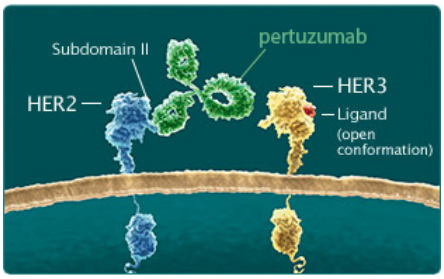
Despite the overall clinical efficacy of trastuzumab, many patients develop resistance, warranting the development of new and mechanistically distinct anti-HER2 agents to avoid cross-resistance and disease relapse.[12,13] Consequently, the recombinant humanised monoclonal antibody, pertuzumab, was developed.

Pertuzumab is the first in a new class of targeted cancer treatments termed HER2 dimerization inhibitors. Pertuzumab binds to the extracellular dimerization domain (Subdomain II) of the HER2 protein and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4 (Figure 1). It inhibits ligand initiated intracellular signalling through two major signal pathways, mitogen activated protein (MAP) kinase and phosphoinositide 3 kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).[14]

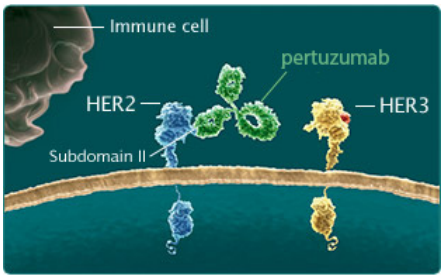
While pertuzumab alone inhibits the proliferation of human tumour cells, the anti-tumour activity is significantly augmented when pertuzumab is used in combination with trastuzumab in HER2-overexpressing xenograft models.[14] Non-clinical data indicate that pertuzumab and trastuzumab bind to distinct epitopes on HER2 without competing with each other and have distinct mechanisms for disrupting HER2 signalling.[5,15] Whereas trastuzumab blocks HER2 cleavage and inhibits ligand-independent signalling,[16] pertuzumab exerts its effects by inhibiting ligand-dependent signalling, particularly between HER2 and HER3, which is known to activate a potent cell survival and proliferation signal.[17,18] These mechanisms are complementary and result in improved anti-proliferative activity in vitro and in vivo when pertuzumab and trastuzumab are given in combination (Figure 1).[18-20]

In the pivotal trial, CLEOPATRA, pertuzumab in combination with trastuzumab and docetaxel was shown to significantly improve progression-free survival (PFS) and overall survival (OS) in patients with first-line metastatic HER2-positive breast cancer.[26] In CLEOPATRA, no drug–drug interactions between pertuzumab and trastuzumab and between pertuzumab and docetaxel were detected in a limited number of patients evaluated.[27]

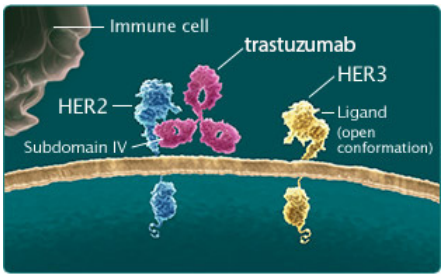
Figure 1. Proposed mechanism of action of pertuzumab with trastuzumab



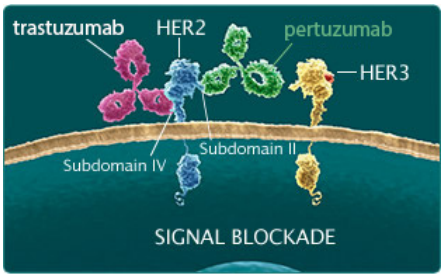
1. Pertuzumab binds to subdomain II and blocks ligand-dependent HER2 heterodimerization with HER1, HER3, and HER4.[21]



2. Pertuzumab inhibits HER2:HER3 dimer formation and downstream signalling, while also mediating ADCC.[21-24]



3. Trastuzumab binds to subdomain IV and disrupts ligand-independent HER2 signalling. Trastuzumab also mediates ADCC.[15,25]



4. Pertuzumab plus trastuzumab provide a dual blockade of HER2-driven signalling pathways.[15,21]

Indication[14]

Neoadjuvant treatment of breast cancer

Pertuzumab is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with inflammatory or locally advanced HER2-positive breast cancer as part of a complete treatment regimen.

