

Pertuzumab

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

ATC codes: L01FD02

Indication	Carcinoma of breast, specialised type	ICD11 code: 2D10
INN	Pertuzumab	
Medicine type	Biological agent	
List type	Complementary	
Formulations	Parenteral > General injections > IV: 240 mg per 14 mL in vial concentrated solution	
EML status history	Application rejected in 2019 (TRS 1021) Application rejected in 2021 (TRS 1035)	
Sex	All	
Age	Adolescents and adults	
Therapeutic alternatives	The recommendation is for this specific medicine	
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org  Read more about patents . 	

Tags

Cancer

Wikipedia

[Pertuzumab](#) 

DrugBank

[Pertuzumab](#) 

Expert Committee recommendation

The Expert Committee noted the meaningful clinical benefit of pertuzumab in metastatic HER2-positive breast cancer when used in combination with trastuzumab and a taxane (e.g. docetaxel). Based on the results of the CLEOPATRA trial, the addition of pertuzumab to trastuzumab and docetaxel for first-line treatment of metastatic breast cancer increased overall survival by about 16 months. The Committee noted the high price of the combination therapy with trastuzumab and pertuzumab, which would present significant financial challenges to patients and health systems, and limit access in many settings. The Committee also considered the requirement of diagnostic molecular tests for determining HER2 status (immunohistochemistry and in-situ hybridization) conducted in highly specialized laboratories and requiring skilled technicians, which may not be widely available and affordable in many low- and middle-income settings. The limited availability of adequate diagnostic infrastructure is a substantial barrier to the appropriate use of HER2 inhibitors and other targeted therapies that should be addressed. The Committee also acknowledged the recommendation against listing of pertuzumab made by the Cancer Working Group based on the concerns outlined in the previous section. The Committee also supported the suggestion of the Cancer Working Group of the need to generate clinical data on the optimal duration of pertuzumab treatment, as shorter treatment duration may make this medicine more affordable. Studies examining this question should be supported as a research priority. The Expert Committee did not recommend the listing of pertuzumab on the EML for the treatment of metastatic HER2-positive breast cancer. Despite the relevant benefit in overall survival when adding pertuzumab to trastuzumab and a taxane shown in the CLEOPATRA trial, the use of combination therapy with trastuzumab + pertuzumab, both high-priced medicines, would be a significant financial challenge for

patients and health systems. Indeed, despite trastuzumab being on the EML since 2015 and the availability of biosimilars, access to and affordability of trastuzumab remains very limited in resource-constrained settings. The increasing number of trastuzumab biosimilars, including those that have been prequalified by WHO, might help increase access. The Committee decided, however, that also adding pertuzumab to the EML at this point could well result in considerable additional expenditure at the country level, using resources that should first be allocated to improving trastuzumab access. The expectation of the Committee is that, in the near future, there will be pertuzumab biosimilars that can be rapidly approved, with the aim of promoting competition among alternatives and allowing for the selection of optimal cheaper combinations of trastuzumab and pertuzumab produced by different companies. The Committee also recommended that WHO continue to work on existing approaches to managing prices and evaluate alternative strategies to improve affordability and access in order to reduce the global burden of cancer.

Background

The Expert Committee considered an application for the inclusion of pertuzumab on the EML for the treatment of early-stage and metastatic HER2-positive breast cancer in 2019, but did not recommend its listing. The Committee considered that the available evidence did not demonstrate a clinically meaningful survival benefit in early stage disease, and that there was important uncertainty about the estimated magnitude of survival benefit in metastatic disease, with results seen in the CLEOPATRA trial not replicated in other trials (1). The Committee acknowledged that pertuzumab was associated with a relevant survival benefit, well beyond the established threshold, as first-line treatment of metastatic breast cancer, based on the results reported in the CLEOPATRA trial. However, the Committee expressed reservations about the generalizability of the results from CLEOPATRA in metastatic breast cancer and consistency of the clinical effectiveness of pertuzumab in studies in both early and metastatic breast cancer. The Committee noted that only about 10% of patients in CLEOPATRA trial had received trastuzumab in the adjuvant or neoadjuvant setting. The Committee was concerned that the observed survival gains may not therefore be generalizable to patients with metastatic disease who have received prior adjuvant or neoadjuvant trastuzumab, making the magnitude of benefit in this population subgroup uncertain. The Committee also noted the results reported in the MARIANNE trial, where pertuzumab in combination with trastuzumab emtansine (T-DM1) was not shown to have greater clinical benefit than trastuzumab plus chemotherapy or T-DM1 alone. The Committee was unable to reconcile the differences in outcomes reported in the MARIANNE and CLEOPATRA trials. The Committee also noted that the relevant survival gains observed in the CLEOPATRA trial for metastatic breast cancer were not replicated in trials of pertuzumab in early stage breast cancer. The Committee accepted that trial results suggest pertuzumab offers a small incremental overall and disease-free survival benefit compared with placebo, based on an analysis at around 3 years median follow-up. The Committee considered that continued follow-up was important to assess long-term overall survival, but thought it unlikely that the magnitude of benefit would be greater with longer follow-up, given that anti-HER2 treatments are typically associated with a reduction in early recurrences, followed by a plateau effect. In the current resubmission, the applicant has consolidated the most recent datasets and published additional scientific information that shows positive results supporting the pertuzumab–trastuzumab combination as the standard of care in first-line treatment of HER2-positive metastatic breast cancer. To complement these data, the application includes supplementary evidence to demonstrate survival benefits in the real-world setting.

