Pertuzumab in neoadjuvant treatment of HER2-positive early breast cancer

See Commentary on page 78

Pertuzumab injection was granted accelerated approval by the US Food and Drug Administration last fall for use in combination with trastuzumab plus docetaxel for neoadjuvant treatment of patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer (either > 2 cm in diameter or node-positive) as part of a complete treatment regimen for early breast cancer.[1] The accelerated approval was based on improvement in pathologic complete response (pCR) rate in a phase 2 trial.[2,3] Data showing improved event-free survival or overall survival are not yet available. Continued approval for this indication is contingent on demonstration of improvement in disease-free survival in a confirmatory trial.

Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (subdomain II) of HER2 and thus blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. Pertuzumab thus inhibits ligand-initiated intracellular signaling through both mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K) signaling pathways, resulting in cell growth arrest and apoptosis, respectively. Pertuzumab also mediates antibody-dependent cell-mediated cytotoxicity.

As part of neoadjuvant therapy, pertuzumab should be administered every 3 weeks for 3-6 cycles as part of one of the following treatment regimens for early breast cancer: 4 preoperative cycles of pertuzumab in combination with trastuzumab plus docetaxel, followed by 3 postoperative cycles of fluorouracil; epirubicin and cyclophosphamide (FEC); 3 preoperative cycles of FEC alone, followed by 3 preoperative cycles of pertuzumab in combination with docetaxel plus trastuzumab; or 6 preoperative cycles of pertuzumab in combination with docetaxel, carboplatin, plus trastuzumab.

What's new, what's important

The US Food and Drug Administration's approval of pertuzumab for the treatment of HER2-positive locally advanced breast cancer in the neoadjuvant setting has generated significant discussion in the oncology community. This is the first time that a drug has been approved on the basis of neoadjuvant data and marks a paradigm shift in drug development in this era of financial constraint. The approval is contingent on the availability of data from the APHINITY trial, a phase 3 UK-based study in the adjuvant setting for which accrual has been completed.

Overall, toxicity of the dual HER2 blockade was minimal. Even with several limitations for the NeoSphere and TRYPHENA trials, the complete pathological responses were impressive. This is consistent with several published studies, which showed a benefit for dual HER2 blockade in the metastatic setting. The preferred regimen we use in the neoadjuvant setting is docetaxel (75 mg/m2) carboplatin AUC of 6, trastuzumab (initial dose 8 mg/kg, followed by 6 mg/kg), and pertuzumab (initial dose 840 mg, followed by 420 mg) – also known as the TCH-P regimen – every 3 weeks for 6 cycles. Pertuzumab can cause infusion reactions such as hypotension, fever, and nausea in a significant number of patients, so we recommend giving the dexamethasone premedication before the pertuzumab infusion.

The approval of pertuzumab gives an excellent option for patients with locally advanced HER2-positive breast cancer. However, it is important that we also have the long-term survival and toxicity data from the adjuvant trials.

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Efficacy

In primary trial

The approval was based on a randomized, multicenter, open-label phase 2 trial in patients with HER2-positive operable, locally advanced, or inflammatory breast cancer (T2-4d).[2,3] Breast tumor samples were required to show HER2 overexpression (IHC 3+ or FISH amplification ratio ≥ 2.0).

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How I treat HER2-positive early breast cancer

The primary goal of therapy in treating early-stage HER-2 positive breast cancer is to eradicate disease, prevent long-term recurrences, minimize toxicity, and improve long-term survival. As such, my primary considerations for treatment are aimed at achieving those objectives. In patients with T1(a-c) N0, T1 N1, or T2 N0, I encourage maximal surgical resection and staging of disease before considering adjuvant therapies. In the adjuvant setting, for pT1c or pN1 or greater stages, I generally offer adjuvant chemotherapy with both anthracyclines and taxanes combined with trastuzumab as per the NSABP B-31 and NCCTG N-9831 trials,[1] with trastuzumab therapy for 1 full year. Although the efficacy of a nonanthracycline regimen, docetaxel, carboplatin, and trastuzumab (TCH), has been well established,[2] I generally reserve this regimen for patients who have potential cardiac risk or other comorbidities that may be compromised by anthracycline therapy. For patients requiring neoadjuvant therapy, such as cT2 N1 or greater, I generally use the same criteria and regimens as already noted here.

