PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pertuzumab (Perjeta) for Metastatic Breast Cancer

August 1, 2013

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of pertuzumab in combination with trastuzumab and a taxane compared to trastuzumab and a taxane (i.e., docetaxel or paclitaxel), in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Pertuzumab is a recombinant humanized monoclonal antibody that binds to the HER2 dimerization domain, preventing dimerizaton of HER2 with other HER receptors (HER3, HER1, and HER4), especially HER3.[1]

Currently pertuzumab has Health Canada approval for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2- positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

The recommended dose of pertuzumab includes a loading dose of 840 mg followed by 420 mg every 3 weeks thereafter. Trastuzumab is to be administered as an IV infusion with an initial loading dose of 8 mg/kg followed by a dose of 6 mg/kg every 3 weeks thereafter. Docetaxel is to be administered as an initial dose of 75 mg/m^2. The dose may be escalated to 100 mg/m^2 if the initial dose is well tolerated or decreased by 25% in case of toxic effects.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

CLEOPATRA was an industry-funded multicentre, double-blind, placebo-controlled randomized controlled trial that compared the safety and efficacy of pertuzumab-trastuzumab-docetaxel (n=402) to placebo-trastuzumab-docetaxel (n=406).[2] The study recruited patients with HER2-positive locally recurrent or metastatic breast cancer who had not received chemotherapy or biologic therapy for their metastatic disease. Patients were ≥18 years old, with an ECOG PS 0-1 and had left ventricular ejection fraction of 50% or more at baseline. Patients may have received one hormonal treatment for metastatic disease before randomization and adjuvant or neoadjuvant chemotherapy with or without trastuzumab, with 12 months or more between the last therapy and the diagnosis of metastatic breast cancer. Both treatment arms were administered until disease progression or unmanageable toxic effects. If treatment was discontinued due to toxic effects, antibody therapy continued until disease progression or unacceptable toxic effects.

Among other exclusion criteria, patients with central nervous system metastases and who had prior cumulative exposure to doxorubicin exceeding 360 mg/m^2 were excluded from the study.

Efficacy

Progression-free survival was the primary endpoint and assessed by an independent review facility, using the RECIST criteria. A statistically and clinically significant difference was demonstrated in the final analysis for the primary outcome, progression free survival in favour of the pertuzumab arm compared to the placebo

arm (median 18.5 vs.12.4 months, respectively; HR 0.62 95% confidence interval [CI] 0.51-0.75; p<0.001) with a median follow-up of 19.3 months.[2] The updated progression-free survival analysis in May 2012 reported similar results (Table 2) after a median follow-up of 29.7 and 30.1 months in the pertuzumab arm and placebo arm, respectively.[3]

Overall survival, defined as the time from randomization to the date of death from any cause, was the secondary endpoint. The fully published analysis of the primary outcome (May 2011) included an interim analysis of overall survival that demonstrated no statistically significant difference (Table 2).[2] In the final overall survial analysis (May 2012), a statistically significant difference in favour of the pertuzumab arm (median not yet reached) compared to the placebo arm (median 37.6 months; HR 0.66 95% CI 0.52-0.84; p=0.0008 [crossed the O'Brien-Fleming stopping boundary]) was demonstrated.[3]

Time to deterioration of health-related quality of life (HRQOL) was evaluated using the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire and deterioration was defined as a decrease of five points from the baseline score in the physical, functional and breast subscales (TOI-PFB subscale). Based on the TOI-PFB subscale, deterioration of HRQOL was experienced by 56.7% vs 59.5% of patients in the placebo compared to pertuzumab arms, respectively.[4] The median time to deterioration was not statistically significant between the placebo and pertuzumab arms (18.3 vs. 18.4 weeks, respectively; HR 0.97, p=0.716). The HRQOL results should be interpreted with caution as they have been published in abstract form only.

Harms

No statistical comparisons were made between the treatment and control arms for any adverse event. The proportion of patients who experienced febrile neutropenia, diarrhea, rash, mucosal inflammation, or dry skin of any grade was higher in the pertuzumab arm than in the placebo arm while the number of deaths from febrile neutropenia/infection was similar in both arms (5 deaths/arm). The rate of withdrawal from the study due to adverse events was identified as a harms outcome that was of particular interest and was similar in both arms (5.7% in the pertuzumab arm versus 5.0% in the placebo arm).

The potential for added cardiotoxicity while on pertuzumab was a concern specifically addressed by the CLEOPATRA study with a separate cardiac safety monitoring board. Baselga et al[2] reported that the proportion of patients who experienced grade 3 or higher left ventricular systolic dysfunction (2.8% vs. 1.2%) was numerically higher in the placebo arm than in the pertuzumab arm respectively.

1.2.2 Additional Evidence

pCODR received input on pertuzumab from the following patient advocacy groups Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (Rethink). Provincial Advisory group input was obtained from five of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

No supplemental issues were identified during the development of the review process.

1.2.3 Interpretation and Guidance

Women with metastatic breast cancer (MBC) have a quoted 5-year survival rate of 15%, though it is recognized there is wide variability between patients and between biological subtypes of breast cancer.[5] Approximately 15-20% of all breast cancers have gene amplification or over-expression (or both) of human epidermal growth factor receptor 2 (HER2), a tyrosine kinase transmembrane receptor, resulting in more aggressive phenotype and a poor prognosis.[6-8] In women with HER2-positive MBC, the use of the anti-HER2 humanized monoclonal antibody trastuzumab, in addition to cytotoxic chemotherapy, as compared to cytotoxic chemotherapy alone, has been found to significantly improve PFS and OS.[9] Thus anti-HER2 treatment is a standard approach for HER2-positive MBC.[10] Despite such therapy, the majority of patients with MBC who initially respond to trastuzumab demonstrate disease progression within 1 year of treatment initiation.[9] As such, there remains the need for new and improved targeted therapies both in terms of efficacy and tolerability for the treatment of MBC.

CLEOPATRA demonstrated a statistically and clinically significant improvement in PFS in favor of the pertuzumab compared to the placebo arm with a median follow-up of 19.3 months.[2] Similar results were reported in the more recent updated analysis.[3] The results from the second interim OS analysis (May 2012) which are the confirmatory and definitive OS results from the CLEOPATRA trial showed a statistically significant difference in favor of the pertuzumab arm (median OS not reached) compared to the placebo arm.[3]

Women with HER2-positive locally recurrent/metastatic breast cancer with an interval of less than 12 months from the completion of the adjuvant or neoadjuvant therapy with trastuzumab were excluded from the CLEOPATRA trial. Although this patient population has important clinical implications in the Canadian environment the benefit of pertuzumab in combination with trastuzumab and docetaxel in this setting was not established.

Health-related quality of life (HRQOL) data were collected and have been reported in abstract form only. The numbers of patients who completed the questionnaire at baseline and throughout therapy were not reported. Cortes et al[4] reported that 56.7% of patients in the placebo arm and 59.5% of patients in the pertuzumab arm experienced deterioration of HRQOL during the study based on the TOI-PFB subscale. The median time to deterioration was 18.3 weeks in the placebo arm versus 18.4 weeks in the pertuzumab arm (HR 0.97, p=0.7161). At Cycle 6, the mean reduction in TOI-PFB score from baseline was -3.5 in the placebo arm and -3.0 in the pertuzumab arm. The authors reported that compliance with reporting the FACT-B questionnaire was ≥75% beyond the first year in both arms. Given the limited information regarding the administration and collection of HRQOL evaluations and the lack of data for quality of life outcomes, the quality of life results need to be interpreted with caution.

The potential for added cardiotoxicity while on pertuzumab was a concern specifically addressed by the CLEOPATRA study with a separate cardiac safety monitoring board. Pertuzumab was not found to increase cardiotoxity in this patient population based on serial LVEF assessments. No statistical comparisons were made between the treatment and control arms for any adverse event.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to pertuzumab in combination with trastuzumab and docetaxel in the first line setting in women with locally advanced/ metastatic HER2-positive breast cancer. This recommendation is based on a single high-quality randomized controlled trial (CLEOPATRA) that demonstrated a clinically and statistically significant benefit in progression free survival and in overall survival. The adverse event profile of pertuzumab was acceptable in view of the clinical benefit.

The Clinical Guidance Panel also considered that from a clinical perspective:

1) Metastatic breast cancer is the second leading cause of cancer death in women and there is a need for new and improved chemotherapeutic/targeted agents, both in terms of efficacy and tolerability.

2) Pertuzumab in combination with trastuzumab and docetaxel demonstrated an improvement in progression free survival and overall survival in women with HER2-positive locally advanced/metastatic breast cancer.

3) Although an increase in some adverse events were noted with pertuzumab (including febrile neutropenia, diarrhea, rash, mucosal inflammation, and dry skin), the rate of treatment withdrawal due to adverse events was similar between those randomized to pertuzumab (5.7%) or placebo (5.0%).

4) Health-related quality of life was not adversely affected by pertuzumab in the CLEOPATRA study (pending final publication); however given the limited QoL data, these results should be interpreted with caution pending final publication.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding pertuzumab (Perjeta) for metastatic breast cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding pertuzumab (Perjeta) conducted by the Breast Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on pertuzumab (Perjeta) and a summary of submitted Provincial Advisory Group Input on pertuzumab (Perjeta) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

In 2011, the estimated number of new cases of Canadian women with breast cancer was 23,600.[11] Deaths from breast cancer account for 14.4% of all annual cancer deaths (second leading cause of cancer deaths in women), with an estimated 5,100 Canadian women dying from breast cancer in 2011.[11] Deaths from breast cancer are attributable to either distant relapse (spread to other organs such as liver or bone) or *de novo* presentation of metastatic breast cancer. In general, women with metastatic breast cancer (MBC) have a median life expectancy of 18-24 months, although there is a wide range based on differences in patient characteristics (e.g age, comorbidites) and subtypes of breast cancer (e.g triple negative).[5]

The goals of systemic therapy in the treatment of MBC are to improve overall survival and to maintain and/or improve quality of life. The treatment of incurable locally advanced or MBC generally involves systemic anti-cancer therapies (e.g. hormonal therapy, chemotherapy, and targeted therapy), supportive systemic therapies (e.g. analgesics, anti-nausea agents, anti-bone resorbtive agents, and steroids), radiation therapy, surgery (e.g. spinal cord compression, hip fractures, limited brain metastases) and the palliative care allied health service team. Over the past several years targeted therapies, designed to block critical pathways involved in cancer cell growth and metastases, have been developed that have led to major clinical advances in the treatment of MBC, partricularly MBC that is positive for the human epidermal growth factor receptor-2 (HER2).

The human epidermal growth factor receptor (HER) family is composed of tyrosine kinase receptors that are involved in the regulation of proliferation and survival of epithelial cells. The family includes four receptors: HER1 (epidermal growth factor receptor (EGFR), HER2 (neu, C-erbB2), HER3 and HER4. HER2 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.[12] Approximately 15-20% of all breast cancers have gene amplification or over-expression (or both) of human epidermal growth factor receptor 2 (HER2), resulting in a more aggressive

phenotype and a poor prognosis.[6-8] In women with HER2-positive MBC, administration of trastuzumab (an anti-HER2 humanized monoclonal antibody) in addition to cytotoxic chemotherapy, was superior (improved progression free and overall survival) compared to cytotoxic chemotherapy alone.[9] Trastuzumab in combination with systemic chemotherapy is now considered a standard approach for HER2-positive MBC.[10] In Canada, the current standard for first-line treatment of HER2-positive locally recurrent unresectable or and metastatic breast cancer includes trastuzumab (Herceptin) in combination with a taxane (e.g., paclitaxel, docetaxel).

Despite such therapy, the majority of patients with MBC who initially respond to trastuzumab demonstrate disease progression within 1 year of treatment initiation.[9] As such, there is a need for new and improved targeted therapies both in terms of efficacy and tolerability for the treatment of MBC.

More recently, a new class of agents, HER dimerization inhibitors that target HER2 dimerization with other receptors in its family, has been developed. Pertuzumab, a recombinant humanized monoclonal antibody binding to the HER2 dimerization domain, prevents dimerizaton of HER2 with other HER receptors (HER3, HER1, and HER4), especially HER3.[1] The mechanism of action of pertuzumab is complementary to trastuzumab in preclinical studies[13] with no increase in cardiotoxicity.[14]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of pertuzumab in combination with trastuzumab and a taxane compared to an appropriate comparator, in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Outcomes of interest included, but were not limited to, overall survival, progression-free survival (PFS), quality of life, and adverse events. Appropriate comparators were trastuzumab in combination with a taxane (i.e., docetaxel or paclitaxel). Additional details on outcomes of interest and other details of the review protocol including further study selection criteria can be found in Table 1 in Section 6.2.1.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

One study (the CLEOPATRA study) was identified that met the eligibility criteria of this review.[2-4,15-24] The CLEOPATRA study was an industry-funded multicentre (in 25 countries), double-blind, placebo-controlled randomized controlled trial that randomized 808 patients with HER2-positive locally recurrent or metastatic breast cancer who had not received chemotherapy or biologic therapy for their metastatic disease, to receive pertuzumab-trastuzumab-docetaxel (pertuzumab arm, n=402) or to placebo-trastuzumab-docetaxel (placebo-arm, n=406).[2] A summary of key trial characteristics can be found in Table 1. The baseline characteristics between the pertuzumab arm and the placebo arm were similar.

