PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Lapatinib (Tykerb) with letrozole for Metastatic Breast Cancer

July 5, 2013

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1.1 Background

The objective of this review is to evaluate the efficacy and safety of lapatinib + letrozole compared with placebo + letrozole in postmenopausal women with hormone receptor (HR)-positive and epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer (MBC). Lapatinib (Tykerb) is a small molecule dual tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR or HER1) and HER2.

Currently lapatinib is approved by Health Canada for use in combination with letrozole for the treatment of postmenopausal patients with hormone receptor positive metastatic breast cancer, whose tumours overexpress the ErbB2 (HER2) receptor, and who are suitable for endocrine therapy.[1]

The Health Canada recommended dose of lapatinib is 1500 mg (6 tablets) in combination with letrozole (2.5 mg) both taken orally once daily.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Four reports presenting data from one unique randomised controlled trial (RCT) (EGF30008) were included in the systematic review. EGF30008 was an international, multicenter, double-blind, phase III RCT that compared the efficacy and safety of lapatinib + letrozole with placebo + letrozole as a first line treatment.[2-4] The study randomised 1286 postmenopausal women (median age 60 years) with HR+ metastatic breast cancer who were suitable for endocrine therapy. Two hundred and nineteen patients (17%) in study EGF30008 were HER2(+) (111 in the lapatinib + letrozole arm and 108 in the placebo + letrozole arm). Prior anti-estrogen therapy was allowed.

Cross-over to the alternate treatment was not permitted at the time of progression and patients with a history of brain metastasis or were HER2-negative were excluded from the study.

Efficacy

The primary endpoint was progression free survival (PFS) in HER2(+) patients. PFS by investigator assessment showed that in the HER2(+) population a statistically significant improvements in PFS was shown in the lapatinib plus letrozole compared to the placebo plus letrozole arms (8.2 months and 3.0 months, respectively, HR 0.71; 95% CI 0.53 to 0.96, p=0.019).

At the time of primary data analysis for PFS in 2008, the OS data were immature. The median OS in the HER2(+) population was 144.7 weeks in the lapatinib + letrozole group compared with 140.3 weeks in the placebo + letrozole group (HR 0.74, 95% CI 0.5 to 1.1, p = 0.113). Post-treatment therapy following discontinuation of study treatment, which may bias OS, was not reported. The manufacturer confirmed that an updated OS analysis is still not available.

HRQoL was measured using the Functional Assessment of Cancer Therapy-Breast (FACT-B), the Functional Assessment of Cancer Therapy-General (FACT-G) and Trial Outcome Index (TOI). Baseline HRQoL scores were similar between the two treatment groups. At week 12, 24, 36 and 48, the differences in average scores of FACT-B, FACT-G and TOI were not

statistically significant between the two groups, for patients who stayed on study (71% at week 12, 47% at week 24, 32% at week 36 and 27% at week 48). Due to the high drop-out rates in the two groups, the HRQoL data should be interpreted with caution.

Harms

There were greater serious adverse events (22% versus 15%, respectively) and grade 3 or 4 diarrhea and rash for the lapatinib + letrozole arm compared to the placebo + letrozole arm. The most common treatment-related serious adverse events (SAEs) in the lapatinib + letrozole group were decreased ejection fraction (3%) and diarrhea (2%), while the most commonly reported treatment-related SAEs in the placebo + letrozole group were decreased ejection fraction and vomiting (1% for each). There were more AEs leading to discontinuation of therapy in the lapatinib + letrozole group (15%) compared with the placebo + letrozole group (6%).

1.2.2 Additional Evidence

pCODR did not receive input on lapatinib with letrozole from any patient advocacy group(s). However, input received for a recent pCODR review of a drug for the treatment of patients with HER2(+) metastatic breast cancer was used to inform this review. Provincial Advisory group input was obtained from five of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

In addition, the following information is discussed as supporting information:

- A meta-analysis of published trials was summarised that evaluated the efficacy of HER2-targeted therapy in addition to standard treatment (chemotherapy and/or hormone therapy) in MBC patients.[5]

- Critical appraisal of an indirect comparison of lapatinib + letrozole (LAP+LET) with trastuzumab + anastrozole (TZ+ANA) was conducted. The indirect analysis made no distinction between HER2(-) and HER2(+) patients in 3 of the 5 trials included (P025, TARGET and North American), and therefore the indirect comparison is based on the assumption that the relative effectiveness of letrozole versus tamoxifen and anastrozole versus tamoxifen is similar in HER2(+) and HER2(-) patients.

Other

Health Canada recently endorsed a public communication regarding the use of lapatinib and trastuzumab in combination with chemotherapy.[6] This communication outlined that in patients with HER2+ metastatic breast cancer, therapy with trastuzumab should be considered a more effective initial treatment than therapy with lapatinib and that patients should only be given the option of lapatinib once they have progressed on a trastuzumab based treatment regimen. The CGP noted that patients receiving lapatinib in combination with chemotherapy are a different patient population than those who would receive lapatinib in combination with hormonal therapy.

1.2.3 Interpretation and Guidance

Metastatic breast cancer is an incurable disease. Within the subtypes of MBC, the HER-2 positive subtype had one of the worst prognoses prior to the use of anti- HER-2 therapy. Approximately 15-20% of all breast cancers have gene amplification or over-expression (or both) of human epidermal growth factor receptor 2 (HER-2), a tyrosine kinase trans-membrane receptor, resulting in more aggressive clinical phenotype and a poorer prognosis. The prevalence of the HER-2+ subtype in MBC is approximately 20-25% historically, though this may be declining due to the efficacy of adjuvant trastuzumab.

In women with HER2-positive MBC, the use of the anti-HER2 humanized monoclonal antibody trastuzumab in combination with cytotoxic chemotherapy (taxane), as compared to cytotoxic chemotherapy alone, has demonstrated a clinically and statistically significant improvement in PFS and OS.[7,8] There however remains the need for new and improved targeted therapies in patients that are either not medically fit or don't require treatment with chemotherapy. In these patients, the use of anti-HER2 therapy (trastuzumab) in combination an AI (anastrozole) may be used (TAnDEM Study).[9] Data from the TAnDEM Study is presented as part of an indirect comparison with Study EGF30008 in the Clinical Guidance Report, which evaluates trastuzumab plus anastrozole.

Study EGF 30008 showed that in the HER2(+) population clinically and statistically significant improvements in PFS was shown by investigator assessment in the lapatinib plus letrozole vs placebo plus letrozole arms. At the time of primary data analysis for PFS, the OS data were immature, however the median OS in the HER2(+) population was similar among both treatment arms. There was greater serious adverse events, grade 3 or 4 diarrhea and rash, and greater drug induced liver toxicity in the lapatinib + letrozole arm. As such, patient would need to acknowledge a greater rate of side effects for the combination of lapatinib and letrozole versus monotherapy with letrozole alone.

Baseline HRQoL scores were not statistically significant between the two groups, for patients who stayed on study. The HRQoL data should however be interpreted with caution, due to the high drop-out rates in the two groups.

As there is no randomised controlled trial directly comparing lapatinib + letrozole with trastuzumab + AI, the comparative efficacy of these regimens is uncertain. However, based on the Clinical Guidance Panel's assessment, it may be reasonable to offer a combination of either lapatinib or trastuzumab with a non-steroidal AI to post-menopausal women with HR+ HER-2+ advanced breast cancer who are not medically fit to receive chemotherapy with trastuzumab. These patients would likely never be medically fit enough to receive chemotherapy. The goal of therapy with these regimens would be to prolong PFS since improvements in OS have not been demonstrated.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit for the combination of lapatinib and letrozole in the treatment of hormone receptor positive (HR+), HER 2 positive MBC in patient's not medically fit to receive chemotherapy with trastuzumab. The CGP based its conclusion on a single RCT, though the cohort of patients of interest (HR+ and HER 2+) numbered only 219. The uncertainty of the CGP's conclusion was due to a modest clinical and statistically significant improvement in progression-free survival for patients receiving lapatinib

and letrozole compared with placebo and letrozole. The uncertainty was primarily due to the absence of a proven overall survival benefit with this regimen.

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

- The standard treatment in the majority of HER 2+ MBC patients is to receive chemotherapy and trastuzumab, a treatment regimen which has demonstrated improvements in overall survival in well performed randomized clinical trials.
- As modest improvements in progression-free survival have not been fully validated as a surrogate outcome for overall survival in MBC, an updated and mature survival analyses be performed and published for EGF30008.
- Subsequent lines of therapy (in particular trastuzumab and chemotherapy) should be documented in the cohorts that received trastuzumab and chemotherapy because they may bias the end-point of overall survival.
- Patients would need to acknowledge a greater rate of side effects for the combination of lapatinib and letrozole versus monotherapy with letrozole alone as greater serious adverse events, grade 3 or 4 diarrhea and rash, and greater drug induced liver toxicity were observed in the lapatinib + letrozole arm.

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 lapatinib (Tykerb) with letrozole for metastatic breast cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.pcodr.ca.

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

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

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Breast cancer is the most common cancer in women and the 2nd most common cause of cancer mortality in Canadian women, with an estimated 5,100 deaths in 2012. In 2012, 22,700 new cases and 5,100 deaths were expected in Canadian women.[10]

Hormone receptor (HR) status and epidermal growth factor receptor 2 (ErbB2 or HER2) are two predictive factors used to estimate the risk of a patient developing recurrent disease. The majority (75%) of women have tumors that overexpress the estrogen receptor and/or the progesterone receptor, and over half of these patients are post-menopausal.[11] HER2, a transmembrane glycoprotein receptor with tyrosine kinase activity, is overexpressed in approximately 20% of breast cancers and is associated with increased disease recurrence and poor prognosis.[12] Approximately half of breast cancers with HER2 over-expression also co-express HRs.[13]

HER2 overexpression is associated with endocrine resistance[14] and as such estrogen deprivation therapy is a principle component in the treatment of hormone-sensitive metastatic breast cancer (MBC). Aromatase inhibitors (AIs) decrease circulating levels of estrogen by blocking the action of the enzyme aromatase, which converts androgens into estrogens. Third generation AIs, such as letrozole and anastrozole, were developed to selectively inhibit the aromatase active site, thereby blocking the synthesis of estrogen, without affecting the production of other adrenal steroids. It is recommended that in patients with estrogen-receptor-positive/HER2-positive breast cancer with no indication for chemotherapy, endocrine therapies should be combined with anti-HER2 therapies, such as lapatinib and trastuzumab.[15]

Lapatinib (Tykerb) is a small molecule dual tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR or HER1) and HER2.

In May 2009, Health Canada approved the use of lapatinib in combination with capecitabine for the treatment of patients with advanced or MBC who have received prior therapy and whose tumours overexpress HER2. Lapatinib in combination with letrozole has been approved by Health Canada for use in postmenopausal patients

with hormone receptor positive metastatic breast cancer, whose tumours overexpress the ErbB2 (HER2) receptor, and who are suitable for endocrine therapy.[1,16] The use of lapatinib in combination with any AI has however not been approved by Health Canada.[17] On January 29, 2010, the U.S. Food and Drug Administration (FDA) granted approval to lapatinib for use in combination with letrozole for the treatment of postmenopausal women with HR (+) MBC that overexpresses the HER2 receptor and for whom hormonal therapy is indicated. In February 2010, the European Medicines Agency (EMA approved lapatinib in combination with letrozole for the same indication as FDA.[18]

The recommended dose is 1500 mg once daily in patients receiving lapatinib in combination with letrozole.[19]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of lapatinib disosylate (Tykerb) in combination with letrozole on patient outcomes compared to standard therapies or placebo in postmenopausal women with hormone receptor-positive (HR+) metastatic breast cancer (MBC) that overexpresses the Human Epidermal Growth Factor Receptor 2 (HER2 receptor), and are suitable for endocrine therapy.

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.

