CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Tucatinib (Tukysa)

Indication: in combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and T-DM1, separately or in combination

Recommendation: Reimburse with Conditions

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CADTH

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TUCATINIB (TUKYSA — SEAGEN CANADA INC.)

Therapeutic Area: Advanced or Metastatic Breast Cancer

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that tucatinib in combination with trastuzumab and capecitabine be reimbursed for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and T-DM1, separately or in combination, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from one double-blind, phase II randomized controlled trial demonstrated that treatment with tucatinib in combination with trastuzumab and capecitabine resulted in added clinical benefit for adult patients with locally advanced unresectable or metastatic HER2-positive breast cancer, with or without brain metastases, who had received prior treatment with trastuzumab, pertuzumab, and T-DM1. The HER2CLIMB trial demonstrated that, when compared with placebo plus trastuzumab and capecitabine, treatment with tucatinib plus trastuzumab and capecitabine was associated with statistically significant and clinically meaningful improvements in progression-free survival (PFS; stratified hazard ratio [HR]=0.54; 95% confidence interval [CI]: 0.42 to 0.71; p-value <0.00001) and PFS among patients with brain metastases (PFS_{BM}; stratified HR=0.48; 95% CI: 0.34 to 0.69, p-value <0.00001), and overall survival (OS; HR=0.66; 95%CI: 0.50 to 0.88; p-value = 0.00480). Input from patient groups indicated that patients desire accessible and affordable treatment options that offer delayed disease progression, effective treatment for brain metastases, improved quality of life, and prolonged survival. Given the totality of the evidence, pERC concluded that tucatinib plus trastuzumab and capecitabine met some of the needs identified by patients as it provides an additional treatment option with improved PFS and OS and no deterioration in quality of life, and fulfills an unmet need for treatment of patients with brain metastases.

Using the sponsor submitted price for tucatinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for tucatinib combination therapy is $512,403 per quality-adjusted life year (QALY) compared with T-DM1 in the second line setting and $381,429 per QALY compared to trastuzumab with capecitabine in the third line setting. Tucatinib combination therapy is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for patients with locally advanced unresectable or metastatic HER2+ breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and T-DM1, separately or in combination. A reduction in price of at least 48% is required for tucatinib combination therapy to be considered cost-effective at a $50,000 per QALY threshold in the second line setting and a reduction in price of at least 94% to be considered cost-effective at a $50,000 per QALY threshold in the third line setting.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Treatment with tucatinib plus trastuzumab and capecitabine should be initiated only in adults who have all of the following: 1.1. Received at least one prior systemic treatment for HER2-positive locally advanced or metastatic breast cancer 1.2. Received prior treatment with trastuzumab, pertuzumab, and T-DM1 1.3. HER2-positive status confirmed using ISH, FISH or IHC methodology	Evidence from the HER2CLIMB trial demonstrated that tucatinib plus trastuzumab and capecitabine resulted in significant improvements in PFS and OS in patients with locally advanced and HER2-positive breast cancer who had previously been treated with all of pertuzumab, trastuzumab, and T-DM1 treatments for breast cancer and had received at least one prior HER2-directed therapy in the advanced/metastatic setting. All patients in the HER2CLIMB trial had a confirmed HER2-positive status using IHC, ISH, or FISH testing methodologies.
2. Patients must have an ECOG PS of 0 or 1.	The CADTH review identified no evidence to demonstrate a benefit of tucatinib in patients with ECOG PS >1 at baseline as these patients were not enrolled in the HER2CLIMB.
3. Patients must have adequate blood counts and organ function.	The CADTH review identified no evidence to demonstrate a benefit of tucatinib in patients with impaired hematologic parameters and organ function as the HER2CLIMB trial only enrolled patients with adequate hematologic parameters and organ function.
Renewal	
4. Assessment for renewal of tucatinib plus trastuzumab and capecitabine should be based on clinical and radiographic evaluation every 6 to 9 weeks for the first 6 months after treatment initiation.	Efficacy assessments in the HER2CLIMB trial were performed every 6 weeks for the first 6 months and every 9 weeks, thereafter.
Discontinuation	
5. Treatment with tucatinib should be discontinued upon the occurrence of any of the following: 5.1. documented disease progression as per IWG response criteria 5.2. Unacceptable toxicity	The CADTH review identified no evidence that continuing treatment with tucatinib in patients whose disease has progressed is effective. Patients who are unable to complete treatment with tucatinib due to unacceptable toxicity would likely not be able to receive further treatment with tucatinib.
6. Treatment with tucatinib can continue if discontinuation is required for either capecitabine or trastuzumab due to toxicity. If trastuzumab and capecitabine are both discontinued, tucatinib must also be discontinued.	This condition reflects the treatment discontinuation criteria used in the HER2CLIMB trial.
Prescribing	
7. Tucatinib plus trastuzumab and capecitabine should only be prescribed by clinicians with expertise and experience in treating breast cancer in approved centres for trastuzumab infusion.	To ensure that tucatinib plus trastuzumab and capecitabine is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.
8. Tucatinib should only be prescribed in combination with trastuzumab and capecitabine for eligible patients.	There is no evidence to suggest an additional benefit of tucatinib as monotherapy or in combination with other treatments; tucatinib was administered in combination with trastuzumab and capecitabine in the HER2CLIMB trial.
Pricing	