Note to indication: this approval is based on improvement in pathological complete response rate.

No improvement in disease-free, progression-free or overall survival has been shown.

Metastatic breast cancer

Pertuzumab is indicated in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease.

Key clinical trials

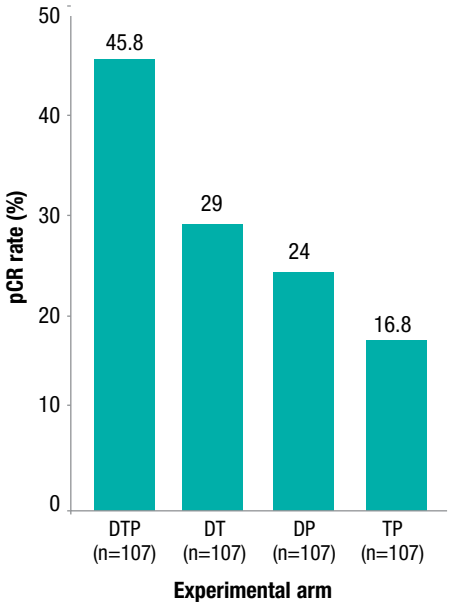
NeoSphere

The NeoSphere study was a randomised, open-label phase II clinical trial that enrolled 417 treatment-naïve HER2-positive breast cancer patients.[28] Inclusion in the study required HER2-positive breast cancer patients to have operable, locally advanced, or inflammatory breast cancer, all of which needed to exceed 2 cm in diameter. Patients were stratified on the basis of their tumour type and its hormone receptor expression status (i.e., estrogen and progesterone receptors), and subsequently were randomised into one of four 12-week neoadjuvant treatment arms: 1) docetaxel, trastuzumab, and pertuzumab (DTP); 2) docetaxel and trastuzumab (DT); 3) docetaxel and pertuzumab (DP); or 4) trastuzumab and pertuzumab (TP). Upon completion of neoadjuvant treatment, most patients underwent surgery, and subsequently received an additional year of adjuvant trastuzumab and anthracycline-based chemotherapy (FEC; 5-fluorouracil, epirubicin, and cyclophosphamide). The primary endpoint was pathologic complete response (pCR), defined as no invasive cells in the breast by microscopic examination at the time of surgery; in situ lesions were permitted.

Pathological complete response rate

As shown in Figure 2, the pCR rate was significantly higher for the DTP regimen compared with the remaining three neoadjuvant arms. Patients given DTP had a significantly improved pCR rate (45.8%) compared with those given DT (29.0%; p=0.0141). The pCR rate was 24.0% in the DP group and 16.8% in the TP group. Extending the pCR definition to include the lack of invasive cancer in all sampled regional lymph nodes, which represents a more conservative definition of pCR, resulted in a modest 5–10% reduction in overall pCR rates across all treatment arms; however, the pCR for the DTP arm (39.3%) remained higher than those observed in the DT (21.5%), DP (17.7%), or TP (11.2%) arms. Finally, significantly higher pCR rates were achieved in women with hormone receptor-negative tumours compared to hormone receptor-positive tumours.

Figure 2. NeoSphere: pathological complete response rate[29]



Abbreviations: pCR = pathological complete response; DTP = docetaxel, trastuzumab and pertuzumab; DT = docetaxel and trastuzumab; DP = docetaxel and pertuzumab; TP = trastuzumab and pertuzumab

Five-year survival analysis

A 5-year analysis showed that an increase in pCR positively correlated with improvements in the extent of patient disease-free survival (DFS) and PFS survival.[30] The 5-year DFS rates were 84% for DTP-treated patients, 81% for DT-treated patients, 75% for DP-treated patients, and 80% for TP-treated patients. Similar success was achieved for the 5-year PFS rates, which were 86% for DTP-treated patients, 81% for DT-treated patients, 73% for DP-treated patients, and 73% for TP-treated patients. This suggests that total pCR could be an early indicator of long-term outcome in early-stage HER2-positive breast cancer.

