

HER2 Dimerization Inhibitor Pertuzumab – Mode of Action and Clinical Data in Breast Cancer

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Keywords

HER2-positive · Dual inhibition · Breast cancer, metastatic · Pertuzumab · Trastuzumab

Summary

The humanized monoclonal antibody pertuzumab prevents the dimerization of HER2 with other HER receptors, in particular the pairing of the most potent signaling heterodimer HER2/HER3, thus providing a potent strategy for dual HER2 inhibition. It binds to the extracellular domain of HER2 at a different epitope than trastuzumab. Pertuzumab and trastuzumab act in a complementary fashion and provide a more complete blockade of HER2-mediated signal transduction than either agent alone. Phase II studies demonstrated that pertuzumab was generally well tolerated as a single agent or in combination with trastuzumab and/or cytotoxic agents, and implied an improved clinical efficacy of the combination of pertuzumab and trastuzumab in early and advanced HER2-positive breast cancer. Results of the pivotal phase III study CLEOPATRA in patients with HER2-positive metastatic breast cancer demonstrated that the addition of pertuzumab to first-line combination therapy with docetaxel and trastuzumab significantly prolonged progression-free and overall survival without increasing cardiac toxicity. Currently, the combination of both antibodies is being explored in the palliative setting as well as in the treatment of early HER2-positive breast cancer. Dual HER2 inhibition with the HER2 dimerization inhibitor pertuzumab and trastuzumab may change clinical practice in HER2-positive first-line metastatic breast cancer treatment.

Schlüsselwörter

HER2-positiv · Duale Inhibition · Mammakarzinom, metastasiertes · Pertuzumab · Trastuzumab

Zusammenfassung

Der humanisierte monoklonale Antikörper Pertuzumab verhindert die Dimerisierung von HER2 mit anderen HER-Rezeptoren, insbesondere die Bildung des im Hinblick auf Signaltransduktionskaskaden potentesten Heterodimers HER2-HER3 und ermöglicht damit eine grundlegend andere Strategie der dualen HER2-Inhibition. Pertuzumab bindet an die extrazelluläre Domäne von HER2, aber einem anderen Epitop als Trastuzumab. Pertuzumab und Trastuzumab erreichen zusammen eine vollständigere Blockade der HER2-vermittelten Signaltransduktion als jede Substanz alleine. Phase-II-Studien konnten zeigen, dass Pertuzumab alleine oder in Kombination gut verträglich ist. Sie legten auch eine verbesserte klinische Wirksamkeit der Kombination von Pertuzumab und Trastuzumab bei primärem und fortgeschrittenem HER2-positivem Brustkrebs nahe. Die Ergebnisse der Phase-III-Studie CLEOPATRA bei Patientinnen mit metastasiertem HER2-positivem Mammakarzinom zeigten, dass die zusätzliche Gabe von Pertuzumab zu einer Erstlinien-Kombinationstherapie mit Docetaxel und Trastuzumab das progressionsfreie Überleben und das Gesamtüberleben signifikant verlängerte ohne Steigerung der kardialen Toxizität. Derzeit wird die Kombination aus beiden Antikörpern in der palliativen Situation und in der Behandlung des frühen HER2-positiven Mammakarzinoms untersucht. Die duale HER2-Inhibition mit Trastuzumab und dem HER2 Dimerisationsinhibitor Pertuzumab könnte die klinische Praxis für die Erstlinientherapie beim metastasierten HER2-positiven Mammakarzinom und möglicherweise auch in früheren Stadien verändern.