Public health relevance

Breast cancer is the leading cause of cancer death in women globally, responsible for 6.6% of all cancer deaths in 2018 (2). High incidence and low mortality rates are seen in high-income countries, with low incidence and high mortality rates recorded in low- and middle-income countries. The overall 5-year survival rates for high-income countries are estimated to be higher than 85%. In comparison, in low- and middle-income countries, 5-year survival rates are reported to range between 38% and 60% (3). While improved early detection and advances in systemic therapy for the early-stage disease have resulted in some decline in breast cancer mortality since 1989, metastatic breast cancer remains largely incurable with a median survival of about 24 months (4). Factors associated with poor survival include age $\geq$ 50 years, visceral disease, shorter disease-free interval, aneuploid tumours, tumours with a high S-phase fraction, p53 accumulation, low BCL2 gene expression, negative hormone receptor status, and positive HER2 status (5). Five-year survival for patients with metastatic disease is about 18% in Europe (6). Many cytotoxic agents are available for the treatment of metastatic breast cancer that are used singly or in combination (anthracyclines, taxanes, alkylating agents and vinca alkaloids). Used as single agents, they produce response rates of 20–80%; however, complete responses are rare and short-lived, and disease progression is almost inevitable (7,8). HER2 is involved in regulating cell growth, survival and differentiation (9), thus the HER2 receptor has emerged as one of the most important targets for breast cancer treatment.

Amplification and/or overexpression of HER2 occurs in about 18–22% of breast cancers (10,11). HER2-positivity is associated with increased tumour aggressiveness, higher rates of recurrence and increased mortality (11–16). The median age of patients presenting with HER2-positive breast cancer is the mid-50s, about 5 years younger than the general breast cancer population (17).