Safety

The most common adverse reactions are shown in Table 1. In the neoadjuvant treatment period, left ventricular dysfunction (LVD) occurred in 3% of patients treated with DTP, and in 1% with DT, 1% with DP and 1% with TP. In the overall treatment period, left ventricular ejection fraction (LVEF) decline >10% and a drop to less than 50% occurred in 8% of patients treated with DTP versus 2% of patients treated with DT. LVEF recovered to ≥50% in all patients. Symptomatic LVD (CHF) occurred in 0.9% of patients treated with TP, and in 0.0% with DTP, DT, and DP.

In the five-year survival analysis there were no new or long-term safety concerns and tolerability was similar across groups (neoadjuvant and adjuvant treatment periods combined).[30] The most common grade 3 or worse adverse events were neutropenia, febrile neutropenia and leukopenia. The number of patients with one or more serious adverse event was similar across groups (19-22 serious adverse events per group in 18-22% of patients).

Table 1. Summary of most common adverse events (all grades and grade ≥3) in NeoSphere[30]

Adverse reaction	Docetaxel + trastuzumab + pertuzumab (n=107)	Docetaxel + trastuzumab (n=107)	Docetaxel + pertuzumab (n=94)	Trastuzumab + pertuzumab (n=108)
10 most common adverse events (all grades) (%)				
Alopecia	68	70	69	55
Neutropenia	64	75	73	44
Nausea	66	65	65	48
Diarrhoea	51	38	56	43
Fatigue	33	33	39	31
Vomiting	36	29	39	29
Mucosal inflammation	31	26	31	17
Rash	28	24	32	20
Myalgia	23	22	23	27
Asthenia	27	21	25	18
10 most common adverse events (grade ≥3) (%)				
Neutropenia	55	66	64	37
Febrile neutropenia	11	9	16	5
Leukopenia	6	12	9	4
Menstruation irregular	4	6	6	6
Diarrhoea	7	4	5	3
Granulocytopenia	1	1	2	5
Vomiting	0	3	4	1
Asthenia	2	1	3	3
Urinary tract infection	2	2	1	1
Radiation skin injury	2	2		2

Table 2. Frequency of adverse reactions occurring in more than 20% of patients in TRYPHAENA[31]

Adverse reaction	Arm 1 FEC + trastuzumab + pertuzumab followed by docetaxel + trastuzumab + pertuzumab (n=72)	Arm 2 FEC followed by docetaxel + trastuzumab + pertuzumab (n=75)	Arm 3 TCH + pertuzumab (n=76)
10 most common adverse events (all grades) (%)			
Diarrhoea	61.1	61.3	72.4
Alopecia	48.6	52.0	53.9
Nausea	52.8	53.3	44.7
Neutropenia	51.4	46.7	48.7
Vomiting	40.3	36.0	39.5
Fatigue	36.1	36.0	42.1
Anaemia	19.4	8.0	6.8
Mucosal inflammation	23.6	20.0	17.1
Constipation	18.1	22.7	15.8
Dyspepsia	25.0	8.0	27.4
10 most common adverse events (grade ≥3) (%)			
Neutropenia	47.2	42.7	46.1
Febrile neutropenia	18.1	9.3	17.1
Leukopenia	19.4	12.0	11.8
Diarrhoea	4.2	5.3	11.8
Anaemia	1.4	2.7	17.1
Thrombocytopenia	0.0	0.0	11.8
Vomiting	0.0	2.7	5.3
Drug hypersensitivity	2.8	0.0	2.6
Fatigue	0.0	0.0	3.9
Alanine aminotransferase increase	0.0	0.0	3.9

FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; TCH = docetaxel, carboplatin, and trastuzumab

EXPERT COMMENTARY ON NEOSPHERE

Sheridan Wilson

The definition of pCR used in the NeoSphere trial (no invasive cells in the breast) is less discriminatory in predicting improved long term outcomes that the more stringent definition of no invasive or in situ cells in the breast and lymph nodes.

