WHO 23rd Expert Committee on the Selection and Use of Essential Medicines – 2021

Application for the addition of pertuzumab on the WHO Model List of Essential Medicines

Submitted by
F. Hoffmann-La Roche Ltd

27 November 2020

F. Hoffmann-La Roche Ltd
Grenzacherstrasse 124
4070 Basel, Switzerland

Table of Contents

1. Summary statement of the proposal for **inclusion**, change or deletion

F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) proposes the **inclusion** of pertuzumab on the complementary list of the WHO Model List of Essential Medicines (EML) for use in combination with trastuzumab and chemotherapy for the treatment of adults with HER2-positive locally recurrent unresectable or metastatic breast cancer (mBC), who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease.

The principal reasons for requesting this inclusion are as follows:

- Significant disease burden of HER2-positive mBC globally, particularly in low- and lower- middle income countries (LMICs) where a higher rate is observed (Francies et al., 2020).
- Treatment with pertuzumab in combination with trastuzumab and chemotherapy has demonstrated superior outcomes vs. trastuzumab and chemotherapy in large randomised clinical trials evaluating the combination in HER2-positive mBC including the pivotal Phase III CLEOPATRA study.
- Besides trastuzumab, there are no other targeted treatments available for the first-line treatment of HER2-positive mBC and treatment of this disease will be significantly improved with wider availability and use of pertuzumab, maximising the chances for optimal access to healthcare.
- Use of pertuzumab for the treatment of HER2-positive mBC is approved by the EMA (PERJETA® SmPC, 2020) and FDA (FDA, 2020). Pertuzumab is recommended by International Clinical Guidelines: ESO-ESMO Guidelines for Advanced Breast Cancer ABC5, 2020 (Cardoso et al., 2020); AGO Guidelines, 2020 (Ditsch et al., 2020); NCCN Breast Cancer Guidelines (v4 – 2020) (NCCN, 2020); ASCO Clinical Practice Guidelines, 2018 (ASCO, 2018).
- The efficacy and safety of pertuzumab is established in HER2-positive breast cancer patients, supported by an extensive clinical trial programme in metastatic and early stages of the disease.
- Data from clinical studies indicate that pertuzumab is well tolerated and it shows manageable safety profile also in combination with trastuzumab and a range of other therapeutic agents. No new or unexpected safety findings have been identified other than those that are known for agents that target the HER family of receptors.

The value of pertuzumab inclusion for HER2-positive mBC treatment should be recognised, especially in LMICs that experience suboptimal diagnoses, inadequate access to treatment, poor health education, lack of screening programmes and many other barriers that are specific to these environments.

Pertuzumab is a recombinant, humanised, immunoglobulin G1K monoclonal antibody, which targets the human epidermal growth factor receptor 2 (HER2, also known as ERBB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab is the first in a class of targeted cancer treatments called HER2 dimerisation inhibitors. By binding to the subdomain 2 epitope of the extracellular domain of HER2, it prevents heterodimerisation of HER2 with other members of the human epidermal receptor (HER) family (HER1, HER3 and HER4). As a result, ligand-activated downstream signalling is blocked by pertuzumab (PERJETA® SmPC, 2020). Pertuzumab is also capable of activating antibody-dependent cell-mediated cytotoxicity (PERJETA® SmPC, 2020).

Pertuzumab and trastuzumab bind distinct epitopes on the HER2 receptor, and therefore do not compete with each other but rather have complementary mechanisms for disrupting HER2 signalling. The result is augmented anti-proliferative activity when both agents are administered in combination (PERJETA® SmPC, 2020).

Pertuzumab is currently indicated for the treatment of HER2-positive mBC, as follows (PERJETA® SmPC, 2020):

Pertuzumab is indicated for use in combination with trastuzumab and docetaxel 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.

Additional studies such as the Phase III PERUSE study, have demonstrated that chemotherapies like paclitaxel are viable alternatives to docetaxel as backbone chemotherapy for all patients with HER2-positive LR/mBC (please refer to section 9.2 for details).

2. Relevant WHO technical department and focal point (if applicable)

N/A

3. Name of organisation(s) consulted and/or supporting the application

F. Hoffmann-La Roche Ltd

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

INN: pertuzumab
ATC code: L01XC13

5. Formulation and strength proposed for inclusion

Concentrate solution for infusion 420mg/14 ml in vial.
The clinical formulation of pertuzumab for intravenous (IV) administration is a sterile, preservative-free, liquid concentrate, provided as a single use formulation containing 30 mg/mL pertuzumab in 20 mM L-histidine acetate, 120 mM sucrose, and 0.02% (w/v) polysorbate 20 at pH 6.0. Each 20 mL drug product vial contains 420 mg of pertuzumab (14.0 mL/vial).

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

Individual medicine.

7. Treatment details (requirements for diagnosis, treatment and monitoring)

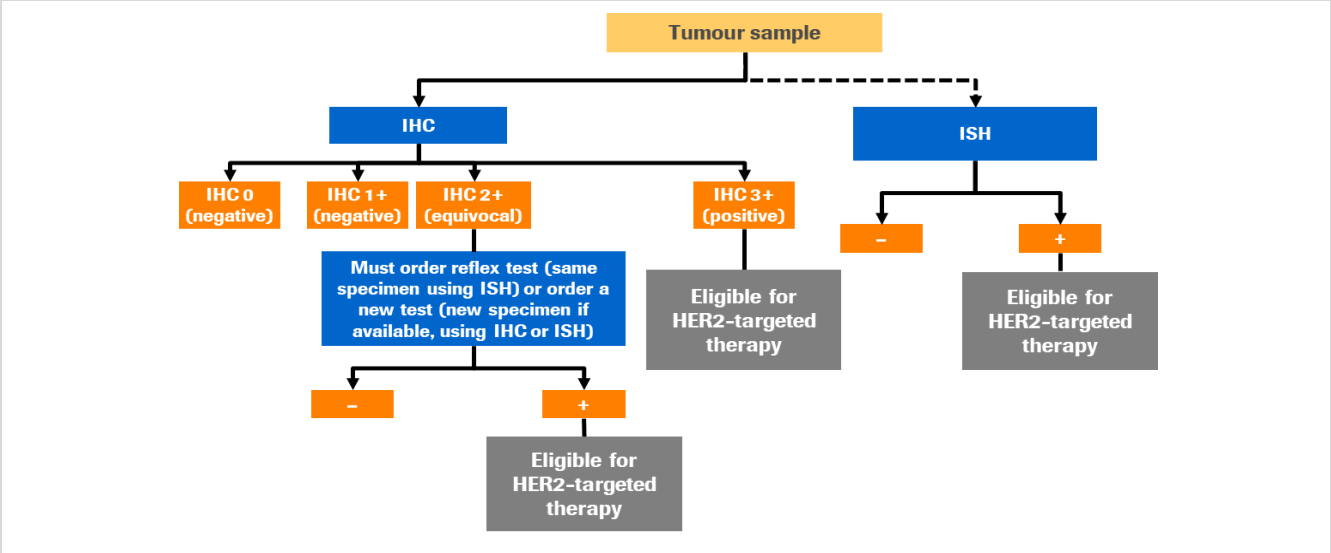
7.1 Need for special diagnostics

HER2 is a tyrosine kinase transmembrane receptor that regulates cell proliferation, migration and survival. A copy number gain (amplification) or an increased expression (overexpression) of HER2 is found in approximately 20% of breast cancers, classifying these as HER2-positive. HER2-positive breast cancer is dependent on the signalling through the HER2 pathway, which promotes tumour growth, but also renders the cells highly sensitive to HER2 blockade by HER2-targeted treatments such as pertuzumab and trastuzumab.

Given its prevalence and worse prognosis factor, the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines recommend that HER2 status must be determined in all patients with invasive breast cancer (Wolff et al., 2018). Testing criteria define HER2-positive status when there is evidence of protein overexpression detected by immunohistochemistry (IHC) or gene amplification by in situ hybridisation (ISH). A confirmed diagnosis of HER2-positive is defined as a score of 3+ in IHC or a positive ISH (ratio of HER2 copy number/chromosome 17 ≥2 or average HER2 copy number ≥6 signals per cell), assessed by a validated test (Figure 1). To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures.

Diagnostic tests for detection of HER2 overexpression have been included in the latest WHO Essential Diagnostic List (World Health Organization; 2019a) by the Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD). This decision signals the recognition of the need for countries to build capacity for appropriate treatment of HER2 positive breast cancer, therefore supporting inclusion of standard of care (SoC) treatments especially for their most advance stages, which disproportionately affect LMICs. Inclusion of these medicines will indeed represent an unprecedented opportunity for capacity building.

Figure 1. HER2-positivity is determined by immunohistochemistry (IHC) and/or in situ hybridisation (ISH)



(Adapted from Hanna & Kwok, 2006; Wolff et al., 2018).

7.2 Treatment, administration requirements, monitoring facilities and skills

Treatment with pertuzumab should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Administration must be performed by a healthcare professional prepared to manage anaphylaxis, in an environment where full resuscitation facilities are immediately available (PERJETA® SmPC, 2020).

Pertuzumab is administered intravenously by infusion. It should not be administered as an intravenous push or bolus. The recommended initial loading dose of pertuzumab is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes. An observation period of 30 to 60 minutes is recommended after completion of each infusion. The observation period should be completed prior to any subsequent infusion of trastuzumab or chemotherapy (PERJETA® SmPC, 2020).

In mBC, pertuzumab should be administered in combination with trastuzumab and docetaxel. Treatment with pertuzumab and trastuzumab may continue until disease progression or unmanageable toxicity even if treatment with docetaxel is discontinued.

The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion may be resumed when symptoms abate. The infusion should be discontinued immediately and permanently if the patient experiences a National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 4 reaction (anaphylaxis), bronchospasm or acute respiratory distress syndrome (PERJETA® SmPC, 2020).

Pertuzumab did not show overall differences in efficacy and safety in patients ≥65 and <65 years of age except for diarrhoea, which had an increased incidence in patients ≥65 years of age. No dose adjustment is necessary in the elderly population ≥ 65 years of age. Limited data are available in patients > 75 years of age. The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥65 years of age, compared to patients aged <65 years of age: decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhoea (PERJETA® Clinical Decision Report (CDS) version 11).

The safety and efficacy of pertuzumab in children and adolescents below 18 years of age and in patients with hepatic impairment have not been established.

Dose adjustments of pertuzumab are not needed in patients with mild or moderate renal impairment and no dose recommendations can be made for patients with severe renal impairment because of the limited pharmacokinetic data available (PERJETA® SmPC, 2020).

Pertuzumab and trastuzumab should be withheld for at least 3 weeks for any signs and symptoms suggestive of congestive heart failure. Pertuzumab should be discontinued if symptomatic heart failure is confirmed (PERJETA®, SmPC 2020).

7.3 Reference to existing clinical guidelines

Current international guidelines recommend the pertuzumab trastuzumab + chemotherapy combination regimen as standard of care (SoC) for the first-line treatment of HER2-positive mBC:

ESO-ESMO (European School of Oncology-European Society for Medical Oncology) International Consensus Guidelines for Advanced Breast Cancer (ABC5 2020) (Cardoso et al., 2020):

- The standard first-line therapy for patients previously untreated with anti HER2 therapy is the combination of chemotherapy + trastuzumab and pertuzumab, because it has proven to be superior to chemotherapy + trastuzumab in terms of Overall Survival (OS) in this population (Level of Evidence - LoE I/A, Consensus 86%).
- In patients previously treated in the (neo)adjuvant setting with anti-HER2 therapy, the combination of chemotherapy + trastuzumab and pertuzumab is an important option for first-line therapy (LoE I/A, Consensus 76%).

AGO (German Gynecological Oncology Group) Guidelines (2020) (Ditsch et al., 2020):

- For first-line treatment in HER2-positive mBC, SoC is trastuzumab and pertuzumab in combination with docetaxel (LoE 1b/A/AGO++) or weekly paclitaxel (LoE 2b/B/AGO++).

ASCO (American Society of Clinical Oncology) Clinical Practice Guidelines (2018):

- Clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes (Type: evidence-based; evidence quality: high; strength of recommendation: strong).

NCCN (National Comprehensive Cancer Network) Breast Cancer Guidelines (v4 – 2020) (NCCN, 2020):

- Pertuzumab+ trastuzumab (intravenous or subcutaneous) + docetaxel (category 1) or paclitaxel for HER2-positive recurrent or stage IV breast cancer as a preferred regimen.

8. Information supporting the public health relevance

8.1 Epidemiology and Natural History of Breast Cancer

The global cancer burden increased to 18.1 million cases, causing 9.6 million deaths in 2018, with most new cancer cases and developing cancer-related mortality occurring in low- and middle-income countries (LMICs). Specifically, breast cancer is the leading cause of cancer death (11.6%) among women globally (Bray et al., 2018). Around 60% of deaths worldwide attributed to breast cancer are estimated to occur in LMICs (Francies et al., 2020). High incidence and low mortality of breast cancer is observed in developed countries, while low incidence and high mortality rates is recorded in LMICs (Francies et al., 2020). The overall 5-year survival rates for high-income countries is estimated to be higher than 85% compared to LMICs like South Africa (53%), Algeria (38.8%), India (60%), Brazil (58.4%) (Francies et al., 2020).

Many factors may explain the lower incidence and higher mortality identified for breast cancer in developing countries. Delayed diagnoses and poor access to treatment may be due to poor health awareness and education, lack of screening programs and different kind of barriers related to cultural misconception and fear of loss of employment (Shulman et al., 2010). Considering the high rate of late stage disease presentation in LMICs, increased disease awareness, implementation of effective guidelines for diagnosis and treatment, enhancement of diagnosis and healthcare systems capacity are key to government collaboration to breast cancer management in these countries (Francies et al., 2020).

While improved early detection and advances in systemic therapy for early stage disease have resulted in some decline in breast cancer mortality since 1989, mBC remains largely incurable with a median survival of approximately 24 months (Surveillance Epidemiology and End Results Program, 2020). Factors associated with poor survival include age ≥ 50 years, visceral disease, shorter disease-free interval (DFI), aneuploid tumours, tumours with a high S-phase fraction, p53 accumulation, low bcl-2 expression, negative hormone receptor status, and positive human epidermal growth factor receptor 2 (HER2) status (Chang et al., 2003).

At the early stage of the disease, breast cancer is usually operable and can be treated with curative intent. However, approximately 20%–35% of patients experience relapse (Darby et al., 2011) and those with metastatic or unresectable disease are generally incurable. Patients with metastatic disease have a 5-year life expectancy of approximately 18% in Europe (Sant et al., 2003). Although the treatment of mBC is usually palliative in intent, this malignancy readily responds to systemic agents, and prolongation of survival and symptom palliation are now possible with modern medical management. Systemic treatments are in continual evolution as more active chemotherapeutic agents became available and biological factors were incorporated into treatment.

There are many agents available for the treatment of mBC that are used singly or in combination, according to the clinical context. The most active drugs are the anthracyclines, taxanes, alkylating agents, and vinca alkaloids. Used as single agents, they produce response rates of 20−80%; however, the rare complete responses are short-lived, and progression of disease is almost inevitable (Bernard-Marty et al., 2003; Chung & Carlson, 2003). The introduction of paclitaxel and docetaxel in the 1990s led to additional improvements in the management of mBC. The now common use of anthracyclines in the adjuvant treatment of early breast cancer (eBC) has both increased the incidence of anthracycline-resistant mBC and restricted the use of anthracyclines in later stages of the disease, in order to avoid dose-limiting toxicity (DLT). There is also an increasing trend toward using taxanes earlier in the management of mBC in patients with no or minimal prior anthracycline exposure or in combination with anthracyclines, or both.

With the growing understanding of the biology of breast cancer, multiple new targets for anti-cancer therapies are being identified. The HER2 receptor has emerged as one of the most important targets for the treatment of breast cancer. HER2 is involved in regulating cell growth, survival, and differentiation (Sundaresan et al., 1999). Amplification and/or overexpression of HER2 occurs in approximately 18%–22% of breast cancers (Wolff et al., 2007; Ross et al., 2009). HER2 amplification/overexpression (HER2-positivity) is associated with increased tumour aggressiveness, higher rates of recurrence, and increased mortality (Ross et al., 2009; Borg et al., 1990; Ross et al., 1998; Menard et al., 2001; Brown et al., 2008; Curigliano et al., 2009).

Trastuzumab, which targets the HER2 receptor, was first approved for use as monotherapy or in combination with chemotherapy in the metastatic setting, and in combination with chemotherapy as adjuvant treatment for HER2-positive breast cancer. This meant that optimal management of mBC now considers not only a patient's general condition, medical history, tumour burden, and receptor status, but also the HER2 status.

As described, the treatment of mBC is palliative rather than curative in intent. However, improvement in survival rates remains an important treatment goal, begging for a significant need for better treatment and management of the disease with advanced mechanisms of action.

8.2 Medical Need and likely impact of improving treatment of HER2-positive breast cancer

Of the 523,000 deaths from breast cancer in Europe each year (Ferlay et al., 2019), approximately 15%–20% (60,000–90,000) are likely to be due to HER2-positive disease. The median age of patients presenting with HER2-positive breast cancer is in the mid-50s, approximately 5 years younger than the general breast cancer population (Neven et al., 2008). At a time when the actuarial survival for women is > 80 years of age, the median loss of life-years per patient is approximately two decades.

Although improved early detection and advances in systemic therapy for early-stage disease have resulted in a decline in breast cancer mortality in recent years (Levi et al., 2005; Malvezzi et al., 2011), mBC (of all subtypes) remains essentially incurable. Despite improvements in Progression-Free Survival (PFS) and Overall Survival (OS) with trastuzumab, lapatinib-, and trastuzumab emtansine-based therapies, some patients with HER2-positive mBC do not respond to these targeted agents, and almost all patients with HER2-positive mBC will eventually progress and die of breast cancer. New active agents are therefore urgently required to improve disease control and extend survival in patients with HER2-positive mBC.

The addition of trastuzumab to standard chemotherapy prolongs time to progressive disease, or Progression-Free Survival (PFS), and improves survival when given with chemotherapy to women with HER2-positive breast cancer (Romond et al., 2005; Slamon et al., 2001). Trastuzumab is well tolerated both as a single agent and in combination with standard chemotherapy for breast cancer (Cobleigh et al., 1998; Slamon et al., 2001). The most significant adverse event observed in patients who receive trastuzumab is cardiac dysfunction, reflected by asymptomatic decreases in left ventricular ejection fraction (LVEF) and, less frequently, by clinically symptomatic congestive heart failure (CHF).

Pertuzumab has a different mechanism of action inhibiting HER2 dimerisation. Pertuzumab is also directed against the extracellular domain of HER2, however, it differs from trastuzumab in the epitope-binding regions of the light chain (12 amino acid differences) and heavy chain (29 amino acid differences). As a result, pertuzumab binds to an epitope within what is known as sub-domain 2 of HER2, while the epitope for trastuzumab is localised to sub-domain 4 (Cho et al., 2003; Franklin et al., 2004). Pertuzumab blocks the association of HER2 with other HER family members, including HER1 (EGFR), HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signalling through two major signal pathways, MAP-kinase and PI3-kinase. Inhibition of these signalling pathways can result in growth arrest and apoptosis, respectively

(Hanahan & Weinberg, 2000). Clinical data generated to date indicate that pertuzumab provides broader HER2 blockade through inhibition of HER2 homo- and heterodimerisation.

Available clinical data for pertuzumab in combination with trastuzumab and chemotherapy demonstrates efficacy with manageable toxicity in patients with HER2-positive breast cancer in the metastatic (Baselga et al., 2012) neoadjuvant (Gianni et al., 2012), and adjuvant settings (von Minckwitz et al., 2017). A summary of key clinical trials is presented in Section 9.

8.3 Target population

HER2-positivity is determined by IHC and/or ISH as described in Section 7.1. Pertuzumab's target population spans HER2-positive metastatic or locally recurrent unresectable breast cancer, neoadjuvant HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence, and adjuvant HER2-positive eBC at high risk of recurrence.

8.4 Assessment of current use

Cumulative exposure from marketing: Since international birth date (IBD), an estimated cumulative total of 517,123 patients have received pertuzumab (PSUR (PBRER), 2020).

Cumulative exposure in clinical trials: 11,982 patients have received pertuzumab (PSUR (PBRER), 2020).

Estimated use of pertuzumab for mBC: 187,623 patients worldwide (PSUR (PBRER), 2020).

8.5 Roche's approach to access to cancer medicines

At Roche we strongly believe in the value our medicines bring to patients and their families. Roche's focus is entirely on developing medicines that respond to unmet medical need and we are fully committed to working hard to make sure that those who need our medicines are able to access and benefit from them. Roche knows that innovation is only truly meaningful when it reaches patients, however we also understand that access to healthcare is a multidimensional challenge and there is no 'one size fits all' solution.

From experience, especially for cancer treatment, Roche believes that awareness, diagnosis, healthcare capacity and funding are determining factors in getting our medicines to patients. Moreover, complex treatments, such as those for cancer, often require sophisticated diagnosis, specialised training and hospital infrastructure for successful treatment. As such, Roche takes a comprehensive approach, first identifying concrete measures and then addressing country-specific challenges to reach patients.

Roche's goal is to facilitate, broad, rapid and sustainable access to its medicines and with that goal in mind we focus our efforts on capacity building, value recognition, outcome certainty and funding. Roche partners with stakeholders across the supply-chain and at different health service delivery points to develop and execute tailored solutions.

8.6 Addressing cancer medicines access challenges holistically: Awareness, Diagnosis, Healthcare Capacity and Funding

In recent years, Roche has supported a number of initiatives to help governments increase patient access by enhancing population awareness, health workforce capacity, early diagnosis and developing flexible pricing solutions to alleviate budgetary pressure.

Roche has also brought its oncology expertise to partnerships in insurance to better cover patients for cancer. In China, Roche teamed up with ten local insurance companies, including the three largest, to help

develop additional insurance policies that include cancer treatment and care, and further developed seminars, forums and campaigns to support educational programs for stakeholders, including insurers and the wider population about cancer treatment regimens.

8.7 Reducing inequality in access to cancer medicines

Inclusion of pertuzumab in the EML would support global efforts undertaken by multiple stakeholders, including Roche, to enable equitable access to healthcare and effective therapies, particularly for HER2-positive breast cancer patients. Indeed, the current standard of care treatment for mBC hasn't improved significantly over the last decades. This means that people suffering from mBC have limited options for treatment, thus increasing inequitable health outcomes for them.

Furthermore, geographic disparities in access to cancer medicines subsist globally, with late stage diagnosis commonly occurring in low- and middle-income countries (LMICs) (Francies et al., 2020).

Roche is particularly committed to bringing innovative medicines to patients in low-resources settings and reducing global inequities in access.

In line with this objective, the development of new formulations, like the subcutaneous form of Roche's key cancer medicines that may be used in combination with pertuzumab, such as trastuzumab, where such combination is approved and the clinical trials that Roche is executing in low-resourced settings, should globally expand patient access to up to date standard of care and cancer treatment in these settings.

Improving global access to healthcare is a Roche core commitment, with the recognition that partnership is key to overcoming this challenge. For this reason, Roche is proud to actively contribute to the global effort of enhancing healthcare access and is keen on making our innovations available for people who need and can benefit from them.

9. Summary of evidence of comparative effectiveness in a variety of clinical settings

In its 2019 decision to not include pertuzumab in the WHO EML, the WHO Expert Committee on Selection and Use of Medicines noted that a large overall survival benefit was observed only in a single trial in the metastatic disease. More specifically, the Committee expressed concerns about the generalisability of the data observed due to the fact that i) only a limited portion of patients had received prior adjuvant or neoadjuvant trastuzumab, and ii) the benefit was not confirmed by another trial at the time (World Health Organization; 2019b).

This latter point was further supported by the assessment made by the WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention (NVI), which pointed notably to the need for more mature clinical and real-world data (World Health Organization; 2019b).

In addition, the WHO Expert Committee recommended that WHO requests access to raw clinical trial data from CLEOPATRA and MARIANNE trials from Roche, for an independent re-analysis by the WHO, with the proposal that this analysis would be undertaken by the suggested-to-be-established working group on transparency and access to clinical trial data(World Health Organization; 2019b).

In the time that has elapsed since the summary data was provided to the WHO in December 2018 and assessed by the WHO Expert Committee in 2019, Roche has consolidated most recent datasets and published additional scientific information that continue to show positive results in support of the pertuzumab-trastuzumab combination being the SoC in first-line HER2-positive mBC.

