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

HECTOR BOIX-PERALES,^a JEANETT BORREGAARD,^b KRISTINA BECH JENSEN,^b JENS ERSBØLL,^b SARA GALLUZZO,^c ROSA GIULIANI,^d CINZIA CICERONI,^d DANIELA MELCHIORRI,^d TOMAS SALMONSON,^e JONAS BERGH,^f JAN H. SCHELLEN,^g FRANCESCO PIGNATTI^a

^aEuropean Medicines Agency, London, United Kingdom; ^bDanish Health and Medicines Authority, København, Denmark; ^cDepartment of Physiology and Pharmacology, Università di Roma "La Sapienza," Rome, Italy; ^dAgenzia Italiana del Farmaco, Rome, Italy;

^eLäkemedelsverket, Medical Products Agency, Uppsala, Sweden; ^fKarolinska Institutet, Stockholm, Sweden; ^gThe Netherlands Cancer Institute, Amsterdam, The Netherlands

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Pertuzumab • Perjeta • Breast cancer • EMA • European Medicines Agency

ABSTRACT

Pertuzumab is a recombinant humanized monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of *HER2*. Based on the positive opinion from the European Medicines Agency (EMA) on March 4, 2013, a marketing authorization valid throughout the European Union (EU) was issued for pertuzumab (Perjeta) for use in combination with trastuzumab and docetaxel for the treatment of adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. The demonstration of clinical benefit for pertuzumab was based on a single, phase III, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel in previously untreated patients with locally advanced or

metastatic HER2-positive breast cancer. In the primary analysis, median progression-free survival was 18.5 months in the pertuzumab group compared with 12.4 months in the placebo group (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.51–0.75; $p < .0001$). For the secondary endpoints, overall survival (HR: 0.66; 95% CI: 0.52–0.84; $p = .0008$) and objective response rate (80.2% vs. 69.3%) were also favored in the pertuzumab group. Toxicity was similar between groups except for higher incidence of diarrhea, rash, mucosal inflammation, dry skin, and neutropenia for pertuzumab compared with placebo. This paper summarizes the scientific review of the application leading to approval in the EU. The detailed scientific assessment report and product information, including the summary of product characteristics, are available on the EMA website (<http://www.ema.europa.eu>). *The Oncologist* 2014;19:766–773

Implications for Practice: Pertuzumab was approved in the European Union for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive breast cancer. The approval is based on a controlled, randomized pivotal study with 808 patients. A statistically significant improvement in PFS was observed in the pertuzumab group compared with the placebo group (18.5 months compared with 12.4 months) and the hazard ratio for overall survival was 0.66. Administration of two HER2 blocking antibodies strongly enhances the effect compared with each antibody on its own. The benefits were considered clinically relevant in patients who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

INTRODUCTION

Breast cancer has a global prevalence of more than 1.3 million patients and a mortality rate of approximately 450,000 deaths per year [1]. In the European Union (EU), 89,000 deaths were predicted to occur from breast cancer in 2013 [2].

The human epidermal growth factor receptor-2 (*HER2*) proto-oncogene (also known as “neu” or “c-erbB-2”) plays a key role in regulating cell growth, survival, and differentiation. *HER2* overexpression or amplification (commonly

Correspondence: Hector Boix-Perales, Ph.D., European Medicines Agency, 7 Westferry Circus, London E14 4HB, United Kingdom. Telephone: 44 20 74 7418 8400; E-Mail: Hector.Boix@ema.europa.eu Received September 5, 2013; accepted for publication April 22, 2014; first published online in *The Oncologist Express* on June 13, 2014. ©AlphaMed Press 1083-7159/2014/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2013-0348>

referred to as “HER2 positivity”) has been associated with higher rates of recurrence and increased mortality. Of the global deaths from breast cancer each year, ~15%–20% are likely due to HER2-positive disease.

The introduction of anti-HER2-based therapies has significantly improved outcomes both in the metastatic setting (trastuzumab, lapatinib) and the adjuvant setting (trastuzumab) for HER2-positive breast cancer patients.