The efficacy and safety of lapatinib 1500 mg plus letrozole 2.5 mg given once daily as a first line therapy were compared with placebo plus letrozole in an international, multicenter, double-blind, phase III RCT (EGF30008).[2-4] The study recruited postmenopausal women (median age 60 years) with HR+ metastatic breast cancer who were suitable for endocrine therapy. Two hundred and nineteen patients (17%) in study EGF30008 were HER2(+). In the HER2(+) subgroup, all patients were predominantly stage IV disease (94-95%), and had visceral or soft tissue involvement (83-86%). All HER2(+) patients were ECOG performance status of 0 (51%) and 1 (49%). Patients with a history of brain metastasis or HER2-negative were excluded from the study. Prior anti-estrogen therapy was allowed. The primary endpoint was progression free survival (PFS) in HER2(+) patients. The secondary endpoints included overall survival (OS), health-related quality of life (HRQoL), and clinical benefit rate (CBR). Safety outcomes included death, serious adverse events (SAEs), adverse events leading to discontinuation, and any adverse events. Efficacy was evaluated in 219 patients [HER2(+), 111 in the lapatinib + letrozole arm and 108 in the placebo + letrozole arm], and safety was evaluated in 219 patients (113 in the lapatinib + letrozole arm and 106 in the placebo + letrozole arm).

At the cut-off date for PFS analysis (June 3, 2008, 1.8 years), there were 177 PFS events, of which 88 were in the lapatinib plus letrozole arm and 89 in the placebo plus letrozole arm. PFS by investigator assessment in the HER2+ population was 8.2 months and 3.0 months in the lapatinib plus letrozole and placebo plus letrozole arms, respectively [hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.53 to 0.96, p=0.019]. Subgroup analyses for PFS in the HER2(+) population showed consistently longer PFS in treatment of lapatinib + letrozole, although a statistically significantly longer PFS was not observed in some subgroups.

The OS data were immature at the time of primary data analysis for PFS. The median OS in the HER2(+) population was 144.7 weeks in the lapatinib + letrozole group compared with 140.3 weeks in the placebo + letrozole group (HR 0.74, 95% CI 0.5 to 1.1, p = 0.113).

HRQoL was measured using the Functional Assessment of Cancer Therapy-Breast (FACT-B), the Functional Assessment of Cancer Therapy-General (FACT-G) and Trial Outcome Index (TOI). Baseline HRQoL scores were similar between the two treatment groups. At week 12, 24, 36 and 48, the differences in average scores of FACT-B, FACT-G and TOI were not statistically significant between the two groups, for patients who stayed on study (71% at week 12, 47% at week 24, 32% at week 36 and 27% at week 48).

The clinical benefit rates (CBR) in the HER2(+) population were 48% and 29% in the lapatinib + letrozole and placebo + letrozole arms, respectively, odds ratio (OR) = 0.4, 95% CI 0.2 to 0.8, p = 0.003.

The most common adverse events in the study were diarrhea, rash, nausea, fatigue and arthralgia, with diarrhea and rash higher in the lapatinib + letrozole group. The most common treatment-related serious adverse events (SAEs) in the lapatinib + letrozole group were decreased ejection fraction (3%) and diarrhea (2%), while the most commonly reported treatment-related SAEs in the placebo + letrozole group were decreased ejection fraction and vomiting (1% for each). There were more AEs leading to discontinuation of therapy in the lapatinib + letrozole group (15%) compared with the placebo + letrozole group (6%). In the safety population, 243 patients (37%) in the lapatinib + letrozole group and 231 patients (37%) in the letrozole + placebo died. Eight deaths (1%) due to SAEs occurred in each group, and three of them were considered study drug-related (one in lapatinib + letrozole, and two in letrozole + placebo). Data of death, SAEs and discontinuation due to adverse events specific for the HER2-positive population are not reported.

Table 1: Key Results from EGF30008 Study (cut-off at June 3, 2008)

Efficacy [HER2(+) population]				
		Median	**HR (95% CI)**	**P value**
OS (immature)	Lap + Let (n=111)	144.7 weeks	0.74 (0.5, 1.1)	0.113
	Pl + Let (n=108)	140.3 weeks		
PFS	Lap + Let (n=111)	8.2 months	0.71 (0.53, 0.96)	0.019
	Pl + Let (n=108)	3.0 months		
Quality of Life*	Between-groups difference (95% CI) at week 48			
FACT-B	-2.6 (-11.0 to 5.8)			
FACT-G	-2.9 (-10.0 to 4.2)			
TOI	-2.9 (-9.4 to 3.5)			
		n (%)	**OR (95% CI)**	**P-value**
CBR	Lap + Let (n=111)	53 (48)	0.4 (0.2, 0.8)	0.003
	Pl + Let (n=108)	31 (29)		

Safety [safety population in EGF30008]		
	LAP+LET n (%)**	**LET+PL n** (%)**
ITT population (LAP+LET: 654, LET+PL: 624)		
All deaths	243 (37)	231 (37)
Fatal AEs	8 (1)	8 (1)
SAEs	144 (22)	94 (15)
Suspected to be drug-related	54 (8)	27 (4)
AEs leading to discontinuation	95 (15)	35 (6)
Any AEs	628 (96)	536 (86)
AEs suspected to be drug-related	548 (84)	343 (55)
AEs of special interest***	533 (81)	228 (37)
HER2-positive population (LAP+LET: 113, LET+PL: 106)		
All deaths	NR	NR
Treatment-related deaths[3]	1 (< 1)	0
SAEs[20]	23 (20)	10 (9)
Suspected to be drug-related	NR	NR
AEs leading to discontinuation[21]	7 (6)	3 (3)
Any AEs[3]	108 (96)	82 (77)
AEs suspected to be drug-related	NR	NR
AEs of special interest***	NR	NR

AE = adverse event; **FACT-B** = the Functional Assessment of Cancer Therapy-Breast; **FACT-G** = the Functional Assessment of Cancer Therapy-General; **SAE** = serious adverse event; **LAP+LET** = lapatinib + letrozole; **LET+PL** = Letrozole + placebo; **n** = number of patients with events; **NR** = not reported; **TOI** = trial outcome index

* HRQoL results were based on 59 patients (32 in LAP+LET, 27 in LET+PL) who completed the assessment at week 48

** calculated by Methods Team

***included rash, diarrhea, nail changes, hepatobiliary events, cardiac events and pulmonary events

Data source for ITT population: Tykerb submission,[16] Johnston 2009,[2] Schwartzberg 2010[3]

At present, a phase III, multi-center, open-label, three-arm study (NCT 01160211) is ongoing to evaluate the efficacy and safety of AI in combination with lapatinib, trastuzumab or both in postmenopausal women with HR(+), HER2(+) metastatic breast cancer. It estimated to enroll 525 patients.

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.

A meta-analysis of published trials evaluated the efficacy of HER2-targeted therapy in addition to standard treatment (chemotherapy and/or hormone therapy) in MBC patients.[5] Eight trials (involving 1848 patients) published from 1996 to December 2009 were included for analysis. HER2-targeted agents were trastuzumab in five trials and lapatinib in three trials. OS, PFS, time to progression (TTP) and response rates were reported in these trials. The meta-analysis indicated that a 22% reduction in the mortality rate with the addition of HER2-targeted agents to standard therapy (HR for OS: 0.78, 95% CI 0.67 to 0.91). The benefit of HER2-targeted therapy over standard therapy was also seen with the secondary outcomes of TTP (HR 0.56, 95% CI 0.48 to 0.64), PFS (HR 0.63, 95% CI 0.53 to 0.74) and ORR (RR 1.67, 95% CI 1.46 to 1.90). This study suggested the benefit of adding HER2-targeted therapy to standard treatment in HER2 (+) MBC.

2.1.5 Summary of Supplemental Questions

Critical appraisal of an indirect comparison of lapatinib + letrozole (LAP+LET) with trastuzumab + anastrozole (TZ+ANA):

Indirect statistical assessments for efficacy among lapatinib + letrozole and trastuzumab + anastrozole therapies were performed using an indirect comparison that employed a Bucher fixed effect model (Riemsma 2012[13]). This analysis found that hazard ratios for PFS, OS, and ORR in postmenopausal HER2+ HR+ MBC patients favored lapatinib + letrozole over trastuzumab + anastrozole, but the differences were not statistically significant. The indirect analysis made no distinction between HER2(-) and HER2(+) patients in 3 of the 5 trials included (P025, TARGET and North American), and therefore the indirect comparison is based on the assumption that the relative effectiveness of letrozole versus tamoxifen and anastrozole versus tamoxifen is similar in HER2(+) and HER2(-) patients. Conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data, and therefore the findings derived from this review should be interpreted with caution.

See section 7.1 for more information.

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

Patient input was not received for lapatinib + letrozole. Input received for a recent pCODR review for the treatment of patients with HER2+ metastatic breast cancer was used to inform this review.

- Current treatment options for HER2(+) MBC are effective at prolonging progression-free disease, but most cases of advanced disease will progress and symptoms will worsen. Patient groups identified their goals of current treatment options for MBC include controlling the progression of the disease (extending their life), and reducing cancer-related symptoms (extending or stabilizing quality of life).
- Patients indicated that the decision to determine what risks and side effects are tolerable must rest in the hands of each individual patient. Each patient will assess the impact of side effect on their quality of life differently.
- Patients with MBC understand the limitations of current treatment options, and seek to live their remaining months and years with the best possible quality of life (both physical and social aspects) that they can achieve.
- There are many financial and psychosocial impacts to the patients and families/caregivers that are affected by MBC diagnosis and treatment.

PAG Input

Input on the Tykerb review was obtained from five of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, the current common therapeutic option for patients who are appropriate for anti-HER2 therapy is trastuzumab + chemotherapy followed by trastuzumab + AI. While lapatinib is not likely to replace the current common therapeutic option in patients where chemotherapy is the preferred option, lapatinib may replace the trastuzumab + AI

regimen. It was also noted that due to lapatinib having an oral route of administration, it may enhance accessibility to patients and reduce chemotherapy clinic and chair time. In addition, the number of patients with HER2+ breast cancer that is non-visceral disease is small and funding implementation would not have a large budgetary impact. However, several barriers to implementation include dosing (six tablets per day may be burdensome for patients), patient monitoring (additional resources towards left ventricular function and liver function tests) and jurisdictional differences in funding of oral treatments (PharmaCare Co/pay versus cancer agency).

Other

Health Canada recently endorsed a public communication regarding the use of lapatinib and trastuzumab in combination with chemotherapy.[6] Two recent studies have shown that the use of lapatinib in combination with chemotherapy is less effective than the use of trastuzumab in combination with chemotherapy.[22,23] This communication outlined that in patients with HER2+ metastatic breast cancer, therapy with trastuzumab should be considered a more effective initial treatment than therapy with lapatinib and that patients should only be given the option of lapatinib once they have progressed on a trastuzumab based treatment regimen. The CGP noted that patients receiving lapatinib in combination with chemotherapy are a different patient population than those who would receive lapatinib in combination with hormonal therapy.

2.2 Interpretation and Guidance

Metastatic breast cancer is an incurable disease. Within the subtypes of MBC, the HER-2 positive subtype had one of the worst prognoses prior to the use of anti- HER-2 therapy. With the use of the monoclonal anti-HER 2 antibody trastuzumab in combination with a taxane as 1st line therapy for HER-2+ MBC, an improvement in overall survival has been demonstrated in both randomized clinical trials and in population based studies. Lapatinib is an oral tyrosine kinase inhibitor of the HER-1 (EGFR) and HER-2 receptor.

Activity of lapatinib has been demonstrated in an RCT combining lapatinib and chemotherapy (capecitabine) in HER-2+ MBC.

Study EGF30008, comparing the combination of letrozole plus lapatinib with letrozole with placebo as 1st line treatment of HR+ MBC, included a population of known HER-2 positive tumors.[2] In the HER-2 positive HR+ cohort, the addition of lapatinib to letrozole improved PFS, but with no difference as of yet seen in OS at the time of the analysis in 2008 (though less than 50% of deaths had occurred at time of analysis). Overall, a hazard ratio of 0.71 in the improvement of PFS for the combination is a modest gain at best. There was however greater serious adverse events, grade 3 or 4 diarrhea and rash, and greater drug induced liver toxicity for the lapatinib + letrozole arm.

As there is no randomised controlled trial directly comparing lapatinib + letrozole with trastuzumab + AI, the comparative efficacy of these regimens is uncertain. However, based on the Clinical Guidance Panel's assessment, it may be reasonable to offer a combination of either lapatinib or trastuzumab with a non-steroidal AI to post-menopausal women with HR+ HER-2+ advanced breast cancer who are not medically fit to receive chemotherapy with trastuzumab. The goal of therapy with these regimens would be to prolong PFS since

improvements in OS have not been demonstrated. Patient would need to acknowledge a greater rate of side effects (diarrhea, rash, liver toxicity) for the combination of lapatinib and letrozole versus monotherapy with an AI alone. These patients would likely never be medically fit enough to receive chemotherapy. In patients with HER2+ MBC, a survival benefit for anti-HER 2 agents have consistently been proven when taken in combination with chemotherapy, thus patients who are medically fit to receive chemotherapy and trastuzumab should do so in the appropriate time frame dictated by the pace of the disease and the patient and oncologist. Upon consideration of feedback received from two eligible stakeholders, the Clinical Guidance Panel did not consider it necessary to add any additional comments or clarifications into the clinical guidance report.