The comprehensive datasets presented under Section 9 intend to address the WHO Expert Committee's concerns raised in 2019 for the mBC indication, with the following updated data summarised below. Details for each trial are expanded in the relevant sub-sections:

- CLEOPATRA: the end-of-study analysis from the Phase lll, randomised, double-blind, placebo-controlled CLEOPATRA study of first-line pertuzumab, trastuzumab and docetaxel in patients with human epidermal growth factor receptor 2 (HER2)-positive mBC (Baselga et al., 2012; Swain et al., 2013; Swain et al., 2015; Swain et al., 2020);

- PUFFIN: a Phase III study to evaluate the efficacy and safety of pertuzumab, trastuzumab and docetaxel versus placebo, trastuzumab and docetaxel in previously untreated HER2-positive mBC (Xu et al., 2020);

- PERUSE: a Phase III study of pertuzumab in combination with trastuzumab and a taxane in first- line treatment in participants with HER2-positive advanced breast cancer (Bachelot et al., 2014; Perez et al., 2016; Miles et al., 2016, Bachelot et al., 2019, Miles et al., 2020);

- PERNETTA: a non-comparative randomised open-label phase II trial of pertuzumab –trastuzumab with or without taxane-based/vinorelbine chemotherapy followed by trastuzumab emtansine (T-DM1) in case of progression (Huober et al., 2018);

- VELVET: a two-cohort, open-label, Phase II, proof-of-concept trial of pertuzumab, trastuzumab and vinorelbine (Cohort 1 – pertuzumab – trastuzumab in separate infusion bags; Cohort 2 – pertuzumab –trastuzumab single infusion bag) (Perez et al.2016);

- PERTAIN: a randomised Phase II trial investigating trastuzumab plus an aromatase inhibitor with or without pertuzumab in hormone receptor-positive disease (induction taxane could be administered at the investigator's discretion) (Rimawi et al., 2018);

- MetaPHER: a Phase IIIb, single-arm safety trial of fixed-dose trastuzumab subcutaneous in combination with pertuzumab intravenous and taxane intravenous (Kümmel et al., 2019);

- SAPPHIRE: a Phase IIIb trial investigating the combination of pertuzumab intravenous with trastuzumab subcutaneous and clinician's choice of taxane chemotherapy (Australian study) (Woodward et al., 2019);

- BO17929: a single-arm, Simon two-stage study of pertuzumab + trastuzumab in case of progression during trastuzumab -based therapy (Cohort 1&2 – pertuzumab q3w + trastuzumab qw or q3w; Cohort 3 – patients received pertuzumab without trastuzumab) (Baselga et al., 2010; Cortés et al., 2012);

- PHEREXA: a randomised Phase III study of trastuzumab plus capecitabine with or without pertuzumab in patients who experienced disease progression during trastuzumab -based therapy (Urruticoechea et al., 2017).

To complement the above trials data, supplementary evidence was collected in the US to demonstrate survival benefits in the real-world setting and is also shared:

- Use of pertuzumab in combination with taxanes for HER2-positive advanced breast cancer: analysis of US electronic health records (Polito et al., 2019).

Finally, Roche is committed to data sharing and believes that disclosure of our clinical study results and data serves the international research community and helps to fully realise the public health benefit of our clinical research.

In line with Roche standard policy for data sharing, and to follow upon the WHO Expert Committee's recommendation to seek access to patient level data and to perform independent re-analyses, Roche invited the WHO [early 2020] to submit its request for access to patient level data from our pertuzumab studies via the dedicated cross-industry platform Vivli.

This platform was designed to enable the sharing of datasets from multiple organisations, including from Roche, upon the assessment and decision of an Independent Review Panel.

9.1 Selection of clinical evidence to support application for inclusion of pertuzumab for the treatment of HER2-positive mBC

Pertuzumab has been studied in several Phase I, Phase II and Phase III clinical trials in solid tumours, including breast, prostate, ovarian, and lung cancer. Study WO20698/TOC4129g (CLEOPATRA) is the Phase III trial that established the pertuzumab + trastuzumab combination plus chemotherapy as the standard of care for first-line HER2-positive mBC. An extensive clinical trial programme provides additional evidence to support the role of pertuzumab in HER2-positive mBC including, but not limited to, Phase III Study YO29296 (PUFFIN) and Phase IIIb Study MO28047 (PERUSE). The PUFFIN and PERUSE trials provide the most robust datasets to support pertuzumab as first-line treatment of mBC and are described in detail below. Other supportive studies are summarised in Table 2. Additional Real-World Evidence analyses have also been performed and reference to these are also made below.

A description of the key evidence for pertuzumab's favourable benefit profile in each of these settings as defined by large, pivotal, and randomised clinical trials is provided in the next section, and safety data will be covered in section 10.

9.2 Summary of Data

9.2.1 Metastatic or Locally Recurrent Unresectable HER2-positive Breast Cancer

The main sources of evidence for efficacy in the mBC setting are: Phase III Study WO20698/TOC4129g (CLEOPATRA) including an End of Study analysis, Phase III Study YO29296 (PUFFIN) and Phase IIIb Study MO28047 (PERUSE). Safety data about these studies are provided in Section 10.

9.2.1.1 Study WO20698/TOC4129g (CLEOPATRA) (Baselga et al., 2012; Swain et al., 2013; Swain et al., 2015; Swain et al., 2020)

The efficacy of pertuzumab was demonstrated in a multicentre, randomised, double-blind, placebo-controlled, Phase III study (WO20698/TOC4129g) in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who had not received previous anti-HER2 therapy or chemotherapy for metastatic disease. A total of 808 patients were enrolled at sites in 25 countries. The primary efficacy endpoint was Independent Review Facility (IRF)-assessed Progression-Free Survival (PFS). Key secondary efficacy endpoints included Overall Survival (OS) and IRF-assessed Overall Response Rate (ORR). Duration of response, investigator-assessed PFS, and time to symptom progression based on the Functional Assessment of Cancer Therapy-Breast quality-of-life questionnaire were also evaluated.

Patients were randomised in a 1:1 ratio to pertuzumab + trastuzumab + docetaxel (n = 402) or placebo + trastuzumab + docetaxel (n = 406). Pertuzumab was given by intravenous (IV) infusion at an initial dose of 840 mg, followed every 3 weeks thereafter by a dose of 420 mg. Placebo was given on the same schedule as pertuzumab. Trastuzumab was given by IV infusion at an initial dose of 8 mg/kg, followed every 3 weeks thereafter by a dose of 6 mg/kg. Docetaxel was given by IV infusion at an initial dose of 75 mg/m^2 every 3 weeks. The dose of docetaxel could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated.

The combination of trastuzumab and a taxane was established from positive results of two large pivotal trials (H0648g, M77001), as first-line for patients with HER2-positive mBC (Slamon et al., 2001; Marty et al., 2005). Docetaxel was included in the standard treatment plan, as it has been proven efficacious when combined with trastuzumab in women with HER2- positive mBC and should provide clinical benefit independent of pertuzumab.

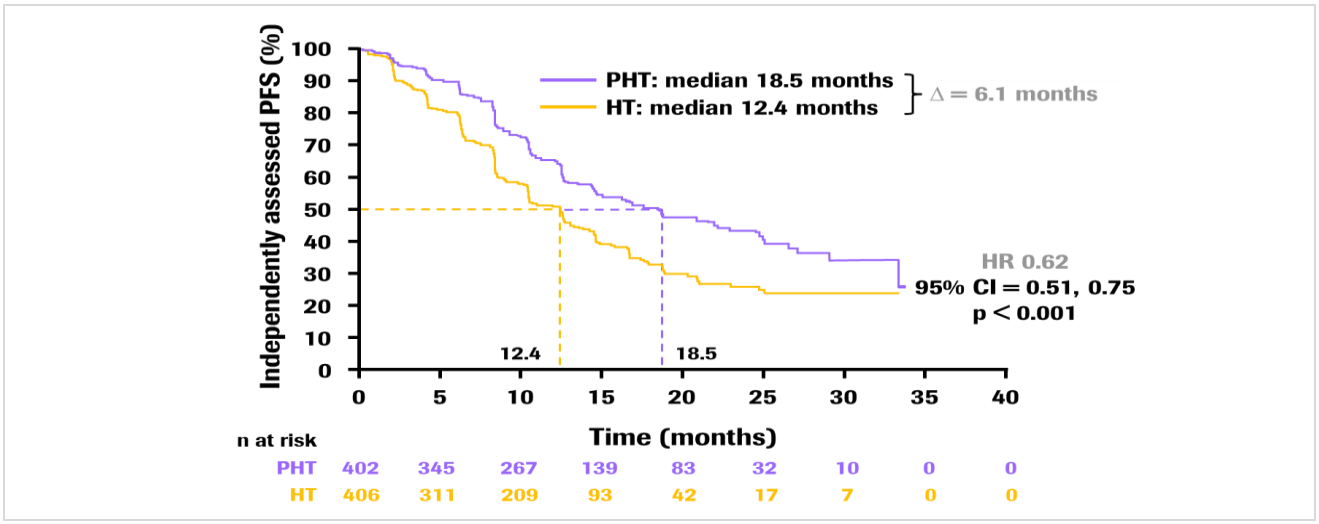
Patients were treated with pertuzumab/ placebo and trastuzumab until disease progression, withdrawal of consent, or unmanageable toxicity. It was recommended that patients be treated with docetaxel for at least six cycles.

Demographic and baseline characteristics were generally well balanced between treatment groups.

At the time of the data cut-off for the primary analysis (13 May 2011), 433 IRF-confirmed PFS events had occurred in 242 patients (59.6%) in the placebo + trastuzumab + docetaxel arm and 191 patients (47.5%) in the pertuzumab + trastuzumab + docetaxel arm.

Study WO20698/TOC4129g demonstrated a statistically significant and clinically meaningful improvement in IRF-assessed PFS in the pertuzumab arm compared with the placebo arm (HR = 0.62; 95% CI: 0.51, 0.75; p < 0.001), with an increase of 6.1 months in median PFS (12.4 months in the placebo arm vs. 18.5 months in the pertuzumab arm). The Kaplan-Meier curve (Figure 2) shows an early separation beginning at the first tumour assessment (9 weeks), which is maintained from this point onwards.

Figure 2. Study WO20698/TOC4129g: Kaplan-Meier Curve for IRF-Assessed Progression-Free Survival (Primary Analysis)



(P = pertuzumab, H = trastuzumab, T = docetaxel)

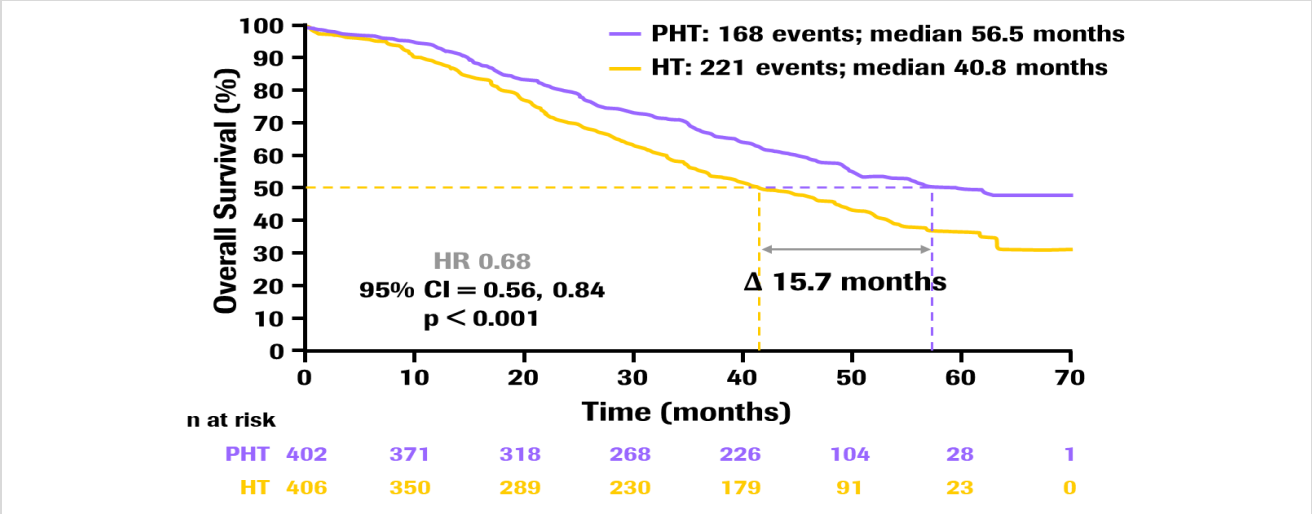
Analyses of PFS by clinically relevant patient subgroups suggested that the benefit of pertuzumab in combination with trastuzumab and docetaxel was observed consistently in all pre-specified subgroups tested, including those based on geographic region, prior treatment, age, race, presence of visceral disease, hormone receptor status, and HER2 immunohistochemistry or fluorescent *in situ* hybridisation status.

The final analysis of OS (data cut-off 11 February 2014), planned to take place after 385 deaths (actual number of deaths at data cut-off, 389) for Study WO20698/TOC4129g (CLEOPATRA) confirmed the results of the second interim analysis of OS, which had demonstrated a statistically significant improvement in survival with pertuzumab + trastuzumab + docetaxel compared with placebo + trastuzumab + docetaxel. The main efficacy findings are as follows:

- The median OS estimates were 40.8 months with placebo + trastuzumab + docetaxel and 56.5 months with pertuzumab + trastuzumab + docetaxel (HR = 0.68; 95% CI: 0.56, 0.84; p < 0.001) (Figure 3).
- Sensitivity analyses defined to explore the impact of crossover on the OS result confirmed the robustness of the results in the intention to treat (ITT) population.
- Exploratory subgroup analyses of final OS were consistent with the analysis in the whole ITT population and confirmed results from previous analyses.
- At the time of data cut-off, 320/406 patients (78.8%) in the placebo + trastuzumab + docetaxel arm and 284/402 patients (70.6%) in the pertuzumab + trastuzumab + docetaxel arm had experienced a PFS event according to the investigator. The treatment benefit of pertuzumab + trastuzumab + docetaxel compared with placebo + trastuzumab + docetaxel was maintained in the updated analysis of investigator assessed PFS (HR = 0.68; 95% CI: 0.58, 0.80; p < 0.001). The median PFS durations of 12.4 months in the placebo arm and 18.7 months in the pertuzumab arm were consistent with results from the previous analyses.
- Exploratory subgroup analyses of investigator assessed PFS indicated treatment benefit with pertuzumab + trastuzumab + docetaxel over placebo + trastuzumab + docetaxel in all subgroups analysed and were consistent with the result in the whole ITT population, and with results from previous analyses.

In conclusion, the OS and PFS improvement demonstrated with pertuzumab + trastuzumab + docetaxel compared with placebo + trastuzumab + docetaxel at the time of the final OS analysis remained clinically meaningful and confirm the results of previous analyses.

Figure 3. Study WO20698/TOC4129g: Kaplan-Meier Curve of Overall Survival (Final OS Analysis, ITT Population)



(P = pertuzumab, H = trastuzumab, T = docetaxel)

CLEOPATRA End of Study Analysis (Swain et al., 2020)

An end-of-study OS analysis was conducted based on a Clinical Cutoff Date (CCOD) of 23 November 2018. These analyses were consistent with the results of the second interim OS analysis and the event-driven final analysis of OS demonstrating that the improvement in survival with pertuzumab + trastuzumab + docetaxel compared with placebo + trastuzumab + docetaxel was maintained. The median survival estimates at the end of study were 40.8 months with placebo + trastuzumab + docetaxel and 57.1 months with pertuzumab + trastuzumab + docetaxel (HR = 0.69; 95% CI: 0.58-0.82; p<0.0001).

The end-of-study exploratory subgroup analyses of OS were consistent with the analysis in the overall ITT population and with the results from previous analyses.

The investigator assessed PFS results were consistent with the results from the previous analyses. The treatment benefit of pertuzumab + trastuzumab + docetaxel over placebo + trastuzumab + docetaxel was maintained in the end-of-study analysis of investigator-assessed PFS (HR = 0.69; 95%% CI: 0.59-0.81; p < 0.0001). The median PFS durations of 12.4 months in the placebo + trastuzumab + docetaxel arm and of 18.7 months in the pertuzumab + trastuzumab + docetaxel arm were consistent with results from the previous analyses.

The exploratory subgroup analyses of investigator assessed PFS indicated treatment benefit with pertuzumab + trastuzumab + docetaxel over placebo + trastuzumab + docetaxel in all subgroups analysed and were consistent with the result in the overall ITT population, and with results from previous analyses.

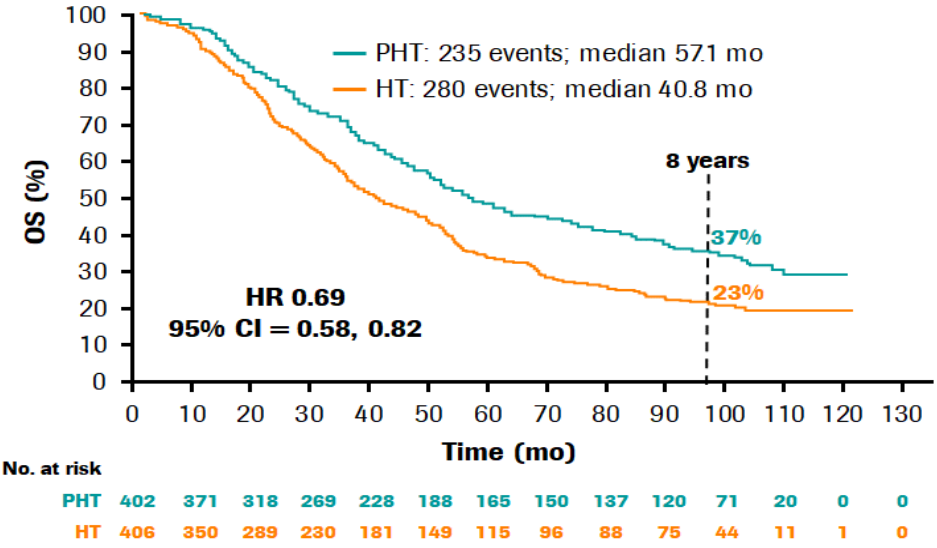
Key efficacy results at all data cuts for this study are provided in Table 1, and Kaplan Meier curves for the End-of-Study Analysis in Figures 4 and 5.

Table 1. Study WO20698/TOC4129g: Overview of efficacy across data cuts (Overall Survival)

	Pla+T+D n=406	Ptz+T+D n=402	HR* [95% CIs]	p-value* (boundary)
	OS events, n(%)	OS events, n(%)		
OS (frirst IA; (13 May 2011)	96 (23.6%)	69 (17.2%)	0.64 [0.47–0.88]	p=0.0050 (p≤0.0012)
OS (Second IA; (14 May 2012)	154 (37.9%)	113 (28.1%)	0.66 [0.52–0.84]	p=0.0008 (p≤0.0138)
OS (final analysis; (11 February 2014)	221 (54.4%)	168 (41.8%)	0.68 [0.56–0.84]	p=0.0002 (N/A)
OS (end of study analysis; (23 November 2018)	280 (69.0%)	235 (58.5%)	0.69 [0.58–0.82]	p<0.0001 (N/A)

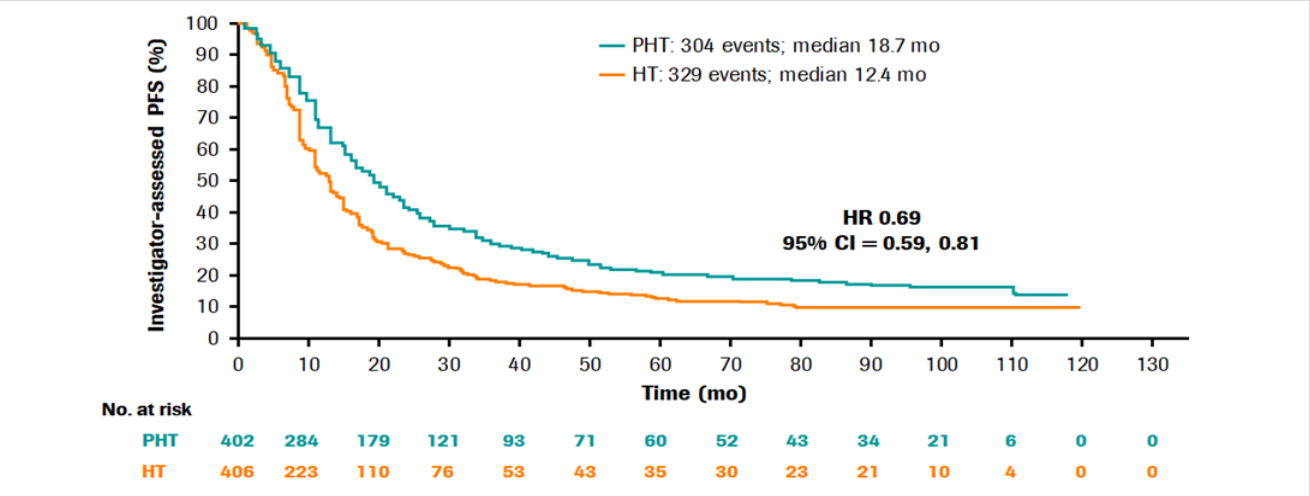
HR = hazard ratio; IA = interim analysis; N/A = not applicable; NR=not reached; OS = overall survival
* Stratified by prior treatment status and region

Figure 4. Study WO20698/TOC4129g End-of-Study analysis: Overall Survival



CI, confidence interval; HR, hazard ratio; HT, trastuzumab + docetaxel; mo, months; OS, overall survival; PHT, pertuzumab + trastuzumab + docetaxel

Figure 5. Study WO20698/TOC4129g End-of-Study analysis: Investigator-assessed Progression-Free Survival



CI, confidence interval; HR, hazard ratio; HT, trastuzumab + docetaxel; mo, months; OS, overall survival; PHT, pertuzumab + trastuzumab + docetaxel.

End of Study Key Points

- Statistically significant improvement in overall survival and investigator-assessed progression-free survival with pertuzumab + trastuzumab + docetaxel versus placebo + trastuzumab + docetaxel maintained after more than 8 years' follow-up.
- Landmark overall survival estimates at 8 years were 37% in the pertuzumab-treated group and 23% in the placebo-treated group.
- To our knowledge, this is the longest follow-up of patients for first-line treatment of HER2-positive mBC (maximum of 120 months).

9.2.1.2 Phase III Study YO29296 (PUFFIN) of pertuzumab + trastuzumab + taxane- based chemotherapy (Chinese bridging study) (Xu B et al., 2020)

PUFFIN is a Phase III, randomised, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab+ docetaxel vs. placebo + trastuzumab + docetaxel in Chinese patients previously untreated HER2-positive mBC, and is a is a bridging study to CLEOPATRA.

Patients were randomised 1:1, stratified by visceral/non-visceral disease and hormone receptor status. The primary endpoint was investigator-assessed Progression-Free Survival (PFS). Secondary endpoints included objective response rate (in patients with measurable baseline disease), overall survival, and safety. The consistency threshold for PFS (hazard ratio [HR] < 0.81) (maintaining ≥ 50% of the risk reduction determined in CLEOPATRA [HR 0.62]) determined the target sample size (n = 240).

At the time of CCOD (27 June 2018), the study met its primary endpoint. Compared with placebo + trastuzumab + docetaxel, treatment with pertuzumab + trastuzumab+ docetaxel resulted in a clinically meaningful improvement in investigator-assessed PFS (stratified HR = 0.69, 95% CI: [0.49, 0.99]), corresponding to a 31% reduction in the risk of disease progression or death (Figure 6). The observed magnitude of treatment effect was consistent with the CLEOPATRA data (Independent Review Committee IRC-assessed PFS HR = 0.62 [95% CI: 0.51, 0.75] in the CLEOPATRA ITT population and HR = 0.68 [95% CI: 0.48, 0.95] in the CLEOPATRA Asian population). The median PFS was 12.4 months in placebo + trastuzumab + docetaxel arm vs. 14.5 months in pertuzumab + trastuzumab+ docetaxel arm. The improvement in investigator assessed PFS was also seen consistently in sensitivity analyses and pre-defined subgroup analyses (Figure 7), including subgroups with prior neo/adjuvant therapy with trastuzumab. All subgroup

analyses were consistent with overall PFS results and efficacy of pertuzumab + trastuzumab + docetaxel observed in CLEOPATRA.