Table 1. Summary of Trial characteristics of the CLEOPATRA Study[2]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT00567190 CLEOPATRA Study 204 sites in 25 countries Patients enrolled from February 2008 through July 2010. Data cutoffs: Primary analysis (Final PFS analysis): May 13, 2011 Updated analysis (Final OS analysis): May 14, 2012 Enrolled: n=808 Randomized: n=808 Double-blind, placebo-controlled RCT Randomized in a 1:1 ratio (pertuzumab:placebo) Randomization was stratified by: A) Geographic area[A] B) Prior treatment status[B] Funded by: F. Hoffmann-La Roche/ Genentech	HER2-positive locally recurrent or metastatic breast cancer who had not received chemotherapy or biologic therapy for their metastatic disease. Patients may have received one hormonal treatment for metastatic disease before randomization. Patients may have received adjuvant or neoadjuvant chemotherapy with or without trastuzumab, with 12 months or more between the last therapy and the diagnosis of metastatic breast cancer. Age ≥18 years, ECOG PS 0-1, left ventricular ejection fraction of 50% or more at baseline. HER2 status was confirmed centrally by immunohistochemistry (with 3+ being positive) or fluorescence in situ hybridization (with amplification ratio ≥2.0 being positive) **Key exclusion criteria:** Central nervous system metastases. Prior cumulative exposure to doxorubicin exceeding 360 mg/m^2.	**Intervention:** Pertuzumab 840 mg loading dose followed by 420 mg every 3 weeks plus trastuzumab 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks plus docetaxel 75 mg/m^2 every 3 weeks. **Control:** Placebo following same schedule as for pertuzumab plus trastuzumab 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks plus docetaxel 75 mg/m^2 every 3 weeks. Both arms were administered until disease progression or unmanageable toxic effects. If discontinuation due to toxic effects, antibody therapy continued until disease progression or unacceptable toxic effects. Docetaxel dose could be increased to 100 mg/m^2 if toxic effects were deemed acceptable. Docetaxel dose could be decreased by 25% due to toxic effects.	**Primary:** Progression-free survival (independent assessment) **Secondary:** Overall survival ORR Progression-free survival (investigator assessed) Safety

ECOG PS = Eastern Cooperative Oncology Group Performance Status; **ORR** = objective response rate; **OS**=overall survival; **PFS**=progression-free survival; **RCT**= randomized controlled trial

[A]Asia, Europe, North America, South America.
[B]Prior adjuvant or neoadjuvant chemotherapy vs. none.

The primary outcome of the trial was progression-free survival. Secondary endpoints included overall survival and objective respone rate. Response was assessed by an independent review facility, using the RECIST criteria, every nine weeks during treatment and every six months in the first year after discontinuation of study treatment, and thereafter once yearly for up to three years. Progression-

free survival was defined as the time from randomization to date of progressive disease or death from any cause. Overall survival was defined as the time from randomization to the date of death from any cause. The study randomized enough patients to meet the sample size requirement of 800 patients for the primary outcome, progression-free survival. The study was also designed with a pre-specified interim analysis of overall survival to be performed at the same time as the final analysis for the primary outcome, progression-free survival. The final analysis for the primary outcome was reported in Baselga et al[2] with a data cut-off of May 13, 2011. An early stopping boundary was applied to the interim analysis of overall survival; if the stopping boundary was not crossed, patients were to continue receiving study treatment, with groups remaining blinded, until the final analysis of overall survival.[25] Baselga et al[2] reported that 385 deaths would be required for the final overall survival analysis. At the San Antonio Breast Cancer Symposium in December 2012, Swain et al[15] reported the results of the second planned interim analysis of overall survival for the CLEOPATRA study with a data cut-off of May 2012. The results of that analysis, the final (May 2012) overall survival analysis, were subsequently fully published in 2013 as Swain, Kim et al.[3]

Overall, the study was well conducted and designed. A potential limitation of the study is the limited information regarding the administration and collection of health-related quality of life evaluations and the lack of data for quality of life outcomes.[4] Given those limitations, the quality of life results need to be interpreted with caution.

The results of the CLEOPATRA study are summarized in Table 2. A statistically significant difference was demonstrated in the final analysis for the primary outcome, progression free survival in favour of the pertuzumab arm (median 18.5 months) compared to the placebo arm (median 12.4 months; HR 0.62 95% confidence interval [CI] 0.51-0.75; p<0.001) with a median follow-up of 19.3 months.[2] The updated progression-free survival analysis in May 2012 reported similar results (Table 2) after a median follow-up of 29.7 months and 30.1 months for the pertuzumab arm and placebo arm, respectively.[3] The fully published primary analysis (May 2011) demonstrated no statistically significant difference in overall survival (Table 2).[2] However, in the fully published final (May 2012) overall survival analysis, a statistically significant difference in overall survival was reported, in favour of the pertuzumab arm (median not yet reached) compared to the placebo arm (median 37.6 months; HR 0.66 95% CI 0.52-0.84; p=0.0008—crossed the predetermined O'Brien-Fleming stopping boundary).[3]

Table 2. Summary of Key Outcomes From the CLEOPATRA Study.[2,3]

Efficacy outcome (ITT population)	Analysis	Intervention	Median [months]	HR (95% CI)	p-value	Median follow-up [months]
Progression-free survival	May 13, 2011 (independent assessment)	Pertuzumab (n=402) Placebo (n=406)	**18.5** **12.4**	**0.62** **(0.51-0.75)**	**p<0.001**	**19.3**
	May 14, 2012 (investigator	Pertuzumab (n=402) Placebo	**18.7**	**0.69** **(0.58-0.81)**	**NR**	**29.7**

Efficacy outcome (ITT population)	Analysis	Intervention	Median [months]	HR (95% CI)	p-value	Median follow-up [months]
	assessed)	(n=406)	**12.4**			**30.1**
Overall survival	May 13, 2011	Pertuzumab (n=402) Placebo (n=406)	NYR; 69 deaths NYR; 96 deaths	0.64 (0.47-0.88)	p=0.005, NS†	19.3
	May 14, 2012	Pertuzumab (n=402) Placebo (n=406)	**NYR: 113 deaths** **37.6: 154 deaths**	**0.66** **(0.52-0.84)**	**p=0.0008 ‡**	**29.7** **30.1**

Harms outcome (safety population)	Pertuzumab (n=407)	Placebo (n=397)
Withdrew due to AE (%)	5.7	5.0
Diarrhea, all grades (%)	66.8	46.3
Constipation, all grades (%)	15.0	24.9
Rash, all grades (%)	33.7	24.2
Mucosal inflammation, all grades (%)	27.8	19.9
Dry skin, all grades (%)	10.6	4.3
Febrile neutropenia, Grade ≥3 (%)	13.8	7.6
Left ventricular systolic dysfunction, Grade ≥3 (%)	1.2	2.8

Notes: Results for outcomes in **BOLD** type are statistically significant; AE=adverse event; CI=confidence interval; HR=hazard ratio; NS=not significant; NR=not reported

†The result was not statistically significant: the O'Brien-Fleming stopping boundary, using a Lan-DeMets alpha spending function, was not met for the interim analysis of overall survival (boundary: HR ≤0.603; p≤0.0012).[2]

‡The final overall survival analysis crossed the O'Brien-Fleming stopping boundary (HR≤0.739; p≤0.0138), and was therefore statistically significant.[3]

Information on health-related quality of life (HRQOL) evaluations in the CLEOPATRA study were reported by Cortes et al[4] at the 2012 ASCO annual conference. Time to deterioration of HRQOL was evaluated using the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire and deterioration was defined as a decrease of five points from the baseline score in the physical, functional and breast subscales (together referred to as the TOI-PFB subscale). Patients completed questionnaires every third cycle three days before each tumour assessment until independently determined progressive disease. The numbers of patients who completed the questionnaire at baseline and throughout therapy were not reported. Cortes et al[4] reported that 56.7% of patients in the placebo arm and 59.5% of patients in the pertuzumab arm experienced deterioration of HRQOL during the study based on the TOI-PFB subscale. The median time to deterioration was 18.3 weeks in the placebo arm versus 18.4 weeks in the pertuzumab arm (HR 0.97, p=0.7161). At Cycle 6, the mean reduction in TOI-PFB score from baseline was -3.5 in the placebo arm and -3.0 in the pertuzumab arm.

The authors reported that compliance with reporting the FACT-B questionnaire was ≥75% beyond the first year in both arms.

Key adverse events and harms outcomes can be found in Table 2. No statistical comparisons were made between the treatment and control arms for any adverse event. The proportion of patients who experienced febrile neutropenia, diarrhea, rash, mucosal inflammation, or dry skin of any grade was higher in the pertuzumab arm than in the placebo arm, while the proportion of patients who experienced any grade of constipation or grade 3 or higher left ventricular systolic dysfunction were higher in the placebo arm than in the pertuzumab arm (Table 2). The rate of withdrawal from the study due to adverse events was similar in both arms (Table 2).

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, access to additional therapies that will stop progression of the disease, even if only for a short amount of time, is an important aspect when consideration is given to treatment. Because there is no cure for metastatic breast cancer, patients are looking for treatments with manageable side effect profiles that will extend life expectancy while offering an acceptable quality of life. Patient advocacy group input also indicated that many patients would be willing to tolerate the potential adverse effects of a treatment if it was found to prolong their survival, even for a short period of time.

PAG Input

Input on the Pertuzumab review was obtained from four of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that Pertuzumab can readily be implemented since it follows a protocol already in place with trastuzumab (eg. cardiac monitoring and dose withholding protocol). PAG also noted that Pertuzumab could be easily accessible in both urban and rural settings and minimal cost and dose wastage is expected due to it fixed dosing regimen. PAG identified some points for clarification regarding combination of Pertuzumab with other drugs in cases where a patient may require an alternative to docetaxel and in second line treatment. As

well, PAG identified the need for clarification around the availability of single vials of Pertuzumab as opposed to kits including trastuzumab.

Other

The product monograph provided by the manufacturer (Hoffmann-La Roche Limited) provides several warnings and precautions including, but not limited to:[26]

Embryo-Fetal Toxicity (Serious Warning and Precaution)

Exposure to Perjeta can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception.

Cardiovascular – Left Ventricular Dysfunction

Decreases in left ventricular ejection fraction (LVEF) have been reported with drugs that block HER2 activity, including Perjeta (pertuzumab). In the pivotal trial, CLEOPATRA, Perjeta in combination with Herceptin and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo and Herceptin and docetaxel. However patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

Perjeta has not been studied in patients with: a pretreatment LVEF value of ≤ 50%; a prior history of congestive heart failure (CHF); decreases in LVEF to <50% during prior Herceptin adjuvant therapy; conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360mg/m2 of doxorubicin or its equivalent.

Candidates for treatment with Perjeta and Herceptin should undergo thorough baseline cardiac assessment including history and physical exam, electrocardiogram (ECG) and either 2D echocardiogram or multiple gated acquisition (MUGA) scan to ensure that LVEF is within the institution's normal limits. A careful risk-benefit assessment should be made before deciding to treat with Perjeta and Herceptin. Cardian assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Perjeta and/or Herceptin.

If LVEF is <40% or 40-45% associated with ≥10% points below the pre-treatment value, PERJETA and HERCEPTIN should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If the LVEF has not improved, or has declined further, discontinuation of Perjeta and Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks

Immune—Infusion-Associated Reactions, and Hypersensitivity Reactions/Anaphylaxis

Perjeta has been associated with infusion and hypersensitivity reactions. Close observation of the patient for 60 minutes, after the first infusion and for 30 minutes following subsequent infusions is recommended following the administration of Perjeta. If a significant infusion-associated reaction occurs, the

infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction.

Febrile Neutropenia

Patients treated with Perjeta, Herceptin and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, Herceptin and docetaxel, especially during the first 3 cycles of treatment.

2.2 Interpretation and Guidance

Burden of Metastatic Breast Cancer

Breast cancer deaths are the second most common cause of cancer mortality in women in Canada, with an estimated 5,100 deaths in 2011. Breast cancer deaths also contribute to the greatest potential life years lost from any illness in Canadian women. Though many end-points are clinically important in the treatment of metastatic breast cancer, an improvement in overall survival (OS) and progression free survival (PFS) are considered to be some of the most important to strive for by: women with breast cancer, health care professionals and regulatory bodies. This is reinforced by the input from the patient advocacy groups on this submission (see section 4).

Effectiveness of Pertuzumab

CLEOPATRA is an industry-funded multicenter, double-blind, placebo-controlled randomized trial that compared the use of pertuzumab-trastuzumab-docetaxel to placebo-trastuzumab-docetaxel.[2] The study population (n=808) included women with HER2-positive locally recurrent or metastatic breast cancer who had not received chemotherapy or biologic therapy for their metastatic disease.