2.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit for the combination of lapatinib and letrozole in the treatment of hormone receptor positive (HR+), HER 2 positive MBC in patient's not medically fit to receive chemotherapy with trastuzumab. The CGP based its conclusion on a single RCT, though the cohort of patients of interest (HR+ and HER 2+) numbered only 219. The uncertainty of the CGP's conclusion was due to a modest clinical and statistically significant improvement in progression-free survival for patients receiving lapatinib and letrozole compared with placebo and letrozole. The uncertainty was primarily due to the absence of a proven overall survival benefit with this regimen.

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

- The standard treatment in the majority of HER 2+ MBC patients is to receive chemotherapy and trastuzumab, a treatment regimen which has demonstrated improvements in overall survival in well performed randomized clinical trials.
- As modest improvements in progression-free survival have not been fully validated as a surrogate outcome for overall survival in MBC, an updated and mature survival analyses be performed and published for EGF30008.
- Subsequent lines of therapy (in particular trastuzumab and chemotherapy) should be documented in the cohorts that received trastuzumab and chemotherapy because they may bias the end-point of overall survival.
- Patients would need to acknowledge a greater rate of side effects for the combination of lapatinib and letrozole versus monotherapy with letrozole alone as greater serious adverse events, grade 3 or 4 diarrhea and rash, and greater drug induced liver toxicity were observed in the lapatinib + letrozole arm.

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 deaths are the 2nd most common cause of cancer mortality in Canadian women, with an estimated 5,100 deaths in 2012. Breast cancer deaths also contribute to the greatest potential life years lost from any illness in Canadian women. The goals of systemic therapy in the treatment of metastatic breast cancer (MBC) are to improve overall survival and to maintain and/or improve quality of life. Despite MBC being such a prevalent disease, of the clinical trials performed in the metastatic setting only a small minority of the randomized controlled trials have actually demonstrated an improvement in overall survival. The ones that have demonstrated an overall survival benefit are important trials to note.

Targeted therapies are designed to block critical pathways involved in cancer cell growth and metastases and have now led to major clinical advances in the treatment of MBC, especially HER2-positive MBC. The human epidermal growth factor receptor (HER) family is composed of tyrosine kinase receptors that are involved in the regulation of proliferation and survival of epithelial cells. The family includes four receptors: HER-1 (epidermal growth factor receptor (EGFR), HER-2 (neu, C-erbB2), HER-3 and HER-4. The HER-2 has emerged as one of the most important targets for the treatment of breast cancer. Approximately 15-20% of all breast cancers have gene amplification or over-expression (or both) of human epidermal growth factor receptor 2 (HER-2), a tyrosine kinase trans-membrane receptor, resulting in more aggressive clinical phenotype and a poorer prognosis. The prevalence of the HER-2+ subtype in MBC is approximately 20-25% historically, though this may be declining due to the efficacy of adjuvant trastuzumab. Despite a quantitative inverse relationship between HER-2 and ER (estrogen receptor) (and PgR [progesterone receptor]), approximately half of all HER-2 positive breast cancers are also hormone receptor positive.[24] HER-2 over-expression confers a worse prognosis in breast cancer, regardless of the accompanying hormone receptor status.

In women with HER2-positive MBC, the use of the anti-HER2 humanized monoclonal antibody trastuzumab in combination with cytotoxic chemotherapy (taxane), as compared to cytotoxic chemotherapy alone, has demonstrated a clinically and statistically significant improvement in PFS and OS.[7,8] Thus anti-HER2 treatment in combination with chemotherapy is a standard approach for HER2-positive MBC for those suitable to received chemotherapy. There however remains the need for new and improved targeted therapies both in terms of efficacy and tolerability for the treatment of MBC.

3.2 Accepted Clinical Practice

Though there may not be a single standard treatment regimen delivered, the standard principle today is the delivery of a taxane-based regimen concurrent with trastuzumab improves overall survival in HER-2+ MBC compared to the chemotherapy backbone alone. In the pivotal study by Slamon et al, the addition of trastuzumab to chemotherapy (either paclitaxel or an anthracycline regimen) improved response rates, time to disease progression and overall survival.[7] Unfortunately the concurrent delivery of a conventional anthracycline (doxorubicin + cyclophosphamide) with trastuzumab had unacceptable rates of cardiotoxicity. In a subsequent trial of the combination of docetaxel + trastuzumab vs. docetaxel alone as 1st line treatment of HER-2 positive MBC, the combination of docetaxel and trastuzumab demonstrated improved response rate, PFS and overall

survival.[8] Lastly, a phase III trial comparing paclitaxel, carboplatin and trastuzumab vs. paclitaxel and trastuzumab alone demonstrated improved response rate and PFS (though no difference in OS) without significantly increased toxicity has led to the use of this triplet.[25] More recently, the experimental arm on CLEOPATRA (docetaxel, trastuzumab + pertuzumab) as a 1st line regimen for HER-2+ MBC demonstrated significantly improved clinical outcomes (PFS and OS) with the addition of pertuzumab to docetaxel and trastuzumab compared to docetaxel and trastuzumab alone.[26]

Not all patients with HER-2 positive MBC are medically fit or require treatment with a taxane or an anti-HER 2 agent(s) at initial presentation/relapse of MBC. Elderly patients, those with significant co-morbidities, and those with limited asymptomatic bone and/or soft tissue metastases (without visceral or brain metastases) that are both hormone receptor positive and HER-2 positive would be candidates to consider for hormonal therapy prior to chemotherapy and trastuzumab.

3.3 Evidence-Based Considerations for a Funding Population

Two phase III randomized controlled trials (RCT) have been performed with the addition of targeted anti-HER 2 therapy in combination with hormonal therapy in HER-2 positive HR+ MBC. The TAnDEM study (n=207) combined trastuzumab with anastrozole versus anastrozole alone as 1st or 2nd line hormonal therapy in advanced stage disease.[9] Prior tamoxifen as adjuvant or hormonal therapy for MBC was allowed, though approximately 35-40% of patients were hormonal therapy naïve on enrollment. Though the addition of trastuzumab to an AI did have a statistically significant impact in improving the hazard ratio for PFS (HR=0.63; 95% CI, 0.47-0.84), the absolute improvement was modest at best (median PFS 4.8 months vs 2.4 months; log rank p=0.0016). Moreover, there was no difference in overall survival between the arms, with the authors stating a likely reason being that 70% of patients on the anastrozole alone arm crossed over to receive a trastuzumab-containing regimen at some point in time post-progression.

The second RCT (EGF30008) to mention is the phase III trial that compared the combination of letrozole plus lapatinib with letrozole with placebo as 1st line treatment of HR+ MBC, which included a population of known HER-2 positive tumors.[2] As there is no randomised controlled trial directly comparing lapatinib + letrozole with trastuzumab + AI, the comparative efficacy of these regimens is uncertain. However, based on the Clinical Guidance Panel's assessment , it may be reasonable to offer post-menopausal women with HR+ HER-2+ advanced breast cancer who are not medically fit to receive chemotherapy with trastuzumab, a combination of either lapatinib or trastuzumab with an non-steroidal AI. Treatment would be with the goal of prolonging PFS however uncertain remains of actually improving OS.

3.4 Other Patient Populations in Whom the Drug May Be Used

In addition to the above criteria, it may be reasonable to use lapatinib + letrozole in the patient populations for which data is limited or excluded on the randomized phase III trial of lapatinib and letrozole vs placebo and letrozole. These include:

- those patients that had prior exposure to an aromatase inhibitor (either non-steroidal or steroidal) in the adjuvant setting. Less than 1% of subjects on the above mentioned clinical trial (EGF 30008) had prior exposure to an AI.

- those patients that had prior exposure to trastuzumab in the adjuvant setting. Less than 1% of subjects on the above mentioned clinical trial (EGF 30008) had prior exposure to an anti-HER 2 agent in the adjuvant setting.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Please note that since patient input was not received on lapatinib (Tykerb) in combination with Letrozole for metastatic breast cancer, the patient input summary from the most recent and relevant pCODR review of a drug for metastatic breast cancer was used to provide information on patient values and experiences with the disease. Two patient advocacy groups, Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (Rethink) collaborated and provided joint input on a treatment of metastatic breast cancer patients and their input is summarized below.

CBCN and Rethink conducted an online survey and key informant interviews to gather information from patients and caregivers about the impact of metastatic breast cancer on their lives and the effect of treatments on their disease. Patients were contacted through the membership databases of CBCN and Rethink. Survey questions comprised of a combination of scoring options and free form commentary. Survey participants were contacted through the membership databases of CBCN and Rethink. A total of 87 respondents completed the survey; of this total, 71 were patients with metastatic breast cancer and 16 were caregivers. Cited responses are included verbatim to provide a deeper insight of the patient and caregiver perspective; cited responses are not corrected for spelling or grammar. A copy of the survey was provided to pCODR. A review of current studies and grey literature was also conducted to identify issues and experiences that are commonly shared among breast cancer patients.

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

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

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients Have with Metastatic Breast Cancer

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

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

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

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

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

4.1.2 Patients' Experiences with Current Therapy for Metastatic Breast Cancer

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

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

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

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

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

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

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

"Many of the next step treatments are very expensive and not covered by government programs and it is a HUGE struggle to get coverage. … When dealing with an incurable disease the last thing you want to have to do is spend time on a letter writing campaign

to argue about whether or not you should receive the drugs recommended by your physician. At about $1500.00 a week, I don't know many who can afford that."

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

- 53% of respondents with children or other dependents indicated there is minimal or no access to appropriate care for their loved ones when they are experiencing debilitating symptoms to their cancer, and 40% identified barriers to accessing quality care during cancer treatment.
- 26% of patients indicated there are minimal or no transportation options in their community when they seek treatment and support for symptoms, and 18% indicated a lack of adequate transportation options to access cancer treatment. One patient indicated that in a rural community, it is difficult to get to the hospital in the winter months.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.1.3 Impact of Metastatic Breast Cancer and Current Therapy on Caregivers

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

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

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

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

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

4.2 Information about the Drug Being Reviewed

There is no information on direct experiences with lapatinib in combination with letrozole since patient input was not received for lapatinib in combination with letrozole.

4.3 Additional Information

No additional comments were received.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input on the lapatinib + letrozole review was obtained from five of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, the current common therapeutic option for patients who are appropriate for anti-HER2 treatment is trastuzumab + chemotherapy followed by trastuzumab + an aromatase inhibitor (AI). While lapatinib is not likely to replace the current common therapeutic option (trastuzumab + chemo) in patients where chemotherapy is the preferred option, lapatinib may replace the trastuzumab + AI regimen. If implemented lapatinib + letrozole as an oral treatment would enhance accessibility to patients and reduce chemotherapy clinic and chair time. PAG also noted that the number of patients with HER2+ breast cancer that is non-visceral disease is small and funding implementation would not have a large budgetary impact.

Potential barriers to implementation were noted by PAG around dosing, patient monitoring and jurisdictional differences in funding of oral treatments. PAG indicated that six tablets per day may be a burdensome regimen for patients suggesting that one large dose may be a preferred option. Likewise, the recommended monitoring of patients on lapatinib + letrozole (left ventricular function and liver function tests) is likely to incur additional clinic and hospital resources. PAG noted that issues around patient access to treatment may arise as cancer drug funding systems vary in provinces (PharmaCare Co/pay versus cancer agency).

Additional points were noted by PAG with regards to the potential for indication creep into subsequent lines of treatment. PAG noted that letrozole is used in subsequent lines of treatment other than first line and lapatinib may be requested in those settings in patients that have failed first line trastuzumab.

