PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Lapatinib (Tykerb) Letrozole for Metastatic Breast Cancer

July 5, 2013

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Tykerb (in combination with Letrozole)
Role in Review:	Manufacturer
Organization Providing Feedback	GlaxoSmithKline

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part ___✓ disagree

The manufacturer disagrees with the initial recommendation and respectfully requests that pERC reconsider its position based on the following reasons:

CLINICAL BENEFIT:

Demonstrated clinical benefit in HER2+HR+ metastatic breast cancer (mBC) patients:

- Health Canada approved the lapatinib+letrozole indication based on progression free survival (PFS) where median PFS in HER2+/HR+ patients was 8.2 months (lapatinib+letrozole) vs 3.0 months (letrozole only) providing a PFS gain of 5.2 months [HR=0.71 (95% CI: 0.53, 0.96; p=0.019)]. This statistically significant improvement in PFS was recognized by the Clinical Guidance Panel (CGP). The CGP also acknowledged improvements in some of the pivotal trial's secondary endpoints (CGR pg 6-7).
- The Tykerb product monograph also highlights that lapatinib + letrozole, *"offered an improvement in objective response rate compared to Letrozole alone (27.9% vs 14.8%) and in Clinical Benefit Rate (47.7% and 28.7%, respectively)"* and that, *"a trend in OS in favour of the TYKERB plus letrozole in the ErbB2 (HER2) positive population was observed."*[1] With less than 50% of OS events recorded (Johnston et al, 2009), median OS in the HER2+ group was 32.3 months vs. 33.3 months for letrozole vs. lapatinib + letrozole (HR = 0.74; 95% CI: 0.5, 1.1; p=0.113). As noted by the CGP, mature OS data is pending.
- The CGP also noted that subgroup analyses "*showed consistently longer PFS in treatment with lapatinib + letrozole although not all differences were statistically significant"* (CGR pg 35)
- These primary and secondary outcomes demonstrate the consistency of results in favour of the lapatinib plus letrozole arm. Thus, the magnitude of the difference in PFS offered by the combination (vs letrozole) should be considered to be of clear clinical benefit in patients with HER2+/HR+ mBC.
- While *"uncertainty was primarily due to the absence of a proven overall survival benefit with this regimen" (CGR pg 4),* there is precedence for pCODR providing positive funding recommendations in the absence of mature OS data (everolimus + exemestane in postmenopausal women with HR+ aBC). Moreover, some provinces, according to the CGP, are funding trastuzumab +anastrozole, even though this combination does not have statistically significant OS data. For lapatinib and letrozole, mature OS data will be forthcoming from the pivotal trial; however, patients in the meantime should be provided access to an option that has been reviewed and recommended by both Health Canada and pCODR.

[1] Canadian Tykerb Product Monograph (March 26, 2013), pg 30.

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- The manufacturer agrees with the conclusion of the Clinical Guidance Panel, *"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 patients not medically fit to receive chemotherapy with trastuzumab"* (CGR pg 3) **pERC should thus reconsider whether the uncertainty introduced by the lack of OS outweighs the strength of the primary and secondary endpoints as well as the patient-based values (see below) and other benefits that may accrue to patients within this population.**

PATIENT-BASED VALUES

Tolerable side effects while maintaining quality of life: Tykerb in combination with letrozole is the only licensed all-oral combination for HER2+HR+ mBC patients that allows effective treatment at home, helps avoid costly iv administration (including patient travel time to clinics etc) and provides an option to patients who are not medically fit to receive chemotherapy. Thus, this combination of drugs aligns with a number of key patient-based values (convenience, lower expense, enhanced choice).