Although the trial was not powered to detect differences in these endpoints, the numerical improvements in 5 year DFS and PFS are not statistically significant but are in line with the improvements in pCR. Taken in the context of the substantial improvement in overall survival seen with the use of the pertuzumab-trastuzumab combination for metastatic HER2-positive breast cancer the NeoSphere results are compelling for the use of this anti-HER2 combination in the neoadjuvant setting. However, adequately powered survival results are needed to definitively establish the benefit of pertuzumab in early breast cancer. The APHINITY trial of adjuvant pertuzumab may provide the required data in this regard.

Ian Campbell

Studies showing better pCR rates and response of locally advanced and inflammatory breast cancer are important. Prior to these therapies, women with inflammatory breast cancer and some with locally advanced disease were essentially inoperable.

With these therapies, not only do the vast majority of these tumours become operable, 5 year survival rates of better than 50% even for inflammatory breast cancers are being obtained. In NeoSphere some 60% of women were operable, just over 30% were locally advanced, and about 7% had inflammatory breast cancer. Median tumour size was over 50 mm, and about 70% of cases were node positive.

Of women who obtained a pCR, only 5.6-7.5% remained node positive at surgery. The proportion of women not responding to treatment was only given for the 2 antibody group (and was about a third). Some of these women may well have responded with longer treatment, judging by time to response in metastatic studies. Six percent of women did not undergo planned surgery (most of which I interpret to mean progressed or did not respond enough, to become operable), and most of these were in the above group with no chemotherapy. No other surgical outcomes are given – in particular, the number of women who were able to receive breast conservation or skin sparing mastectomy as a result of these treatments.

TRYPHAENA

The TRYPHAENA study[31] was a randomised, open-label phase II clinical trial that enrolled 225 patients using the same criteria as those employed in the NeoSphere trial. Patients were randomly allocated to receive one of three 18-week neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with trastuzumab and pertuzumab (Arm 1); 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with pertuzumab (Arm 2); or 6 cycles of docetaxel, carboplatin, and trastuzumab (TCH) in combination with pertuzumab (Arm 3). Upon completion of neoadjuvant treatment, all patients underwent surgery, and subsequently continued to receive adjuvant trastuzumab treatment to 1 year. Unlike the NeoSphere trial, the primary endpoint of the TRYPHAENA trial aimed to determine the cardiac toxicities associated with co-administering pertuzumab and trastuzumab in the absence or presence of anthracyclines. Cardiac tolerability was measured by incidence of left ventricular systolic dysfunction (LVSD), as well as by a decline of ≥10% points from baseline to <50% in LVEF. The secondary endpoint was the pCR rate, which again was defined as the absence of histological evidence of invasive cancer in the breast.

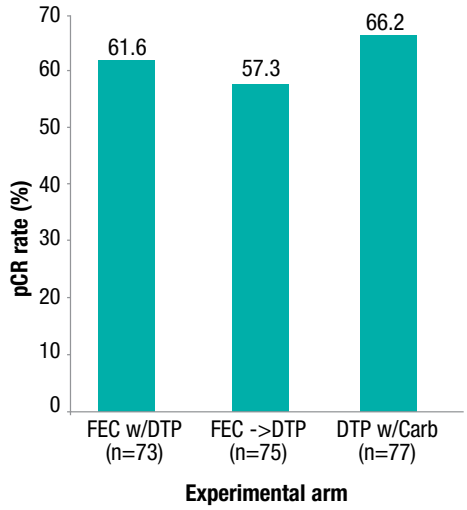
Cardiac safety

The combination of pertuzumab with trastuzumab and standard chemotherapy resulted in low rates of symptomatic LVSD. During neoadjuvant treatment, two patients (2.7%; Arm 2) experienced symptomatic LVSD and 11 patients (Arm 1: 5.6%; Arm 2: 5.3%; Arm 3: 3.9%) had declines in LVEF of ≥10% points from baseline to <50%. Other adverse events are shown in Table 2.