5.1 Factors Related to Comparators

PAG noted that the current therapeutic option for treatment of HER2 positive metastatic breast cancer is trastuzumab + chemotherapy (e.g. paclitaxel or docetaxel) followed by trastuzumab + an aromatase inhibitor (AI). Although lapatinib + letrozole in the first line setting would be an alternative therapeutic option, it is unlikely to displace the current therapeutic option in patients where chemotherapy is the preferred option; however lapatinib/letrozole may be an alternative to trastuzumab + AI.

PAG noted that although lapatinib as an oral treatment will increase accessibility of treatment to patients, it is more expensive than the current therapeutic option and as such presents a potentially challenge to funding.

5.2 Factors Related to Patient Population

PAG noted that as most jurisdictions fund more than one AI, there is a potential for lapatinib to be requested in combination with funded AI's other than letrozole. Likewise, although the main study supporting efficacy is limited to patients in the first line setting, there may also be a potential risk for indication creep in further lines of therapy after failure on trastuzumab, as letrozole is generally not restricted to use in the first line setting.

As an enabler to implementation, PAG noted that the patient population with HER2 positive advanced breast cancer with non-visceral disease (i.e. not in need of chemotherapy) is small. This means that implementing a funding decision will have a small budgetary impact.

5.3 Factors Related to Accessibility

PAG noted that lapatinib tablets are currently packaged into bottles and need dispensing at a pharmacy, a change from the unit dose blister packaging in the past. This has raised concerns around drug exposure to individuals that prepare patient prescriptions and family members as well as the inconvenience to patients. PAG indicated that these concerns present a barrier to funding and indicated that the unit dose blistering many need to be reinstituted.

PAG noted that lapatinib is an oral medication, and in some jurisdictions, oral medications are not covered in the same way as intravenous cancer medications, which may limit accessibility of treatment to patients. For these jurisdictions, patients would first require an application to their pharmacare program, and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of- pocket expenditure.

As an enabler to implementations, PAG noted that the availability of an oral drug in comparison to the current therapeutic option which is available as an iv therapy, will allow for improved accessibility of the drug to patients especially in less urban and rural communities.

5.4 Factors Related to Dosing

PAG noted that the current indication for lapatinib requires patients to take six tablets per day. Although as an oral therapy lapatinib is more accessible to patients, PAG noted that the number of tablets to be taken per dose may be a regimen that could be burdensome to patients.

5.5 Factors Related to Implementation Costs

If implemented, PAG noted that if lapatinib became available as first line treatment, it may be used instead of the current therapeutic option, the trastuzumab + chemotherapy regimen. This will result in reduced chemotherapy clinic and chair time.

PAG also noted that management of toxicities and associated dose adjustments may require additional hospital resources and costs. Patients may require monitoring of left

ventricular ejection fraction (LVEF) and need liver function tests (LFT) every 4-6 weeks, procedures that are likely to represent additional costs. However, as endocrine therapy (alone) and lapatinib + capcitabine are already available, management of toxicities and dose adjustments will not be completely new. PAG also noted that there will be an addition to pharmacy workload as patients would now be getting two prescriptions (lapatinib + letrozole).

5.6 Other Factors

PAG noted that if lapatinib + letrozole is implemented, the current treatment algorithms and criteria for those treatments already funded will need modification.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of lapatinib disosylate (Tykerb) in combination with letrozole on patient outcomes compared to standard therapies or placebo in postmenopausal women with hormone receptor-positive (HR+) metastatic breast cancer (MBC) that overexpresses the Human Epidermal Growth Factor Receptor 2 (HER2 receptor), and are suitable for endocrine therapy (see Table 1 in Section 6.2.1 for outcomes of interest and comparators).

A supplemental question(s) 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.

- Critical appraisal of an indirect comparison (provided by manufacturer) of treatments in patients with MBC that are both HR(+) and HER2(+)

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
Published and unpublished RCT	Postmenopausal women with HR+ metastatic breast cancer that overexpresses HER2, and are suitable for endocrine therapy HER2-negative patients will be excluded.	lapatinib 1500 mg QD orally + letrozole 2.5mg QD orally	endocrine therapy (AI / tamoxifen / fulvestrant) Trastuzumab + endocrine therapy (AI / tamoxifen / fulvestrant)	• **OS** • **PFS** • **HRQoL** • CBR • TTP • Time to brain metastasis • SAE • AE • WDAE
AE=adverse events; **AI**=aromatase inhibitor; **CBR**=clinical benefit rate; **HER2**=Human Epidermal Growth Factor Receptor 2; **HR+**= hormone receptor-positive; **HRQoL**=health-related quality of life; **OS**=overall survival; **PFS**= progression-free survival; **QD**=once daily**; RCT**=randomized controlled trial; **SAE**=serious adverse events; **TTP**=time to progression; **WDAE**=withdrawal due to adverse events				

** 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 (1974-) with daily updates via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 3 of 12) 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 lapatinib/Tykerb/Tyverb and letrozole/Femara/Letoval.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of April 1, 2013.

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

6.2.3 Study Selection

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

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

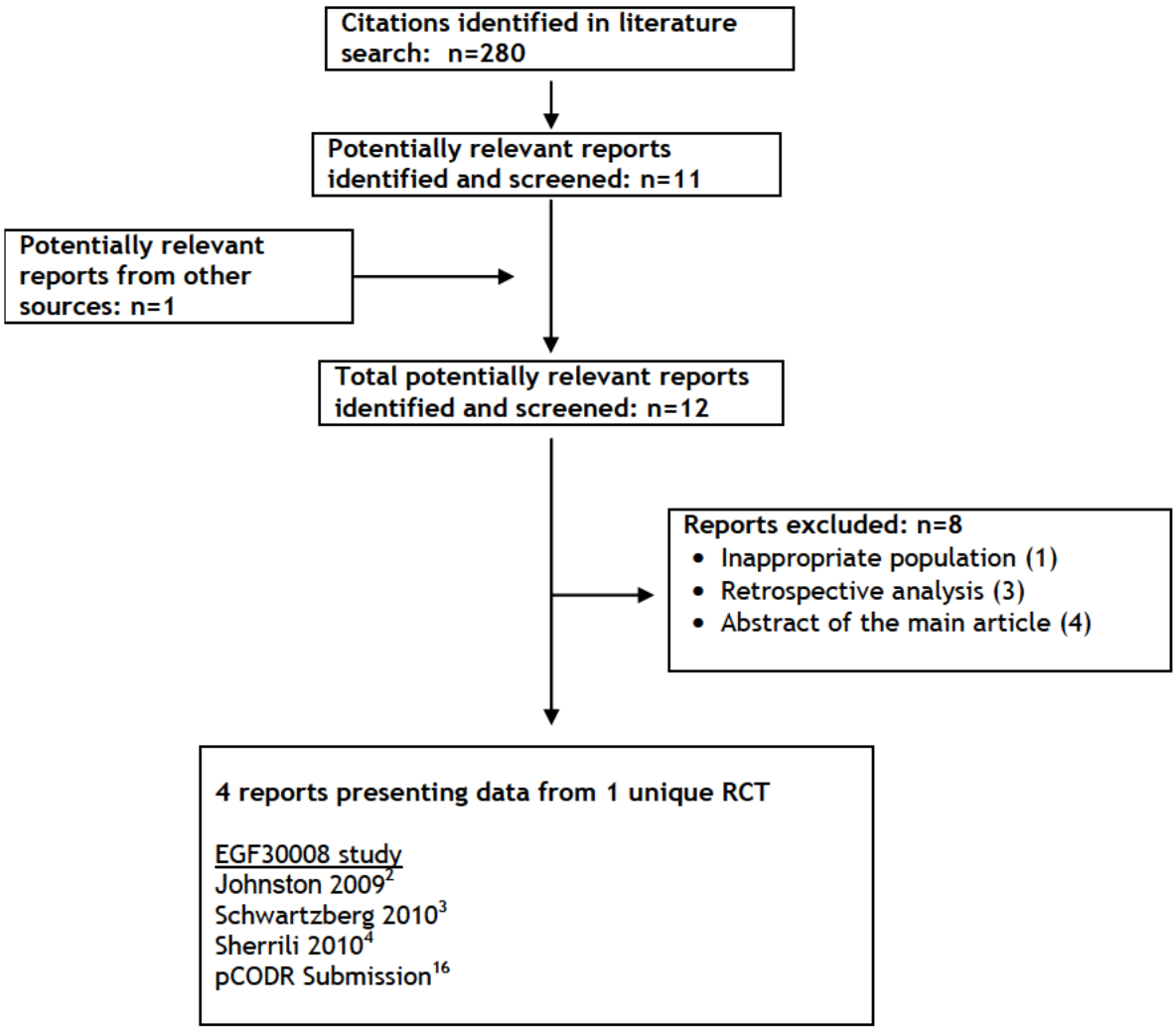
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

6.3 Results

6.3.1 Literature Search Results

Of the 12 potentially relevant reports identified, 4 reports were included in the pCODR systematic review[2-4,16] and 8 reports were excluded. Reports were excluded because they were abstract of the main study,[27-30] inappropriate population,[31] and retrospective analysis of the main study.[32-34]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of the EGF30008 Trial[2-4]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
International, DB, parallel phase III RCT 210 centers in multiple countries (including Canada)[35] Randomization period: Dec 9, 2003 – Dec 29, 2006 Randomization at 1:1 ratio was stratified on the basis of: • Sites of metastatic disease (soft tissue or visceral vs. bone-only disease) • Interval since completion of prior adjuvant antiestrogen therapy (≥6 months or no prior endocrine therapy vs. <6 months) Data cut-off for primary analysis: Jun 3, 2008 n=1286 randomized (219 with HER2+) n=1286 analyzed Funded by: GlaxoSmithKline	Postmenopausal women with stage IIIB/IIIC or IV ER/PgR-positive MBC ECOG PS 0 or 1 Normal organ function **Exclusion criteria:**[35] Extensive symptomatic visceral disease History of other malignancy Central nervous system metastases or leptomeningeal carcinomatosis Prior therapy for advanced or metastatic disease Prior antiestrogen therapy (AI/trastuzumab) < 1 year	Lapatinib 1500 mg + letrozole 2.5 mg, orally QD Letrozole 2.5 mg + placebo, orally QD	Primary • Progression free survival in HER2+ population Secondary • Overall survival • Clinical benefit rate • Overall response rate • HRQoL • Safety

AI= aromatase inhibitor; **CR**= complete response; **DB**= double-blind; **ECOG**= Eastern Cooperative Oncology Group; **ER**= estrogen receptor; **HER2**= Human Epidermal Growth Factor Receptor 2; **HR**= hormone receptor; **HRQoL**= health-related quality of life; **MBC**= metastatic breast cancer; **PgR**= progesterone receptor; **PS**= performance status; **QD**= once daily; **RCT**= randomized controlled trial

a) Trials

One phase III, double-blind, placebo-controlled RCT (EGF30008) was included in this review (see Table 2).[2-4] The purpose of this study was to evaluate the efficacy and safety of the combination of lapatinib and letrozole in postmenopausal women with HR-positive metastatic breast cancer that overexpresses HER2. The study was conducted at 210 centers in multiple countries worldwide including Canada. It was sponsored by the manufacturer, who played a role in study design, data collection and data analysis.

Patients were randomized to receive treatment with either oral lapatinib (1500 mg daily) plus oral letrozole (2.5 mg daily) or placebo plus letrozole. Randomization was stratified by the sites of metastatic disease and by the interval since completion of

prior adjuvant antiestrogen therapy. Randomization period was from December 9, 2003 through December 29, 2006. The methods of randomization and blinding were not provided in the published reports.

A total of 1280 HR-positive patients were required to ensure that 218 patients with HER2-positive tumors were enrolled to obtain 173 PFS events with 80% power to detect a hazard ratio of 0.645 (α=0.05).

b) Populations

Overall, baseline characteristics were balanced between two treatment groups, in both ITT population and HER2-positive population. The median age was 60 years for the combination therapy group (range 44-85) and 59 years for the monotherapy group (range 45-87). Majority of the patients (95% in the combination therapy group and 94% in the monotherapy group) were in stage IV of the disease. Half of the patients were of ECOG performance status of 0 and the other patients had performance status of 1. All patients had ER/PgR-positive tumors, and 17% had HER2-positive disease. Previous treatments included endocrine therapy and chemotherapy in HER2-positive population. More patients in the lapatinib + letrozole group (55%) than in the letrozole + placebo group (47%) had received previous chemotherapy. Approximately one third of the patients received adjuvant antiestrogen therapy within 6 months of study entry. Table 3 provides details of the baseline patient and trial characteristics in HER2-positive population.