Introduction

According to a current analysis of more than 18,000 results of HER2 testing in clinical routine practice, $16.7 \pm 3.2\%$ (95% confidence interval (CI) 16.6–16.8) of patients with early breast cancer have HER2-positive tumors [1]. HER2 positivity is correlated with aggressive breast tumor behavior and associated with reduced response to standard therapies and decreased breast cancer survival [2, 3]. The introduction of targeted therapy against HER2 has significantly changed the prognosis of patients with HER2-positive breast cancer, transforming HER2 positivity from a negative prognostic to a positive predictive disease marker. Trastuzumab has become the standard of care that significantly improves outcomes in patients with HER2-positive early breast cancer [4–9] and HER2-positive metastatic breast cancer (MBC) [10, 11]. Yet, despite the proven efficacy of trastuzumab plus chemotherapy, some patients with HER2-positive breast cancer do not respond, and the disease in the majority of patients with MBC progresses within 1 year. The medical need for targeted therapy for advanced disease is being addressed through intensive research efforts. Dual therapy targeting HER2 has been identified as a promising treatment strategy [12]. The humanized monoclonal antibody pertuzumab binds to the extracellular domain of HER2. It prevents the dimerization of HER2 with other HER receptors, especially HER3 [13] and allows for a fundamentally different strategy of dual HER2 inhibition.

HER Family and HER2-HER3 Heterodimer

The 4 type 1 transmembrane tyrosine kinase receptors EGFR (or HER1), HER2, HER3 and HER4 constitute the HER family. HER1, HER2 and HER3 are all implicated in the development and progression of cancer [14]. In principle, each receptor consists of an extracellular domain that binds ligands, a transmembrane region and a cytoplasmic domain with kinase activity, with the exceptions that there is no known ligand to HER2, and HER3 does not exert tyrosine kinase activity. Ligand binding induces conformational rearrangements of the receptors, and promotes association of both homodimers and heterodimers. This is followed by internalization, phosphorylation and further downstream signaling, thus regulating many cellular processes including cell growth, proliferation and survival [15].

Not all of the 10 possible dimers are fully biologically active. HER2 and HER3 are highly complementary to each other: HER3 binds ligand yet lacks intrinsic kinase activity; HER2 has intrinsic tyrosine kinase activity but no identified ligand [14]. The HER2/HER3 heterodimer is considered the most potent HER dimer pair with respect to strength of interaction, ligand-induced tyrosine phosphorylation and downstream signaling [16, 17]. In vitro, reduction of HER3 expres-

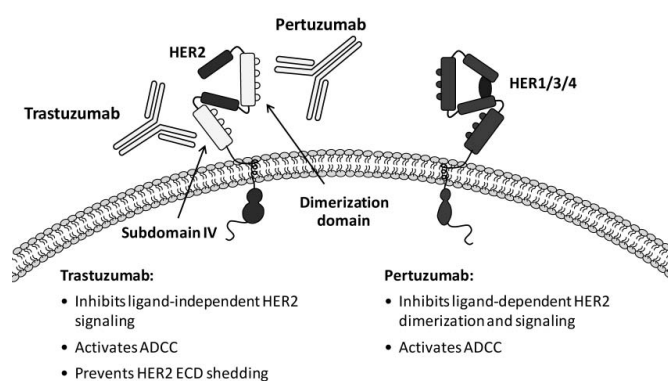


Fig. 1. Complementary mechanisms of action of pertuzumab and trastuzumab. Adapted from Baselga J et al. [40]

ADCC = antibody-dependent cell-mediated cytotoxicity; ECD = extracellular domain.

sion decreased cell proliferation to the same extent as reduction of HER2 expression [18]. Also, HER3 provides an escape route for breast cancer when HER1 and HER2 are inhibited by tyrosine kinase inhibitors [19, 20].

Pertuzumab – Mode of Action and Rationale for Combination with Trastuzumab

Pertuzumab is a humanized monoclonal antibody that binds to the dimerization domain of HER2. Blocking the pairing of the most potent signaling HER dimer, HER2-HER3, affects key signaling pathways [13, 17, 20, 21]. As it binds to the extracellular domain of HER2 pertuzumab can also activate immune effector functions such as antibody-dependent cell-mediated cytotoxicity [22].

