Review Article

Pertuzumab: Unprecedented benefit in human epidermal growth factor receptor 2-positive breast cancer

ABSTRACT

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is a more aggressive subtype of breast cancer and targeting the HER2 receptor has proven effective in improving the prognosis of these patients. Pertuzumab, a recombinant humanized monoclonal antibody and the first in a class of HER2 dimerization inhibitors approved for treating HER2+ breast cancer. It blocks ligand-dependent heterodimerization and ligand-independent homodimerization of HER2 with other HER members. When used in combination with trastuzumab and taxane, pertuzumab complements the action of trastuzumab and results in a comprehensive blockade of HER2 signaling pathway. This review article traces the development of pertuzumab from concept to its current use in HER2+ breast cancer treatment. A search of Medical Literature Published since 2007 was performed in PubMed using the keywords "pertuzumab," "HER2+ breast cancer," "HER2 targeted therapy," "metastatic breast cancer," and in search engines for ongoing trials with pertuzumab and incidence of cancer and breast cancer in India. A total of 35 publications and abstracts from the American Society of Clinical Oncology were selected for this review. Pertuzumab is approved in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ metastatic BC, who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The dual HER2 blockade of pertuzumab and trastuzumab is now accepted worldwide as a standard of care by various guidelines.

Key words: Breast cancer; human epidermal growth factor receptor 2; pertuzumab.

Introduction

In 2012, breast cancer accounted for 25% of all cancers in women and was the leading cause of mortality among women.[1,2]

In India, breast cancer is becoming a silent epidemic with 23/100,000 women being diagnosed with it and is estimated to become the leading cancer in women in all parts of India by 2020.[3] Every year there has been a rise in the incidence of 0.5–2% across all regions of India and by 2030, one-fifth of the world's cancer cases are expected to be in India and mortality predicted to reach almost 120,000 annually by the year 2035.[3] India's 5-year survival rate is low (~50%) in comparison to the USA (90%) and China (82%). Due to lack of awareness and inadequate screening measures, breast cancer is diagnosed at a relatively advanced stage in India. The quality of care for breast cancer patients widely depends on where the patient gets treated. There are some super specialty centers that diagnose and treat breast cancer according to standardized protocols, but the majority of patients avail treatment at centers with inadequate infrastructure and specialists thereby delaying the diagnosis and timely treatment.[4]

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The prognosis of breast cancer largely depends on its subtypes, i.e. hormone receptor status and human epidermal growth factor receptor 2 (HER2) status and the accurate diagnosis and treatment is necessary for optimal treatment of breast cancer.

Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer

HER2 gene is amplified in about 15–30% of breast cancers[5-10] defined as 3+ immunohistochemistry or fluorescence *in situ* hybridization amplification ratio ≥2.0. HER2+ breast cancers tend to be more aggressive than other types of breast cancer with a higher chance of metastasis and poor clinical outcomes. It serves as a predictive marker indicating increased sensitivity to taxanes, anthracyclines, and decreased sensitivity to tamoxifen and HER2 receptor is also a target for anti-HER2 agents.[11,12]

Human Epidermal Growth Factor Receptor Family Receptors

The HER family consists of four main receptors - HER1, HER2, HER3, and HER4.[5,6,13] Each receptor has an extracellular domain, an alpha helical transmembrane segment, and an intracellular protein kinase domain.[13] The extracellular domain is further subdivided into four subdomains I, II, III, and IV.[13]

Activation of HER2 gene, a tyrosine kinase receptor, mediates signaling pathways including the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) and Ras-dependent mitogen-activated protein kinase (MAPK) pathways involved in cellular proliferation, differentiation, migration, and apoptosis.[5,6,11-13]

Currently Approved Anti-human Epidermal Growth Factor Receptor 2 Agents

Targeting the HER family of tyrosine kinase inhibitors has proved to be effective in improving the prognosis of the HER2+ breast cancer patients. Trastuzumab (Genentech, Inc., CA, USA; a wholly owned subsidiary of Roche Group), Pertuzumab (Genentech, Inc., CA, USA) humanized monoclonal antibodies, and Trastuzumab Emtansine (Genentech, Inc., CA, USA) an antibody drug conjugate, and Lapatinib (GlaxoSmithKline; London, UK) a tyrosine kinase inhibitor are approved by the United States Food and Drug Administration (US FDA) for treating HER2+ metastatic breast cancer (mBC).[7-9,14]