Table 3. Baseline Patient Demographics and Clinical Characteristics in EGF30008 (HER2-positive population)

Demographic or clinical characteristics	Lapatinib + Letrozole (N=111) n (%)	Letrozole + placebo (N=108) n (%)
Age, years		
Median	60	59
Range	44-85	45-87
ECOG performance status		
0	59 (53)	51 (47)
≥1	51 (46)	57 (53)
Hormone Receptor status		
ER/PgR positive	74 (67)	69 (64)
ER positive/PgR negative	19 (17)	20 (19)
Disease stage		
IIIB or IIIC	5 (5)	7 (6)
IV	106 (95)	101 (94)
Number of metastatic sites		

Demographic or clinical characteristics	Lapatinib + Letrozole (N=111) n (%)	Letrozole + placebo (N=108) n (%)
Median	2	2
Range	1-7	1-7
Metastatic sites		
Bone only	16 (14)	18(17)
Visceral or soft tissue	95 (86)	90 (83)
Previous therapy		
Endocrine	60 (54)	62 (57)
Chemotherapy	61 (55)	51 (47)
Interval since prior adjuvant antiestrogen therapy		
≥ 6 months or no prior therapy	73 (66)	67 (62)
< 6 months	38 (34)	41 (38)

ECOG= Eastern Cooperative Oncology Group; **ER**= estrogen receptor; **PgR**= progesterone receptor

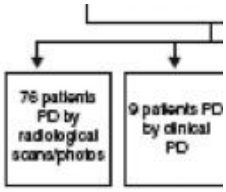


Figure 1. Treatment Population in EGF30008 – HER2-positive only

Data source: Schwartzberg 2010[3]

c) Interventions

Patients received combination of lapatinib 1500 mg plus letrozole 2.5 mg orally daily or letrozole 2.5 mg plus matching lapatinib placebo orally daily. Treatment continued until disease progression was determined using Response Evaluation Criteria in Solid Tumors (RECIST 1.0), or withdrawal from the study as a result of unacceptable toxicity or other reasons.[2,4] Lapatinib dose adjustment was allowed (no details were provided on how the dose was adjusted), while no dose adjustments were allowed for letrozole.[3] Cross-over to the alternate treatment was not permitted at the time of progression. At the clinical data cut-off date (June 3, 2008), 18 patients in the HER2-positive population still received study treatment.[2,3] The median follow-up time in EGF30008 was 1.8 year. The median treatment duration was 40 weeks in the letrozole-lapatinib group and 38 weeks in the letrozole arm, with compliance (pill count agreement of > 80%) of more than 95% in both arms, in the ITT population.[2] Post-

treatment therapy following discontinuation of study treatment was not reported either.

d) Patient Disposition

The ITT population (1286 patients) in EGF30008 included all randomly assigned patients regardless of whether they received study medication. Of the 219 patients with HER2-positive status, 111 were assigned to the combination therapy with lapatinib plus letrozole, and 108 were assigned to the monotherapy with letrozole.

Figure 1 presents the study population and patient disposition in EGF30008.

The safety population (1278 patients) included all patients who received at least one dose of randomized therapy. In the HER2-positive population, 219 patients were included in safety analysis. Two subjects randomized to the letrozole + placebo arm actually received letrozole + lapatinib, therefore the HER2 (+) safety population reported on 106 and 113 patients, respectively.[3]

As of the data cut-off date on June 3, 2008, 18 patients were still on treatment, and 201 discontinued treatment in the HER2-positive population: 76% for progression, 6% for consent withdrawal, 5% for adverse event, 1% for protocol violation, < 1% for death, and 3% for other seasons.[2,3] Patient disposition in each treatment arm was not reported in the published reports. According to the information provided by submitter at checkpoint meeting, more patients in the letrozole + lapatinib group (6%) discontinued the study because of adverse events than those in the letrozole + placebo group (3%), while slightly more patients in the letrozole + placebo group (79%) withdrew due to disease progression than the letrozole + lapatinib group (74%).[20]

e) Limitations/Sources of Bias

EGF30008 was a phase III randomized double-blind controlled trial. The patient characteristics at baseline were balanced between treatment groups. The study was designed by academic investigators and by representatives of the sponsor, GlaxoSmithKline. A central randomization was conducted according to the submitter. Methods of blinding was not reported in the published articles, but was provided in the checkpoint meeting which was presented by submitter to provide additional information. Patients and investigators were blinded to the treatment allocation.[20]

The primary endpoint (PFS) was evaluated by local investigators only. Cross-over to the alternate group was not allowed at the time of progression. Other strengths of the study included an appropriate sample size and power calculation.

Potential limitations in the EGF30008 study include:

- The study efficacy endpoints were assessed by local investigators only, without being supplemented by an independent committee. Safety data was monitored by an independent data monitoring committee on an ongoing basis.
- Various post-progression treatment modalities may bias OS. Post-treatment therapy following discontinuation of study treatment was not reported.
- There were no sufficient details in result reporting, such as safety data for HER2(+) population in each treatment group.

- The effectiveness and safety of the study drug in patients with ECOG performance status ≥2 (when they may benefit from the study drug) remain unknown since they were not included in Study EGF30008.
- The HRQoL data should be interpreted with caution, due to the high drop-out rates in the two groups. At week 48, only 25-30% of patients in the HER2-positive population completed the HRQoL questionnaire. In addition, post-progression quality of life benefit could not be evaluated, since the assessments were stopped after withdrawal of the study treatment.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The primary endpoint was investigator-assessed progression-free survival (PFS) in the HER2-positive population as determined by RECIST. Efficacy was assessed every 12 weeks and at the time of study treatment withdrawal, after which patients were followed only for survival.[3] HRQoL was assessed at screening, every 12 weeks, and at withdrawal using the Functional Assessment of Cancer Therapy-Breast (FACT-B).[4]

The safety analysis was conducted in the safety population, in which patients must receive at least one dose of study treatment. Toxicity was assessed every 4 weeks according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0), and cardiac function was assessed every 8 weeks. Beginning at week 108, toxicities and cardiac function were assessed every 12 weeks.[3]

The cut-off date for the primary analysis of progression-free survival (PFS) was June 3, 2008 (median follow-up 1.8 years), at which the overall survival results were still immature.

Table 4: Summary of Key Trial Outcomes (Efficacy) from the EGF30008 Study (HER2-positive population, lapatinib plus letrozole, N=111; placebo plus letrozole, N=108)

PFS by investigator assessment	**Median (months)**	**HR (95% CI)**	**P-value**
	LAP+LET: 8.2 LET+PL: 3.0	0.71 (0.53, 0.96)	0.019
OS	**Median (weeks)**	**HR (95% CI)**	**P-value**
	LAP+LET: 144.7 LET+PL: 140.3	0.74 (0.5, 1.1)	0.113
Quality of Life*	**Between-groups difference (95% CI) at week 48**		
FACT-B	-2.6 (-11.0 to 5.8)		
FACT-G	-2.9 (-10.0 to 4.2)		
TOI	-2.9 (-9.4 to 3.5)		
CBR	**n** (%)**	**OR (95% CI)**	**P-value**
	LAP+LET: 53 (48) LET+PL: 31 (29)	0.4 (0.2, 0.8)	0.003

CBR = clinical benefit rate; **CI** = confidence interval; **FACT-B** = the Functional Assessment of Cancer Therapy-Breast; **FACT-G** = the Functional Assessment of Cancer Therapy-General; **HR** = hazard ratio; **LAP+LET** = lapatinib + letrozole; **LET+PL** = Letrozole + placebo; **n** = number of patients with the events; **OR** = odds ratio; **OS** = overall survival; **PFS** = progression free survival; **TOI** = trial outcome index
* HRQoL results were based on 59 patients (32 in LAP+LET, 27 in LET+PL) who completed the assessment at week 48
** Calculated by Methods Team

Sources: Johnston 2009,[2] Schwartzberg 2010[3]

Table 5: Summary of Key Trial Outcomes (Safety) from the EGF30008 Study

	LAP+LET n* (%)	LET+PL n* (%)
ITT population (LAP+LET: 654, LET+PL: 624)		
All deaths	243 (37)	231 (37)
Fatal AEs	8 (1)	8 (1)
SAEs	144 (22)	94 (15)
Suspected to be drug-related	54 (8)	27 (4)
AEs leading to discontinuation	95 (15)	35 (6)
Any AEs	628 (96)	536 (86)
AEs suspected to be drug-related	548 (84)	343 (55)
AEs of special interest**	533 (81)	228 (37)
HER2-positive population (LAP+LET: 113, LET+PL: 106)		
All deaths	NR	NR
Treatment-related deaths[3]	1 (< 1)	0
SAEs[20]	23 (20)	10 (9)
Suspected to be drug-related	NR	NR
AEs leading to discontinuation[21]	7 (6)	3 (3)
Any AEs[3]	108 (96)	82 (77)
AEs suspected to be drug-related	NR	NR
AEs of special interest**	NR	NR

AE = adverse event; **SAE** = serious adverse event; **LAP+LET** = lapatinib + letrozole; **LET+PL** = Letrozole + placebo; **n** = number of patients with events; NR = not reported

* calculated by Methods Team

**included rash, diarrhea, nail changes, hepatobiliary events, cardiac events and pulmonary events

Data source for ITT population: Tykerb submission,[16] Johnston 2009[2]

Efficacy Outcomes

a) Overall survival (OS)

OS was the secondary endpoint in the EGF30008 study. It was defined as the time from the date of randomization to the date of death due to any cause. Kaplan-Meier methods were used to estimate the distribution function of OS, with the stratified log-rank test used for comparisons between treatment arms. The published article by Johnston et al. 2009[2] reported that the OS results were immature at the analysis for PFS. At that time, there were a total of 104 deaths (47%) in the HER2-positive population: 50 (45%) in the lapatinib + letrozole group, and 54 (50%) in the letrozole + placebo group.[16] The median OS in this population at cut-off date of June 3, 2008 was 144.7 weeks in the lapatinib + letrozole group compared with 140.3 weeks in the letrozole + placebo group [hazard ratio (HR) = 0.74, 95% confidence interval (CI) 0.5 to 1.1, p = 0.113] (Figure 2).[2] There was no statistically significant difference in OS between the two treatment groups by the Cox regression model (HR=0.77, 95% CI: 0.52 to 1.14, p=0.185).[16] An updated OS analysis was requested from the manufacturer but was not available at the time of this report.

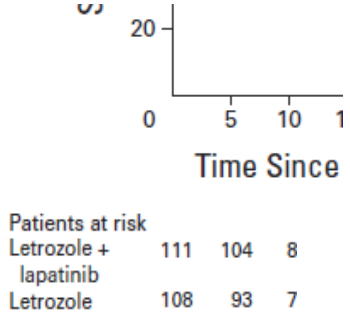


Figure 2. Kaplan-Meier estimates of overall survival in EGF30008 (source: Johnston 2009[2])

b) Progression-free survival (PFS)

PFS was defined as time from random assignment until the earliest date of disease progression or death as a result of any cause. It was summarized using the Kaplan-Meier method, with the stratified log-rank test used for comparisons between treatment arms. Cox regression analysis was used to assess the prognostic significance of PFS for the known prognostic baseline characteristics after retaining treatment and stratification factors: age, ECOG performance status score, number of metastatic sites, site of disease, interval since prior chemotherapy, interval since prior adjuvant antiestrogen therapy, etc.[3] PFS in the HER2-positive population was the primary endpoint in EGF30008, and PFS in the ITT population was the secondary endpoint.

As of June 3, 2008 cut-off (median follow-up 1.8 years), the median PFS on the basis of investigator assessment in the HER2-positive population was 8.2 months for lapatinib + letrozole versus 3.0 months for letrozole + placebo (HR 0.71; 95% CI 0.53 to 0.96, p=0.019). Kaplan-Meier plots of progression free survival is shown in Figure 3.

Results from the Cox regression analysis for PFS adjusting for known baseline prognostic factors were consistent with the Kaplan-Meier method: HR = 0.65, 95% CI 0.47 to 0.89, p = 0.008. After retaining treatment and stratification factors, age (younger), performance status (0), and baseline serum soluble HER2 extracellular domain were identified as being significant.

Subgroup analyses for PFS in the HER2-positive population showed consistently longer PFS in treatment with lapatinib + letrozole although not all differences were statistically significant (Figure 4).