In vitro studies have shown that trastuzumab and pertuzumab bind to different epitopes on the HER2 protein [13]. Concomitant binding of both antibodies has also been demonstrated in vivo [22]. The modes of action of trastuzumab and pertuzumab are complementary (fig. 1). Trastuzumab inhibits ligand-independent HER2 signaling, prevents HER2 activation by extracellular domain shedding, and flags cells for destruction by the immune system [22–24]; however, it cannot prevent ligand-activated HER2/HER3 or HER2/HER1 heterodimerization, a potential escape mechanism for tumor cells from the inhibitory effects of trastuzumab [13, 21, 25]. There is preclinical evidence for the synergy of trastuzumab and pertuzumab in HER2-overexpressing tumors and specifically in HER2-overexpressing breast cancer. It was demonstrated that trastuzumab and pertuzumab synergistically inhibited the survival of HER2-overexpressing BT474 breast cancer cells in vitro [24]. In vivo, the combination of trastuzumab and pertuzumab dramatically enhanced the anti-tumor effect in an HER2-overexpressing breast cancer xenograft model compared to each antibody as a single agent [22].

In addition, the combination of pertuzumab and trastuzumab was effective following progression on trastuzumab [22].

Clinical Data

Monotherapy with Pertuzumab

Single-agent pertuzumab has been evaluated in 2 phase I studies in 39 patients with solid tumors. The results demonstrated that pertuzumab was well tolerated and had a pharmacokinetic profile supporting 3-week dosing [26]. The maximum tolerated dose (MTD) was not reached up to the dose level of 25 mg/kg [27]. Results also implied potential flat dosing.

Five phase II studies in unselected patients with advanced prostate, non-small cell, ovarian and breast cancer demonstrated a modest clinical activity of single-agent pertuzumab [28–32]. Pertuzumab was generally well tolerated. Most adverse events were grade 1–2. Diarrhea, rash, asthenia, vomiting, nausea and abdominal pain were most common. A pooled analysis of 598 patients from 14 studies with pertuzumab as a single agent, or in combination with capecitabine, docetaxel, gemcitabine, carboplatin, paclitaxel, erlotinib or trastuzumab showed an at least similar cardiac safety as trastuzumab. 23 of 331 patients across all studies with single-agent pertuzumab developed asymptomatic left ventricular systolic dysfunction and 1 (0.3%) symptomatic heart failure [33]. There was no notable increase in cardiac side effects when pertuzumab was given in combination with non-anthracycline cytotoxics, erlotinib or trastuzumab.

A phase II study performed in 79 patients with HER2-negative breast cancer evaluated pertuzumab given once every 3 weeks with a loading dose of 840 mg followed by either 420 mg or 1,050 mg. Pharmacokinetic data supported a fixed dose of pertuzumab once every 3 weeks [32]. Analysis of pooled data from 153 patients from 3 clinical studies in which pertuzumab was either administered every 3 weeks as a weight-based or fixed dose (420 or 1,050 mg) indicated that pharmacokinetic profiles were similar, thus proving the feasibility of administering pertuzumab as a fixed dose [34].

Dual HER2 Inhibition with Pertuzumab and Trastuzumab – Phase II Studies

A phase II study in patients with HER2-positive MBC with progression during prior trastuzumab therapy provided the first evidence that the combination of the 2 antibodies pertuzumab and trastuzumab, without additional chemotherapy, was clinically active and well tolerated [35]. The overall response rate for the 66 patients treated with the combination of both antibodies was 24.2%. Complete response (CR) was seen in 4 (6.1%), partial response (PR) in 12 (18.2%), and stable disease (SD) for 6 months in 17 (25.8%) patients. Median progression-free survival (PFS) was 5.5 months. Adverse events were generally grade 1 or 2 and included

diarrhea, fatigue, nausea, and rash. 4 patients experienced treatment-related adverse events of grade 3 or higher. There were no significant cardiac events. Only 3 patients had a decrease in left ventricular ejection fraction (LVEF) of > 10% points from baseline or to < 50% of the absolute value. No patient withdrew due to cardiac-related adverse events [35].