Regarding the secondary endpoints, OS data was not considered mature at the time of CCOD. 25 deaths had occurred (13 deaths [10.7%] in placebo + trastuzumab + docetaxel arm vs. 12 deaths [9.8%] in pertuzumab + trastuzumab + docetaxel arm). The median time to death had not been reached in either treatment arm at the time of the cut-off. In those patients who achieved an overall response of Complete Response (CR) or Partial Response (PR), the Duration of Response (DoR) was longer in patients receiving pertuzumab compared with placebo (median DoR: 10.4 months in placebo + trastuzumab + docetaxel arm vs. 12.4 months pertuzumab + trastuzumab+ docetaxel arm).

Figure 6. YO29296 (PUFFIN) Investigator-assessed progression- free survival in the intention-to-treat population

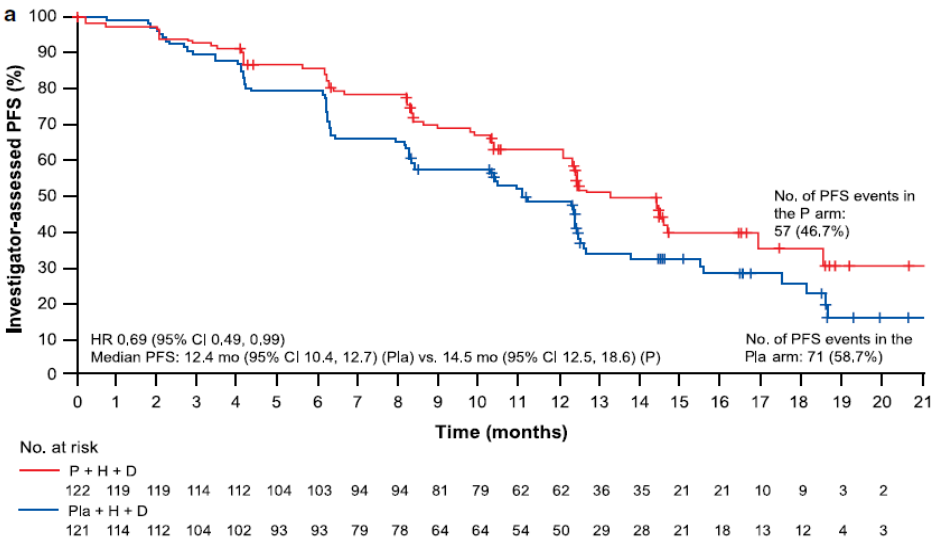
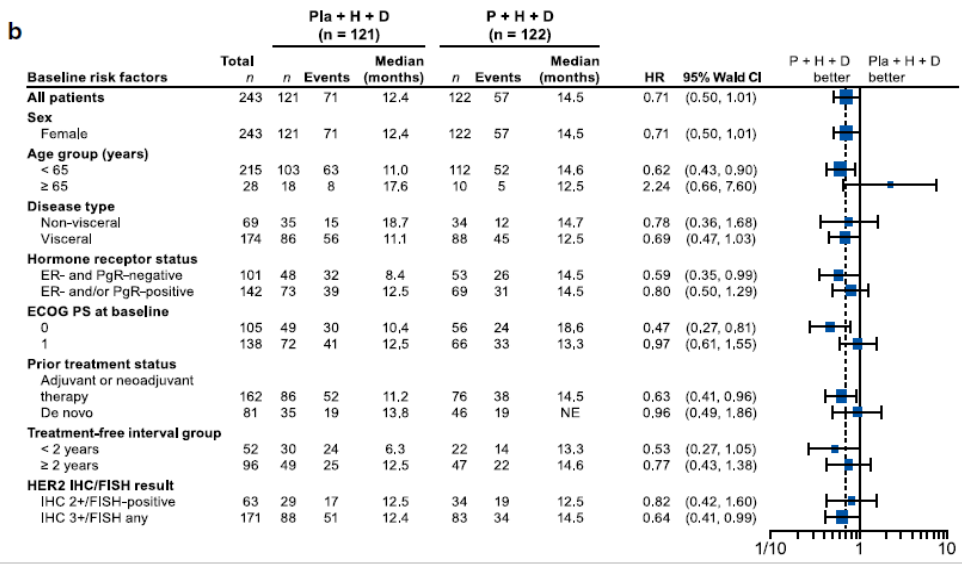


Figure 7. YO29296 (PUFFIN) Investigator-assessed progression- free survival in subgroups



9.2.1.3 Phase III Study MO28047 (PERUSE) of pertuzumab + trastuzumab + taxane (physician's choice) in HER2-positive mBC (Bachelot et al., 2014; Perez et al., 2016; Miles et al., 2016; Bachelot et al., 2019; Miles et al., 2020)

Study MO28047 (PERUSE) was designed to assess the safety and efficacy of investigator-selected taxane with pertuzumab and trastuzumab in first-line therapy for HER2-positive mBC. Patients with inoperable HER2-positive advanced breast cancer (locally recurrent/metastatic) (LR/mBC) and no prior systemic therapy for LR/mBC (except endocrine therapy) received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab [8mg/kg loading dose, then 6mg/kg every 3weeks (q3w)] and pertuzumab (840mg loading dose, then 420mg q3w) until disease progression or unacceptable toxicity. The primary end point was safety. Secondary end points included Overall Response Rate (ORR) and Progression-Free Survival (PFS).

A preliminary safety analysis (CCOD: 8 May 2015) was performed on a population of 1436 patients, after a median duration of follow-up of 12.2 months (Bachelot et al., 2014). A safety update (CCOD: 1 April 2016) was performed on the same population, after a median duration of follow-up of 17.2 months (Bachelot et al., 2016). The initial taxane selected by the investigator was docetaxel in 54.2% of patients, paclitaxel in 41.2% of patients, and nab-paclitaxel in 4.5% of patients. The median exposure to treatment was 16.1 months (range: <0.1, 45.9) for pertuzumab and 16.0 months (range: <0.1, 45.9) for trastuzumab. The median exposure to treatment with docetaxel, paclitaxel, or nab-paclitaxel was 3.8 (range: <0.1, 24.2), 4.2 (range: <0.1, 36.6), and 3.9 (range: <0.1, 17.3) months, respectively. The median number of cycles of pertuzumab and trastuzumab were 24.0 (range: 1, 64) and 24.0 (range: 1, 67), respectively. The median number of cycles of docetaxel, paclitaxel and nab-paclitaxel were 6.0 (range: 1, 34), 7.0 (range: 1, 51) and 6.0 (range: 1, 26), respectively.

Overall, 1,436 patients received at least one treatment dose (initially docetaxel in 775 patients, paclitaxel in 589, nab-paclitaxel in 65; 7 discontinued before starting taxane). Median age was 54 years; 29% had received prior trastuzumab. Median treatment duration was 16 months for pertuzumab and trastuzumab and 4 months for taxane. At this preliminary analysis (52 months' median follow-up), median PFS was 20.6 [95% confidence interval (CI) 18.9–22.7] months overall (19.6, 23.0 and 18.1 months with docetaxel, paclitaxel and nab-paclitaxel, respectively). ORR was 80% (95% CI 78%–82%) overall (docetaxel 79%, paclitaxel 83%, nab-paclitaxel 77%).

These preliminary findings from PERUSE after a median follow-up of > 4 years suggested that the safety and efficacy of first-line pertuzumab, trastuzumab and taxane for HER2-positive LR/mBC are consistent with results from CLEOPATRA. Paclitaxel appeared to be a valid alternative taxane backbone to docetaxel, offering similar PFS and ORR with a predictable safety profile.

Final results from PERUSE were recently presented (Miles et al., 2020; Huober et al., 2018; ESMO, 2020). Overall, 1436 patients were treated in PERUSE (1009 in Europe, 177 in Asia, 121 in South America, 71 in Africa, 34 in North America and 24 in Australia). 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% confidence interval [CI] 67.5–69.3; range 0.0–87.3 months), corresponding to 5.7 years.

The taxane chosen by the investigator was:

- Docetaxel in 775 patients (54%)
- Paclitaxel in 588 patients (41%)
- Nab-paclitaxel in 65 patients (5%).

Patients received a median of 16.2 months of study treatment (range 0.0–86.4 months):

- 4.2 months of taxane therapy
- 16.1 months of anti-HER2 therapy

Median treatment exposure was longer in:

- Patients aged ≤65 than >65 years (17.5 vs 11.1 months, respectively)
- Patients with no prior trastuzumab than prior trastuzumab (17.9 vs 13.2 months, respectively).

By the final data cut-off, PFS events had been recorded in 872 patients (61%) and deaths in 658 patients (46%; of which 581 [88%] were from progressive disease). Median PFS was 20.7 months (95% CI 18.9–23.1 months) (Figure 8). Subgroup analyses showed similar PFS irrespective of hormone receptor status or taxane backbone (Figure 9). PFS in patients with prior (neo)adjuvant trastuzumab (n=400) was consistent with results in CLEOPATRA (median PFS 18.7 months).

Median OS was 65.3 months (95% CI 60.9–70.9 months) and was more favorable in patients with hormone receptor-positive disease. OS was similar with all three taxane backbones (Figure 10). OS in patients with prior (neo)adjuvant trastuzumab (54 months) was also consistent with CLEOPATRA (median OS 57.1 months).

Among 1,198 patients with measurable disease, the ORR was 79.5% (95% CI 77.1–81.7%). Median DoR in 952 responding patients was 20.0 months (95% CI 18.2–22.2 months).

Figure 8. Study MO28047 (PERUSE) Final Analysis Progression Free Survival

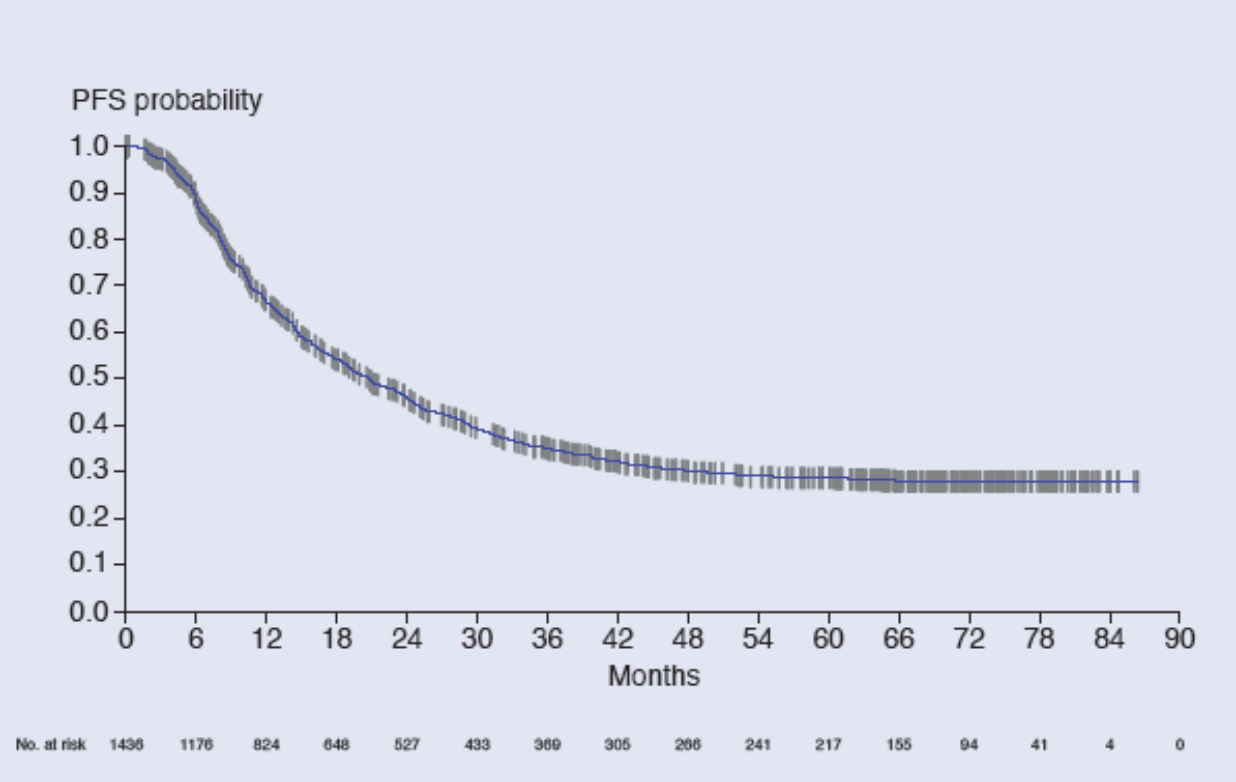


Figure 9. Study MO28047 (PERUSE) Final Analysis Progression Free Survival by selected taxane

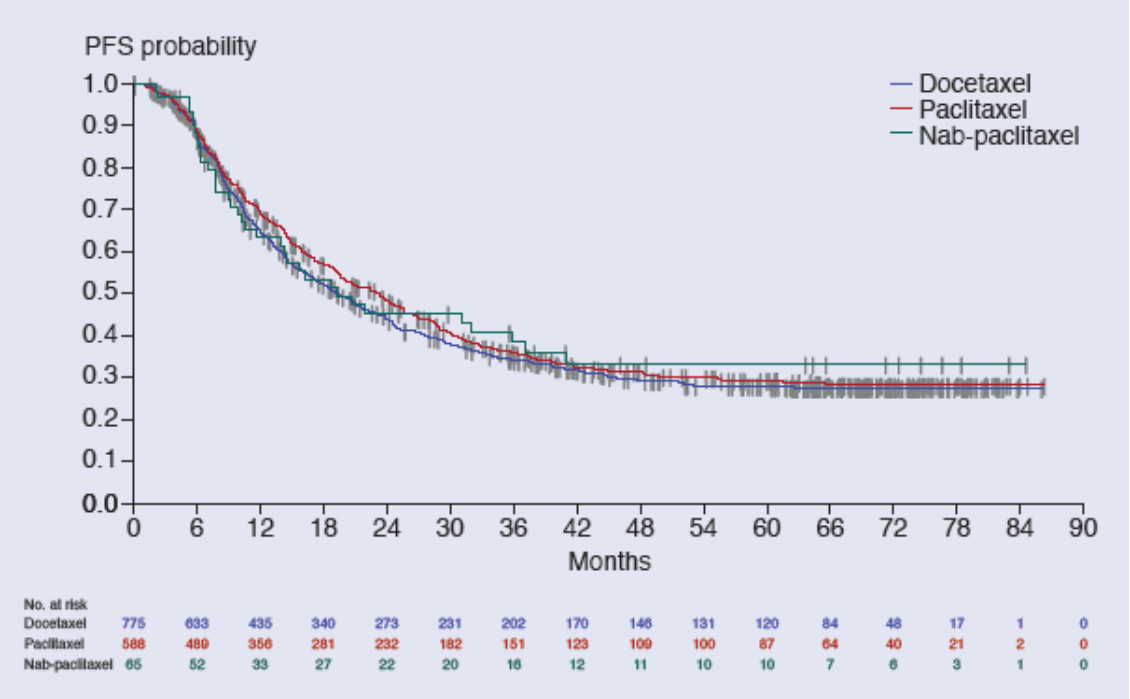
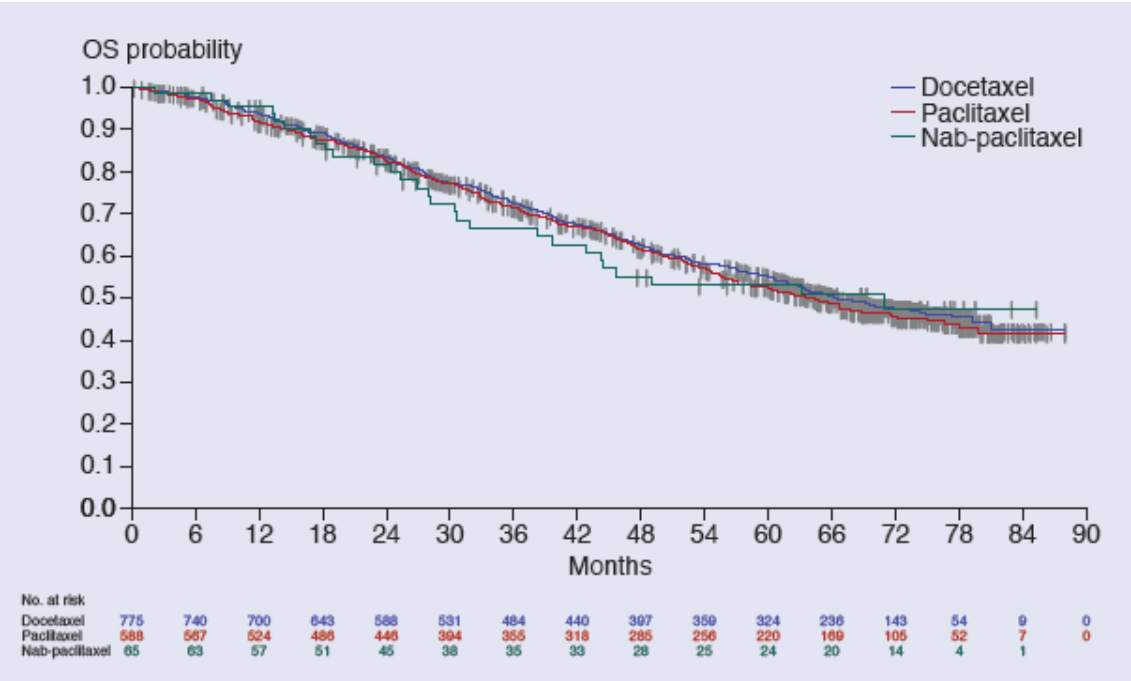


Figure 10. Study MO28047 (PERUSE) Final Analysis Overall Survival by selected taxane



Overall, efficacy results are consistent with CLEOPATRA (median PFS 20.7 months in PERUSE vs 18.7 months in CLEOPATRA; median OS 65.3 vs 57.1 months, respectively). Maintenance endocrine therapy, which was allowed in PERUSE but not in CLEOPATRA, may explain the more favorable OS in patients with HER2-positive disease in PERUSE.

In conclusion, the PERUSE final analysis further confirms the efficacy of pertuzumab + trastuzumab + taxane therapy in first-line treatment of HER2-positive LR/mBC, as previously demonstrated in the pivotal CLEOPATRA study, which established pertuzumab + trastuzumab + docetaxel as SoC in this setting. The study

demonstrates that paclitaxel is a viable alternative to docetaxel as backbone chemotherapy for all patients with HER2-positive LR/mBC. PERUSE is an important study as its data may enable access to pertuzumab + trastuzumab in patients where paclitaxel is the preferred chemotherapy backbone due to toxicity concerns with docetaxel.

9.2.2 Additional Supportive Studies for pertuzumab in HER2-positive mBC

An extensive clinical trial programme provides additional data to support the role of pertuzumab in HER2-positive mBC. Table 2 provides an overview of additional supportive studies with relevant references to the respective presentations.

Table 2. Additional supportive studies for pertuzumab in HER2-positive mBC

STUDY	DESCRIPTION	KEY FINDINGS	REFERENCES
Expanding the pertuzumab *–trastuzumab safety and efficacy dataset as first-line treatment of mBC*			
PERNETTA	Non-comparative randomised open-label Phase II trial of pertuzumab –trastuzumab with or without taxane-based/vinorelbine chemotherapy followed by trastuzumab emtansine (T-DM1) in case of progression	Pertuzumab **+** trastuzumab alone as first-line treatment followed by trastuzumab emtansine (T-DM1) is a reasonable therapeutic strategy in HER2-positive mBC	Huober J, *et al*. *Ann Oncol* 2018; **29**(suppl_8):viii90-viii121; Miles DW, *et al. Ann Oncol* 2020; **31**: s356-s7
Combining pertuzumab *–Trastuzumab with alternative chemotherapy partners asfirst-line treatment of mBC*			
VELVET	Two-cohort, open-label, Phase II, proof-of-concept trial of pertuzumab, trastuzumab and vinorelbine (Cohort 1 – pertuzumab – trastuzumab in separate infusion bags; Cohort 2 – pertuzumab – trastuzumab single infusion bag)	Pertuzumab + trastuzumab + vinorelbine is a suitable alternative to pertuzumab + trastuzumab + docetaxel, and the combination can be safely administered together in a single infusion bag	Perez EA, *et al. Breast Cancer Res* 2016; **18**:126; Andersson M, *et al. Oncologist* 2017; **22**:1160–1168
Combining pertuzumab *–Trastuzumab with endocrine therapy as first-line treatment of mBC*			
PERTAIN	Randomised Phase II trial investigating trastuzumab plus an aromatase inhibitor with or without pertuzumab in hormone receptor-positive disease (induction taxane could be administered at the investigator's discretion)	Pertuzumab + trastuzumab combined with an aromatase inhibitor is effective for patients HER2-positive, hormone receptor-positive mBC	Rimawi M, *et al. J Clin Oncol* 2018; **36**:2826–2835
Pertuzumab *IV–Trastuzumab SC + taxane as first-line treatment of mBC*			
MetaPHER	Phase IIIb, single-arm safety trial of fixed-dose trastuzumab SC in combination with pertuzumab IV and taxane IV	Safety profile of pertuzumab IV + trastuzumab SC + docetaxel is consistent with the safety in CLEOPATRA /no new safety signals	Kümmel S, *et al.* SABCS 2019 (abstract P1-18-05)
SAPPHIRE	Phase IIIb trial investigating the combination of pertuzumab IV with trastuzumab SC and clinician's choice of taxane chemotherapy (Australian study)	Pertuzumab IV + trastuzumab SC plus clinician's choice taxane, most commonly nab-paclitaxel, has acceptable safety and tolerability	Woodward N, *et al. Clin Breast Cancer* 2019; **19**:216–224
Pertuzumab *–trastuzumab as second-line treatment of mBC*			
BO17929	Single-arm, Simon two-stage study of pertuzumab + trastuzumab in case of progression during trastuzumab -based therapy (Cohort 1&2 **–** pertuzumab q3w + trastuzumab qw or q3w; Cohort 3 **–** patients received pertuzumab without trastuzumab)	Pertuzumab + trastuzumab is active and well tolerated in patients with HER2-positive mBC who had progression during prior trastuzumab therapy	Baselga J, *et al. J Clin Oncol* 2010; **28**:1138–1144 Cortés J, *et al. J Clin Onco*l 2012; **30**:1594–1600
PHEREXA	Randomised Phase III study of trastuzumab plus capecitabine with or without pertuzumab in patients who experienced disease progression during trastuzumab -based therapy	Addition of pertuzumab to trastuzumab and capecitabine has no significant effect on PFS or OS; it was well tolerated with no new safety signals	Urruticoechea A, *et al. J Clin Oncol* 2017; **35**:3030–3038

9.2.3 Real World study on the use of pertuzumab in combination with taxanes for first-line treatment of HER2-positive mBC

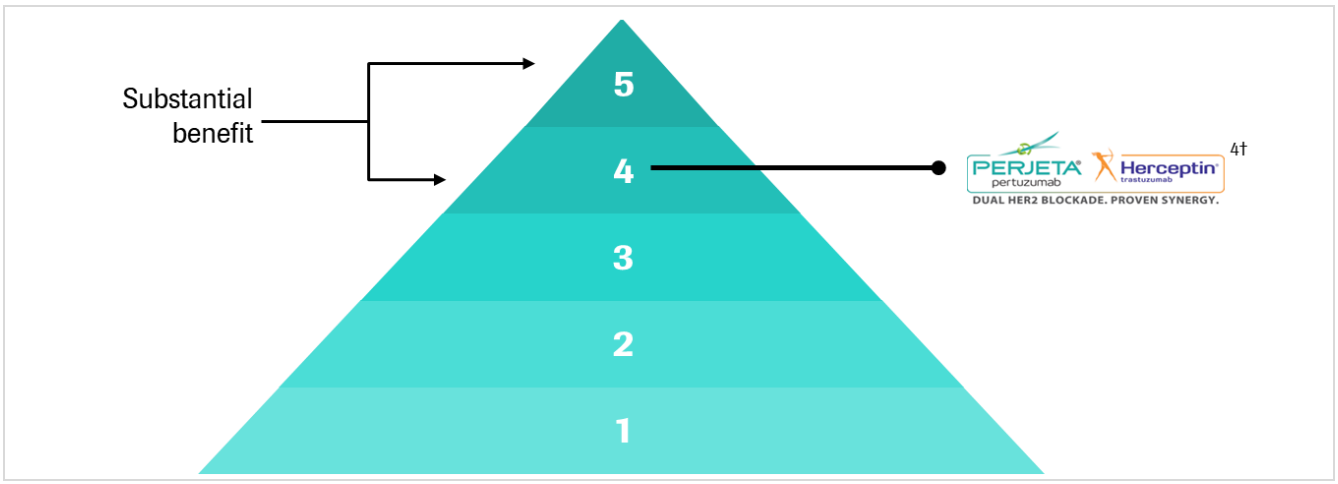
An evaluation of the use of taxanes with pertuzumab + trastuzumab and patient outcomes was performed after pertuzumab-trastuzumab plus docetaxel or paclitaxel was administered as first-line treatment for HER2-positive mBC in a real-world setting using data from Flatiron Health Electronic Health Records. This was the first study to address the real-world use of paclitaxel and to evaluate the effectiveness of pertuzumab-trastuzumab combinations with paclitaxel or docetaxel as first-line treatment for HER2-positive mBC. This analysis supports the evidence from the PERUSE trial suggesting that paclitaxel is a valid alternative taxane backbone to docetaxel and extends the evidence to a more heterogenous population (Polito et al., 2019).