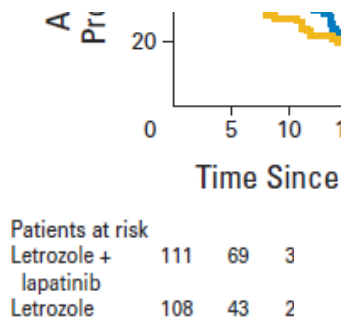


Figure 3. Kaplan-Meier estimates of progression-free survival in EGF30008 (source: Johnston 2009[2])

Figure 4. Subgroup analysis for PFS in EGF30008 – HER2-positive population (source: Schwartzberg 2010[3])

c) Health-related quality of life (HRQoL)

HRQoL in EGF30008 was assessed using FACT-B in HER2-positive population. Patients had to have completed the baseline FACT-B questionnaire and at least one follow-up questionnaire to be included in analyses. FACT-B is a self-reporting instrument consisting of FACT-General (FACT-G, 27 general questions combined into 4 subscales, score ranges from 0 to 108) and breast cancer subscale (BCS, 10 breast cancer-specific

questions, score ranges from 0 to 36). The FACT-B total score ranges from 0 to 136. The trial outcome index (TOI) is an efficient summary index of physical/functional outcomes, which is the sum of two subscales in FACT-G, physical well-being (PWB) and functional well-being (FWB), and BCS scores. It ranges from 0 to 92. FACT-B total score and FACT-G score are calculated only when patients respond to at least 80% of the items that constituted the relevant score. The minimal clinically meaningful difference (MCID) was estimated to be 2 to 3 points for the BCS, 8 points for the FACT-B total score, and 6 points for the FACT-G. The higher the score, the better the quality of life.[28,36]

Since the quality of life assessments were stopped after treatment termination or disease progression, few patients completed the questionnaire after week 48; the HRQoL results were available for the visits up to week 48.

Baseline HRQoL scores were similar between the two treatment groups. Changes in HRQoL from baseline were similar in both groups with generally stable results on all measures for patients who stayed in the study (the results were graphically presented in the published article). When comparing the two groups, the differences in average scores of FACT-B, FACT-G and TOI were not statistically significant at week 12, 24, 36 and 48, for patients who stayed in study (71% at week 12, 47% at week 24, 32% at week 36 and 27% at week 48). Table 6 shows the results at week 48.

Table 6. Summary of HRQoL Results by Treatment Group in EGF30008 (HER2-positive population)

	LAP+LET (n=111)	LET+PL (n=108)
Baseline, mean (SD)		
FACT-B total	99.3 (19.2)	101.1 (19.3)
FACT-G	75.9 (15.7)	77.4 (15.6)
BCS	23.2 (5.2)	23.6 (6.0)
TOI		
Between-group difference at week 48, (LAP+LET) – (LET+PL) , mean (95% CI)*		
FACT-B total	-2.6 (-11.0 to 5.8), p=0.533	
FACT-G	-2.9 (-10.0 to 4.2), p=0.416	
TOI	-2.9 (-9.4 to 3.5), p=0.364	

BCS=breast cancer subscale; **CI**=confidence interval; **FACT-B**=Functional Assessment of Cancer Therapy-Breast; **FACT-G**=Functional Assessment of Cancer Therapy-General; **LAP+LET**=lapatinib+letrozole; **LET+PL**=letrozole+placebo; **SD**=standard deviation; **TOI**=trial outcome index

* The endpoint values at week 48 were not reported

d) Clinical benefit rate (CBR)

CBR was defined as the proportion of patients with complete response, partial response, or stable disease for ≥ 6 months. The CBRs (95% CI) in HER2-positive population were 48% and 29% in the lapatinib + letrozole and letrozole + placebo arms, respectively, odds ratio (OR) = 0.4, 95% CI 0.2 to 0.8, p = 0.003 (Figure 5).

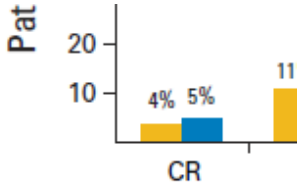


Figure 5. Response rates and Clinical benefit rates in EGF30008 (source: Johnston 2009[2])

Harms Outcomes

The safety analysis population consisted of 1278 patients in ITT population and 219 patients in HER2-positive population (113 in the lapatinib + letrozole arm and 106 in the letrozole + placebo arm). Adverse events were monitored continuously throughout the study and graded using the NCI-CTCAE.

As of June 3, 2008, the median duration of exposure was 40 weeks in the lapatinib + letrozole group and 38 weeks in the letrozole + placebo group.

Similar to the overall population, HER2(+) patients who were treated with letrozole + lapatinib experienced more adverse events, serious adverse events and discontinuation due to adverse events, compared with those treated with letrozole + placebo.

a) Death

In the safety population, 243 patients (37%) in the lapatinib + letrozole group and 231 patients (37%) in the letrozole + placebo died. Of those, the primary cause of all deaths was disease progression. Eight deaths (1%) due to SAEs occurred in each group, and three of them were considered study drug-related (one in lapatinib + letrozole, and two in letrozole + placebo).[2,16] Data specific for the HER2-positive population are not reported.

b) Serious Adverse Events

Reported serious adverse events (SAEs) were more common in the lapatinib + letrozole group (n=144, 22%) compared with the letrozole + placebo group (n=94, 15%) in the safety population. Fifty-four patients (8%) and 27 patients (4%) had SAEs considered to be related to study drug by the investigator in the two groups respectively. The most common treatment-related SAEs in the lapatinib + letrozole group were decreased ejection fraction (3%) and diarrhea (2%), while the most commonly reported treatment-related SAEs in the comparison group were decreased ejection fraction and vomiting (1% for each).[16] In the HER2-positive population, more patients in the letrozole + lapatinib group (20%) reported SAEs compared with those in the letrozole + placebo group (9%).[20]

c) Adverse Events Leading to Discontinuation

There were more AEs leading to discontinuation of therapy in the lapatinib + letrozole group (n=95, 15%) compared with the letrozole + placebo group (n=35, 6%), in the safety population. The most common reason for discontinuation in lapatinib + letrozole group were diarrhea (24 patients, 4%) and vomiting (11 patients, 2%).[16] In the HER2(+) population, more patients in the letrozole + lapatinib group (6%) withdrew due to adverse events compared with those in the letrozole + placebo group (3%).[20]

d) Any Adverse Events

More patients in the lapatinib + letrozole group experienced at least one adverse event than those in the letrozole + placebo group (safety population: 628, 96% versus 536, 86%; HER2-positive population: 108, 96% versus 82, 77%).[3,16] Of those, 84% in the lapatinib + letrozole group (n=548) and 55% in the letrozole + placebo (n=343) were suspected to be drug related in safety population. The most common adverse events in the study were diarrhea, rash, nausea, fatigue and arthralgia, when diarrhea and rash were higher in the lapatinib + letrozole group. These adverse events in the safety population and HER2-positive population are shown in Table 6. Adverse events by grade in the HER2-positive population are shown in Table 7.

Table 6. Adverse Events (%) in EGF30008

	Safety population (N=1278)		HER2-positive population (N=219)	
	LAP+LET	LET+PL	LAP+LET	LET+PL
Diarrhea	64	20	68	8
Rash	44	13	46	8
Nausea	31	21	27	18
Fatigue	21	18	22	14
Arthralgia	19	23	18	20

LAP+LET = lapatinib + letrozole; **LET+PL** = letrozole + placebo

Table 7. Adverse Events in HER2-positive Population in EGF30008

Alanine aminotransf increase	
Aspartate aminotran increase	
Shown are events re addition of the incid	

Source: Schwartzberg 2010[3]

6.4 Ongoing Trials

At present, one related on-going trial was identified.[37]

Status	Study
Active	Title: Ph III Trial to Compare Safety and Efficacy of Lapatinib Plus Trastuzumab Plus Aromatase Inhibitor (AI) vs. Trastuzumab Plus AI vs. Lapatinib Plus AI as 1st Line in Postmenopausal Subjects With Hormone Receptor+ HER2+ MBC Who Received Trastuzumab and Endocrine Therapy in Neo- and/or Adjuvant Setting Study ID: NCT01160211 Design: multi-center, open-label, three-arm N= 525, estimated Primary Objective: evaluate the efficacy and safety of AI in combination with lapatinib, trastuzumab or both in postmenopausal women with HR+, HER2(+) metastatic breast cancer. Treatment arms: Lapatinib + trastuzumab + AI Trastuzumab + AI Lapatinib + AI Primary outcome: OS of lapatinib/trastuzumab/AI combination vs. trastuzumab/AI combination (time frame: approximately 6 years) Secondary outcomes: OS of trastuzumab/AI vs. lapatinib/AI and trastuzumab/lapatinib/AI (time frame: approximately 6 years), PFS of lapatinib/trastuzumab/AI vs. trastuzumab/AI and lapatinib/AI vs. trastuzumab/AI, ORR, time to response, CBR, safety and tolerability of all 3 treatment groups, QoL Start date: May 2011 End date: December 2017

7 SUPPLEMENTAL QUESTIONS

7.1 Critical Appraisal of an Indirect Comparison of Lapatinib + Letrozole with Anastrozole + Trastuzumab

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

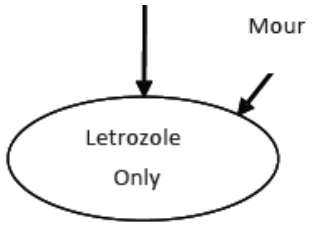
7.1.1 Objective

The manufacturer submitted an indirect comparison of lapatinib + letrozole (LAP+LET) versus trastuzumab + anastrozole (TZ+ANA) in order to evaluate the cost-effectiveness of these two therapies for the treatment of postmenopausal women with HER2+ and HR+ MBC. An indirect comparison can provide information in the situation where trials have not been designed to directly compare the specific treatments. The section of this report provides a summary and critical appraisal of the methods and findings of this indirect comparison.

7.1.2 Findings

A network diagram of studies used for the indirect comparison in the manufacturer's cost-effectiveness analysis is shown in Figure 6. The manufacturer employed this analysis to compare LAP+LET with TZ+ANA as studied in the EGF30008 and TAnDEM trials.[2,9] Both EGF30008 and TAnDEM included postmenopausal women with histologically confirmed HR+ MBC. TAnDEM only included patients who were HER2+, while 17% of the patients in the EGF30008 trial were HER2+. Crossover from LET + placebo to LAP+LET was not allowed in EGF30008, while patients in TAnDEM were able to switch from the anastrozole arm to trastuzumab once disease progressed.

Figure 6. Network diagram of studies used for cost-effectiveness analysis



Source: Tykerb submission,[16] economic evaluation

The indirect comparison submitted by the manufacturer was based on a systematic review and indirect comparison conducted by Riemsma et al. in 2012.[13] In the systematic review, RCTs

assessing the efficacy and safety of first-line treatments for postmenopausal women with HR+ HER2+ MBC who had not received prior therapy for advanced or metastatic disease were included.

Five unique studies were included in this indirect comparison: EGF30008,[2] P025,[38,39] TARGET,[40] North American[41] and TAnDEM.[9] The EGF30008 trial[2] compared lapatinib+letrozole with letrozole+placebo, the P025 trial[38] compared letrozole with tamoxifen, both the TARGET and North American trials compared tamoxifen with anastrozole and were prospectively designed to allow for combined data analysis, and the TAnDEM trial compared anastrozole with trastuzumab+anastrozole. Approximately 21% of patients in the TARGET Trial, 11% of patients in the North American trial, and 44% of patients in the P025 Trial had unknown HR status. HER2 status was not specified in the P025, TARGET, and North American trials. Study characteristics are listed in Table 8.

Table 8. Summary of studies used for indirect comparison.