The primary clinical end-point was progression-free survival with a number of secondary endpoints including overall survival and objective response rate. The study demonstrated a statistically significant improvement in PFS in favor of the pertuzumab arm (median 18.5 months) compared to the placebo arm (median 12.4 months; HR 0.62 95% CI 0.51-0.75; p<0.001) with a median follow-up of 19.3 months.[2] Similar results were reported in the more recent updated analysis. In the first interim analysis[2] (fully published primary analysis), OS did not reach statistically significance, however, in the updated final overall survival analysis (May 2012), OS showed a statistically significant difference in favor of the pertuzumab arm (median OS not reached) compared to the placebo arm (median 37.6 months; HR 0.66 95% CI 0.52-0.84; p=0.0008).[3] The results from the second interim OS analysis are the confirmatory and definitive OS results from the CLEOPATRA trial.

The study was conducted in the appropriate patient population (first line metastatic HER2-positive locally recurrent or metastatic breast cancer) with an appropriate comparator (taxane with trastuzumab). The study was placebo-controlled and double blinded. Health-related quality of life data were collected and have been reported in abstract form only.[4]

Safety of Pertuzumab

The proportion of patients who experienced febrile neutropenia (13.8% vs. 7.6%), diarrhea (66.8% vs. 46.3%), rash (33.7% vs. 24.2%), mucosal inflammation (27.8% vs. 19.9%), or dry skin (10.6% vs. 4.3%) of any grade was higher in the pertuzumab arm than in the placebo arm respectively. The proportion of patients who experienced any grade of constipation (24.9% vs. 15%) or grade 3 or higher left ventricular systolic dysfunction (2.8% vs. 1.2%) was numerically higher in the placebo arm than in the pertuzumab arm respectively. No statistical comparisons were made between the treatment and control arms for any adverse event. Adverse events leading to discontinuation occurred in 5.7% of patients on pertuzumab and 5.0% of patients on placebo; the number of deaths from febrile neutropenia/infection was similar in both arms (5 deaths/arm).

The potential for added cardiotoxicity while on pertuzumab was a concern specifically addressed by the CLEOPATRA study with a separate cardiac safety monitoring board. Pertuzumab was not found to increase cardiotoxity in this patient population based on serial LVEF assessments.

Limitations of the Evidence

The Clinical Guidance Panel determined that there is one subgroup in which there may be insufficient evidence from the CLEOPATRA trial to extrapolate from that has clinical implications in the Canadian environment. Women with HER2-positive locally recurrent/metastatic breast cancer with an interval of less than 12 months from the completion of the adjuvant or neoadjuvant therapy with trastuzumab were excluded from the CLEOPATRA trial. The benefit of pertuzumab in combination with trastuzumab and docetaxel in this setting has not been established.

Need and Therapeutic Options

The strengths of this agent, as has been studied so far and published or publicly available include: an improvement in progression free survival and overall survival in the first line setting in women with locally advanced or metastatic HER2-positive breast cancer. When compared to the standard arm (placebo + docetaxel + trastuzumab), the toxicity profile was acceptable with no apparent difference in QOL between the arms of the study as measured. More importantly, there was no increase in cardiotoxicity. The agents delivered in the placebo arm (trastuzumab and docetaxel) are in keeping with the available chemotherapeutic agents and HER2 targeted therapies available and used in Canadian practice today.

Based on the currently available data, pertuzumab (in combination with a docetaxel and trastuzumab) should be considered as a standard of care option in the treatment of women with incurable locally advanced/metastatic HER2-positive breast cancer in the first line setting. The use of other taxanes (e.g. paclitaxel, nab-paclitaxel) in combination with pertuzumab/trastuzumab could potentially produce similar benefits based on the known synergy between taxanes and anti-HER2 therapies however, the magnitude of potential benefit and associated toxicities have not yet been established. The impact of downstream use of anti-HER2 therapies on overall survival following progression on pertuzumab has not been formally evaluated.

Patients in the CLEOPATRA study could have received one line of hormonal therapy prior to pertuzumab in the metastatic setting. The role of pertuzumab following endocrine therapy and lapatinib has not been determined. The combination of pertuzumab with other chemotherapeutic agents (such as vinorelbine, cyclophosphamide) and antibody-drug conjugates (eg. trastuzumab emtansine) is currently being investigated. Future clinical trials of pertuzumab in combination with other systemic agents and in earlier lines of therapy (e.g. early stage breast cancer) will help

to elucidate the specific role and benefit of this agent in the full spectrum of breast cancer treatment.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to pertuzumab in combination with trastuzumab and docetaxel in the first line setting in women with locally advanced/ metastatic HER2-positive breast cancer. This recommendation is based on a single high-quality randomized controlled trial (CLEOPATRA) that demonstrated a clinically and statistically significant benefit in progression free survival and in overall survival. The adverse event profile of pertuzumab was acceptable in view of the clinical benefit.

The Clinical Guidance Panel also considered that from a clinical perspective:

1) Metastatic breast cancer is the second leading cause of cancer death in women and there is a need for new and improved chemotherapeutic/targeted agents, both in terms of efficacy and tolerability.
2) Pertuzumab in combination with trastuzumab and docetaxel demonstrated an improvement in progression free survival and overall survival in women with HER2-positive locally advanced/metastatic breast cancer.
3) Although an increase in some adverse events were noted with pertuzumab (including febrile neutropenia, diarrhea, rash, mucosal inflammation, and dry skin), the rate of treatment withdrawal due to adverse events was similar between those randomized to pertuzumab (5.7%) or placebo (5.0%).
4) Health-related quality of life was not adversely affected by pertuzumab in the CLEOPATRA study (pending final publication); however given the limited QoL data, these results should be interpreted with caution pending final publication.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Breast Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Breast cancer is the most commonly diagnosed malignancy in Canadian women, with an estimated incidence of 23,600 new cases in Canada in 2011.[11] Deaths from breast cancer account for 14.4% of all annual cancer deaths (second leading cause of cancer deaths in women) with an estimated 5,100 Canadian women dying from breast cancer in 2011. Deaths from breast cancer are attributable to either distant relapsed or *de novo* presentation of metastatic breast cancer, which is considered an incurable situation. In general, women with metastatic breast cancer (MBC) have a quoted 5-year survival rate of 15%, though it is recognized there is wide variability between patients and between biological subtypes of breast cancer.[5]

The goals of systemic therapy in the treatment of MBC are to improve overall survival and to maintain and/or improve quality of life. More than in any other malignancy, the past 10-15 years has seen a number of novel systemic agents for the treatment of MBC. The use of sequential chemotherapy has been favoured over concurrent therapy with multiple agents to primarily limit toxicities. More recently, this practice has been challenged by the introduction of new targeted agents. Targeted therapies are designed to block critical pathways involved in cancer cell growth and metastases and have led to major clinical advances in the treatment of MBC, especially HER2-positive MBC.

The human epidermal growth factor receptor (HER) family is composed of tyrosine kinase receptors that are involved in the regulation of proliferation and survival of epithelial cells. The family includes four receptors: HER1 (epidermal growth factor receptor (EGFR), HER2 (neu, C-erbB2), HER3 and HER4. The HER2 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.[12] Approximately 15-20% of all breast cancers have gene amplification or over-expression (or both) of human epidermal growth factor receptor 2 (HER2), a tyrosine kinase transmembrane receptor, resulting in more aggressive phenotype and a poor prognosis.[6-8] In women with HER2-positive MBC, the use of the anti-HER2 humanized monoclonal antibody trastuzumab, in addition to cytotoxic chemotherapy, as compared to cytotoxic chemotherapy alone, has been found to significantly improve PFS and OS.[9] Thus anti-HER2 treatment is a standard approach for HER2-positive MBC.[10] Despite such therapy, the majority of patients with MBC who initially respond to trastuzumab demonstrate disease progression within 1 year of treatment initiation.[9] As such, there remains the need for new and improved targeted therapies both in terms of efficacy and tolerability for the treatment of MBC.

3.2 Accepted Clinical Practice

The treatment of incurable locally advanced or MBC generally involves systemic anti-cancer therapies (e.g. hormonal therapy, chemotherapy, and targeted therapy), supportive systemic therapies (e.g. analgesics, anti-nausea agents, anti-bone resorbtive agents, and steroids), radiation therapy, surgery (e.g. spinal cord compression, hip fractures, limited brain metastases) and the palliative care allied health service team. The prevalence of use of these various therapeutic modalities clearly vary by patient disease characteristics, patient co-medical conditions, patient preferences, physician recommendations and availability of the various treatment options.

An improvement in overall survival is still considered the gold standard as evidence of a therapeutic benefit from any systemic agent in the treatment of breast cancer. In a recent review

of randomized trials in MBC published between 1998-2007, 76 phase III trials were identified.[27] Of these 76 trials, only 15 (19.7%) demonstrated a statistical improvement in overall survival. Thus the ability to demonstrate an actual improvement in overall survival is challenging in the setting of MBC because of disease heterogeneity, cross-over to the experimental arm (in some trials) and the ability to receive standard treatment post progression.

First line therapy for HER2-positive MBC

Trastuzumab (Herceptin) is the first agent developed to target the HER2 pathway.[28] Trastuzumab is a recombinant, humanized monoclonal antibody that binds to domain IV on the juxtamembrane region of the extracellular domain of HER2 and inhibits tumor cell growth in vitro and in vivo via several mechanisms.[29] In women with HER2-positive MBC, the use of trastuzumab in the fist-line setting has been shown to improve progression-free and overall survival when administered in combination with chemotherapy (taxane) versus chemotherapy alone (taxane). In the pivotal trial by Slamon et al., the addition of trastuzumab to chemotherapy in women with HER2-positive MBC, significantly increased RR (32 versus 50%) median duration of response (6 versus 9 months), and overall survival (OS) (20 versus 25 months, P<0.01).[9] Based on this evidence and confirmatory trials, trastuzumab in combination with a taxane is now recommended as first-line therapy for women with HER2/neu-overexpressing MBC. Trastuzumab combination therapy is most effective in women with the highest level of HER2/neu protein overexpression, as indicated by an immunohistochemistry score of 3+ (moderate/strong membrane staining in at least 10% of tumour cells) or by HER2/neu gene amplification (defined as HER2/CEP17$\geq$ 2 by fluorescence in situ hybridization – FISH).

Lapatinib (Tykerb) is a dual tyrosine kinase inhibitor of both HER1 and HER2. In the first line setting for hormone sensitive, HER2-positive MBC, lapatinib in combination with letrozole is currently under review with pCODR. If shown to have a clinically important benefit when compared to letrozole alone, the use of lapatinib with an aromatase inhibitor in this setting may likely be considered in patients suitable for endocrine therapy. Lapatinib in combination with a taxane has been compared to trastuzumab in combination with a taxane in the first line setting for HER2-positive MBC.[30] Other trials of lapatinib have been done following progression on trastuzumab.

More recently, a new class of agents targeting HER2 dimerization with other receptors in its family has been developed (HER dimerization inhibitors). Pertuzumab, a recombinant humanized monoclonal antibody binding to the HER2 dimerization domain, prevents dimerizaton of HER2 with other HER receptors (HER3, HER1, and HER4), especially HER3.[1] The mechanism of action of pertuzumab is complementary to trastuzumab in preclinical studies[13] with no increase in cardiotoxicity.[14] In the CLEOPATRA (the CLinical Evaluation Of Pertuzumab And TRAstuzumab) study, the effectiveness and safety of combination pertuzumab and trastuzumab with docetaxel was shown in women with HER-2 positive MBC in the first line setting.[2] In the second interim analysis of the CLEOPATRA study, a significant overall survival benefit was observed with a HR of 0.66, 95% CI 0.52-0.84, p=0.0008.[15] This is a very important study to consider with potential impact on clinical practice. The combination of pertuzumab with other targeted therapies and chemotherapies in first line setting for HER2-positive MBC is currently ongoing (i.e. T-DM1, vinorelbine, metronomic chemotherapy). Other anti-HER2 therapies are currently being developed and tested but not in clinical use.

3.3 Evidence-Based Considerations for a Funding Population

The evidence based population suitable for consideration of pertuzumab for the treatment of HER2-positive MBC would be the same patient population included in the clinical trial (CLEOPATRA).[2] These would be women with either metastatic breast cancer or incurable locoregionally recurrent HER2-positive breast cancer defined by immunohistochemistry (with 3+) or fluorescence in situ hybridization (with amplification ratio $\geq$ 2). Patients may have received one

hormonal treatment for metastatic disease before randomization. Patients may have received adjuvant or neoadjuvant chemotherapy with or without trastuzumab, with 12 months or more between the last therapy and the diagnosis of MBC. Patients should have a good performance status (ECOG score of 0-1), and have adequate left ventricular ejection fraction of 50% or more at baseline (determined by echocardiography or multiple-gated acquisition scanning).

Treatment with pertuzumab and trastuzumab would continue until disease progression, unacceptable toxicity, or patient or physician recommendation (as was done in the CLEOPATRA study).

It is also important to recognize that in the CLEOPATRA trial 71.1% of patients randomized to the pertuzumab arm in fact received further anti-HER2 targeted therapy following progression on pertuzumab. It is likely that a proportion of patients in clinical practice with progression on pertuzumab will receive further anti-HER2 therapies (e.g. lapatinib).

