pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pertuzumab (Perjeta) Neoadjuvant Breast Cancer

July 16, 2015

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

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1 GUIDANCE IN BRIEF

1.1 Background

In 2014 approximately 24,400 women in Canada were diagnosed with breast cancer, the majority of whom presented with early stage disease.[1,2] In general, primary operable breast cancers are categorized as Stage I-II and locally advanced breast cancers as Stage III. Overall, the 5-year relative survival from breast cancer is 88%, though this varies based on disease stage and subtype. According to the National Cancer Institute, approximately 20-25% of all breast cancers are human epidermal growth factor receptor-2 (HER2) positive.[1,2] HER2-positive breast cancer has a poorer prognosis than HER2-negative disease because they have a greater likelihood of relapse and poorer survival.[3]

Pertuzumab (Perjeta) targets the HER2 protein and binds to a different epitope than trastuzumab and prevents the pairing of HER2 with other members of the human epidermal growth factor receptor family, which reduces cell signalling and division.[4]

The objective of this review was to evaluate the effectiveness and safety of pertuzumab in combination with trastuzumab and chemotherapy in the neoadjuvant setting for the treatment of patients with HER2-positive locally advanced, inflammatory, or early stage breast cancer who have not received any previous cancer therapy for their disease.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two randomized phase II trials met the criteria for inclusion in this review. The NeoSphere study was a four arm phase II open-label trial that randomized patients with HER2-positive locally advanced, inflammatory, or primary operable breast cancer to trastuzumab plus docetaxel (n=107); pertuzumab plus trastuzumab plus docetaxel (n=107); pertuzumab plus trastuzumab (n=107) or; pertuzumab plus docetaxel (n=96). Pertuzumab was administered at a loading dose of 840 mg, followed by a 420 mg dose every 3 weeks. Trastuzumab was administered at a loading dose of 8 mg/kg, followed by a 6 mg/kg dose every 3 weeks. Docetaxel was administered at a dose of 75 mg/m^2 (with escalation to 100 mg/m^2, if tolerated) every 3 weeks.[5] The primary endpoint was pathological complete response (pCR).

The TRYPHAENA study was a three arm phase II trial that randomized patients with HER2-positive primary operable, locally advanced or inflammatory breast cancer to pertuzumab and trastuzumab in cycles 1-6 plus FEC-5 (fluorouracil, epirubicin, cyclophosphamide) in cycles 1-3 and docetaxel in cycles 4-6 (Arm A; n=73); FEC-5 in cycles 1-3 followed by pertuzumab, trastuzumab, and docetaxel in cycles 4-6 (Arm B; n=75), or; pertuzumab, trastuzumab, docetaxel, and carboplatin in cycles 1-6 (Arm C; n=77). Pertuzumab was administered at a loading dose of 840 mg, with subsequent doses of 420 mg. Trastuzumab was administered at a loading dose of 8 mg/kg, with subsequent doses of 6 mg/kg.[6] The primary endpoint of the study was cardiac safety (incidence of symptomatic left ventricular systolic dysfunction [LVSD]; decline in left ventricular ejection fraction [LVEF] of ≥10% points from baseline to <50% over course of neoadjuvant treatment). No hypothesis testing was conducted for this study.

Efficacy

In the NeoSphere study, the rate of pCR(breast) was statistically significantly higher in the pertuzumab plus trastuzumab plus docetaxel group compared with the tratuzumab plus docetaxel group (45.8% versus [vs.] 29%, respectively; p=0.0141).[7] The rate of pCR was 16.8% in the pertuzumab plus docetaxel group and 24% in the pertuzumab plus docetaxel group. In patients with T2-T3 tumours expected to undergo a mastectomy at baseline, the rate of conversion to breast conserving surgery was 23.2% in the pertuzumab plus trastuzumab plus docetaxel arm and 22.6% in the trastuzumab plus docetaxel arm.[8] Data on three-year progression-free survival (PFS) and disease-free survival (DFS) provided by the Submitter, and subsequently presented at ASCO 2015 demonstrated no statistically significant differences between the pertuzumab plus trastuzumab plus docetaxel arm (90% and 92%, PFS and DFS rates, respectively) compared with the trastuzumab plus docetaxel arm (86% and 85%), with hazard ratio (HR) of 0.69 (95% confidence interval [CI]) 0.34 to 1.40 for PFS and HR of 0.60 (95% CI 0.28-1.27) for DFS.[9] Of note, the trial was not powered to detect differences in either of those outcomes.

In the TRYPHAENA study, all arms received pertuzumab. The rate of pCR(breast) was 61.6% in Arm A, 57.3% in Arm B, and 66.2% in Arm C. The rate of pCR(breast and nodes) was 56.2% in Arm A, 54.7% in Arm B, and 63.6% in Arm C. The rate of conversion to breast conserving surgery was 21.7% in Arm A, 16.7% in Arm B, and 27.0% in Arm C.[6]

Harms

Grade 3 or higher adverse events in the NeoSphere trial were similar between the treatment groups that received docetaxel, but lower in the group that received trastuzumab plus pertuzumab alone. The most common grade 3 or higher adverse events were neutropenia (range 45%-57% in docetaxel arms vs. 1% in the arm without docetaxel), febrile neutropenia (range 7%-8% in docetaxel arms vs. none in the arm without docetaxel), and leukopenia (range 5%-12% in docetaxel arms vs. none in the arm without docetaxel). Of note, no significant change in mean maximum left ventricular ejection fraction (LVEF) was detected when pertuzumab was added to trastuzumab and no patient experienced an LVEF decrease to less than 40% at any time during the study. During neoadjuvant treatment, no patients withdrew due to an adverse event in the group that received trastuzumab plus docetaxel or in the group that received pertuzumab plus trastuzumab plus docetaxel, while two patients in each of the remaining treatment groups did so.[7]

In the TRYPHAENA study, neutropenia, febrile neutropenia, and leukopenia were the most frequently reported grade 3 or higher adverse events. The rates of febrile neutropenia were 18.1% in Arm A, 9.3% in Arm B, and 17.1% in Arm C. The rates of grade 3 or higher LVSD were 0% in Arm A, 2.7% in Arm B, and 0% in Arm C. The rates of decline in LVEF ≥10% from baseline to <50% were 5.6% in Arm A, 5.3% in Arm B, and 3.9% in Arm C.[6]

1.2.2 Additional Evidence

pCODR received input on pertuzumab for the neoadjuvant treatment of HER2-positive early stage breast cancer from one patient advocacy group, Canadian Breast Cancer Network (CBCN). Provincial Advisory Group input was obtained from nine of the nine provinces participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of pertuzumab in the neoadjuvant treatment of HER2-positive early stage breast cancer and is discussed as supporting information:

- Pathological complete response as a surrogate for long-term survival in patients with early stage breast cancer.
    - A summary and critical appraisal of a pooled analysis of pathological complete response and long-term outcomes in breast cancer was conducted.[10] Cortazar et al conducted a systematic review for trials of neoadjuvant treatment of breast cancer. A total of 12 trials with 11,955 patients were identified and included. The authors reported an association between pCR and event-free survival (EFS) and overall survival that was strongest in patients with total pCR (no invasive disease in breast and nodes, i.e., ypT0/is ypNO or ypT0 ypN0). The association was strongest in patients with triple-negative breast cancer and in patients with HER2-positive, hormone-receptor negative breast cancer. At a trial level, little association was demonstrated between the frequency of pCR and either EFS or overall survival. Potential limitations of this analysis included: i) variation in definition of pCR between the trials; ii) inclusion of non-randomized trials which might limit generalizability of the results, and; iii) different preoperative treatments were used given the differences in inclusion criteria between the trials (e.g., HER2-positive versus HER2-negative). If different subtypes of breast cancer have different responses to the same treatment, the association between pCR and long-term outcomes could be obscured. Although an association between pCR and EFS and between pCR and overall survival was demonstrated at the individual level, the data did not demonstrate that, at a trial level, pCR is associated with either EFS or overall survival. Further study is required in order for pCR to be validated as a surrogate for EFS or overall survival.

1.2.3 Interpretation and Guidance

Burden of Illness

In 2014, approximately 24,400 women were diagnoses with breast cancer in Canada. Approximately 95% of new cases of breast cancer are stage 0-III. Overall, the 5-year relative survival from breast cancer is 88%, though this varies based on stage and subtype. For Stage I disease, approximately 15% are HER2-positive, while 18-20% of Stage II-III cases are HER2-positive. Despite the use of anti-HER2 directed therapies (ie. trastuzumab), the risk of relapse in women with node positive locally advanced HER2-positive breast cancer is higher than in those with HER2-negative disease. The estimated 10-year DFS is 73.7% in patients treated with adjuvant trastuzumab.[11] After a median follow-up of 5.4 years, the 5-year EFS was 58% in the neoadjuvant chemotherapy plus trastuzumab arm of the NOAH study, which enrolled patients with locally advanced or inflammatory breast cancer.[7] Women with HER2-positive breast cancer treated with chemotherapy and anti-HER2 directed therapy remain at ongoing risk of relapse.

Effectiveness

The most relevant trial on which to base conclusions is the NeoSphere trial, as it is the only trial in which part of a current standard of care was included (i.e., the trastuzumab plus docetaxel arm). The NeoSphere study demonstrated significant differences in the rate of pCR(breast) in favour of the pertuzumab plus trastuzumab plus docetaxel arm compared with the trastuzumab plus docetaxel arm. In addition, a higher rate of pCR(breast and nodes) was observed in the pertuzumab-trastuzumab-docetaxel arm (39.3%) than in the trastuzumab-docetaxel arm (21.5%). Although no significant differences in DFS or PFS were reported for the comparison of pertuzumab-trastuzumab-docetaxel to trastuzumab-docetaxel, the trial was not powered to detect differences in either outcome.[9]

Slightly higher rates of pCR(breast and nodes) were seen in all three arms of the TRYPHAENA study ; however, the study lacked an arm without pertuzumab which limits the extrapolation of these results to other studies and to distinguish the additional benefit of pertuzumab.[6]

Safety

The rates of adverse events were similar in the arms containing pertuzumab compared with trastuzumab-docetaxel arm, with the exception of slight numerical increases in diarrhea, rash and mucosal inflammation. The most frequently occurring adverse events were alopecia, neutropenia, diarrhea, nausea, fatigue, rash, and mucosal inflammation. The rates of grade 3 or higher adverse events were similar with or without pertuzumab. The addition of pertuzumab did not increase the rate of clinically significant cardiac toxicity. Similar rates of adverse events were observed in the TRYPHAENA study, with neutropenia, febrile neutropenia, and leukopenia reported as the most frequently occurring grade 3 or higher adverse events.[6]

Need

One of the strongest prognostic factors in early stage breast cancer is stage at presentation. In the NOAH study, all enrolled patients had locally advanced or inflammatory breast cancer. After a median follow-up of 5.4 years, the 5-year EFS was 58% (95% CI 48% to 66%) in the neoadjuvant chemotherapy plus trastuzumab arm.[7] Thus despite the addition of concurrent trastuzumab to an anthracycline/taxane neoadjuvant regimen – almost half of HER-2 positive LABC patients still experienced an event at 5 years. A need still exists to improve the outcome in this cohort of patients.

In primary operable breast cancer, the long term outcomes can be extrapolated from trials of adjuvant trastuzumab. Most studies report a 5-year DFS >90% in patients with node-negative disease. Eight-year follow-up from the HERA and the NSABP B-31/NCCTG N9831 trials reported DFS of 76% and 74%, respectively.

1.3 Conclusions

The Clinical Guidance Panel concluded that there *may be* a net overall clinical benefit to the addition of pertuzumab to trastuzumab and a taxane (docetaxel) as part of a neoadjuvant regimen in HER2-positive node positive (Stage IIB) and locally advanced/inflammatory (Stage III) breast cancer. This conclusion is based on a single

randomized phase II trial (NeoSphere) that demonstrated a clinically and statistically significant increase in total pathological complete response rate (tpCR; no invasive disease in breast and nodes, ypT0ypN0) for the addition of four cycles of neoadjuvant pertuzumab to trastuzumab and docetaxel.[5] A second randomized phase II trial (TRYPHAENA) provides supportive data of comparably high tpCR rates in pertuzumab containing neoadjuvant regimens (however there was not an arm without pertuzumab in this trial). The adverse event profile was generally similar with or without pertuzumab (as from NeoSphere). There does not appear to be added clinically significant cardiac toxicity with the addition of pertuzumab.[6] Furthermore, the Clinical Guidance Panel agreed that, based on a clear demonstration of poorer outcome in node positive (Stage IIB) and locally advanced or inflammatory breast cancer (Stage III disease), even in the era of neoadjuvant trastuzumab, it would seem appropriate to first consider pertuzumab in this cohort of patients. While the NeoSphere study did include primary operable node negative breast cancers, and it would be safe to assume improvements in pCR are similar in this cohort of patients, prognostically the long-term outcomes for these two groups of patients are different. Clinical stage II disease includes node negative breast cancers with a T size just over 2 cm, to multiple node positive disease (as long as not clinical N2 disease [matted nodes]. Thus the need, or room for improvement, in primary operable HER2-positive breast cancers is more variable.

The Clinical Guidance Panel also considered that:

- The benefit of the addition of pertuzumab to trastuzumab and a taxane, pre-operatively, is likely the greatest in the HER-2 positive, hormone receptor negative (ER-/PR-) cohort; however, the Panel agreed that it should not be restricted to only hormone receptor negative HER-2 positive LABC. The Clinical Guidance Panel noted that the greatest differential improvement in tpCR and the strongest association for achieving tpCR to improved long term clinical outcomes is in this cohort of patients.
- Based on extrapolation from a large pooled analysis (CTNeoBC) demonstrating that the association between tpCR and long-term outcomes was strongest in HER-2 positive, hormone receptor negative tumours that received neoadjuvant trastuzumab (EFS: HR 0.15; 0.09-0.27; OS: HR 0.08; 0.03-0.22).
- The conclusions of the CGP may need to be revisited when the results of the large randomized trial of adjuvant pertuzumab in patients who have received surgery for breast cancer (the APHINITY trial) become available.
- Pertuzumab should NOT be delivered adjuvantly, regardless of response to the neoadjuvant component, as this was not done in either of the randomized phase II trials.

