Pertuzumab: new hope for patients with HER2-positive breast cancer

M. Capelan1,2, L. Pugliano1,3, E. De Azambuja1,2, I. Bozovic1,2, K. S. Saini1,3, C. Sotiriou1,4, S. Loi3,4 & M. J. Piccart-Gebhart1,3*

1Department of Medicine, Institute Jules Bordet, L’Université Libre de Bruxelles, Brussels; 2BreAST Data Center, Institute Jules Bordet, l’Université Libre de Bruxelles, Brussels; 3Breast International Group (BIG), Brussels; 4Breast Cancer Translational Research Laboratory (BCTL) JC Heuson, Institut Jules Bordet, Brussels, Belgium

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Background: Human epidermal growth factor receptor 2 (HER2) overexpression is detected in approximately 15% to 20% of all breast cancers (BCs). A revolutionary change in the prognosis of this subgroup of patients has occurred since trastuzumab therapy was introduced into daily clinical practice. However, because trastuzumab resistance is common, new molecules with complementary and/or synergistic mechanisms of action have been developed. Pertuzumab is a new anti-HER2 humanized monoclonal antibody that prevents the formation of HER2 dimers.

Material and methods: A computer-based literature search was carried out using PubMed (keywords: breast neoplasm, dimerization, HER-2, pertuzumab); data reported at international meetings are included.

Results: This paper describes pertuzumab’s mechanism of action, safety, and role in HER2-positive BCs. It also explores the role of pertuzumab as a single agent or combined with trastuzumab by reviewing data from preclinical research to ongoing clinical trials. Recently published trials, particularly the CLEOPATRA study, highlight the efficacy, tolerability, and increase in disease-free survival associated with this novel agent when combined with trastuzumab.

Conclusion: The pertuzumab and trastuzumab anti-HER2 dual blockade is likely to represent a substantial advance for patients with HER2-positive BCs and a new milestone on the way to personalized medicine.

Key words: breast neoplasm, dimerization, HER2, pertuzumab

introduction

Approximately 15% to 20% of patients with breast cancer (BC) have human epidermal growth factor receptor 2 (HER2) overexpression or amplification, associated with poorer prognosis [1–3]. The humanized monoclonal antibody trastuzumab, now used in the metastatic and the adjuvant settings, has changed the approach to treat patients with HER2-positive BC and the prognosis of the disease [4–8].

Nevertheless, not all patients benefit from trastuzumab. Around 15% of women relapse after trastuzumab-based therapy, indicating the presence of de novo or acquired resistance to trastuzumab [9]. This is the basis for exploration into additional therapeutics [10], including lapatinib, neratinib, afatinib, trastuzumab emtansine (formerly known as trastuzumab-DM1), heat shock protein 90, histone deacetylase inhibitors, and pertuzumab [11–17].

Pertuzumab is a humanized monoclonal antibody that binds to the extracellular domain II of HER2. Its mechanism of action is complementary to trastuzumab, inhibiting ligand-dependent HER2–HER3 dimerization and reducing signaling via intracellular pathways such as phosphatidylinositol 3-kinase (PI3K/Akt). Pertuzumab has shown antitumor activity in both the metastatic and the neoadjuvant settings and is now being tested as adjuvant therapy [18–22]. In this review, we will discuss both pertuzumab and trastuzumab and their mechanisms of action, explore current evidence and potential benefits of treatment with these antibodies, and describe completed and ongoing clinical trials.

methods

A computer-based literature search was carried out using PubMed. Articles were selected using the key words ‘pertuzumab’, ‘breast neoplasm’, and ‘HER2’. Only papers published in English before May 2012 were reviewed. Published abstracts from international meetings and ongoing trials were also included.

background

the HER family receptors

HER2 family receptors consist of four transmembrane tyrosine kinase receptors present on the surface of normal cells: epidermal growth factor receptor (EGFR, also known as HER1, ErbB1), HER2 (HER2/neu or ErbB2), HER3 (ErbB3), and...
HER4 (ErbB4) (Figure 1) [23, 24]. Each receptor is characterized by three domains: an extracellular domain, an alpha helical transmembrane segment, and an intracellular protein kinase domain [25]. The extracellular domain is subdivided into four further domains. Of importance are domain I, the ligand-binding site; domain II, the dimerization site, that is the pertuzumab-binding site; and domain IV, the site for trastuzumab binding.