Pertuzumab is a recombinant, humanized, IgG monoclonal antibody that targets HER2 [3]. Pertuzumab acts by blocking the dimerization of HER2 with other HER family members, including HER1 (EGFR), HER3, and HER4 (“dimerization inhibitor”). Pertuzumab differs from trastuzumab in the epitope-binding regions of the light chain (12 amino acid differences) and the heavy chain (29 amino acid differences). Although both pertuzumab and trastuzumab bind the HER2 receptor, they differ in their binding of HER2 epitopes, and this partly explains their different mode of action (Fig. 1).

The applicant company Roche Registration Ltd. submitted an initial marketing authorization application for pertuzumab (Perjeta; Omnitarg; RO4368451; rhuMab 2C4) to the European Medicines Agency (EMA). The review was conducted by the Committee for Medicinal Products for Human Use (CHMP), and a marketing authorization was granted in the EU on March 4, 2013, for pertuzumab for use in combination with trastuzumab and docetaxel for the treatment of adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

This article summarizes the scientific review of the application leading to the approval of pertuzumab in the EU. The detailed scientific assessment report and product information are available on the EMA website (<http://www.ema.europa.eu>).

NONCLINICAL ASPECTS

In BT-474 breast cancer cells, combination treatment of trastuzumab with pertuzumab resulted in a synergistic and dose-dependent downregulation of total and phosphorylated HER2 expression levels. The levels of phospho-Akt were also downregulated in contrast to phospho-ERK1/2, which was not inhibited [5]. Further, in vitro experiments with a panel of human tumor cell lines showed that pertuzumab activated antibody-dependent cellular cytotoxicity with potency identical to that of trastuzumab [6].

Pertuzumab was able to induce apoptosis in cells that have low to moderate HER2 expression (MDA-MB-175-VII cells) but did not induce apoptosis in breast cancer cell lines with high HER2 expression (BT-474 cells and SK-BR-3 cells). This finding raises questions about the extent to which pertuzumab-mediated tumor cell apoptosis occurs in the in vivo setting.

Pertuzumab was able to induce apoptosis in cells that have low to moderate HER2 expression but did not induce apoptosis in breast cancer cell lines with high HER2 expression. This finding raises questions about the extent to which pertuzumab-mediated tumor cell apoptosis occurs in the in vivo setting.

The antitumor activity of pertuzumab was evaluated in nude mice implanted with patient-derived tumors representing breast cancer, ovarian cancer, and non-small cell lung cancer (NSCLC). Pertuzumab exhibited 13%–45% tumor growth inhibition in 1 of 6 tested breast tumor xenograft models, 1 of 4 ovarian cancer tumor xenograft models, and 4 of 18 NSCLC tumor xenograft models. Although both pertuzumab and trastuzumab as single agents exhibited antitumor activity against HER2-overexpressing Calu-3 NSCLC xenografts (85% and 82% tumor growth inhibition), the combination of the two was superior compared with monotherapy, resulting in tumor regression and, in some cases, complete remission. Moreover, although not statistically significant, combined treatment with pertuzumab and trastuzumab appeared to result in higher tumor growth inhibition in the breast cancer cell line MDA-MB-175-VII xenograft model than the individual drugs alone. Nonclinical models suggested that >80% suppression of tumor growth was achieved at steady-state trough concentrations of ~5–25 µg/mL [7].

Placental transfer of pertuzumab after i.v. administration to pregnant monkeys resulted in exposures in fetuses of approximately one-third of the maternal exposure. Maternal and fetal toxicity was observed in all pertuzumab-treated groups. The main findings consisted of low amniotic fluid volume; high fetal lethality; retarded development; and external, visceral, and skeletal abnormalities. These results are consistent with the expression of HER2 in renal tissue and the role of HER2 in the regulation of growth, differentiation, and morphogenesis of the kidney. Although the observed external, visceral, and skeletal abnormalities were considered secondary to intrauterine restriction resulting from low amniotic fluid volume, it is possible that the ventricular abnormalities observed in the toxicity study may also be a direct effect of pertuzumab treatment.