Trastuzumab is the first humanized monoclonal antibody which binds with the HER2 (extracellular domain receptors IV) and reduces tumor cell proliferation and survival.[6,13] It is recommended along with chemotherapy as the first-line treatment for HER2+ mBC;[5,6,8] neoadjuvant and adjuvant treatment of HER2+ early breast cancer. The development of trastuzumab revolutionized the treatment of HER2+ breast cancer and it yielded promising results when used in combination with chemotherapy. It is evident from numerous studies that trastuzumab improved overall survival (OS), progression-free survival (PFS), and mortality outcomes.[7,8,15,16] However, it was seen that despite an initial response to trastuzumab therapy, approximately 50% of patients with HER2+ mBC experience disease progression within a year[17] with a median survival of 2–2.5 years[17,18] in patients after diagnosis of HER2+ mBC.

The HER2/HER3 heterodimer is considered the most potent HER dimer pair with respect to the strength of interaction, ligand-induced tyrosine phosphorylation, and downstream signaling.[19] Blocking this dimer pair affects the key signaling pathways.[19] Trastuzumab blocks homodimerization but cannot inhibit heterodimerization, i.e. it inhibits ligand-independent HER2 signaling, prevents HER2 activation by extracellular domain shedding, and flags cells for destruction by the immune system; 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.[19,20] In preclinical studies, HER2/HER3 signaling was required for the proliferation of HER2-amplified cancer cells, as a consequence, blockade of ligand-induced HER2/HER3 heterodimers in combination with inhibition of ligand-independent homodimerization of HER2 offers a promising synergistic therapeutic strategy for HER2+ breast cancer.[18] Thus, there is a need for a potential agent, such as pertuzumab, which can also prevent heterodimerization, resulting in more potent growth inhibition.[20]

This review article traces the development of pertuzumab from concept to its current use in HER2+ breast cancer treatment. A search of published medical literature was performed following the principles of evidence-based medicine. The search strategy included a search using the keywords: Pertuzumab, HER2+ breast cancer, HER2 targeted therapy, mBC in PubMed and standard search engines.

Pertuzumab - Brief Overview

Pertuzumab is the first drug in a novel class of therapeutic antibodies, referred to as HER2 dimerization inhibitor.[9,21]

Pertuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture.

Pertuzumab targets the extracellular dimerization domain (subdomain II) of the HER2 receptor and blocks ligand-dependent heterodimerization of HER2 with other HER members (HER1, HER3, and HER4) and homodimerization with other HER2 receptors in the presence of heregulin (HRG), which activates PI3K/Akt signaling pathways.[8,9,21,22] This results in inhibition of MAPK and PI3K signal pathways thereby causing cell growth arrest and apoptosis.[21] HRG, a secreted growth factor, is involved in cell proliferation, invasion, survival, and differentiation of normal and malignant tissues and induces tumorigenicity and metastasis of breast cancer cells.[23] Disruption of the physiological balance between HRG ligands and their HER is implicated in the formation of a variety of human cancers.[23]

Pertuzumab also mediates antibody-dependent cell-mediated cytotoxicity.[9,13,21] The mechanism of action of pertuzumab is complementary to trastuzumab.[9,13] Pertuzumab binds to HER2 subdomain II, that is, essential for dimerization while trastuzumab binds to domain IV.[13] The unique characteristic of pertuzumab is to inhibit tumors with HER2/HER3 activation *in vitro*, that is, not displayed by trastuzumab.[13] Pertuzumab (not trastuzumab) inhibits HRG-induced phosphorylation, essential for HER2+ breast cancer tumorigenesis.[13] Trastuzumab does not block HRG-induced signaling pathways, suggesting that the pertuzumab is superior to trastuzumab in blocking ligand-activated HER2 signaling.[24,25]

Promising Evidence of Human Epidermal Growth Factor Receptor 2 Targeted Approach with Pertuzumab for Metastatic Breast Cancer

Preclinical data

Treatment of KPL-4 breast cancer xenografts with either trastuzumab or pertuzumab inhibited tumor growth with treatment-to-control ratios (TCRs) of 0.67 and 0.65, respectively. Combining trastuzumab and pertuzumab induced strongly enhanced antitumor activity compared with either agent alone (TCR 0.04) resulting in tumor regression and, in six of ten animals, complete tumor remission.[26] The combination of pertuzumab and trastuzumab can induce apoptosis *in vitro* and tumor regression *in vivo*.[27]