9.3 ESMO Magnitude of Clinical Benefit Scale ranking for pertuzumab in mBC

The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a screening tool that helps to identify cancer treatments with therapeutic value. It consists of a validated and reproducible scale that is applicable across the full range of solid tumours in oncology. It incorporates a structured, rational and valid approach to data interpretation and analysis that reduces the tendency to have judgements affected by bias or uninformed and/or idiosyncratic data interpretation that has been developed in accordance with the public policy standard of “accountability for reasonableness” (Cherny et al., 2015; Cherny, 2017).

The scale considers overall survival, progression-free survival, disease free survival, hazard ratio, response rate, quality of life, prognosis of the condition and toxicity. The highest grades of the ESMO-MCBS in the curative setting are A and B and in the non-curative setting 5 and 4, which indicate a substantial magnitude of clinical benefit. Drugs are given an initial score based on efficacy (maximum score of 4 in the metastatic setting), which is then adjusted for Quality of Life (QoL) and toxicity.

Figure 11. Pertuzumab benefits from a Score of 4 for the treatment of HER2-positive mBC in the ESMO-MCBS (ESMO, 2020), highlighting the substantial benefit provided by pertuzumab for patients with HER2-positive mBC



9.4 Characterisation of benefits

9.4.1 Metastatic or Locally Recurrent Unresectable Breast Cancer

Study WO20698/TOC4129g (CLEOPATRA) established the baseline efficacy of pertuzumab in combination with trastuzumab and docetaxel for the treatment of 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 benefit profile of pertuzumab in patients with metastatic or locally recurrent unresectable breast cancer remains unchanged from that demonstrated by the pivotal trial, WO20698/TOC4129g (CLEOPATRA). This is further supported the longer follow up reported in the End of Study analysis and by data from other significant studies evaluating pertuzumab in HER2-positive mBC, including Phase III studies PUFFIN and PERUSE.

9.5 Other data: the MARIANNE trial

Additional clinical trials involving pertuzumab include the Phase III MARIANNE trial. A description of the study is provided below for information only. Roche does not intend to include the MARIANNE trial as part of the clinical package to support the role of pertuzumab - trastuzumab as first-line treatment of HER2-positive mBC.

Instead, Roche intends to clarify some of the concerns expressed by the Expert Committee in 2019 in reference to the difference in the reported outcomes of CLEOPATRA and MARIANNE.

As reported in the WHO Technical Report Series No. 1021 (TRS 1021), the Expert Committee commented "[…] Notably, in MARIANNE, the median OS of patients treated with trastuzumab and a taxane (50.9 months) was longer than that reported in the CLEOPATRA trial for trastuzumab plus docetaxel (40.8 months) and closer to the median OS of 56.5 months reported in CLEOPATRA for trastuzumab, docetaxel and pertuzumab". (World Health Organization; 2019b).

Please note that cross-trial comparisons should not be made between the Phase III MARIANNE study and the trials evaluating pertuzumab-trastuzumab + taxane as first-line treatment of HER2-positive mBC (CLEOPATRA, PERUSE, PUFFIN) which support the role of pertuzumab-trastuzumab plus chemotherapy as SoC for the first-line treatment of HER2-positive mBC.

9.4.1 Rationale for the MARIANNE Study

The aim of MARIANNE was to investigate whether T-DM1 given alone or in combination with pertuzumab as first-line treatment of HER2-positive mBC showed benefit, while minimising the side effects of traditional chemotherapy, compared with trastuzumab plus taxane.

When the MARIANNE study was planned, there were positive preclinical data for the combination of T-DM1 and pertuzumab from animal models, as well as preliminary clinical data from a Phase Ib/II trial in the first-line setting (TDM4373g). Safety and initial efficacy data were also available from a Phase II study comparing T-DM1 to trastuzumab plus taxane chemotherapy in the first line setting (TDM4450g).

At the time when the MARIANNE trial was designed (2009), the SoC was trastuzumab plus docetaxel or paclitaxel, as endorsed by health authorities, which was the comparator implemented in the study. The CLEOPATRA results were not available at that time.

9.4.2 MARIANNE study design

The Phase III MARIANNE study was an international, randomised, multicentre study that was designed to evaluate the following three HER2-targeted regimens:

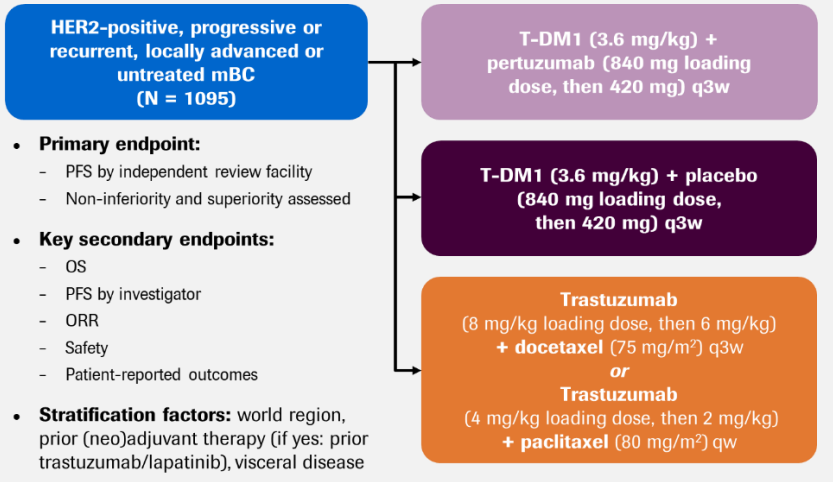
- T-DM1 in combination with pertuzumab
- T-DM1 alone (in combination with pertuzumab-placebo)
- Trastuzumab plus taxane chemotherapy (docetaxel or paclitaxel) at standard doses

The study included 1,095 people with previously untreated (first line) HER2-positive advanced/metastatic breast cancer (mBC). Patients with centrally assessed, HER2-positive, progressive/recurrent, previously untreated locally advanced or metastatic breast cancer with a ≥6-month interval since treatment in the (neo)adjuvant setting were randomised 1:1:1 to the three groups (Figure 12).

The primary endpoint was Progression-Free Survival (PFS) assessed by an independent review facility (IRF). Secondary efficacy endpoints included Overall Survival (OS), PFS by investigator and Objective Response Rate (ORR).

Statistical analysis was performed independently for each of the T-DM1-containing treatment arms versus the trastuzumab plus taxane arm, and also between the two T-DM1-containing arms. Hierarchical statistical testing was performed in a pre-specified sequential order. PFS was tested first for non-inferiority and then for superiority only if non-inferiority was achieved. The statistical design meant that, if superior PFS was not shown, all subsequent tests were descriptive only.

Figure 12. MARIANNE evaluated T-DM1 + pertuzumab vs. trastuzumab + taxane in first-line mBC

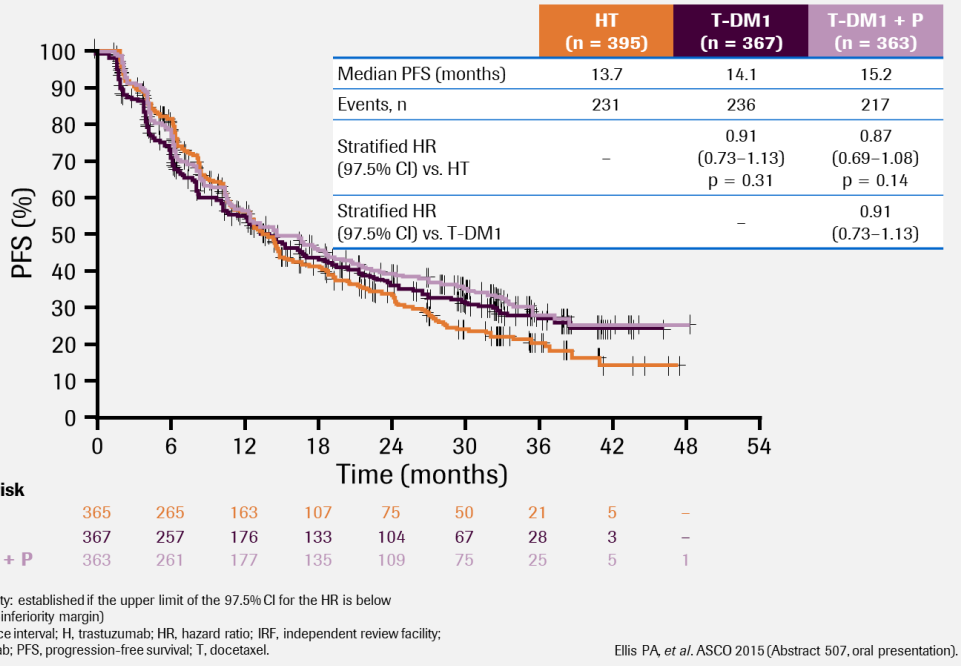


9.4.3 MARIANNE Results

9.4.3.1 Efficacy

The study met the PFS non-inferiority endpoint as assessed by an IRF, but the T-DM1 containing regimens did not show superiority compared with the trastuzumab plus taxane arm (Figure 13). This means that the three treatment regimens helped patients live without their disease worsening for a similar amount of time, but neither of the T-DM1-containing regimens significantly improved PFS compared with trastuzumab plus taxane.

Figure 13. MARIANNE study. Progression- Free Survival assessed by an Independent Review Facility (IRF)-



Non-inferiority: established if the upper limit of the 97.5% CI for the HR is below 1.1765 (non-inferiority margin)
CI, confidence interval; H, trastuzumab; HR, hazard ratio; IRF, independent review facility; P, pertuzumab; PFS, progression-free survival; T, docetaxel.

Ellis PA, *et al*. ASCO 2015 (Abstract 507, oral presentation).

The response rate for T-DM1 or T-DM1 plus pertuzumab was numerically slightly lower than the other arms; however, duration of response was longer with T-DM1 (20.7 months) and T-DM1 plus pertuzumab (21.2 months) than with trastuzumab plus taxane (12.5 months).

9.4.3.2 Safety

The T-DM1-based regimens in MARIANNE were better tolerated than trastuzumab plus taxane (Figure 14), having yielded fewer high-grade adverse events, fewer adverse events leading to discontinuation of chemotherapy, as well as lower rates of taxane associated adverse events that are particularly bothersome to patients, such as diarrhoea, neuropathy and alopecia. In addition, health-related quality of life was maintained for longer with T-DM1.

Figure 14. MARIANNE study. Overview of Adverse Events (AEs)

AEs, %	HT (n = 353)	T-DM1 (n = 361)	T-DM1 + P (n = 366)
Any AE	98.6	98.9	98.6
Grade ≥3 AE	54.1	45.4	46.2
AE leading to death	1.7	1.1	1.9
AE leading to discontinuation of any treatment component	29.7	18.3	9.1
LVEF <50% and ≥15%-point decrease from baseline	4.5	0.8	2.5

9.4.4 Results from MARIANNE should not be compared with those of CLEOPATRA

It is not appropriate to draw comparisons between the CLEOPATRA and MARIANNE studies due to differences in study design and patient populations.

CLEOPATRA was designed to evaluate pertuzumab in combination with trastuzumab and docetaxel vs trastuzumab + docetaxel:

- The results from CLEOPATRA showed significant clinical benefit for pertuzumab plus trastuzumab and docetaxel in first-line mBC
- Comprehensive HER2 blockade using pertuzumab + trastuzumab significantly increased OS compared with single blockade with trastuzumab alone
- These results established the comprehensive HER2 blockade and chemotherapy, using pertuzumab plus trastuzumab and docetaxel, as first-line standard of care for patients with HER2-positive mBC.

Conversely, MARIANNE was designed to evaluate T-DM1 alone or in combination with pertuzumab as first-line treatment for HER2-positive mBC compared with trastuzumab + taxane.

In conclusion, as per the information provided above, the different objectives and design of MARIANNE make impossible to compare this study with trials evaluating the combination of pertuzumab + trastuzumab + chemotherapy in HER2-positive mBC. The data on MARIANNE are presented here for information purposes only.

10. Evidence on safety

10.1 Estimate of total patient exposure to date

Overall, data from 19 clinical studies indicate that pertuzumab is well tolerated and in combination with trastuzumab and a range of other therapeutic agents shows acceptable safety profile. No new or unexpected safety findings have been encountered other than those that are known for agents that target the HER family of receptors. Diarrhoea, fatigue, and nausea are the most frequently reported Adverse Events (AEs) with single-agent pertuzumab, and the incidence of hematologic toxicities such as leukopenia and febrile neutropenia is low. A low level of cardiac toxicities, predominantly asymptomatic declines in left ventricular ejection fraction (LVEF), has been reported.

In the pivotal Phase III trial WO20698/TOC4129g (CLEOPATRA), the rates of symptomatic and asymptomatic left ventricular systolic dysfunction were not higher in patients receiving pertuzumab + trastuzumab + docetaxel than in those receiving placebo + trastuzumab + docetaxel (Baselga et al., 2012). However, patients who have received prior anthracyclines or radiotherapy to the chest area may be at higher risk of decreased LVEF.

10.2 Description of adverse effects/reactions

The safety of pertuzumab has been evaluated in more than 6,000 patients in Phase I-III trials in patients with various malignancies, and predominantly treated with pertuzumab in combination with other antineoplastic agents. Those studies included the pivotal trials CLEOPATRA (n=808), NEOSPHERE (n=417), TRYPHAENA (n=225), and APHINITY (n=4,804) (Table 3). The safety of pertuzumab was generally consistent across studies, although the incidence and most common adverse drug reactions (ADRs) varied depending on whether pertuzumab was administered as monotherapy or in combination with other antineoplastic agents.

Other studies that provide supporting evidence are Phase IIIb Study MO28047 (PERUSE), Phase II study MO27775 (PERTAIN), Phase II trial MO27782 (VELVET), Phase III study MO22324 (PHEREXA), Phase II study WO20697 (NEOSPHERE) and Phase II study WO29217 (BERENICE).

Table 3 summarizes the ADRs from the pertuzumab -treatment arms of the following pivotal clinical trials:

- CLEOPATRA, in which pertuzumab was given in combination with trastuzumab and docetaxel to patients with mBC (n=453).
- NEOSPHERE (n=309) and TRYPHAENA (n=218), in which neoadjuvant pertuzumab was given in combination with trastuzumab and chemotherapy to patients with locally advanced, inflammatory or eBC.
- APHINITY, in which adjuvant pertuzumab was given in combination with trastuzumab and anthracycline-based or non-anthracycline-based, taxane containing chemotherapy to patients with eBC (n=2,364).

It is important to note that the trials above include both the use of pertuzumab in eBC and mBC settings.

The following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

The most common ADRs (≥30%) from this pooled data were diarrhoea, alopecia, nausea, fatigue, neutropenia, and vomiting. The most common NCI-CTCAE Grade 3-4 ADRs (≥10%) were neutropenia and febrile neutropenia (PERJETA® CDS version 11).

Table 3. Summary of Adverse Drug Reactions (ADRs) in patients treated with pertuzumab^ (PERJETA® CDS version 11)

ADR (MedDRA Preferred Term) System Organ Class	Pertuzumab + trastuzumab + chemotherapy^^ n = ^^^3344 (100%) Frequency rate %		Frequency category
	All Grades %	Grades 3-4 %	
Blood and lymphatic system disorders			
Neutropenia	31.4	24.2	Very common
Anaemia	24.8	5.7	Very common
Febrile neutropenia*	11.9	11.8	Very common
Leukopenia	10.8	6.1	Very common
Cardiac disorders			
Left ventricular dysfunction**	1.4	0.3	Common
Cardiac failure congestive**	0.1	<0.1	Uncommon
Eye disorders			
Lacrimation increased	12.1	-	Very common
Gastrointestinal disorders			
Diarrhoea	67.9	8.9	Very common
Nausea	60.8	1.9	Very common
Vomiting	30.0	1.7	Very common
Stomatitis	24.9	1.6	Very common
Constipation	24.5	0.4	Very common
Dyspepsia	13.2	<0.1	Very common
Abdominal pain	11.7	0.4	Very common
General disorders and administration site conditions			
Fatigue	44.3	3.3	Very common
Mucosal inflammation	23.2	1.5	Very common
Asthenia	20.9	1.5	Very common
Pyrexia	18.9	0.6	Very common
Edema peripheral	16.2	<0.1	Very common
Immune system disorders			
Hypersensitivity	3.3	0.4	Common
Drug hypersensitivity	2.5	0.4	Common
Infections and infestations			
Nasopharyngitis	12.8	<0.1	Very common
Upper respiratory tract infection	9.5	0.3	Common
Paronychia	3.9	<0.1	Common
Metabolism and nutrition disorders			
Decreased appetite	23.1	0.8	Very common
Musculoskeletal and connective tissue disorders			
Arthralgia	24.6	0.7	Very common
Myalgia	24.3	0.8	Very common
Pain in extremity	10.0	0.2	Very common
Nervous system disorders			
Dysgeusia	22.7	<0.1	Very common
Headache	21.8	0.4	Very common
Peripheral sensory neuropathy	15.7	0.5	Very common
Neuropathy peripheral	14.7	0.7	Very common
Dizziness	11.2	0.1	Very common
Paresthesia	10.2	0.4	Very common

Cont. Table 3. Summary of Adverse Drug Reactions (ADRs) in patients treated with pertuzumab^ (PERJETA® CDS version 11)

ADR (MedDRA Preferred Term) System Organ Class	Pertuzumab + trastuzumab + chemotherapy^^ n = ^^^3344 (100%) Frequency rate %		Frequency category
	All Grades %	Grades 3-4 %	
Psychiatric disorders			
Insomnia	15.9	0.2	Very common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	15.6	<0.1	Very common
Cough	15.5	<0.1	Very common
Dyspnea	11.5	0.5	Very common
Pleural effusion	0.9	<0.1	Uncommon
Skin and subcutaneous tissue disorders			
Alopecia	63.1	<0.1	Very common
Rash	26.4	0.5	Very common
Nail disorder	12.9	0.3	Very common
Pruritus	12.9	<0.1	Very common
Dry skin	11.7	<0.1	Very common
Vascular disorders			
Hot flush	15.7	0.1	Very common

^ Pooled data from the overall treatment period in CLEOPATRA (data cutoff 11 February 2014; median number of cycles of pertuzumab was 24); from the neoadjuvant treatment period in NEOSPHERE (median number of cycles of pertuzumab was 4, across all treatment arms) and TRYPHAENA (median number of cycles of pertuzumab was 3 in the FEC/Ptz+T+D arm and 6 in the Ptz+T+FEC/Ptz+T+D and Ptz+TCH arms); and from the treatment period of APHINITY (median number of cycles of pertuzumab was 18) [70].
^ ^ In NEOSPHERE, 108 patients received pertuzumab + trastuzumab alone without docetaxel and 94 patients received pertuzumab + docetaxel without trastuzumab.
^ ^ ^ In CLEOPATRA, 45 patients who were randomised to receive placebo and who had no prior exposure to pertuzumab, had crossed over to receive pertuzumab and are included in the 3,344 patients treated with pertuzumab.
* In this table this denotes an adverse reaction that has been reported in association with a fatal outcome.
** The incidence of left ventricular dysfunction and cardiac failure congestive reflect the MedDRA Preferred Terms reported in the individual studies.

10.3 Further information on selected adverse drug reactions (PERJETA® CDS version 11)

10.3.1 Left ventricular dysfunction

In the pivotal trial CLEOPATRA, the incidence of left ventricular dysfunction (LVD) during study treatment was higher in the placebo-treated group than the pertuzumab-treated group (8.6% and 6.6%, respectively). The incidence of symptomatic LVD was also lower in the pertuzumab treated group (1.8% in the placebo-treated group vs. 1.5% in the pertuzumab treated group).

10.3.2 Infusion-related reactions

An infusion-related reaction was defined in the pivotal trials as any events reported as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. In the pivotal trial CLEOPATRA, the initial dose of pertuzumab was given the day before trastuzumab and docetaxel to allow for the examination of pertuzumab associated reactions. On the first day when only pertuzumab was administered, the overall frequency of infusion-related reactions was 9.8% in the placebo-treated group and 13.2% in the pertuzumab -treated group, with the majority of reactions being mild or moderate. The most common infusion-related reactions (≥1.0%) in the pertuzumab treated group were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting.

During the second cycle when all drugs were administered on the same day, the most common infusion related reactions (≥1.0%) in the pertuzumab -treated group were fatigue, drug hypersensitivity, dysgeusia, hypersensitivity, myalgia, and vomiting.

In neoadjuvant and adjuvant trials, pertuzumab was administered on the same day as the other study treatment drugs. Infusion-related reactions occurred in 18.6% - 25.0% of patients on the first day of pertuzumab administration (in combination with trastuzumab and chemotherapy). The type and severity of events were consistent with those observed in CLEOPATRA, with a majority of reactions being mild or moderate (PERJETA® CDS version 11).

10.3.3 Hypersensitivity reactions/anaphylaxis

In the pivotal trial CLEOPATRA, the overall frequency of hypersensitivity/anaphylaxis reported events was 9.3% in the placebo-treated patients and 11.3% in the pertuzumab- treated patients, of which 2.5% and 2.0% were NCI-CTCAE (version 3) grade 3-4, respectively. Overall, 2 patients in placebo treated group and 4 patients in the pertuzumab -treated group experienced anaphylaxis (PERJETA® CDS version 11).

Overall, most of hypersensitivity reactions was mild or moderate in severity and resolved upon treatment. Based on modifications made to study treatment, most reactions were assessed as secondary to docetaxel infusions.

In neoadjuvant and adjuvant trials, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA.

10.3.4 Laboratory Abnormalities

In the pivotal trials CLEOPATRA, NEOSPHERE, and APHINITY the incidence of NCI-CTCAE Grade 3-4 decreases in neutrophil counts were balanced in the pertuzumab -treated and control groups (PERJETA® CDS version 11).

10.4 Identification of variation in safety due to health systems and patient factors

The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥65 years of age, compared to patients aged <65 years of age: decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhoea (PERJETA® CDS version 11).

Per the pertuzumab EU SmPC, there is limited amount of data from the use of pertuzumab in pregnant women. Studies in animals have shown reproductive toxicity and pertuzumab is not recommended during pregnancy and in women of childbearing potential not using contraception. Pharmacovigilance actions relating to risk in pregnancy include a global enhanced pregnancy pharmacovigilance program (PERJETA® SmPC 2020).

10.5 Summary of clinical trials involving trastuzumab + pertuzumab in patients with HER2-positive tumours

The risk profile for pertuzumab in the treatment of metastatic or locally recurrent unresectable breast cancer is based on an extensive clinical trial programme with main sources of evidence from Phase III pivotal trial WO20698/TOC4129g (CLEOPATRA), Phase III Study YO29296 (PUFFIN) and Phase IIIb Study MO28047 (PERUSE).

10.5.1 Study WO20698/TOC4129g (CLEOPATRA) (Baselga et al., 2012; Swain et al., 2013; Swain et al., 2015; Swain et al., 2020)

In the completed Phase III pivotal trial WO20698/TOC4129g (CLEOPATRA) in patients with HER2-positive mBC (N = 808), the safety profile of pertuzumab + trastuzumab + docetaxel at the time of the end of the study (23 November 2018) was generally similar to that of placebo + trastuzumab + docetaxel. No new safety concerns were identified. There was no evidence of cumulative or late toxicity. Treatment with pertuzumab + trastuzumab + docetaxel did not increase the incidence of cardiac disorders, in particular LVD and symptomatic LVD, in comparison with treatment with placebo + trastuzumab + docetaxel.