CLINICAL PHARMACOLOGY

Across all clinical studies, the volume of distribution of the central compartment and the peripheral compartment in the typical patient was 3.11 L and 2.46 L, respectively. The median clearance of pertuzumab was 0.235 L/day, and the median half-life was 18 days. Pertuzumab displayed linear pharmacokinetics (PK) within the recommended dose range. No dedicated renal impairment study was presented, but mild to moderate renal impairment had no effect on pertuzumab PK; therefore, no dose adjustment is recommended for patients with this level of renal impairment.

No PK interactions were observed between pertuzumab and trastuzumab or docetaxel. Four studies have evaluated the effects of pertuzumab on the PK of the following coadministered cytotoxic agents: docetaxel [8], gemcitabine [9], erlotinib [10] and capecitabine [11]. There was no evidence of any PK interaction between pertuzumab and any of these agents.

Based on the results of early clinical development and a phase I study (TOC2297g), a loading dose of 840 mg i.v. followed by a 420 mg i.v. maintenance dose every 3 weeks was proposed [12]. Population PK modeling showed that the target serum concentration was achieved by the continued use of fixed, non-weight-based dosing in female patients [13]. Phase II studies in advanced ovarian cancer and hormone-refractory prostate cancer [14, 15] showed that a higher dose (1,050 mg every 3 weeks, no loading dose) did not differ significantly in terms of efficacy or safety.

Figure 1. Dual HER2 blockade with trastuzumab and pertuzumab in HER2-amplified breast cancer [4].

Abbreviations: HER-2, human epidermal growth factor-2; HER-3, human epidermal growth factor-3; HRG, heregulin; P, phosphorylation; PI3K, phosphatidylinositol 3-kinase.

Table 1. Summary of baseline patient and disease characteristics (pivotal study WO20698/TOC4129g)

Characteristic	Placebo + T + D (n = 406)	Pertuzumab + T + D (n = 402)	Total (n = 808)
Female sex, n (%)	404 (99.5)	402 (100)	806 (99.8)
Age			
Median	54	54	54
≥65, n (%)	67 (16.5)	60 (14.9)	127 (15.7)
ECOG PS, n (%)			
0	248 (61.1)	274 (68.2)	522 (64.6)
1	157 (38.7)	125 (31.1)	282 (34.9)
LVEF, mean	65.5	64.9	65.2
Prior treatment, adjuvant or neoadjuvant, n (%)	192 (47.3)	184 (45.8)	376 (46.5)
Prior therapy, trastuzumab, n (%)	41 (10.1)	46 (11.4)	87 (10.8)
Visceral disease type, n (%)	90 (22.2)	88 (21.9)	178 (22)
Measurable disease status (IRF) , n (%)	336 (82.8)	343 (85.3)	679 (84)
Histology, n (%)			
Anaplastic	1 (0.2)	2 (0.5)	3 (0.4)
Moderately differentiated	132 (32.5)	132 (32.8)	264 (32.7)
Poorly differentiated	125 (30.8)	130 (32.3)	255 (31.6)
Unknown	131 (32.3)	124 (30.8)	255 (31.6)
Well differentiated	16 (3.9)	14 (3.5)	30 (3.7)
ER/PgR status, n (%)			
Negative	196 (48.3)	212 (52.7)	408 (50.5)
Positive	199 (49)	189 (47)	388 (48)
Unknown	11 (2.7)	1 (0.2)	12 (1.5)
HER2 status IHC 3+, n (%)	371 (91.4)	350 (87.1)	721 (89.2)
HER2 status FISH-positive, n (%)	383 (94.3)	384 (95.5)	767 (94.9)
Ductal breast cancer subtype, n (%)	368 (90.6)	368 (91.5)	736 (91.1)

Abbreviations: D, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; IRF, independent review facility; LVEF, left ventricular ejection fraction; T, trastuzumab.