Pathological complete response rate

The pCR rates were similar across all experimental arms: 61.6% (Arm 1), 57.3% (Arm 2), and 66.2% (Arm 3) (Figure 3). These findings were mirrored when analysing pCR rates according to the more conservative definition (i.e., no invasive cancer in breast and lymph nodes). Likewise, incorporation of anthracyclines also failed to impact the pCR rates achieved by dual administration of trastuzumab and pertuzumab. Finally, and as expected, pCR rates were significantly higher in hormone receptor-negative tumours as compared with their hormone receptor-positive counterparts.

Figure 3. TRYPHAENA: pathological complete response rate[32]



Abbreviations: pCR = pathological complete response; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; DTP = docetaxel, trastuzumab and pertuzumab; Carb = carboplatin

EXPERT COMMENTARY ON TRYPHAENA

Sheridan Wilson

The TRYPHAENA results show impressive pCR rates across the 3 arms, however the study was designed to assess a cardiac endpoint and lacked an arm without pertuzumab which limits the extrapolation of these results and the ability of this study to distinguish the additional benefit of pertuzumab over a standard-of-care regimen. Nonetheless the TRYPHAENA data can be viewed as supportive of the pCR improvements seen in NeoSphere and provide confidence in the cardiac tolerability of the pertuzumab-trastuzumab combination in the neoadjuvant population.

Ian Campbell

Entry criteria for TRYPHAENA were similar to NeoSphere, but in this study conversion from initial planned mastectomy to breast conservation was a planned secondary endpoint. This occurred in 17-27% of cases in the 3 arms. Only one patient progressed on treatment after only 1 cycle of FEC.

Most breast surgeons in NZ are now experienced at managing women undergoing neoadjuvant therapy, but a few points are worth noting for those new to this approach.

Pretreatment marking of the tumour with a clip is really important in all cases. This is especially the case for women where breast conservation is a goal, so that with a complete clinical response, the tumour bed can still be identified and removed reliably at surgery. It is also important with mastectomy, so that the pathologists can also reliably identify the original tumour site for careful examination. Especially for women with locally advanced disease and inflammatory breast cancer, I like to photograph the breast with the palpable tumour marked and the extent of peau d'orange, to assist with subsequent surgical planning, especially when the tumour response is not so good.

If, on resection of the tumour bed with a breast conservation approach, diffuse viable cells are found throughout the specimen, and/or good margins cannot be obtained, then mastectomy should be performed. This is a different situation to the adjuvant setting – these women are demonstrating that they have aggressive disease, and there is usually no more chemotherapy planned to mop up residual disease.

EXPERT COMMENTARY ON PATHOLOGICAL COMPLETE RESPONSE AS A SURROGATE ENDPOINT

Sheridan Wilson

Ultimately the outcome of most relevance in the (neo)adjuvant setting is survival and there is ongoing debate regarding the association of pCR and long-term clinical outcome measures such as DFS and OS. An early surrogate marker for these traditional measures of efficacy is appealing as a means to fast-track the development and evaluation of novel therapies. Neoadjuvant trials using pCR as a primary endpoint require a comparatively smaller trial population than is necessary in the adjuvant setting to assess the impact of systemic treatment and offer relatively easier access to tissue that can facilitate the development of companion biomarkers to finesse treatment decisions.

A number of studies have shown that the cohort of patients who achieve a pCR (irrespective of which treatment they receive) enjoy more favourable long-term outcomes and the patient level correlation between pCR and clinical outcome is widely accepted for the more aggressive breast cancer subtypes including the HER2-positive, hormone-receptor negative group. For this group it can be argued that by increasing the chance of a pCR a patient's chance of improved survival are increased. The patient level prognostic impact of pCR is less clear in HER2-positive, hormone receptor-positive breast cancer. However, what magnitude of pCR improvement is required to significantly improve long term outcomes and how this differs across breast cancer sub-groups is not established at a trial level.