The most common AE in both arms combined was alopecia (an AE associated with docetaxel), followed by diarrhoea, neutropenia, nausea, fatigue and rash. The safety profile of pertuzumab + trastuzumab and docetaxel in patients who crossed over (after initially being treated with placebo + trastuzumab and docetaxel) was consistent with the safety profile observed in patients treated with pertuzumab + trastuzumab + docetaxel from the beginning of the study. The majority of AEs following crossover from placebo to pertuzumab were Grade 1–2. No new safety signals were identified in these patients.

The incidences of diarrhoea, rash, mucosal inflammation, headache, anaemia, upper respiratory tract infection, pruritus, febrile neutropenia, dry skin, and muscle spasms were higher (≥ 5% difference) in the pertuzumab + trastuzumab + docetaxel arm compared with the placebo + trastuzumab + docetaxel arm, whereas constipation was more common in the placebo + trastuzumab + docetaxel arm (Table 4).

Based on the safety analysis population, more deaths occurred in the placebo + trastuzumab + docetaxel arm (65.9%) compared with the pertuzumab + trastuzumab + docetaxel arm (58.3%). The majority of deaths in both arms were due to disease progression.

Table 4. Study WO20698/TOC4129g: Overview of Adverse Events (Latest Clinical Cutoff: 23 November 2018)

	HT	PHT
n (%)	n = 396	n = 408
Any AE	391 (98.7%)	408 (100.0%)
Grade ≥ 3	291 (73.5%)	317 (77.7%)
Related	381 (96.2%)	397 (97.3%)
SAE	116 (29.3%)	160 (39.2%)
AE leading to discontinuation of study medication	114 (28.8%)	131 (32.1%)
AE leading to dose interruption/modification	217 (54.8%)	265 (65.0%)
AE resulting in death	12 (3.0%)	8 (2.0%)
Events to monitor		
Symptomatic LVD assessed by the investigator	7 (1.8%)	6 (1.5%)
Left ventricular dysfunction	34 (8.6%)	32 (7.8%)

(P = pertuzumab, H = trastuzumab, T = docetaxel)

Conclusion: For CLEOPATRA study, the cumulative safety profile with longer follow-up was similar to the safety profile reported at previous data cutoffs. There was no evidence of cumulative or late toxicity.

The magnitude of clinical benefit and the acceptable safety profile with pertuzumab + trastuzumab + docetaxel compared with placebo + trastuzumab + docetaxel in patients with HER2-positive locally recurrent, unresectable, or mBC, who had not received chemotherapy or biologic therapy for their metastatic disease, were maintained with longer follow-up. These data confirmed the positive benefit-risk profile of pertuzumab + trastuzumab + docetaxel in the studied indication.

10.5.2 Phase III Study YO29296 (PUFFIN) of pertuzumab + trastuzumab + taxane- based chemotherapy (Chinese bridging study) (Xu B et al., 2020)

In the Phase III, randomised, double-blind, placebo-controlled clinical trial (PUFFIN), the safety of pertuzumab + trastuzumab+ docetaxel vs. placebo + trastuzumab + docetaxel in Chinese patients previously untreated HER2-positive mBC was studied.

The safety profile during the treatment period is shown in Table 5. Overall, safety was consistent with the known pertuzumab safety profile.

Table 5. YO29296 (PUFFIN) Safety summary in the safety population

Patients with at least one event:	Pertuzumab plus trastuzumab plus docetaxel ($n=122$)	Placebo plus trastuzumab plus docetaxel ($n=120$)
Most common adverse events (all grades)[a], *n* (%)		
Leukopenia	89 (73.0)	86 (71.7)
Neutropenia	86 (70.5)	84 (70.0)
Anemia	64 (52.5)	57 (47.5)
Alopecia	50 (41.0)	40 (33.3)
Alanine aminotransferase increased	35 (28.7)	50 (41.7)
Diarrhea	56 (45.9)	26 (21.7)
Aspartate aminotransferase increased	33 (27.0)	42 (35.0)
Asthenia	25 (20.5)	20 (16.7)
Pyrexia	26 (21.3)	18 (15.0)
Pain	18 (14.8)	22 (18.3)
Cough	23 (18.9)	14 (11.7)
Decreased appetite	15 (12.3)	14 (11.7)
Peripheral edema	10 (8.2)	18 (15.0)
Nail discoloration	12 (9.8)	15 (12.5)
Nausea	13 (10.7)	14 (11.7)
Upper respiratory tract infection	12 (9.8)	13 (10.8)
Blood bilirubin increased	10 (8.2)	13 (10.8)
Hypokalemia	15 (12.3)	7 (5.8)
Vomiting	13 (10.7)	9 (7.5)
Hypoesthesia	13 (10.7)	8 (6.7)
Weight increased	4 (3.3)	15 (12.5)
Stomatitis	14 (11.5)	4 (3.3)
Grade 3 or higher adverse events[b], *n* (%)		
Neutropenia	67 (54.9)	70 (58.3)
Leukopenia	60 (49.2)	56 (46.7)
Febrile neutropenia	5 (4.1)	7 (5.8)
Diarrhea	5 (4.1)	3 (2.5)
Anemia	6 (4.9)	0 (0)

Table includes adverse events with onset from first dose of study drug through 42 days after last dose of study drug
[a] Reported in ≥ 10% of patients in either arm
[b] Reported in ≥ 3% of patients in either arm

Conclusion: In summary, PUFFIN reinforce the existing large body of evidence for pertuzumab in HER2-positive breast cancer and support the favourable benefit–risk profile of the pertuzumab-based regimen in Chinese patients in first-line metastatic setting.

10.5.3 Study PERTAIN (Rimawi et al., 2018; Final CSR REPORT No. 1100067, 2020)

In the completed randomised, two-arm, open-label, multicenter Phase II study MO27775 (PERTAIN) assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first-line treatment of patients with receptor 2 (HER2)–positive and hormone receptor–positive metastatic/ locally advanced breast cancer (mBC/LABC), all-grade AEs occurred in 96.1% in Arm A (pertuzumab + trastuzumab + aromatase inhibitor [AI] and 98.4% in Arm B [trastuzumab + AI]). The incidence of Grade ≥ 3 AEs was higher in the pertuzumab treatment arm (56.7% in Arm A and 41.1% in Arm B).

The most frequently reported AEs of CTCAE grade ≥3 (occurring in at least 3% of patients) were: Arm A, hypertension (15 patients, 11.8%), diarrhoea (12 patients, 9.4%), anaemia, pneumonia (each 6 patients, 4.7%), and asthenia, febrile neutropenia, left ventricular dysfunction, and neutropenia (each 4 patients, 3.1%); and Arm B, hypertension (13 patients, 10.5%), neutropenia (9 patients, 7.3%), and asthenia (4 patients, 3.2%).

In the selected AE category of “Congestive Heart Failure”, the incidence of AEs suggestive of CHF (preferred terms: cardiac failure, left ventricular dysfunction, and ejection fraction decreased) was low in both treatment arms: 5 patients (3.9%, 5 events) in Arm A and 1 patient (0.8%, 1 event) in Arm B. The median time to onset was not reached in either treatment arm.

There were not clinically relevant (i.e., at least 10% points below baseline) mean changes from baseline in LVEF over time in either treatment arm. Later in the study, when data were available for only 1 patient in Arm A, at Cycle 117, that patient had a change in LVEF of -11% from baseline, which represented a mean change of -11% (and therefore was >10% points below baseline).

Conclusion: For PERTAIN study, there were no new safety concerns at the final analysis of safety data. The safety profile at a median of follow-up of 6 years was consistent with previous trials of pertuzumab and trastuzumab. Pertuzumab plus trastuzumab and an AI was effective and tolerable for the treatment of patients with receptor 2 (HER2)–positive and hormone receptor–positive metastatic/ locally advanced breast cancer (mBC/LABC). This study provided additional evidence on the role of pertuzumab plus trastuzumab in first-line HER2+ mBC patients and suggests that there may be patients who would benefit from treatment with pertuzumab, trastuzumab, and AI without induction chemotherapy.

10.5.4 Study VELVET (Andersson et al., 2015; Final Clinical Study Report Report No 1070752, 2016)

In the completed, two-cohort, non-randomised, open-label, Phase II trial MO27782 (VELVET) in patients with HER2-positive mBC, the safety profile of pertuzumab, trastuzumab, and vinorelbine in combination has been acceptable, with no new safety signals observed. At the end of the study, the most common AEs (≥ 20% of patients) in Cohort 1 (pertuzumab and trastuzumab administered sequentially in separate infusion bags, followed by vinorelbine) were diarrhoea, neutropenia, nausea, asthenia, pyrexia, fatigue, anaemia, constipation, vomiting, chills, alopecia, rash, leukopenia, decreased appetite, and weight decreased. In Cohort 2 (pertuzumab and trastuzumab administered together in a single infusion bag, followed by vinorelbine), the most common AEs (≥ 20% of patients), at the end of the study were diarrhoea, neutropenia, nausea, fatigue, constipation, hypertension, asthenia, pain in extremity, pyrexia, muscle spasms, alopecia, back pain, headache, mucosal inflammation, dyspnea, stomatitis, vomiting, cough, decreased appetite, neuropathy peripheral, abdominal pain upper, and weight decreased.

Conclusion: For VELVET study, no new safety signals were identified and administering trastuzumab and pertuzumab sequentially or in the same infusion bag did not appear to impact safety.

10.5.5 Study PERUSE (Final CSR Report No. 1101598, 2020; Perez et al., 2016; Miles et al., 2016; Bachelot et al., 2014)

In the completed Phase IIIb multicenter, open-label, single-arm study MO28047 (PERUSE) designed to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane in first-line treatment of patients with HER2-positive advanced (metastatic or locally recurrent) breast cancer, 1,419 (98.8%) patients experienced at least one AE (any grade), the most frequent being diarrhoea (68.5%), alopecia (48.3%), nausea (35.7%), fatigue (31.9%) and asthenia (29.8%).

Overall, 59.8% of AEs were Grade 3–4 in the study. In total, 31 patients experienced a Grade 5 AE.

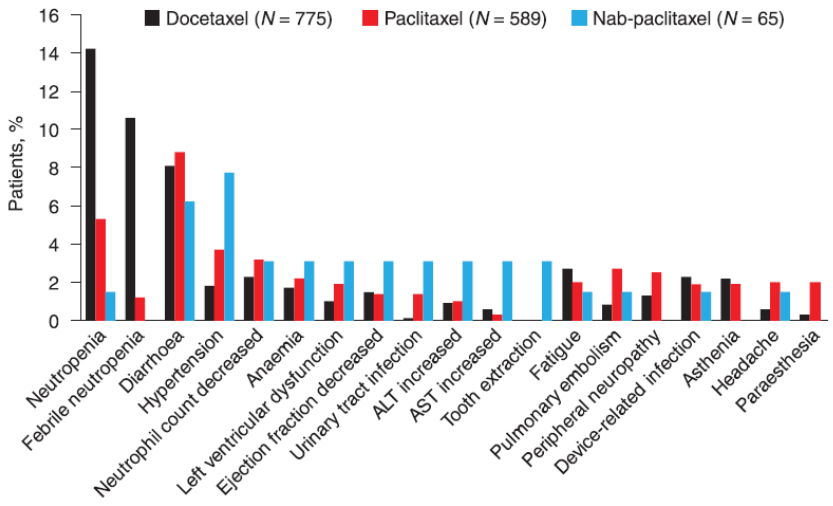
The most frequently reported (≥2% of patients) Grade ≥3 AEs by PT were neutropenia (10.1%), diarrhoea (8.4%), febrile neutropenia (6.3%), hypertension (3.2%), neutrophil count decreased (2.6%), fatigue (2.5%), and asthenia and anaemia (2.0% each).

Thirty-five (2.4%) patients died due to 37 AEs. AEs leading to pertuzumab treatment interruption or discontinuation occurred in 33% of patients; the most common AEs were ejection fraction decreased, diarrhoea, neutropenia and LVD.

Ninety (6.3%) patients experienced a decline in LVEF (98 events). Of these, 75 (5.2%) patients experienced decreased ejection fraction, eight (0.6%) experienced left ventricular dysfunction, seven (0.5%) experienced cardiac failure and one (0.1%) patient experienced congestive heart failure. In total, 85 events were considered related to both pertuzumab and trastuzumab, ten events were considered related to trastuzumab only, and three events were considered related to pertuzumab, trastuzumab and taxane. Fifty cardiac AESI resulted in discontinuation of treatment and 28 resulted in dose interruption. Of the 98 cardiac AESI, 78 (79.6%) are resolved, eight (8.2%) are resolved with sequela, 12 (12.2%) are ongoing and one (1.0%) is reported as unknown.

AEs to monitor were reported in 91.9% patients. The most common (occurring in ≥5% of patients) AEs to monitor by category were infusion-related reactions / administration-related reactions (1096 [76.3%] patients, 4,894 events), rash / skin reactions (668 [46.5%] patients, 1,415 events), mucositis (618 [43.0%] patients, 1,200 events), cardiac dysfunction (478 [33.3%] patients, 764 events), neutropenia / febrile neutropenia (439 [30.6%] patients, 1,238 events), anaphylaxis and hypersensitivity (124 [8.6%] patients, 136 events), and diarrhoea Grade ≥3 (120 [8.4%] patients, 155 events) (Figure 15).

Figure 15. Study MO28047 (PERUSE) Most common (>2% of patients in any subgroup) grade ≥3 adverse events by initially selected taxane. ALT, alanine aminotransferase; AST, aspartate aminotransferase



Safety was assessed by the following subgroups: region, age, Eastern Cooperative Oncology Group (ECOG) performance status at baseline, type of taxane, visceral disease at baseline, prior neoadjuvant chemotherapy, hormone receptor status, and previous trastuzumab therapy. The frequency of Grade ≥3 Treatment Emergent Adverse Events (TEAEs) in each subgroup was as expected for the populations analysed. No new safety signals were identified.

Conclusion: For PERUSE study, no new safety signals were identified and the safety profile of pertuzumab in combination with trastuzumab was consistent with the previous findings.

10.5.6 Study BO17929 (Baselga et al., 2010; Cortes et al., 2012; Final Clinical Study Report No 1066980, 2016)

In the completed Phase II, two-stage single-arm study BO17929 in patients with HER2-positive mBC receiving pertuzumab and trastuzumab (N = 66), the most common AEs were diarrhoea, fatigue, nausea and rash (Table 6).

Table 6. Study BO17929: Summary of Common Adverse Events, (all grades): Primary Analysis

Patients, n (%)	Cohorts 1+2 PH (n = 66)
Diarrhoea	42 (64)
Fatigue	22 (33)
Nausea	18 (27)
Rash	17 (26)
Headache	13 (20)
Arthralgia	11 (17)
Cough	9 (14)
Anorexia	9 (14)
Asthenia	8 (12)
Dizziness	8 (12)

Patients, n (%)	Cohort 3 P (n = 29)	Cohort 3 P→PH (n = 17)
Diarrhoea	14 (48.3)	5 (29)
Nausea	10 (34.5)	5 (29)
Vomiting	7 (24)	4 (24)
Fatigue	5 (17)	4 (24)
Asthenia	5 (17)	2 (12)
Back pain	5 (17)	2 (12)
Musculoskeletal chest pain	3 (10)	0 (0)
Abdominal distension	3 (10)	0 (0)
Abdominal pain, upper	3 (10)	1 (6)
Decreased appetite	3 (10)	2 (12)

Conclusion: In the study BO17929, combined therapy was well tolerated, with most adverse events of severity Grade 1 or 2. Single-agent pertuzumab was also well tolerated, with most adverse events of NCI-CTCAE Grade 1 or 2. The safety profile of dual-agent treatment in Cohort 3 was consistent with that seen in Cohorts 1 and 2, confirming that addition of trastuzumab to pertuzumab did not notably increase toxicity.

10.5.7 Study PHEREXA (Final CSR Report No. 1081437, 2018; Urruticoechea et al., 2017)

In the completed Phase III study MO22324 (PHEREXA) the safety profile of the pertuzumab- containing regimen was consistent with the previous studies of pertuzumab and no new safety signals were observed.

Almost all patients experienced an AE. The safety and tolerability of pertuzumab + trastuzumab + capecitabine (Arm B) was comparable with that of trastuzumab + capecitabine (Arm A) in terms of the incidence and severity of any AE (the majority were Grade 1-2 in severity), Serious Adverse Events (SAEs), discontinuations due to AEs, and AEs leading to death. The most common AEs were diarrhoea, palmar-plantar erythrodysesthesia (PPE) syndrome and nausea. The incidence of diarrhoea was higher in those patients that received pertuzumab. The incidence of Grade ≥ 3 AEs was lower in those patients that received pertuzumab. The incidence of SAEs was similar in the two treatment arms. As expected, events to monitor, including diarrhoea, rash/skin reactions (excluding PPE syndrome) and mucositis were more common in the pertuzumab- containing arm. The incidence of cardiac disorders, particularly LVD, was higher in patients that received pertuzumab (3.2% vs. 7.5%). There was a total of 270 deaths 136 patients in Arm A and 134 patients in Arm B), the majority of which were due to disease progression.

Conclusion: In the PHEREXA study, no new safety signals were observed and overall, the safety profile of the pertuzumab regimen was consistent with the previous studies. No late cardiac safety issues were observed.

10.5.8 Safety overall conclusion

The benefit that pertuzumab brings to patients was demonstrated and proven in the pivotal trials in the first-line treatment of patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, in the neoadjuvant treatment of patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer and the adjuvant treatment of eBC at high risk of recurrence (PSUR (PBRER), 2020).

Based on the CLEOPATRA study (WO20698/TOC4129g), pertuzumab + trastuzumab + docetaxel is considered the current standard of care for first-line treatment of HER2-positive mBC, as per the most recent international and local Breast Cancer Guidelines: NCCN Breast Cancer Guidelines (v4 – 2020) (NCCN, 2020), AGO Guidelines from the German Gynecological Oncology Group (AGO 2018) (Wolff et al., 2018) as well as European Society for Medical Oncology Guidelines (ESMO) 2018 (Cardoso et al., 2017).

Overall, data from clinical studies indicate that pertuzumab is well tolerated and in combination with trastuzumab and a range of other therapeutic agents shows manageable safety profile. No new or unexpected safety findings have been identified other than those that are known for agents that target the HER family of receptors. Diarrhoea, fatigue, and nausea are the most frequently reported AEs with single agent pertuzumab, and the incidence of hematologic toxicities such as febrile neutropenia is low (PSUR (PBRER), 2020).

11. Summary of available data on comparative cost and cost-effectiveness of the medicine

The application submitted for consideration in 2018 did not provide costs/cost-effectiveness data in the context of mBC. Considering the relevance and importance of this information for a comprehensive review of pertuzumab and the assessment of its suitability for inclusion in the WHO Essential Medicines List, data have been added for consideration by the Expert Committee.

11.1 Range of costs of the proposed medicine

11.1.1 Roche's pricing approach

Roche pricing approach reflects the WHO definition of 'Fair Pricing', balancing the need for affordability to healthcare systems and patients and sufficient market incentives for industry to invest in future innovation.

Three main factors are taken into consideration when setting a price and at its core, Roche's pricing approach is based on the health impact that a medicine brings to the patient, their families and broader society.

Secondly, the context of individual healthcare systems is considered, factoring in different priorities and burdens of disease; varying abilities to pay; local regulatory environments and cost-effectiveness assessments when applicable.

Thirdly, this approach enables Roche to invest year after year into high risk and complex areas of medicines for developing future innovation.

Together with healthcare system partners, Roche uses tailored pricing solutions and believes that this responsible approach to pricing enables broad, rapid and equitable access for patients today and innovation for patients tomorrow.

11.1.2 US and Europe price ranges

The US list of Wholesale Acquisition Cost (WAC) price for one vial of pertuzumab 420mg is $5,292 per vial / $100,548 per Episode of Care (EoC) (18 cycles).

In France, Germany, Italy, Spain and UK, list ex-factory prices for pertuzumab range from €2,221 – €3,037 per vial, or €42,199 – €57'703 per EoC.

11.1.3 Low- and lower- middle income countries (LMICs)

At a global level, Roche is committed to broadening access for patients to its medicines in low- and lower-middle income countries (LMICs). To this end, Roche is developing comprehensive, scalable and adapted solutions to ensure that people in these countries have affordable access to the care they deserve, and that Roche supports the journey towards Universal Health Coverage (UHC).

Non-communicable diseases (NCDs), in particular cancer, have become a major disease burden globally, and Roche wants to continue to support the growing number of governments that are taking action against NCDs, particularly in countries with more limited resources.

For several years now, Roche has pioneered International Differential Pricing (IDP), allowing our local organisations to adjust prices to reflect a country's relative income and ability to pay. This helps to ensure that our innovations are fairly priced and therefore reach patients in need.

As part of a wider Roche commitment to doing more to address affordability challenges, Roche's IDP model has been strengthened this year with a broadened scope to make it more reflective of the local economic situation. This model aligns innovative medicine prices (including pertuzumab) to a purchasing parity-adapted formula, factoring in gross domestic product per capita, as well as public healthcare investment and the United Nations' Human Development Index to ensure that the prices are as fair as possible.

Roche IDP model was applied in several LMIC countries, either through public funding or the Out-of-Pocket Paying (OoP) sector, where pricing was added to non-pricing support in the form of patient assistance programmes. These programmes included components such as medicine doses and diagnostic tests donations, patient awareness educational campaigns involving healthcare practitioners, patient assistance to treatment adherence, and health service delivery improvements.

This comprehensive set of interventions resulted in greater access to patients who otherwise could not afford treatment with pertuzumab in mBC. To date, and with the implementation of a greater price flexibility, as part of its IDP model, Roche was able to support governments and private institutions in LMICs in providing access to patients for pertuzumab in mBC in Albania, Armenia, Bosnia Herzegovina, Egypt, Georgia, India, Indonesia, Malaysia, Mexico, Moldova, Myanmar, Pakistan, Thailand and Ukraine.

Due to its broadened scope and implementation in additional countries, Roche new strengthened IDP model will continue to allow access to pertuzumab mBC treatment for even more patients.

Few examples below illustrate such collaboration and the establishment of special prices agreement.

Uruguay - In supporting the government to address significant budget challenges and overcome cost hurdles, and with close collaboration with stakeholders, Roche was able to structure breast cancer treatment reimbursement through payment facilitation mechanisms over agreed periods of time, and with the development of guidelines defining treatment protocols, inclusion/exclusion and end-of-treatment criteria, patient follow-up, and shared treatment data.

Brazil - In 2018, pertuzumab received a favorable reimbursement recommendation in the mBC setting from the Brazilian health technology assessment agency, the National Committee for Health Technology Incorporation (CONITEC) which enabled Roche and the Brazilian Ministry of Health to reach a price agreement in 2020 that addresses the needs of the healthcare system to serve high numbers of breast cancer patients.

Morocco - Pertuzumab was granted reimbursement in 2017 by the Agence Nationale de l'Assurance Maladie (ANAM) from Morocco's Ministry of Health. Public reimbursement was gained following strong clinical data from the PERUSE study carried out in Morocco on pertuzumab, successful experience and feedback from the medical community, and price adjustment to reflect the country's ability to afford this treatment option. Prior to reimbursement, access to specialty care medicines was limited and requests were granted on a case-by-case basis by ANAM. A broader access is now possible.

Lebanon - To ensure HER2-positive breast cancer patients in Lebanon have access to pertuzumab, Roche worked with the Ministry of Public Health (MoPH) and the National Social Security Fund (NSSF) to address the needs of key healthcare professionals in specific regions. Tailored pricing solutions per healthcare centre/payer were offered as of 2015, including personalised reimbursement models for the NSSF and combination pricing for the MoPH.

11.2 Cost-effectiveness of pertuzumab

The application of cost-effectiveness to innovative technologies has relevant limitations and there are cases in which highly effective and essential medicines result not to be cost-effective, even if they would be zero priced. This has been observed in many case studies that considered the costs incurred during periods of additional survival related to either the technology being appraised or the condition the technology was intending to treat (Davis et al., 2014, Fleeman et al., 2015). However, despite falling in the above mentioned category, thanks to special price agreements specifically tailored to the country context and needs, the pertuzumab + trastuzumab combination in HER2 mBC was supported by HTA recommendations, leading to positive reimbursement decisions in several countries, including Norway (Nye Metoder et al., 2019), UK (NICE, 2018; SMC, 2019)), Ireland (NCPE, 2020), France (HAS, 2019), Germany (G-BA, 2013) and Spain (MSCBS, 2020).