Three elements are required for pathway signaling from HER receptors: a ligand, an HER receptor, and a dimerization partner. A ligand binds to domain I, inducing a conformational change in the ligand-bound receptor and exposing the dimerization domain. Dimerization is vital and results in either a homodimer or a heterodimer and HER2 represents the preferred dimerization partner [26].

Determining which dynamic signaling pathway is activated depends on the ligand that is bound and the dimerization partner [27]. Homodimers form the weakest signal transduction units, while heterodimers, especially the HER2–HER3 dimer, produce the most potent signaling for the activation of the PI3K/Akt pathway [28–31]. Beyond the PI3K/Akt pathway, other pathways known to play an essential role in the development of BC include Ras-dependent mitogen-activated protein kinase (Ras/MAPK) and Janus kinase signal transducer and activator of transcription (JAK-STAT) (Figure 1) [25, 26, 32–36].

Trastuzumab is a recombinant monoclonal antibody that binds to the extracellular domain IV of HER2, which results in the down-regulation of the PI3K/Akt pathway [37]. Trastuzumab has different mechanisms of action, including antibody-dependent cell-mediated cytotoxicity, prevention of HER2 extracellular domain shedding, and angiogenesis inhibition; however, inhibition of signaling transduction is thought to be its main mechanism of action (Figure 1) [38]. Junttila et al. [39] have shown how trastuzumab, more strongly than pertuzumab, is able to inhibit ligand-independent activation of the PI3K/Akt pathway in overexpressed HER2 cell lines. Nevertheless, de novo and acquired trastuzumab resistance occurs and several resistance mechanisms have been described (Table 1) [40–58].

Pertuzumab inhibits the formation of both heterodimers and homodimers in the presence of an HER2 ligand; more specifically, it inhibits the potent HER2–HER3 interaction in the presence of heregulin (HRG), which activates the PI3k/Akt signaling pathway. Like trastuzumab, it also induces ADCC as one of its major mechanisms of action [60, 61].

**pharmacokinetics**

In the animals studied, the terminal half-life of pertuzumab was ~10 days, and the volume of distribution was 40 ml/kg [60]. In humans, pooled analysis from one phase IA and two phase II studies in advanced disease evaluated pertuzumab pharmacokinetic parameters demonstrated minor interpatient variability in clearance and volume distribution when pertuzumab was administered with a fixed dose or based on weight (mg/kg). This supports the use of fixed dosing of pertuzumab, with an initial loading dose (840 mg) followed by a fixed dose of 420 mg every 3 weeks [62].

**preclinical data**

HRG, a ligand of HER3, is believed to promote cell proliferation and tumorigenesis and play a role in metastasis in vivo [63]. Cell line studies have revealed that pertuzumab inhibits HRG-mediated morphogenesis on breast cell lines more than trastuzumab. By using BT474MI and MCF-7 breast cell lines treated with HRG and the two antibodies, Agus et al. [64] showed the superiority of pertuzumab in disrupting HRG-induced signaling. Whereas pertuzumab inhibited HRG-induced phosphorylation, vital for HER2-positive BC tumorigenesis, trastuzumab did not.

Similarly, BC tumors developed on originating from MDA-MB-175 cell lines depend on a paracrine HRG loop that activates HER2/HER3 and pertuzumab response in vitro, but not trastuzumab response. The ability of pertuzumab to inhibit tumors with HER2/HER3 activation in vitro is a unique characteristic that is not displayed by trastuzumab [65].