Clinical Efficacy

The pivotal efficacy study WO20698/TOC4129g (CLEOPATRA), a multicenter, randomized, double-blind, placebo-controlled phase III clinical trial, recruited patients with histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease and who were candidates for chemotherapy [16]. Patients were enrolled in

Europe (37.9%), Asia (31.3%), North America (16.7%), and South America (14.1%). Only approximately half of patients had received prior adjuvant or neoadjuvant treatment, and only 11% of patients had received prior adjuvant or neoadjuvant therapy with trastuzumab. Most of these patients had received prior anthracycline therapy, and 43% of patients in both treatment groups had previously received radiotherapy.

Table 2. Summary of efficacy results (pivotal study WO20698/TOC4129g)

Parameter	Placebo + T + D (n = 406)	Pertuzumab + T + D (n = 402)	HR (95% CI)	p value
PFS ^a				<.0001
Events, no. (%)	242 (59)	191 (47.5)		
Median (months)	12.4	18.5	0.62 (0.51–0.75)	
Overall survival				.0008 ^b
Events, no. (%)	154 (37.9)	113 (28.1)		
Median (months)	37.6	Not reached	0.66 (0.52–0.84)	
ORR ^a				.0011
Measurable disease (no.)	336	343		
ORR, % (95% CI)	69.3 (64.1–74.2)	80.2 (75.6–84.3)	Difference in ORR: 10.8 (4.2–17.5)	
Complete response (%)	4.2	5.5		
Partial response (%)	65.2	74.6		
Stable disease (%)	20.8	14.6		
Progressive disease (%)	8.3	3.8		
Duration of response, ^a median (weeks)	54.1	87.6		

^aPFS, ORR, and duration of response are based on tumor assessments by independent review facilities.

^bThe *p* value met the boundary for the interim analysis of overall survival (*p* ≤ .0138).

Abbreviations: CI, confidence interval; D, docetaxel; ORR, objective response rate; PFS, progression-free survival; T, trastuzumab.

For the majority of patients (>90%), the HER2 status was tested only in the primary tumor specimen. About half of tumors were ER/PgR positive, which is in line with previous findings in HER2-positive breast cancer populations. In general, baseline characteristics were well balanced between treatment arms (Table 1).

Patients received trastuzumab plus docetaxel plus either placebo or pertuzumab. Pertuzumab (loading dose of 840 mg i.v., followed by a 420 mg i.v. maintenance dose every 3 weeks) and trastuzumab (loading dose of 8 mg/kg i.v., followed by a 6 mg/kg i.v. maintenance dose every 3 weeks) were given until disease progression, withdrawal of consent, or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m² as an i.v. infusion every 3 weeks for at least six cycles and could be escalated to 100 mg/m² at the investigator's discretion.

The primary endpoint of the study was progression-free survival (PFS) as assessed by an independent review facility (performing blinded independent review) and defined as the time from the date of randomization to the date of disease progression (Response Evaluation Criteria In Solid Tumors version 1) or death (from any cause) if the death occurred within 18 weeks of the last tumor assessment.

In total, 808 patients were randomized to the placebo group (*n* = 406) or the pertuzumab group (*n* = 402). The efficacy results are summarized in Table 2 and Figures 2 and 3. A statistically significant improvement in PFS was observed in the pertuzumab group compared with the placebo group (18.5 months vs. 12.4 months; hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.51–0.75; *p* < .0001). The effect was consistent across most subgroups (prior treatment status, geographical region, age group, race, ER/PgR, HER2 immunohistochemistry status, and fluorescence in situ hybridization status), except for visceral disease (visceral disease subgroup: HR: 0.55; 95% CI: 0.45–0.68; nonvisceral disease subgroup: HR: 0.96; 95% CI: 0.61–1.52; interaction *p* = 0.0332). In the second

interim analysis of overall survival (OS; data cutoff of May 14, 2012, and also considered the final analysis), the HR was 0.66 (95% CI: 0.52–0.84, *p* = .0008). Exploratory subgroup analyses by biomarker (serum markers, HER ligands and receptor tyrosine kinases, and intracellular pathway markers) did not identify any predictive or prognostic association between biomarker level and pertuzumab for PFS [17].