12. Summary of regulatory status and market availability of the medicine

The summary of market availability of pertuzumab has been added to complement the information provided in the 2018 application.

Pertuzumab (PERJETA®) was first granted marketing approval for mBC in the United States (U.S.) on 8 June 2012, which marks the IBD. PERJETA® was approved for use in mBC in the European Union (EU) on 4 March 2013 and in Japan on 28 June 2013.

Pertuzumab (PERJETA®) was granted approval for use in the neoadjuvant eBC setting in the U.S. on 30 September 2013 and in the EU on 28 July 2015, and subsequently for use in the adjuvant eBC setting in the U.S. on 20 December 2017 and EU on 31 May 2018.

As of 7 June 2020, pertuzumab (PERJETA®) has been approved in:

- more than 117 countries worldwide for mBC
- more than 106 countries for neoadjuvant treatment of eBC
- more than 97 counties for adjuvant treatment of eBC

A list of the global marketing authorisations for pertuzumab (PERJETA®) is provided in Appendix 1.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

There are no pharmacopoeial standards specific for pertuzumab. The drug product does comply with the European Pharmacopoeia monographs, “Pharmaceutical Preparations (2619)”, “Parenteral Preparations (0520)”, and “Substances for Pharmaceutical Use (2034)”.

14. Comprehensive reference list and in-text citations

- *American Society of Clinical Oncology. Clinical Practice Guidelines 2018. ASCO; 2018. [Available at: https://www.asco.org/research-guidelines/quality-guidelines/guidelines/breast-cancer]. Access date: November 25, 2020.*
- *Andersson M, López-Vega JM, Petit T, Zamagni C, Donica M, Kamber J, et al. The co-administration of pertuzumab (P) and trastuzumab (T) as a single infusion, followed by vinorelbine (V), in first-line (1L) treatment of HER2-positive locally advanced or metastatic breast cancer (MBC) patients (pts): VELVET study interim analysis [Conference Abstract]. Journal of Clinical Oncology. 2015;33(15_suppl):586.*
- *Andersson M, Lopez-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.*
- *Arnedos M, Gligorov J. St. Gallen International Consensus Guidelines in early breast cancer: experts to prevent patients' overtreatment and breaking the bank? Ann Oncol. 2019;30(10):1533-5.*
- *Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L. Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol. 2011;9(1):16-32.*
- *Attard CL, Pepper AN, Brown ST, Thompson MF, Thuresson PO, Yunger S, et al. Cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer in Canada. J Med Econ. 2015;18(3):173-88.*
- *Babigumira J, Santos E, Antao V, Wang B, Portera C, Kamath T, et al. Projecting the cost-effectiveness of pertuzumab with trastuzumab and docetaxel in the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory or early breast cancer. Journal of Clinical Oncology. 2014;32:642.*
- *Bachelot T, Ciruelos E, Peretz-Yablonski T, Puglisi F, Schneeweiss A, Campone M, et al. First-line pertuzumab (P), trastuzumab (H), and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC): Interim safety results (N=704) from PERUSE [Conference Abstract]. Journal of Clinical Oncology. 2014;32(15_suppl):548.*
- *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.*
- *Baselga J, Cortes 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.*
- *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.*
- *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.*
- *Borg A, Tandon AK, Sigurdsson H, Clark GM, Ferno M, Fuqua SA, et al. HER-2/neu amplification predicts poor survival in node-positive breast cancer. Cancer Res. 1990;50(14):4332-7.*
- *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.*
- *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.*
- *Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC3). Breast. 2017;31:244-59.*
- *Cardoso F., Kyriakides S., Ohno S., Penault-Llorca F., Poortmans P., Rubio I. T., et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019(30): 1194-1220.*

- *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 (ABC5). Annals of Oncology. 2020(12):1623-49.*
- *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.*
- *Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard JY, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol. 2017;28(10):2340-66.*
- *Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol. 2015;26(8):1547-73.*
- *Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. Oncologist. 2003;8(6):514-20.*
- *Cobleigh MA, Vogel CL, Tripathy D, et al. Efficacy and safety of Herceptin (humanized anti-HER2 antibody) as a single agent in 222 women with HER2 overexpression who relapsed following chemotherapy for metastatic breast cancer [Conference Abstract]. Proceedings of the American Society of Clinical Oncology. 1998;17:97a.*
- *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.*
- *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.*
- *Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707-16.*
- *Davis S. Assessing Technologies That Are Not Cost-Effective at a Zero Price [Internet]. London: National Institute for Health and Care Excellence (NICE); 2014 [updated July 2014. Available from: https://www.ncbi.nlm.nih.gov/books/NBK310371/].*
- *Dawood S, Merajver SD, Viens P, Vermeulen PB, Swain SM, Buchholz TA, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol. 2011;22(3):515-23.*
- *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.*
- *European Society for Medical Oncology. ESMO-MCBS Scorecards: Pertuzumab [Internet]: ESMO, 2020. [Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-4-1].*
- *F. Hoffmann-La Roche Ltd. PERJETA® Periodic Benefit-Risk Evaluation Report/ Periodic Safety Update Report. 2018.*
- *F. Hoffmann-La Roche Ltd. PERJETA® CDS version 11: Folleto de Información al Profesional. 2020.*
- *F. Hoffmann-La Roche Ltd. Pherexa Final CSR Report. April 2018. Report No.: 1081437.*
- *F. Hoffmann-La Roche Ltd. PERJETA®/Pertuzumab Periodic Benefit-Risk Evaluation Report/ Periodic Safety Update Report. Period June 8, 2019 to June 7, 2020. Grenzach-Wyhlen, German; August 2020. Report No.: 1101895.*
- *F. Hoffmann-La Roche Ltd. PERJETA® SmPC 2020 [Internet] June 2020 [Available from: https://www.ema.europa.eu/en/documents/product-information/perjeta-epar-product-information_en.pdf].*
- *F. Hoffmann-La Roche Ltd. Pertain Final CSR Report. June 2020. Report No.: 1100067.*
- *F. Hoffmann-La Roche Ltd. Peruse Final CSR Report.; May 2020. Report No.: 1101598.*

- *F. Hoffmann-La Roche Ltd. BO17929 Final Clinical Study Report. n.d. Report No.: 1066980.*
- *F. Hoffmann-La Roche Ltd. NEOSPHERE Final Clinical Study Report. n.d. Report No.: 1062325.*
- *F. Hoffmann-La Roche Ltd. TRYPHAENA Final Clinical Study Report. n.d. Report No.: 1069778.*
- *F. Hoffmann-La Roche Ltd. PERJETA® SmPC 2018 [Internet] October 2018 [Available from: https://www.ema.europa.eu/documents/product-information/PERJETA®-epar-product-information_en-0.pdf].*
- *F. Hoffmann-La Roche Ltd. Cleopatra Final CSR. September 2019. Report No.: 1092200.*
- *Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53.*
- *Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.*
- *Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.*
- *Fleeman N, Bagust A, Beale S, Dwan K, Dickson R, Proudlove C, et al. Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer. Pharmacoeconomics. 2015;33(1):13-23.*
- *Food and Drug Administration. Highlights of prescribing information: PERJETA [Internet]: Food and Drug Administration; 2020 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf].*
- *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.*
- *Gemeinsamer Bundesausschuss. Nutzenbewertung nach § 35a SGB V: Nutzenbewertungsverfahren zum Wirkstoff Pertuzumab (Mammakarzinom, HER2+, Kombination mit Trastuzumab und Docetaxel). Resolution: October 1st, 2013 [Internet]: Gemeinsamer Bundesausschuss; 2013 [Available from: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/65/].*
- *Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(1):25-32.*
- *Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791-800.*
- *Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32(19):2078-99.*
- *Gradishar WJ, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(4):452-78.*
- *Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. NCCN Guidelines Insights Breast Cancer, Version 1.2016. J Natl Compr Canc Netw. 2015;13(12):1475-85.*
- *Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57-70.*
- *Hanna WM, Kwok K. Chromogenic in-situ hybridization: a viable alternative to fluorescence in-situ hybridization in the HER2 testing algorithm. Mod Pathol. 2006;19(4):481-7.*
- *Haute Autorité de Santé. Perjeta [Internet]: Haute Autorité de Santé; 2019 [updated 21 June 2019. Available from: https://www.has-sante.fr/jcms/pprd_2984015/fr/perjeta].*
- *Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol. 2007;25(15):2127-32.*

- *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). Annals of Oncology. 2018;29.*
- *International Agency for Research on Cancer. Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018 [Internet]: International Agency for Research on Cancer; 2018 [updated December 2018. Available from: https://www.iarc.fr/featured-news/latest-global-cancer-data-cancer-burden-rises-to-18-1-million-new-cases-and-9-6-million-cancer-deaths-in-2018].*
- *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 MetaPHER study [Conference Abstract]. Cancer Research. 2020;80(4 Supplement):P1-18-05.*
- *Levi F, Bosetti C, Lucchini F, Negri E, La Vecchia C. Monitoring the decrease in breast cancer mortality in Europe. Eur J Cancer Prev. 2005;14(6):497-502.*
- *Malvezzi M, Arfe A, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2011. Ann Oncol. 2011;22(4):947-56.*
- *Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23(19):4265-74.*
- *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.*
- *Miles D, Schneeweiss A, Peretz-Yablonski T, Ciruelos E, Puglisi F, Easton V, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy in patients ≥ 65 years with HER2-positive locally recurrent/metastatic breast cancer: subgroup analyses of the PERUSE study. [Poster P4-21-07]. 39th Annual San Antonio Breast Cancer Symposium; 2016 December 6-10; San Antonio, TX.*
- *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). Annals of Oncology. 2020;31:S356-S7.*
- *Ministerio de Sanidad Consumo y Bienestar Social. Buscador de la Información sobre la situación de financiación de los medicamentos: Pertuzumab (Perjeta®) [Internet]: Gobierno de Espana; 2020 [Available from: https://www.mscbs.gob.es/profesionales/medicamentos.do?metodo=verDetalle&cn=697235].*
- *National Centre for Pharmacoeconomics Ireland. Pertuzumab (Perjeta®) [Internet]: NCPE Ireland; 2020 [Available from: http://www.ncpe.ie/drugs/pertuzumab-perjeta/].*
- *National Comprehensive Cancer Network. Breast cancer (Version 4, 2020). NCCN; 2020. [Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf]. Access date: November 25, 2020*
- *National Institute for Health and Care Excellence. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer. Technology appraisal guidance [TA509] [Internet]: NICE; 2018 [Available from: https://www.nice.org.uk/guidance/ta509/documents/breast-cancer-her2-positive-metastatic-pertuzumab-with-trastuzumab-and-docetaxel-appraisal-consultation-document].*
- *National Institute for Health and Care Excellence. Single Technology Appraisal: Pertuzumab for adjuvant treatment of early HER2-positive breast cancer [ID1192] [Internet] NICE; 2018 [Available from: https://www.nice.org.uk/guidance/ta569/documents/committee-papers-2].*
- *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.*
- *Nye Metoder. Pertuzumab (Perjeta) [Internet]: Nye Metoder; 2019 [Available from: https://nyemetoder.no/metoder/pertuzumab-perjeta].*

- *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.*
- *Piccart M, Procter M, Fumagalli D, Azambuja E, Clark E, Ewer M, et al. Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer [Conference Abstract]. Cancer Research. 2020;80(4 Supplement):GS1-04.*
- *Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659-72.*
- *Polito L, Shim J, Du Toit Y, et al. Use of pertuzumab in combination with taxanes for HER2+ metastatic breast cancer: Analysis of U.S. electronic health records. [Poster]. 42nd Annual San Antonio Breast Cancer Symposium; 2019 December 10–14; San Antonio, TX.*
- *Pradelli L, Zaniolo O, Caputo A, Roussel M, Tournier C. Cost-Utility Analysis Of Adjuvant Pertuzumab-based Regimen In Women With HER2-Positive Breast Cancer In Italy [Conference Abstract]. Value in Health. 2018;21:S45.*
- *Rimawi M, Ferrero JM, de la Haba-Rodriguez 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.*
- *Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84.*
- *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.*
- *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.*
- *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. International Journal of Cancer. 2003;106(3):416-22.*
- *Schleich W, Tournier C, Campagnoli E, Era S. 1225 Potential long-term cost savings due to significant clinical benefit of pertuzumab in combination with trastuzumab for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer. European Journal of Cancer. 2015;51:S180-S1.*
- *Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013;24(9):2278-84.*
- *Shulman LN, Willett W, Sievers A, Knaul FM. Breast cancer in developing countries: opportunities for improved survival. J Oncol. 2010;2010:595167.*
- *Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Rolski J, et al. Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC→T) with Doxorubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab (AC→TH) with Docetaxel, Carboplatin and Trastuzumab (TCH) in Her2neu Positive Early Breast Cancer Patients: BCIRG 006 Study [Conference Abstract]. Cancer Research. 2009;69(24 Supplement):62.*
- *Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-92.*
- *Sundaresan S, Penuel E, Sliwkowski MX. The biology of human epidermal growth factor receptor 2. Curr Oncol Rep. 1999;1(1):16-22.*

- *Surveillance Epidemiology and End Results Incidence Data,1975-2017 [Internet]. National Cancer Institute. Bethesda, MD. 2020 [cited November 23, 2020]. Available from: https://seer.cancer.gov/data/.*
- *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.*
- *Swain SM, Ewer MS, Viale G, Delaloge S, Ferrero JM, Verrill M, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol. 2018;29(3):646-53.*
- *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.*
- *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.*
- *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.*
- *von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-31.*
- *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.*
- *Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018;36(20):2105-22.*
- *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.*
- *World Health Organization. Second WHO model list of essential in vitro diagnostics (WHO/MVP/EMP/2019.05). World Health Organization; 2019a. [Available from: https://who.int/medical_devices/publications/EDL_2_0_Standalone.pdf?ua=1].*
- *World Health Organization. The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). WHO Technical Report Series, No. 1021. World Health Organization; 2019b. [Available from: https://apps.who.int/iris/bitstream/handle/10665/330668/9789241210300-eng.pdf?ua=1].*
- *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.*

Appendix 1

Table A1. Summary of regulatory status and market availability of PERJETA®

	Country	Worldwide market approvals
	Albania	29 March 2016
	Algeria	7 January 2018
	Argentina	25 April 2013
	Armenia	31 January 2013
	Aruba	27 September 2000
	Australia	2 May 2013
	Austria	4 March 2013
	Azerbaijan	13 December 2013
	Bahrain	8 July 2013
	Bangladesh	29 June 2014
	Belarus	25 March 2014
	Belgium	4 March 2013
	Bolivia (Plurinational State of)	18 September 2013
	Bosnia-Herzegovina	30 May 2014
	Brazil	27 May 2013
	Brunei Darussalam	6 June 2018
	Bulgaria	4 March 2013
	Canada	12 April 2013
	Chile	21 October 2013
	China	17 December 2018
	Colombia	26 June 2014
	Costa Rica	3 April 2013
	Croatia	4 March 2013
	Cuba	7 January 2014
	Curacao	23 July 2013
	Cyprus	4 March 2013
	Czech Republic	4 March 2013
	Denmark	4 March 2013
	Dominican Republic	20 May 2013
	Ecuador	22 January 2013
	Egypt	31 December 2015
	El Salvador	20 July 2013
	Estonia	4 March 2013
	Finland	4 March 2013
	France	4 March 2013

	Country	Worldwide market approvals
	Georgia	29 March 2016
	Germany	4 March 2013
	Ghana	29 May 2020
	Greece	4 March 2013
	Guatemala	15 July 2013
	Honduras	9 March 2013
	Hong Kong	8 April 2014
	Hungary	4 March 2013
	Iceland	4 March 2013
	India	27 April 2015
	Indonesia	31 October 2016
	Ireland	4 March 2013
	Israel	10 February 1203
	Italy	4 March 2013
	Jamaica	19 February 2015
	Japan	28 June 2013
	Jordan	29 December 2015
	Kazakhstan	14 August 2015
	Kyrgyzstan	19 April 2019
	Republic of Korea	29 May 2013
	Kosovo	31 January 2013
	Kuwait	6 February 2013
	Latvia	4 March 2013
	Lebanon	3 July 2014
	Lithuania	4 March 2013
	Luxembourg	4 March 2013
	Macao	15 May 2014
	Macedonia	16 July 2013
	Malaysia	29 November 2013
	Malta	4 March 2013
	Mauritius	23 May 2017
	Mexico	19 September 2012
	Republic of Moldova	24 February 2014
	Montenegro	10 March 2014
	Morocco	2 August 2017
	Myanmar	6 February 2015
	Namibia	21 March 2019

	Country	Worldwide market approvals
	Netherlands	4 March 2013
	New Zealand	28 June 2013
	Nicaragua	17 September 2014
	Nigeria	13 May 2019
	Norway	4 March 2013
	Oman	15 February 2015
	Pakistan	20 December 2017
	Palestine, State of	4 June 2018
	Panama	13 February 2014
	Paraguay	20 September 2013
	Peru	27 March 2014
	Philippines	16 October 2013
	Poland	4 March 2013
	Portugal	4 March 2013
	Qatar	9 May 2013
	Romania	4 March 2013
	Russian Federation	21 August 2015
	Saudi Arabia	21 September 2014
	Serbia	27 December 2013
	Singapore	5 February 2014
	Sint Maarten	9 March 2016
	Slovakia	4 March 2013
	Slovenia	4 March 2013
	South Africa	25 March 2019
	Spain	4 March 2013
	Sri Lanka	9 October 2019
	Sweden	4 March 2013
	Switzerland	13 August 2012
	Syrian Arab Republic	2 May 2016
	Taiwan	14 June 2013
	Thailand	24 January 2014
	Trinidad & Tobago	14 April 2015
	Tunisia	23 April 2019
	Turkey	18 February 2016
	Turkmenistan	2 May 2014
	Ukraine	20 January 2014
	United Arab Emirates	10 November 2016

	Country	Worldwide market approvals
	United Kingdom	4 March 2013
	United States of America	8 June 2012
	Uruguay	26 December 2012
	Uzbekistan	8 July 2016
	Bolivarian Republic of Venezuela	30 October 2014
	Vietnam	27 March 2017
	Zimbabwe	17 September 2019

Appendix 2

Supportive information: Benefit of pertuzumab in early breast cancer (eBC)

In its 2019 assessment, the WHO Expert Committee concluded on a lack of mature clinical evidence and conclusive meaningful survival benefit of pertuzumab in the early disease stage (World Health Organization; 2019b).

While this year's submission is seeking the inclusion of pertuzumab in the WHO EML as first-line treatment of mBC only, the evidence below is nevertheless considered useful as supportive information to enable the Expert Committee having a comprehensive review of the value and actual use of pertuzumab worldwide in eBC.

1. Introduction

In addition to mBC, pertuzumab is also indicated for the treatment of HER2-positive eBC (PERJETA® SmPC 2020):

Pertuzumab is indicated for use in combination with trastuzumab and chemotherapy in:

- the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.
- the adjuvant treatment of adult patients with HER2-positive eBC at high risk of recurrence.

2. Treatment, administration requirements, monitoring facilities and skills

In eBC, pertuzumab can be used in neoadjuvant or adjuvant settings as part of a complete regimen for eBC treatment. Neoadjuvant treatment usually foresees 3 to 6 cycles in combination with trastuzumab and chemotherapy. In the adjuvant protocol pertuzumab should be administered in combination with trastuzumab for a total of 1 year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first) as part of a complete regimen for eBC and regardless of the timing of surgery. Treatment should include standard anthracycline- and/or taxane-based chemotherapy. Pertuzumab and trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (PERJETA® SmPC 2020).

3. Reference to existing clinical guidelines

3.1 International Clinical Guidelines also recommend use of pertuzumab in the eBC setting: Neoadjuvant SoC for patients with T >2 cm and/or N+ disease is pertuzumab + trastuzumab + chemotherapy

ESMO Guidelines for eBC (2019) (Cardoso et al., 2019):

- Dual blockade with trastuzumab–pertuzumab can be considered in high-risk patients (node-positive or ER-negative) for 1 year, starting before or after surgery [I, A; ESMO-MCBS v1.1 score: B].

AGO Guidelines (2020) (Ditsch et al., 2020):

- If chemotherapy is indicated, systemic treatment before surgery (neoadjuvant) should be preferred. Pertuzumab plus trastuzumab in combination with chemotherapy is recommended for patients at high risk of recurrence (node positive AGO++).

St. Gallen Guidelines (2019) (Arnedos and Gligorov, 2019):

- Neoadjuvant systemic therapy is the preferred initial approach in stage 2 or 3 HER2-overexpressing or triple-negative breast cancer. Chemotherapy in combination with trastuzumab and pertuzumab is the preferred approach for stage 2 or 3 HER2-positive tumours in adjuvant and neoadjuvant settings.

NCCN Breast Cancer Guidelines (v4 – 2020) (NCCN, 2020):

- Patients with HER2-positive tumours should be treated with preoperative systemic therapy incorporating trastuzumab. A pertuzumab-containing regimen may be administered preoperatively to patients with ≥T2 or ≥N1, HER2-positive eBC.

3.2 Adjuvant continuation of pertuzumab + trastuzumab to complete 18 cycles in the adjuvant setting for patients who achieve a pathologic complete response (pCR):

ESMO Guidelines for eBC (2019) (Cardoso et al., 2019):

- Grade A recommendation.
- If pCR: Complete up to 1 year of HER2-targeted therapy with trastuzumab ± pertuzumab for cases initially node-positive or hormone receptor-negative.

AGO Guidelines (2020):

- If pCR: Pertuzumab + trastuzumab for patients at high risk disease (node-positive) to complete 12 months (LoE 2b).

St. Gallen Guidelines (2019) (Arnedos and Gligorov, 2019):

- If pCR: Adjuvant trastuzumab or trastuzumab plus pertuzumab as originally offered in the patient's initial neoadjuvant systemic treatment regimen.

NCCN Breast Cancer Guidelines (v4 – 2020):

- Category 1 listing. If pCR or no preoperative therapy (or if T-DM1 is discontinued in the event of toxicity): Complete up to 1 year (18 cycles) of HER2-targeted therapy with trastuzumab ± pertuzumab.

4. Medical need and likely impact of improving treatment of HER2-positive breast cancer

In the eBC setting, surgery is the main modality of local treatment for breast cancer, and surgery and/or radiotherapy can control loco-regional disease in the majority of patients. Neoadjuvant therapy is given prior to surgery and has become a standard treatment option for many patients with newly diagnosed breast cancer. Neoadjuvant therapy is the primary modality of therapy for patients with inflammatory breast cancer, regardless of tumour size (Dawood 2011). Although improvements have been made, many patients with HER2-positive eBC still relapse after standard of care with trastuzumab and chemotherapy. New active agents are therefore urgently required for patients with HER2-positive eBC, when the disease is still localised to the breast and regional lymph nodes, to offer the chance of potentially curing the disease, as well as delaying disease recurrence and death in those who are not cured.

5. Selection of clinical evidence to support application for inclusion of pertuzumab for the treatment of HER2-positive eBC

Pertuzumab benefits from indications in the eBC setting, where it is recommended by international clinical guidelines. Data summaries from key clinical trials in this setting are provided as additional supporting evidence for the comprehensive role of pertuzumab + trastuzumab in HER2-positive breast cancer.

6. Summary of Data

The main sources of evidence for efficacy in the eBC setting are: Phase II Studies WO20697 (NEOSPHERE) and BO22280 (TRYPHAENA) in the neoadjuvant setting, Phase III Study BO25126 (APHINITY) in the adjuvant setting, including an updated analysis.

6.1 Neoadjuvant Treatment of Locally Advanced, Inflammatory, or Early-Stage Breast Cancer: Study WO20697 (NEOSPHERE) (Gianni 2012, Gianni 2016)

The efficacy of pertuzumab as neoadjuvant treatment was demonstrated in Study WO20697, a multicentre, randomised, open-label, Phase II study conducted in patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer. A total of 417 patients were enrolled at sites in 16 countries. The primary efficacy endpoint was rate of breast pathologic Complete Response (bpCR), defined as the proportion of patients with an absence of invasive neoplastic cells in the breast following primary systemic therapy (*in situ* disease might remain; nodal status not considered), also known as ypT0/is. Secondary efficacy endpoints included clinical response rate, time to clinical response and Breast-Conserving Surgery (BCS) rate.