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 the neoadjuvant treatment of HER2-positive previously untreated 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.cadth.ca/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding Pertuzumab (PERJETA) conducted by the Breast Cancer 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

There were roughly 24,400 new breast cancer cases in Canada, in 2014[1] According to the National Cancer Institute approximately 20 to 25 percent of all breast cancers are HER2-positive. HER2-positive refers to the fact that breast cancer may overexpress a protein called HER2 (human epidermal growth factor receptor-2), which causes this particular form of breast cancer to have a poorer prognosis compared to breast tumours that do not overexpress HER2. HER2-positive disease is an aggressive, fast growing form of breast cancer that has a greater likelihood of relapse after going into remission.[4]

The survival rates of HER2-positive breast cancer are not the same as they are for HER2-negative breast cancer. The HER2-positive form of the disease has a greater likelihood of recurring after first remission and is associated with a decrease in survival as compared to HER2 negative breast cancer.[3]

Pertuzumab is a recombinant, humanized, IgG monoclonal antibody (mAb) that targets the extracellular domain (Subdomain II) of the HER2 protein and binds to a different epitope (domain II) than trastuzumab (T) and prevents dimerisation of HER2 with other members of the human epidermal growth factor receptor family (HER1 [i.e.,EGFR], HER3 and HER4). These dimers (homodimerisation or heterodimerisation) are responsible for signal transduction via critical pathways (MAP kinase and PI3K) that are involved in the survival, growth and division of breast cancer cells. Pertuzumab results in a more complete inhibition of the HER2 axis when combined with trastuzumab (dual HER2 blockade). Pertuzumab is also able to induce antibody-dependent cell-mediated cytotoxicity (ADCC).[12]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of pertuzumab in combination with trastuzumab and chemotherapy, on patient outcomes compared with appropriate comparators in treatment of patients with previously untreated, HER2-positive locally advanced, inflammatory, or early stage breast cancer. Only randomised controlled trials were considered for inclusion in this review. Overall survival, disease-free survival (DFS), relapse-free survival, pathological complete response (pCR), adverse events, and quality of life werere outcomes of interest. Please see Table 1 in section 6.2.1 for a complete list of outcomes of interest.

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.

Two trials met the inclusion criteria for this review. The Neoshpere trial[5] is a four arm study that examined the use of pertuzumab in combination with chemotherapy (docetaxel), trastuzumab, or both. Four hundred and seventeen patients were randomized into four treatment arms. These treatment arms were well balanced in terms of baseline characteristics as well as node status, tumor size, and hormone receptor status. Pathological complete response is the primary endpoint, with safety and adverse events being secondary endpoints.

Pathological complete response was highest in the pertuzumab in combination with trastuzumab and docetaxel group (Treatment Arm B) at 45.8%.[5] Pathological complete response of 16.8% and 24% was found in pertuzumab & trastuzxuamb (Treatment Arm C), and pertuzumab & docetaxel arms (Treatment Arm D) respectively. Pathological complete response occurred in 29% of patients in the control arm (Treatment Arm A) which was treated with trastuzumab & docetaxel. This study was not designed for hypothesis testing and the primary endpoint was pathological complete response. Significant differences were found between; Arm B versus Arm A ($p=0.0141$); between Arm C versus Arm A ($p=0.0198$), and; between Arm D and Arm B ($p=0.003$). Testing was done with $\alpha=0.2$.[5]

Three year disease free survival (DFS) was analysed between the trastuzumab and docetaxel group (Arm A) versus the pertuzumab and trastuzumab and docetaxel group (Arm B) using a standard methodology. Results indicated that there was improvement in estimated 3-year survival but results were not statistically significant.[9] Estimated survival rates were 85% versus 92% with a HR 0.60 and a 95% CI of 0.28-1.27.[9] No power calculation was presented, and the trial was not powered to detect a significant difference in DFS

Three-year progression free survival (PFS) was also analysed between treatment arms A and B. Results were similar with improvements in estimated 3-year PFS, with estimated survival rates of 86% and 90%.[9] Results were also not statistically

significant with a hazard ratio of 0.69 and a 95% CI extending from 0.34 to 1.40.[9] No power calculation was presented, and the trial was not powered to detect a significant difference in PFS.[9]

A pooled analysis of patients achieving tpCR versus not achieving tpCR was also conducted. The 3-year DFS HR was 0.68 with 95% CI between 0.36-1.26. The 3-year PFS HR was 0.54 with a 95% CI between 0.29-1.00. No power calculation was conducted.[9]

The mean maximum decrease in LVEF measurement was low (4–5%) and was balanced across treatment groups. No significant change was detected when pertuzumab was added to trastuzumab and no patient experienced an LVEF decrease to less than 40% at any time during the study.[5]
Adverse events were similar between groups and the most common adverse events of grade 3 or higher were neutropenia, febrile neutropenia, and leucopenia, which is as expected for treatment with docetaxel.[5]

The main limitation with this study was that it is an open label trial indicating that response assessment may have been subject to by bias due to the fact that neither participants or researchers were blinded to treatments.

The TRYPHAENA study is a three arm study.[6] Two arms examined the use of fluorouracil, epirubicin, cyclophosphamide (FEC) followed by docetaxel, trastuzumab and pertuzumab given concurrently, in different permutations. The third arm used carboplatin and docetaxel in combination with trastuzumab and pertuzumab. Two hundred and twenty five patients were randomized between the three treatment arms. The median overall time on study including post treatment follow-up ranged from 20 -21 months across arms. Baseline characteristics were well balanced with small differences noted in increased proportion of white race patients randomised into Arm C, more patients with locally advanced disease in Arm C, more patients with hormone receptor negative tumors in Arm B, and higher proportion of patients with HER2 IHC2+ tumors in Arm A.[6]

Cardiac safety was the main endpoint in the study with incidence of LVSD, and decline in LVEF ≥10% points from baseline to <50% over course of neoadjuvant treatment being the specific definition of outcomes under review. Pathological compete response, response rate, time to clinical response, rate of breast conserving surgery, and adverse events were secondary endpoints.[6]

The highest proportion of patients achieving pathological complete response by any definition, either (ypT0/is), (ypT0/is ypN0), or (ypT0 ypN0), occurred in Arm C. Proportions achieving pCR for those three definitions were 66.2%, 63.6% and 51.9% respectively.[6]

One patient in Arm C experienced symptomatic LVSD during adjuvant trastuzumab treatment. During neoadjuvant treatment, four patients (5.6%) in Arm A, four patients (5.3%) in Arm B, and three patients (3.9%) in Arm C experienced LVEF declines of ≥10% points from baseline to <50%.[6]

Neutropenia was the most frequently occurring ≥grade 3 adverse event with 47.2%, 42.7%, and 46.1% of patients having this event in Treatment arms A, B, and C respectively. Following Neutropenia, febrile neutropenia, leucopenia, diarrhea, anemia, thrombocytopenia, and vomiting were most frequently occurring. No information was found on other endpoints that were to be reported by this trial.[6]

The main limitations associated with this trial are that there was no hypothesis testing meaning differences found between treatment arms can only be interpreted as occurring randomly, and that enrolment was low leading to reduced ability to generalize results to a population.

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

The APHINITY trial is an ongoing randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive Primary Breast Cancer. The primary endpoint of the trial is invasive disease free survival. Secondary endpoints include disease free and overall survival, recurrence-free interval, distant recurrence free interval, cardiac and overall safety, and quality of life. This study examines patients in the adjuvant treatment setting in patients with operable disease. The estimated study completion date for this trial is December, 2023.[13]

NeoALLTO was an open-label randomized phase III trial in which 455 women with HER2-positive early breast cancer were randomized 1:1:1 to receive either lapatinib (1500 mg/day), trastuzumab (4 mg/kg loading dose followed by 2 mg/kg), or lapatinib (1000 mg/day) plus trastuzumab (same dose as for single-agent use), for 6 weeks, followed by an additional 12 weeks of the assigned regimen in combination with weekly paclitaxel (80 mg/m^2).[14] Four weeks after the last dose of paclitaxel, patients underwent definitive surgery followed by 3 cycles of FEC (fluorouracil 500 mg/m^2 plus epirubicin 100 mg/m^2 plus cyclophosphamide 500 mg/m^2) followed by 34 weeks of the assigned anti-HER2 regimen. This study was published in 2014, after the meta-analysis by Cortazar et al was conducted. The primary endpoint was pCR and secondary endpoints included event-free survival, overall survival, and the association between pCR and event-free survival or overall survival (30 weeks after randomization). No statistically significant differences in 3-year event-free survival (median follow-up 3.77 years) or 3-year overall survival (median follow-up 3.84 years) were demonstrated between the three treatment arms; however, the trial was not powered to detect differences in either of those outcomes. The analysis of an association between patients who achieved pCR compared with those who did not demonstrated a statistically significant improvement in 3-year event-free survival (HR 0.38, 95% CI 0.22 to 0.63; p0.0003) and in 3-year overall survival (HR 0.35, 95% CI 0.15 to 0.70; p=0.005).[14]

2.1.5 Summary of Supplemental Questions

Pathological Complete Response as a Surrogate for Long-Term Survival in Patients with Early Stage Breast Cancer

A review was conducted on the following pooled analysis to determine whether pathological complete response is valid as a surrogate endpoint for these outcomes: *Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 2;384(9938):164-7, Cortazar P, Zhang L, et al.*[10]

Methods used in this analysis included a systematic review to generate the population sample, HR estimation and log rank testing for event free survival analysis and overall survival analysis of pooled population and subgroups, and cox regression for relationship between baseline characteristics and pathological complete response.

A review of the methods and information used in the pooled analysis reveal possible sources of bias and error. These included: i) variation in definition of pCR; ii) non-randomized trials were included making generalizability and reliability of results questionable, and; iii) different preoperative treatments used in studies which may affect both response and long-term outcomes. This reduces generalizability and reliability as not all patients were HER2 positive, making it impossible to make statement for this subgroup, and the relatively short follow up makes statements about overall survival less reliable.

Conclusions in the pooled analysis indicated that a positive relationship between pCR and EFS and OS for responders (individuals). However, responder analyses are independent of treatment group and are not useful for comparisons at a trial level. When analysed between treatment groups, at a trial level, the positive relationship between pCR and EFS and OS was not found.

Although a positive correlation does exist at the individual level, particularly for the hormone negative subgroups, this relationship requires further analysis in order for pCR to be validated as a surrogate for overall survival or event-free survival.[10]

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

One patient advocacy group, Canadian Breast Cancer Network (CBCN), provided input on pertuzumab (Perjeta) in combination with trastuzumab and chemotherapy prior to surgery for the treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter or node positive) as part of a complete treatment regimen for early stage breast cancer, and their input is summarized below.

CBCN obtained the information using a number of approaches. CBCN conducted one-on-one interviews with three patients from Ontario and Saskatchewan. Of the three patients, one patient had experience with the treatment under review. CBCN also conducted literature review of printed sources reports with breast cancer patients, including results from the clinical trials for pertuzumab and information obtained from Hoffman-LaRoche.

From a patient perspective, managing early-stage HER2 and inflammatory breast cancer is always a challenge, as patients have very limited treatment options available to them. CBCN noted that the disease usually develops quickly and progresses aggressively and in general the prognosis of patients living with inflammatory breast cancer is less favourable than other types of breast cancer. According to CBCN, many of the symptoms have the ability to impact daily life, primarily fatigue, pain and nausea. As such, CBCN believes that providing patients with this treatment combination in the earliest disease setting could delay or prevent cancer recurrences and ensure optimal health outcomes for cancer patients. CBCN indicated that the primary aspect to control for patients with HER2 positive breast cancer is reducing the risk of recurrence and disease progression to improve patients' overall survival. CBCN suggested that pertuzumab could serve to meet the gap in available treatment options for those patients suffering from trastuzumab resistance by offering these high-risk patients additional options to combat cancer recurrence and boost the efficacy of current treatments.

PAG Input

Input was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of pertuzumab in the neoadjuvant treatment of breast cancer:

Clinical factors:

- The unknown long-term clinical benefits
- Clarity on the group of patients who would benefit from the addition of pertuzumab
- Clarity on treatment duration (number of treatments)
- Request for re-use in the adjuvant setting

Economic factors:

- High cost of pertuzumab

2.2 Interpretation and Guidance

Burden of disease:

Breast cancer is the most common malignancy diagnosed in women in Canada. In 2014 approximately 24,400 women were diagnosed with breast cancer in Canada. This represents 26% of all new cancer cases diagnosed in 2014. Approximately 95% of incident cases of breast cancer are stage 0-III. Data from British Columbia in 2002 demonstrated a

stage distribution of 32% Stage II presentation and 8% Stage III presentation. [2] Overall the 5-year relative survival from breast cancer is 88%, though this varies based on stage and subtype. For stage I breast cancer approximately 15% are HER-2 positive and for stage II-III approximately 18-20% of cases are determined to be HER-2 positive. Prior to the use of adjuvant anti-HER2 directed therapy (trastuzumab), women with HER2-positive breast cancer had a worse clinical outcome. However, since the adoption of adjuvant trastuzumab in 2005,the clinical outcomes for women with HER2-positive breast cancer in Canada have become significantly more favourable.[15] The risk of relapse, however, is still sufficiently high in women with node positive and locally advanced HER2-positive breast cancer to warrant the investigation and use of new and more effective therapies. Results from the combined analyses of NSABP B-31 and NCCTG N9831 (2 adjuvant breast cancer trials), demonstrate that breast cancer relapses continue to occur at a relatively constant rate over time in the trastuzumab treated arm(s) – with an estimated 10-year DFS of 73.7%.[11] An initial similar EFS (71%) was seen in the trastuzumab treated arm of the NOAH study, which enrolled patients with locally advanced/inflammatory breast cancer.[16] With longer follow up, to 5.4 years median, the 5 year event free survival rate was 58% in the chemotherapy plus trastuzumab arm in the NOAH trial[7], thus demonstrating that women with HER2-positive breast cancer treated with chemotherapy and anti-HER2 directed therapy remain at ongoing risk of relapse.