Over the last 5 years two large analyses have been conducted to further assess the relationship between pCR and survival outcomes. Cortazar et al. conducted a systematic review of 12 trials, comprising 11,955 patients.[32] The authors reported an association between pCR and event free survival (EFS) and OS that was strongest in patients with total pCR (tpCR; no invasive disease in breast and nodes); and that the association between tpCR and long-term outcomes was strongest in HER2-positive, hormone receptor-negative tumours that received neoadjuvant trastuzumab (EFS: HR 0.15; 0.09-0.27; OS: HR 0.08; 0.03-0.22). Although an association between pCR and EFS and between pCR and OS was demonstrated at the individual level, the data did not demonstrate that, at a trial level, pCR is associated with either EFS or OS.

The German breast group performed a similar analysis and found that no invasive *and* no in situ disease in the breast and nodes was the strongest predictor of improved outcome and agreed that pCR was a less compelling endpoint in HER2-positive, hormone receptor-positive breast cancer.[33] That pCR is a less suitable endpoint in hormone receptor-positive disease may reflect the important impact on long term outcome conferred by years of adjuvant endocrine therapy that is poorly captured in a neoadjuvant trial.

Neoadjuvant studies help to refine the patient population and may provide 'stop-go' signals to inform the design of adjuvant trials. Although the surrogacy of pCR for long term outcomes is strengthening in the HER2-positive, hormone receptor-negative subgroup we still need documentation of relapse and survival impacts from large adjuvant studies.

Ian Campbell

For surgeons and radiation oncologists, the big question regarding pCR is: How much more local treatment is required?

There are no randomised trials of this in the breast for surgery with cancer outcome results available yet. Generally we accept that breast conservation is appropriate with pCR although reporting on local recurrence is not ideal by surgical approach.

For the axilla, we have some surrogate endpoints from the SENTINA, ACOSOG Z1071 and SN FNAC studies which performed sentinel node biopsy and axillary dissection after chemotherapy in women with clinically or biopsy proven nodal disease at diagnosis (Pilewskie M, Morrow M. JAMA Oncol. 2017;3(4):549-555).

Overall, the false negative rate (i.e. the proportion of women with residual involved nodes that were missed by sentinel node biopsy) was 13-14%. This rate dropped to 5-9% if at least 3 negative sentinel nodes were found and removed. It is important to note that this does not mean picking out extra non sentinel nodes to make sure 3 have been examined. The false negative rate was also approximately halved by using dual tracer technique i.e. radiotracer and blue dye. Long term cancer outcomes from this approach are awaited, though the better systemic therapy gets, the better these local treatment outcomes are also likely to get.

Trials are underway assessing the most appropriate radiotherapy approach to the breast or chest wall and regional nodes after pCR, but in the meantime, treatment is generally based on the pre-chemo clinical stage, with some limited non randomised evidence that recurrence rates may be higher if a more conservative approach using less or no radiotherapy is taken.

Highlights of prescribing information[14]

The following is a summary of the prescribing information for pertuzumab. These highlights do not include all the information needed to use pertuzumab safely and effectively. See full prescribing information for pertuzumab (http://www.medsafe.govt.nz/profs/datasheet/p/perjetainf.pdf).

Dosage and administration

Pertuzumab is for intravenous infusion only. Do not administer as an intravenous push or bolus. The initial pertuzumab dose is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion.

Neoadjuvant early breast cancer: Administer pertuzumab, trastuzumab, and docetaxel by intravenous infusion preoperatively every 3 weeks for 3 to 6 cycles. The safety of pertuzumab administered for greater than 6 cycles for the neoadjuvant treatment of breast cancer has not been established. Following surgery, patients should be treated with adjuvant trastuzumab to complete 1 year of treatment. The safety of pertuzumab as part of a doxorubicin-containing regimen has not been established. There is insufficient evidence to recommend concomitant administration of an anthracycline with pertuzumab.

Metastatic breast cancer: Administer pertuzumab, trastuzumab, and docetaxel by intravenous infusion every 3 weeks. It is recommended that patients are treated with pertuzumab until disease progression or unmanageable toxicity.

Contraindications

Pertuzumab is contraindicated in patients with known hypersensitivity to pertuzumab, Chinese hamster ovary cell proteins or to any other component of the product.