- As noted by the CGP, *"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" (CGP pg 15).*
- The PAG noted that, *"If implemented lapatinib + letrozole as an oral treatment would enhance accessibility to patients and reduce chemotherapy clinic and chair time"*(CGR pg 21). pERC also noted that this combination may benefit those who are not medically fit for chemotherapy, including the elderly among others (Rec pg 5). Despite this observation, "*pERC did not consider this need to be great enough to justify a funding recommendation for this very limited patient population."*
- pERC pointed to the availability of *"other treatment options that are currently available for this population, which have demonstrated overall survival benefit"* (CGR pg 3). However, available first-line therapies for post-menopausal patients with HR+ErbB2+ mBC have been either associated with limited clinical benefit (AIs) or with convenience and toxicity issues (trastuzumab + chemotherapy).
- Of note, trastuzumab + anastrozole has not been granted an indication by Health Canada for use in HER2+HR+ mBC patients. Thus, the lack of an approved indication from Health Canada and no formal review/recommendation by pCODR has resulted in variable access for patients in Canada as provinces may have reservations funding therapies off-label.
- Importantly, lapatinib + letrozole provides a safe, effective, on-label alternative for a small, defined group of metastatic breast cancer patients. The CGP also identified that anti-HER2+AIs may be suitable for patients "*who are not medically fit to receive chemotherapy with trastuzumab*" (CGR pg 10) and go on to state that the, *"goal of therapy with these regimens would be to prolong PFS since improvements in OS have not been demonstrated."* (CGP pg 10-11) which aligns to the indication.
- The manufacturer acknowledges that the combination of lapatinib+letrozole is associated with higher AEs, but these AEs are both predictable and manageable. pERC speculated that given the uncertain clinical benefit of lapatinib plus letrozole, *"there may be less tolerance among patients for the additional toxicity (eg serious diarrhea and rashes) associated with lapatinib plus letrozole"*. However, the CGP also recognized that "*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."(CBR pg 15).* Indeed, "*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."* (CBR pg 9)
- Overall, lapatinib + letrozole provides an all-oral regimen that delays progression in HR+ErbB2+ mBC

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patients without a detrimental effect on tolerability or quality of life. Moreover, this combination provides a Health Canada-approved therapeutic choice to a small patient population who may not be able to tolerate the aggressive and highly toxic chemotherapy regimens or the travel time associated with going to a clinic to receive trastuzumab.

ECONOMIC EVALUATION

As trastuzumab + anastrozole is not indicated for this condition and OS data is also lacking, the economic comparison to lapatinib+letrozole should not feature so prominently in the economic evaluation section of the recommendation summary (pg 6), nor should it be used as a basis for funding decision, particularly as trastuzumab+anastrozole has no indication for this population.

- The manufacturer agrees that due to lack of data comparing lapatinib + letrozole with trastuzumab + anastrozole, the estimate of effect is uncertain. However, the manufacturer disagrees with pCODR that assuming equal efficacy is a conservative assumption since the two combination drugs do not have the same mechanism of action. The EGP provides no basis for such assumption (EGR pg 2).

Within the CGR, "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."

- Lapatinib + letrozole is expected to have a small budget impact, since the indication is for a limited patient population (ie: post-menopausal HER2+HR+ women with MBC, who are suitable for endocrine therapy, who have not received prior chemotherapy, hormonal therapy, immunotherapy, biologic therapy, or anti-ErbB1/ ErbB2 therapy for metastatic disease, and who are without extensive symptomatic visceral or rapidly progressing or life threatening disease).

ADOPTION FEASIBILITY

Lapatinib + letrozole provides the only all-oral on-label alternative to trastuzumab + anastrozole as well as a more convenient alternative for patients unable to tolerate chemotherapy.

- pERC notes that "accessibility to trastuzumab + anastrozole is limited as it is not funded in many jurisdictions". To improve access to a safe, effective and well-tolerated therapy, pCODR should reconsider its funding recommendation for lapatinib + letrozole.
- While we agree with the PAG who noted that, "lapatinib as an oral treatment will increase accessibility of treatment to patients", we disagree that as a therapeutic option, it would present "a potentially [sic] challenge to funding." (CGR pg 21) since the patient population is small (see above).
- Concerns that *"access would still be limited for patients in remote areas"* as the *"need for monitoring of adverse events and dose adjustments associated with lapatinib plus letrozole"* may only apply to patients starting on therapy as these AEs are predictable and manageable. Even in remote areas, the number of patients who might require dose adjustments due to AE complications would be small, given that less than 20% of the Canadian population lives remotely. Hence, the accessibility benefits offered by the oral administration of lapatinib plus letrozole outweigh the limitations posed by therapy adjustments and monitoring in remote areas.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

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____ Support conversion to final recommendation.

Recommendation does not require reconsideration by pERC.

_✓__ Do not support conversion to final recommendation.

Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	**Section Title**	**Paragraph, Line Number**	**Comments and Suggested Changes to Improve Clarity**
			See comments above
22	Accessibility	1-6	Tykerb is not a cytotoxic agent. Thus, concern about drug exposure due to the switch from blister packs to high density polyethylene (HDPE) bottles is unwarranted.

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About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

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e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½″ by 11″ paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.

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