Phase I and II clinical studies

In a Phase I trial, 21 patients of advanced solid tumors were treated with pertuzumab with escalating dose starting from 0.5 mg/kg. Pertuzumab infusions given every 3 weeks at doses >5.0 mg/kg ensured that serum concentrations remained in excess of 20 μg/mL.[28] Pertuzumab demonstrated linear pharmacokinetics at a dose range of 225 mg/kg, with the median clearance of 0.24 L/day and the median half-life of 18 days.[10,21] The steadystate concentration of pertuzumab was reached after the first maintenance dose.[21]

The early phase pharmacokinetic analysis demonstrated that pertuzumab serum concentration over time was similar after intravenous administration of fixed-dose pertuzumab (840 mg followed by 420 mg on days 21, 42, and 63) weight-based pertuzumab (12.2 mg/kg followed by 6.1 mg/kg on days 21, 42, and 63) body surface area-based pertuzumab (485 mg/m^2 followed by 242.5 mg/m^2 on days 21, 42, and 63.[29] Dose adjustments are not needed as there are no pharmacokinetic differences based on age, gender, ethnicity, or disease status (neoadjuvant or metastatic).[21]

Based on the limited activity of the single agent in Phase I trials, the clinical development of pertuzumab thereafter focused on its use in combination with other anti-HER2 agents.[7]

The Phase II trial evaluated pertuzumab in combination with trastuzumab in HER2+ mBC patients who progressed on trastuzumab. The overall response rate 24.2% and the combination of pertuzumab and trastuzumab was well-tolerated and adverse events (AEs) were mild to moderate.[30]

A number of Phase II trials are exploring the various regimens combining pertuzumab and trastuzumab with other active cytotoxics (paclitaxel, capecitabine, and vinorelbine) [Table 1].[31]

Phase III clinical studies

The efficacy and safety of pertuzumab in combination with trastuzumab in mBC have been demonstrated in a Phase III clinical trial. A randomized, double-blind, placebo-controlled Phase III clinical trial CLinical Evaluation of Pertuzumab and TRAstuzumab (CLEOPATRA) evaluated the role of the dual anti-HER2 blockade in 808 patients who were not previously treated with chemotherapy or biological for their metastatic disease. The patients were randomly assigned to receive docetaxel + trastuzumab + placebo (n = 406; control group) or docetaxel + trastuzumab + pertuzumab (n = 402; pertuzumab group).[32] Of 808 patients, 376 patients (184 in study arm and 192 in control arm) had received treatment in the adjuvant or neoadjuvant setting and 88 of them had received prior trastuzumab (47 in study arm and 41 in control arm). The primary endpoint was an independent assessment of PFS. The results of this study showed that pertuzumab in combination with trastuzumab and docetaxel as a first-line treatment for HER2+ mBC significantly prolonged PFS with

Table 1: Ongoing Phase II clinical trials with pertuzumab

NCT number	Phase	Drugs	Indication	Trial design	Estimated number of patients	Primary objective
NCT01276041	2	Pertuzumab + trastuzumab + paclitaxel	Stage IV HER2+ breast cancer	Interventional, nonrandomized, open-label	69	PFS at 6 months or later
NCT01491737 (PERTAIN)	2	Pertuzumab + trastuzumab + aromatase inhibitor Trastuzumab + aromatase inhibitor + induction chemotherapy	HER2+ and hormone receptor-positive breast cancer	Randomized, multicenter, first-line setting	258	PFS
NCT01565083 (VELVET)	2	Pertuzumab + trastuzumab + vinorelbine (single or sequential administration)	Metastatic or locally advanced HER2+ breast cancer	Two-cohort, open-label, multicenter, first line	213	ORR
NCT01912963	2	Pertuzumab + trastuzumab + Eribulin mesylate	Metastatic, unresectable locally advanced, or locally recurrent HER2+ breast cancer	Interventional, open-label, single group assignment	81	Safety profile, ORR