Exploratory subgroup analyses by biomarker (serum markers, HER ligands and receptor tyrosine kinases, and intracellular pathway markers) did not identify any predictive or prognostic association between biomarker level and pertuzumab for PFS.

Clinical Safety

The safety of pertuzumab has been evaluated in more than 1,400 patients in trials conducted in patients with various malignancies and predominantly treated with pertuzumab in combination with other antineoplastic agents.

An overview of adverse events (AEs) from the pivotal trial is presented in Table 3. The toxicity was similar between groups except for higher incidences of diarrhea (66.8% vs. 46.3%), rash (33.7% vs. 24.2%), mucosal inflammation (27.8% vs. 19.9%), dry skin (10.6 vs. 4.3), and neutropenia (52.8% vs. 49.6%) for pertuzumab compared with the placebo arm. Grade ≥3 leukopenia was more frequent in the pertuzumab group compared with placebo (58.2% vs. 53.4%). Febrile neutropenia was also more frequent in the pertuzumab group (13.8% vs. 7.6%) although below the recommended threshold for prophylactic granulocyte colony-stimulating factor (febrile neutropenia risk ≥20%), based on the European Society for Medical Oncology guidelines [18]. In patients with a leukopenia

Figure 2. Study WO20698/TOC4129g: Kaplan-Meier plot of independent review facility-assessed progression-free survival (intention-to-treat population).
Abbreviations: D, docetaxel; Pla, placebo; Ptz, pertuzumab; T, trastuzumab.

Figure 3. Kaplan-Meier curve of overall survival.
Abbreviations: D, docetaxel; Pla, placebo; Ptz, pertuzumab; T, trastuzumab.

event at any cycle, the median time to the most severe event was 29 days in both treatment groups.

Diarrhea was more commonly reported in patients treated in the pertuzumab group (68.1%) compared with

placebo (47.6%). Although diarrhea episodes also lasted longer in the pertuzumab group (median duration of the longest episode was 17 days compared with 8 days in the control arm), most of these events were mild or moderate in

Table 3. Summary of adverse events (National Cancer Institute Common Terminology Criteria, version 3) occurring in $\geq 10\%$ of patients in any group (pivotal study WO20698/TOC4129g)

Adverse event	Placebo + T + D (n = 397), n (%)	Pertuzumab + T + D (n = 407), n (%)
Alopecia	241 (60.7)	247 (60.7)
Diarrhea	189 (47.6)	277 (68.1)
Neutropenia	198 (49.9)	215 (52.8)
Nausea	169 (42.6)	177 (43.5)
Fatigue	147 (37.0)	154 (37.8)
Rash	96 (24.2)	145 (35.6)
Asthenia	121 (30.5)	108 (26.5)
Decreased appetite	106 (26.7)	119 (29.2)
Edema peripheral	121 (30.5)	98 (24.1)
Vomiting	98 (24.7)	101 (24.8)
Mucosal inflammation	79 (19.9)	112 (27.5)
Myalgia	95 (23.9)	96 (23.6)
Nail disorder	92 (23.2)	93 (22.9)
Anemia	76 (19.1)	96 (23.6)
Headache	74 (18.6)	94 (23.1)
Neuropathy peripheral	80 (20.2)	88 (21.6)
Cough	77 (19.4)	89 (21.9)
Constipation	101 (25.4)	62 (15.2)
Leukopenia	82 (20.7)	75 (18.4)
Pyrexia	72 (18.1)	77 (18.9)
Stomatitis	61 (15.4)	80 (19.7)
Dysgeusia	62 (15.6)	75 (18.4)
Arthralgia	65 (16.4)	67 (16.5)
Upper respiratory tract infection	55 (13.9)	70 (17.2)
Dyspnea	63 (15.9)	57 (14.0)
Pain in extremity	51 (12.8)	68 (16.7)
Insomnia	55 (13.9)	59 (14.5)
Lacrimation increased	55 (13.9)	58 (14.3)
Nasopharyngitis	56 (14.1)	53 (13.0)
Abdominal pain	49 (12.3)	59 (14.5)
Back pain	46 (11.6)	60 (14.7)
Dizziness	52 (13.1)	53 (13.0)
Peripheral sensory neuropathy	56 (14.1)	49 (12.0)
Pruritus	40 (10.1)	64 (15.7)
Dyspepsia	48 (12.1)	52 (12.8)
Edema	49 (12.3)	46 (11.3)
Febrile neutropenia	30 (7.6)	56 (13.8)
Abdominal pain upper	40 (10.1)	39 (9.6)
Paresthesia	41 (10.3)	38 (9.3)
Hypertension	32 (8.1)	41 (10.1)
Dry skin	19 (4.8)	44 (10.8)