Benefits

The main sources of evidence for efficacy of pertuzumab in treatment of metastatic breast cancer presented in the application were from the CLEOPATRA, PUFFIN and PERUSE trials. CLEOPATRA (18–21) This was a multicentre, randomized, double-blind, placebo-controlled, phase III study in participants with HER2-positive metastatic or locally recurrent non-resectable breast cancer who had not previously received anti-HER2 therapy or chemotherapy for metastatic disease. The primary efficacy endpoint was progression-free survival assessed by an independent review facility. Key secondary efficacy endpoints included overall survival and overall response rate assessed by an independent review facility. A total of 808 participants were randomized in a 1:1 ratio to pertuzumab + trastuzumab + docetaxel (n = 402) or placebo + trastuzumab + docetaxel (n = 406). Results showed a statistically significant and clinically meaningful improvement in progression-free survival assessed by an independent review facility in the pertuzumab arm compared with the placebo arm (hazard ratio (HR) 0.62; 95% confidence interval (CI) 0.51 to 0.75; $P < 0.001$), with an increase of 6.1 months in median progression-free survival (12.4 months in the placebo arm versus 18.5 months in the pertuzumab arm). Analyses of progression-free survival by clinically relevant patient subgroups suggested that the benefit of pertuzumab in combination with trastuzumab and docetaxel was observed consistently in all prespecified subgroups tested, including those based on geographic region, prior treatment, age, race, presence of visceral disease, hormone receptor status, and HER2 immunohistochemistry or fluorescent in situ hybridization status. The final analysis of overall survival from the CLEOPATRA trial (data cut-off 11 February 2014) found that the median overall survival estimates were 40.8 months with placebo + trastuzumab + docetaxel and 56.5 months with pertuzumab + trastuzumab + docetaxel (HR 0.68, 95% CI 0.56 to 0.84). At the time of data cut-off, 320/406 (78.8%) participants in the placebo + trastuzumab + docetaxel arm and 284/402 (70.6%) participants in the pertuzumab + trastuzumab + docetaxel arm had experienced a progression-free survival event, according to the investigator. The median progression-free survival duration of 12.4 months in the placebo arm and 18.7 months in the pertuzumab arm was consistent with the previous analyses. An end-of-study analysis of the CLEOPATRA trial was conducted based on a clinical cut-off date of 23 November 2008 (21). Median overall survival estimates at the end of study (> 8 years of follow-up) were 40.8 months with placebo + trastuzumab + docetaxel and 57.1 months with pertuzumab + trastuzumab + docetaxel (HR 0.69, 95% CI 0.58 to 0.82; $P < 0.0001$). The 8-year landmark overall survival rates were 37% in the pertuzumab-treated group and 23% in the placebo-treated group. PUFFIN (22) This was a randomized, double-blind, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel versus placebo + trastuzumab + docetaxel in 243 Chinese participants with previously untreated HER2-positive metastatic breast cancer; it is a bridging study to CLEOPATRA. The primary endpoint was investigator-assessed progression-free survival; secondary endpoints included overall response rate (in participants with measurable baseline disease), overall survival and safety. Compared with placebo + trastuzumab + docetaxel, treatment with pertuzumab + trastuzumab + docetaxel resulted in a clinically meaningful improvement in investigator-assessed progression-free survival (stratified HR 0.69, 95% CI 0.49 to 0.99), corresponding to a 31% reduction in the risk of disease progression or death. The observed magnitude of treatment effect was not fully consistent with the CLEOPATRA data. Median progression-free survival was 12.4 months in the placebo + trastuzumab + docetaxel arm versus 14.5 months in the pertuzumab + trastuzumab + docetaxel arm. Overall survival data were not considered mature at the time of the clinical cut-off date. The median time to death had not been reached in either treatment arm at the time of the cut-off. PERUSE (23,24) This was a multicentre single-arm phase IIIb study to assess the safety and efficacy of physician's choice taxane with pertuzumab and trastuzumab as first-line therapy for HER2-positive locally recurrent or metastatic breast cancer. Patients with inoperable HER2-positive advanced locally recurrent or metastatic breast cancer and no prior systemic therapy (except endocrine therapy) received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab and pertuzumab until disease progression or unacceptable toxicity. The primary endpoint was safety; secondary endpoints included overall response rate and progression-free survival. Participants received a median of 16.2 months of study treatment (4.2 months of taxane therapy and 16.1 months of anti-HER2 therapy). At the date of the clinical cut-off for the final analysis (26 August 2019), the median duration of follow-up was 68.7 months (95% CI 67.5 to 69.3 months), corresponding to 5.7 years. Survival results were consistent with the CLEOPATRA trial: median progression-free survival 20.7 months (95% CI 18.9 to 23.1 months) in PERUSE versus 18.7 months in CLEOPATRA; median overall survival 65.3 months (95% CI 60.9 to 70.9 months) in PERUSE versus 57.1 months in CLEOPATRA. Maintenance endocrine therapy, which was allowed in PERUSE but not in CLEOPATRA, may explain the more favourable overall survival in participants with HER2-positive disease in PERUSE. The

application included an overview of additional supportive studies for pertuzumab in HER2-positive metastatic breast cancer (25–33), including a real-world study on the use of pertuzumab plus trastuzumab and taxane as first-line treatment of HER2-positive metastatic breast cancer (34).