Data for the efficacy and safety of the combination of pertuzumab and trastuzumab also come from 2 large randomized studies in the neoadjuvant setting. 417 patients with locally advanced, inflammatory or early HER2-positive breast cancer were enrolled in the international randomized phase II trial NeoSphere [36]. Patients were randomized into 4 arms and received trastuzumab plus docetaxel in arm A, pertuzumab, trastuzumab plus docetaxel in arm B, pertuzumab and trastuzumab in arm C and pertuzumab plus docetaxel in arm D. Study drugs were given every 3 weeks for 4 cycles before surgery. Trastuzumab was given with a loading dose of 8 mg/kg and at 6 mg/kg subsequently, pertuzumab at a loading dose of 840 mg and then at 420 mg, and docetaxel at 75 mg/m² escalating if tolerated to 100 mg/m². The highest pathological CR (pCR) of 45.8% was achieved with the combination of pertuzumab, trastuzumab plus docetaxel as compared to 29% for trastuzumab plus docetaxel ($p = 0.0141$) and 24.0% with pertuzumab plus docetaxel ($p = 0.003$). Of note, patients treated with the chemotherapy-free combination of pertuzumab and trastuzumab had a pCR of 16.8%. Fewer pCRs were seen in hormone receptor-positive tumors across all study arms. The most frequent adverse events were mostly grade 1–2 and were alopecia, neutropenia, diarrhea, nausea, fatigue rash and mucosal inflammation. The lowest incidence of adverse events $\geq$ grade 3 was recorded for the combination of pertuzumab and trastuzumab. The mean maximum decrease in LVEF was low (4–5%) and balanced across treatment arms. Adding pertuzumab to trastuzumab did not result in an increase of cardiac toxicity [36]. Extensive biomarker analyses have been performed but so far have not yielded clinically useful assays for patient or regimen selection in addition or alternatively to conventional HER2 assessment used at present [37].

Another 223 patients with HER2-positive locally advanced, inflammatory or early stage breast cancer were assigned to 3 arms of 6 cycles of neoadjuvant treatment in the TRYPHAENA study, an international randomized phase II study [38]. Patients in arm A received FEC (5-fluorouracil, epirubicin, cyclophosphamide) in cycles 1–3 and docetaxel in cycles 4–6 plus pertuzumab and trastuzumab from cycles 1–6. Patients in arm B were treated with FEC from cycles 1–3 and docetaxel from cycles 4–6 plus pertuzumab and trastuzumab from cycles 4–6 only. In arm C, patients received docetaxel and carboplatin plus pertuzumab and trastuzumab from cycles 1–6. Study drugs were administered every 3 weeks. Pertuzumab was given at a loading dose of 840 mg and at 420 mg subsequently, and trastuzumab at a loading dose of 8 mg/kg and at 6 mg/kg subsequently. Following surgery, patients received trastuzumab to complete 1 year of treatment. The primary endpoint

of the study was cardiac safety, assessed by a thorough follow-up of 15 LVEF assessments up to 60 months post randomization. Cardiac toxicity was generally mild in all treatment arms with symptomatic left ventricular systolic dysfunction (LVSD) $\geq$ grade 3 in 0%, 2.7% and 0%, and LVEF decline $\geq$ 10% points from baseline or to $<$ 50% in 4.2%, 5.3% and 3.9% of patients for arms A, B, and C, respectively. There was no difference in cardiac side effects for concurrent administration of pertuzumab plus trastuzumab with epirubicin compared with sequential administration or the anthracycline-free regimen. Neutropenia, febrile neutropenia, leukopenia, and diarrhea were most frequently reported adverse events of $\geq$ grade 3 across all arms. Regardless of chemotherapy chosen, the combination of pertuzumab with trastuzumab in the neoadjuvant setting resulted in high pCR rates of 61.6%, 57.3% and 66.2% for arms A, B, and C, respectively [38].