Effectiveness:

Pertuzumab, a humanized monoclonal antibody that inhibits dimerization of HER2 with other HER receptors, has been evaluated in two randomised phase II studies in the neoadjuvant setting. In the NeoSphere trial, 417 women with HER2-positive primary operable (60% of study population)/LABC (40% of study population) disease were randomized to receive either 4 cycles of neoadjuvant trastuzumab (8mg/kg loading dose, followed by 6mg/kg every 3 weeks), docetaxel (75mg/m^2 escalating to 100mg/m^2 as tolerated) and pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks), or trastuzumab plus docetaxel, or pertuzumab and trastuzumab (without chemotherapy), or pertuzumab plus docetaxel.[5] The combination of dual HER2-targeted therapies and docetaxel induced a pCR (breast) in 45.8% (95%CI: 36.1-55.7) compared with 29% of those randomized to trastuzumab and docetaxel (95%CI: 20.6–38.5; p=0.0141). pCR in both breast and lymph nodes (ypT0/is ypN0) was 39.3% (95% CI: 30-49.2%) in the pertuzumab, trastuzumab and docetaxel arm compared to 21.5% (95% CI: 14.1%-30.5%) in the trastuzumab and docetaxel arm. After surgery all patients received 3 cycles of FEC and the remainder of 1 year of trastuzumab. pCR was achieved for 24.0% of those receiving pertuzumab and docetaxel and 16.8% of women who were treated with dual HER2-targeted therapy in the absence of chemotherapy. Neither short nor long-term clinical outcomes (EFS and OS) have been publicly reported from NeoSphere; however, data provided by the Submitter at the Checkpoint Meeting, and subsequently presented at ASCO 2015, demonstrated no statistically significant differences between the trastuzumab and docetaxel group (Arm A) compared with the pertuzumab, trastuzumab and docetaxel group (Arm B) in either 3-year DFS (85% vs. 92% [HR 0.60; 95% CI 0.28-1.27]; respectively) or PFS (86% vs. 90% [HR 0.69; 95% CI 0.34-1.40]), but the study was not powered to detect differences in either outcome.[9]

The TRYPHAENA trial was a phase II study with cardiac safety as the primary end-point of the study.[6] All 225 participants received dual HER2 targeting with trastuzumab and pertuzumab. In this study approximately 73% of the population was defined as primary

operable, with the remaining 27% as locally advanced. The three study arms comprised randomization to 5-fluorouracil/epirubicin/cyclophosphamide, 500mg/100mg/600mg/m^2 (FEC_{100}) for 3 cycles followed by docetaxel for 3 cycles (75 mg/m^2) concurrent with trastuzumab and pertuzumab for all 6 cycles (Arm A), FEC_{100} X 3 followed by docetaxel X 3 (75 mg/m^2) with trastuzumab and pertuzumab given only alongside docetaxel (Arm B) or 6 cycles of docetaxel, carboplatin, trastuzumab and pertuzumab (Arm C). In this trial pCR (breast) was a secondary end-point, with rates ranging between 57.3% and 66.2%, in keeping with results seen elsewhere. When pCR was defined as ypT0ypN0, the rates were as follows: 50.7% (Arm A), 45.3% (Arm B) and 51.9% (Arm C). When pCR was defined as ypT0/is ypN0, the rates were 56.2% (Arm A), 54.7% (Arm B), and 63.6% (Arm C). The lack of an arm without pertuzumab limits the extrapolation of these results to other studies and to distinguish the added benefit of pertuzumab. No clinical outcomes such as EFS or DFS have been presented on TRYPHAENA.

The relevant clinical outcomes for the addition of pertuzumab concurrent with 4-6 cycles of a taxane and trastuzumab from the two randomized phase II trials (NeoSphere and TRYPHAENA) are outlined in Table 1. The most relevant trial on which to base conclusions is the NeoSphere trial, for this is the only trial in which part of a current standard of care treatment arm was included (docetaxel + trastuzumab arm).

Table 1. Outcomes from the two randomized phase II trials (NeoSphere and TRYPHAENA).

	NeoSphere [5]		**TRYPHAENA [6]**		
	DH x 4	DH+P x 4	FECHP x 3-DHP x 3	FEC x 3-DHP x 3	TCH+P x 6
ypT0/is ypN0	21.5%	39.3%	56.2%	54.7%	63.6%
ypT0ypN0	-	-	50.7%	45.3%	51.9%
ER-/PR-*	36.8%	63.2%	79.4%	65%	83.8%
ER+ and/or PR+*	20%	26%	46.2%	48.6%	50%
Conversion to BCS #	22.6%	23.2%	21.7%	16.7%	27%

* ypT0/is (breast); # from planned mastectomy
D(docetaxel); H (trastuzumab); P (pertuzumab); FEC (5-FU, epirubicin, cyclophosphamide)
TCH (docetaxel, carboplatin, trastuzumab)					

The improvement in total pathological complete response (tpCR; i.e., no invasive disease in breast or nodes) appears predominantly in the hormone receptor negative cohort. However no difference in breast conservation rates in patients initially deemed to be mastectomy candidates was seen.

Safety:

In the NeoSphere trial the most frequently occurring adverse events were alopecia, neutropenia, diarrhea, nausea, fatigue, rash and mucosal inflammation. In terms of comparing between group A (docetaxel + trastuzumab) vs group B (docetaxel, trastuzumab + pertuzumab) no apparent differences in common AE grade 3 or higher was seen. The rate of febrile neutropenia was similar between these arms (7% and 8% respectively). Numerically a slight increase in the rates of diarrhea (34% vs 46%), rash (21% vs 26%) and

mucosal inflammation (21% vs 26%) was seen for the addition of pertuzumab. One death was seen in group B (fatal hepatitis) with no death seen in group A. No significant change in LVEF was detected when pertuzumab was added to trastuzumab. No patient had an LVEF decrease to < 40%. There was no mention of alterations in dose intensity of docetaxel for the addition of pertuzumab (either group B or C). During the neoadjuvant period no patients withdrew due to an adverse event in group A or group B, while 2 patients in each of groups C and D did so. [5]

In TRYPHAENA neutropenia, febrile neutropenia (FN) and leukopenia were the most frequently reported grade ≥3 AE. The rates of FN were 18.1%, 9.3% and 17.1% across Arms A-C respectively. Diarrhea, anemia, thrombocytopenia, vomiting, drug hypersensitivity and fatigue (grade ≥3) were numerically higher in arm C (TCH+P) than in the other arms. No deaths were reported during neoadjuvant treatment. The rates of symptomatic LVSD or LVEF decline ≥10% from baseline to <50% during neoadjuvant treatment were 5.6%, 5.3% and 3.9% across Arms A-C respectively. As in NeoSphere, where was no mention of alterations in dose intensity of chemotherapy for the addition of pertuzumab or an inability to proceed to definitive surgery due to toxicity in any of the arms of the study.[6]

Need:

One of the strongest prognostic factors in early stage breast cancer is still stage at presentation. In the landmark NOAH trial, all patients enrolled presented with locally advanced/inflammatory breast cancer. Approximately 42% had T4 non-inflammatory disease and 27% had Stage IIIB inflammatory (T4d) disease. After a median follow-up of 5.4 years, the 5-year event free survival rate was 58% (95% CI: 48-66%) in the chemotherapy plus trastuzumab arm. [7] Thus despite the addition of concurrent trastuzumab to an anthracycline/taxane neoadjuvant regimen – almost half of HER2-positive LABC patients still experience an event at 5 years. Clearly a need still exists to improve the outcome in this cohort of patients.

In primary operable breast cancer, the long-term outcomes can be extrapolated from the adjuvant trastuzumab trials. Most studies suggest favorable outcomes (>90% DFS at 5 years follow-up) in patients with node negative disease treated with adjuvant trastuzumab. Eight-year follow up from the HERA and the NSABP B-31/ NCCTG N9831 trials reported DFS of 76% and 74% respectively.

Both the NeoSphere and TRYPHAENA studies enrolled patients with either primary operable or locally advanced breast cancer. A minimum T size of ≥2 cm regardless of nodal status was required. However, based on the favourable prognosis in women with node negative disease, greater consideration of this regimen should be given to those with node positive (Stage IIB) or locally advanced/inflammatory breast cancer disease (Stage III). Adjuvant trials such as APHINITY (pertuzumab) and KAITLAN (TDM1) will help to further define the role of these agents in the treatment of HER2-positive breast cancer particularly in the node positive population.

2.3 Conclusions

The Clinical Guidance Panel concluded that there *may be* a net overall clinical benefit to the addition of pertuzumab to trastuzumab and a taxane (docetaxel) as part of a neoadjuvant regimen in HER2-positive node positive (Stage IIB) and locally advanced/inflammatory (Stage III) breast cancer. This conclusion is based on a single randomized phase II trial (NeoSphere) that demonstrated a clinically and statistically significant increase in pathological complete response rate (tpCR; no invasive disease in breast and nodes, ypT0/is ypN0) for the addition of four cycles of neoadjuvant pertuzumab to trastuzumab and docetaxel. A second randomized phase II trial (TRYPHAENA) provides supportive data of comparably high tpCR rates in pertuzumab containing neoadjuvant regimens (however there was not an arm without pertuzumab in this trial). The adverse event profile was generally similar with or without pertuzumab (as from NeoSphere). There does not appear to be added clinically significant cardiac toxicity with the addition of pertuzumab. Furthermore, the Clinical Guidance Panel agreed that, based on a clear demonstration of poorer outcome in node positive (Stage IIB) and locally advanced or inflammatory breast cancer (Stage III disease), even in the era of neoadjuvant trastuzumab, it would seem appropriate to first consider pertuzumab in this cohort of patients. While the NeoSphere study did include primary operable node negative breast cancers, and it would be safe to assume improvements in pCR are similar in this cohort of patients, prognostically the long-term outcomes for these two groups of patients are different. Clinical stage II disease includes node negative breast cancers with a T size just over 2 cm, to multiple node positive disease (as long as not clinical N2 disease [matted nodes]. Thus the need, or room for improvement, in primary operable HER2-positive breast cancers is more variable.

The Clinical Guidance Panel also considered that:

- The benefit of the addition of pertuzumab to trastuzumab and a taxane, pre-operatively, is likely the greatest in the HER-2 positive, hormone receptor negative (ER-/PR-) cohort; however, the Panel agreed that it should not be restricted to only hormone receptor negative HER-2 positive LABC. The Clinical Guidance Panel noted that the greatest differential improvement in tpCR and the strongest association for achieving tpCR to improved long term clinical outcomes is in this cohort of patients.
- Based on extrapolation from a large pooled analysis (CTNeoBC) demonstrating that the association between tpCR and long-term outcomes was strongest in HER-2 positive, hormone receptor negative tumours that received neoadjuvant trastuzumab (EFS: HR 0.15; 0.09-0.27; OS: HR 0.08; 0.03-0.22).
- The conclusions of the CGP may need to be revisited when the results of the large randomized trial of adjuvant pertuzumab in patients who have received surgery for breast cancer (the APHINITY trial) become available.
- Pertuzumab should NOT be delivered adjuvantly, regardless of response to the neoadjuvant component, as this was not done in either of the randomized phase II trials.

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 presentation in industrialized nations and those with organized screening mammography programs, is predominantly an early stage disease presentation. In 2014 approximately 24,400 women were diagnosed with breast cancer in Canada[17] the majority of whom presented with early stage disease. Approximately 95% of incident cases of breast cancer are stage 0-III. Data from British Columbia in 2002 demonstrated a stage distribution of 38% Stage I, 32% Stage II, and 8% Stage III presentation[2]. In general, primary operable breast cancers are categorized as Stage I-II and locally advanced breast cancers as stage III (particularly Stage IIIB-C). Overall the 5-year relative survival from breast cancer is 88%, though this varies based on stage and subtype of breast cancer. Prior to the use of adjuvant anti-HER2-directed therapy (trastuzumab), the HER2-positive cohort had the worse outcome. However, since the use of adjuvant trastuzumab in standard clinical practice since 2005, the clinical outcomes (disease free survival and overall survival) in Canada have become significantly more favourable.[18] However the risk of relapse is still sufficiently high in node positive (Stage IIB) and locally advanced breast cancer (Stage III) to warrant the investigation and the use of new and more effective therapies.

The standard clinical use of neoadjuvant chemotherapy today can be categorized into two populations of patients: the locally advanced breast cancers (LABC) and the primary operable breast cancers (POBC). The purpose for the use of neoadjuvant chemotherapy for LABC is to convert a baseline inoperable state to an operable state.[19] This typically applies to some Stage IIIa (clinical $T_{0\text{-}3}N_2M_0$) and all Stages IIIb and IIIc (which include clinical $T_4N_{0\text{-}2}M_0$ and $T_{0\text{-}4}N_3M_0$) breast cancers. LABC (which includes inflammatory breast cancer) is heterogeneous both in clinical presentation and in biological subtypes. Unfortunately, there are few randomized clinical trials which specifically address the management of this population of patients. One such landmark study in a full LABC population was the NOAH trial.[16] This randomized trial of neoadjuvant trastuzumab in combination with chemotherapy (both anthracycline and taxanes) in HER2-positive LABC demonstrated a significant increase in pathological complete response (pCR) with the addition of concurrent trastuzumab, that also translated to an improvement in event free survival (EFS).

The standard clinical use of neoadjuvant chemotherapy in primary operable breast cancer (POBC) is based on two principles. Firstly, the potential to downstage a tumour and thus convert a baseline mastectomy candidate to a breast conservation candidate. Based on the Early Breast Cancer Trialists Collaborative Group (EBCTCG) overview of neoadjuvant trials, there is an 18% chance of breast conservation with a neoadjuvant strategy [Oxford, September 7, 2006, unpublished]. The second principle, based on primarily the NSABP B-18 study, and the EBCTCG meta-analyses of neoadjuvant trials, is that it is clear that standard chemotherapy regimens (anthracyclines +/- taxanes) whether given pre-operatively or post-operatively (adjuvant) provided the same long term clinical outcomes in these patients. [20] POBC is generally considered to include Stage I to IIIa disease – however the use of neoadjuvant chemotherapy is generally not considered in Stage I disease.

The last consideration in the realm of neoadjuvant systemic therapy is that of the prognostic role of achieving pathological complete response (pCR) as a surrogate indicator of long-term clinical outcomes. It has long been described that achieving a pCR (absence of invasive disease in breast +/- lymph nodes) to neoadjuvant chemotherapy is associated with a better disease free and overall survival. Two recent large pooled analyses have been performed addressing this topic, with an overall similar conclusion but somewhat differing subgroup analyses. The German Breast Group (GBG) correlated the long term outcome with pathological response in 6,377 patients with primary breast cancer treated with neoadjuvant chemotherapy (anthracycline and taxane +/- trastuzumab) in seven randomized trials.[21] This analysis clearly demonstrated an association between pCR and long-term outcomes. They concluded that a pCR definition of no invasive disease and no in situ disease in breast (and nodes) best discriminated with favourable outcome. Lastly they also distinguished that a pCR in HER2-positive (hormone receptor negative) and in triple negative breast cancers (TNBC) was associated with an excellent prognosis. However, a pCR in the HER2-positive (hormone receptor positive) subtype did not correlate with an improved disease free survival (DFS). The FDA (US) performed a pooled analysis (CTNeoBC of 11,955 patients from 12 international trials (including the seven from the GBG trial). [10] This pooled analysis concluded that a pCR definition of no invasive disease (regardless of presence of in situ disease) in breast and lymph nodes (ypT0/is ypN0) was better associated with improved EFS. Again, the association between pCR and long-term outcomes was strongest in TNBC and HER2-positive/ER-negative breast cancers. This analysis however did show an association between pCR and EFS in the HER2-positive/ER-positive subtype. Lastly they found little association between increases in frequency of pCR and EFS.