HER2+ - Human epidermal growth factor receptor 2 positive; PFS - Progression-free survival; ORR - Overall response rate

an increase of 6.1 months (hazard ratio [HR]: 0.62; $P < 0.001$) when compared with trastuzumab + taxane alone. The median OS was 40.8 months in the control group and 56.5 months in the pertuzumab group, with a difference of 15.7 (HR: 0.68; $P < 0.0002$) months.[32,33] About 78.9% patients in the control arm and 77% patients in study arm received treatment after progression on study drugs the postprogression treatment was evenly balanced in both arms and included anti HER2 agents (trastuzumab, trastuzumab emtansine, and lapatinib) chemotherapy (taxanes, cyclophosphamide, anthracyclines, and capecitabine vinorelbine) and hormonal treatment. The median independently assessed PFS was 10.4 months in the control group and 16.9 months in the pertuzumab group (HR: 0.62) among the patients ($n = 88$) who had received neoadjuvant or adjuvant chemotherapy with trastuzumab. Among the 288 patients who had received neoadjuvant or adjuvant chemotherapy without trastuzumab, the median independently assessed PFS was 12.6 months in the control group and 21.6 months in the pertuzumab group (HR: 0.60). The addition of pertuzumab to trastuzumab and docetaxel also prolonged the time to worsening of breast cancer symptoms. A median time to deterioration in breast cancer symptoms was 18.3 weeks in the control group compared with 26.7 weeks in the pertuzumab group (HR: 0.77; $P = 0.0061$).[9] In another Phase III study, MARIANNE pertuzumab was tried in combination with trastuzumab emtansine for patients of first-line HER2+ mBC. The combination was found to be noninferior to trastuzumab plus taxane, but the quality of life parameters were better in the trastuzumab emtansine and pertuzumab arm therefore making it an alternative treatment option to treat patients who are not suitable for chemotherapy.[34]

An ongoing single-arm Phase IIIb trial PERUSE is evaluating the safety and efficacy of first-line pertuzumab in combination with trastuzumab and a broader range of taxanes (investigator's choice of docetaxel, paclitaxel, or nab-paclitaxel) in patients with HER2+ locally recurrent cancer or mBC.[35] Further details of ongoing Phase III studies with pertuzumab are provided in Table 2.[31]

Clinical Trials in the Neoadjuvant Setting

The dual HER2 blockade by pertuzumab and trastuzumab combination was evaluated in two Phase II studies in combination with or without chemotherapy in early breast cancer. NeoSphere (NCT00545688) a randomized Phase II study ($n = 417$) in a neoadjuvant setting compared the pathological complete response (pCR) rates as well as clinical response rate, disease free survival, breast conservation rate, and a biomarker evaluation.[32] A higher pCR rates (45.8%) with pertuzumab + trastuzumab + docetaxel, compared to trastuzumab + docetaxel (29%) or pertuzumab + trastuzumab (16.8%), or pertuzumab + docetaxel (24%).[36]

TRYPHAENA (NCT00976989) was a multicenter, randomized Phase II study that evaluated the combination of pertuzumab and trastuzumab given concurrently or sequentially with an anthracycline-based, or concurrently with a carboplatin-based chemotherapy regimen in 225 locally, advanced, inflammatory, or early stage patients with HER2+ breast cancer. Results from TRYPHAENA indicate a low incidence of symptomatic and asymptomatic left ventricular systolic dysfunction across all arms during the neoadjuvant and adjuvant periods. Concurrent administration of pertuzumab plus trastuzumab with epirubicin resulted in similar cardiac tolerability compared with the sequential administration or the anthracycline-free regimen. Regardless of chemotherapy chosen, the combination of pertuzumab with trastuzumab in the neoadjuvant setting resulted in high pCR rates (57-66%).[37]