Patients were randomised in a 1:1:1:1 ratio to one of four neoadjuvant regimens:

Trastuzumab + docetaxel (n = 107), pertuzumab + trastuzumab + docetaxel (n = 107), pertuzumab + trastuzumab (n = 107), or pertuzumab + docetaxel (n = 96). Randomisation was stratified by neoadjuvant/adjuvant treatment and geographic region.

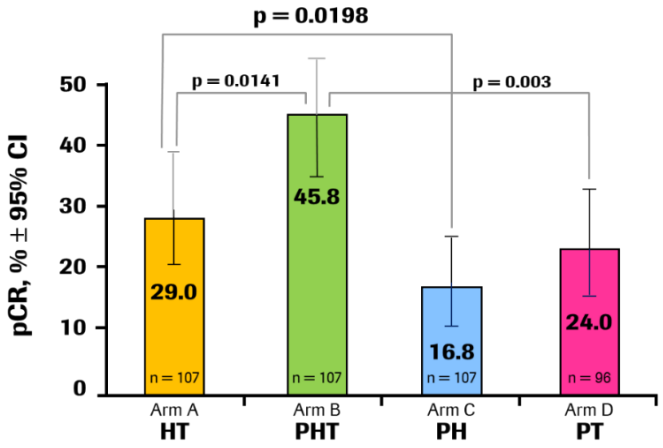
Prior to surgery, patients received treatment by IV infusion every 3 weeks for four cycles. Pertuzumab was given at an initial dose of 840 mg, followed by doses of 420 mg. Trastuzumab was given at an initial dose of 8 mg/kg, followed by doses of 6 mg/kg. Docetaxel was given at an initial dose of 75 mg/m^2 and escalated if tolerated to 100 mg/m^2.

After surgery, all patients received 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), cyclophosphamide (600 mg/m^2) (FEC) in combination with trastuzumab. FEC was given by IV infusion every 3 weeks for three cycles, and trastuzumab was given by IV infusion every 3 weeks for 1 year total After surgery but prior to FEC, patients in the pertuzumab + trastuzumab arm received docetaxel every 3 weeks for four cycles, so that all patients received equivalent cumulative doses of chemotherapeutic agents and trastuzumab.

Demographic and baseline characteristics were generally well balanced among the treatment groups. Overall, 7% of patients had inflammatory breast cancer, 32% had locally advanced breast cancer, and 61% had operable breast cancer. Approximately half of the patients in each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR-positive disease).

The efficacy results for the primary endpoint (9 March 2012 clinical cut-off date) are summarised in Figure A2.1. A statistically significant and clinically meaningful improvement in bpCR rate (ypT0/is) was observed in patients receiving pertuzumab + trastuzumab + docetaxel compared with patients receiving trastuzumab + docetaxel as neoadjuvant therapy (45.8% vs. 29.0%, p = 0.0141). A consistent pattern of results was observed regardless of pCR definition, with a higher tpCR (ypT0/is N0) rate also reported in patients receiving pertuzumab + trastuzumab + docetaxel compared with trastuzumab + docetaxel (39.3% vs. 21.5%).

Figure A2.1. Study WO20687: Efficacy Results (Primary Analysis)



(H = trastuzumab; P = pertuzumab; pCR = pathological complete response; T = docetaxel)

bpCR rates were lower in the subgroup of patients with hormone receptor-positive disease (ranging from 5.9% to 26.0% among the four arms) than in the subgroup with hormone receptor-negative disease (ranging from 27.3% to 63.2%), but the difference in pCR still favoured pertuzumab + trastuzumab + docetaxel compared with trastuzumab + docetaxel.

The overall PFS (defined as the time from the date of randomisation to the first documentation of progressive disease or death, equivalent to the commonly recognised definition of Event-Free Survival, EFS) and Disease-Free Survival (DFS) results from the 5-year analysis for Study WO20697 are consistent with and supportive of the benefit shown from the addition of pertuzumab to trastuzumab plus docetaxel in the primary analysis of pCR (regardless of the definition of pCR used). The main efficacy findings from the 5-year analysis are as follows:

- In the PFS (as defined above) and DFS analyses, point estimates for hazard ratios were 0.69 (0.34, 1.40) and 0.60 (0.28, 1.27), respectively, indicating a lower risk of PFS and DFS events in the pertuzumab + trastuzumab + docetaxel arm compared with the trastuzumab + docetaxel arm.

- Subgroup analyses were consistent with overall PFS and DFS results.

In conclusion, these findings support the use of pertuzumab in combination with neoadjuvant trastuzumab and docetaxel in HER2-positive eBC.

6.2 Neoadjuvant Treatment of HER2-positive locally advanced, inflammatory, or early-stage breast cancer: Study BO22280 (TRYPHAENA) (Schneeweiss 2013)

Supportive evidence for the efficacy of pertuzumab as neoadjuvant treatment was provided in Study BO22280, a multicentre, randomised, open-label, Phase II study conducted in patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer. A total of 225 patients were enrolled at sites in 19 countries. The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study. The key efficacy endpoint was pCR rate (ypT0/is). Additional efficacy endpoints included clinical response rate, time to clinical response, Breast-Conserving Surgery (BCS) rate, DFS, PFS, and OS.

Patients were randomised in a 1:1:1 ratio to receive one of three neoadjuvant regimens: three cycles of pertuzumab + trastuzumab + FEC followed by three cycles of pertuzumab + trastuzumab + docetaxel (Ptz + T + FEC/Ptz + T + D), three cycles of FEC followed by three cycles of pertuzumab + trastuzumab + docetaxel (FEC/Ptz + T + D), or six cycles of carboplatin + pertuzumab + trastuzumab + docetaxel (C + Ptz + T + D).

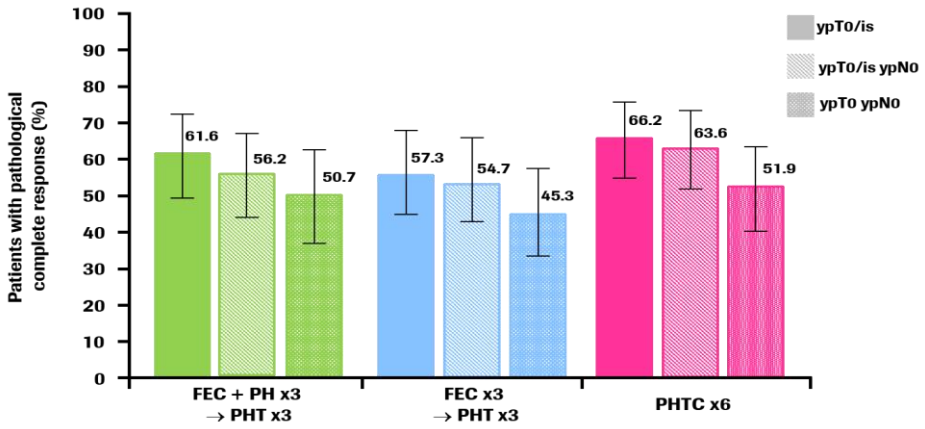
Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and hormone receptor status (ER- and/or PgR-positive vs. ER- and PgR-negative).

Prior to surgery, patients received treatment by IV infusion every 3 weeks for six cycles. Pertuzumab was given at an initial dose of 840 mg, followed by doses of 420 mg. Trastuzumab was given at an initial dose of 8 mg/kg, followed by doses of 6 mg/kg. FEC consisted of 5-fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2). Docetaxel was given at an initial dose of 75 mg/m^2, with the option to escalate to 100 mg/m^2 at the investigator's discretion in the Ptz + T + FEC/Ptz + T + D and FEC/Ptz + T + D arms (no escalation in the carboplatin + pertuzumab + trastuzumab + docetaxel arm). The carboplatin dose was calculated using the Calvert formula (AUC 6). After surgery, all patients received trastuzumab by IV infusion q3w for 1-year total.

Demographic and baseline characteristics were generally well balanced among the treatment groups. Overall, 6% of patients had inflammatory breast cancer, 25% had locally advanced breast cancer, and 69% had operable breast cancer. Approximately half of the patients in each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR-positive disease).

High pCR rates were observed in all three treatment arms (Figure A2.2). A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive disease (ranging from 46.2% to 50.0% in the three arms) than in patients with hormone receptor-negative disease (ranging from 65.0% to 83.8%).

Figure A2.2. Study BO22280: Efficacy Results (Primary Analysis)



(C = carboplatin; FE =, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P = pertuzumab; pCR = pathological complete response; T = docetaxel).

6.3 Adjuvant Treatment of eBC with a High Risk of Recurrence: Study BO25126 (APHINITY) (von Minckwitz et al., 2017)

Pertuzumab was approved for the adjuvant treatment of eBC at high risk of recurrence based on data from the pivotal study, BIG 4-11/BO25126/TOC4939g (APHINITY) (von Minckwitz 2017). Study BO25126 was a randomised multicentre, double blind, placebo-controlled comparison of chemotherapy + trastuzumab + pertuzumab (Ptz + T + Chemo) vs. trastuzumab + placebo + chemotherapy (Pla + T + Chemo) as adjuvant therapy in patients with operable HER2-positive primary breast cancer.

The primary efficacy endpoint in Study BO25126 was invasive disease-free survival (IDFS), defined as time from randomisation to ipsilateral invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, or death due to any cause. IDFS is the considered to be most accurate efficacy measure

in adjuvant setting and as such was broadly adopted in newly designed adjuvant studies. Of note, this definition does not include Second Primary Non-Breast Cancers (SPNBCs) as events. In this way, the definition of IDFS used in Study BO25126 differed from the definition of IDFS recommended by the National Cancer Institute (NCI) working group in 2007 (Hudis 2007). The rationale for excluding SPNBCs is based on consideration that these events are not related to breast cancer disease or study treatment under investigation to treat breast cancer and as such have potential to dilute treatment effect under investigation. However, IDFS according to the NCI working group definition (i.e., including second primary non-breast cancers as events [IDFS-SPNBC]) was evaluated as a secondary endpoint in the study. Other efficacy endpoints were: DFS, OS, Recurrence-Free Interval (RFI), Distant Recurrence-Free Interval (DRFI). These are standardly used in oncology studies to assess the efficacy. Other secondary endpoints were cardiac safety, overall safety, and Health-Related Quality of Life (HRQoL). The primary analysis was conducted when 379 IDFS events were reported.

A total of 4,805 patients were enrolled and randomised in a 1:1 ratio to one of two treatment arms: Pertuzumab + trastuzumab plus chemotherapy (Ptz + T + Chemo; n = 2,400) or placebo + trastuzumab plus chemotherapy (Pla + T + Chemo; n = 2,405). Pertuzumab was given by IV infusion at an initial dose of 840 mg, followed q3w thereafter by a dose of 420 mg. Placebo was given according to the same schedule as pertuzumab. trastuzumab was given by IV infusion at an initial dose of 8 mg/kg, followed q3w thereafter by a dose of 6 mg/kg. Investigators' choice of trastuzumab -containing adjuvant chemotherapy for early stage breast cancer could be either with an anthracycline-containing regimen or a non-anthracycline-containing regimen, administered for 6–8 cycles. Full details regarding the dosage and administration of the chemotherapy regimens are summarised in Table A2.1.

Table A2.1. Study BO25126: Protocol Approved Chemotherapy Regimens

REGIMEN	DOSE	FREQUENCY
Anthracycline therapy: FEC (or FAC) → T		
3 or 4 cycles x FEC (or FAC) → 3 or 4 cycles x docetaxel	F: 500 to 600mg/m² E: 90 to 120mg/m² or A: 50mg/m² C: 500 to 600mg/m²	Q3W
	Followed by: Docetaxel: 100mg/m² OR Docetaxel: 75mg/m² for 4 cycles [a] OR Docetaxel: 75mg/m² in the first cycle, escalating to 100mg/m² in subsequent cycles	Q3W Q3W Q3W
3 or 4 cycles x FEC (or FAC) → 12 weekly cycles of paclitaxel	F: 500 to 600mg/m² E: 90 to 120mg/m² or A: 50mg/m² C: 500 to 600mg/m²	Q3W
	Followed by: Paclitaxel: 80mg/m²	q1w
Anthracycline therapy: AC (or EC) → T		
4 cycles x AC [b] (or EC) → 3 or 4 cycles x docetaxel	A: 60mg/m² or E: 90 to 120mg/m² C: 500 to 600mg/m²	Q3W
	Followed by: Docetaxel: 100mg/m² OR Docetaxel: 75mg/m² for 4 cycles [a] OR Docetaxel: 75mg/m² in the first cycles, escalating to 100mg/m² in subsequent cycles	Q3W
4 cycles x AC [b] (or EC) → 12 weekly cycles of paclitaxel	A: 60mg/m² or E: 90 to 120mg/m² C: 500 to 600mg/m²	Q3W
	Followed by: Paclitaxel: 80mg/m²	q1w

Cont. Table A2.1. Study BO25126: Protocol Approved Chemotherapy Regimens

Non-Anthracycline therapy: Docetaxel/carboplatin as in BCIRG 006 [c]		
6 x docetaxel plus carboplatin	Docetaxel: 75 mg/m^2 Carboplatin: AUC 6 (900-mg maximum dose)	Q3W

A = doxorubicin; AUC = area under the curve; C = cyclophosphamide, E = epirubicin, F = 5-fluorouracil; T = taxane; q1w = every week; Q3W = every 3 weeks.

[a] If docetaxel 75 mg/m^2 was used and not escalated to 100mg/m^2, then 4 cycles had to be given.

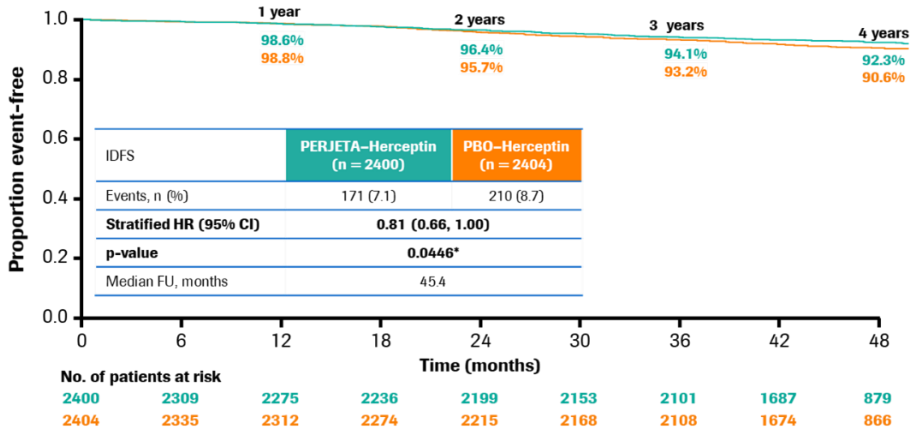
[b] EC or AC could be given at the same dose (A: 60mg/m^2 or E: 90 to 120mg/m^2) every 2 weeks (dose dense) with G-CSF support, for a total of 4 cycles.

[c] Phase III randomized Herceptin (H) trial comparing AC→T with AC→TH and with TCH in the adjuvant treatment of node positive and high risk node negative patients with operable breast cancer containing the HER2neu alteration.

The study met its primary endpoint. At the clinical cut-off date, IDFS events had occurred in 171 patients (7.1%) in the Ptz + T + Chemo arm compared with 210 patients (8.7%) in the Pla + T + Chemo arm. Treatment with Ptz + T + Chemo resulted in a statistically significant and clinically meaningful improvement in IDFS, corresponding to a 19% reduction in the risk of relapse or death (HR = 0.81, 95% CI [0.66, 1.00], p = 0.045), as compared with Pla + T + Chemo. Estimates of IDFS event-free rates were 94.1% vs. 93.2% at 3 years and 92.3% vs. 90.6% at 4 years in the Ptz + T + Chemo vs. Pla + T + Chemo arms, respectively. The Kaplan-Meier plot of IDFS is presented in Figure A2.3. On visual inspection, the curves begin to separate around 24 months after randomisation and separation becomes more distinct with further follow-up.

The majority of recurrences were distant and visceral (lungs, liver, and CNS) in both treatment arms. The addition of pertuzumab to trastuzumab and chemotherapy reduced the rate of distant recurrences as first site of recurrence (Ptz + T + Chemo: 112/2400 [4.7%] vs. Pla + T + Chemo: 139/2404 [5.8%]) and at any time in the study (119/2400 [5.0%] vs. 145/2404 [6.0%]).

Figure A2.3. Study BO25126: Efficacy Results (Primary Analysis) - Kaplan-Meier Curve for IDFS



Stratification factors are nodal status and protocol version, intended adjuvant chemotherapy and central hormone receptor status.
* The p-value shown in this table is based on stratification factor data taken from the eCRF. In a sensitivity analysis based on stratification factor data from the IxRS system (FDA Preferred Analysis), the p-value from the stratified log-rank test was 0.0471.
HR was estimated by Cox regression; HR, hazard ratio.

Table A2.2. Study BO25126: Secondary endpoint results

	3-year absolute rates			
	PERJETA–Herceptin n = 2400	Placebo–Herceptin n = 2404	Hazard ratio (95% CI)	p-value
IDFS (primary endpoint), %	94.1	93.2	0.81 (0.66, 1.00)	0.0446
Key secondary efficacy endpoints, %				
IDFS incl. second primary non-BC events (STEEP definition)	93.5	92.5	0.82 (0.68, 0.99)	0.0403
DFS	93.4	92.3	0.81 (0.67, 0.98)	0.0327
OS (first interim analysis)*	97.7	97.7	0.89 (0.66, 1.21)	0.467
DRFI†	95.7	95.1	0.82 (0.64, 1.04)	0.101

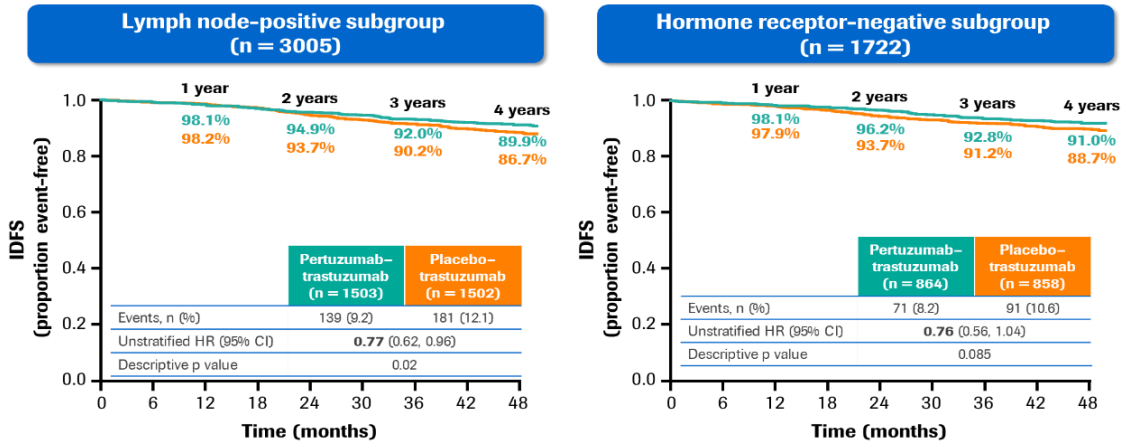
A testing hierarchy was used to control the overall type I error rate of the secondary endpoints at 5%.
* First OS IA at 26% of the target events for the final OS analysis
† DRFI not included in the hierarchical testing procedure
Analyses were based on the ITT population.
DRFI, distant recurrence-free interval; HR, hazard ratio.

Key secondary endpoints showed statistically significant improvement in IDFS including SPNBC (IDFS-SPNBC) and in DFS. The interim OS results numerically favoured patients receiving Ptz + T + Chemo, but with only 26% of the events required for the final planned OS analysis, the data were immature at the primary data cut-off. Overall, the secondary endpoint results were consistent with and supportive of the primary endpoint results (Table A2.2).

Subgroup analysis across multiple, pre-specified, clinically relevant subgroups showed that the IDFS improvements were seen in the great majority of the subgroups. Patients with node-positive disease showed clear benefit with Ptz + T + Chemo treatment with IDFS event-free rates of 91.99% vs. 90.15% at 3 years (HR = 0.77, 95% CI [0.62, 0.96]), indicating a 23% reduction in the risk of recurrence or death, as compared with Pla + T + Chemo (Figure A2.4). The IDFS rates at 4 years were 89.9% vs. 86.7%, respectively. In the low-risk node-negative subgroup, only 3.4% of patients had experienced an IDFS event by the CCOD (HR = 1.13, 95% CI [0.68, 1.86]), compared to 10.6% of patients in the node-positive subgroup. Due to such a small number of events in the node-negative subgroup, the CI for the HR ratio is wide.

Improved IDFS was observed irrespective of the hormone receptor status, but the benefit of adding pertuzumab to trastuzumab and chemotherapy was more marked in patients with hormone receptor-negative disease (HR = 0.76, 95% CI [0.56, 1.04]) than for patients with hormone receptor-positive disease (HR = 0.86, 95% CI [0.66, 1.13]), indicating a 24% and 14% reduction in the risk of recurrence or death, respectively.

Figure A2.4. Study BO25126: Efficacy Results (Primary Analysis) - Kaplan-Meier Curves for IDFS in high-risk subgroups



6.4 APHINITY Updated Analysis: 6 years follow up (Piccart et al., 2019)

A second, pre-planned and time-driven interim analysis for OS, as well as updated pre-planned descriptive IDFS and safety results in APHINITY with a median follow-up of 74 months, were presented at SABCS 2019 (Piccart M 2019).

This analysis was a pre-planned efficacy and safety analysis of APHINITY, based on a time-driven second interim OS analysis and provides descriptive updates of IDFS from the ITT population and in relevant subgroups as well as updates on cardiac safety. The clinical cut-off date for this efficacy analysis was 19 June 2019, 2.5 years after the primary analysis. Definitions of all endpoints were provided in the primary analysis. The median follow-up time is 74.1 months, 28.7 months longer than at the primary analysis (which had a clinical cut-off date of 19 Dec 2016). Patients who received at least one dose of study treatment were included in the safety analysis, according to the treatment given. Primary cardiac events included heart failure or cardiac death; secondary cardiac events included asymptomatic or mildly symptomatic LVEF decrease.

Results showed:

- Fewer deaths in the pertuzumab arm (5.2% vs 6.1%), however statistical significance was not reached at this interim analysis.

- The hazard ratio for overall survival was 0.85; 95% confidence interval (CI) 0.67-1.07; 6-year OS 94.78% vs 93.93% (0.85% difference).

- **The IDFS benefit from pertuzumab has been maintained**
  - IDFS results at primary analysis were: Hazard ratio, 0.81; 95% CI 0.66-1.00; 3-year IDFS 94.1% vs 93.2% (0.9% difference).
  - Current updated IDFS results are: Hazard ratio, 0.76; 95% CI 0.64-0.91; 6-year IDFS 90.6% vs 87.8% (2.8% difference) (Figure A2.5).

- The hazard ratio for the node positive cohort was 0.72; 95% CI 0.59-0.87; 6 years IDFS 87.89% vs 83.36% (with 28% reduction in the risk of recurrence associated with Δ4.5% in IDFS), confirming the benefit of PH in node-positive disease (Figure A2.6).

- With longer follow-up the benefit of pertuzumab is observed regardless of hormone receptor status of the primary tumour (Figure A2.7).

- No new cardiac safety concerns emerged after a median follow up of 74 months.

- Continued follow-up of patients is very important to fully assess OS benefit.