Dual HER2 Inhibition with Pertuzumab and Trastuzumab – Pivotal Phase III Study in First-line MBC Treatment

In the pivotal phase III trial CLEOPATRA, 808 patients with centrally confirmed HER2-positive locally recurrent, unresectable, or metastatic breast cancer were randomized [39, 40]. For inclusion, patients could have had only a prior hormonal regimen for MBC. Prior neoadjuvant or adjuvant systemic therapy, including trastuzumab and/or taxanes, was allowed if the disease-free interval was $\geq$ 12 months. Patients were treated until the time of disease progression or the development of unacceptable toxicity either with a combination of docetaxel, trastuzumab and placebo in the control group or docetaxel, trastuzumab and pertuzumab in the experimental arm (fig. 2). The recommendation was to administer at least 6 cycles of chemotherapy. If chemotherapy was discontinued due to toxicity, antibody therapy could be continued until disease progression or onset of unacceptable toxicity. 75% of all patients discontinued docetaxel but continued to receive pertuzumab or placebo plus trastuzumab treatment. The median number of treatment cycles per patient was 15 (range 1–50) in the control and 18 (range 1–56) in the pertuzumab

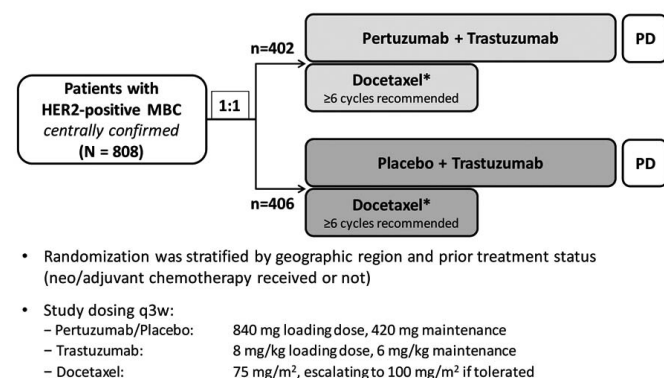


Fig. 2. CLEOPATRA: Study design. Adapted from Baselga J et al. [40]. MBC = metastatic breast cancer; PD = progressive disease.

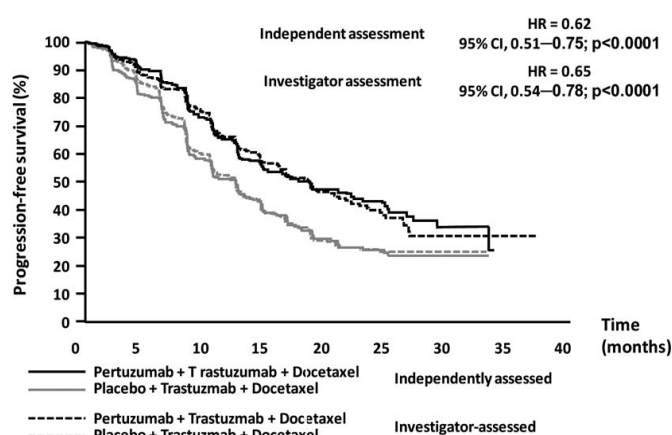


Fig. 3. Independently and investigator-assessed progression-free survival. Adapted from Baselga J et al. [39, 40].

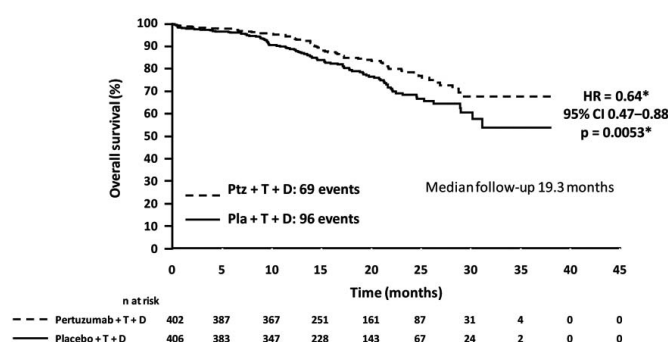


Fig. 4. CLEOPATRA: Predefined interim analysis of overall survival (n=165 events). Adapted from Baselga J et al. [39, 40].

