Clinical Cancer Research

FDA Approval Summary: Pertuzumab for Adjuvant Treatment of HER2-Positive Early Breast Cancer

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Abstract

On December 20, 2017, the FDA granted regular approval to pertuzumab in combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer (EBC) at high risk of recurrence. Approval was based on data from the APHINITY trial, which randomized patients to receive pertuzumab or placebo in combination with trastuzumab and chemotherapy. After 45.4-month median follow-up, the proportion of invasive disease-free survival (IDFS) events in the intent-to-treat population was 7.1% ($n = 171$) in the pertuzumab arm and 8.7% ($n = 210$) for placebo [hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.67–1.00; $P = 0.047$]. The proportion of IDFS events in patients with hormone receptor–negative disease was 8.2% ($n = 71$) and 10.6% ($n = 91$) in the pertuzumab and placebo arms, respectively (HR, 0.76; 95% CI, 0.56–1.04). The proportion of IDFS events for patients with node-positive disease was 9.2% ($n = 139$) and 12.1% ($n = 181$) in the pertuzumab and placebo arms, respectively (HR, 0.77; 95% CI, 0.62–0.96). Adverse reactions in ≥30% of patients receiving pertuzumab were diarrhea, nausea, alopecia, fatigue, peripheral neuropathy, and vomiting. From a regulatory standpoint, the benefits of the addition of pertuzumab to adjuvant treatment outweighed the risks for patients with EBC at high risk of recurrence.

Introduction

Approximately 20% of breast cancers strongly overexpress human epidermal growth factor receptor 2 (HER2), a gene associated with more aggressive disease and increased recurrence (1). Despite advances in treatment of patients with HER2-positive early breast cancer (EBC), a proportion of patients continue to develop distant recurrences associated with significant morbidity, functional decline, and mortality (2).

Pertuzumab (Perjeta; Genentech, Inc.) is a recombinant humanized mAb that targets the extracellular dimerization domain (subdomain II) of HER2. Pertuzumab binds to a different region than trastuzumab, another monoclonal HER2 antibody, and inhibits the ligand-dependent activation of the HER2 signaling pathway, blocking the dimerization of HER2 with HER3 and other HER family receptors. Pertuzumab and trastuzumab activate the immune system via antibody-dependent cell-mediated cytotoxicity (ADCC). On the basis of preclinical studies, the combination of trastuzumab and pertuzumab demonstrates greater antitumor effect combined as compared with either agent alone (3, 4).

Pertuzumab was initially granted regular approval by the FDA on June 8, 2012, for the treatment of patients with HER2-positive metastatic breast cancer (MBC) with no prior treatment for metastatic disease based on results from the CLEOPATRA study evaluating docetaxel and trastuzumab with pertuzumab or placebo. The final analysis from CLEOPATRA demonstrated an estimated median 15.7-month improvement in overall survival (OS) with the addition of pertuzumab [hazard ratio (HR), 0.68; 95% confidence interval (CI), 0.56–0.84; ref. 5]. On September 30, 2013, the FDA granted pertuzumab accelerated approval for use in combination with docetaxel and trastuzumab as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or EBC (either greater than 2 cm or lymph node positive) as part of a complete treatment regimen for EBC based on an increased rate in pathologic complete response (pCR; ref. 6). This approval was based on two trials, NEOSPHERE, demonstrating a statistically significant improvement in pCR with the addition of pertuzumab to chemotherapy and trastuzumab when compared with trastuzumab alone (39.3% compared with 21.5%, $P = 0.0063$), and TRYPHAENA, demonstrating high rates of pCR and evidence of cardiac safety. At the time of the neoadjuvant approval, Study BO25126 (APHINITY, NCT01358877) was underway. This summarizes the FDA review and data from APHINITY supporting the approval of pertuzumab as a part of adjuvant treatment of patients with HER2-positive EBC at high risk of recurrence.