Harms

Safety data from 19 clinical studies indicate that pertuzumab, combined with trastuzumab and a range of other therapeutic agents, has an acceptable safety profile. No new or unexpected safety findings were encountered other than those side-effects known for agents that target the HER family of receptors; these include diarrhoea, fatigue and nausea as the most frequently reported adverse events with single-agent pertuzumab. The incidence of haematological toxicities such as leukopenia and febrile neutropenia is low. A low level of cardiac toxicities, predominantly asymptomatic declines in left ventricular ejection fraction, has been reported. In the CLEOPATRA study, the rates of symptomatic and asymptomatic left ventricular systolic dysfunction were not higher in participants receiving pertuzumab + trastuzumab + docetaxel than in those receiving placebo + trastuzumab + docetaxel (18). However, participants who have received prior anthracyclines or radiotherapy to the chest area may be at higher risk of decreased left ventricular ejection fraction. The safety of pertuzumab has been evaluated in more than 6000 participants in phase I–III trials in both early and metastatic breast cancer settings including CLEOPATRA (n = 808), NEOSPHERE (n = 417), TRYPHAENA (n = 225) and APHINITY (n = 4804). The safety of pertuzumab was generally consistent across the studies. However, the incidence and most common adverse drug reactions varied depending on whether pertuzumab was administered as monotherapy or in combination with other antineoplastic agents. Pooled safety data from these studies indicate that the most common adverse events (all grades) with pertuzumab occurring in at least 30% of patients were diarrhoea (67.9%), alopecia (63.1%), nausea (60.8%), fatigue (44.3%), neutropenia (31.4%) and vomiting (30.0%). The most common grade 3 and 4 adverse events occurring in at least 10% of patients were neutropenia (24.2%) and febrile neutropenia (11.8%).

Cost / cost effectiveness

In the United States, the wholesale acquisition cost of one vial of pertuzumab 420 mg is US\$ 5292 per vial and US\$ 100 548 per episode of care (18 cycles). In France, Germany, Italy, Spain and the United Kingdom of Great Britain and Northern Ireland, ex-factory list prices for pertuzumab range from € 2221 to € 3037 per vial, or € 42 199 to € 57 703 per episode of care. In low- and lower-middle-income countries, the manufacturer (Roche) has developed an international differential pricing model which aligns innovative medicine prices (including pertuzumab) to a purchasing parity-adapted formula, factoring in gross domestic product per capita, public health care investment and the United Nations Human Development Index to ensure that the prices are as fair as possible. This model was applied in several low- and middle-income countries together with patient assistance programmes. However, information about the effect of this model on accessibility and affordability is limited. Reimbursement agreements involving special pricing were reached with governments in Brazil, Lebanon, Morocco and Uruguay. Special price agreements have also been negotiated and resulted in positive reimbursement decisions for the combination of pertuzumab plus trastuzumab for metastatic HER2-positive breast cancer in several high-income countries including France, Germany, Ireland, Spain and the United Kingdom.

WHO guidelines

WHO guidelines for treatment of metastatic HER2-positive breast cancer are not available. The combination regimen of pertuzumab, trastuzumab plus taxane chemotherapy is recommended for first-line treatment of HER2-positive metastatic breast cancer in several international guidelines (35–38).

Availability

As of June 2020, pertuzumab has been approved in more than 117 countries worldwide for treatment of metastatic breast cancer.

Other considerations

MARIANNE (39) In consideration of the application for pertuzumab in 2019, the Expert Committee noted the overall survival results from the MARIANNE trial, a randomized multicentre phase III study designed to evaluate TDM-1 alone or in combination with pertuzumab compared with trastuzumab plus taxane chemotherapy as first-line treatment of HER2-positive metastatic