Clinical cutoff date: November 7, 2011.

Abbreviations: D, docetaxel; T, trastuzumab.

severity and few patients actually discontinued study medication because of diarrhea. Many patients experienced diarrhea early in the course of treatment. A higher incidence of diarrhea was observed in Asian patients, patients with a history of bowel disease, and patients receiving concomitant chemotherapy.

No significant differences were observed between the two treatment groups in terms of incidence of cardiac AEs. Left ventricular dysfunction was the most common cardiac AE. After 1 year of additional follow-up (clinical cutoff date of May 14, 2012), left ventricular dysfunction occurred at a frequency of $<10\%$ in the pivotal clinical trial (5.4% in the pertuzumab group and 8.6% in the placebo group, including symptomatic left ventricular systolic dysfunction in 1.2% and 3.3% of patients, respectively). In the pivotal trial, prior anthracycline therapy (HR: 2.21; 95% CI: 1.27–3.86; $p = .0053$) and prior radiotherapy (HR: 2.43; 95% CI: 1.37–4.31; $p = .0025$) were identified as potentially important risk factors associated with time to first asymptomatic or symptomatic left ventricular systolic dysfunction (according to the investigator's assessment). The cardiac dysfunction was reversible in the majority of patients and recovered >9 weeks after the decline (the assessment of left ventricular ejection fraction [LVEF] was scheduled every 9 weeks). Patients with clinically important cardiac risk factors (current uncontrolled hypertension or unstable angina; history of congestive heart failure of any New York Heart Association criteria or serious cardiac arrhythmia requiring treatment, except for atrial fibrillation and paroxysmal supraventricular tachycardia; history of myocardial infarction within 6 months of randomization; history of LVEF decline to below 50% during or after prior trastuzumab neoadjuvant or adjuvant therapy) were not eligible to enroll in this study.

The incidence of serious AEs was higher in the pertuzumab group (35.6%) compared with the placebo group (28.0%). AEs resulting in death occurred in 2.0% in the pertuzumab arm compared with 2.8% in the placebo arm and were related mainly to febrile neutropenia or infection.

Patients in the pivotal trial were tested at multiple time points for antibodies to pertuzumab. Approximately 2.8% (11 of 386) of pertuzumab-treated patients and 6.2% (23 of 372) of placebo-treated patients tested positive. Anaphylaxis or hypersensitivity reactions (occurring at any time and regardless of causality) were reported for 9.1% of patients in the placebo arm compared with 10.8% of patients in the pertuzumab arm. These events were severe in 2.5% and 2.0% of patients, respectively. A potential loss of efficacy based on anti-therapeutic antibodies in individual patients cannot be ruled out. Immunogenicity information from ongoing and planned clinical trials will be collected and reviewed by the Agency.

BENEFIT-RISK ASSESSMENT

The lack of a pertuzumab and docetaxel treatment arm in the pivotal trial was discussed during the scientific advice procedure. The applicant argued that nonclinical data as well as data from the supportive studies, in particular, study WO20697, clearly indicated that the combination regimen was more active than either agent alone. Consequently, it was agreed that it would be unethical to include a pertuzumab-and docetaxel-only arm.