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Clinical Trial Design

The APHINITY trial was a randomized, multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo or pertuzumab as adjuvant therapy for patients with operable HER2-positive primary breast cancer. The primary objective was to compare invasive disease-free survival (IDFS; excluding second nonbreast cancers) in patients with HER2-positive EBC randomized to chemotherapy plus 1 year of trastuzumab plus placebo or chemotherapy plus 1 year of trastuzumab plus pertuzumab. Permitted chemotherapy regimens included FEC or FAC followed by docetaxel or paclitaxel; or AC, followed by docetaxel or paclitaxel; or docetaxel in combination with carboplatin (7). IDFS was defined as the time from randomization to the first occurrence of one of the following events: invasive breast cancer recurrence in the breast, axilla, regional lymph nodes, chest wall, or skin; distant recurrence; or death attributable to any cause. Secondary objectives were to compare IDFS including second primary nonbreast cancers, disease-free survival (DFS) including ductal carcinoma *in situ* (DCIS), OS, recurrence-free interval, distant recurrence-free interval, cardiac safety, overall safety, and health related quality of life. Pertuzumab was administered as an 840 mg i.v. loading dose followed by 420 mg i.v. every 3 weeks. Trastuzumab was administered as an 8 mg/kg i.v. loading dose followed by 6 mg/kg i.v. every 3 weeks.

Results

Efficacy

Baseline demographics for patients in the intent-to-treat (ITT) population of APHINITY are shown in Table 1. The trial randomized 2,400 patients to the pertuzumab arm and 2,404 to placebo. Most patients were <65 with only a few patients ≥75 ($n = 56$, 1.2%). Eleven (0.2%) patients were male. Baseline disease characteristics for patients in the ITT population are shown in Table 2.

APHINITY demonstrated a statistically significant improvement in IDFS with the addition of pertuzumab to standard adjuvant chemotherapy and trastuzumab with an HR of 0.82 (95% CI, 0.67–1.00; $P = 0.047$; Table 3). The 3-year IDFS rate was 94.1% in the pertuzumab arm and 93.2% in the placebo arm (Fig. 1). Subgroup analyses suggested that certain high-risk subgroups such as those with node-positive disease (HR, 0.77; 95% CI, 0.62–0.96; 3-year IDFS rate of 92.0% in the pertuzumab arm and 90.2% in the placebo arm) as well as hormone receptor–negative disease (HR, 0.76; 95% CI, 0.56–1.04; 3-year IDFS rate of 92.8% in the pertuzumab arm and 91.2% in the placebo arm) may benefit more from therapy. At the time of the first interim OS analysis, 96.7% in the pertuzumab and 96.3% in the placebo arm were alive (HR, 0.89, 95% CI, 0.66–1.21). These data were immature. The final OS analysis will be conducted when 640 deaths have occurred.

Safety

No new safety signals were identified. The safety profile was consistent with the known profile of pertuzumab in the metastatic and neoadjuvant settings. The most common treatment-emergent adverse events (TEAE; >30%) were diarrhea, nausea, alopecia, fatigue, peripheral neuropathy, and vomiting. Grade 3 and 4

Table 1. APHINITY demographics

Demographic parameters	Chemotherapy, trastuzumab and pertuzumab $N = 2,400$, *n* (%)	Chemotherapy, trastuzumab and placebo $N = 2,404$, *n* (%)
Sex		
Male	3 (0.1)	8 (0.3)
Female	2,397 (99.9)	2,396 (99.7)
Age		
Mean years (SD)	51.7 (10.9)	51.4 (10.7)
Median (years)	51	51
Min, max (years)	22, 86	18, 85
Age group		
<65 years	2,085 (86.9)	2,111 (87.8)
≥65 years	315 (13.1)	293 (12.2)
≥75 years	30 (1.3)	26 (1.1)
Race		
White	1,705 (71.0)	1,694 (70.5)
Black or African American	32 (1.3)	41 (1.7)
Asian	590 (24.6)	598 (24.9)
American Indian or Alaska Native	57 (2.4)	56 (2.3)
Native Hawaiian or other Pacific Islander	3 (0.1)	7 (0.3)
Other[a]	13 (0.5)	8 (0.3)
Ethnicity		
Hispanic or Latino	45 (1.9)	42 (1.7)
Not Hispanic or Latino	432 (18.0)	386 (16.1)
Not reported/unknown	1,923 (80.1)	1,976 (82.2)
Region		
United States	296 (12.3)	294 (12.2)
Rest of the world	2,104 (87.7)	2,110 (87.8)
Canada	64 (2.7)	46 (1.9)
Central and South America	60 (2.5)	64 (2.7)
Europe	1,345 (56.0)	1,340 (55.7)
Asia	573 (23.9)	573 (23.8)
Australia/New Zealand	53 (2.2)	75 (3.1)
Africa (South Africa)	9 (0.4)	12 (0.5)

[a]Data on ethnicity were collected primarily at U.S. sites.