3.4 Other Patient Populations in Whom the Drug May Be Used

Patients with HER2-positive MBC previously treated with more than one endocrine therapy in the metastatic setting are likely to be a patient population in which pertuzumab may be considered but that did not meet the eligibility criteria of those enrolled in the CLEOPATRA study.

Another patient population where pertuzumab could also be considered is in the treatment of patients with HER2-positive MBC who have relapsed within 6-12 months of receiving trastuzumab in the adjuvant setting.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (Rethink) collaborated and provided joint input on pertuzumab for the treatment of metastatic breast cancer patients and their input is summarized below.

CBCN and Rethink conducted an online survey and key informant interviews to gather information from patients and caregivers about the impact of metastatic breast cancer on their lives and the effect of treatments on their disease. Patients were contacted through the membership databases of CBCN and Rethink. No patients surveyed had direct experience with the treatment under review. Survey questions comprised of a combination of scoring options and free form commentary. Survey participants were contacted through the membership databases of CBCN and Rethink. A total of 87 respondents completed the survey; of this total, 71 were patients with metastatic breast cancer and 16 were caregivers. Cited responses are included verbatim to provide a deeper insight of the patient and caregiver perspective; cited responses are not corrected for spelling or grammar. A copy of the survey was provided to pCODR. Phone interviews were conducted with two patients that had direct experience with the treatment under review. Both participants participated in the CLEOPATRA clinical trial in Canada. A presentation about the clinical trial and its outcomes was presented to CBCN and Rethink by a clinician who supervised the patients in the Canadian portion of the study. A review of current studies and grey literature was also conducted to identify issues and experiences that are commonly shared among breast cancer patients.

From a patient perspective, access to additional therapies that will stop progression of the disease, even if only for a short amount of time, is an important aspect when consideration is given to treatment. Because there is no cure for metastatic breast cancer, patients are looking for treatments with manageable side effect profiles that will extend life expectancy while offering an acceptable quality of life. Patient advocacy group input also indicated that many patients would be willing to tolerate the potential adverse effects of a treatment if it was found to prolong their survival, even for a short period of time.

Please see below for a summary of specific input received from the patient advocacy groups.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients Have with Metastatic Breast Cancer

Metastatic breast cancer is the spread of cancerous cell growth from the place where it first started to another place in the body. The most common site of breast cancer metastasis is to the bones, but can also spread to the lungs, liver, brain and skin. Current treatment options for HER2+ metastatic breast cancer are effective at prolonging progression-free disease, but most cases of advanced disease will progress and symptoms will worsen.

From a patient perspective, quality of life while living with metastatic breast cancer is an important consideration. Patients with metastatic breast cancer understand the limitations of current treatment options, and seek to live their remaining months and years with the best possible quality of life that they can achieve. The 71 patients who participated in the survey provided an answer to the question *How have the symptoms of metastatic cancer affected their quality of life?* Fatigue, insomnia, pain, problems concentrating and depression were the most frequently reported symptoms of the disease that impact a patient's quality of life. Other physical symptoms that

were identified by patients included: early menopause, mood swings, loss of appetite, neuropathy, loss of balance, incontinence and skin bruising.

Metastatic breast cancer also impacts many social aspects of a patient's life, including restricting an individual's ability to work, to care for children and dependents, and to be social and meaningfully participate in their community. The survey asked *what kind of impact living with metastatic breast cancer has had on their quality of life*. Other experiences identified by patients: guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of impact of the cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, martial stress/loss of fidelity and affection from husband. The responses to both survey questions are summarized in the table below.

Affect on Quality of Life		**Significant or Debilitating Impact (N = 71 patients)**	**Moderate Impact (N = 71 patients)**
How have the symptoms of metastatic cancer affected your quality of life?	Fatigue	54%	40%
	Insomnia	39%	46%
	Pain	37%	44%
	Problems Concentrating	31%	59%
	Depression	26%	53%
How has living with metastatic cancer restricted your ability to participate in the following areas?	Work	71% of those employed	-
	Provide Caregiving Responsibilities	21% of those with children or dependents	53% of those with children or dependents
	Exercise	49%	38%
	Pursue Hobbies and Personal Interests	42%	42%
	Participate in Social Events and Activities	41%	41%
	Volunteer	31%	46%
	Self-Manage Other Chronic Diseases on Health Issues	25%	43%
	Spend Time with Loves Ones	22%	52%

4.1.2 Patients' Experiences with Current Therapy for Metastatic Breast Cancer

Patient groups identified their goals of current treatment options for metastatic breast cancer include controlling the progression of the disease (extending their life), and reducing cancer-related symptoms (extending or stabilising quality of life). Treatment options and their effectiveness vary among type of cancer, location of cancer, and how symptoms are experienced by patients.

Patients report that the financial burden associated with living with breast cancer extends far beyond any loss of income during a temporary or permanent absence from employment. In addition to the loss of income during illness, breast cancer patients can incur substantial costs associated with treatment and disease management.

Literature published by the Canadian Breast Cancer Network about the financial impact of breast cancer on patients identified the following:

- 80% of breast cancer patients report a financial impact due to their illness. Patients who are self-employed frequently do not have health care coverage that will cover the cost of treatment for the breast cancer, nor medication and alternative treatments such as massage, acupuncture and nutritional counselling to manage side effects.
- Many patients are not eligible for their corporate health care plan, or face confusing and time-consuming application processes to access corporate or government assistance plans.
- 44% of patients have used their savings, and 27% have taken on debt to cover costs.
- Breast cancer results in high out of pocket expenses related to devices and family care costs. Examples of common costs include:
    - childcare when ill, when receiving clinic-based clinics, and when travelling to receive treatment in another community or region
    - parking costs during treatment and medical appointments; and
    - transportation and accommodation costs when patients must travel to receive treatment.

These findings were consistent with the responses to the survey of CBCN and Rethink:

- Nearly one third of patients indicated that the cost of medication, the cost of alternative treatments (i.e. massage, physiotherapy, etc.) to manage symptoms and side effects, and the time required to travel to treatment had a significant or debilitating impact on their quality of life.
- 24% of patients indicated that the costs associated with travel had a significant or debilitating impact on their quality of life, and 41% of patients indicated that it had some or moderate impact on their quality of life.

Other barriers that were included in the survey responses were: not qualifying for insurance at work, inability to change employers due to loss of insurance, and the prohibitive cost of new treatment options.

"Many of the next step treatments are very expensive and not covered by government programs and it is a HUGE struggle to get coverage. … When dealing with an incurable disease the last thing you want to have to do is spend time on a letter writing campaign to argue about whether or not you should receive the drugs recommended by your physician. At about $1500.00 a week, I don't know many who can afford that."

In response to questions on the survey relating to the availability of support services such as childcare, transportation, and alternative treatments in their community:

- 53% of respondents with children or other dependents indicated there is minimal or no access to appropriate care for their loved ones when they are experiencing debilitating symptoms to their cancer, and 40% identified barriers to accessing quality care during cancer treatment.

- 26% of patients indicated there are minimal or no transportation options in their community when they seek treatment and support for symptoms, and 18% indicated a lack of adequate transportation options to access cancer treatment. One patient indicated that in a rural community, it is difficult to get to the hospital in the winter months.

When asked *what level of side effects and how much impact on one's quality of life would be worth extending progression-free disease by six months*, the responses clearly indicated that this assessment can only be determined by an individual patient in this circumstance.

When asked to rate *how much impact different symptoms of cancer and cancer treatment would be considered tolerable*:

- Almost two-thirds of patients indicated that fatigue, nausea, depression, problems with concentration, memory loss, diarrhea and insomnia, some or a moderate impact on one's quality of life would be considered acceptable, and approximately one quarter of patients indicated that a strong or debilitating impact would be considered acceptable.
- 70% of patients indicated that some or moderate pain would be considered acceptable, and 27% of patients indicated that strong or debilitating pain would be considered acceptable.

One patient indicated that for her, side-effects were not a big factor in assessing whether she would begin a new treatment. Other than hair loss, she was able to work with her physician to identify and receive medication to adequately manage and in some cases, eliminate side-effects.

Based on comments provided in the open-ended portion of the survey, patients made two observations:

- Some patients felt they did not understand the wording of the question.
- Some patients did not feel that they had the capacity to respond to a hypothetical question of this nature.

"My preference is for access to lots of treatments so I can live for long time. Less side effects are preferable, but if there is no option I will put up with symptoms of treatment in order to live longer."

"Not all patients suffer the same way. […] It was a difficult task to answer that question."

When asked in the survey about their willingness to tolerate risk with a new treatment:

- 34% were willing to accept serious risk with treatment if it would control the disease
- 45% were willing to accept some risk with treatment
- 21% were very concerned and felt less comfortable with serious risks with treatment.

The responses to the open ended question the key informant interviews confirmed that the decision to determine what risks and side effects are tolerable must rest in the hands of each individual patient. While a side-effect such as hair loss, nausea and fatigue for a medication may be common across patients, each patient will assess its impact on their quality of life differently.

"I think patients (ESPECIALLY young patients) should be given more decision making power in terms of access to radical treatments to control disease. […] With two small children, I am determined to access any treatment that can extend my life and I hate struggling with doctors for this access."

"It has been very frustrating that doctors do not address the more subjective symptoms such as pain related to chemotherapy (muscle and joint), which persists after chemotherapy"

"I believe that I would prefer to tolerate severe restrictions in the quality of my life, if it meant that I would be able to have a longer period without progression."

"Had you asked me some of these questions four years ago, the answers would have been different. My oncologist tells me that I am running out of treatment options. […] It is very scary to face the day (soon) when I will have no treatment and the cancer will be allowed to run its course."

4.1.3 Impact of Metastatic Breast Cancer and Current Therapy on Caregivers

While caregivers provide loving support, they experience a significant negative impact on their quality of life. Caregiver respondents reported experiencing a number of symptoms of stress, as well as a negative impact on their ability to continue their daily routines, responsibilities, and self-care for personal health issues.

- 77% of caregivers indicated that anxiety, fatigue, and problems with concentration had a negative impact on their quality of life
- 67% of caregivers indicated that depression and insomnia had a negative impact on their quality of life, and
- 55% of caregivers indicated that memory loss and physical pain such as muscle tension had a negative impact on their quality of life.

All caregivers reported that their role has resulted in a negative impact on their personal, social, and professional lives. 100% of caregivers identified restrictions to their employment, their ability to pursue personal interests and hobbies, their ability to travel, and their ability to exercise. One respondent indicated that there was a clear impact on his or her ability to fulfill his job responsibilities and negatively impacted on his or her career progression.

- 89% of caregivers identified restrictions to their ability to participate in social events and activities
- 75% of caregivers identified restrictions to their ability to volunteer
- 67% of caregivers identified restrictions to their ability to spend time with loved ones, and
- 44% of caregivers identified restrictions to their ability to care for children and dependents.

"I do not want to be a burden on my family. I would not want my family to decline/lose good opportunities in their careers & restrict them in anyway on my behalf/condition."

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Pertuzumab

Patients expect that this drug will extend survival among patients living with HER2+ breast cancer by a 6.1 month improvement in median progression free survival, from 12.4 to 18.5 months. Patient group input states that results from the clinical trial suggest that there is no known toxicity associated with pertuzumab. The most common side effects reported by patients in the clinical trial were diarrhea, hair loss, a decrease in infection-fighting white blood cells, nausea, fatigue, rash, and nerve damage. However, Canadian based participants in the CLEOPATRA trial indicated that these symptoms were minimal, or were not experienced at all.

By delaying the progression of the disease, this treatment can relieve cancer-related symptoms, and improve or stabilise a patient's quality of life. When living with no or with minimal cancer-related symptoms, and with minimal side effects from the treatment, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn income, spend time with loved ones and participate in their life in a meaningful way by engaging in social activities, travelling, maintaining friendships, and pursuing personal interests.

Patients living with metastatic breast cancer are aware that their advanced disease will progress with worsening symptoms until death, and embrace opportunities to try new treatment, even if benefits may be as little as a six month extension of progression-free disease. In their responses to the survey, patients expressed hope and relief to be able to have six additional months with their loved ones, and to be able to experience at least the family milestones that would come with that six months. A number of patients expressed concern over the costs of the treatment, indicating that new treatments often come with high costs which must be covered by patients out of pocket, or which require lengthy processes for public and private insurance to secure approval for the expense.

Two Canadian patients living with HER2+ metastatic breast cancer participated in the CLEOPATRA study and accessed the treatment under review. Both patients indicated that the drug was responsible for slowing down the progression of the disease to the point that there was some shrinkage of the cancer, and is responsible for extending their life. Both patients indicated that their quality of life while taking this treatment was very good. Before participating in the clinical trial, both patients were made aware of the possible risks associated with the treatment. Given the stage of disease and treatment options that were available to them, both felt that the potential benefit outweighed any possible risk. Currently, both patients feel very strongly that the benefits of the treatment have outweighed any risks. Both recommend this treatment to other patients.

"In some ways there was a risk, supposedly, to do this, but my feeling is you gotta try to do everything you can to treat this illness.[…] I feel very fortunate to have had this opportunity to participate in this clinical trial."