Table 2: Ongoing selected Phase III clinical trials with pertuzumab

NCT number	Drugs	Indication	Trial design	Estimated number of patients	Primary objective
NCT01120184 (MARIANNE)	T-DM1 + pertuzumab T-DM1 + pertuzumab + placebo Trastuzumab + docetaxel or paclitaxel	Recurrent locally advanced or previously untreated mBC	Randomized, double blind parallel, multicenter	1095	PFS
NCT01358877 (APHINITY)	Chemotherapy + trastuzumab + placebo Chemotherapy + trastuzumab + pertuzumab as adjuvant therapy	Operable HER2+ primary breast cancer	Large, prospective, 2-arm, randomized double-blind, placebo-controlled, multicenter, multinational	4805 across 42 countries	Improvement in IDFS with pertuzumab and trastuzumab
NCT02514681 (PRECIOUS)	Trastuzumab + chemotherapy Pertuzumab + trastuzumab + chemotherapy	HER2+ metastatic locally advanced and mBC	Randomized, double-blind, Placebo-controlled, parallel	370	PFS
NCT02003209	Neoadjuvant therapy: Docetaxel, carboplatin, TCHP with or without estrogen deprivation	Hormone receptor-positive, HER2+ operable or locally advanced breast cancer	Randomized, open-label, parallel	312	Rate of pCR in the breast and posttherapy lymph nodes
NCT01026142 (PHEREXA)	Pertuzumab + trastuzumab + capecitabine Trastuzumab + capecitabine	HER2+ breast cancer whose disease has progressed following previous trastuzumab treatment	Randomized, double-blind,	450	PFS
NCT01966471	Pertuzumab + trastuzumab + taxane + anthracycline Pertuzumab + T-DM1 + anthracycline	Operable HER2+ primary breast cancer	Two-arm, randomized, open-label, parallel, multicenter	2500	Invasive disease free survival
NCT01572038 (PERUSE)	Pertuzumab + trastuzumab + taxanes in first line treatment	HER2+ locally recurrent cancer or mBC	Multicenter, open-label, single arm study	1500	Safety
NCT01996267 (TRAIN-2)	Neoadjuvant PTC + pertuzumab preceded by FEC-T + pertuzumab or PTC + pertuzumab	HER2+ breast cancer	Randomized, open-label, parallel	437	pCR
NCT02586025	Trastuzumab + pertuzumab + docetaxel Trastuzumab + placebo + docetaxel	Early-stage or locally advanced HER2+ breast cancer	Randomized, double blind, parallel	328	Total pCR
NCT02019277 (IIIb)	Pertuzumab + trastuzumab + taxanes (docetaxel, paclitaxel or nab-paclitaxel) as first-line therapy	Advanced HER2+ breast cancer	Open-label, multicenter	50	Safety profile
NCT02131064	Docetaxel + carboplatin + trastuzumab + pertuzumab T-DM1 + pertuzumab	HER2+ breast cancer	Randomized, multicenter, open-label, two-arm study	444	pCR
NCT02568839 (PREDIX HER2)	Docetaxel + trastuzumab sc + pertuzumab Trastuzumab emtansine	HER2+ breast cancer	Randomized, open-label, parallel	200	Pathological objective response
NCT02402712	Pertuzumab + trastuzumab + docetaxel	Advanced HER2+ breast cancer	Open-label, single-arm, multicenter	400	Safety profile
NCT02344472	Chemo- versus endocrine therapy in combination with trastuzumab + pertuzumab	HER2+ and hormone-receptor positive mBC	Randomized, open-label, parallel, multicenter	270	Safety profile

FEC-T - 5 Fluorouracil, epirubicin, cyclophosphamide-docetaxel; HER2+ - Human epidermal growth factor receptor 2 positive; IDFS - Invasive disease free survival; ORR - Overall response rate; pCR - Pathological complete response; PFS - Progression-free survival; PTC - Paclitaxel, trastuzumab, carboplatin; T-DM1 - Trastuzumab emtansine; TCHP - Trastuzumab, and pertuzumab; mBC - Metastatic breast cancer

Approval for treating human epidermal growth factor receptor 2+ breast cancer

The early approval of pertuzumab in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ mBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease by the US FDA was based on significant and clinically meaningful improvements in PFS and OS, as well as an acceptable safety profile in the CLEOPATRA trial.[9]

The FDA also granted accelerated approval for pertuzumab in combination with trastuzumab and docetaxel as a neoadjuvant treatment for breast cancer that is HER2+ and locally advanced, inflammatory, or early-stage (either >2 cm in diameter or positive lymph node); in patients who have a high-risk cancer recurrence and metastasis. The accelerated approval was based on the totality of evidence provided by the improvement in pCR in the NeoSphere and TRYPHAENA trials as well as supported by the efficacy and safety data from CLEOPATRA.[9,21,38]

Pertuzumab is currently not recommended for treatment in adjuvant setting and cycles greater than six for neoadjuvant treatment of early breast cancer.[21]

Pertuzumab is currently approved for treating breast cancer in 93 countries (Roche data on file).