Table 2. Baseline disease characteristics for the APHINITY study

	Chemotherapy, trastuzumab and pertuzumab $N = 2,400$, *n* (%)	Chemotherapy, trastuzumab and placebo $N = 2,404$, *n* (%)
Nodal status		
Negative	897 (37.4)	902 (37.5)
1–3 Positive	907 (37.8)	900 (37.4)
≥4 positive	596 (24.8)	602 (25.0)
Pathologic tumor size and nodal status		
<1 cm and node negative	58 (2.4)	60 (2.5)
≥1–<2 cm and node negative	417 (17.4)	391 (16.3)
≥2 cm and node negative	421 (17.5)	450 (18.7)
<1 cm and node positive	86 (3.6)	68 (2.8)
≥1–<2 cm and node positive	416 (17.3)	425 (17.7)
≥2 cm and node positive	999 (41.6)	1,007 (41.9)
Hormone receptor status		
ER and/or PR positive	1,536 (64.0)	1,546 (64.3)
ER and PR negative	864 (36.0)	858 (35.7)
HER2 status (central)		
0	6 (0.3)	2 (<0.1)
1+	16 (0.7)	9 (0.4)
2+	193 (8.0)	200 (8.3)
3+	2,184 (91.0)	2,190 (91.2)
Primary surgery		
Breast conservation	1,118 (46.7)	1,076 (44.8)
Mastectomy	1,280 (53.3)	1,327 (55.2)
Anthracycline-based chemotherapy regimen	1,865 (77.7)	1,877 (78.1)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

Table 3. FDA's analysis of IDFS, in the ITT population of APHINITY

	Chemotherapy, trastuzumab and pertuzumab *N* = 2,400, *n* (%)	Chemotherapy, trastuzumab and placebo *N* = 2,404, *n* (%)
IDFS events (*n*)	171 (7.1%)	210 (8.7%)
Distant recurrence	112	139
Locoregional recurrence	26	34
Contralateral breast cancer	5	11
Death without prior IDFS events	28	26
3-yr IDFS rate (95% CI)	94.06% (93.09–95.03)	93.24% (92.21–94.26)
Stratified HR (95% CI)[a]	0.82 (0.67–1.00)	
Stratified log-rank *P* value[a]	0.047	

Abbreviation: yr, year.

[a]Stratified by randomization stratification factors collected from IxRS: nodal status, hormone receptor status, chemotherapy regimen, and protocol version.

adverse events (AE; ≥2%) were neutropenia, febrile neutropenia, diarrhea, leukopenia, anemia, fatigue, nausea, and stomatitis. All grade diarrhea was greater in the pertuzumab arm (71%) versus the placebo arm (45%). The incidence of grade 3 and 4 AEs was similar in the treatment arms except for diarrhea (pertuzumab 9.9% vs. placebo 3.7%). Almost all diarrhea serious AEs (SAE) required hospitalization (56 patients in the pertuzumab arm and 18 patients in the placebo arm). For the treatment phase when only targeted therapy was administered, the incidence of all grade diarrhea in both arms was less than when administered with chemotherapy, but the rate remained higher in the pertuzumab arm (pertuzumab 18.1% vs. placebo 9.2%; ref. 8). No patients on the pertuzumab arm were hospitalized for diarrhea during targeted therapy alone. Primary cardiac events, defined as heart failure (NYHA class III or IV) or cardiac deaths, were low in each treatment arm, 0.7% for pertuzumab and 0.3% for placebo, almost all were heart failure events. Secondary cardiac events, defined as a change in left ventricular ejection fraction (LVEF) of ≥10 points from baseline and to <50%, were comparable in both arms (2.7% and 2.8%, respectively). Most secondary cardiac events were reported in patients who received anthracycline-based therapy. However, 96.9% of patients who received anthracycline-based therapy did not experience a secondary cardiac event. There was no increase in death due to AEs between the arms any time during the study period.