The results of xenograft experiments support those of the above cell-line studies and also offer insight into pertuzumab’s mechanistic pathway. When pertuzumab was combined with other agents, particularly with trastuzumab, it showed a synergistic effect when compared with pertuzumab monotherapy [66]. Sustained complete responses were seen in 60% of KPL-4 xenograft models when both agents were combined, and the effect was independent of HER2 expression [66]. This antitumor effect was greater than that observed with either pertuzumab or trastuzumab as a single agent (0% complete response in both cases) in tumors progressing on trastuzumab. Furthermore, these studies demonstrated a sustained (>99 days) prevention of metastatic tumor spread to lungs and the liver, a finding not seen with either of these agents alone. Similar results were reported with a BT474MI xenograft model [65, 66]. Tumor regression was comparable for trastuzumab, pertuzumab, and their combination, but subsequent tumor re-growth was less common with the combination than with either agent alone, although this result did not reach statistical significance. Scheuer et al. [66] have also shown that the combination of pertuzumab and trastuzumab was able to keep antitumor activity after progression on trastuzumab in KPL-4 and Calu-3 xenografts. Given recent preclinical data on the up-regulation of HER3 as...
important feedback mechanism on PI3K/Akt inhibition, it could be expected that blockade of HER3 would be important for the prevention of resistance mechanism in HER2-overexpression disease [67, 68].

Of particular interest is the ability of pertuzumab in preclinical models to inhibit tumor growth independently from the level of expression of HER2. Agus et al. [64] demonstrated a 59% inhibition of tumor growth (P < 0.001) with low HER2 levels in MCF7 xenograft models. However, this has not been confirmed by clinical studies [69].

Both trastuzumab and pertuzumab induce the activation of the ADCC pathway as part of their antitumor activity [66]. Early studies, however, did not reveal an additive effect on the activation of the ADCC pathway when using both antibodies in combination. Therefore, enhanced antitumor activity seems to arise from the complementary and different mechanisms of action of both antibodies.

**clinical data**

In the clinic, pertuzumab is revealing both its efficacy and its favorable toxicity profile, and has been—or is—the subject of numerous trials in the metastatic, adjuvant, and neoadjuvant settings. Most striking are the promising results of trials evaluating the dual anti-HER2 blockade with pertuzumab and trastuzumab.

**the metastatic setting**

Several phase I clinical trials testing pertuzumab as monotherapy or in combination with chemotherapy (CT) or trastuzumab in patients with metastatic breast cancer (MBC) refractory to standard treatment have been conducted (supplementary Table S1, available at Annals of Oncology online) [16, 17, 70–73]. In these trials, although the maximum tolerated dose was not reached, pertuzumab was generally well...
The most common adverse events (asthenia, diarrhea, vomiting, and rash) were of grades 1–2.

Two single-arm phase II studies evaluating pertuzumab in combination with trastuzumab without CT in patients with HER2-positive MBC who had progressed during prior trastuzumab-based therapy have been reported (Table 3) [18, 19]. The smaller of the two studies, conducted by Portera et al. [18], was stopped early because of cardiac toxicity. Designed with a target recruitment of 37 patients, the trial was halted when 6 of 11 (54%) patients experienced a decline in the left ventricular ejection fraction (LVEF). In the Baselga trial [19], 3 of 66 (4.5%) patients experienced a decreased LVEF ≥10% points and <50% absolute LVEF value; however, none of these patients suffered any cardiac symptoms. Regarding efficacy, the Baselga and Portera studies showed similar objective response rates (ORR) and clinical benefit rates (CBR) (ORR 18% and 24.5% and CBR 45.5% to 50%, respectively). The small difference in efficacy can be accounted for by the fact that the Portera study [18] included a poorer prognosis group of patients and fewer patients overall.