Safety

The safety of pertuzumab has been evaluated in more than 1400 patients in clinical trials.[10] The most frequently (>30%) reported AEs with pertuzumab treatment were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, vomiting, and peripheral neuropathy.[10,13,21] The most common NCI-CTCAE v3.0 Grade 3–4 adverse reactions (>2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue.[10,21]

In CLEOPATRA trial, a significant drop in left ventricular ejection fraction (LVEF) defined as LVEF drop of 10% or more from the baseline or an absolute value less than 50% occurred in 6.1% in pertuzumab group and 7.1% in control group. The decline in LVEF was reversible in 87.5% patients.[39]

The addition of pertuzumab to trastuzumab and docetaxel was well-tolerated, and the AEs profile was generally balanced between the two treatment groups.[9,32] Pertuzumab in combination with trastuzumab and chemotherapy showed a favorable cardiac toxicity profile when appropriate monitoring was conducted.[13]

Prior exposure to anthracyclines and prior left ventricular dysfunction with trastuzumab treatment may be potential risk factors of cardiac toxicity for patients who are treated with trastuzumab plus pertuzumab.[40] Another trial conducted by Baselga *et al*.[30] also showed that 3/66 (4.5%) patients experienced a decreased LVEF ≥10% points. Similar results are reported in the NeoSphere and TRYPHAENA studies.[9,32,36,37] It has been shown that HRG stimulated proliferation and inhibited apoptosis of neonatal and adult cardiac myocytes that persistently expressed HER2 and HER4. Thus, targeting HER2 may alter the signals necessary for the survival of cardiac myocytes leading to cardiac toxicity.[40]

A meta-analysis was performed using six randomized trials evaluating the cardiac toxicity between anti-HER2 monotherapy (trastuzumab, or pertuzumab, or lapatinib) and anti-HER2 combination therapy (trastuzumab + pertuzumab, or trastuzumab + lapatinib) with or without chemotherapy in breast cancer patients, regardless of treatment setting (metastatic or neoadjuvant). The study showed that dual HER2 blockade does not significantly increase the risk of cardiac AEs compared to anti-HER2 monotherapy.[41] The incidence of decline in LVEF to <50% was 3.1% of patients treated with combined anti-HER2 therapy, compared with 2.9% of patients in the monotherapy group.[41]

Brain metastases are common in patients with HER2+ mBC, with up to half of the patients experiencing it and its treatment remains a great challenge in HER2+ mBC.[27,42] The incidence is increasing over time and could be attributed partly to a marked reduction in mortality as a result of HER2 inhibition and control of noncentral nervous system (CNS) metastatic progression. Results of the exploratory analyses from CLEOPATRA study suggests that pertuzumab, trastuzumab, and docetaxel delays the onset of CNS disease compared with placebo, trastuzumab, and docetaxel with the median time to development of CNS metastases as the first site of disease progression was 11.9 months versus 15 months in the placebo and pertuzumab arms, respectively; and median OS was 26.3 months versus 34.4 months in the placebo and pertuzumab arms, respectively.[43] Current research is focused on various approaches including the use of small molecule inhibitors that have the potential to cross the BBB (e.g. afatinib and everolimus), using molecules concurrently with radiation, and lastly utilizing immunotherapy before and after radiotherapy based on the efficacy noted in melanoma patients with brain metastases.[27]

Recommended Dose

Pertuzumab is given as intravenous infusion with an initial loading dose of 840 mg (administered as a 60 min infusion), followed by 420 mg (administered as a 30–60 min infusion) every 3 weeks.[21] The recommended dose was based on the results of early clinical development Phase I study and the efficacy and safety data demonstrated in the Phase II and CLEOPATRA trial.[10]

Clinical Practice Based Recommendations

The NCCN guidelines recommend pertuzumab plus trastuzumab in combination with a taxane as a preferred option for first-line treatment in patients with HER2+ mBC. Pertuzumab plus trastuzumab in combination with docetaxel is category 1, whereas in combination with paclitaxel is category 2A recommendation.[44]

The American Society of Clinical Oncology clinical practice guidelines strongly recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes based on high-quality evidence.[42]

The European School of Oncology-European Society of Medical Oncology and Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) guidelines recommend pertuzumab and

trastuzumab in combination with docetaxel in previously untreated HER2+ mBC based on the OS benefit demonstrated in CLEOPATRA study.[45]

Conclusion

HER2+ breast cancer is a more aggressive subtype of breast cancer and targeting the HER2 receptor has proved to be effective in improving the prognosis of these patients. The HER2/HER3 heterodimer is considered the most potent HER dimer pair. Pertuzumab binds to subdomain II, a different site of HER2 receptor and blocks ligand-dependent heterodimerization and ligand-independent homodimerization of HER2 with other HER members as compared to trastuzumab which binds to subdomain IV therefore complementing the action of trastuzumab and resulting in a comprehensive blockade of HER2 signaling pathway. The proof of concept for dual HER2 blockade was provided by CLEOPATRA trial which demonstrated unprecedented OS advantage with the acceptable safety profile and also improved the quality of life of these patients. Pertuzumab is approved in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ mBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The dual HER2 blockade of pertuzumab and trastuzumab is now accepted worldwide as a standard of care by various guidelines. The way forward for anti-HER2 treatment is to determine the optimum sequence of anti-HER2 therapies and preferred chemotherapy partners for anti-HER2 agents to maximize favorable treatment outcomes.