Patients ≥65 years of age (n = 302) who were treated with pertuzumab compared with those age <65 years had a greater incidence of grade 3 and 4 AEs: 72.5% versus 62.9%, and a greater incidence of SAEs: 43.7% versus 27.2%. The incidence of all grade diarrhea was increased in patients ≥65, 77.2% versus 70.3%. The incidence of grade 3 and 4 diarrhea was 15.9% in patients ≥65 and 8.9% in patients <65.

Patient-reported outcomes

Patient-reported outcomes (PRO) were assessed using three instruments: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), its breast cancer–specific module (EORTC QLQ-BR23), and EuroQol 5 Dimension (EQ-5D-3L). Responses to all questionnaires were to be collected at screening/baseline, end of anthracycline (only for patients receiving anthracyclines), end of taxane (week 10, 13, or 19 depending on the chemotherapy regimen), week 25, end of study treatment, and follow-up months 18, 24, and 36. The completion rates on both arms were 85% or higher at all scheduled assessments. These data informed the review of safety and tolerability.

The mean of change from baseline for functional domains and relevant symptoms of EORTC QLQ-C30 was evaluated. Although the study was not designed to compare outcomes statistically between treatment arms, the results suggested that patients in both treatment groups reported comparable declines in physical function from baseline while on chemotherapy. Mean physical function scores began to recover during the targeted therapy alone; however, they did not return to baseline until follow-up off treatment. There were no notable differences in physical function scores measured by the 5-item physical function scale between the two treatment arms throughout the study (Fig. 2A).

Longitudinal data on patient-reported diarrhea were analyzed to further explore the Common Terminology Criteria for Adverse Events (CTCAE) safety findings. Patient-reported diarrhea was worse in the pertuzumab arm throughout the time on study treatment, but returned to baseline during off-treatment follow-up (Fig. 2B). The increased incidence of rash in the

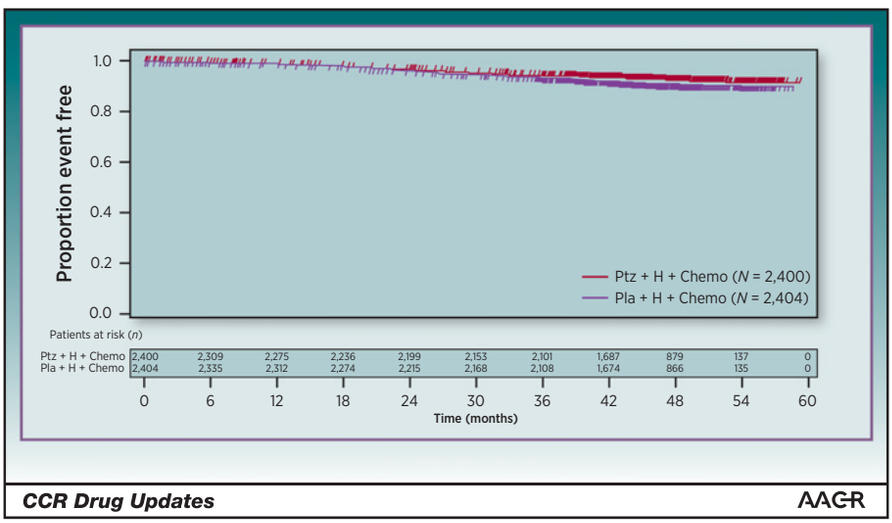

Figure 1.
Kaplan–Meier curves for IDFS in the ITT population of APHINITY. Pla + H + Chemo, placebo + trastuzumab + chemotherapy; Ptz + H + Chemo, pertuzumab + trastuzumab + chemotherapy.