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**Table 1.** Trastuzumab: potential mechanisms of resistance

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Pathway</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired access of trastuzumab to the binding site</td>
<td>p95HER [52, 55, 56]</td>
<td>Cleavage of HER2 results in a truncated p95 protein (also called p95 HER2) that lacks the receptor site for trastuzumab. p95 HER2 may further add to resistance by independently phosphorylating HER3 and initiating signaling via the PI3K/Akt pathway</td>
</tr>
<tr>
<td>Membrane masking proteins [50, 51]</td>
<td>MUC 4 is a membrane-associated mucin that can conceal surface proteins on HER2, making it difficult for trastuzumab to identify the appropriate binding site</td>
<td></td>
</tr>
<tr>
<td>HER2 shedding</td>
<td>Shedding of the HER2 receptor with high levels of serum HER2 binds trastuzumab, reducing the amount of therapeutic trastuzumab</td>
<td></td>
</tr>
</tbody>
</table>

**Alternate signaling**

| Cross-talk [47, 53] | HER3 receptor has more specific direct binding sites than HER2 for the activation of the PI3K/Akt pathway |
| IGF-1R activation [48, 49, 57] | Insulin-like growth factor 1 receptor (IGF-1R) is a tyrosine kinase receptor that can very efficiently activate the PI3K/Akt pathway independently of HER2. IGF-1R decreases G1/S cell-cycle arrest via p27. Evidence of increased expression of IGF-1R in resistant clones |
| MET activation [46, 58] | MET is a tyrosine kinase implicated in resistance to EGFR inhibitors gefitinib and erlotinib and may play a part in trastuzumab resistance via increased levels of MET and its ligand, HRG. Trastuzumab exposure can increase the expression of MET |

**HER2-independent activation of downstream signaling**

| PTEN [43, 44] | PTEN is a negative regulator of the PI3K/Akt pathway. The absence of PTEN may lead to trastuzumab resistance |
| PI3K/Akt activating mutations [41, 42] | Most frequent are E542K or E545K and H1047R on exon 9 and 20, occurring in up to 40% of breast cancers. They represent gain-of-function mutations |
| Reduced p27 expression [40] | p27 interacts with the cell cycle to produce G1/S cell-cycle arrest. Reduced expression of p27 in trastuzumab-resistant cell lines |

**Table 2.** Trastuzumab and pertuzumab comparisons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trastuzumab</th>
<th>Pertuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Recombinant humanized monoclonal antibody, IgG1 (κ)</td>
<td>Fully humanized monoclonal antibody, human IgG1 (κ)</td>
</tr>
<tr>
<td></td>
<td>Two heavy chains (451 residues) and two light chains (214 residues)</td>
<td>Two heavy chains (449 residues) and 2 light chains (214 residues)</td>
</tr>
<tr>
<td></td>
<td>Produced in CHO cell culture</td>
<td>Produced in CHO cell culture</td>
</tr>
<tr>
<td>Epitope-binding region</td>
<td>Extracellular domain of HER2 (domain IV)</td>
<td>Extracellular domain of HER2 (domain II)</td>
</tr>
<tr>
<td>Half-life</td>
<td>25.5 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intravenous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Type of inhibitor</td>
<td>–</td>
<td>Dimerization</td>
</tr>
<tr>
<td>Induces ADCC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibitor of HER2–HER3 dimer formation in a ligand-induced fashion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibitor of HER2–HER3 dimer formation in a ligand-independent fashion</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prevents HER2 extracellular domain shedding</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Efficacy affected by formation of p95HER2</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reduces cross-talk, resistance</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
pertuzumab and trastuzumab was well tolerated in both studies [18, 19]. 

Cortes et al. [74] have published the third cohort of the above study by Baselga et al. to assess the efficacy of pertuzumab monotherapy and the reintroduction of trastuzumab in combination with pertuzumab in patients who had already progressed on both drugs. Surprisingly, the ORR and CBR were 3.4% and 10.3%, respectively, in the 29 patients who received pertuzumab monotherapy, whereas the ORR and CBR were 17.6% and 41.2%, respectively, in the patients who received dual blockade after progression on pertuzumab. These results were comparable with the first cohort of patients. Treatment was also well tolerated with no relevant cardiac toxicity. These results form the rationale for the PHEREXA study (discussed below) and raise the question of why pertuzumab monotherapy is largely ineffective and why the reintroduction of HER2 blockade can be effective for some women despite previous progression.