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Conflicts of interest

Dr. Amit Rauthan, Dr. P. S. Dattatreya, Dr. Manish Singhal, and Dr. Ram Prabu have received honoraria for consulting and lectures from Roche Products (India) Pvt. Ltd. in the past. Dr. Anil Kukreja and Dr. Siddharth Naik are employees of Roche Products (India) Pvt. Ltd.

References

1. World Cancer Research Fund International. Breast Cancer Statistics; 2015. Available from: http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics. [Last accessed on 2015 Dec 04].
2. American Cancer Society. Global Cancer Facts and Figures. 3rd ed. Atlanta, Georgia: American Cancer Society. Available from: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-044738.pdf. [Last accessed on 2015 Dec 04].
3. Shah A. Breast Cancer in India – Scope of the Issue and Reasons for Hope 2015. Available from: https://www.ketto.org/campaigns_pdf/anushis_report_edited.docx. [Last accessed on 2015 Dec 08].
4. Agarwal G, Ramakant P. Breast cancer care in India: The current scenario and the challenges for the future. Breast Care (Basel) 2008;3:21-7.
5. Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (HER 2) in cancers: Overexpression and therapeutic implications. Mol Biol Int 2014;9.
6. Wang WJ, Lei YY, Mei JH, Wang CL. Recent progress in HER2 associated breast cancer. Asian Pac J Cancer Prev 2015;16:2591-600.
7. Gradishar WJ. Emerging approaches for treating HER2-positive metastatic breast cancer beyond trastuzumab. Ann Oncol 2013;24:2492-500.
8. Nielsen DL, Kümler I, Palshof JA, Andersson M. Efficacy of HER2-targeted therapy in metastatic breast cancer. Monoclonal antibodies and tyrosine kinase inhibitors. Breast 2013;22:1-12.
9. Moya-Horno I, Cortés J. The expanding role of pertuzumab in the treatment of HER2-positive breast cancer. Breast Cancer (Dove Med Press) 2015;7:125-32.
10. Boix-Perales H, Borregaard J, Jensen KB, Ersbøll J, Galluzzo S, Giuliani R, *et al.* The European Medicines Agency Review of Pertuzumab for the treatment of adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer: Summary of the scientific assessment of the committee for medicinal products for human use. Oncologist 2014;19:766-73.
11. Hanna W, Gelmon KA. Review of the literature on HER2/neu testing and the role of HER2/neu as a prognostic and predictive factor in breast cancer – Update December 2000 to July 2001. Curr Oncol 2002;9:S2-17.
12. Ross JS, Fletcher JA, Linette GP, Stec J, Clark E, Ayers M, *et al.* The Her-2/neu gene and protein in breast cancer 2003: Biomarker and target of therapy. Oncologist 2003;8:307-25.
13. Capelan M, Pugliano L, De Azambuja E, Bozovic I, Saini KS, Sotiriou C, *et al.* Pertuzumab: New hope for patients with HER2-positive breast cancer. Ann Oncol 2013;24:273-82.
14. FDA Approved Drugs for Oncology. Available from: https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology. [Last accessed on 2015 Dec 04].
15. Balduzzi S, Mantarro S, Guarneri V, Tagliabue L, Pistotti V, Moja L, *et al.* Trastuzumab-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev 2014;6:CD006242.
16. Bria E, Cuppone F, Fornier M, Nisticò C, Carlini P, Milella M, *et al.* Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: The dark side of the moon? A meta-analysis of the randomized trials. Breast Cancer Res Treat 2008;109:231-9.
17. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, *et al.* Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 study group. J Clin Oncol 2005;23:4265-74.
18. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-92.
19. Harbeck N, Beckmann MW, Rody A, Schneeweiss A, Müller V, Fehm T, *et al.* HER2 dimerization inhibitor pertuzumab – Mode of action and clinical data in breast cancer. Breast Care (Basel) 2013;8:49-55.