Based on the results of the primary analysis, there was a favorable outcome for PFS in patients treated with

pertuzumab in combination with trastuzumab and docetaxel compared with placebo in combination with trastuzumab and docetaxel. The secondary analyses for OS also showed a difference in favor of the pertuzumab arm (for updated OS results, see [19]). The evidence presented was statistically compelling and clinically relevant. A number of sensitivity analyses confirmed the robustness of the result. The effect was consistent across most subgroups, except for visceral disease. This was somewhat unexpected from a mechanistic point of view and considered likely to be a chance finding.

There were concerns about the selected patient population because only ~11% of patients had received prior trastuzumab in the neoadjuvant or adjuvant setting compared with the majority of patients expected on the basis of current standard of care. In an exploratory post hoc analysis in patients with prior adjuvant or neoadjuvant trastuzumab ($n = 88$), the median PFS in the placebo group ($n = 41$) and the pertuzumab group ($n = 47$) was 10.4 months and 16.9 months, respectively (HR: 0.62; 95% CI: 0.35–1.07; log-rank $p = .08$). Despite the known limitations of exploratory analyses, these results provided reassurance about the efficacy of pertuzumab in the target population. However, the EMA has imposed obligations to conduct post-authorization studies to further confirm the effect size associated with pertuzumab in patients pretreated with trastuzumab. The results of the ongoing studies MO22324, a randomized phase II study of trastuzumab plus capecitabine with or without pertuzumab in second-line HER2-positive metastatic breast cancer after one line of trastuzumab-based therapy in the metastatic setting (PHER-EXA), and MO28047, a single-arm study of pertuzumab in combination with trastuzumab and a taxane in first-line HER2-positive advanced breast cancer (PERUSE), are expected by March 2015 and December 2016, respectively.

Treatment with pertuzumab was associated with increased toxicity compared with the placebo arm. The main adverse drug reactions were diarrhea, rash, mucosal inflammation, and neutropenia, including febrile neutropenia. Important safety information to be addressed after approval as part of the risk management plan relate to patients aged 75 years or older; pregnant or lactating women; safety in male patients and risk

of AEs in the male reproductive system; and patients with cardiovascular, hepatic, or renal impairment or immunogenicity.

CONCLUSION

Pertuzumab for use in combination with trastuzumab and docetaxel offered substantial and clinically relevant benefits in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Although added toxicity was observed for the pertuzumab combination, the safety and tolerability of pertuzumab combination treatment was acceptable in view of the magnitude of the benefits.

ACKNOWLEDGMENTS

The scientific assessment summarized in this report is based on the marketing authorization application submitted by the applicant company and on important contributions from, among others, the rapporteur and co-rapporteur assessment teams, members of the Committee for Medicinal Products for Human Use, and additional experts. We thank Silvy da Rocha Dias for reviewing the manuscript. This publication is a summary of the European Public Assessment Report and the summary of product characteristics. See the EMA website for up-to-date information on this marketing authorization (<http://www.ema.europa.eu>). Jonas Bergh and Jan H. Schellens are members of the EMA Scientific Advisory Group on Oncology and did not participate in the Committee for Medicinal Products for Human Use review of pertuzumab. The authors remain solely responsible for the opinions expressed in this publication.

AUTHOR CONTRIBUTIONS

Data analysis and interpretation: Jeanett Borregaard, Kristina Bech Jensen, Jens Ersbøll, Sara Galluzzo, Rosa Giuliani, Cinzia Ciceroni, Daniela Melchiorri

Manuscript writing: Hector Boix-Perales, Francesco Pignatti

Final approval of manuscript: Hector Boix-Perales, Jeanett Borregaard, Kristina Bech Jensen, Jens Ersbøll, Sara Galluzzo, Rosa Giuliani, Cinzia Ciceroni, Daniela Melchiorri, Tomas Salmonson, Jonas Bergh, Jan H. Schellens, Francesco Pignatti

DISCLOSURES

The authors indicated no financial relationships.