Trial, Publications	Study design	Patient population	Intervention and Comparator	Outcomes
EGF30008 Johnston et al 2009[2]	Multinational, multicenter, parallel-group, DB RCT	1286 postmenopausal women with HR+ MBC (219 HER2+)	Lapatinib 1500 mg + Letrozole 2.5 mg, orally QD (n=642) Letrozole 2.5 mg + Placebo, orally QD (n=644)	Primary: PFS in HER2+ Secondary: OS, CBR, ORR, QoL, Safety
P025 Mouridsen et al 2003[38] Mouridsen et al 2007[39]	Multinational, multicenter, DB DD RCT Crossovers allowed	907 postmenopausal women with ER+ and/or PgR+ (44% with both receptors unknown) MBC (unknown # HER2+)	Letrozole 2.5 mg, orally QD (n=453) Tamoxifen 20 mg, orally QD (n=454)	Primary: TTP Secondary: OS, ORR, TTR, TTC, TTF, Safety
TARGET Boneterre et al 2000[40]	Multinational, multicenter, DB RCT	668 postmenopausal women with ER+ and/or PgR+ (21% with both receptors unknown) MBC (unknown # HER2+)	Anastrozole 1 mg, orally QD (n=340) Tamoxifen 20 mg, orally QD (n=328)	Primary: TTP, ORR Secondary: OS, TTF, response duration, clinical benefit duration
North American Nabholtz et al 2003[41]	Multinational, multicenter, DB RCT	353 postmenopausal women with ER+ and/or PgR+ (11% with both receptors unknown) MBC (unknown # HER2+)	Anastrozole 1 mg, orally QD (n=171) Tamoxifen 20 mg, orally QD (n=182)	Primary: TTP, ORR Secondary: TTF, response duration, clinical benefit duration
TAnDEM Kaufman et al 2009[9]	Multinational, multicenter, open-label RCT Crossover allowed	207 postmenopausal women with HR+ HER2+ MBC	Anastrozole 1 mg (n=104) Anastrozole 1 mg orally QD + Trastuzumab 4 mg/kg loading dose, 2 mg/kg/week (n=103)	Primary: PFS Secondary: CBR, ORR, TTP, TTR, response duration, OS, 2-year survival rate

CBR=clinical benefit ratio; **DB=**double blind; **DD=**double dummy; **ER=**estrogen receptor; **HER2=**human epidermal growth factor receptor 2; **HR=**hormone receptor; **MBC**=metastatic breast cancer; **ORR=**overall objective response rate; **OS=**overall survival; **PFS=**progression free survival; **PgR=**progesterone receptor; **QD=**once daily; **QoL=**quality of life; **RCT=**randomized controlled trial; **TTC=**time to chemotherapy; **TTF=**time to treatment failure (progression, death, or withdrawal); **TTR=**time to response; **TTP=**time to progression

The Bucher method was used to perform indirect comparisons in this systematic review, which is an adjusted indirect comparison approach using aggregate data. The effect measure comparing two treatments within an RCT is used rather than the individual results for each treatment group in order to partially maintain the strength of randomization. One assumption of this model is that the relative efficacy of a treatment is similar in all trials included in the indirect comparison.

A summary of results of the indirect comparison between LAP+LET and TZ+ANA for progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) in patients with postmenopausal HER2+ HR+ MBC are presented in Table 9. According to these results, hazard ratios for PFS, OS, and ORR in postmenopausal HER2+ HR+ MBC patients favored LAP+LET over TZ+ANA, but the differences were not statistically significant.

Table 9. Summary of indirect comparison results for PFS and OS

TTP/PFS		
Treatment	**Hazard Ratio**	**95% CI**
LAP+LET vs. TZ+ANA	0.89	0.54-1.47
OS		
Treatment	**Hazard Ratio**	**95% CI**
LAP+LET vs. TZ+ANA	0.85	0.47-1.54
ORR		
Treatment	**Hazard Ratio**	**95% CI**
LAP+LET vs. TZ+ANA	0.92	0.24-3.48

ANA=anastrozole; **CI=**confidence interval; **LAP=**lapatinib; **LET=**letrozole; **ORR=**objective response rate; **PFS=**progression free survival; **TTP=**time to progression; **TZ=**trastuzumab

Limitations

The systematic review did not include a meta-regression analysis to assess potential sources of heterogeneity due to the limited number of studies per comparison. Different inclusion criteria and trial design were used in the studies included in the indirect comparison. The EGF30008 and TAnDEM trial specified patients who had HER2+ status, while the P025, TARGET and North American trials did not identify these patients and or analyze them separately. The P025 and TAnDEM allowed for patients to crossover to the alternate treatment upon disease progression, while the other trials did not allow for this. There were large differences in the number of patients with unknown HR status among the included studies, ranging from 11% to 44% in the P025, TARGET, and North American trials. The authors intended to include the effect of unknown HR status as a variable in a meta-regression analysis, but there was insufficient data in the network to do this. Due to the variability in patient population and trial design, results should be interpreted with caution.

In addition, there was no distinction between HER2(-) and HER2(+) patients in the P025, TARGET and North American trials, and therefore the indirect comparison of LAP+LET versus TZ+ANA is based on the assumption that the relative effectiveness of letrozole versus tamoxifen and anastrozole versus tamoxifen is similar in HER2(+) and HER2(-) patients.

Patients were allowed to crossover to the alternative study treatment upon disease progression in the P025 and TAnDEM trials, which may affect overall survival data. In the TAnDEM trial, 70% patients crossed over from anastrozole to trastuzumab post-progression.

The quality of the manufacturer-submitted indirect analyses was assessed according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[42] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 10.

Table 10. Appraisal of the indirect comparison analyses using ISPOR criteria[42]

ISPOR Checklist Item	Details and Comments
1. Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an indirect comparison analysis and the study objectives were clearly stated.
2. Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for RCTs were clearly stated: first line-treatment for postmenopausal women with HR+ and/or HER2+ MBC who had not received prior therapy for advanced or metastatic disease • A computerized literature search of Medline, Embase, CDSR, Central, DARE and HTA was conducted from inception to January 2009. A detailed search strategy was presented. • Two reviewers screened titles and abstracts of identified references and full articles were obtained and inspected for potential inclusion. Disagreements were resolved through discussion. • Data was extracted as follows: dichotomous data extracted as number of individuals with the outcome of interest and total numbers of individuals in the intervention and control group; continuous data extracted as mean and standard deviation for the intervention and control group • Quality assessment of included studies was carried out independently by two reviewers using the Cochrane Collaboration quality assessment checklist.
3. Are the outcome measures described?	• Outcomes assessed in the indirect comparison analysis (overall survival, OS; progression-free survival, PFS; time-to-progression, TTP; objective response rate, ORR; quality of life; adverse events, AE) were clearly stated. • Justification of the outcome measures analyzed in the indirect comparison were provided: ORR, OS, and PFS/TTP, but not for the remaining outcomes
4. Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• The Bucher method was used for the indirect comparisons between lapatinib+letrozole and comparator treatments, both for narrative and statistically indirect comparisons. • Dichotomous data were analyzed by calculating relative risk for each trial using the DerSimonian and Laird method and the corresponding 95% confidence intervals or the odds ratio using the Mantel-Haenszel method. • Continuous data were analyzed using the weighted mean difference between groups and the corresponding 95% confidence interval.

ISPOR Checklist Item	Details and Comments
	• Survival data were analyzed by using the hazard ratio and its standard error. • A random-effects model was used for the calculation of relative risks of weighted mean differences to account for anticipated heterogeneity. Heterogeneity was assessed by measuring the degree of inconsistency in the studies' results (I^2). • Description and justification of using the Bucher method was not provided.
5. Are sensitivity analyses presented?	• No sensitivity analyses were reported.
6. Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• The selection process of included studies was reported. • A table summarizing patient characteristics of the studies used for the indirect comparisons was provided. Detailed information included the proportion of patients with unknown HR status and the number of HER2+ patients (if known) was included. • Three of the included studies (P025, TARGET, North American) included patients with unknown HR status and did not differentiate/specify patients with HER2+ status. • A figure showing the network of studies was provided, but forest plots were not provided as a formal network meta-analysis was not performed due to the lack of data. • Two studies (P025, TAnDEM) allowed patient crossover upon disease progression. • A table with raw data by study and treatment was not provided for the indirect comparison analysis.
7. Does the study describe an assessment of model fit? Are competing models being compared?	• Neither assessment of model fit nor comparison of competing models was reported.
8. Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for three outcome measures (ORR, PFS/TTP, OS) including point estimates and 95% confidence intervals as a measure of uncertainty.
9. Sensitivity/scenario analyses	• No sensitivity analysis was reported.

7.1.3 Summary

Indirect statistical assessments for efficacy among LAP+LET and TZ+ANA therapies were performed using an indirect comparison that employed a Bucher fixed effect model. This analysis found that the hazard ratios for PFS, OS, and ORR in postmenopausal HER2(+) HR(+) MBC were not statistically significant. In addition, three of the included studies (P025, TARGET, North American) included patients with unknown HR status and did not differentiate/specify patients with HER2+ status. Conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data, and therefore the findings derived from this review should be interpreted with caution.

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 lapatinib (Tykerb) with letrozole for metastatic breast cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

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

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.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Embase 1974-present – daily update (oemezd). Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE (R) 1946-present (pmez)

#	Searches	Results
1	(lapatinib* or tykerb* or tyverb* or GW 282974X or GW282974X or GW572016 or GW 572016 or GSK 572016 or GSK572016).ti,ab,ot,sh,hw,rn,nm.	6746
2	(0VUA21238F or 231277-92-2 or 388082-78-8).rn,nm.	5574
3	or/1-2	6746
4	(letrozole* or femara* or CGS20267 or CGS 20267 or CCRIS 8822 or CCRIS8822 or HSDB 7461 or HSDB7461 or Letoval).ti,ab,ot,sh,hw,rn,nm.	8161
5	(7LKK855W8I or 112809-51-5).rn,nm.	7013
6	or/4-5	8161
7	3 and 6	675
8	exp *drug toxicity/	68067
9	exp *drug hypersensitivity/	45120
10	*abnormalities, drug-induced/	43908
11	exp *postoperative complications/	334836
12	exp *intraoperative complications/	20031
13	exp *adverse drug reaction/	175844
14	exp *drug safety/	11362
15	exp *side effect/	47098
16	exp *postoperative complication/	334386
17	exp *peroperative complication/	20031
18	(safe or safety).ti.	186991

19	side effect*.ti.	28804
20	(adverse or undesirable or harm* or toxic or injurious or risk or risks or reaction* or toxic or toxicit* or toxologic* or complication* or noxious or tolerability or poison* or teratogen* or intoxication or warning*).ti.	1572940
21	((drug or chemically) adj induced).ti.	25322
22	quinazolines/ae	2005
23	quinazolines/po	135
24	quinazolines/to	359
25	or/8-24	2323493
26	3 and 25	452
27	7 or 26	1092
28	27 use pmez	176
29	*lapatinib/	890
30	(lapatinib* or tykerb* or tyverb* or GW 282974X or GW282974X or GW572016 or GW 572016 or GSK 572016 or GSK572016).ti,ab.	2737
31	or/29-30	2827
32	*letrozole/	1384
33	(letrozole* or femara* or CGS20267 or CGS 20267 or CCRIS 8822 or CCRIS8822 or HSDB 7461 or HSDB7461 or Letoval).ti,ab.	3834
34	or/32-33	4118
35	31 and 34	106
36	exp *drug toxicity/	68067
37	exp *drug hypersensitivity/	45120
38	*abnormalities, drug-induced/	43908
39	exp *postoperative complications/	334836
40	exp *intraoperative complications/	20031
41	exp *adverse drug reaction/	175844

42	exp *drug safety/	11362
43	exp *side effect/	47098
44	exp *postoperative complication/	334386
45	exp *peroperative complication/	20031
46	(safe or safety).ti.	186991
47	side effect*.ti.	28804
48	(adverse or undesirable or harm* or toxic or injurious or risk or risks or reaction* or toxic or toxicit* or toxologic* or complication* or noxious or tolerability or poison* or teratogen* or intoxication or warning*).ti.	1572940
49	((drug or chemically) adj induced).ti.	25332
50	or/36-49	2321520
51	31 and 50	156
52	35 or 51	257
53	52 use oemezd	187
54	28 or 53	363
55	exp animals/	35049346
56	exp animal experimentation/ or exp animal experiment/	1686725
57	exp models animal/	1072833
58	nonhuman/	4026291
59	exp vertebrate/ or exp vertebrates/	34142927
60	or/55-59	36224180
61	exp humans/	27029266
62	exp human experimentation/ or exp human experiment/	322183
63	or/61-62	27031336
64	60 not 63	9194425
65	54 not 64	356

66	remove duplicates from 65	281

2. Literature search via PubMed

Search	Most Recent Queries	Result
#7	Search **#4 OR #6**	3
#6	Search **#1 AND #5 AND publisher [sb]**	2
#5	Search **adverse*[ti] OR complication*[ti] OR harm[ti] OR harmful[ti] OR harmfull[ti] OR harming[ti] OR injurious[ti] OR risk*[ti] OR side effect*[ti] OR treatment outcome*[ti] OR undesirable[ti] OR tolerability[ti] OR teratogen*[ti] OR toxicity[ti] OR interaction[ti] OR interactions[ti] OR reaction[ti] OR reactions[ti] OR tolerability[ti] OR toxic[ti] OR safety[ti] OR safe[ti] OR safeties[ti]**	912752
#4	Search **#3 AND publisher [sb]**	1
#3	Search **#1 AND #2**	33
#2	Search **letrozole OR femara OR CGS20267 OR "CGS 20267" OR "CCRIS 8822" OR CCRIS8822 OR "HSDB 7461" OR HSDB7461 OR letoval OR 7LKK855W8I**	1749
#1	Search **lapatinib OR tykerb OR tykerb OR "GW 282974X" OR GW282974X OR GW572016 OR "GW 572016" OR "GSK 572016" OR GSK572016 OR 0VUA21238F**	1116

3. Cochrane Central Register of Controlled Trials (Central)

Search for trials. Issue 3 of 12, March 2013.