breast cancer. A total of 1095 participants were randomized 1:1:1 to the three treatment arms. In particular, the Committee noted that overall survival was similar in all three treatment arms, with all regimens resulting in median overall survival longer than 50 months. For the trastuzumab plus taxane arm, median overall survival was 50.9 months (1). In contrast, in the CLEOPATRA trial, the median overall survival was 40.8 months in the trastuzumab plus docetaxel arm, and 57.1 months in the pertuzumab plus trastuzumab plus docetaxel arm. To clarify concerns raised by the Expert Committee in 2019, the current application included information about the MARIANNE trial, including rationale, study design, efficacy results for progression-free survival (the primary endpoint) and safety. It concluded that it was not appropriate to draw comparisons between the CLEOPATRA and MARIANNE studies due to differences in study design, objectives and patient populations. Comments from the EML Cancer Medicines Working Group The Working Group acknowledged that the updated data from the CLEOPATRA trial and additional evidence presented from PERUSE and PUFFIN trials, demonstrated relevant benefit in overall survival of pertuzumab (in combination with trastuzumab) in treatment of metastatic breast cancer. The Working Group considered that the inclusion of pertuzumab on the EML for treatment of metastatic HER2-positive breast cancer, in combination with trastuzumab and a taxane, could be supported from a clinical perspective. However, the Working Group acknowledged that the use of combination therapy with trastuzumab and pertuzumab, both high-priced medicines, would be a financial challenge for patients and health systems, and access in many settings would be limited. The Working Group also noted that affordability of and access to trastuzumab (included on the EML model list since 2015) remains very limited in many resource-constrained settings, and the addition of another high-priced biological medicine would likely compound this problem. Increasing the availability of biosimilars will be critical to improving affordability and access. The Working Group therefore concluded that financial considerations precluded its support for inclusion of pertuzumab on the EML. In addition, the Working Group highlighted that future consideration should be given to the optimal duration of pertuzumab treatment for patients with metastatic breast cancer. Clinical data on this question are currently lacking and should be supported as a research priority by research funding agencies. Comments were received from the WHO Department of Noncommunicable Diseases. The technical department noted that there was evidence of clinical benefit for pertuzumab. The feasibility of the inclusion of pertuzumab in national EMLs, particularly for low- and middle-income countries, is uncertain, when access to trastuzumab remains limited because of costs and diagnostic capacity. The addition of pertuzumab, in light of the increased focus on and availability of trastuzumab biosimilars, has an opportunity cost that may further limit inclusion of HER2-positive targeted therapies in national EMLs and benefit packages as part of universal health coverage. The duration of therapy with pertuzumab is uncertain, which may also affect its accessibility in low- and middle-income countries. Given these considerations, increasing access to trastuzumab, including through WHO prequalification, should be considered a priority before reconsidering the inclusion of pertuzumab on the EML.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; <https://apps.who.int/iris/handle/10665/330668>, accessed 9 June 2021).
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
3. Francies FZ, Hull R, Khanyile R, Dlamini Z. Breast cancer in low-middle income countries: abnormality in splicing and lack of targeted treatment options. *Am J Cancer Res*. 2020;10(5):1568–91.
4. Surveillance epidemiology and end results incidence data, 1975–2017 [internet]. Bethesda, MD: National Cancer Institute; 2020 (<https://seer.cancer.gov/data/>, accessed 23 November 2020).
5. Chang JC, Wooten EC, Tsimelzon A, Hilsenbeck SG, Gutierrez MC, Elledge R, et al. Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer. *Lancet*. 2003;362(9381):362–9.
6. Sant M, Allemani C, Capocaccia R, Hakulinen T, Aareleid T, Coebergh JW, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. *Int J Cancer*. 2003;106(3):416–22.
7. Bernard-Marty C, Cardoso F, Piccart MJ. Use and abuse of taxanes in the management of metastatic breast cancer. *Eur J Cancer*. 2003;39(14):1978–89.
8. Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. *Oncologist*. 2003;8(6):514–20.
9. Sundaresan S, Penuel E, Sliwkowski MX. The biology of human epidermal growth factor receptor 2. *Curr Oncol Rep*. 1999;1(1):16–22.
10. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*. 2007;25(1):118–45.
11. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist*. 2009;14(4):320–68.
12. Borg A, Tandon AK, Sigurdsson H, Clark GM, Fernö M, Fuqua SA, et al. HER-2/neu amplification predicts poor survival in node-positive breast cancer. *Cancer Res*. 1990;50(14):4332–7.
13. Ross JS, Fletcher JA. The HER-2/neu oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. *Stem Cells*. 1998;16(6):413–28.
14. Ménard S, Fortis S, Castiglioni F, Agresti R, Balsari A. HER2 as a prognostic factor in breast cancer. *Oncology*. 2001;61(Suppl 2):67–72.
15. Brown M, Tsodikov A, Bauer KR, Parise CA, Caggiano V. The role of human epidermal growth factor receptor 2 in the survival of women with estrogen and progesterone receptor-negative, invasive breast cancer: the California Cancer Registry, 1999–2004. *Cancer*. 2008;112(4):737–47.
16. Curigliano G, Viale G, Bagnardi V, Fumagalli L, Locatelli M, Rotmensz N, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol*. 2009;27(34):5693–9.