3.2 Accepted Clinical Practice

Accepted clinical practice for stage II (particularly node positive) and stage III breast cancer is for an anthracycline and taxane based regimen. In general, 6-8 cycles of neoadjuvant chemotherapy is accepted as a standard based on inferior outcomes in node positive disease for 4 cycles compared to 8 cycles (NSABP B-30).[22] Based historically on what has evolved from clinical trials (e.g. NSABP B-18) and based on being a standard arm across various neoadjuvant and adjuvant trials (E1199, NSABP B-30) – one commonly accepted neoadjuvant regimen is $A_{60}C_{600}$ x 4 cycles followed by docetaxel (100 mg/m^2) x 4 cycles.

In HER2-positive disease, the same principle holds true except for the addition of trastuzumab. The first landmark trial investigating the benefit of neoadjuvant trastuzumab in the LABC setting was the NOAH trial.[16] NOAH randomised 228 HER2-positive patients to a neoadjuvant regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) with or without concurrent trastuzumab (throughout the entire chemotherapeutic regimen). The trastuzumab-treated cohort demonstrated a significantly superior rate of pathological complete responses (pCR) in breast and nodes (tpCR) (38% vs. 19%; P= 0.001), which ultimately translated to an improved 3-year event free survival (71% vs 56% hazard ratio 0.59 95% CI: 0.38-0.90).

Secondly, it would seem both practical and also potentially more efficacious to deliver the trastuzumab concurrent with the taxane. In the NCCTG N9831 study, one arm delivered paclitaxel (weekly) concurrent with trastuzumab (arm C) while in another arm the trastuzumab was delivered sequential (arm B).[22] Though there was a numerical increase in

DFS in favour of the concurrent arm (84.4% vs 80.1%), this did not meet statistical significance based on the interim analyses criteria (arm C/arm B hazard ratio 0.77; 95% CI 0.53-1.11). However, as there was no difference in toxicity between these two arms, and for convenience and earlier completion of therapy it would be overall advantageous to deliver the trastuzumab concurrent with the taxane.

Lastly, as several neoadjuvant trials in the HER2-positive population delivered trastuzumab concurrent with both the anthracycline and taxane component, the questions remained whether there was an additional advantage and safety to do so versus concurrent with the taxane alone pre-operatively. The Z1041 trial addressed this exact question in 282 women with operable HER2-positive primary disease. [23] One treatment arm was $FE_{75}C$ x 4 followed sequentially by weekly paclitaxel concurrent with trastuzumab and the other treatment arm was weekly paclitaxel concurrent with trastuzumab followed by $FE_{75}C$ x 4 concurrent with trastuzumab. pCR rates (breast) was 56.5% (95% CI: 47.8-64.9%) for the sequential arm vs 54.2% (95% CI: 45.7-62.6%) for the concurrent arm. No difference was observed for breast conservation rates between the arms (37.7% vs 39.1% respectively).

In summary, accepted clinical practice for Stage II-III HER2-positive primary operable and locally advanced disease would include: $A_{60}C$ x 4 followed by docetaxel$_{100}$/trastuzumab x 4; $A_{60}C$ x 4 followed by paclitaxel/trastuzumab x 4; $T_{75}CH$ x 6 (docetaxel/carboplatin/trastuzumab) and possibly $FE_{100}C$ x 3 followed by docetaxel$_{100}$/trastuzumab x 3. The total duration of trastuzumab is 12 months (including the component given concurrent with the taxane if so given).

3.3 Evidence-Based Considerations for a Funding Population

The evidence based suitable population for consideration of funding should at a minimum fit the inclusion criteria of NeoSphere and TRYPHAENA. HER2-positive by either IHC or FISH (as per ASCO/CAP criteria), medically fit to receive chemotherapy, normal baseline left ventricular ejection fraction and adequate baseline haematological and non-hematologic panel.

Both studies allowed patients with either primary operable or locally advanced breast cancer. A minimum T size of ≥2 cm regardless of nodal status was required. Thus Stage II-III disease (including inflammatory breast cancer) would be eligible. However based on underlying risk:benefit ratio and the concern of 'over-treatment' in node negative disease, a greater consideration of this regimen could be given to node positive disease (Stage IIB) and locally advanced/inflammatory breast cancer disease (Stage III).

3.4 Other Patient Populations in Whom the Drug May Be Used

No other potential uses of the drug that may impact on its utilization were identified.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Canadian Breast Cancer Network (CBCN), provided input on pertuzumab (Perjeta) in combination with trastuzumab and chemotherapy prior to surgery for the treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter or node positive) as part of a complete treatment regimen for early stage breast cancer, and their input is summarized below.

CBCN obtained the information using a number of approaches. CBCN conducted one-on-one interviews with three (3) patients from Ontario and Saskatchewan. Of the three patients, one patient had experience with the treatment under review. CBCN also conducted literature review of printed sources reports with breast cancer patients, including results from the clinical trials for pertuzumab and information obtained from Hoffman-LaRoche.

From a patient perspective, managing early-stage HER2 and inflammatory breast cancer is always a challenge, as patients have very limited treatment options available to them. CBCN noted that the disease usually develops quickly and progresses aggressively and in general the prognosis of patients living with inflammatory breast cancer is less favourable than other types of breast cancer. According to CBCN, many of the symptoms have the ability to impact daily life, primarily fatigue, pain and nausea. As such, CBCN believes that providing patients with the treatment combination in the earliest disease setting could delay or prevent cancer recurrences and ensure optimal health outcomes for cancer patients. CBCN indicated that the primary aspect to control for patients with HER2-positive breast cancer is reducing the risk of recurrence and disease progression to improve patients' overall survival. CBCN suggested that pertuzumab could serve to meet the gap in available treatment options for those patients suffering from trastuzumab resistance by offering these high-risk patients additional options to combat cancer recurrence and boost the efficacy of current treatments.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission and have not been corrected.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Neoadjuvant Breast Cancer

According to CBCN, a diagnosis of early-stage, human epidermal growth factor receptor (HER2) positive breast cancer has a significant impact on the day-to-day life of the patient. The diagnosis of HER2-positive breast cancer, as well as the treatments that are used, impact both the emotional and physical well-being of a patient.

CBCN indicated that the primary aspect to control for patients with HER2-positive breast cancer is reducing the risk of recurrence and disease progression to improve patients' overall survival.

CBCN reported that for patients with HER2-positive, inflammatory breast cancer, treatment concerns are augmented. In view of the aggressive nature of this disease, CBCN

noted that accessing targeted therapies is of critical concern for patients to manage their disease.

CBCN suggested that some of the side effects of HER2-positive breast cancer and the therapies used to manage this disease include: cardiac toxicity, fever, cough, muscle pain, fatigue, diarrhea and nausea.

CBCN noted that many of these symptoms have the ability to impact daily life; primarily fatigue, pain and nausea. Therefore, CBCN believes it is important for patients to have access to therapies that will extend their life expectancy without significantly increasing side effects that will negatively impact their daily lives.

4.1.2 Patients' Experiences with Current Therapy for Neoadjuvant Breast Cancer

CBCN reported that managing early-stage HER2 and inflammatory breast cancer is always a challenge, as patients have very limited treatment options available to them. It was noted that most patients receive a combination of the anti-HER2 therapy, trastuzumab, in addition to standard chemotherapy.

According to CBCN, while prognosis on this treatment regimen is generally favourable, patients must cope with a range of side effects from this treatment combination. Common side effects with this treatment regimen include: cardiac toxicity, fever, cough, muscle pain, fatigue, diarrhea and nausea.

In addition to the more common side effects experienced by patients undergoing a treatment regimen of pertuzumab in combination with chemotherapy, CBCN noted that some patients also experience resistance to trastuzumab.

For these patients, who are already quite limited in their treatment options, CBCN indicated it is very important to have access to other treatments, such as, dual-blockade medications, which can target the HER2 signaling pathway and allow trastuzumab, to have increased efficacy.

In addition to the cost of drugs, breast cancer has a financial burden that impacts the patient and their families significantly. 88% of breast cancer patients experience a financial impact from the disease, 44% of breast cancer patients use savings and 27% take on debt due to the disease.

4.1.3 Impact of Neoadjuvant Breast Cancer and Current Therapy on Caregivers

CBCN noted that breast cancer greatly impacts the caregivers, because they not only have to increase their care for the patient but deal with the emotional aspect of a cancer diagnosis. According to CBCN, there is often a significant financial burden placed on the caregiver as they are taking additional time off of work and are often times assisting in covering financial costs associated with the disease that are not covered under public or private health benefits.

Additionally, patients experience increased anxiety and stress due to the additional responsibility of looking after a loved one. Because breast cancer primarily affects women there is a very large impact on the family as a whole since women often are the primary

caregivers for the family. Spouses are required to assume a lot of the caretaking responsibilities for the patient but also for the whole family unit.

CBCN reported that by increasing the life expectancy of women with breast cancer, this eases some of the psychosocial burden assumed by caregivers.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Pertuzumab

According to CBCN, pertuzumab in combination with trastuzumab plus chemotherapy offers patients significantly improved pathological complete response rates without substantial differences in tolerability. Therefore, CBCN believes that providing patients with this treatment combination in the earliest disease setting could delay or prevent cancer recurrences and ensure optimal health outcomes for cancer patients.

Moreover, CBCN noted that this treatment combination could also serve to meet the gap in available treatment options for those patients suffering from trastuzumab resistance by offering these high-risk patients additional options to combat cancer recurrence and boost the efficacy of current treatments. One patient stated: "*This drug has the potential to prevent stage 2 cancer developing into metastasised cancer. I am not sure how you can put a value on it. But I know for me, it was literally the opportunity of a long life rather than the prospect of an early death*."

CBCN indicated that when compared to other existing therapies, pertuzumab has a convenient dosing schedule, typically given every 3 weeks, on the same day as trastuzumab and docetaxel, and during the same visit, allowing patients greater ease in their treatment schedules.

CBCN reported that the most common grade 3 – 4 adverse reactions (more than 2 percent) were neutropenia, febrile neutropenia, leukopenia, and diarrhea. Other significant adverse reactions reported with pertuzumab include left ventricular dysfunction, infusion-related reactions, hypersensitivity reactions, and anaphylaxis.

One patient stated: "*It is hard to gauge how the side effects compared as I was on other chemotherapies simultaneously. However I believe they were not nearly as severe as the Docetaxel side effects*."

"*Chemo therapy is rough. No matter how you look at it, treatment is difficult. It is impossible to compare the side effects versus the outcomes. Life-saving treatment is worth every throat ulcer, aching bones and nausea. As soon as I knew about this drug I reviewed the research and consulted with my oncologist. It became apparent that this drug gave me a much better outcome than without. Thankfully I have an amazing community that pulled together and funded this treatment for me. I am truly grateful for the ability to access this drug. Others have not been so lucky. If we want to prevent privatized health care we need to make lifesaving drugs available to all members of society not just those with friends and family willing to pay*."

CBCN suggested that because of the manageable toxicity profile of pertuzumab with trastuzumab and chemotherapy, the positive results of a prolonged life would outweigh the side negative side effects of this therapy. As such, CBCN believes that the lives of patients, families and their caregivers will be enhanced by this drug because it can improve the prognosis of the patient and give the patient more time with their loved ones.

4.3 Additional Information

No additional comments were received.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of pertuzumab in the neoadjuvant treatment of breast cancer:

Clinical factors:

- The unknown long-term clinical benefits
- Clarity on the group of patients who would benefit from the addition of pertuzumab
- Clarity on treatment duration (number of treatments)
- Request for re-use in the adjuvant setting

Economic factors:

- High cost of pertuzumab

Details of these factors and other factors are outlined below.

5.1 Factors Related to Comparators

PAG noted that the current standard of care for neoadjuvant treatment of HER2-positive breast cancer is trastuzumab plus chemotherapy in most of the provinces. PAG is seeking information on whether the trial results can be generalized to other anthracylcine chemotherapy combinations.

PAG noted the phase II trial shows an improvement in pathological complete response when pertuzumab is added in the neoadjuvant setting. PAG is seeking information on how this correlates to cure rates, increases in survival and reduction in risk of recurrence since the doubling of pathological complete response observed in the NeoALTTO trial did not correspond to improved survival outcomes.

5.2 Factors Related to Patient Population

PAG noted that patients with HER2-positive, locally advanced and inflammatory breast cancer is clearly indicated for neoadjuvant treatment; however, the early stage breast cancer population encompasses a wider range of patients and PAG is requesting clarity on the group of patients who would benefit from the addition of pertuzumab. In addition, PAG is seeking information on the re-use of pertuzumab in the metastatic setting for patients who have received pertuzumab previously in the neoadjuvant setting.

PAG indicated there will be requests for use in the adjuvant setting and is seeking information on the use of pertuzumab in the adjuvant setting.

5.3 Factors Related to Dosing

PAG noted that the dose of pertuzumab and the frequency of treatment in the neoadjuvant setting are the same as in the metastatic setting. These are enablers to implementation.

5.4 Factors Related to Implementation Costs

PAG noted several enablers to implementation of pertuzumab in the neoadjuvant setting. Pertuzumab is an add-on drug to existing treatment and patients are already in the chemotherapy clinics for the existing treatment. Drug wastage is not a concern since pertuzumab vials contain the amount of the fixed dose.

Barriers to implementation include the high cost of pertuzumab, additional preparation time and the additional chair time for the infusion. PAG also noted that pertuzumab is administered for four to six cycles before surgery and given the high cost of pertuzumab, there is a significant difference between four cycles and six cycles. PAG is requesting clarity on the appropriate number of cycles.