For patients with either T1a or T1b N0 disease or with significant comorbidities that may limit the ability to use combination chemotherapy, I have begun to use the regimen that was reported by Tolaney and colleagues at the 2013 San Antonio Breast Cancer Symposium using paclitaxel and trastuzumab given weekly for 12 weeks.[3] This regimen is very well tolerated, and now we have data to support that it is efficacious as well in preserving long-term survival outcomes. However, patient selection, based on comorbidities, tumor histology and long-term risk of recurrence, is extremely important in this setting, and not all patients necessarily require chemotherapy with trastuzumab with such early-stage disease.

Ultimately, the choice of therapy for early-stage HER2-positive breast cancer patients is driven by unique patient specific factors. However, the common theme is to offer HER2-targeted therapies to this susceptible population to maximize long-term outcomes. As with adjuvant endocrine therapy in hormone-sensitive patients, the greatest sin that an oncologist could commit would be to not offer or consider HER2-targeted therapies to this population. With the advent of dual blockade HER2-targeted therapies, as noted in the accompanying Commentary on page 78, I expect that the choices available for this population will continue to expand, leading to better outcomes.

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A total of 417 patients were randomized to receive 1 of 4 neoadjuvant regimens: trastuzumab plus docetaxel (n = 107), pertuzumab and trastuzumab plus docetaxel (n = 107), pertuzumab plus trastuzumab (n = 107), or pertuzumab plus docetaxel (n = 96). Pertuzumab (initial dose 840 mg, followed by 420 mg), trastuzumab (initial dose 8 mg/kg, followed by 6 mg/kg), and docetaxel (75 mg/m^2, escalated to 100 mg/m^2 at investigator discretion) were administered preoperatively by IV infusion every 3 weeks for a total of 4 cycles. Following surgery, all patients received 3 cycles of FEC IV every 3 weeks, and trastuzumab was administered IV every 3 weeks to complete 1 year of therapy. The primary endpoint of the study was pCR rate defined as the absence of invasive cancer in the breast (ypT0/is). The FDA-preferred definition of pCR is the absence of invasive cancer in the breast and lymph nodes (ypT0/is ypN0).

The 4 treatment groups were generally balanced for age (median, 49-50 years), ethnic origin (64%-75% white, 21%-26% Asian), Eastern Cooperative Oncology Group performance status (0 in 83%-94%, 1 in 6%-17%), estrogen receptor (ER)- or progesterone receptor (PR)-positive disease (47%-48%), ER- and PR-negative disease (52%-53%), operable disease (60%-63%), locally advanced disease (30%-34%), inflammatory disease (5%-9%), lymph node status (N0 in 29%-30%, N1 in 43%-50%, N2 in 21%-23%, N3 in 0%-5%), and median tumor size at clinical examination (50-55 mm).

pCR was observed in 49 of 107 women (45.8%) who received pertuzumab, trastuzumab, and docetaxel, compared with 31 of 107 (29.0%) who received trastuzumab plus docetaxel (P = .0141) on the study definition of pCR,[3] and in 42 (39.3%) and 23 (21.5%; P = .0063), respectively, on the FDA-preferred definition.[1,2] pCR rates were 24.0% in patients who received pertuzumab and docetaxel and 16.8% in those who received pertuzumab and trastuzumab on the study definition,[3] and 17.7% and 11.2% on the FDA-preferred definition.[2] The pCR rates and magnitude of improvement with pertuzumab and trastuzumab plus docetaxel compared with trastuzumab and docetaxel were lower in the subgroup of patients with hormone receptor (HR)-positive tumors (22.0% vs 12.0%, respectively, on FDA-preferred definition;[2] 26.0% vs 20.0% on study definition[3]) compared with the subgroup with HR-negative tumors (54.4% vs 29.8% on FDA-preferred definition; 63.2% vs 36.8% on study definition).