REFERENCES

1. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–2917.
2. Malvezzi M, Bertuccio P, Levi F et al. European cancer mortality predictions for the year 2013. *Ann Oncol* 2013;24:792–800.
3. Adams CW, Allison DE, Flagella K et al. Humanization of a recombinant monoclonal antibody to produce a therapeutic HER dimerization inhibitor, pertuzumab. *Cancer Immunol Immunother* 2006;55:717–727.
4. Franklin MC, Carey KD, Vajdos FF et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell* 2004;5:317–328.
5. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Res* 2004;64:2343–2346.
6. Scheuer W, Friess T, Burtscher H et al. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res* 2009;69:9330–9336.
7. Malik S, Totpal K, Balter I et al. Dose-response studies of recombinant humanized monoclonal antibody 2C4 in tumor xenograft models [abstract 773]. *Proc Am Assoc Cancer Res* 2003;44:150.
8. Attard G, Kitzen J, Blagden SP et al. A phase Ib study of pertuzumab, a recombinant humanised antibody to HER2, and docetaxel in patients with advanced solid tumours. *Br J Cancer* 2007;97:1338–1343.
9. Makhija S, Amler LC, Glenn D et al. Clinical activity of gemcitabine plus pertuzumab in platinum-resistant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. *J Clin Oncol* 2010;28:1215–1223.
10. Felip E, Ranson M, Cedres S et al. A phase Ib, dose-finding study of erlotinib in combination with a fixed dose of pertuzumab in patients with advanced non-small-cell lung cancer. *Clin Lung Cancer* 2012;13:432–441.
11. Albanell J, Montagut C, Jones ET et al. A phase I study of the safety and pharmacokinetics of the combination of pertuzumab (rhuMab 2C4) and capecitabine in patients with advanced solid tumors. *Clin Cancer Res* 2008;14:2726–2731.
12. Agus DB, Gordon MS, Taylor C et al. Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. *J Clin Oncol* 2005;23:2534–2543.
13. Ng CM, Lum BL, Gimenez V et al. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. *Pharm Res* 2006;23:1275–1284.
14. Gordon MS, Matei D, Aghajanian C et al. Clinical activity of pertuzumab (rhuMab 2C4), a HER dimerization inhibitor, in advanced ovarian

cancer: Potential predictive relationship with tumor HER2 activation status. *J Clin Oncol* 2006;24:4324–4332.

15. de Bono JS, Bellmunt J, Attard G et al. Open-label phase II study evaluating the efficacy and safety of two doses of pertuzumab in castrate chemotherapy-naïve patients with hormone-refractory prostate cancer. *J Clin Oncol* 2007;25:257–262.

16. Baselga J, Cortes J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;366:109–119.

17. Baselga J, Cortés J, Im SA et al. Biomarker analyses in CLEOPATRA: A phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer (MBC). *Cancer Res* 2012;72(suppl 3):S5-1.

18. Crawford J, Caserta C, Roila F. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. *Ann Oncol* 2010;21(suppl 5):v248–v251.

19. Swain SM, Kim SB, Cortés J et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2013;14:461–471.

For Further Reading:

Sunil Verma, Anil A. Joy, Daniel Rayson et al. HER Story: The Next Chapter in HER-2-Directed Therapy for Advanced Breast Cancer. *The Oncologist* 2013;18:1153–1166.

Implications for Practice:

HER-2-directed therapy remains one of most promising areas of development in the management of advanced breast cancer (ABC). Results of eight trials investigating new HER-2-directed therapy regimens have been published or presented since 2012. Multiple HER-2-directed therapies have demonstrated significant and clinically meaningful survival benefits in the treatment of HER-2-positive ABC, including pertuzumab-combinations, trastuzumab-lapatinib combinations, and the antibody-cytotoxic conjugate, trastuzumab-emtansine. With the increased number of HER-2-directed therapy options, optimal sequencing of these regimens across multiple lines of therapy is integral to providing the best possible care for our patients. Consideration should also be given to management of central nervous system metastases and ensuring cardiac safety.