5.5 Factors Related to Health System

Pertuzumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of infusion related reactions. Intravenous chemotherapy drugs would be funded fully in all jurisdictions for eligible patients.

In provinces that fund pertuzumab in the metastatic setting, healthcare providers are already familiar with the preparation, administration and monitoring of pertuzumab infusions.

5.6 Factors Related to Manufacturer

The high cost of pertuzumab would be a barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of pertuzumab in combination with trastuzumab and chemotherapy in the neo-adjuvant setting for the treatment of patients with HER2-positive locally advanced, inflammatory, or early stage breast cancer who have not received any previous cancer therapy for their disease, with tumour >2cm.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

1. An understanding of relationship between pathological complete response and long term outcomes associated with HER2-positive, early stage breast cancer is required to determine whether pCR can be used as clinical efficacy surrogate for survival outcomes.

A critical appraisal and summary of the results from the Cortazar, 2014 systematic review and meta-analysis of the relationship between pathological complete response and long-term outcomes; EFS, and OS, in early stage breast cancer will provide insight into the use of pathological complete response as a surrogate for survival.[10]

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 the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table # 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized Controlled trials	Prior to surgery for patients with HER2-positive locally advanced, inflammatory, or early stage breast cancer who have not received prior anti-HER2 therapy or chemotherapy from metastatic disease , with tumor >2cm	pertuzumab ***AND*** trastuzumab ***AND*** Chemotherapy	trastuzumab ***OR*** Chemotherapy ***OR*** trastuzumab ***AND*** Chemotherapy	**Overall survival** (OS**), disease free survival** (DFS), **relapse free survival**, pathological complete response (pCR), grade 3-4 adverse events, withdrawal due to adverse events, hematologic/non-hematologic

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
				adverse events, febrile neutropenia, infusion reactions, infections, rash, fatigue, diarrhea, increased white blood cell count, treatment related deaths, Left ventricular dysfunction, Other cardiac events (CHF, MI, primary arrhythmia), frequency of change from inoperable disease to operable disease, frequency of mastectomy avoidance, quality of life
OS-Overall Survival, DFS-Disease Free Survival, RFS-Relapse Free Survival, pCR-Pathological Complete Response, CHF-Chronic Heart Failure, MI-Myocardial Infarction				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

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 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 Breast Cancer mesh with text word "HER2".

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical. 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 April 6, 2015.

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 ESMO 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.

FDA and EPAR sites were searched for reports and HTA assessments on current submission agents. These documents are used to inform members on relevant issues and are examined to see if the contain more exhaustive reported results.

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 (December 29th, 2014).

6.2.6 Writing of the Review Report

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

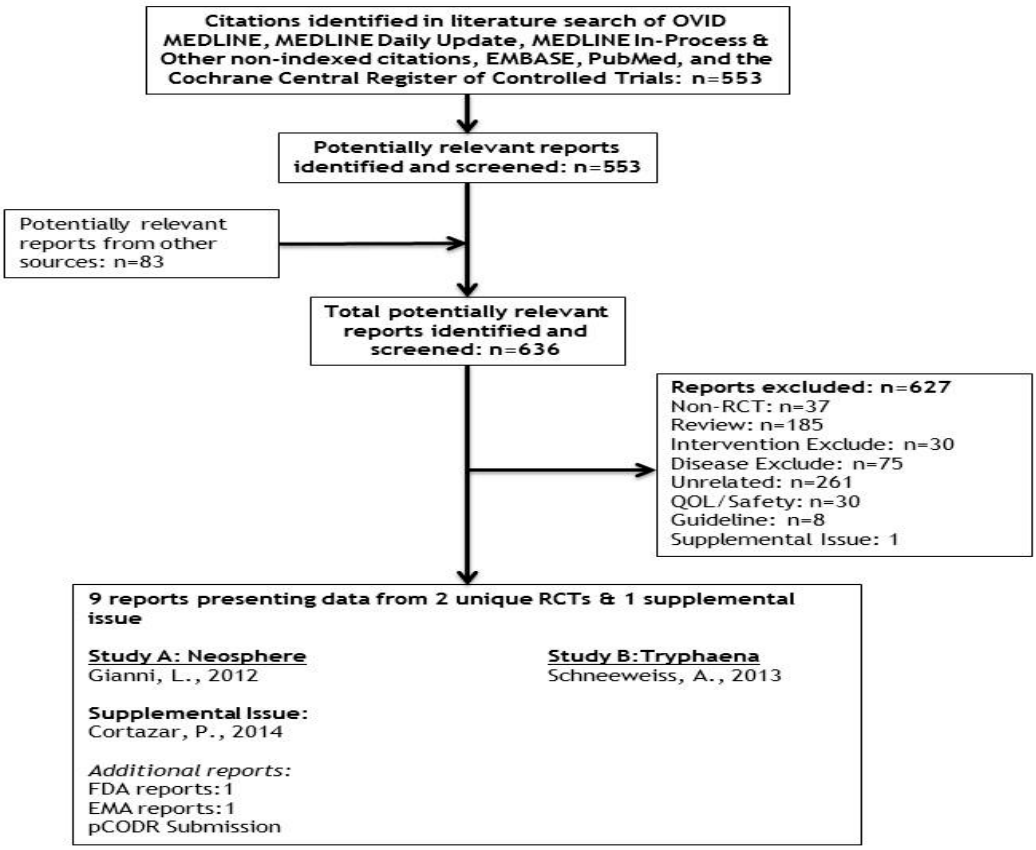
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions 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

Of the 636 potentially relevant reports identified, 2 studies were included in the pCODR systematic review[5,6] Studies were excluded because of ineligible study design (37), content unrelated to topic of interest (261), unrelated disease type or disease area (75), ineligible interventions (30), ineligible article type (guidelines 8), ineligible outcome of interest analysed (safety as primary outcome in a non-randomzied study (30)). One document was retrieved upon request from the review team because it contained information related to the supplemental issue addressed within this review.[10]

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



Note: Additional information was obtained from the Submission to pCODR. [24]

6.3.2 Summary of Included Studies

Two randomized trials met the inclusion criteria and were selected for inclusion. NEOSPHERE (WO20697)[5] is an open-label, 4 arm multicenter trial that examined pertuzumab in combination with trastuzumab and docetaxel in patients with locally advanced, inflammatory or early stage HER2-positive breast cancer. The primary tumour had to be over 2cm in diameter and centrally confirmed as HER2-positive. Interventions were assigned to treatment arms as follows: Arm A - trastuzumab + docetaxel (T+D); Arm B - pertuzumab + trastuzumab + docetaxel (Ptz+T+D); Arm C - pertuzumab + trastuzumab (Ptz+T); Arm D - pertuzumab + docetaxel (Ptz+D). The primary endpoint of the intention-to-treat (ITT) population was pCR in the breast (ypT0/is), which is defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery. Remaining in-situ lesions were allowed. Axillary lymph node status at time of surgery was also assessed so that the frequency of total pCR (yp T0/is ypN0), which is defined as the absence of invasive neoplastic cells in the breast and axillary lymph nodes regardless of DCIS, could be determined.[5]

TRYPHAENA (BO22280)[6] is a phase II randomized, multicenter, open-label, three-arm study to evaluate the tolerability and activity associated with pertuzumab and trastuzumab in combination with anthracyclines or carboplatin-based neoadjuvant systemic chemotherapy in patients with HER2-positive primary (operable, locally advanced or inflammatory) breast cancer. Arm A included: pertuzumab plus trastuzumab plus FEC, followed by pertuzumab plus trastuzumab plus docetaxel (Ptz+T+FEC/Ptz+T+D). Arm B included: FEC, followed by pertuzumab plus trastuzumab plus docetaxel (FEC/Ptz+T+D) Fluorouracil, epirupicin, and cyclophosphamide for three cycles, followed by three cycles of docetaxel, trastuzumab, and pertuzumab. Arm C included: Pertuzumab plus TCH (Ptz+TCH) Docetaxel, carboplatin, trastuzumab and pertuzumab for six cycles.[6]

6.3.2.1 Detailed Trial Characteristics

Table 2. Trial Characteristics

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NeoSphere 2012[5] Four arm, open label, Randomized Control trial N=417 Funded by: Hoffman LaRoche	Patients who have not undergone previous therapy, who are undergoing neoadjuvant treatment containing chemotherapy and who have: • Early-stage HER2-positive breast cancer. • Primary tumor ≥2 cm. • (ECOG) performance status of 0 or 1 • baseline left ventricular ejection fraction (LVEF) of 55% or more, as measured by echocardiography or multiple gated acquisition (MUGA).	4 neoadjuvant cycles prior to surgery **Arm A**: Trastuzumab and Docetaxel **Arm B**: pertuzumab and trastuzumab plus docetaxel. **Arm C:** pertuzumab and trastuzumab **Arm D:** pertuzumab plus docetaxel Trastuzumab (T) loading dose of 8 mg/kg, followed by maintenance doses of 6 mg/kg every three weeks. Docetaxel (D) was given at 75 mg/m^2, escalating, if tolerated, to 100 mg/m^2 every three weeks. Pertuzumab (Ptz) loading dose was 840 mg, which was followed by doses of 420 mg every three weeks.	***Primary:*** Pathological complete response ***Secondary***: clinical response rate, time to clinical response, BCS rate, DFS, PFS, evaluation of biomarkers
TRYPHAENA, ***2013***[6] Three arm, open label, randomized Control trial	HER2-positive, locally advanced, inflammatory and operable (T2-4d) breast cancer, scheduled for neoadjuvant therapy. • Early-stage HER2-positive breast cancer. • Primary tumor >2 cm.	**Arm A**: H+P (cycles 1−6) with FEC (cycles 1−3) and docetaxel (T) (cycles 4−6)	***Primary:*** symptomatic cardiac events (Grade 3, 4 or 5 symptomatic LVSD), and clinically significant left ventricular ejection fraction (LVEF) declines (defined

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
N=225 Funded by: Hoffman La-Roche	• (ECOG) performance status of 0 or 1 • baseline left ventricular ejection fraction (LVEF) of 55% or more, as measured by echocardiography or multiple gated acquisition (MUGA).	**Arm B**: FEC (cycles 1−3) followed by T+H+P (cycles 4−6) **Arm C**: T+H+P+carboplatin (Cb) (cycles 1−6) Trastuzumab was given at an initial dose of 8 mg/kg, followed by 6 mg/kg; pertuzumab was given at an initial dose of 840 mg, followed by 420 mg. docetaxel: 75 mg/m2, escalating to 100 mg/ m2 if no dose-limiting toxic effect occurred during cycle 4 FEC dose was the same in arms A and B. 5-fluorouracil: 500 mg/m2; epirubicin: 100 mg/m2; cyclophosphamide: 600 mg/m2	as a decline of ≥ 10% points from baseline and to a value of < 50%) over the course of the neoadjuvant treatmentperiod. ***Secondary:*** bpCR, clinical response rate, BCS rate, DFS, PFS, OS evaluation of biomarkers associated with response.
T-Docetaxel, **H**-trastuzumab, **P**-Pertuzumab, **FEC**-**5**-fluorouracil, epirubicin, cyclophosphamide , **bpCR:** breast pathological complete response rate, **LVEF**-left ventricular ejection fraction, **LVSD**-left ventricular systolic dysfunction, cb-carboplatin			

a) Trials

Two randomized controlled trials were found for this review. NeoSphere[5] is a four arm, open label comparative trial. Patients were randomized on a 1:1:1:1 basis performed centrally with stratification by operable, locally advanced, inflammatory breast cancer, and positivity for estrogen or progesterone receptors. A pre-planned descriptive intent-to-treat analysis was conducted 5 years after randomization of the last patient, to evaluate disease-free survival (DFS; time from surgery until progression or death) and progression-free survival (PFS; time from randomization until progression or death, equivalent to the commonly used definition of event-free survival). A pre-planned pooled analysis, across all four treatment arms was also reported. This analysis compared l patients who achieved tpCR versus all patients who did not achieve tpCR. The data cutoff for this primary study report of the neoadjuvant phase

of the trial occurred at the last patient's surgery or withdrawal in December, 2009.

TRYPHAENA[6] is a phase II randomized, multicenter, open-label, three-arm study to evaluate the tolerability and activity associated with pertuzumab and trastuzumab in combination with anthracyclines- or carboplatin-based neoadjuvant systemic chemotherapy in patients with HER2-positive primary (operable, locally advanced or inflammatory) breast cancer. Patients in each arm were stratified by operable, locally advanced, and inflammatory breast cancer and also by estrogen or progesterone receptor positivity status. As indicated, patients were required to have a baseline LVEF of at least 55% and no significant cardiovascular co-morbidities that could impair left ventricular function, since the study was primarily designed to evaluate cardiac safety.

The primary analysis for the TRYPHAENA study provides data up to the clinical cutoff date of June 2011 (by which time all patients had completed the neoadjuvant phase). An updated analysis provides safety data up to the clinical cutoff date of July 4, 2012, by which time all patients had completed the adjuvant therapy with trastuzumab and 97% of patients (201/225) were still in follow-up.

b) Populations

NeoSphere[5] enrolled 608 patients at 59 centers in 16 countries. Four hundred and seventeen of these patients were determined to be eligible and were randomized to one of the four treatment arms. Treatment groups were well balanced with respect to baseline characteristics. The median age was 50 years in groups A and B and 49 years in groups D and C. The majority of patients had ECOG score of 0: 94%; 90%; 86%; 83%, for groups A to D, respectively, with remaining group proportions having an ECOG score of 1. Forty seven percent of patients in arms A & B and 48% in arms C & D were ER or PR positive.

TRYPHAENA[6] recruited a total of 225 patients from 44 centres in 19 countries between Dec. 2009 and Jan. 2011, with 73 patients randomized to Arm A, 75 to Arm B, and 77 to Arm C. Baseline characteristics were well-balanced across treatment arms with the exception that there were more white patients randomised to arm C.