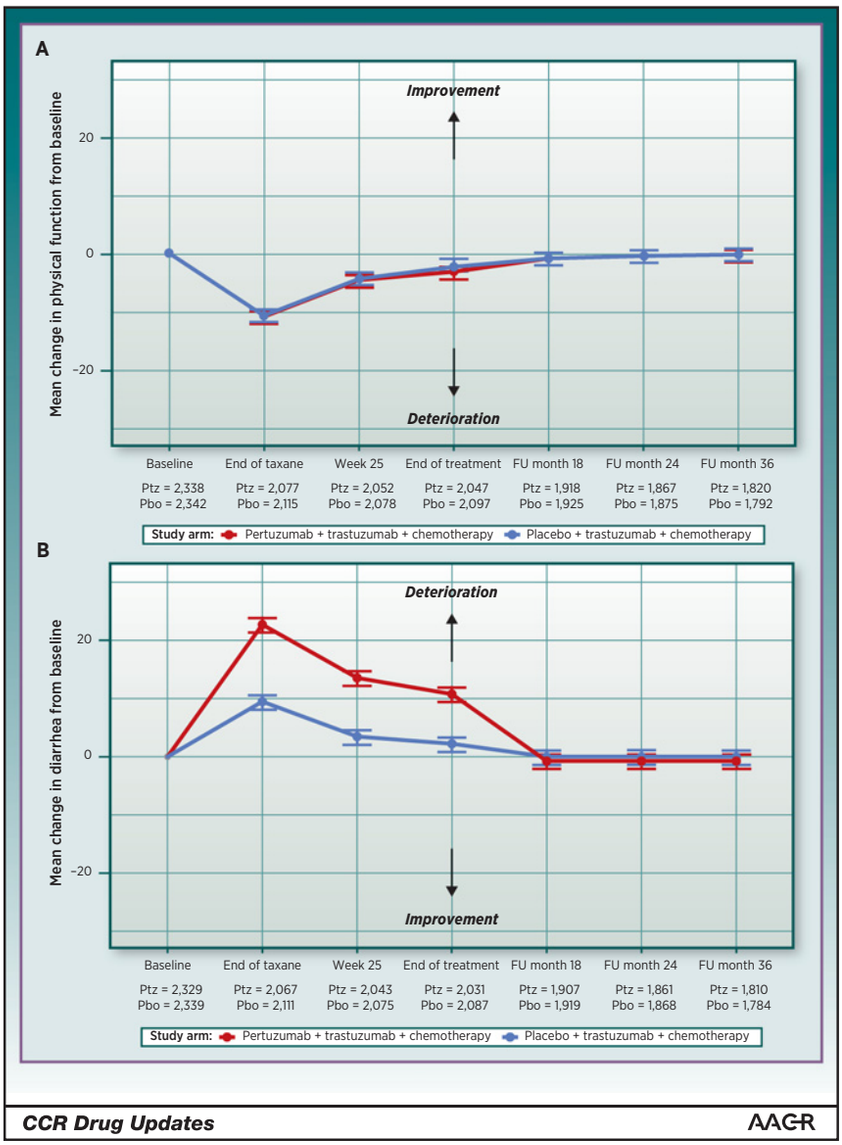

Figure 2.
Analysis of change in patient-reported physical function and diarrhea in the APHINITY study. **A,** Mean change in physical function from baseline using EORTC QLQ-C30. **B,** Mean change in diarrhea from baseline using EORTC QLQ-C30. FU, follow-up; Pbo, placebo; Ptz, pertuzumab.

pertuzumab arm as assessed by CTCAE could not be further characterized by PRO as the instruments selected did not assess this AE.

Regulatory Insights

While APHINITY demonstrated a statistically significant improvement in IDFS with the addition of pertuzumab to standard adjuvant chemotherapy and trastuzumab, the overall benefit was modest with a 0.9% absolute improvement in median IDFS. One potential reason for this small improvement is that APHINITY enrolled patients with a broad range of tumor sizes and included tumors at least 1 cm as well as tumors 0.5–1 cm that were hormone receptor negative, histologic grade 3, or where the patient was younger than 35 years old. The recurrence risk for patients in the APHINITY study overall was lower than that of patients who were included in the neoadjuvant NEOSPHERE study, which required patients to have a primary tumor size of greater than 2 cm or evidence of lymph node involvement, with 19.3% of patients in the APHINITY trial ($n = 926$) having no evidence of lymph node involvement and a primary tumor size less than 2 cm. As the prognosis for patients with small tumors with no nodal involvement is already excellent, this likely resulted in a ceiling effect where it was difficult to show benefit from additional therapy (9). In higher risk subgroups, such as those with node-positive or hormone receptor–negative disease, a larger benefit was observed. The absolute improvement of IDFS in these subgroups is comparable with other historic adjuvant approvals including paclitaxel, anastrozole, letrozole, and neratinib with IDFS benefits ranging from approximately 2% to 4% (10, 11, 12, 13).