17. Neven P, Van Calster B, Van den Bempt I, Van Huffel S, Van Belle V, Hendrickx W, et al. Age interacts with the expression of steroid and HER-2 receptors in operable invasive breast cancer. *Breast Cancer Res Treat.* 2008;110(1):153–9.
18. 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(2):109–19.
19. Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, 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(6):461–71.
20. 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(8):724–34.
21. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020;21(4):519–30.
22. Xu B, Li W, Zhang Q, Shao Z, Li Q, Wang X, et al. Pertuzumab, trastuzumab, and docetaxel for Chinese patients with previously untreated HER2-positive locally recurrent or metastatic breast cancer (PUFFIN): a phase III, randomized, double-blind, placebo-controlled study. *Breast Cancer Res Treat.* 2020;182(3):689–97.
23. Bachelot T, Ciruelos E, Schneeweiss A, Puglisi F, Peretz-Yablonski T, Bondarenko I, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent or metastatic breast cancer (PERUSE). *Ann Oncol.* 2019;30(5):766–73.
24. Miles DW, Ciruelos EM, Schneeweiss A, Puglisi F, Peretz-Yablonski T, Campone M, et al. Final results from PERUSE, a global study of pertuzumab (P), trastuzumab (H) and investigator's chosen taxane as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mbc). *Ann Oncol.* 2020;31:S356–S7.
25. Huober J, Weder P, Veyret C, Thürlimann B, Xyrafas A, Vanlemmens L, et al. PERNETTA: A non-comparative randomized open-label phase II trial of pertuzumab (P) + trastuzumab (T) with or without chemotherapy both followed by T-DM1 in case of progression, in patients with HER2-positive metastatic breast cancer (MBC): (SAKK 22/10 / UNICANCER UC-0140/1207). *Ann Oncol.* 2018;29.
26. Perez EA, López-Vega JM, Petit T, Zamagni C, Easton V, Kamber J, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. *Breast Cancer Res.* 2016;18(1):126.
27. Andersson M, López-Vega JM, Petit T, Zamagni C, Easton V, Kamber J, et al. Efficacy and safety of pertuzumab and trastuzumab administered in a single infusion bag, followed by vinorelbine: VELVET cohort 2 final results. *Oncologist.* 2017;22(10):1160–8.
28. Rimawi M, Ferrero JM, de la Haba-Rodríguez J, Poole C, De Placido S, Osborne CK, et al. First-line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2-positive and hormone receptor-positive metastatic or locally advanced breast cancer (PERTAIN): a randomized, open-label phase ii trial. *J Clin Oncol.* 2018;36(28):2826–35.
29. Kümmel S, Tondini CA, Abraham J, Nowecki Z, Itrych B, Hitre E, et al. Subcutaneous trastuzumab and hyaluronidase-oysk with intravenous pertuzumab and docetaxel in HER2-positive advanced breast cancer: final analysis of the phase iiib, multicenter, open-label, single-arm metaphor study [Conference Abstract]. *Cancer Res.* 2020;80(4 Suppl):P1–18-05.
30. Woodward N, De Boer RH, Redfern A, White M, Young J, Truman M, et al. Results from the first multicenter, open-label, phase iiib study investigating the combination of pertuzumab with subcutaneous trastuzumab and a taxane in patients with her2-positive metastatic breast cancer (SAPPHIRE). *Clin Breast Cancer.* 2019;19(3):216–24.
31. 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(7):1138–44.
32. Cortés J, Fumoleau P, Bianchi GV, Petrella TM, Gelmon K, Pivot X, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol.* 2012;30(14):1594–600.
33. Urruticoechea A, Rizwanullah M, Im SA, Ruiz ACS, Láng I, Tomasello G, et al. Randomized phase iii trial of trastuzumab plus capecitabine with or without pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who experienced disease progression during or after trastuzumab-based therapy. *J Clin Oncol.* 2017;35(26):3030–8.
34. Polito L, Shim J, Toit YD, Do T, Knott A, Sanglier T. Abstract P1-18-14: Use of pertuzumab in combination with taxanes for HER2+ metastatic breast cancer: analysis of U.S. electronic health records. *Cancer Res.* 2020;80(4 Suppl):P1–18-04.
35. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, Andre F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol.* 2020(12):1623–49.
36. Ditsch N, Untch M, Kolberg-Liedtke C, Jackisch C, Krug D, Friedrich M, et al. AGO recommendations for the diagnosis and treatment of patients with locally advanced and metastatic breast cancer: update 2020. *Breast Care (Basel).* 2020;15(3):294–309.
37. NCCN Clinical Practice Guidelines in Oncology. Breast cancer. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2021 (<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419>, accessed 17 May 2021).
38. Giordano SH, Temin S, Chandarlapaty S, Crews JR, Esteva FJ, Kirshner JJ, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO clinical practice guideline update. *J Clin Oncol.* 2018;36(26):2736–40.
39. Perez EA, Barrios C, Eiermann W, Toi M, Im YH, Conte P, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase II MARIANNE study. *J Clin Oncol.* 2017;35(2):141–8.