In another important study, Gianni et al. [69] examined the effect of pertuzumab in 79 patients with HER2-negative disease. Patients were randomly assigned to receive two different doses of pertuzumab as a single agent. Unfortunately, the ORR was 2.5% with a CBR of 7.7%, indicating limited efficacy of pertuzumab in HER2-negative BC patients, despite the promising preclinical data previously published (Table 3).

CLEOPATRA [Clinical Evaluation Of Pertuzumab And Trastuzumab (NCT00567190)] is a phase III, randomized, double-blind, placebo-controlled study evaluating the role of the dual anti-HER2 blockade. Eight hundred and eight previously untreated patients in metastatic setting were randomly assigned to receive T-DM1 and pertuzumab, T-DM1 and pertuzumab-placebo or trastuzumab and docetaxel.

PHEREXA [Pertuzumab HERceptin Evaluation with Xeloda® (NCT01026142)] is an ongoing, randomized, multicenter phase III trial exploring the role of pertuzumab in combination with T-DM1, another potentially interesting dual blockade [75]. A total of 1092 patients with recurrent locally advanced or previously untreated MBC are being randomly assigned to receive T-DM1 and pertuzumab, T-DM1 and pertuzumab-placebo or trastuzumab and docetaxel.

Other trials for MBC which have yet to release results include MARIANNE (NCT01120184) and PHEREXA (NCT01026142). MARIANNE is a randomized, multicenter phase III trial exploring the role of pertuzumab in combination with T-DM1, another potentially interesting dual blockade [75]. A total of 1092 patients with recurrent locally advanced or previously untreated MBC are being randomly assigned to receive T-DM1 and pertuzumab, T-DM1 and pertuzumab-placebo or trastuzumab and docetaxel.

The neoadjuvant setting
The neoadjuvant setting offers a unique opportunity to rapidly assess the antitumor efficacy of new agents in patients with BC, thus also the potential of a pertuzumab and trastuzumab dual HER2 blockade. An example of this approach, the randomized phase II study NeoSphere [Neoadjuvant Study of Pertuzumab and Herceptin in Early Regimen Evaluation (NCT00545688)], evaluated the combination of pertuzumab with docetaxel and trastuzumab in 417 patients with HER2-positive BC (supplementary Figure S2, available at Annals of Oncology online).
online). The primary end point was a comparison of the pathological complete response (pCR) rates defined according to the National Surgical Adjuvant Breast and Bowel Project (NASABP) guidelines (i.e. no invasive cancer in the breast or only non-invasive in situ cancer in the breast specimen). Secondary end points included clinical response rate (CRR), DFS, breast conservation rate (BCR), and a biomarker evaluation [22].

In NeoSphere, the combination of docetaxel, trastuzumab, and pertuzumab (DTP) was able to nearly double the pCR rate (45.8%) when compared with the other study arms which generated the following pCR results: 29% (P = 0.0141) for docetaxel plus trastuzumab (DT); 16.8% (P-value not reported) for trastuzumab plus pertuzumab (TP); and 24% (P = 0.003) for docetaxel plus pertuzumab (DP). As expected, pCR rates were higher in patients who, at surgery, were node-negative rather than node-positive (21.5% versus 7.5%, 39.3 versus 6.5%, 11.2% versus 5.6%, and 17.7% versus 6.3% for DT, DTP, TP, and DP, respectively).