pCR can be used as an endpoint to support accelerated approval in patients with breast cancer who are at high risk for disease recurrence and death despite available systemic therapy (6). The accelerated approval of pertuzumab in the neoadjuvant setting was based on a totality of evidence including the substantial

improvement in PFS and OS seen in the metastatic setting, and the improvement in pCR in the neoadjuvant setting, which was deemed to be reasonably likely to predict a benefit in DFS. However, questions remain regarding the use of pCR as a surrogate endpoint, including what magnitude of improvement in pCR might correspond to an improvement in IDFS, and why, despite the large OS benefit seen with pertuzumab in the metastatic setting, the benefit in the adjuvant setting was modest. For future applications, the totality of evidence of the activity of the agent in other treatment settings can be employed to address some of the residual questions regarding pCR (6, 14).

At the initial neoadjuvant approval, the use of pertuzumab had not been evaluated in combination with doxorubicin, and the FDA label indicated that the safety of pertuzumab as part of a doxorubicin-containing regimen had not been established. In the APHINITY study, over 75% of patients received a regimen containing epirubicin or (adriamycin) doxorubicin. Cardiac safety was similar between treatment arms and the addition of pertuzumab did not increase the risk of cardiotoxicity. These data demonstrated the safety of adding pertuzumab to doxorubicin-containing regimens, and the label language regarding the lack of safety data in this setting was removed.

Because of the modest improvement in IDFS, FDA paid close attention to the risk–benefit profile and safety analysis during the review. Another piece of the risk–benefit profile is how patients felt during and after therapy; thus, the PRO data submitted with this application were closely analyzed. There was no notable difference in physical or role function demonstrated in the chemotherapy, trastuzumab, and pertuzumab arm as compared with the chemotherapy, trastuzumab, and placebo arm. However, there was a difference in patient-reported diarrhea in patients who received pertuzumab. There were several issues when considering adding a summary of physical and role functioning language to the drug product label. FDA analysis noted a ceiling effect, defined as patients reporting the highest level of functioning, at baseline for multiple items including those in the physical function scale. A large percentage of patients scored at the highest end of the physical function scale, which may make differences between the treatment arms more difficult to detect. To support a claim of "no difference," the sensitivity of a measure is particularly important, and it was uncertain whether differences could not be detected because of the ceiling effect noted with the 5-item scale. The same concern applies to the two-question assessment of role function. As there was no formal noninferiority hypothesis for