Both clinical trial patients were unable to identify an alternative treatment that would have resulted in a similar positive impact on the progression of their disease. They expressed that had this treatment not been available to them, they would have had to rely on existing treatments which, as had been explained to them by their oncologist, would have not been able to prevent the disease from progressing. Both patients indicated that they would likely already be deceased had they not been able to participate in this trial.

Neither patient was able to identify an adverse effect or symptom that had a serious negative impact on her personal quality of life, nor on the quality of life of her caregiver/loved ones. The following symptoms were identified by one or both patients, however, they were all identified as being very minor, and/or easily managed/treated: hair loss, fatigue (which was identified by one patient as possibly attributable to the cancer, to age, or to the treatment), insomnia, peripheral neuropathy (which was described as neither painful, nor problematic), and mood swings.

Both patients expressed that since being on the drug, they experienced a very good quality of life, and indicated that the therapy had no negative impact on the following activities:

- Managing household responsibilities
- Spending time with loved ones
- Maintaining friendships, enjoying social activities, travelling and pursuing hobbies
- Volunteering
- Self-managing other health concerns.

Both patients indicated it was not apparent to others that they were ill when observing their appearance or lifestyle. One patient expressed that very few people outside her circle of family and friends were aware that she was living with cancer. One patient indicated that her physician was very surprised at how healthy she appeared.

"I spend a lot of time with family – three children and grandchildren. Lots of friends, I'm very socially active. The treatment has had zero impact on my social life."

The only financial impact that was identified with participating in this trial was the parking. Both patients indicated that they lived in close proximity to the site of the clinical trial and expressed that they felt lucky to have not had to travel to another community or region.

Both patients indicated that while the clinic-based intravenous administration of the drug was less convenient than oral treatments they had used in the past, it did not impact on their quality of life. It was noted by both participants, however, that they lived in close proximity to the clinic and did not have to travel between cities or to another region/area. They also both indicated that they have strong support networks, and if they were not able to drive themselves, they were able to rely on family or friends to provide transportation.

Both patients had experienced a number of oral and intravenous-based treatments for cancer, and indicated that the adverse effects were comparable to, or less noticeable than the effects associated with other treatments.

Both patients expressed that they felt very lucky to have been given the opportunity to participate in this clinical trial. They both indicated that while they were cognizant that the duration of the drug's effectiveness on their cancer is unknown, testing of their disease continues to demonstrate positive results.

4.3 Additional Information

No information was provided in this section by CBCN and Rethink

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for pertuzumab (Perjeta) for metastatic breast cancer. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the Pertuzumab review was obtained from four of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that pertuzumab can readily be implemented since it follows a protocol already in place with trastuzumab. PAG also noted that pertuzumab could be easily accessible in both urban and rural settings and minimal cost and dose wastage is expected due to it fixed dosing regimen. PAG identified some points for clarification regarding combination of pertuzumab with other drugs in cases where a patient may require an alternative to docetaxel and in second line treatment. As well, PAG identified the need for clarification around the availability of single vials of Pertuzumab as opposed to kits including herceptin.

5.1 Factors Related to Comparators

PAG noted that the current standard of care for treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer is trastuzumab + chemotherapy. PAG indicated pertuzumab presents as an add-on therapy to trastuzumab. This was noted to potentially present a challenge to funding.

5.2 Factors Related to Patient Population

PAG noted the number of patients with HER2 positive advanced breast cancer is not large, however duration of therapy and number of treatments per patient is high with trastuzumab. If recommended, PAG noted that pertuzumab may not accrue more additional treatment visits.

PAG noted a few potential barriers for use of pertuzumab in the current patient population. PAG was not clear if pertuzumab, in the metastatic setting, could also be reasonably used with other taxanes than docetaxel (eg. Nab-paclitaxel, paclitaxel) or other chemo (vinorelbine, if taxanes cannot be given). Similairly, trastuzumab is used in combination with other drugs other than docetaxel (e.g. paclitaxel, capecitabine, vinorelbine, platinum drugs). PAG also noted the possibility for indication creep into the adjuvant settings.

PAG also noted that the current funding policy in some Canadian jurisdictions for trastuzumab + docetaxel is specific for use in the metastatic setting and does not specify use in locally recurrent unresectable breast cancer. As such, PAG would like clarity on the funding in the latter setting for pertuzumab.

5.3 Factors Related to Accessibility

PAG notes that currently trastuzumab is available to patients in all locations and so pertuzumab would also be available in urban and rural settings. PAG also noted that although pertuzumab would increase chemotherapy clinic time, it would so in established patients already on the regimen of trastuzimab and docetaxel.

5.4 Factors Related to Dosing

PAG noted that fixed dosing of pertuzumab will minimize drug wastage and this is considered to be a main enabler. PAG also noted that pertuzumab follows the dosing, cardiac monitoring and dose withholding protocol of trastuzumab and so implementation would likely be similar.

5.5 Factors Related to Implementation Costs

PAG noted several areas where pertuzumab therapy will not accrue additional implementation costs. The first involved HER2 testing and cardiac monitoring which are already implemented for trastuzumab therapy and thus will not require additional costs with pertuzumab therapy. In additional, since pertuzumab is administered in a fixed dose, costs associated with potential wastage of the drug will be avoided, as noted above.

PAG noted that additional costs may be accrued with pertuzumab therapy through the requirement of additional pharmacy time for IV drug preparation and increased need for refrigeration space for appropriate drug storage. PAG also noted that there will be an increase in chemotherapy clinic time as pertuzumab has longer IV infusion times than trastuzumab and it also has more IV dose administrations per patient.

5.6 Other Factors

PAG noted that clarification is required around the availability of pertuzumab in single vials as opposed to the kit along with trastuzumab. PAG indicated that in large centers, the option of acquiring the single vial would be more cost effective.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of pertuzumab in combination with trastuzumab and a taxane compared to an appropriate comparator, in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Outcomes of interest and appropriate comparators can be found in Table 1 in Section 6.2.1.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 3 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT	• HER2-positive metastatic breast cancer that has not been previously treated with either anti-HER2 therapy or chemotherapy for metastatic disease.‡ • HER2-positive locally recurrent unresectable breast cancer.	Pertuzumab + trastuzumab + a taxane†	Trastuzumab + taxane†	**OS** PFS **QOL** **Adverse events** Withdrawal from study (due to toxicity or progression) Cardiac toxicity
HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; QOL=quality of life.				

Note: Outcomes in bold are those considered most important to patients, based on input from patient advocacy groups.
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*
†Taxanes include: docetaxel, paclitaxel, or nab-paclitaxel.
‡Patients could have received anti-HER2 therapy or chemotherapy as adjuvant treatment.

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 4) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pertuzumab (Perjeta) and metastatic or advanced breast cancer.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of May 2, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

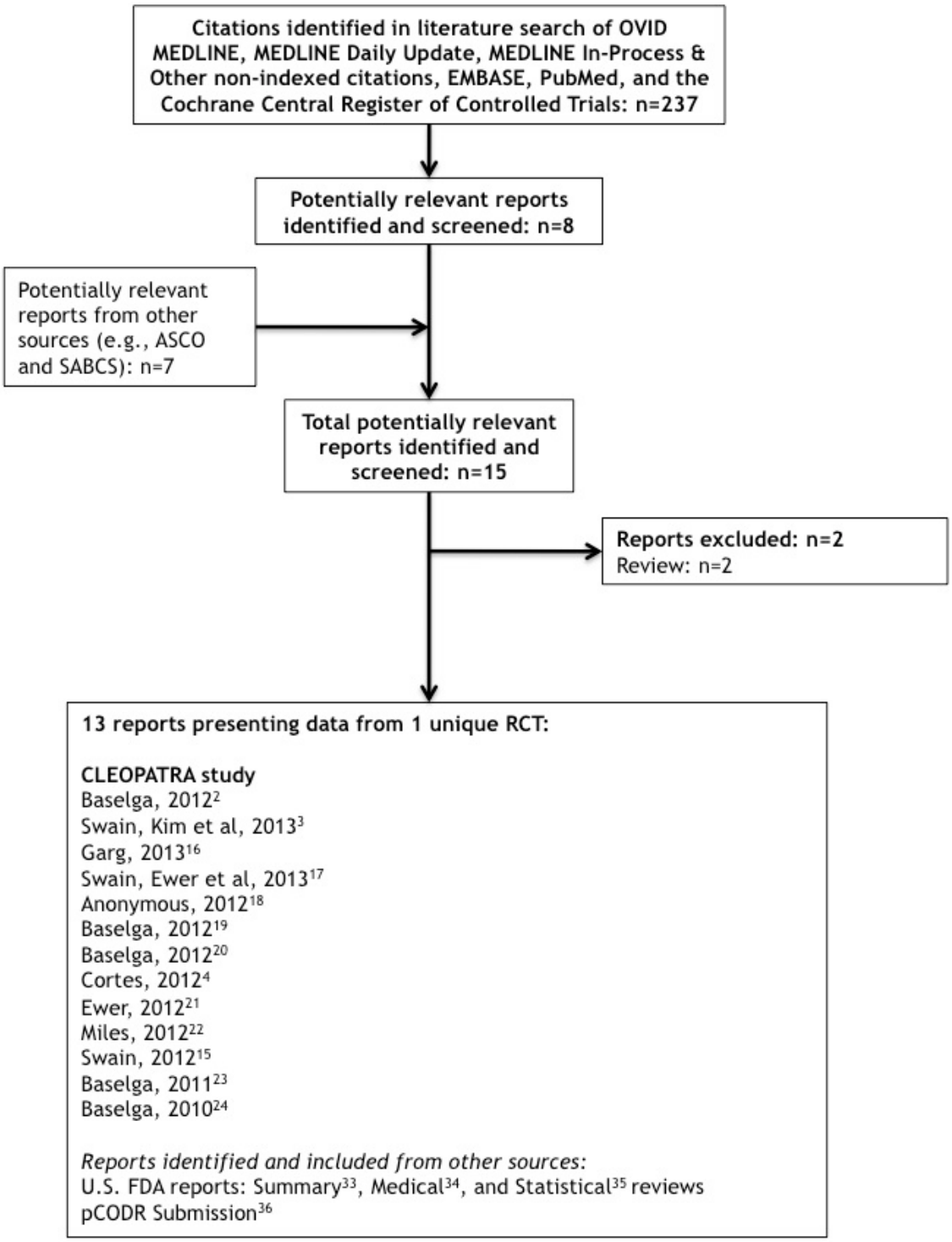
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

A total of 237 citations were identified through searches of MEDLINE, MEDLINE Daily Update, MEDLINE In-Process & Other Non-indexed Citations, EMBASE, Cochrane Central Register of Controlled Trials, and PubMed (Figure 1). An additional seven abstracts were identified through searches of ASCO and the SABCS conference proceedings. Of those 244 citations, 15 potentially relevant reports were retrieved for full-text review. Thirteen studies were included in the pCODR systematic review[2-4,15-24] and two studies were excluded because they were reviews.[31,32] Additional reports were identified from the United States Food and Drug Administration (US FDA).[33-35] The US FDA reviews did not contain any additional information and thus are not discussed further. In addition, the submission was included as a source of information.[36]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the CLEOPATRA study was also obtained through requests to the Submitter by pCODR.[25]

6.3.2 Summary of Included Studies

Only one study was identified that met the eligibility criteria of this systematic review (Table 1).

6.3.2.1 Detailed Trial Characteristics

a) Trials

Only one study, the CLEOPATRA trial[2] met the eligibility criteria for the systematic review (Table 1). The trial was a double-blind, placebo-controlled randomized trial that compared therapy with pertuzumab, trastuzumab, and docetaxel versus therapy with placebo, trastuzumab, and docetaxel in patients with HER2-positive locally recurrent or metastatic breast cancer who had not received prior chemotherapy or biologic therapy for their metastatic disease. The study was conducted in 204 centres in 25 countries in Asia, Europe, and North and South America. Both patients and investigators were blinded to pertuzumab or placebo assignment. An appropriate method of randomization was reported by Baselga et al.[2] Randomization was stratified by geographic area and by prior treatment status (prior adjuvant or neoadjuvant treatment vs. none). The study was funded by F. Hoffmann-La Roche and Genentech.[2] The data cut-off for the final analysis of the primary outcome was May 13, 2011. Of note, the study remained blinded after the final PFS analysis and was to remain blinded until the final analysis for overall survival, therefore no patients were permitted to cross over to the pertuzumab arm after the final PFS analysis.[25] An interim, and subsequently the final, analysis of overall survival was conducted on May 14, 2012 and was reported in a full publication by Swain, Kim et al in 2013.[3]

The primary outcome of the study was progression-free survival. Secondary endpoints included overall survival and objective response rate. Response was assessed by an independent review facility, using the RECIST criteria, every nine weeks during treatment and every six months in the first year after discontinuation, and thereafter once yearly for up to three years. Progression-free survival was defined as the time from randomization to date of progressive disease (first radiographical documentation) or death from any cause. Overall survival was defined as the time from randomization to the date of death from any cause. Objective response was defined as complete response or partial response.