The treatment groups were also analyzed according to estrogen receptor (ER) status, with higher pCR in ER-negative than in ER-positive tumors. In the DTP arm, patients with ER-negative disease attained a pCR of 63.2% compared with 26% for patients with ER-positive BC. The study arm using both monoclonal antibodies alone without docetaxel (TP), which demonstrated a pCR of 16.8% overall, but a pCR of 31% in patients with BC identified as ER-negative. This lends support to the hypothesis that it may be possible to identify a subgroup of patients who can be spared CT; however, this will require further validation [22].

Another trial of interest is TRYPHAENA (NCT00976989), a multicenter, randomized, phase II study that evaluated the combination of pertuzumab and trastuzumab given to 225 patients with HER-2-positive BC in one of the three following arms: arm 1, concurrently with an anthracycline-taxane regimen [FEC (5-fluorouracil, epirubicine, and cyclophosfamide) followed by docetaxel]; arm 2, sequentially to FEC, but concurrently with docetaxel; or arm 3, concurrently with both docetaxel and carboplatin (supplementary Figure S3, available at Annals of Oncology online). The study’s primary end point was to assess cardiac toxicity, and its secondary end points were tolerability, pCR, CRR, and BCR.

The pCR rates, as defined by NASABP guidelines, were quite similar across the three arms: 61.6% in arm 1, 57% in arm 2, and 66.2% in arm 3. pCR was analyzed according to the ER status and showed higher pCR in ER-negative tumors than in ER-positive ones in all three arms: 79.4% versus 46.2% in arm 1; 65.0% versus 48.6% in arm 2; and 83.8% versus 50.0% in Arm 3 [21].

the adjuvant setting

Based on the promising data of trastuzumab and pertuzumab combination in metastatic and neoadjuvant settings, APHINITY was developed for the adjuvant setting. APHINITY is a prospective, two-arm, randomized, multicenter, multinational, double-blind, placebo-controlled study aiming to enroll 3806 patients with HER2-positive early BC. Patients will be randomly assigned (1:1 ratio) to receive either anthracycline or non-anthracycline-containing adjuvant CT (investigators’ choice) and either trastuzumab plus pertuzumab or trastuzumab plus a placebo for a total of 12 months. Patients will be stratified according to nodal status, adjuvant CT type, hormone receptor status, and geographical region (Figure 2) [77].

APHINITY’s primary objective is to show an improvement in invasive disease-free survival with the two anti-HER2 monoclonal antibodies (HR of 0.76). Patients will be followed for 10 years, and the study’s secondary objectives include second non-Bcs, DFS, OS, recurrence-free interval, distant recurrence-free interval, cardiac safety, overall safety, and health-related quality of life. In addition, foreseen translational research will evaluate several biomarkers with the aim of identifying patients whose disease is more likely to respond to treatment or those who likely to experience toxicity. The first patient was recruited in October 2011.

safety data

Many BC patients have now been treated with pertuzumab in reported phase I or II metastatic clinical trials [17-19, 69-73, 78]. The most common toxic effects were diarrhea, asthenia, nausea, and rash, the majority being grades 1–2, which indicates that pertuzumab is well tolerated. In the phase III CLEOPATRA study, the most common toxic effects at any grade were the same as in the phase I or II trials, most manageable grades were 1–2. Some of these adverse events showed ≥5% higher incidence of any grade in the docetaxel plus trastuzumab and pertuzumab arm compared with the one without pertuzumab. The adverse events were diarrhea (66.8% versus 46.3%), rash (33.7% versus 24.2%), mucosal inflammation (27.8% versus 19.9%), febrile neutropenia (13.8% versus 7.8), and dry skin (10.6% versus 4.3%). Adverse events grade ≥3 such as neutropenia (48.9% versus 45.8%), febrile neutropenia (13.8 versus 7.6%), leucopenia (16.6 versus 12.3%), and diarrhea (7.9% versus 5%) were also slightly higher in the docetaxel plus pertuzumab and trastuzumab arm (Table 4) [20].