Table 3. Patient Characteristics NeoSphere[5]

Characteristic	Trastuzumab & Docetaxel	Trastuzumab, Docetaxel & Pertuzumab	Trastuzumab & Pertuzumab	Docetaxel & Pertuzumab
	(n = 107)	(n = 107)	(n = 107)	(n = 96)
ER positive or PR positive,	50 (47%)	50 (47%)	51 (48%)	46 (48%)

Characteristic	Trastuzumab & Docetaxel	Trastuzumab, Docetaxel & Pertuzumab	Trastuzumab & Pertuzumab	Docetaxel & Pertuzumab
	(n = 107)	(n = 107)	(n = 107)	(n = 96)
or both (n (%))				
Operable (n(%))	64 (60%)	65 (61%)	65 (61%)	60 (63%)
Locally Advanced n (%))	36 (34%)	32 (30%)	35 (33%)	31 (32%)
Inflammatory (n (%))	7 (7%)	10 (9%)	7 (7%)	5 (5%)
Lymph node status (n (%))				
No	32 (30%)	31 (29%)	32 (30%)	28 (29%)
N1	48 (45%)	53 (50%)	46 (43%)	41 (43%)
N2	22 (21%)	22 (21%)	24 (22%)	22 (23%)
N3	5 (5%)	0 (0%)	5 (5%)	5 (5%)
Median tumour size mm (range)	50 (20-200)	55 (20-150)	50 (20-200)	50 (0-180)

Table 4. Patient Characteristics TRYPHAENA[6]

	Arm A (n=73)	**Arm B**(n=75)	**Arm C**(n=75)
Characteristic			
Median Age, (range)	49.0 (27-77)	49.0 (24-75)	50.0 (30-81)
ECOG Score (n (%))			
0	66 (90.4%)	66 (88.0%)	68 (88.3%)
1	6 (8.2%)	9 (12.0%)	9 (117%)
NA	1 (1.4%)	0	0
ER positive or PR positive (n (%))	39 (53.4%)	35 (46.7%)	40 (51.%)
Disease Stage			
Operable (n (%))	53 (72.6%)	54 (72.0%)	49 (63.6%)

	Arm A (n=73)	Arm B(n=75)	Arm C(n=75)
Locally Advanced (n (%))	15 (20.5%)	17 (22.7%)	24 (31.2%)
Inflammatory (n (%))	5 (6.8%)	4 (5.3%)	4 (5.2%)
Median tumour size mm (range)	53 (10-220)	49 (19-120)	50 (15-200)

c) *Interventions*

In the NeoSphere[5] study patients received trastuzumab every 3 weeks at 8 mg/kg (cycle 1), followed by 6 mg/kg. The pertuzumab loading dose was 840 mg, followed by 420 mg every 3 weeks. Docetaxel was given at 75 mg/m^2, escalating, if tolerated, to 100 mg/m^2 every 3 weeks. After completion of four neoadjuvant treatment cycles, eligible patients underwent surgery and adjuvant FEC therapy (three cycles of fluorouracil 600 mg/m^2 intravenously, epirubicin 90 mg/m^2 intravenously, and cyclophosphamide 600 mg/m^2 intravenously every 3 weeks) in all groups except for group C, in which patients received four cycles of docetaxel before FEC. All patients received concomitant trastuzumab every 3 weeks for 1 year. Radiotherapy and standard hormone treatment for patients positive for oestrogen receptor were prescribed as per local guidelines. Patients underwent physical examination prior to surgery and specimens were examined for pathological complete response. Pathologists followed guidelines for assessment of pCR and independent analysis was conducted intermittently to ensure consistency.

In the TRYPHAENA[6] study drugs were administered intravenously on a 3-weekly schedule and given consecutively on the same day in the following sequence: trastuzumab, followed by pertuzumab, FEC, carboplatin, and docetaxel. Trastuzumab was given at an initial dose of 8 mg/kg, followed by 6 mg/kg; pertuzumab was given at an initial dose of 840 mg, followed by 420 mg. In Arms A and B, the doses administered were 5-fluorouracil: 500 mg/m^2; epirubicin: 100 mg/m^2; cyclophosphamide: 600 mg/m2; docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if no dose-limiting toxic effect occurred during cycle 4. In Arm C, carboplatin was administered at a dose of AUC6 (area under the plasma concentration-time curve) and docetaxel was given at 75 mg/m^2 (no dose escalation allowed). Dose modifications for trastuzumab and pertuzumab were not permitted. Docetaxel dose reductions to 75 mg/m^2 then to 60 mg/m^2 were allowed; re-escalation was not permitted. Dose reductions of FEC and carboplatin were allowed as per local prescribing information.[6]

d) *Patient Disposition*

In the NeoSphere[5] trial 417 patients were enrolled across 59 centres in 16 countries from Dec 17, 2007, to Dec 22, 2009. Four, 5, 14, and 6 patients from treatment arms A, B, C, and D respectively, withdrew from the study. Of 417 eligible patients, 392 underwent surgery as planned, and all those who did so had a valid assessment of pathological response.

Two patients died during the neoadjuvant phase. One death occurred in group B and was caused by fulminant hepatitis possibly related to treatment, which began after treatment cycle 4. This patient had a high body-mass index, hypertension, and type 2 diabetes. The other death occurred in group D; this patient died of lung metastases and progressive disease. Four patients withdrew due to adverse events. The majority of patients received all scheduled cycles of neoadjuvant treatment (Arm A = 95.8%; Arm B =88.0%, Arm C = 92.1%).[5]

In the TRYPHAENA study 225 patients were recruited from 44 centers in 19 countries between December 2009 and January 2011; 73 patients were randomized to Arm A, 75 to Arm B, and 77 to Arm C. At the time of data-cutoff all patients had completed neoadjuvant and adjuvant treatment and therefore, 1 year of trastuzumab therapy. There were no deaths reported during neoadjuvant treatment.[6]

e) Limitations/Sources of Bias

NeoSphere[5]

I. Breast cancer status and hormone receptor status were baseline stratification factors. However there were no power calculations that would confirm level of confidence in results. Subgroup results should be used with caution.

II. NeoSphere was not powered to determine predictive role of pCR according to hormone receptor status.

III. NeoSphere results should be used with caution due to technical, statistical issues. Comparative testing used alpha (α) = 0.2 which indicates a higher likelihood that results may not be accurate. A higher alpha level in comparative testing indicates we cannot be as certain that we are correctly rejecting the null hypothesis.

IV. There is no power calculation for the NeoSphere survival analysis, and it is a descriptive analysis.

V. Disease-free survival and progression-free survival results were provided by submitter. Conclusions drawn in the NeoSphere survival analysis do not match statistical conclusions. Clinical improvements benefits were seen, but statistical difference was not found between treatments.

VI. Pooled analysis used response (tpCR) versus non-response (tpCR) cohort and conclusion indicated results supported primary endpoint bpCR.

VII. No power analysis was conducted on pooled analysis and there is no detail regarding preplanning of pooled analysis.

VIII. Follow up in NeoSphere not long enough to determine cardiac feasibility. Safety concerns may be greater than reported due to short observation/follow-up period.

TRYPHAENA[6]

IX. TRYPHAENA has small number of patients which affects generalizability of the results.

X. TRYPHAENA was not designed for hypothesis testing and no comparative testing was completed.

XI. No survival analysis was conducted in TRYPHAENA. Given that the relationship between long term survival and pathological complete response is not certain efficacy results from the trial remain unclear in drawing conclusion about long term survival.

XII. Both trials are phase two studies and involved comparisons of different treatment combinations. This creates limitations about specific efficacy conclusions that can be made regarding pertuzumab since all treatment arms included pertuzumab.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 5. Efficacy Outcomes - NeoSphere[5,9]

Efficacy Outcomes				
Outcome	**Group A** **N=107**	**Group B** **N=107**	**Group C** **N=107**	**Group D** **N=96**
Pathological complete response in ITT population n(%, 95% CI)	31 (29.0%) (20.6-38.5)	49 (45.8%) (36.1-55.7) P=0.0141	18 (16.8%) (10.3%-25.3%) P=0.0198	23 (24.08%) (15.8%-33.7%) P=0.003 vs gr B
Pathological complete response in Node negative population at surgery n(%, 95% CI)	n=23 (21.5%, 14.1–30.5)	n=42 (39.3%, 30.0–49.2)	n=12 (11.2%, 5.9–18.8)	n=17 (17.7%, 10.7–26.8)
Pathological complete response in Node positive^{+ve} population at surgery n(%, 95% CI)	n=8 (7.5%, 3.3–14.2)	n=7 (6.5%, 2.7–13.0)	n=6 (5.6%, 2.1–11.8)	n=6 (6.3%, 2.3–13.1)
Pathological complete response in ER positive or PR positive, or both, women n/N(%, 95% CI)	10/50, 20.0% (10.0%-33.7%)	13/50, 26.0% (14.6%-40.3%)	3/51, 5.9% (1.2%-16.2%)	8/46, 17.4% (7.8%-31.4%)
Complete or partial response in primary breast tumor n/# with clinical breast examination (%, 95% CI)	79/99, 79·8% (70.5%–87.2%)	89/101, 88.1% (80.2%–93.7%)	69/102, 67.6% (57.7%–76.6%)	65/91, 71.4% (61.0%–80.4%)

Complete or partial response in all breast tumors & nodes n/# with clinical breast examination (%, 95% CI)	79/97, 81.4% (72.3%–88.6%)	88/100, 88.0% (80.0%–93.6%)	65/98, 66.3% (56.1%–75.6%)	65/88, 73.9% (63.4%–82.7%)
ITT=intention to treat; n=number of patients; %=proportion of patient group; 95% CI=95 percent confidence interval; n/N=number of patient events divided by number of patients in subgroup.				
Efficacy Outcomes – NeoSphere (cont'd)				
Outcome	**Group A** **N=107**	**Group B** **N=107**	**Group C** **N=107**	**Group D** **N=96**
3 yr - Disease Free Survival (DFS) Estimated Survival Rate HR and 95% CI	85%	92% HR=0.60 95% CI (0.28-1.27) ***versus group A***	88%	84%
3 yr Progression Free Survival (PFS) Estimated Survival Rate HR and 95% CI	86%	90% HR=0.69 95%CI (0.34-1.40) ***versus group A***	81%	82%
Efficacy Outcomes - NeoSphere Pooled Analysis (pooled by tpCR)				
Pooled analysis – Disease Free Survival	***(Achieve tpCR vs. Not achieve tpCR)*** HR=0.68 (95% CI, 0.36–1.26)			

Pooled analysis – Progresion Free Survival	***(Achieve tpCR vs. Not achieve tpCR)*** HR=0.54 (95% CI, 0.29–1.00)
tpCR=total pathological response rate	

Table 6. Efficacy Outcomes - TRYPHAENA [6,8]

Efficacy Outcomes			
Outcome	**Arm A** (FEC + H+ P ×3 →T+H+P ×3) N=72	**Arm B** (FEC ×3 →T +H+P ×3) N=75	**Arm B** (TCH + P ×6) N=76
Pathological complete response in ITT population (Tumor size 0)	61.6%	57.3%	66.2%
Pathological complete response in ITT population (Tumor size 0 and node 0)	56.2%	54.7%	63.6%
Clinical Complete Response (ITT)	50.7%	28.0%	40.3%
Hormone Receptor Negative (ER and PgR negative)			
	Arm A (FEC + H+ P ×3 →T+H+P ×3)	**Arm B** (FEC ×3 →T +H+P ×3)	**Arm B** (TCH + P ×6)

	N=34	N=40	N=37
% of patients achieving bpCR (ypT0/is)	79.4%	65.0%	83.8%
% of patients achieving tpCR (ypT0/is ypN0)	73.5%	62.5%	81.1%
FEC= 5-fluorouracil & epirubicin &cyclophosphamide; H=trastuzumab; P=pertuzumab; T= docetaxel; TCH=docetaxel, carboplatin, trastuzumab; ER=estrogen receptor; PgR= Progeseteron receptor; tpCR = total pathological complete response, bpCR = breast pathological complete response			

Table 6 cont'd. Efficacy Outcomes - TRYPHAENA[6, 8]

Hormone Receptor Positive (ER and PgR positive)			
Outcome	**Arm A** (FEC + H+ P ×3 →T+H+P ×3) N=39	**Arm B** (FEC ×3 →T +H+P ×3) N=35	**Arm B** (TCH + P ×6) N=40
% of patients achieving tpCR (ypT0/is)	46.2%	48.6%	50.0%
% of patients achieving tpCR (ypT0/is ypN0)	41.0%	45.7%	47.5%
ITT Population			
Outcome	**Arm A** (FEC + H+ P ×3 →T+H+P ×3) N=46	**Arm B** (FEC ×3 →T +H+P ×3) N=36	**Arm B** (TCH + P ×6) N=37
Breast Conserving Surgery	21.7%	16.7%	27.0%

Efficacy Outcomes

Pathological Complete Response

Of 417 eligible patients in the NeoSphere study, 392 underwent surgery as planned, and all those who did so had a valid assessment of pathological response. Pathological complete response was noted in 31 of 107 women (29.0%, 95% CI 20.6–38.5) given trastuzumab plus docetaxel (group A) compared with 49 of 107 (45.8%, 36.1–55·7) in group B that was given pertuzumab, trastuzumab, and docetaxel. This produced a p-value of p=0.0141 when compared using a Mantel Haenszel test. Twenty-three of 96 women (24.0%) given pertuzumab plus docetaxel (group D) had a pathological complete response, as did 18 of 107 (16.8%) women treated with both anti-HER2 antibodies but without chemotherapy, from Group C.[5] In the FDA review of pertuzumab, pCR(breast and nodes) results for group A compared with group B were reported for the subgroups of patients with primary operable disease (n=129), locally advanced disease (n=69), and inflammatory disease (n=17). All three subgroup analyses favoured the pertuzumab arm. The difference in pCR(breast and nodes) between Group A compared with Group B (i.e., a positive number favours Group B [pertuzumab arm]) was 0.21 (95% CI 0.06 to 0.37) for patients with primary operable disease; 0.13 (95% CI -0.10 to 0.35) for patients with locally advanced disease, and; 0.16 (95% CI -0.23 to 0.54) for patients with inflammatory disease.[8]

Within the ITT population of the TRYPHAENA study (n=225), the majority of patients were found to have achieved pCR in the breast (ypT0/is). The bpCR rates were similar across treatment arms in the ITT population (61.6% in arm A, 57.3% in arm B, and 66.2% in arm C) with similar results being found when pCR defined as both T0 & N0. Among these patients, 21.7% (Arm A), 16.7% (Arm B), and 27.0% (Arm C) were able to undergo breast conserving surgery following neoadjuvant systemic therapy.[6]

Objective Response

In the NeoSphere trial most patients achieved an objective response (complete response or partial response) in the primary lesion. As noted for pathological complete responses, the greatest clinical response was reported in group B. Few patients had insufficient therapeutic response (as per investigators' decision) during the neoadjuvant treatment period, although numbers were higher in group C where patients received both anti-HER2 antibodies without chemotherapy (no patients in group A, one [0·9%] patient in group B, seven [6·5%] in group C, and one [1·0%] in group D).[5]