A total of 800 patients were required to be enrolled to provide 381 events (progression or death from any cause within 18 weeks after the last tumour assessment), to provide 80% power to detect a 33% improvement in median progression-free survival in the pertuzumab arm compared to the placebo arm (Hazard Ratio [HR], 0.75) with a two-sided significance of 5%. The log-rank test, stratified by prior treatment status and region was used to compare the progression-free survival between the treatment arms. The Kaplan-Meier method was used to estimate the progression-free survival curves and the Cox proportional hazards model, with stratification by prior treatment status and region, was used to estimate the HR and 95% confidence intervals (95% CI). Of note, the study was designed with a pre-specified interim analysis of overall survival to be performed at the same time as the primary analysis for progression-free survival. A Lan-DeMets alpha spending function with an O'Brien-Fleming stopping boundary was applied to the interim analysis of overall survival. If the stopping boundary was not crossed, patients were to continue receiving study treatment, with groups remaining blinded, with planned interim analyses until the required number of events (deaths) occurred or the stopping boundary was crossed. Baselga et al[2] reported

that 385 deaths would be required for the final analysis of overall survival, providing 80% power to detect a 33% improvement in overall survival in the pertuzumab arm compared to the placebo arm. The early stopping boundary for the final analysis of overall survival was p≤0.0138 and a HR≤0.739.[3] In the analysis reported by Swain, Kim et al 2013[3] the comparison of overall survival between the two trial arms was analyzed using the log-rank test, stratified by previous treatment status and geographical region. The Kaplan-Meier method was used to estimate the median overall survival. The HR and its 95% CI were estimated using the Cox proportional hazards model with stratification by previous treatment status and geographical region. Analyses of overall survival by predetermined subgroups (previous treatment status, geographical region, age group, ethnic origin, visceral versus non-visceral disease, hormone receptor status, and HER2 status) were also conducted.[3]

Objective response was analyzed using the Mantel-Haenszel Chi-squared test stratified by prior treatment status and region. Adverse events were evaluated descriptively in the safety population, which was defined as all patients who received at least one dose of a study drug.

b) Populations

A total of 808 patients were enrolled and randomized in a 1:1 ratio to either pertuzumab/trastuzumab/docetaxel (n=402) or to placebo/trastuzumab/docetaxel (n=406). The baseline characteristics between the two groups were similar (Table 4).

Table 4. Baseline Patient Characteristics in the CLEOPATRA study.[2]

Characteristic	Pertuzumab	Placebo
n	402	406
Sex (%)		
Female	100.0	99.5
ECOG PS (%)		
0	68.2	61.1
1	31.1	38.7
≥2	0.7	0.2
Age (years)		
Median	54.0	54.0
Minimum-maximum	22-82	27-89
Race or ethnic group (%)		
Asian	31.8	32.8
Black	2.5	4.9
White	60.9	57.9
Other	4.7	4.4
Region (%)		
Asia	31.1	31.5
Europe	38.3	37.4
North America	16.7	16.7
South America	13.9	14.3
Disease type at screening (%)		
Nonvisceral	21.9	22.2
Visceral	78.1	77.8
Hormone-receptor status (%)		

Characteristic	Pertuzumab	Placebo
ER-positive, PgR-positive, or both	47.0	49.0
ER-negative and PgR-negative	52.7	48.3
Unknown	0.2	2.7
HER2 status, assessed by immunohistochemistry (%)		
0 or 1+	1.0	0.5
2+	11.7	7.9
3+	87.1	91.4
Data not available	0.2	0.2
HER2 status, assessed by FISH (%)		
Positive	95.5	94.3
Negative	0.2	1.0
Data not available	4.2	4.7
Prior adjuvant or neoadjuvant chemotherapy (%)		
No	54.2	52.7
Yes†	45.8	47.3
Anthracycline	37.3	40.4
Hormone	26.4	23.9
Taxane	22.6	23.2
Trastuzumab	11.7	10.1

Notes: ECOG PS=Eastern Cooperative Oncology Group performance status; ER=estrogen receptor; FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor receptor 2; n=number of patients randomized; PgR=progesterone receptor.

†Patients may have received more than one type of adjuvant or neoadjuvant chemotherapy.

c) Interventions

All 808 patients in the trial were to receive either placebo or pertuzumab, in combination with trastuzumab and docetaxel.[2] All drugs were administered intravenously. Trastuzumab was to be given at a loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression, as assessed by the investigator or the development of toxic effects that could not be managed. Dose reductions of trastuzumab were not permitted. Docetaxel was to be given at 75 mg/m^2 every 3 weeks. At the discretion of the investigator, the dose of docetaxel could be increased to 100 mg/m^2 if the side-effects were acceptable. The protocol also allowed the investigator to reduce the dose by 25% if the drug had toxic effects. It was recommended that patients receive six cycles of docetaxel.

Four hundred two patients out of the total 808 patients were randomized to receive pertuzumab in combination with trastuzumab and docetaxel and 406 patients were randomized to receive placebo in combination with trastuzumab and docetaxel. Pertuzumab or placebo was administered at a loading dose of 840 mg followed by 420 mg every 3 weeks until disease progression or the development of toxic effects that could not be managed. Dose reductions of pertuzumab or placebo were not permitted.

The median number of treatment cycles per patient was 15 (range, 1-50) in the placebo arm and 18 (range, 1-56) in the pertuzumab arm. The median duration of study treatment was 11.8 months in the placebo arm and 18.1 months in the pertuzumab arm. Patients received docetaxel for a median of eight cycles (range, 1-41) in the placebo arm and eight cycles (range, 1-35) in the pertuzumab arm. In the safety population (placebo arm, n=397; pertuzumab arm, n=407), the dose of

docetaxel was increased to 100 mg/m^2 for one or more cycles in 15.4% of patients in the placebo arm and in 11.8% of patients in the pertuzumab arm. The median dose intensity of docetaxel was 24.8 mg/m^2 per week in the placebo arm and 24.6 mg/m^2 per week in the pertuzumab arm.

Following discontinuation of study treatment, 76.9% of 338 patients who received placebo, and 75.5% of 298 patients who received pertuzumab received subsequent treatments.[3] Table 5 provides details regarding the subsequent treatments received by patients in each study arm following discontinuation of study treatment.

Table 5. Subsequent Treatments Received Following Discontinuation of Study Treatment.[3]

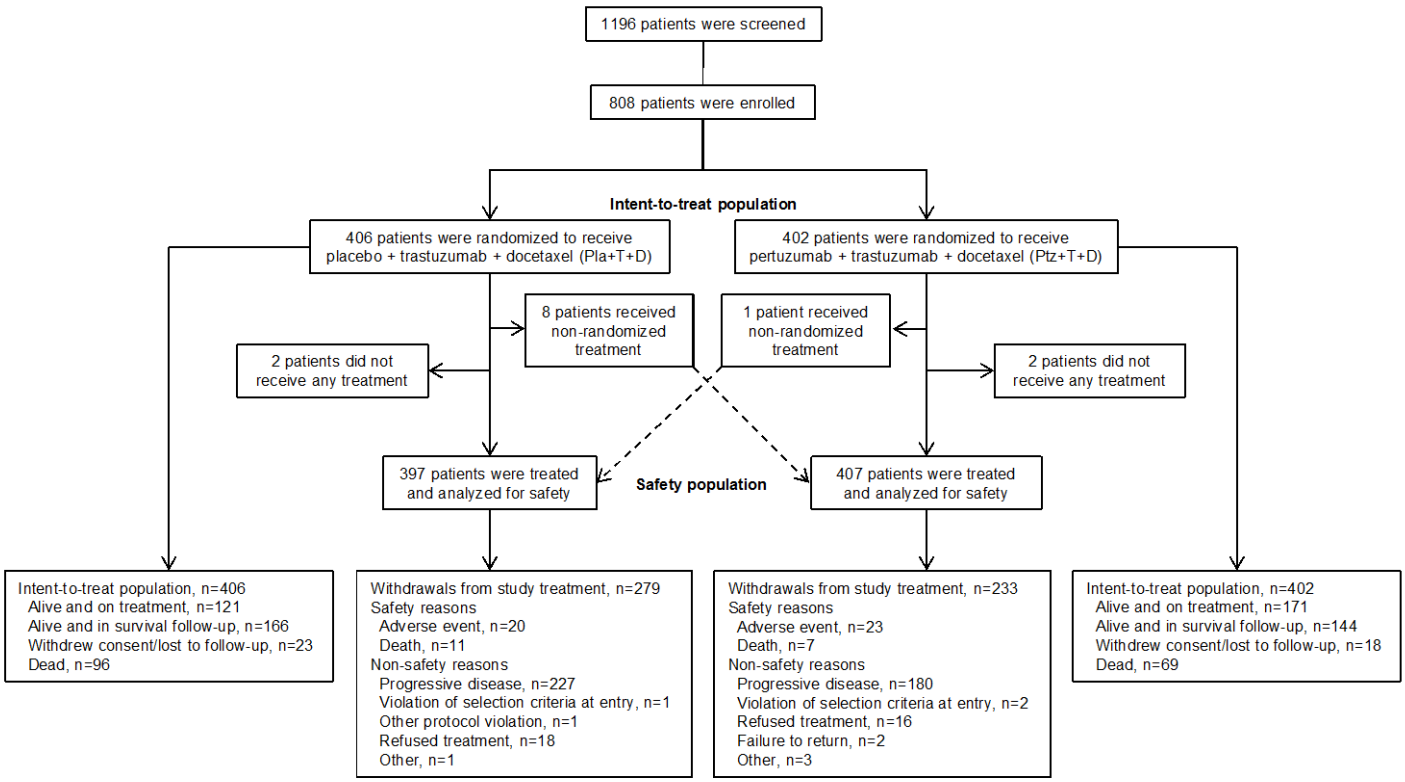
Treatment	Pertuzumab-arm n=225	Placebo-arm (n=260)
Any HER2-targeted therapy, n(%)	160 (71.1)	178 (68.5)
Trastuzumab, n(%)	106 (47.1)	104 (40.0)
Laptinib, n(%)	93 (41.3)	114 (43.8)
Trastuzumab emtansine, n(%)	21 (9.3)	26 (10.0)
Capecitabine, n(%)	113 (50.2)	140 (53.8)
Vinorelbine, n(%)	51 (22.7)	70 (26.9)
Cyclophosphamide, n(%)	30 (13.3)	43 (16.5)
Doxorubicin, n(%)	29 (12.9)	46 (17.7)
Paclitaxel, n(%)	21 (9.3)	32 (12.3)
Docetaxel, n(%)	13 (5.8)	11 (4.2)

Note: Table is reproduced, in a modified form, from Swain, Kim et al, 2013.[3]

d) Patient Disposition

The disposition of the patients, for both the intent-to-treat population and the safety population can be found in Figure 2.

Figure 2. Patient disposition in the CLEOPATRA study.[2]



Note: Figure reproduced from supplementary material for Baselga et al, 2012[2], available online at http://www.nejm.org.

At the primary analysis (May 2011), of the 406 patients randomized to the placebo arm, two patients did not receive any treatment and eight received pertuzumab instead of placebo. In addition, 23 patients withdrew consent and/or were lost to follow-up. Of the 402 patients randomized to the pertuzumab arm, two patients did not receive any treatment and one patient received placebo instead of pertuzumab. In addition, 18 patients withdrew consent and/or were lost to follow-up. In total, at the time of analysis, 96 patients had died in the placebo arm and 69 patients had died in the pertuzumab arm.

At the May 2012 overall survival final analysis, 338 of 406 (83.3%) patients in the placebo group and 298 of 402 (74.1%) patients in the pertuzumab group had discontinued study treatment.[3] Swain, Kim et al[3] did not report data on patient disposition for the time period between the primary (May 2011) analysis and the final (May 2012) overall survival analysis. The submitter was asked to provide information on the proportion of patients who withdrew or dropped out during that time period. The proportion of patients who withdrew because they refused treatment (defined as 'did not cooperate' or 'withdrew consent') was similar between the two study arms and the proportions reported for each study arm were relatively unchanged from those reported in the primary (May 2011) analysis.[25]

e) Limitations/Sources of Bias

The CLEOPATRA study[2] was a well designed and conducted double-blind placebo-controlled randomized trial. Both the patients and investigators were blinded to

study treatment. The primary outcome was progression free survival with a planned interim analysis for overall survival data when the primary analysis for progression-free survival was conducted. A total of 41 of 808 patients withdrew consent, were lost to follow-up, or both—Baselga et al[2] did not report further information. However, even if all 41 patients were lost to follow-up, they represent approximately 5% of the total study population and would therefore have only a small impact on the study results. Another potential limitation is the lack of information regarding the administration and collection of the health-related quality of life evaluations and the limited data on quality of life outcomes. Given the limited information reported for the quality of life evaluations, the reported results need to be interpreted with caution.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

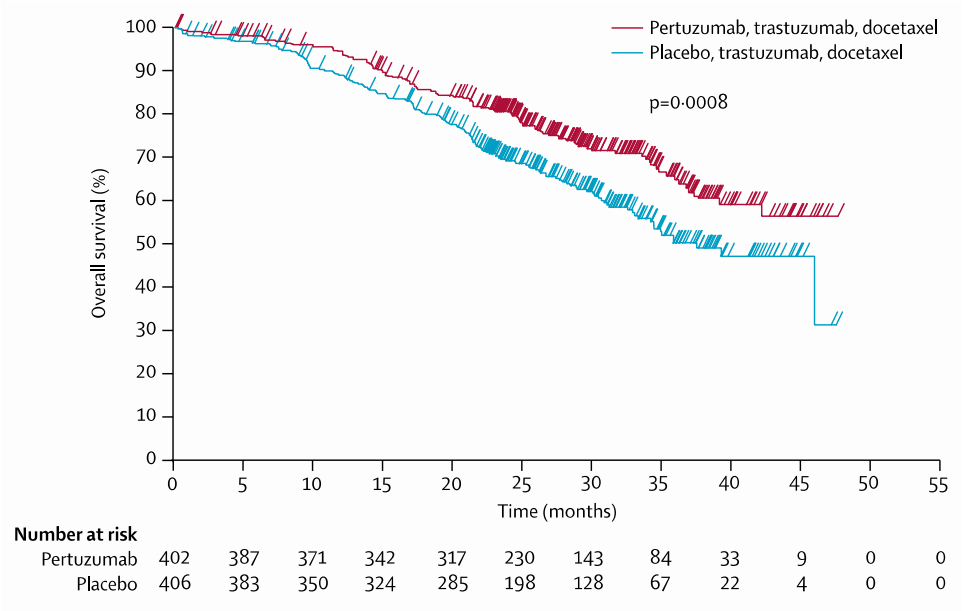
A total of 808 patients (402 patients in the pertuzumab arm and 406 patients in the placebo arm) were included in the intent-to-treat efficacy analysis.[2] Table 2 summarizes the key efficacy outcomes for the CLEOPATRA study.