Figure A2.5. APHINITY Updated Analysis: Pertuzumab + trastuzumab + chemotherapy significantly increased IDFS rates for HER2-positive eBC in the adjuvant setting with 6 years' follow-up

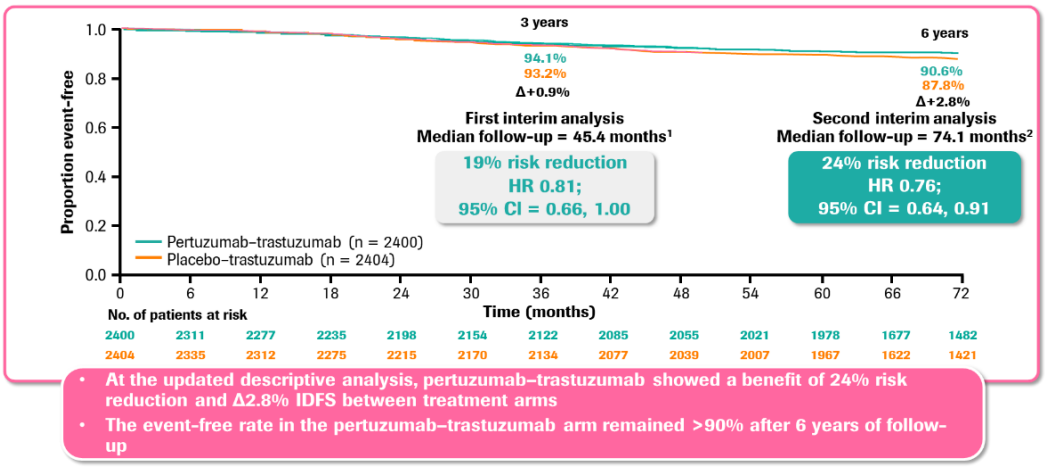


Figure A2.6. APHINITY Updated Analysis: The node-positive subgroup showed the most pronounced IDFS benefit with pertuzumab + trastuzumab

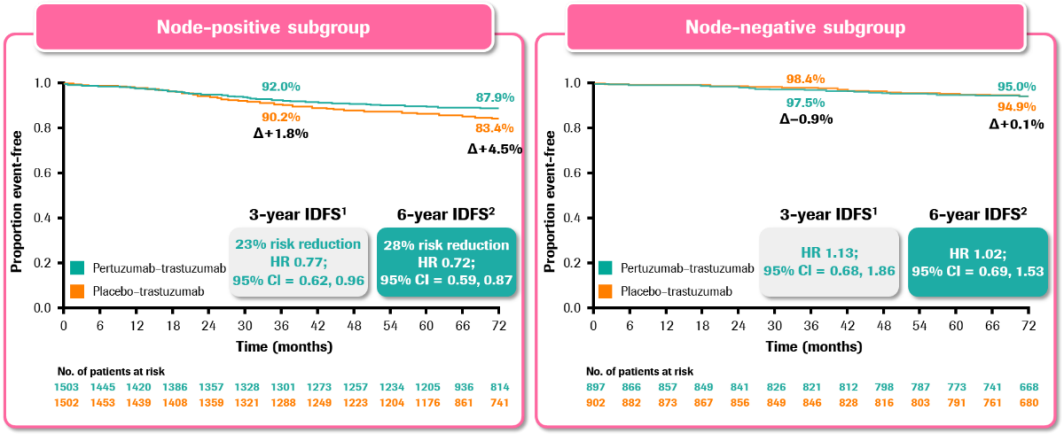
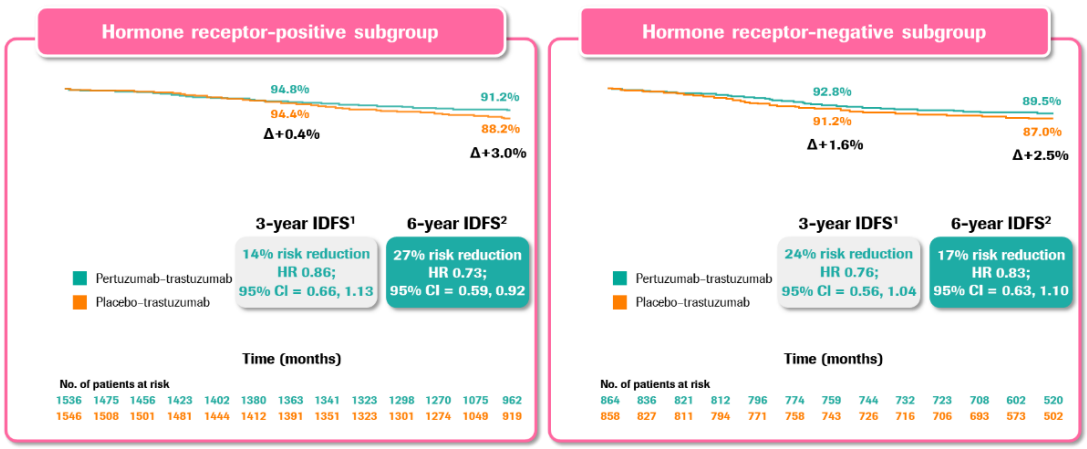


Figure A2.7. APHINITY Updated Analysis: With longer follow-up, the benefit of 18 cycles pertuzumab + trastuzumab was seen in patients at high risk of recurrence, regardless of hormone receptor status



In conclusion, the benefits of comprehensive HER2 blockade using pertuzumab and trastuzumab in the adjuvant setting for patients with node-positive disease observed at the primary analysis are reinforced in the updated analysis of IDFS. The longer-term benefit of pertuzumab no longer appears to depend upon hormone receptor status. No cardiac safety concerns have emerged.

6.5 Neoadjuvant therapy in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer: Study WO29217 (BERENICE) (Swain et al., 2018)

Study WO29217 (BERENICE), is a non-randomised, open-label, multicentre, multinational, Phase II trial including two parallel groups of patients, and was primarily designed to evaluate the cardiac safety of two neoadjuvant anthracycline/taxane-based regimens given in combination with pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (with primary tumours >2 cm in diameter or node-positive disease) who were scheduled to receive neoadjuvant therapy.

The main efficacy endpoint was tpCR (ypT0/is ypN0), other efficacy endpoints included: bpCR, GBG pCR, EFS, iDFS and OS. A total of 397 patients were enrolled at 75 centres; 199 patients to Cohort A and 198 to Cohort B to receive the following treatment:

- **ddAC→ T + PH (Cohort A):** Dose-dense doxorubicin and cyclophosphamide (ddAC) given every 2 weeks (q2w) for four cycles with granulocyte-colony stimulating factor (G-CSF) support as needed according to local guidelines, followed by weekly paclitaxel (T) for 12 weeks, with pertuzumab and trastuzumab (PH) given q3w from the start of paclitaxel (Cohort A).

- **FEC→ D + PH (Cohort B):** 5-fluorouracil, epirubicin and cyclophosphamide (FEC) given q3w for four cycles, followed by docetaxel (D) given q3w for four cycles, with pertuzumab and trastuzumab (PH) given q3w from the start of docetaxel (Cohort B).

Following surgery, patients in both treatment cohorts were to receive further adjuvant pertuzumab and trastuzumab q3w (13 cycles), so that a total of 17 cycles of pertuzumab and trastuzumab therapy were given during the study.

All analyses were descriptive, and no comparisons were made between the efficacy results of the two treatment cohorts.

Although not the primary objective of this study, the assessment of pCR rate in the breast and lymph nodes (tpCR; ypT0/is ypN0) was the key efficacy endpoint. Both treatment regimens were active, with the majority of patients achieving pCR; 61.8% (95% CI: 54.7–68.6) in Cohort A and 60.7% (95% CI: 53.6–67.5) in Cohort B. Both treatment regimens were active both in hormone receptor-positive and hormone receptor-negative patients. However, as has been previously observed for neoadjuvant treatment, pCR rates were higher in those patients with hormone receptor-negative disease than in patients with hormone receptor-positive disease. These results are in line with pCR rates observed in TRYPHAENA following dual HER2 neoadjuvant treatment with pertuzumab and trastuzumab (Schneeweiss et al., 2013).

Exploratory analyses also looked at local pathologist-determined pCR rates in breast and lymph nodes (ypT0/is ypN0). pCR rates in breast and nodes as determined by the local pathologist (63.8% [95% CI: 56.7 − 70.5]) in Cohort A and 61.2% [95% CI: 54.1 − 68.0] in Cohort B) iDFS and OS data were not mature at the time of primary analysis.

7. Characterisation of benefits

7.1 Neoadjuvant treatment of Locally Advanced, Inflammatory, or Early-Stage Breast Cancer

Studies WO20697 (NEOSPHERE) and BO22280 (TRYPHAENA) established the baseline efficacy of pertuzumab in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer as part of an FEC- or carboplatin-containing regimen. The results of the 5-year analysis for Study WO20697 (NEOSPHERE) (Final CSR February 2015, data cut-off 20 October 2014) provide information on PFS and DFS in the pivotal Phase II study in the approved indication of HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (Gianni 2016). The PFS and DFS benefit demonstrated with Ptz + T + D compared with T + D are consistent with and supportive of earlier efficacy analyses that showed a significant improvement in pCR rate with the addition of pertuzumab to neoadjuvant trastuzumab and docetaxel. (Gianni et al., 2016). The neoadjuvant therapy was associated with a bpCR rate of 45.8%, (Gianni et al., 2012), which was similar to reported rates in the Study BO22280 (TRYPHAENA) (Schneeweiss et al., 2013).

The primary analysis of Study WO29217 (BERENICE) (Primary CSR December 2016, data cut-off 3 March 2016) provided information for two neoadjuvant anthracycline/taxane-based regimens given in combination with pertuzumab and trastuzumab (ddAC → T + PH and FEC → D + PH) in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (with primary tumours >2 cm in diameter or node-positive disease) (Swain et al., 2018). Both treatment regimens were active with the majority of patients in both cohorts achieving similar high tpCR rates (61.8% in Cohort A and 60.7% in Cohort B), these results are in line with pCR rates observed in TRYPHAENA (Schneeweiss et al., 2013). The benefit profile of pertuzumab in the neoadjuvant breast cancer setting remains unchanged from that demonstrated by Studies WO20697 (NEOSPHERE) BO22280 (TRYPHAENA) and WO29217 (BERENICE) (Gianni at al., 2012; Schneeweiss et al., 2013; Swain et al., 2018).

7.2 Adjuvant treatment of eBC with a High Risk of Recurrence

Study BO25126 (APHINITY) established the baseline efficacy of pertuzumab in combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive eBC at high risk of recurrence (Von Minckwitz at al., 2017). At the clinical cut-off date, IDFS events had occurred in 171 patients (7.1%) in the Ptz + T + Chemo arm compared with 210 patients (8.7%) in the Pla + T + Chemo arm. Treatment with Ptz + T + Chemo resulted in a statistically significant and clinically meaningful improvement in IDFS, corresponding to a 19% reduction in the risk of relapse or death (HR = 0.81, 95% CI [0.66, 1.00], p = 0.045), as compared with Pla + T + Chemo. Estimates of IDFS event-free rates were 94.1% vs. 93.2% at 3 years and 92. 38% vs. 90.58% at 4 years in the Ptz + T + Chemo vs. Pla + T + Chemo arms, respectively (Von Minckwitz at al., 2017). Results from secondary endpoints were consistent with the primary endpoint results and supportive of the clinical benefit of Ptz + T + Chemo vs. Pla + T + Chemo. The efficacy data in the APHINITY study supports the adjuvant treatment of patients with HER2-positive eBC with Ptz + T + Chemo. After longer follow up, an additional interim analysis at 6 years confirmed the benefit of pertuzumab for all N + patients in the eBC setting, with no new safety signals.

8. Evidence on safety

8.1 Left ventricular dysfunction

In NEOSPHERE, in which patients received four cycles of pertuzumab as neoadjuvant treatment, the incidence of LVD (during the overall treatment period) was higher in the pertuzumab, trastuzumab and docetaxel-treated group (7.5%) compared to the trastuzumab and docetaxel-treated group (1.9%). There was one case of symptomatic LVD in the pertuzumab and trastuzumab -treated group.

In TRYPHAENA, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with pertuzumab + trastuzumab + 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by pertuzumab + trastuzumab + docetaxel; 9.3% in the group treated with pertuzumab + trastuzumab + docetaxel following FEC; and 6.6% in the group treated with pertuzumab in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with pertuzumab + trastuzumab + docetaxel following FEC (this excludes a patient that experienced symptomatic LVD during FEC treatment prior to receiving pertuzumab plus trastuzumab + docetaxel) and also 1.3% in the group treated with pertuzumab in combination with TCH. No patients in the group treated with pertuzumab + trastuzumab and FEC followed by pertuzumab + trastuzumab + docetaxel experienced symptomatic LVD.

In the neoadjuvant period of the BERENICE trial, the incidence of NYHA Class III/IV symptomatic LVD (congestive heart failure according to NCI-CTCAE v.4) was 1.5% in the group treated with dose dense AC followed by pertuzumab + trastuzumab and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by pertuzumab in combination with trastuzumab and docetaxel. The incidence of asymptomatic LVD (PT ejection fraction decrease according to NCI-CTCAE v.4) was 7% in the group treated with dose dense AC followed by pertuzumab + trastuzumab and paclitaxel and 3.5% in the group treated with FEC followed by pertuzumab + trastuzumab and docetaxel.

In APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to <50% was <1% (0.6% of pertuzumab -treated patients vs 0.2% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 46.7% of pertuzumab -treated patients and 66.7% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. The majority of the events were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10%-points from baseline and to <50% were reported in 2.7% of pertuzumab -treated patients and 2.8% of placebo-treated patients, of whom 79.7% of pertuzumab -treated patients and 80.6% of placebo-treated patients had recovered at the data cutoff (PERJETA® CDS version 11).

8.2 Hypersensitivity reactions/anaphylaxis

In NEOSPHERE, two patients in the pertuzumab and docetaxel-treated group experienced anaphylaxis. In both TRYPHAENA and APHINITY, the overall frequency of hypersensitivity/anaphylaxis was highest in the pertuzumab and TCH treated group (13.2% and 7.6% respectively), of which 2.6% and 1.3% of events, respectively were NCI-CTCAE Grade 3-4 (PERJETA® CDS version 11).

9. HER2-positive eBC evidence

Evidence of safety in the eBC setting are: Phase II Studies WO20697 (NEOSPHERE) and BO22280 (TRYPHAENA), Phase II study WO29217 (BERENICE) and Phase III Study BO25126 (APHINITY).

9.1 Study NEOSPHERE (Gianni at al., 2012; Final Clinical Study Report No 1062325, 2015)

In the completed Phase II study WO20697 (NEOSPHERE; N = 417), the most frequently occurring AEs during neoadjuvant treatment were alopecia, neutropenia, diarrhoea, nausea, fatigue, rash and mucosal inflammation (Table A2.3). The overall safety profile of pertuzumab, trastuzumab and docetaxel (Arm B) was comparable to that of trastuzumab plus docetaxel (Arm A). The tolerability of pertuzumab plus docetaxel (Arm D) was also broadly comparable to that of Arm B. Patients receiving trastuzumab and pertuzumab only (Arm C) reported fewer AEs across most body systems compared to patients who also received chemotherapy. At the final clinical cut-off date, the safety profile observed was consistent with what has been previously reported for the neoadjuvant, adjuvant and post-treatment follow-up periods, indicating

that the combination of trastuzumab, pertuzumab and docetaxel was generally well tolerated (Table A2.4). In addition, no late safety concerns (including delayed cardiac toxicity) have emerged.

Table A2.3. Study WO20697: Summary of 10 most common adverse events in neoadjuvant phase

Patients n, (%)	Arm A **HT** (n = 107)	Arm B **PHT** (n = 107)	Arm C **PH** (n = 108)	Arm D **PT** (n = 94)
Alopecia	70 (65)	68 (64)	1 (1)	63 (67)
Neutropenia	67 (63)	54 (50)	1 (1)	59 (63)
Diarrhoea	36 (34)	49 (46)	30 (28)	51 (54)
Nausea	39 (36)	41 (38)	15 (14)	34 (36)
Fatigue	29 (27)	28 (26)	13 (12)	24 (26)
Rash	23 (21)	28 (26)	12 (11)	27 (29)
Mucosal inflammation	23 (21)	28 (26)	3 (3)	24 (26)
Myalgia	24 (22)	24 (22)	10 (9)	19 (20)
Asthenia	19 (18)	22 (21)	3 (3)	15 (16)
Headache	12 (11)	12 (11)	15 (14)	12 (13)

(P = pertuzumab, H = trastuzumab, T = docetaxel)

Table A2.4. Study WO20697: Tolerability of neoadjuvant and adjuvant treatment – 10 common grade ≥3 AEs (safety population)

	Neoadjuvant				Adjuvant			
Patients, n (%)	**HT** (n = 107)	**PHT** (n = 107)	**PH** (n = 108)	**PT** (n = 94)	**HT** (n = 103)	**PHT** (n = 102)	**PH** (n = 94)	**PT** (n = 88)
Neutropenia and granulocytopenia	62 (57.9)	49 (45.8)	1 (0.9)	54 (57.4)	24 (23.3)	25 (24.5)	45 (47.9)	21 (23.9)
Febrile neutropenia	8 (7.5)	9 (8.4)	0	7 (7.4)	3 (2.9)	3 (2.9)	5 (5.3)	10 (11.4)
Diarrhoea	4 (3.7)	6 (5.6)	0	4 (4.3)	0	1 (1.0)	3 (3.2)	1 (1.1)
Asthenia	0	2 (1.9)	0	2 (2.1)	1 (1.0)	0	3 (3.2)	1 (1.1)
Rash	2 (1.9)	2 (1.9)	0	1 (1.1)	–	–	–	–
Drug hypersensitivity	0	1 (0.9)	2 (1.9)	0	–	–	–	–
ALT increased	3 (2.8)	0	0	1 (1.1)	–	–	–	–
Vomiting	–	–	–	–	3 (2.9)	0	1 (1.1)	2 (2.3)
Nausea	–	–	–	–	2 (1.9)	1 (1.0)	1 (1.1)	0
Radiation skin injury	–	–	–	–	2 (1.9)	2 (2.0)	2 (2.1)	0

Conclusion: For NEOSPHERE trial, the final safety profile for the overall study period was consistent with the safety profiles previously reported for the neoadjuvant, adjuvant and post-treatment follow-up periods, indicating that the combination of trastuzumab, pertuzumab and docetaxel was generally well tolerated. No new safety signals were identified and despite a median duration of time on study (including post-treatment follow-up) of approximately 5 years, no late safety concerns (including delayed cardiac toxicity) have emerged.

9.2 Study TRYPHAENA (Schneeweiss at al., 2013; Final Clinical Study Report No 1069778, 2016)

In the completed Phase II study BO22280 (TRYPHAENA; N = 223), where neoadjuvant trastuzumab and pertuzumab were given in addition to commonly used anthracycline-based or carboplatin-based chemotherapy neoadjuvant regimens, the most common AEs were diarrhoea, alopecia, nausea, neutropenia, vomiting, fatigue, anaemia, dyspepsia and thrombocytopenia (Table A2.5).

Table A2.5. Study BO22280: Overview of Cardiac Safety Data during the Neoadjuvant, Adjuvant and the Post-Treatment Periods

Patients, n (%)	FEC + PH x3 → PHT x3	FEC x3 → PHT x3	PHTC x6
Neoadjuvant treatment period	**n = 72**	**n = 75**	**n = 76**
LVSD (all grades)	4 (5.6)	3 (4.0)	2 (2.6)
Symptomatic LVSD (grade ≥3, SAE)	0 (0.0)	2 (2.7)	0 (0.0)
LVEF decline ≥10% from baseline to <50%	4 (5.6)	4 (5.3)	3 (3.9)
Adjuvant treatment period	**n = 68**	**n = 65**	**n = 67**
LVSD (all grades)	4 (5.9)	5 (7.7)	3 (4.5)
Symptomatic LVSD (grade ≥3, SAE)	0 (0.0)	0 (0.0)	1 (1.5)
LVEF decline ≥10% from baseline to <50%	4 (5.9)	8 (12.3)	3 (4.5)
Follow-up period	**n = 70**	**n = 75**	**n = 74**
LVSD (all grades)	1 (1.4)	2 (2.7)	1 (1.4)
Symptomatic LVSD (grade ≥3, SAE)	0 (0.0)	1 (1.3)	0 (0.0)
LVEF decline ≥10% from baseline to <50%	3 (4.3)	4 (5.3)	2 (2.7)

Conclusion: In TRYPHAENA study, pertuzumab and trastuzumab were generally well tolerated, with low and similar rates of symptomatic LVSD, regardless of whether they were given sequentially after or concomitantly with anthracycline treatment, or concomitantly with carboplatin-based treatment. The overall safety profile of each regimen was consistent with the known toxicities of the individual treatments' regimens, and there were few patients who had to withdraw from study treatment due to an AE.

9.3 Study BERENICE (Swain et al., 2018)

In the ongoing, non-randomised Phase II study WO29217 (BERENICE) where two neoadjuvant anthracycline/taxane-based regimens were given in combination with pertuzumab and trastuzumab, the most common AEs were nausea, diarrhoea, alopecia, fatigue, constipation, asthenia, vomiting, mucosal inflammation, stomatitis, anaemia, myalgia, epistaxis, and headache. Overall, the AEs reported were as expected and generally well balanced between the two cohorts and there were no unexpected safety signals. The incidence of Grade ≥ 3 AEs was similar in both cohorts. Approximately one quarter of all patients experienced at least one SAE, with febrile neutropenia and diarrhoea being the most commonly reported.

There were no deaths reported during the neoadjuvant period of the study. The number of patients discontinuing any study medication due to AEs was low in both cohorts and the cardiac safety profiles of both treatment regimens were consistent with the know cardiac safety profiles of pertuzumab and trastuzumab.

9.4 Study APHINITY (von Minckwitz et al., 2017)

In the ongoing Phase III study (Study BO25126/TOC4939g [APHINITY]) which compared chemotherapy + trastuzumab + placebo versus chemotherapy + trastuzumab + pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer, the most common AEs (≥ 30% in either treatment arm) were diarrhoea, nausea, alopecia, fatigue, vomiting, arthralgia, and constipation. The incidence of most of the common AEs was similar between treatment arms except for diarrhoea, nausea and fatigue, which were higher in the pertuzumab + T + Chemo arm, and arthralgia, which was higher in the Pla + T + Chemo arm. The incidence of Grade ≥3 AEs during the overall study treatment period was higher in the pertuzumab + T + Chemo arm than in the Pla + T + Chemo arm (64.2% patients in the pertuzumab + T + Chemo arm and 57.3% patients in the Pla + T + Chemo arm). The proportion of patients who experienced at least one AE that led to the withdrawal of pertuzumab or placebo was similar in the two treatment arms.

The cardiac event rates were low in both treatment arms (Table A2.6).

Table A2.6. Most common AEs, all-grade with >10% incidence and Δ ≥3% between arms

Patients, %	PERJETA–Herceptin n = 2364	Placebo–Herceptin n = 2405
Diarrhoea	71.2	45.2
Stomatitis	28.4	24.0
Rash	25.8	20.3
Mucosal inflammation	23.4	18.4
Nausea	69.0	65.5
Fatigue	48.8	44.3
Arthralgia	28.7	32.5
Myalgia	26.0	29.5
Anaemia	27.8	23.3
Dysgeusia	26.0	21.5
Decreased appetite	23.9	19.9
Epistaxis	18.2	13.6
Oedema peripheral	17.1	20.1
Pruritus	14.0	9.0

10. Overall conclusion

In the neoadjuvant treatment of HER2-positive breast cancer, international guidelines recognise the improvements in the pathologic complete response (pCR) rate provided by the concomitant use of two anti-HER2 therapies in combination with chemotherapy when compared with chemotherapy associated with one anti-HER2 agent only based on the NEOSPHERE and TRYPHAENA neoadjuvant studies. The 2015 NCCN Guidelines (Gradishar et al., 2015) recommend the addition of pertuzumab to a number of chemotherapy regimens in the neoadjuvant setting and consider it also reasonable to include pertuzumab in a number of adjuvant regimens, if the patient did not receive pertuzumab as a part of neoadjuvant therapy.

Assessing treatment effect and benefit in the metastatic and the early stage breast cancer settings

It is not possible to compare treatment effects in mBC where the goal is to extend life vs in eBC where the intent is to rid the patient off the disease.

Efficacy in mBC is measured in terms of the delay of progression of the disease; while in eBC, it is measured in terms of reduction of the risk of recurrence or death, with iDFS identifying the proportion of patients without recurrence of invasive breast cancer or death. In this curative setting, any significant improvement in the risk of recurrence vs the SoC is clinically meaningful.

The difference between the treatment arms was estimated at 3-year iDFS rates, and now with longer follow up at 6-year iDFS rates. At 6 years a difference of 2.8% was observed vs the initial 0.9% between treatment arms at 3 years. A larger effect was seen in the N+ subgroup, where the difference in IDFS increased from 1.8% at 3 years to 4.5% at 6 years. These data points demonstrate that the differences between the APHINITY treatment arms are not only sizable, they are growing.

The significant reduction in the risk of recurrence or death is also recognised by the ESMO MCBS, and additional preplanned analyses are expected in 2022 and 2026 (final analysis), at which point new trends (expected to be stronger) may emerge.