ID	Search	Hits
#1	lapatinib* or tykerb* or tyverb* or GW 282974X or GW282974X or GW572016 or GW 572016 or GSK 572016 or GSK572016 or 0VUA21238F or 231277-92-2 or 388082-78-8	87
#2	letrozole* or femara* or CGS20267 or CGS 20267 or CCRIS 8822 or CCRIS8822 or HSDB 7461 or HSDB7461 or Letoval or 7LKK855W8I or 112809-51-5	392
#3	#1 AND #2	11

4. Grey Literature search via:

Clinical trial registries:

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

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

Search terms: (lapatinib OR tykerb OR tyverb) AND (letrozole OR femara)

Select international agencies including:

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

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Search terms: (lapatinib OR tykerb OR tyverb) AND (letrozole OR femara)

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

San Antonio Breast Cancer Symposium (SABCS)
http://www.sabcs.org/

Search terms: (lapatinib OR tykerb OR tyverb) AND (letrozole OR femara)
/ last 5 years

REFERENCES

1. Tykerb® lapatinib tablets (as lapatinib ditosylate): 250 mg [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2012 Mar 26.

2. Johnston S, Pippen J Jr, Pivot X, Lichinitser M, Sadeghi S, Dieras V, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol [Internet]. 2009 Nov 20 [cited 2013 Apr 5];27(33):5538-46. Available from: http://jco.ascopubs.org/content/27/33/5538.full.pdf+html

3. Schwartzberg LS, Franco SX, Florance A, O'Rourke L, Maltzman J, Johnston S. Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer. Oncologist [Internet]. 2010 [cited 2013 Jan 25];15(2):122-9. Available from: http://theoncologist.alphamedpress.org/content/15/2/122.full.pdf+html

4. Sherrill B, Amonkar MM, Sherif B, Maltzman J, O'Rourke L, Johnston S. Quality of life in hormone receptor-positive HER-2+ metastatic breast cancer patients during treatment with letrozole alone or in combination with lapatinib. Oncologist. 2010;15(9):944-53.

5. Harris CA, Ward RL, Dobbins TA, Drew AK, Pearson S. The efficacy of HER2-targeted agents in metastatic breast cancer: a meta-analysis. Ann Oncol [Internet]. 2011 Jun [cited 2013 Jan 25];22(6):1308-17. Available from: http://annonc.oxfordjournals.org/content/22/6/1308.full.pdf+html

6. GlaxoSmithKline Inc. Tykerb (lapatinib ditosylate) - updated information on efficacy - for the public [Internet]. Ottawa: Health Canada; 2013 Mar 25. [cited 2013 Apr 5]. (Healthy Canadians: recalls & alerts). Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/26287a-eng.php

7. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med [Internet]. 2001 Mar 15 [cited 2013 Apr 5];344(11):783-92. Available from: http://content.nejm.org/cgi/reprint/344/11/783.pdf

8. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol [Internet]. 2005 Jul 1 [cited 2013 Apr 5];23(19):4265-74. Available from: http://jco.ascopubs.org/cgi/content/full/23/19/4265

9. Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol [Internet]. 2009 Nov 20 [cited 2013 Apr 5];27(33):5529-37. Available from: http://jco.ascopubs.org/content/27/33/5529.full.pdf+html

10. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian cancer statistics 2012 [Internet]. Toronto: Canadian Cancer Society; 2012 May. [cited 2013 Apr 5]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2012---English.pdf

11. Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database. Breast Cancer Res Treat. 2002 Nov;76(1):27-36.

12. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987 Jan 9;235(4785):177-82.

13. Riemsma R, Forbes CA, Amonkar MM, Lykopoulos K, Diaz JR, Kleijnen J, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer (MBC). Curr Med Res Opin. 2012 Aug;28(8):1263-79.

14. National Comprehensive Cancer Network. Breast cancer [Internet]. Version 1. Fort Washington (PA): NCCN; 2013. [cited 2013 Feb 7]. (NCCN Clinical Practice Guidelines in Oncology). Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf Registration required.

15. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E, ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2012 Oct [cited 2013 Feb 7];23 Suppl 7:vii11-vii19. Available from: http://annonc.oxfordjournals.org/content/23/suppl_7/vii11

16. pan-Canadian Oncology Drug Review manufacturer submission: Tykerb® (lapatinib ditosylate); Company: GlaxoSmithKline. Mississauga (ON): GlaxoSmithKline; 2012 Dec 14.

17. Health Canada. Summary basis of decision (SBD) for Tykerb™. Lapatinib ditosylate, 250 mg tablet. GlaxoSmithKline Inc. Submission control number: 110294 [Internet]. Ottawa: Health Canada, Health Products and Food Branch; 2009 Nov 3. [cited 2013 Feb 7]. Available from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/sbd-smd/phase1-decision/drug-med/sbd_smd_2009_tykerb_110294-eng.pdf

18. European Medicines Agency. EPAR summary for the public: Tyverb (lapatinib) [Internet]. London: EMA; 2010 May. [cited 2013 Feb 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000795/WC500044958.pdf

19. U.S. Food and Drug Administration. Tykerb [Internet]. Silver Spring (MD): FDA; 2010 Mar 8. [cited 2013 Feb 25]. Available from: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm203522.htm

20. GlaxoSmithKline response to February 4, 2013 pCODR Expert Review Committee request for additional information for Tykerb pCODR checkpoint meeting: Tykerb™ (lapatinib) in postmenopausal patients with metastatic breast cancer [internal manufacturer's report]. Mississauga (ON): GlaxoSmithKline; 2013 Feb 19.

21. European Medicines Agency. Assessment report for Tyverb. International non-prorietary name/common name: lapatinib [Internet]. Variation assessment report. London: EMA; 2010 Feb 18. [cited 2013 Feb 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000795/WC500091824.pdf

22. Gelmon KA, Boyle F, Kaufman B, Huntsman D, Manikhas A, Di Leo A, et al. Open-label phase III randomized controlled trial comparing taxane-based chemotherapy (Tax) with lapatinib (L) or trastuzumab (T) as first-line therapy for women with HER2+ metastatic breast cancer: interim analysis (IA) of NCIC CTG MA.31/GSK EGF 108919 [abstract]. J Clin Oncol. 2012;30(18 Suppl 1):abstract LBA671.

23. Pivot X, Semiglazov V, Zurawski B, Allerton R, Fabi A, Ciruelos E, et al. CEREBEL (EGF111438): an open label randomized phase III study comparing the incidence of CNS metastases in patients (pts) with HER2+ metastatic breast cancer (MBC), treated with lapatinib plus capecitabine (LC) versus trastuzumab plus capecitabine (TC) [abstract]. Ann Oncol. 2012;23(Suppl 9):ixe5. Abstract LBA11.

24. Konecny G, Pauletti G, Pegram M, Untch M, Dandekar S, Aguilar Z, et al. Quantitative association between HER-2/neu and steroid hormone receptors in hormone receptor-positive primary breast cancer. J Natl Cancer Inst. 2003 Jan 15;95(2):142-53.

25. Robert N, Leyland-Jones B, Asmar L, Belt R, Ilegbodu D, Loesch D, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol. 2006 Jun 20;24(18):2786-92.

26. Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012 Jan 12;366(2):109-19.

27. O'Rourke L, Pegram M, Press M, Pippen J, Pivot X, Gomez H, et al. First-line lapatinib combined with letrozole versus letrozole alone for hormone receptor positive (HR+) metastatic breast cancer (MBC): subgroup analyses of borderline FISH+, IHC 2+, HER2 unknown (UNK), and treatment-naive (TN) populations from EGF30008 [abstract]. J Clin Oncol. 2009;27(15 Suppl):56. Abstract 1062.

28. Sherif BN, Sherrill B, Amonkar M, Wu Y, Maltzman J, O'Rourke L, et al. Lapatinib plus letrozole compared with letrozole alone as first-line therapy in hormone receptor positive HER2+ metastatic breast cancer (MBC): A quality-of-life (QOL) analysis [abstract]. J Clin Oncol. 2009;27(15 Suppl):abstract 1039.

29. Johnston S, Arteaga C. Lapatinib (Tykerb) plus letrozole (Femara) or letrozole alone for postmenopausal hormone receptor-positive metastatic breast cancer. PT. 2009;34(2):102.

30. Davis A, Sabesan S, Gill G, Beadle G. First-line therapy with lapatinib combined with letrozole versus letrozole alone in hormone receptor positive metastatic breast cancer: an update of results from the phase III double blind EGF30008 trial [abstract]. Asia Pac J Clin Oncol. 2009;5 Suppl 1:A55-A56.

31. Zembryki D, Gomez H, Koehler M, Johnston S, Pippen J, Florance A, et al. Cardiac safety of the lapatinib/letrozole combination as first-line therapy in patients (pts) with metastatic breast cancer (MBC) [abstract]. J Clin Oncol. 2009;27(15 Suppl 1):abstract 1095.

32. Sherrill B, Sherif B, Amonkar MM, Maltzman J, O'Rourke L, Johnston S. Quality-adjusted survival analysis of first-line treatment of hormone-receptor-positive HER2+ metastatic breast cancer with letrozole alone or in combination with lapatinib. Curr Med Res Opin. 2011 Dec;27(12):2245-52.

33. Pivot X, Maltzman J, O'Rourke L, Florance A, Johnston S. Lapatinib plus letrozole vs. letrozole alone in patients (pts) with endocrine sensitive, HER2+, previously untreated metastatic breast cancer (MBC) with multiple (>3 sites) or liver metastases [abstract]. Eur J Cancer Suppl. 2009;7(2):283-4.

34. Sherrill B, Amonkar M, Sherif B, Maltzman J, O'Rourke L, Johnston S. A Q-TWiST analysis of lapatinib plus letrozole compared with letrozole alone as first-line therapy in hormone receptor positive (HR+) metastatic breast cancer (MBC) [abstract]. Eur J Cancer Suppl. 2009;7(2):275.

35. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT00073528, Study comparing GW572016 and letrozole versus letrozole in subjects with advanced or metastatic breast cancer; 2012 Nov 21 [cited 2013 Feb 7]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00073528

36. Frank-Stromborg M, Olsen SJ, editors. Instruments for clinical health-care research. 3rd ed. Sudbury (MA): Jones and Bartlett Publishers, Inc.; 2004.

37. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01160211, A study to compare the safety and efficacy of an aromatase inhibitor in combination with lapatinib, trastuzumab or both for the treatment of hormone receptor positive, HER2+ metastatic breast cancer; 2013 Jan 31 [cited 2013 Feb 7]. Available from: http://clinicaltrials.gov/show/NCT01160211

38. Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol. 2003 Jun 1;21(11):2101-9.

39. Mouridsen HT. Letrozole in advanced breast cancer: the PO25 trial. Breast Cancer Res Treat [Internet]. 2007 [cited 2013 Apr 5];105 Suppl 1:19-29. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2001219

40. Bonneterre J, Thurlimann B, Robertson JF, Krzakowski M, Mauriac L, Koralewski P, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol. 2000 Nov 15;18(22):3748-57.

41. Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol. 2000 Nov 15;18(22):3758-67.

42. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011 Jun;14(4):417-28.