Overall Survival

At the data cut-off for the interim overall survival analysis, after a median follow-up of 19.3 months, a total of 69 of 402 patients died in the pertuzumab arm compared to 96 deaths of 406 patients in the placebo arm.[2] The interim analysis for overall survival demonstrated that this difference was not statistically significant (Table 2).

The final analysis for overall survival was reported at the SABCS in 2012[15], and was subsequently fully published in 2013 as Swain, Kim et al.[3] That analysis used a data cut-off of May 14 2012, nearly a year after the final analysis for the primary outcome, with a median follow-up of 30.1 months in the placebo arm and 29.7 months in the pertuzumab arm.[3] That analysis crossed the O'Brien-Fleming stopping boundary and the overall survival analysis was deemed statistically significant. The median overall survival was not yet reached in the pertuzumab arm (113 deaths) compared to 37.6 months in the placebo arm (154 deaths), with a HR of 0.66, 95% CI 0.52-0.84, p=0.0008 (Table 2).[3] See Figure 3 for the Kaplan-Meier curves of overall survival reported by Swain, Kim et al 2013.[3]

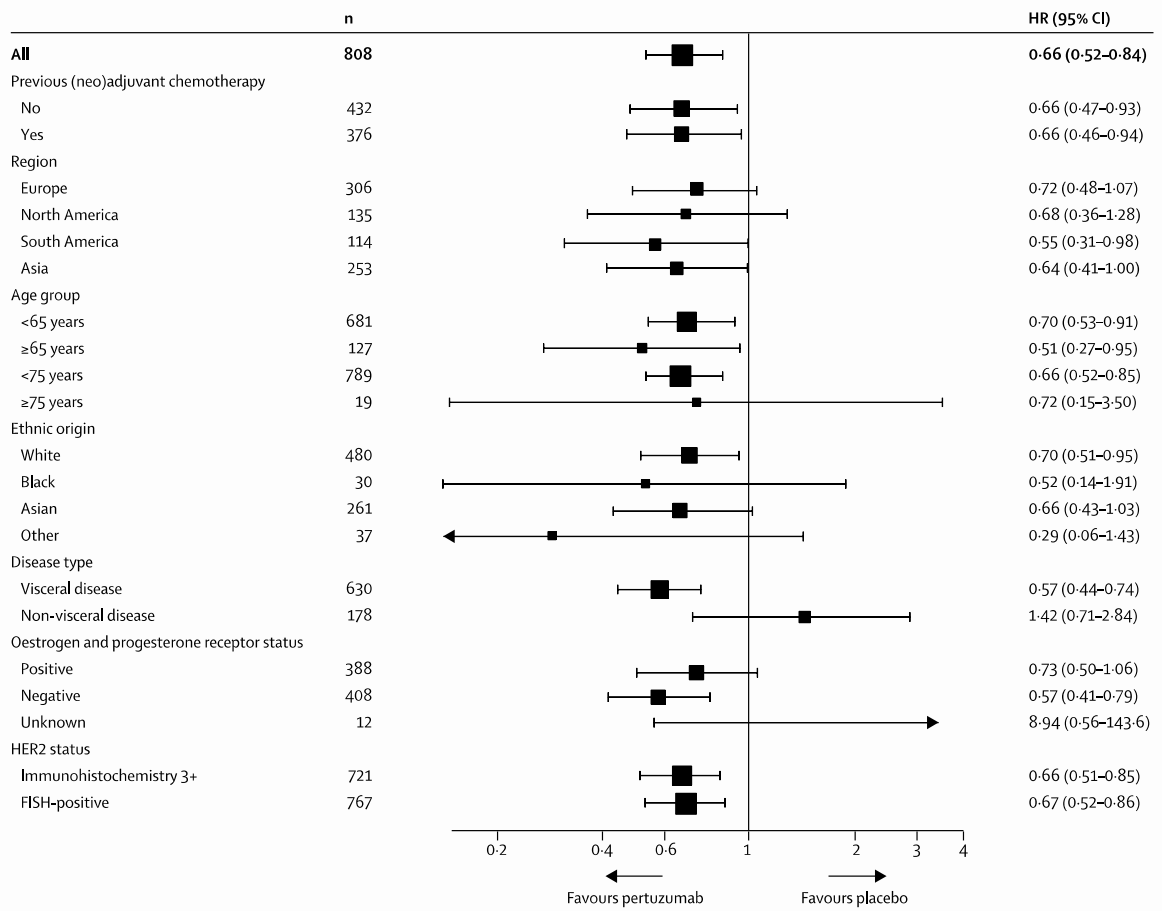
Figure 3. Kaplan-Meier Estimates of Overall Survival, as Reported in the Final Overall Survival Analysis for the CLEOPATRA study.[3]



Note: Reproduced from Swain, Kim et al, 2013 *Lancet Oncology*.[3]

Swain, Kim et al 2013 also reported subgroup analyses across several pre-defined subgroups.[3] See Figure 4 for a Forest Plot of subgroup analyses of overall survival for prespecified subgroups as reported by Swain, Kim et al 2013.[3] The benefit of pertuzumab compared to placebo with respect to overall survival was seen in each of the subgroups, with the exception of nonvisceral disease, which favoured the placebo arm; however, the result was not statistically significant for that subgroup.

Figure 4. Forest Plot of Overall Survival Across Prespecified Subgroups, as Reported in the Final Overall Survival Analysis for the CLEOPATRA Study.[3]

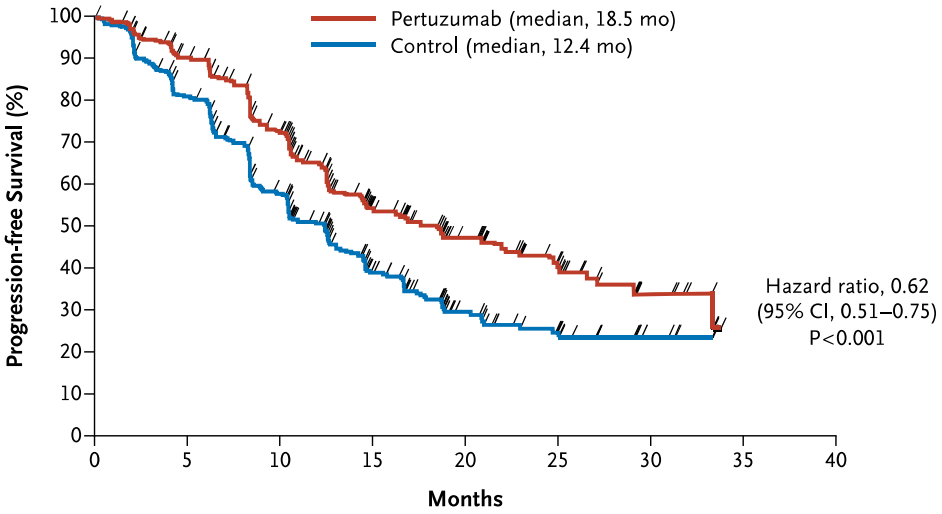


Note: Reproduced from Swain, Kim et al, 2013 *Lancet Oncology*.[3]

Progression-Free Survival

At the date of the primary analysis (May 2011) and after a median follow-up of 19.3 months, independently assessed median progression-free survival, stratified by prior treatment and region, was significantly longer in the pertuzumab arm (18.5 months) compared to the placebo arm (12.4 months), with a hazard ratio (HR) of 0.62 and a 95% confidence interval (CI) of 0.51-0.75; p<0.001.[2] Please see Figure 5 for the Kaplan-Meier curves of progression-free survival reported in the full publication.

Figure 5. Kaplan-Meier Estimates of Progression-free Survival Based on Independent Tumour Assessments, as Reported in the Primary Publication of the CLEOPATRA Study.[2]

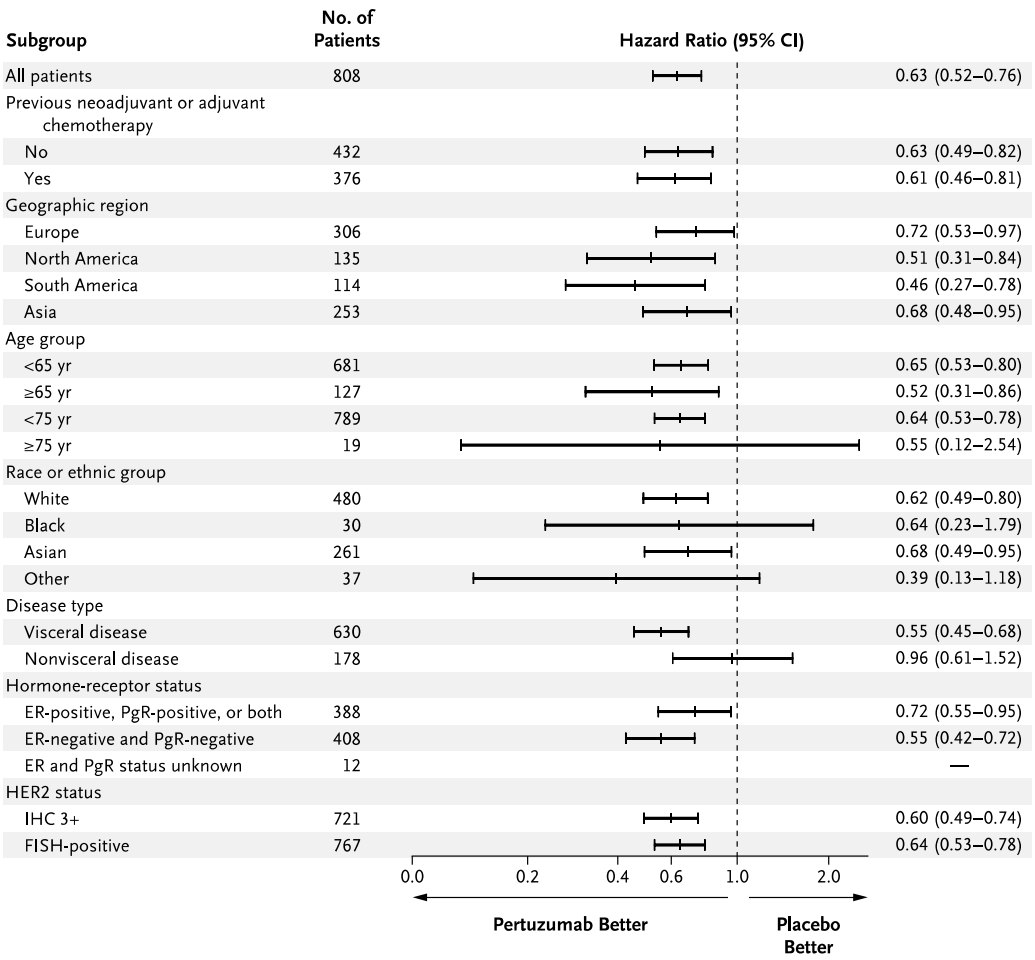


No. at Risk									
Pertuzumab	402	345	267	139	83	32	10	0	0
Control	406	311	209	93	42	17	7	0	0

Note: Reproduced from Baselga et al, 2012.[2]

Baselga et al[2] also reported analyses of progression-free survival across several pre-defined subgroups (Figure 6). The benefit of pertuzumab/trastuzumab/docetaxel was consistent across all subgroups with the exception of patients aged ≥75 years, patients who are Black, patients whose race was defined as 'Other', and patients with nonvisceral disease. Of note, those four subgroups consisted of a small number of patients compared to the other subgroups within their respective categories.