Table 4. FDA risk–benefit analysis

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	• In 2017, it is estimated that breast cancer will be diagnosed in 252,710 women in the United States. Of these, approximately 15% to 20% of new diagnoses will have overexpression of HER2, which is associated with increased risk of disease recurrence.	• HER2-positive EBC breast cancer is a serious and life-threatening condition.
Current treatment options	• The treatment of EBC is curative in nature with a goal to prevent disease relapse and improve OS. Current treatment options for patients with early HER2-positive breast cancer include surgery, radiotherapy, adjuvant/neoadjuvant chemotherapy with trastuzumab ± pertuzumab and adjuvant neratinib.	• Despite advances in treatment of patients with HER2-positive EBC, there remain a proportion of patients who go on to develop distant recurrence. • There is an unmet need to improve the outcomes of patients with HER2-positive operable breast cancer.
Benefit	• Clinical data from the randomized, double-blind, placebo-controlled phase III trial (APHINITY) in women with operable HER2-positive breast cancer presented in this sBLA demonstrate an improvement in 3-year IDFS for pertuzumab + trastuzumab + chemotherapy as compared with placebo + trastuzumab + chemotherapy. The 3-year estimated IDFS rate was 94.1% in the pertuzumab + trastuzumab + chemotherapy arm and 93.2% in the placebo + trastuzumab + chemotherapy arm (HR, 0.82; 95% CI,0.67–1.00; $P = 0.047$). Subgroup analyses showed the following results for node-positive disease and hormone receptor–negative disease: HR, 0.77; 95% CI, 0.62–0.96; 3-year IDFS rate of 92.0% in the pertuzumab arm and 90.2% in the placebo arm, and HR, 0.76; 95% CI, 0.56–1.04; 3-year IDFS rate of 92.8% in the pertuzumab arm and 91.2% in the placebo arm. OS data were not mature at the time of analysis with 96.7% of patients in the pertuzumab + trastuzumab + chemotherapy arm and 96.3% of patients in the placebo + trastuzumab + chemotherapy arm alive at the time of analysis (HR, 0.89; 95% CI, 0.66–1.21).	• The IDFS benefit derived from pertuzumab is statistically significant. • It is most clinically meaningful in patients with high risk for disease recurrence, including but not limited to those patients with lymph node involvement. • Supportive secondary endpoint results and subgroup analyses further substantiate the evidence of pertuzumab benefit, particularly in higher risk subgroups. • OS is immature; final OS analysis will be submitted as a postmarketing commitment.
Risk and risk management	• The addition of pertuzumab to standard chemotherapy and trastuzumab increased the incidence of AEs, including diarrhea, fatigue, anemia, and rash. The incidence of grade 3–4 AEs was similar in the treatment arms except for diarrhea (10% vs. 4%). In the 302 patients age ≥65 years treated with pertuzumab compared with those age <65 years, the older patients had a higher incidence of grade 3 and 4 TEAEs, SAEs, all grades of diarrhea, and grade 3 and 4 diarrhea. There were only 30 patients age ≥75 years in the pertuzumab treatment arm.	• The safety profile of pertuzumab is acceptable for the intended population. • In view of the toxicity observed with pertuzumab for patients age ≥65 years and limited data for patients age ≥75 years, caution is indicated. • The safe use of pertuzumab can be managed through accurate labeling and routine oncology care. • No REMS is indicated.

Abbreviations: REMS, Risk Evaluation and Mitigation Strategy; sBLA, supplemental biologics license application.

these assessments as a part of this study, the result of "little or no difference" is a challenging finding to convey accurately in product labeling. For these reasons, no specific PRO findings were included in FDA labeling. (15).

The definition of IDFS used in APHINITY was time from randomization to the date of the first occurrence of a breast cancer–specific recurrence, whether in the breast, locoregional, or distant recurrence as well as all deaths due to any cause. This definition excludes second primary nonbreast cancers and *in situ* carcinomas including DCIS, lobular carcinoma *in situ* (LCIS), and nonmelanoma skin cancers. This differs from the standardized definitions for efficacy endpoints (STEEP) criteria, which include second primary nonbreast cancers to capture possible treatment-related second cancers (e.g., acute myeloid leukemia) and assure a distant breast cancer diagnosis is not missed (16). FDA considers each definition acceptable as an adjuvant breast cancer trial endpoint as long as prospectively determined. Analyses from APHINITY demonstrated minimal differences between the two definitions at the 3-year timepoint.

Conclusions

In summary, pertuzumab demonstrated a statistically significant improvement in IDFS in a large, randomized, double-blind clinical study. Despite immature OS data, in patients with high-risk HER2-positive EBC such as those patients with hormone receptor–negative disease or lymph node involvement, this IDFS improvement represents a clinically meaningful benefit. The addition of pertuzumab to standard chemotherapy increased the incidence of AEs, including diarrhea, fatigue, anemia, and rash, and increased AEs in patients $\geq$65 years (6). However, the safety profile is acceptable in the intended population. PRO data demonstrated the impact of diarrhea as an AE, but suggest that the addition of pertuzumab to trastuzumab and chemotherapy in the adjuvant setting did not result in additional detriment to physical function. The risk–benefit profile for pertuzumab in the adjuvant treatment of patients with HER2-positive EBC at high risk of recurrence was favorable from a regulatory perspective (Table 4). Important questions that remain unanswered include whether patients who achieve a pCR need a full year of adjuvant pertuzumab in addition to trastuzumab, and whether adjuvant neratinib confers additional clinical benefit in patients who receive trastuzumab and pertuzumab in the adjuvant setting. Labeling allows healthcare providers and patients the flexibility to incorporate this therapy based on assessment of individual risk–benefit.

Disclosure of Potential Conflicts of Interest

B.L. King-Kallimanis was an associate director at Pharmerit International. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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