Regarding the combination of pertuzumab and CT in the neoadjuvant setting, NeoSphere indicates that this regimen is generally well tolerated, showing only slightly higher rates of diarrhea and asthenia than with CT alone. The rates of neutropenia or rash were not increased by adding pertuzumab to any regimen, a finding also present in other earlier trials. The number of serious adverse events in the DTP arm totaled 14%, and 17% in the DT arm. DTP toxicity comprised neutropenia (44.9%), febrile neutropenia (8.4%), asthenia (1.9%), and rash (1.9%) (Table 4) [22]. In TRYPHAENA, the toxicity reported was almost the same, independent of the type of CT used in combination with the anti-HER2 dual blockade. The most common grade ≥3 adverse events were neutropenia, febrile neutropenia, leucopenia, and diarrhea (Table 4) [21].

cardiac safety

Lenihan et al. [79] examined cardiotoxicity in 554 patients included in pertuzumab phase II trials of different solid tumors. Of these, 331 patients received pertuzumab as a single agent, 93 patients received pertuzumab and trastuzumab in
combination, and 130 patients received pertuzumab with non-anthracycline CT or erlotinib. The addition of pertuzumab to trastuzumab did not lead to substantial LVEF reduction (6.5% patients receiving combination treatment versus 6.9% treated with single-agent pertuzumab); however, there was a small increase in the percentage of patients who experienced symptoms of congestive heart failure (CHF) (1.1% versus 0.3%). Nevertheless, the incidence is extremely low, and the majority of patients showed substantial improvement or return to baseline LVEF [79]. Similar results were seen in the CLEOPATRA, NeoSphere, and TRYPHAENA studies.

In CLEOPATRA, left ventricular systolic dysfunction (LVSD) of any grade was more frequent in the trastuzumab plus CT arm than in the trastuzumab plus pertuzumab and CT arm (8.3% versus 4.4%). LVEF grade 3 was also higher in that arm (2.8% versus 1.2%) [20]. In NeoSphere, CHF did not

Table 4. Adverse events grade ≥ 3 in pertuzumab and trastuzumab studies in combination with chemotherapy

<table>
<thead>
<tr>
<th>Adverse events grade ≥ 3 (%)</th>
<th>Neoadjuvant phase II</th>
<th>Metastatic phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TRYPHAENA [21] (n = 225)</td>
<td>NeoSphere [22] (n = 417)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>47.2</td>
<td>42.7</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>18.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>19.4</td>
<td>12.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Rash</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

C, carboplatin; FEC, 5-fluorouracil, epirubicine, and cyclophosphamide; D, docetaxel; P, pertuzumab; Pla, placebo; T, trastuzumab.

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Figure 2. APHINITY is a prospective phase III study evaluating the role of trastuzumab plus pertuzumab combination versus trastuzumab plus placebo with anthracycline and non-anthracycline-based chemotherapy in HER2-positive breast cancer patients in the adjuvant setting. A, anthracycline; DC, docetaxel and carboplatin; Tax, taxane-based chemotherapy (either docetaxel or paclitaxel).
increase with the addition of pertuzumab [22]. As already mentioned, TRYPHAENA’s primary end point was to evaluate the cardiac safety of the pertuzumab and trastuzumab combination, either with anthracycline-containing CT, concurrently or sequentially or with non-anthracycline CT. Low incidence of symptomatic or asymptomatic cardiac toxicity was observed across the three arms. Furthermore, LVSD at any grade was almost the same when anthracyclines were administered concurrently or sequentially with trastuzumab and pertuzumab (5.6% and 4%), respectively. LVEF decrease (defined as ≥10% and ≤50%) was slightly higher in the anthracycline arms, but all patients recovered during the adjuvant treatment [21]. In conclusion, pertuzumab and trastuzumab in combination with CT has to date shown a safe and favorable cardiac toxicity profile when patients are well selected and appropriate monitoring is conducted during and after treatment. The large APHINITY trial hopefully will confirm the low cardiotoxic potential of the pertuzumab–trastuzumab combination.

discussion

Pertuzumab, an HER2 dimerization inhibitor, displays mechanistic advantages that distinguish it from trastuzumab. Pertuzumab’s clinical efficacy has been low when used alone but very striking when used in combination with trastuzumab [70–73]. The generally non-overlapping toxicity profiles of these two drugs are conducive to their combination. For example, gastrointestinal, skin, and asthenia side-effects are more commonly associated with pertuzumab than with trastuzumab.