Figure 6. Forest Plot of Progression-free Survival Based on Independent Tumour Assessments Across Prespecified Subgroups, as Reported in the Primary Publication of the CLEOPATRA Study.[2]



Notes: ER=estrogen receptor; FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; PgR=progesterone receptor.
Reproduced from Baselga et al, 2012.[2]

In an updated analysis with a data cut-off of May 14, 2012, Swain, Kim et al 2013[3] reported that progression-free survival was relatively unchanged from the original final analysis and the result was still statistically significant in favour of the pertuzumab arm compared to the placebo arm (Table 2).

Objective Response

Baselga et al[2] reported a statistically significant difference in the rate of objective response in favour of the pertuzumab arm (80.2% of 343 evaluable patients) compared to the placebo arm (69.3% of 336 evaluable patients; p=0.001).

Quality of Life

Information on health-related quality of life (HRQOL) evaluations in the CLEOPATRA study were reported by Cortes et al[4] at the 2012 ASCO annual conference. Time to

deterioration of HRQOL was evaluated using the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire and was defined as a decrease of five points from the baseline score in the physical, functional and breast subscales (together referred to as the TOI-PFB subscale). Patients completed questionnaires every third cycle three days before each tumour assessment until independently determined progressive disease. The numbers of patients who completed the questionnaire at baseline and throughout therapy were not reported; however, 75% or more of patients in each arm completed the questionnaire beyond the first year.[4] Cortes et al[4] reported that 56.7% of patients in the placebo arm and 59.5% of patients in the pertuzumab arm experienced deterioration of HRQOL during the study based on the TOI-PFB subscale. The median time to deterioration was 18.3 weeks in the placebo arm versus 18.4 weeks in the pertuzumab arm (HR 0.97, p=0.7161). At Cycle 6, the mean reduction in TOI-PFB score from baseline was -3.5 in the placebo arm and -3.0 in the pertuzumab arm. The authors reported that compliance with reporting the FACT-B questionnaire was ≥75% beyond the first year in both arms.

Adverse Events

Key adverse events and harms outcomes can be found in Table 2. No statistical comparisons were made between the treatment and control arms for any adverse events.[2] The adverse events found in Table 2 include those reported in the publication by Baselga et al, for the primary analysis (May 2011) where there was a difference between the treatment arms of 5% or more.[2] All grades of diarrhea, rash, mucosal inflammation, and dry skin occurred in a greater proportion of patients in the pertuzumab arm compared to the placebo arm (Table 2). In addition, the rate of febrile neutropenia occurred in a higher proportion of patients in the pertuzumab arm compared to the placebo arm. The rate of all grades of constipation and the rate of grade 3 or higher left ventricular systolic dysfunction were both higher in the placebo arm than the pertuzumab arm (Table 2). Table 6 presents the rates of all grades of adverse events with an incidence of at least 25% or more in either arm or at least a 5% difference in incidence between the arms as well as the rates of Grade 3 or higher adverse events with an incidence of at least 2%.

The rate of withdrawal from the study due to adverse events was identified as a harms outcome that was of particular interest: the proportional of patients was similar in both treatment arms (5.7% in the pertuzumab arm versus 5.0% in the placebo arm).

Cardiac toxicity was also identified as a harms outcome of particular interest. Baselga et al[2] reported that the proportion of patients with Grade 3 or higher left ventricular systolic dysfunction was 1.2% of 407 patients who received pertuzumab in combination with trastuzumab and docetaxel while the proportion was 2.8% of 397 in patients who received placebo in combination with trastuzumab and docetaxel. Swain, Ewer et al, 2013 reported cardiac tolerability for patients in the CLEOPATRA study.[17] The authors reported that left ventricular ejection fraction (LVEF) was assessed by echocardiogram (ECHO) in 77% of 804 patients included in the cardiac tolerability report (the study safety population), by Multi Gated Acquisition Scan (MUGA) in 18%, and by both ECHO and MUGA in 5%. LVEF was measured at baseline then every nine weeks during study treatment, then at study discontinuation, and every six months for one year following discontinuation and annually thereafter for three years. A clinically significant decline in LVEF was defined as a greater than or equal to 10% decrease from baseline to an absolute value less than 50%. The mean LVEF at baseline was similar in both arms; 65.6% in the placebo arm and 64.8% in the pertuzumab arm. A clinically significant decline in LVEF occurred in 25 of 397 (6.6%) patients in the placebo arm and in 15 of 407 (3.8%) patients in the pertuzumab arm. Of those patients, the LVEF

value recovered to 50% or greater in 18 patients (72.0%) in the placebo arm and in 13 patients (86.7%) in the pertuzumab arm. Swain, Kim et al 2013 reported updated results for LVEF decline and recovery.[3] A clinically significant decline in LVEF occurred in 28 of 396 patients (7.1%) in the placebo arm and in 18 of 408 patients (4.4%) in the pertuzumab arm.[3] A recovery of LVEF to 50% or more occurred in 25 of 28 patients (89.3%) in the placebo arm and in 16 of 18 patients (88.9%) in the pertuzumab arm.[3]

Swain, Kim et al 2013[3] reported in the final overall survival analysis (May 2012) that there were a total of 152 deaths out of 396 patients who received placebo. Of those, five (1.3%) were due to febrile neutropenia or infection and that 12 patients (3.0%) died due to adverse events. In the pertuzumab arm, there were a total of 113 deaths out of 408 patients, of which five (1.2%) deaths were attributable to febrile neutropenia or infection, and eight deaths (2.0%) were due to adverse events. In addition, 13 patients in the placebo arm and 11 patients in the pertuzumab arm died due to unknown or other causes.[15]

Table 6. Adverse Events in the CLEOPATRA Study as Reported in the Full Publication.[2]

Adverse Event	Pertuzumab, trastuzumab, docetaxel; n=407 (%)	Placebo, trastuzumab, docetaxel; n=397 (%)
All grades		
Diarrhea	66.8	46.3
Alopecia	60.9	60.5
Neutropenia	52.8	49.6
Nausea	42.3	41.6
Fatigue	37.6	36.8
Rash	33.7	24.2
Decreased appetite	29.2	26.4
Mucosal inflammation	27.8	19.9
Asthenia	26.0	30.2
Peripheral edema	23.1	30.0
Constipation	15.0	24.9
Dry skin	10.6	4.3
Grade 3 or higher		
Neutropenia	48.9	45.8
Febrile neutropenia	13.8	7.6
Leukopenia	12.3	14.6
Diarrhea	7.9	5.0
Peripheral neuropathy	2.7	1.8
Anemia	2.5	3.5
Asthenia	2.5	1.5
Fatigue	2.2	3.3
Granulocytopenia	1.5	2.3
Left ventricular systolic dysfunction	1.2	2.8
Dyspnea	1.0	2.0

Note: Reproduced from Baselga et al, 2012.[2]

6.4 Ongoing Trials

Two ongoing RCTs were identified investigating the use of pertuzumab in patients with HER2-positive locally recurrent of metastatic breast cancer who have not received chemotherapy or biologic therapy for their metastatic disease through a search of clinical trial registries: NCT01597414 and NCT01120184. Details of the trials can be found in Tables 7 and 8.

Table 7. Study NCT01597414: Pertuzumab + trastuzumab (PH) versus PH plus metronomic chemotherapy (PHM) in the elderly HER2+ metastatic breast cancer population who may continue on T-DM1 alone following disease progression while on PH/PHM: an open-label multicentre randomized phase II selection trial of the EORTC Elderly Task Force and Breast Cancer Group.[37]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01597414 Open-label, active control, randomized phase II trial. Start date: Not yet open to recruitment Expected completion date: Unknown Estimated enrolment: 80 Sponsor: European Organization for Research and Treatment of Cancer (EORTC) Collaborator: Hoffmann-La Roche	Female patients with histologically proven HER2-positve newly diagnosed or recurrent (after surgery) stage IV disease. Patients must have measurable (RECIST criteria) or evaluable disease. WHO PS 0-3 Age ≥70 years, or age ≥60 years with required number of dependencies (not reported).	**Two arms:** Pertuzumab loading dose 840 mg on cycle 1, followed by 420 mg for subsequent cycles, every 3 weeks + trastuzumab loading dose 8 mg/kg of body weight on cycle 1, followed by a maintenance dose of 6 mg/kg every 3 weeks. ***Or*** Pertuzumab + trastuzumab (as above) + cyclophosphamide daily dose of 50 mg/day Patients in both arms will be offered option of T-DM1 after progression: 3.6 mg/kg intravenously, every 3 weeks.	Primary outcomes: Progression-free survival Secondary outcomes: Overall survival Tumour response Health-related quality of life

Available from: http://clinicaltrials.gov/ct2/show/NCT01597414?term=nct01597414&rank=1.

Table 8. Study NCT01120184: A study of trastuzumab-DM1 (T-DM1) plus pertuzumab versus trastuzumab (Herceptin) plus a taxane in patients with metastatic breast cancer.[38]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01120184 Active control, multicenter randomized phase III trial. Arm 1 is open-label and	Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease and a candidate	**Three arms:** ***Arm 1: Patients received either Trastuzumab (Herceptin) +***	Primary outcomes: Progression-free survival (independent tumour assessments) Incidence of adverse

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Arms 2&3 are blinded (subject, investigator, outcome assessors) Start date: July 2010 Expected completion date: April 2016 Estimated enrolment: 1095 Sponsor: Hoffmann-La Roche. Collaborators: Genentech	for chemotherapy. HER2-positive disease. Patients with locally advanced disease must have recurrent or progressive disease that is not resectable. Disease must be measurable or evaluable by RECIST criteria. ECOG PS 0-1 Age ≥18 years Excluded: Patients with prior trastuzumab emtansine (T-DM1) or pertuzumab therapy	***docetaxel (Arm 1a) or Herceptin + paclitaxel (Arm 1b)***: Arm 1a: Herceptin 8 mg/kg i.v. on cycle 1 followed by 6 mg/kg every 3 weeks in subsequent cycles + docetaxel 75 mg/m^2 or 100 mg/m^2 i.v. (on same day as Herceptin) every 3 weeks for a minimum of 6 cycles. Arm 1b: Herceptin 4 mg/kg i.v. on day 1 of cycle 1 followed by 2 mg/kg weekly starting on day 8 of cycle 1 + paclitaxel 80 mg/m^2 i.v. weekly for a minimum of 18 weeks. ***Or*** ***Arm 2:*** T-DM1 3.6 mg/kg i.v. every 3 weeks + pertuzumab 840 mg i.v. on day 1 of cycle 1 followed by 420 mg i.v. every 3 weeks in subsequent cycles. ***Or*** ***Arm 3:*** T-DM1 3.6 mg/kg i.v. every 3 weeks + pertuzumab placebo 840 mg i.v. on day 1 of cycle 1 followed by 420 mg i.v. every 3 weeks in subsequent cycles.	events <u>Secondary outcomes:</u> 1-year survival rate Overall survival Time-to-treatment failure Objective response rate Duration of response

Available from: http://clinicaltrials.gov/ct2/show/NCT01120184?term=nct01120184&rank=1.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Breast Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on pertuzumab (Perjeta) for metastatic breast cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Breast Clinical Guidance Panel is comprised of three medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. (pertuzumab: or perjeta: or 2C4:).ti,ab,rn,nm,sh,hw,ot.
2. 380610-27-5.rn,nm.
3. 1 or 2
4. Exp Breast Neoplasms/
5. (cancer: Or carcinoma: Or neoplasm: Or tumo?r:).ti,ab,sh,hw,ot.
6. (breast: Or mammary).ti,ab,sh,hw,ot.
7. 5 and 6
8. 4 or 7
9. (metasta: or advanc:).ti,ab,sh,hw,ot.
10. 8 and 9
11. 3 and 10

Ovid EMBASE

1. exp *pertuzumab/
2. (pertuzumab: or perjeta: or 2C4:).ti,ab.
3. 1 or 2
4. exp *breast neoplasms/
5. (cancer: Or carcinoma: Or neoplasm: Or tumo?r:).ti,ab.
6. (breast: Or mammary).ti,ab.
7. 5 and 6
8. 4 or 7
9. (metasta: or advanc:).ti,ab.
10. 8 and 9
11. 3 and 10

2. Literature Search via PubMed

PubMed

1. pertuzumab* or perjeta* or 2C4*
2. publisher[sb]
3. 1 and 2

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Search terms: (pertuzumab* or perjeta* or 2C4*) AND (breast cancer*) in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: pertuzumab, perjeta, breast cancer

Select International Agencies:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
www.ema.europa.eu

Search terms: pertuzumab, perjeta

Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search

Search terms: pertuzumab, perjeta, breast cancer

San Antonio Breast Cancer Symposium (SABCS)
via the *Cancer Research* search portal: http://cancerres.aacrjournals.org/search
The abstracts for each year of the SABCS are published in the following issues:
Cancer Research 2012;72(24 Suppl 3)
Cancer Research 2011;71(24 Suppl 3)
Cancer Research 2010:70(24 Suppl 2)
Cancer Research 2009:69(24 Suppl 1)
Cancer Research 2008:69(2 Suppl 1)
Poster presentations of identified abstract, if available, were obtained from the SABCS website: http://www.sabcs.org/

Search terms: pertuzumab, Perjeta

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