In the TRYPHAENA trial, objective response was reported in 89.6%–94.7% of patients. Clinical complete response was achieved by 50.7% of patients in Arm A, 28.0% in Arm B, and 40.3% in Arm C.[6]

Breast Conserving Surgery

Overall rates of BCS were similar across treatment arms in the NeoSphere study. Results were not reported specifically for the ER positive subgroup. However, results were similar across treatment arms and with those in the Ptz+D arm having slightly higher likelihood of undergoing BCS (33.0% of patients) compared with patients in the other three arms (25.0% in the T+D arm, 27.8% in the Ptz+T+D arm and 26.0% in the Ptz+T arm).[24] Rates of BCS in patients with T2-T3 tumours expected to undergo a mastectomy at baseline were similar: T+D 22.6%; Ptz+T+D 23.2%; Ptz+T 18.0%; and Ptz+D 31.7%.[8]

In the TRYPHAENA trial BCS rates were very similar in the three treatment arms, ranging from 32.9%-33.8%. Mastectomy was planned for 46, 36, and 37 patients in Arms A, B, and C, respectively. Considering patients with T2-T3 disease for whom a mastectomy was planned at baseline, rates of BCS were higher in the two treatment arms in which 6 cycles of pertuzumab and trastuzumab were given following neoadjuvant systemic therapy, prior to surgery (21.7% in Arm A, 16.7% in Arm B and 27.0% in Arm C.[6]

Disease Free Survival

In the NeoSphere trial, disease-free survival was defined as time from surgery until progression or death. The Submitter provided updated time-to-event results for the NeoSphere study at the Checkpoint Meeting that were subsequently reported at ASCO 2015. This analysis was a comparative assessment between patients in Group A (traztuzumab & docetaxel), and Group B (pertuzumab & trastuzumab & docetaxel). Results showed non-significant difference between these treatment arms with a hazard ratio of 0.60 with a 95% confidence interval extending from 0.28 – 1.27, with an estimated 92% of patients alive and disease-free at 3 years in Group B and 85% in Group A, although these were estimates. No power calculation was provided.[9]

No information on disease-free survival was available for the TRYPHAENA study.[6]

Progression-Free Survival

Progression-free survival was defined as the time from randomization until progression or death. This analysis was a comparative assessment between patients in Group A (traztuzumab & docetaxel), and Group B (pertuzumab & trastuzumab & docetaxel). Results showed a statistically non-significant difference between these treatment arms with a hazard ratio of 0.69 with a 95% confidence interval extending from 0.34 – 1.40, with an estimated 90% of patients alive and progression-free at 3 years in Group B and 86% in Group A, although these were estimates. No power calculation was provided.[27]

No information on progression-free survival was available for the TRYPHAENA study.[6]

Overall Survival

No information on overall survival was available for either study.

Harms Outcomes

In the NeoSphere study, alopecia, neutropenia, diarrhea, nausea, fatigue, rash, and mucosal inflammation were the most frequently occurring adverse events and most were determined to be related to treatment. Most events were grade 1 or 2 and nearly all of the most frequent adverse events were deemed possibly related to study treatment. The most common adverse events of grade 3 or higher were neutropenia, febrile neutropenia, and leucopenia, as expected for treatment with docetaxel.

The overall incidence of adverse events of grade 3 or higher was lowest in group C (eight [2%] of 326 events), in which no chemotherapy was given and ranged from 12% (97 of 803 events; group B) to 14% (110 of 806 events; group A) in the other three treatment groups. The number of serious adverse events was similar in groups A, B,

and D (15–20 serious adverse events per group in 10–17% of patients), but lower in group C (four serious adverse events in 4% of patients; table 5). Neutropenia and febrile neutropenia were the most frequent serious adverse events.[5]

In the Trypaena study, Alopecia, diarrhoea, nausea, were the most frequently occurring adverse events opccurring in greater than 50% of patients. Neutropenia, febrile neutropenia, and leucopenia were the most commonly occurring ≥ grade 3 adverse events. The incidence of SAEs in the TRYPHAENA study was highest in Arm C (35.5%), followed by Arm A (27.8%) and Arm B (20.0%).[6]

Cardiac Tolerability

In the NeoSphere study the mean maximum decrease in LVEF measurement was low (4-5%) and was balanced across treatment groups. No significant change was detected when pertuzumab was added to trastuzumab and no patient had an LVEF decrease to less than 40% at any time during the study. Four patients (one in group A and three in group B) showed LVEF declines of 10-15% from baseline and to less than 50% during the neoadjuvant period. One patient in group C and one in group D had decreases of at least 15% from baseline to less than 50%.[5]

In TRYPHAENA the incidence of symptomatic LVSD and significant declines in LVEF (≥10% points from baseline to <50%) was low across all Arms. Two patients (2.7%) in Arm B experienced symptomatic LVSD (dyspnea on exertion) during neoadjuvant treatment. One of these patients experienced the event during FEC-only treatment; therefore, only 1 of 223 patients (0.4%) who received trastuzumab and pertuzumab in combination with standard chemotherapy developed symptomatic LVSD during the neoadjuvant treatment period. Both events resolved after study treatment discontinuation and medication for the event. During neoadjuvant treatment, four patients (5.6%) in Arm A, four (5.3%) in Arm B, and three (3.9%) in Arm C experienced LVEF declines of ≥10% points from baseline to <50%. Measurements had improved to ≥50% in all patients at data cutoff.[6]

Table 7. Cardiac Tolerability Outcomes - TRYPHAENA[6]

Outcome	Arm A (FEC + H+ P ×3 →T+H+P ×3) N=72	Arm B (FEC ×3 →T +H+P ×3) N=75	Arm B (TCH + P ×6) N=76
N (%) Symptomatic LVSD (Grade ≥ 3)	0 (0%)	2 (2.7%)	0 (0%)
N (%) LSVD (All Grades)	4 (5.6%)	3 (4.0%)	2 (2.6%)
N (%) Decline in	4 (5.6%)	4 (5.3%)	3 (3.9%)

Outcome	Arm A (FEC + H+ P ×3 →T+H+P ×3) N=72	Arm B (FEC ×3 →T +H+P ×3) N=75	Arm B (TCH + P ×6) N=76
LVEF ≥ 10% from BL to < 50%			
LVD -left ventricular dysfunction, **LVEF**- left ventricular ejection fraction, **LVSD** - left ventricular systolic dysfunction			

Patient Deaths

In the NeoSphere study two patients died during the neoadjuvant phase. One death occurred in group B and was caused by fulminant hepatitis possibly related to treatment, which began after treatment cycle 4. This patient had a high body-mass index, hypertension, and type 2 diabetes. The other death occurred in group D; this patient died of lung metastases and progressive disease.[5]

In the TRYPHAENA study there were no deaths reported during the noeadjuvant treatment period. There were 5 patient deaths in the follow-up period.[6]

Discontinuation of treatment

In NeoSphere the highest frequency of patient withdrawal was in group C where 14 patients discontinued treatment. Four, 5 and 6 patients discontinued treatment in arms A, B, and D.[5] The frequency of serious adverse events was similar in groups A, B, and D (15-20 serious adverse events per group in 10-17% of patients), but lower in group C (four serious adverse events in 4% of patients; table 5).[5]

TRYPHAENA reported that 5.6%, 6.7%, and 7.9% of patients in treatment arms A, B, and C respectively had an adverse event leading to discontinuation of treatment. Also reported was 36.1%, 29.3%, and 50% of patients that had an adverse event leading to dose modification or interruption.[6]

Table 8. AE's of Special Interest: most common ≥3 grade & Serious AE[5]

Most Common ≥3 grade AE's – NeoSphere				
	Group A N=107	Group B N=107	Group C N=108	Group D N=94
Adverse Event				
Neutropenia	61 (57%)	48 (45%)	1 (1%)	52 (55%)
Febrile Neutropenia	8 (7%)	9 (8%)	0 (0%)	7 (7%)

Leucopenia	13 (12%)	5 (5%)	0 (0%)	7 (7%)
Diarrhea	4 (4%)	6 (6%)	0 (0%)	4 (4%)
Asthenia	0	2 (2%)	0 (0%)	2 (2%)
Granulocytopenia	1 (1%)	1 (1%)	0 (0%)	2 (4%)
Rash	2 (2%)	2 (2%)	0 (0%)	1 (1%)
Menstruation Irregular	1 (1%)	1 (1%)	0 (0%)	4 (4%)
Drug Sensitivity	0	1 (1%)	2 (2%)	0 (0%)
ALT Increased	3 (3%)	0 (0%)	0 (0%)	1 (1%)

Serious Adverse Events (defined as any AE that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was medically significant or required intervention to prevent one or more of the outcomes listed)

	Group A N=107	Group B N=107	Group C N=108	Group D N=94
Adverse Event				
All Serious AE's	20	15	4	16
Neutropenia	1 (1%)	4 (4%)	0 (0%)	6 (6%)
Febrile Neutropenia	7 (7%)	6 (6%)	0 (0%)	6 (6%)
Neutropenic infection	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Neutropenic sepsis	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Pyrexia	1 (1%)	1 (1%)	0 (0%)	0 (0%)
Diarrhea	2 (2%)	0 (0%)	0 (0%)	1 (1%)
Heart Failure$_{congestive}$	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Fulminant hepatitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Other	8 (7%)	2 (2%)	3 (3%)	3 (3%)

Table 9. AE's of Special Interest: most common AE's (Any grade, ≥3) - TRYPHAENA[6]

***Most Common* AE's Any grade - TRYPHAENA**			
	Group A N=72	**Group B N=75**	**Group C N=76**
Adverse Event n(%)			
Diarrhea	44 (61.1%)	46 (61.3%)	55 (72.4%)
Alopecia	35 (48.6%)	39 (52.0%)	41 (53.9%)
Nausea	38 (52.8%)	40 (53.3%)	34 (44.7%)
Neutropenia	37 (51.4%)	35 (46.7%)	37 (48.7%)
Vomiting	29 (40.3%)	27 (36.0%)	30 (39.5%)
Fatigue	26 (36.1%)	27 (36.0%)	32 (42.1%)
Anemia	14 (19.4%)	6 (8.0%)	28 (36.8%)
Mucosal Inflammation	17 (23.6%)	15 (20.0%)	13 (17.1%)
Constipation	13 (18.1%)	17 (22.7%)	12 (15.8%)
Dyspepsia	18 (25.0%)	6 (8.0%)	17 (22.4%)
Most Common AE's ≥grade 3 - TRYPHAENA			
Adverse Event n(%)			
Neutropenia	34 (47.2%)	32 (42.7%)	35 (46.1%)
Febrile Neutropenia	13 (18.1%)	7 (9.3%)	13 (17.1%)
Leucopenia	14 (19.4%)	9 (12.0%)	9 (11.8%)
Diarrhea	3 (4.2%)	4 (5.3%)	9 (11.8%)
Anemia	1 (1.4%)	2 (2.7%)	13 (17.1%)
Thrombocytopenia	0 (0%)	0 (0%)	9 (11.8%)
Vomiting	0 (0%)	2 (2.7%)	4 (5.3%)
Drug Hypersensitivity	2 (2.8%)	0 (0%)	2 (2.6%)
Fatigue	0 (0%)	0 (0%)	3 (3.9%)
ALT increase	0 (0%)	0 (0%)	3 (3.9%)

Neutropenia

The incidence of neutropenia was highest in the group A when the event was grade 3 or above and it was highest in group D when the event grade 4 or above.[5]

In the Trypahena study Neutropenia was one of the most commonly reported adverse events of any grade, as well as those ≥ grade 3. Neutropenia was reported as an SAE in 2.8% (Arm A), 4.0% (Arm B), and 1.3% (Arm C).[6]

Febrile Neutropenia

The incidence of febrile neutropenia was similar across all chemotherapy treatment groups (A,B,D) in NeoSphere trial, and the proportion of patients who had an event was 7–8% in groups A, B,and D when events were classified by "any grade". The proportion was 6%-7% when events were classified as "serious". There were no events in the pertuzumab/transtuzumab combination arm C.[5]

Febrile neutropenia was one of the most common serious adverse events in the TRYPHAENA study; grade 3 or higher febrile neutropenic events occurred in 18.1%, 9.3%, and 17.1% of patients in treatment arms A, B, and C, respectively.[6]

Congestive Heart Failure (CHF)

There was one episode of CHF in Neoshpere that occurred in study arm C. It was reported that the patient had enrolled with a prior cardiac condition.[5]

Congestive heart failure was not reported in the TRYPHAENA Study.[6]

Hematologic Adverse Events

In the NeoSphere trial there were two hematologic adverse events identified which fit this category for reporting purposes. There was no aggregate reporting for this group in literature.

Leukopenia occurred at the highest rate in group A with a frequency of 13 (12%). Treatment arm A contained trastuzumab and docetaxel. Rates across arms B and D were similar with counts and frequency of 5 (5%) and 7 (7%).

Incidence of granulocytopenia was similar between treatment arms, and was relatively low. There were no events in treatment arm c, and there were 1, 1, and 2 events in arms A, B, and D respectively.[5]

In the TRYPHAENA study ≥grade 3 Leukopenia occurred in 19.4%, 12.0%, and 11.8% of arms A, B, and C respectively while thrombocytopenia was found in 0%, 0%, and 11.8%.[6]

Non-Hematologic Adverse Events

Rash

The incidence rates of Rash were similar across treatment arms in the NeoSphere study with 21%, 26%,11%, and 29% of patients having events of any grade, in arms A, B, C, and D respectively. These were events reported as any grade. Grade 3 or

greater events occurred at 2%, 2% and 1% in arms A, B, and D respectively. No events were seen in arm C, which is a non-docetaxel arm.[5]

There were no events reported for the TRYPHAENA study.[6]

Fatigue

In the Neoshpere study fatigue was consistent across treatment arms containing docetaxel and was lowest in arm C that did not contain docetaxel. Proportion of patients with any grade fatigue was 27%, 26%, 12%, and 26% in treatment arms A, B, C, and D respectively. Asthenia was reported as a ≥ grade 3 adverse event in 2% of patients in arms B and D respectively.[5]

Fatigue was reported as a common adverse event of any grade, as well as ≥ grade 3, in the TRYPHAENA study. It was consistent across treatment arms in both categories, but was highest in treatment arm C.[6]

Fever

Pyrexia occurred relatively infrequently in treatment arms A and B, and were reported as serious adverse events (≥ grade 3).