20. Recondo G, Dìaz Canton E, de la Vega M, Greco M, Recondo G, Valsecchi ME. Therapeutic options for HER-2 positive breast cancer: Perspectives and future directions. World J Clin Oncol 2014;5:440-54.
21. PERJETA™ (pertuzumab) Injection, for Intravenous Use [Package Insert]. South San Francisco, CA: Genentech, Inc.; 2012. Available from: http://www.gene.com/download/pdf/perjeta_prescribing.pdf. [Last accessed on 2015 Dec 04].
22. Barthélémy P, Leblanc J, Goldbarg V, Wendling F, Kurtz JE. Pertuzumab: Development beyond breast cancer. Anticancer Res 2014;34:1483-91.
23. Breuleux M. Role of heregulin in human cancer. Cell Mol Life Sci 2007;64:2358-77.
24. Metzger-Filho O, Winer EP, Krop I. Pertuzumab: Optimizing HER2 blockade. Clin Cancer Res 2013;19:5552-6.
25. Hubalek M, Brantner C, Marth C. Role of pertuzumab in the treatment of HER2-positive breast cancer. Breast Cancer (Dove Med Press) 2012;4:65-73.
26. Scheuer W, Friess T, Burtscher H, Bossenmaier B, Endl J, Hasmann M. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. Cancer Res 2009;69:9330-6.
27. Singh JC, Jhaveri K, Esteva FJ. HER2-positive advanced breast cancer: Optimizing patient outcomes and opportunities for drug development. Br J Cancer 2014;111:1888-98.
28. Agus DB, Gordon MS, Taylor C, Natale RB, Karlan B, Mendelson DS, *et al.* Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. J Clin Oncol 2005;23:2534-43.
29. Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23:1275-84.
30. Baselga J, Gelmon KA, Verma S, Wardley A, Conte P, Miles D, *et al.* Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol 2010;28:1138-44.
31. ClinicalTrials.gov. Available from: https://www.clinicaltrials.gov/ct2/home. [Last accessed on 2015 Nov 05].
32. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, *et al.* Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
33. Swain SM, Kim S, Cortes J, Ro J, Semiglazov V, Campone M, *et al*. Confirmatory overall survival analysis of CLEOPATRA: A randomized, double-blind, placebo-controlled phase III study with pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive first-line mBC. Cancer Res 2012;72:P5-18-26.
34. Ellis PA, Barrios CH, Eiermann W, Toi M, Im YH, Conte PF, *et al*. Phase III, Randomized Study of Trastuzumab Emtansine (T-DM1) ± Pertuzumab (P) vs. Trastuzumab + Taxane (HT) for First-line Treatment of HER2-positive MBC: Primary Results from the MARIANNE Study. American Society of Clinical Oncology Annual Meeting; Sep 25-27 2015; Chicago IL. Abstract 507; 2015.
35. Bachelot T, Ciruelos E, Peretz-Yablonski T, Puglisi F, Schneeweiss A, Campone M, *et al*. First-line Pertuzumab, Trastuzumab, and Taxane Therapy for HER2-positive Locally Recurrent/Metastatic Breast Cancer: Interim Safety Results (N = 704) from PERUSE. Presented at: The 50th American Society of Clinical Oncology Annual Meeting; May 30-June 3, 2014; Chicago, IL. Poster #548; 2014.
36. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, *et al.* Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.
37. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, *et al.* Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: A randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278-84.
38. Pertuzumab. National Cancer Institute. Available from: http://www.cancer.gov/about-cancer/treatment/drugs/pertuzumab. [Last accessed on 2015 Dec 04].
39. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, *et al.* Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372:724-34.
40. Portera CC, Walshe JM, Rosing DR, Denduluri N, Berman AW, Vatas U, *et al.* Cardiac toxicity and efficacy of trastuzumab combined with pertuzumab in patients with [corrected] human epidermal growth factor receptor 2-positive metastatic breast cancer. Clin Cancer Res 2008;14:2710-6.
41. Valachis A, Nearchou A, Polyzos NP, Lind P. Cardiac toxicity in breast cancer patients treated with dual HER2 blockade. Int J Cancer 2013;133:2245-52.
42. Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, *et al.* Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:2078-99.
43. Swain SM, Baselga J, Miles D, Im YH, Quah C, Lee LF, *et al.* Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: Results from the randomized phase III study CLEOPATRA. Ann Oncol 2014;25:1116-21.
44. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, *et al.* Breast cancer version 2.2015. J Natl Compr Canc Netw 2015;13:448-75.
45. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, *et al.* ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 2014;25:1871-88.