Regarding cardiotoxicity, pertuzumab shows a low incidence of cardiac events, similar to the cardiotoxicity associated with trastuzumab [80]. Substantial LVEF reduction, defined as a decrease of ≥10% below baseline and to an absolute value of <50%, was reported in the HERA trial as 7.03% for a single substantial LVEF drop in the trastuzumab arm [81]. This definition was also employed in the pooled cardiotoxicity analysis of pertuzumab completed by Lenihan et al. [79], which revealed a comparable rate of LVEF reduction of 6.9% for pertuzumab as a single agent, and 6.5% when pertuzumab was combined with trastuzumab. The CLEOPATRA study reported similar results: a substantial LVEF decrease of 8.3% in the trastuzumab plus CT arm compared with 4.4% in the pertuzumab and trastuzumab combination with CT. Based on these data, pertuzumab alone or in combination with trastuzumab demonstrates a safe cardiac profile [20]. The APHINITY study will provide a clearer perspective on this issue [77].

The potential in pertuzumab lies in the dual anti-HER2 blockade with trastuzumab. Several trials have evaluated patient benefit from various combinations of anti-HER2 therapies, mostly in the metastatic setting, although further promising evidence derives from the neoadjuvant setting. In NeoSphere and in NeoALTTO studies, which evaluated the role of lapatinib in combination with trastuzumab and paclitaxel, the pCR of dual anti-HER2 therapy with CT was ~50%, almost doubled when compared with single-agent anti-HER2 treatment with CT. Furthermore, in TRYPHAENA, pCR reached 57.3% to 66.2%, probably because of the addition of a second CT agent (carboplatin or anthracycline) to the dual blockade [21, 22, 82].

Another issue to take into consideration is the different results according to ER status observed in the neoadjuvant setting. TRYPHAENA, NeoSphere, and NeoALTTO, all demonstrated enhanced pCR in the subgroup of patients with ER-negative BC who received the dual anti-HER2 therapy combined with CT: 65.0% to 83.8% versus 46.2% to 50% (TRYPHAENA), 63.2% versus 26.0% (NeoSphere), and 61.3% versus 41.4% (NeoALTTO) for ER-negative and ER-positive tumors, respectively [21, 22, 82]. Results were similar in the Translational Breast Cancer Research Consortium (TBCRC 006) phase II trial, with pCR higher for patients with ER-negative tumors (42%) than those with ER-positive ones (21%) treated with lapatinib and trastuzumab [83]. There are different possible explanations for this observation: (i) an intrinsically greater chemosensitivity of ER-negative BC; (ii) a greater number of salvage pathways in ER-positive BC, with the ER pathway being the number one suspect.

One of the most important challenges for the future is the definition of which subgroups of HER2-positive patients require which combination of dual anti-HER2 therapy. Also of high interest is the report from the NeoSphere trial, which established a pCR of 16.8% using pertuzumab and trastuzumab alone, with another provocative result from the TBCRC 006 trial, which observed a pCR of 28% for the combination of lapatinib and trastuzumab without CT [22, 83]. These data suggest that a subgroup of women do not require combination cytotoxic CT. Progress in the translational research in HER2-positive disease will need to be made rapidly in the next years, as many other anti-HER2 molecules are currently in clinical development. With respect to pertuzumab, trials such as APHINITY will contribute to establishing the drug’s role in the complex framework of HER2-positive BC and will add to our growing scientific and biological understanding of the disease.

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references