In supporting trial

The approval of pertuzumab in the current indication was supported by another randomized phase 2 study conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess cardiac safety when FEC or carboplatin is incorporated into the neoadjuvant regimen.[2,4] Patients were randomized to receive 3 cycles of FEC followed by 3 cycles of docetaxel, all in combination with pertuzumab and trastuzumab (n = 73), or 3 cycles of FEC alone, followed by 3 cycles of docetaxel and trastuzumab in combination with pertuzumab (n = 75), or 6 cycles of docetaxel, carboplatin, and trastuzumab in combination with pertuzumab (n = 77). Patients had a median age of 49 to 50 years, 76% were white, 6% had inflammatory cancer, 25% had locally advanced cancer, and 69% had operable cancer, with approximately half the patients in each group having ER-positive or PR-positive disease.

The pCR rates using the FDA-preferred definition (ypT0/is ypN0) were 56.2% with pertuzumab plus trastuzumab and FEC followed by pertuzumab and trastuzumab plus docetaxel, 54.7% with FEC followed by pertuzumab and trastuzumab plus docetaxel, and 63.6% with pertuzumab plus docetaxel, carboplatin, and trastuzumab. The pCR rates were lower in patients with HR-positive tumors (41.0%, 45.7%, and 47.5%) than in those with HR-negative tumors (73.5%, 62.5%, and 81.1%).

Safety

In primary trial

In the primary trial supporting approval,[2,3] the most common adverse events of any grade with pertuzumab combined with trastuzumab plus docetaxel were alopecia (65% vs 66% with trastuzumab plus docetaxel), neutropenia (51% vs 64%), diarrhea (46% vs 34%), and nausea (39% vs 36%).[2] The most common grade 3 or 4 adverse events were neutropenia (45% vs 59%), febrile neutropenia (9% vs 7%), leukopenia (5% vs 11%), and diarrhea (6% vs 4%).[2] Treatment was discontinued owing to adverse events in 1 patient (< 1%) in the pertuzumab and trastuzumab plus docetaxel group. Left ventricular dysfunction was observed in 2.8% of patients receiving pertuzumab and trastuzumab plus docetaxel (0.9% in the trastuzumab and docetaxel group), with no patients having symptomatic left ventricular dysfunction. Other significant adverse events reported with pertuzumab included infusion-related reactions, hypersensitivity reactions (5.9% in the pertuzumab and trastuzumab plus docetaxel group), and anaphylaxis (1.9% in the pertuzumab and trastuzumab plus docetaxel group).

In supporting trial

In the supporting trial,[2,4] the most common adverse events of any grade in patients who received pertuzumab in combination with trastuzumab and docetaxel for 3 cycles following 3 cycles of FEC were diarrhea (61%), nausea (53%), alopecia (52%), neutropenia (47%), vomiting (36%), and fatigue (36%). The most common grade 3 or 4 adverse events were neutropenia (43%), leukopenia (12%), febrile neutropenia (9%), and diarrhea (5%). Adverse events led to treatment discontinuation in 6.7% of patients. The most common adverse events of any grade in those receiving pertuzumab in combination with docetaxel, carboplatin, and trastuzumab were diarrhea (72%), alopecia (54%), neutropenia (49%), nausea (45%), fatigue (42%), vomiting (40%), and anemia (37%).[4]

The most common grade 3 or 4 adverse events were neutropenia (46%), febrile neutropenia (17%), anemia (17%), leukopenia (12%), diarrhea (12%), thrombocytopenia (12%), and vomiting (5%). Adverse events led to treatment discontinuation in 7.9% of patients. Left ventricular dysfunction occurred in 5.6% of patients receiving pertuzumab plus trastuzumab plus FEC followed by pertuzumab and trastuzumab plus docetaxel, 4.0% of those receiving FEC followed by pertuzumab and trastuzumab plus docetaxel, and 2.6% of those receiving pertuzumab plus docetaxel, carboplatin, and trastuzumab, including symptomatic left ventricular systolic dysfunction in 0%, 2.7%, and 0%. The frequency of hypersensitivity and anaphylaxis was highest in the pertuzumab and docetaxel plus carboplatin, and trastuzumab (13.2%, grade 3 or 4 in 2.6%).

Pertuzumab is marketed as Perjeta by Genentech Inc. It carries a boxed warning for cardiomyopathy and embryo-fetal toxicity. Pertuzumab also has warnings and precautions f or embryo-fetal toxicity, left ventricular dysfunction, infusion-related reactions, hypersensitivity reactions and anaphylaxis, and HER2 testing. HER2 testing should be performed with the use of FDA-approved tests by laboratories with demonstrated proficiency.

References

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