Warnings and precautions

- **Left ventricular dysfunction:** Decreases in left ventricular ejection fraction (LVEF) have been reported with drugs that block HER2 activity, including pertuzumab. Monitor LVEF and withhold dosing as appropriate.
- **Infusion-related reactions:** Pertuzumab has been associated with infusion reactions. Close observation of the patient during, and for 60 min after the first infusion and during, and for 30 min following subsequent infusions, is recommended following the administration of pertuzumab. Monitor for signs and symptoms. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies.
- **Hypersensitivity reactions/anaphylaxis:** monitor for signs and symptoms. If a severe hypersensitivity reaction/anaphylaxis occurs, discontinue the infusion immediately and administer appropriate medical therapies.
- **Febrile neutropenia:** patients treated with pertuzumab, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel. If treatment is necessary, it should be administered in accordance with local guidelines, and administration of colony-stimulating factors (G-CSF) should be considered. Any signs of concomitant infection should be treated as appropriate.
- **Tumour Lysis Syndrome (TLS):** to date, while no cases have been reported from clinical trials, cases suggestive of TLS have been reported in the post-marketing setting. There is no confirmed causal association between TLS and pertuzumab in these cases, however patients at risk of TLS should be monitored closely and appropriate precautions taken.
- **Use in pregnancy - Category D:** pertuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. Women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving pertuzumab and for 6 months following the last dose of pertuzumab. In animal studies, exposure to pertuzumab resulted in embryo-foetal death and birth defects.

Adverse reactions

Neoadjuvant treatment of breast cancer

In NeoSphere, the most common adverse drug reactions (≥50%) seen with pertuzumab in combination with trastuzumab and docetaxel were alopecia and neutropenia. The most common grade 3-4 adverse drug reaction (≥10%) was neutropenia.

In TRYPHAENA, when pertuzumab was administered in combination with trastuzumab and docetaxel for three cycles following three cycles of FEC, the most common adverse drug reactions (≥50%) were diarrhoea, nausea and alopecia. The most common grade 3-4 adverse drug reactions (≥10%) were neutropenia and leukopenia. Similarly, when pertuzumab was administered in combination with docetaxel, carboplatin and trastuzumab for six cycles, the most common adverse drug reactions (≥50%) were diarrhoea and alopecia. The most common grade 3-4 adverse drug reactions (≥10%) were neutropenia, febrile neutropenia, anaemia, leukopenia and diarrhoea.

Metastatic breast cancer

In CLEOPATRA, the most common adverse drug reactions (>50%) seen with pertuzumab in combination with trastuzumab and docetaxel were diarrhoea, alopecia and neutropenia. The most common grade 3-4 adverse drug reactions (>10%) were neutropenia, febrile neutropenia and leukopenia. After discontinuation of docetaxel, adverse drug reactions in the pertuzumab and trastuzumab treatment group occurred in <10% of patients with the exception of diarrhoea, rash, upper respiratory tract infection, headache, nasopharyngitis, pruritus, fatigue, asthenia, nausea, arthralgia, pain in extremity, back pain and cough.

TAKE HOME MESSAGES FROM THE EXPERTS

Sheridan Wilson

- Despite improvements conferred by the use of adjuvant trastuzumab women with HER2-positive breast cancer remain at ongoing risk of relapse and most patients receiving trastuzumab in the neoadjuvant setting do not achieve a pCR. Thus a significant unmet need persists for patients with high risk HER2-positive disease.
- Dual HER2 targeting with trastuzumab and pertuzumab is associated with superior pCR rates in the neoadjuvant setting and is well tolerated.
- The prognostic value of pCR is not uniform across subtypes and whether a particular rate of pCR is required to achieve a clinically meaningful survival benefit has not been established. The greatest pCR rates and strongest association with long term outcome is seen in HER2-positive, hormone-negative breast cancer.
- The adjuvant APHINITY data is awaited to understand what survival benefit the addition of pertuzumab confers in the context of early breast cancer.
- Neoadjuvant therapy trials provide an important window of opportunity for screening novel targeted agents prior to evaluation in larger adjuvant trials.

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