Reimbursement Condition	Reason
9. A reduction in price	The ICER for tucatinib combination therapy is $512,403 per QALY compared T-DM1 in the second line setting and $381,429 per QALY compared to trastuzumab with capecitabine in the third line setting. A price reduction of 48% would be required for tucatinib combination therapy to be able to achieve an ICER of $50,000 per QALY compared to T-DM1 in the second line setting. A price reduction of 94% would be required for tucatinib combination therapy to be able to achieve an ICER of $50,000 per QALY compared to trastuzumab with capecitabine in the third line setting.

FISH = Fluorescence in situ hybridization; HER2 =human epidermal growth factor receptor 2; ICER =incremental cost-effectiveness ratio; IHC = immunohistochemistry; ISH =in situ hybridization; IWG = the International Working Group; QALY = quality-adjusted life years

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by pERC and the drug plans are summarized in Table 2.

Table 2. Implementation Guidance from pERC

Condition #	Implementation Considerations and Guidance
1	All patients in HER2CLIMB were pre-treated with trastuzumab, pertuzumab, and T-DM1. Input from public drug programs indicated that, in Canada, pertuzumab (in combination with trastuzumab) is only funded in the metastatic and relapsed setting. pERC recognized that the subgroup of patients who have not received pertuzumab as part of a previous treatment regimen have a specific clinical need for an effective treatment in locally advanced or metastatic setting. Therefore, pERC agreed with the clinical experts in that combination therapy with tucatinib plus trastuzumab and capecitabine could fill a treatment gap in patients who cannot receive pertuzumab or T-DM1, due to contraindications or toxicity issues, and patients who relapse early on T-DM1 or trastuzumab in the adjuvant setting. pERC noted that the public drug programs may need to consider addressing the variability in funding of pertuzumab across jurisdictions to help facilitate an equitable access to tucatinib plus trastuzumab and capecitabine.
2	While patients enrolled in the HER2CLIMB trial were required to have an ECOG PS of 0 or 1, pERC agreed that clinicians may consider using tucatinib plus trastuzumab and capecitabine for patients with an ECOG PS of 2. The decision to use this treatment for patients with an ECOG PS of 2 should be based on the judgement of the treating physician.
4	In HER2CLIMB, CT or MRI occurred every 6 weeks for 24 weeks, and every 9 weeks thereafter, to assess disease status using RECIST v1.1 criteria. Patients with brain metastases were required to be assessed using MRI. pERC agreed with the clinical experts that MRI is the preferred modality for brain imaging. However, for patients with brain metastases, CT may be considered where an MRI is not available. The clinical experts indicated that, in clinical practice, imaging assessments are typically performed every 3 to 6 months, based on a clinical judgement. pERC agreed that follow-up intervals and imaging assessments may be prolonged at the discretion of the treating physician.
7	As tucatinib and capecitabine both have potential for drug-drug interactions and dose adjustments in the event of toxicities, pERC noted that jurisdictions may need to provision adequate pharmacy resources to ensure accurate and safe administration of this regimen.
	Input from public drug programs indicated that combination therapy with tucatinib plus trastuzumab and capecitabine, which includes both oral and IV agents, would need to be reimbursed through different drug

Condition #	Implementation Considerations and Guidance
	programs in most jurisdictions. Some jurisdictions may have a co-pay for patients as part of funding for tucatinib and capecitabine**.** pERC noted that, upon implementation of the tucatinib reimbursement, jurisdictions would need to fund trastuzumab, in the 3rd line setting, for patients who are eligible to receive tucatinib in combination with trastuzumab and capecitabine.
8	The public drug program expressed a concern with complexity of administration of oral tucatinib and capecitabine due to differing their cyclical days of administration, twice daily dosing, and multiple tablets required per drug per dose. pERC recognized that jurisdictions may need to establish a detailed patient and caregiver education to address potential issues around outpatient dosing schedules and pill burden.
9	CADTH reanalyses estimated the incremental budget impact of reimbursing tucatinib combination therapy to be $64,395,873 in Year 1, $80,786,751 in Year 2, and $99,110,926 in Year 3, for a three-year expected total budget impact of $244,293,549. Therefore, the feasibility of reimbursing tucatinib combination therapy must be addressed.