Overall the incidence rates of GI perforation were within the known safety profile of the drug: up to 2% across all labelled indication within the current product information.[5]

There were no events reported for the TRYPHAENA study.[6]

Wound Healing Complications

No information was reported on wound healing complications in either study. Further information was requested from submitter but it was not provided as the Submitter indicated that none was available.[5,6]

Infusion reactions

No information was reported on infusion reactions in either study. Further information was requested from submitter regarding NeoSphere trial results, but it was not provided as the Submitter indicated that none was available.[5,6]

Withdrawal due to adverse events

Four patients withdrew due to adverse events; two in treatment arm C, and two in treatment arm D.[5]

In TRYPHAENA four patients withdrew from treatment arm A due to adverse events. Two patients in arm B and zero patients in Arm C withdrew from treatment due to an adverse event.[6]

Infections

No information was reported on infections in either study. Further information was requested from submitter regarding NeoSphere trial results, but it was not provided as the Submitter indicated that none was available.[5,6]

Increased white blood cell count

No information was reported on increase white blood cell count in either study. Further information was requested from submitter regarding NeoSphere trial results, but it was not provided as the Submitter indicated that none was available.[5,6]

Other cardiac events (CHF, MI, primary arrhythmia),

Congestive heart failure was reported in 1 patient, in arm C in the NeoSphere study.[5] No information was reported for CHF, MI, or primary arrhythmia in the TRYPHAENA study. Primary endpoints in Tryaphaena were related to cardiac tolerability & safety and included specifically symptomatic left ventricular systolic dysfunction (LVSD) as assessed by the investigator, and decline in the left ventricular ejection fraction (LVEF) of ≥10% points from baseline to <50% over the course of neoadjuvant treatment. Further information was requested from submitter but it was not provided as the Submitter indicated that none was available.[6]

Quality of life

No information was reported on Quality of life. Further information was requested from submitter but none was available.[5,6]

6.4 Ongoing Trials

102 studies were returned in Clinicaltrials.gov.

- 100 studies were excluded because they were not randomized control trials, patients did not have early stage breast cancer, and treatment phase was not neo-adjuvant.

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
The Impact of HER2 Heterogeneity on the Treatment of Early-stage HER2-positive Breast Cancer: a Phase II Study of T-DM1 in Combination With Pertuzumab in the Preoperative Setting[25]			
Study ID#: NCT02326974 Estimated Enrollment:160 Study Start Date: 12/2014 Estimated Study Completion Date: 04/2022 The Impact of HER2 Heterogeneity on the Treatment of Early-stage HER2-positive Breast Cancer: a Phase II Study of T-DM1 in Combination With Pertuzumab in the Preoperative Setting	• Patients must have HER2-positive Stage II or III histologically confirmed invasive carcinoma of the breast. A minimum tumor size of 2 cm determined by physical exam or imaging is required. • HER2-positive, confirmed by central ER/PR determination is required. • Bilateral breast cancers are allowed if both cancers are HER2-positive. • Patients with multifocal or multicentric disease are eligible as long as one area meets eligibility criteria. • Breast imaging should include the ipsilateral axilla. For subjects with a clinically negative axilla, a sentinel lymph node biopsy will be performed either before or after preoperative therapy at the discretion of the subject's physicians. For subjects with a clinically positive axilla, a needle aspiration, core biopsy or SLN procedure will be performed to determine the presence of metastatic disease in the lymph nodes. • Men and women (with any menopausal status) ≥ 18 years of age • ECOG performance status 0 or 1 • Required laboratory values: a. ANC ≥1500/mm3 b. Hemoglobin ≥ 9 g/dl c. Platelets ≥100,000/mm3 d. Serum creatinine < 1.5 X ULN (institutional) e. Total bilirubin ≤ 1.0 X ULN (institutional) For patients with Gilbert syndrome, the direct bilirubin should be within the institutional normal range. f. AST and ALT ≤ 1.5x ULN (institutional)	T-DM1 and Pertuzumab T-DM1 via IV every 3 weeks for 6 doses and Pertuzumab loading dose via IV on Cycle 1 Day 1 followed by maintenance dose via IV every 3 weeks for 6 doses. Excision of tumor/mastectomy of biopsy residual tumor	**Primary Outcome Measures:** Pathological complete response **Secondary Outcome Measures:** Intratumor heterogeneity of HER2 amplification, clinical response, safety & tolerability, Enrichment for HER2-negativity or HER2 heterogeneity in residual tumors treated with T-DM1 plus pertuzumab preoperative therapy, DFS, OS

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	g. Alkaline phosphatase ≤1.5x ULN (institutional) • Documentation of hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies is required: this includes hepatitis B surface antigen (HBsAg) and/or total hepatitis B core antibody (HBcAb) in addition to HCV antibody testing. • Left ventricular ejection fraction (LVEF) ≥ 55% • Premenopausal women must have a negative serum pregnancy test, including women who have had a tubal ligation and for women less than 12 months after the onset of menopause. • Women of childbearing potential and men with partners of childbearing potential must be willing to use one highly effective form of non-hormonal contraception or two effective forms of non-hormonal contraception by the patient and/or partner and continue its use for the duration of the study treatment and for 7 months after the last dose of study treatment. • Potent CYP3A4 inhibitors, such as ketoconazole and erythromycin, should be avoided during the study treatment period with T-DM1. • Excessive alcohol intake should be avoided (occasional use is permitted). • Patients with a history of ipsilateral DCIS are eligible. • Patients undergoing breast conservation therapy (i.e. lumpectomy) must not have any contraindications to radiation therapy. • Willing and able to sign informed consent. • Willing to provide tissue for research purposes.		
Optimizing Neoadjuvant Systemic Treatment for HER2 Positive Breast Cancer - the TRAIN-2 Study[26]			
Study ID#: NCT01996267 Estimated Enrollment:437	• Histologically confirmed infiltrating breast cancer • Stage II or stage III disease. Nodal status must be examined by ultrasound, fine needle aspiration, sentinel node biopsy, or FDG-PET scan.	Intervention: PTC+Pertuzumab Paclitaxel; 80 mg/m2; day 1,8 Trastuzumab; 6 mg/kg (loading dose 8 mg/kg); day 1 Carboplatin;	Primary endpoint: Pathological complete response.

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study Start Date: 12/2013 Estimated Study Completion Date: 12/2019 Optimizing Neoadjuvant Systemic Treatment for HER2-Positive Breast Cancer - the TRAIN-2 Study	• Overexpression and/or amplification of HER2 in an invasive component of the core biopsy, according to one of the following definitions: • >30% of invasive tumor cells showing strong complete circumferential membrane staining (score 3+) • HER2 gene amplification defined as >6 HER2 gene copies per nucleus by in situ hybridization. • Age ≥18 • Eastern Cooperative Oncology Group performance status ≤1 • Adequate bone marrow function (ANC >1.5 x 109/l, platelets >100 x 109/l) • Adequate hepatic function (ALAT, ASAT and bilirubin <2.5 times upper limit of normal) • Adequate renal function (creatinine clearance >50 ml/min) • LVEF ≥50% measured by echocardiography or MUGA • Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance. Absence of any medical condition that would place the patient at unusual risk. • Signed written informed consent	AUC=6; day 1 Pertuzumab; 420 mg (loading dose 840 mg); day 1 Cycle repeated every 21 days Comparator: FEC-T +Pertuzumab Fluorouracil; 500 mg/m2; day 1 Epirubicine; 90 mg/m2; day 1 Cyclophosphamide; 500 mg/m2; day 1 Trastuzumab; 6 mg/kg (loading dose 8 mg/kg) Pertuzumab; 420 mg (loading dose 840 mg); day 1 Cycle is repeated every 21 days	Secondary endpoint: Safety, prognostic and predictive biomarkers.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of pertuzumab in early stage, HER2-positive, breast cancer:

- Is pathological complete response an appropriate surrogate for long term survival in patients with early stage breast cancer?

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Pathological Complete Response as a Surrogate for Long-Term Survival in Patients with Early Stage Breast Cancer.

7.1.1 Objective

Pathological complete response has been proposed as a surrogate endpoint for long-term survival outcome such as event-free survival (EFS), and overall survival (OS). Even with information regarding this relationship, there is uncertainty regarding the appropriateness of using pCR as surrogate. Due to this uncertainty a review was conducted on the following pooled analysis to determine whether pathological complete response is valid as a surrogate endpoint for these outcomes: Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-7

7.1.2 Findings

Methods used in the analysis reported by Cortazar et al[10] included a systematic review to generate the population sample, HR estimation and logrank testing for event free survival analysis and overall survival analysis of pooled population and subgroups, and Cox regression for relationship between baseline characteristics and pathological complete response. Due to variance in definition of pathological complete response, three different definitions were used to develop subgroups for analysis. These were; i) ypT0 ypN0 (i.e., absence of invasive cancer and in-situ-cancer in the breast and axillary nodes), ii) ypT0/is ypN0 (i.e., absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ), iii) ypT0/is (i.e., absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement).

A search of OVID (Medline, Embase) and Pubmed was conducted. Eligibility criteria included studies having at least 200 patients with primary breast cancer treated with preoperative chemotherapy followed by surgery. Studies were required to have available data for pathological complete response, EFS, and OS, and have a median follow-up of at least 3 years. Twelve studies were identified and data from these studies was pooled for analysis.

Results found that eradication of tumour from both the breast and axillary lymph nodes (ypT0 pN0 and ypT0/is ypN0) was better associated with improved EFS and OS than was eradication of invasive tumour from the breast alone. It was also found that the most favourable outcomes after pathological complete response were recorded in patients with HER2-positive, hormone receptor-negative tumours who received trastuzumab (EFS: 0.15, 0.09–0.27; OS: 0.08, 0.03–0.22), and in the triple-negative subgroup (EFS: HR 0·24, 95% CI 0·18–0·33; OS: 0·16, 0·11–0·25). These results were consistent at the individual level but were not consistent when analyzed at the trial (population) level.

A review of the methods used in the pooled analysis found that there were problems which affect the ability to use the conclusions found in the analysis. These issues are summarized briefly below.

This search would highlight the most mature data available from trials and would provide the most valid outcomes in terms of analyses and length of follow-up.

There was considerable variation in how pCR was defined amongst the studies included in the analysis. Although definitions were standardized to form subgroups, there was limited discussion of how progression was assessed. Given the lack of information it is most prudent to consider that pathological complete response may have been misreported, leading to the conclusion that the relationship to long term outcomes was not verified, and that the relationship between pCR and long-term outcomes may not have been valid.
Also, in terms of progression assessment and potential bias, two hundred and seventeen patients from the TECHNO study were not randomized and the trial was not designed to provide comparative outcomes. These results may be biased because response was assessed with full knowledge of treatment. Overall, the assessment of pathological complete response between studies may have been different providing heterogeneous disease characteristics for patients achieving/not achieving pCR, within the pooled population.

Most preoperative treatments were not similar between studies included in the analysis and this may have an effect on likelihood of relapse and death within the pooled patient population. Heterogeneous population within the study sample creates unreliable results and increases likelihood that variance in outcomes would be found in reality. There was also an issue with post-operative treatment being provided in some studies. Particularly the NOAH trial where trastuzumab was given preoperatively, though the relationship between pCR and long-term outcome is confounded by the postoperative use of trastuzumab in the investigational arm, at 3.2 years of median follow-up, the 3-year EFS was 71 percent in the trastuzumab arm and 56 percent in the chemotherapy-alone arm (HR 0.58, adjusted p=0.013). There was no statistically significant difference in OS, but fewer deaths occurred in the trastuzumab arm (18 versus 26; HR 0.62)[8,27].

Not all patients in the studies included in the pooled analysis were HER2-positive and information about HER2 receptor status was not available for four trials (AGO-1, NSABPB-18, NSABP B-27, and ECTO). The HER2-positive subgroup may not be complete and it remains unclear as to whether it is possible to make a statement about this subgroup from the analysis.

Longer follow up would help to confirm results as 5 year relative survival is quite high for early stage patients in general.

7.1.3 Summary

An association between pCR and EFS and between pCR and OS was demonstrated at the individual level. This association was strongest in HER2-positive, hormone-receptor negative breast cancer and in triple-negative breast cancer. However, a relationship between the frequency of pCR and improvement in long-term outcomes has not been established at a trial level indicating that a positive correlation between pCR and survival was not found at a population level, only at the individual level. Given these issues, further investigation is required before pCR is considered a validated surrogate for either EFS or OS.

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 the neoadjuvant treatment of 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.cadth.ca/pcodr).

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.

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.cadth.ca/pcodr). 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. breast, cancer.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
2. (HER2 or Receptor 2).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
3. 1 and 2
4. (pertuzumab or perjeta).ti,ab,rn,nm,sh,hw,ot. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
5. *pertuzumab/
6. or/4-5
7. 3 and 6
8. exp animals/
9. exp animal experimentation/
10. exp models animal/
11. exp animal experiment/
12. nonhuman/
13. exp vertebrate/
14. or/8-13
15. exp humans/
16. exp human experiment/
17. or/15-16
18. 14 not 17
19. 7 not 18
20. (randomized controlled trial or controlled clinical trial).pt.
21. randomized controlled trial/
22. randomized controlled trials as topic/
23. controlled clinical trial/
24. controlled clinical trials as topic/
25. randomization/
26. random allocation/
27. double-blind method/
28. double-blind procedure/
29. double-blind studies/
30. single-blind method/
31. single-blind procedure/
32. single-blind studies/
33. placebos/
34. placebo/
35. control groups/
36. control group/
37. (random: or sham or placebo:).ti,ab,hw.
38. ((singl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
39. ((tripl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
40. (control: adj3 (study or studies or trial:)).ti,ab.
41. (nonrandom: or non random: or non-random: or quasi-random: or quasirandom:).ti,ab,hw.
42. allocated.ti,ab,hw.
43. ((open label or open-label) adj5 (study or studies or trial:)).ti,ab,hw.
44. or/20-43
45. 19 and 44
46. remove duplicates from 45
47. limit 46 to english language

1. Literature search via PubMed

   "Breast Cancer AND Pertuzumab OR Perjeta"

2. Cochrane Library

   "Breast Cancer AND Pertuzumab OR Perjeta"

3. Grey Literature Search via
   ASCO, ESMO,

   "Breast Cancer AND Pertuzumab OR Perjeta"

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