D = docetaxel; OS = overall survival; Pla = placebo; Ptz = pertuzumab; T = trastuzumab.

group. Median duration of study treatment was 11.8 and 18.1 months, respectively. A median of 8 cycles of docetaxel were administered in both groups.

The primary endpoint of independently assessed PFS was met. Pertuzumab increased PFS by 6.1 months from 12.4 months in the control group to 18.5 months in the experimental arm (fig. 3). The treatment benefit was consistent across all prespecified subgroups except for the subgroup of patients with non-visceral disease. In particular, there was a clear treatment benefit in both hormone receptor-negative and -positive patients. In the 288 patients who had received adjuvant or neoadjuvant therapy without trastuzumab, independently assessed PFS was 12.6 months for the control and 21.6 months for the pertuzumab group (hazard ratio (HR) = 0.60; 95% CI, 0.43–0.83). For the 88 patients with prior neoadjuvant or adjuvant trastuzumab, median independently assessed PFS was 10.4 and 16.9 months (HR = 0.62; 95% CI, 0.35–1.07), respectively.

Analysis of the secondary endpoint, overall survival, is event-driven. A preplanned interim analysis performed after 165 events and a median follow-up of 19.3 months showed a

Table 1. CLEOPATRA: Cardiac tolerability^a

	Placebo + trastuzumab + docetaxel	Pertuzumab + trastuzumab + docetaxel
n	397	407
Investigator-assessed symptomatic LVSD ^b	1.8%	1.0%
Independently adjudicated symptomatic LVSD ^b	1.0%	1.0%
Fall in LVEF to < 50% or by ≥ 10% points from baseline	6.6%	3.8%

LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction.

^aAdapted from Baselga J et al. [40].

^bSymptomatic LVSD was defined as New York Heart Association (NYHA) class III/IV.

strong trend toward a survival benefit with pertuzumab-trastuzumab-docetaxel with an HR of 0.64 (95% CI, 0.47–0.88) (fig. 4). The confirmatory overall survival analysis performed after 267 deaths and a median follow-up of 30 months in both arms confirmed a significant survival benefit for the combination of pertuzumab, trastuzumab and docetaxel (HR = 0.66; 95% CI, 0.52–0.84, $p = 0.0008$) [41]. There was also a significant increase in objective response rate from 69.3% in the control to 80.2% in the pertuzumab group ($p = 0.001$).

The combination of pertuzumab and trastuzumab plus docetaxel increased rates of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. These adverse events were primarily grades 1 or 2 and manageable [39, 40]. The great majority of events (all grades and grades ≥ 3) occurred during concomitant antibody and docetaxel administration with a substantial reduction in rates of the most common adverse events following discontinuation of docetaxel. After stopping administration of docetaxel febrile neutropenia was no longer reported in the placebo or the pertuzumab arm [42]. Importantly, there was no increase in cardiac adverse events or LVSD with the addition of pertuzumab (table 1). A univariate Cox regression analysis demonstrated that development of LVSD was associated with prior therapy with anthracyclines and prior radiotherapy. There was no significant association between prior trastuzumab therapy and development of LVSD [43].

Quality of life was similar for both study arms. An exploratory analysis showed that the combination of pertuzumab, trastuzumab and docetaxel was associated with a substantial delay in the time to onset of specific breast cancer symptoms with a median time to deterioration of symptoms of 18.3 weeks for placebo, trastuzumab and docetaxel compared to 26.7 weeks for the pertuzumab, trastuzumab and docetaxel arm (HR = 0.77; 95% CI 0.64–0.93, $p = 0.0061$) [44].

Pertuzumab – Ongoing and Planned Studies

There are a number of ongoing and planned studies aimed at evaluating the combination of pertuzumab and trastuzumab in different settings of HER2-positive breast cancer. The ongoing randomized phase II study PHEREXA is evaluating the efficacy and safety of trastuzumab plus capecitabine with

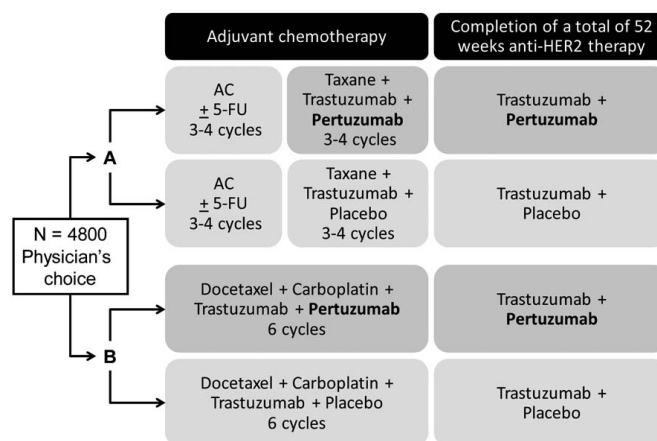


Fig. 5. APHINITY: Study design. Trastuzumab loading dose at first cycle 8 mg/kg, dose of 6 mg/kg 3-weekly in subsequent cycles. Pertuzumab loading dose of 840 mg i.v., dose of 420 mg i.v. 3-weekly in subsequent cycles. Placebo i.v. 3 weekly. A limited number of standard anthracycline or non-anthracycline (TCH) regimens are allowed.

or without the addition of pertuzumab in the treatment of patients with HER2-positive MBC who progressed after 1 line of trastuzumab-based therapy. The planned randomized phase II study VELVET will evaluate how the addition of pertuzumab affects efficacy and safety of the combination of trastuzumab and vinorelbine as a first- or second-line treatment of patients with HER2-positive MBC.

The German Breast Group started the randomized phase III trial, GEPARSepto, comparing neoadjuvant paclitaxel to nanoparticle albumin-bound (nab)-paclitaxel and evaluating dual inhibition with trastuzumab plus pertuzumab in HER2-positive patients. Moreover, surrogate markers for early response to dual inhibition with trastuzumab and pertuzumab will also be evaluated in the WSG ADAPT Trial (www.wsg-online.com). Finally, the large international phase III study APHINITY (fig. 5) will evaluate the added value of pertuzumab for the adjuvant treatment of patients with HER2-positive early breast cancer. In this trial, following an upfront physicians' choice between an anthracycline-based and a non-anthracycline platinum-based adjuvant chemotherapy regimen, patients will be randomized to standard adjuvant trastuzumab plus pertuzumab or adjuvant trastuzumab plus placebo.

Conclusions

Due to their different mechanisms of action, pertuzumab and trastuzumab act in a complementary fashion and provide a more complete blockade of HER2-mediated signal transduction than either agent alone. Proof of principle of the efficacy of dual HER2 inhibition with the dimerization inhibitor pertuzumab and trastuzumab has been provided by the data of the pivotal phase III study CLEOPATRA, which has shown a significant and clinically relevant prolongation of PFS by 6.1 months with the addition of pertuzumab in first-line HER2-positive MBC, resulting in a significant survival benefit. Most importantly, several studies demonstrated that adding pertuzumab is not associated with increased cardiac toxicity. Currently, the combination of both antibodies is being explored in the palliative setting as well as in the treatment of early HER2-positive breast cancer. Dual HER2 inhibition with pertuzumab and trastuzumab may change clinical practice in HER2-positive first-line MBC, and beyond, in HER2-positive breast cancer.

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The following conflicts of interest were disclosed: NH honoraria for consulting and lectures from Roche and GSK; MB participation in advisory boards for GSK, Astra Zeneca, Novartis, Pfizer, Sanofi-Aventis, Amgen, Roche; AR participation in an advisory board for Roche, AS honoraria for consulting and lectures from Roche; VM honoraria for lectures from Amgen, Celgene, Sanofi-Aventis, Pierre-Fabre, Roche and research funding from Roche; TF member of the advisory board of Roche; NM member of the advisory board of Roche; OG member of the advisory board and the speakers' bureau of Roche; CJ member of the advisory board and the speakers' bureau of Roche. IS and MU had no conflict of interest to declare with this publication.

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