CT = computerized tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; MRI = magnetic resonance imaging

Discussion Points

- Based on input from clinical experts, pERC acknowledged that there is an unmet treatment need for patients with advanced or metastatic HER2-positive breast cancer in the third line setting because no standard of care is currently available for these patients following disease progression on second line therapy. The clinical experts noted that HER2-positive breast cancer patients with brain metastases do not have effective systemic treatment options and are often excluded from clinical trials, resulting in significant unmet need in this patient subgroup.

- pERC discussed the results of a randomized phase II (HER2CLIMB) trial that demonstrated significant improvements in PFS and OS. The trial results showed greater improvement in PFS among a subgroup of patients with brain metastases, a group of patients with limited effective treatment options available. pERC agreed that the available evidence supports the comparative efficacy of tucatinib in combination with trastuzumab and capecitabine over trastuzumab plus capecitabine alone in the treatment of patients who are often difficult to treat using current treatment options in the Canadian practice.

- pERC acknowledged that there was a lack of direct evidence to show the comparative effectiveness of tucatinib plus trastuzumab and capecitabine versus other alternative therapies. One sponsor-submitted ITC suggested that combination therapy with tucatinib plus trastuzumab and capecitabine may be more efficacious than capecitabine, neratinib, lapatinib plus capecitabine, and trastuzumab plus capecitabine. However, there were several significant limitations to the submitted ITC which introduced uncertainty to its overall results. Specifically, the sponsor's ITC included studies which reported heterogeneity in trial and patient characteristics, lack of adjustment for relevant effect modifiers (e.g., prior exposure to treatments, line of therapy, and presence of brain metastases), and violation of the proportional hazard assumption, particularly for the analysis of PFS. While these sources of bias introduced uncertainty to the magnitude of the estimates for between-treatment comparisons, pERC agreed with the CADTH review team that the overall direction of ITC estimates could be considered reliable. However, the committee acknowledged that many of the treatment options included in the ITC are not currently reimbursed by public drug plans for patients with locally advanced unresectable or metastatic HER2-positive breast cancer in Canada.

- No differences in HRQoL (as measured using the EQ-5D-5L) were observed in the HER2CLIMB trial between the tucatinib and placebo combination groups. Overall pERC agreed that tucatinib did not result in deterioration of patients' quality of life. However, pERC noted that the patient-reported outcomes in HER2CLIMB were exploratory in nature for which only descriptive results were presented. Therefore, only limited interpretations could be made on the available quality of life data.

- Input from patient groups indicated that patients desire accessible and affordable treatment options that offer delayed disease progression, effective treatment for brain metastases, improved quality of life, and prolonged survival. pERC concluded that the tucatinib plus trastuzumab and capecitabine aligns with some of the patient needs as it offers meaningful improvements in PFS and OS with no deterioration in quality of life, and fulfills an unmet need in patients with brain metastases by providing them with an effective and tolerable systemic treatment option. However, different funding mechanisms for oral medications across Canada and the high cost of tucatinib may lead to administrative and financial

barriers to access to this combination for many patients. In addition, the complexity of administration of oral tucatinib and capecitabine will require additional pharmacy resources to provide patient and caregiver education to ensure appropriate use and to understand how to monitor toxicities.

- pERC discussed the safety profile of tucatinib and noted that, in the HER2CLIMB trial, Grade 3 or higher adverse events and serious adverse events were reported in similar proportion of patients in the tucatinib and placebo combination groups. pERC also noted that most adverse events observed in the pivotal trial were Grade 1 and 2 in severity, with the most commonly reported adverse events in the tucatinib group being diarrhea, hand-foot syndrome, nausea, fatigue, and vomiting. Overall, pERC agreed that tucatinib was associated with a manageable toxicity profile.

- Input submitted to CADTH by the provincial advisory group (PAG) indicated that, in Canada, pertuzumab (in combination with trastuzumab) is only funded in the metastatic and relapsed setting. PAG noted that patients with disease relapse during adjuvant trastuzumab or within 6 months of completing adjuvant trastuzumab therapy are eligible to receive T-DM1 at disease relapse but are not eligible for funding for pertuzumab-trastuzumab in some jurisdictions. PAG identified that this subset of patients was not addressed in the HER2CLIMB population and sought guidance on the appropriateness of the tucatinib combination with patients who have not received prior treatment with pertuzumab if subsequent disease progression occurs after treatment with T-DM1. pERC acknowledged that no evidence was included in the review to show the efficacy and safety of the tucatinib combination therapy in the subgroup of patients who have not received pertuzumab as part of a previous treatment regimen. However, the committee felt that unequal funding for pertuzumab across jurisdictions may not be equitable to all Canadian patients in terms of treatment options. pERC noted that patients who cannot receive pertuzumab or T-DM1, due to contraindications or toxicity issues, and patients who relapse early on T-DM1 or trastuzumab in the adjuvant setting, would benefit from the tucatinib combination; and therefore, suggested that the variability in funding practices for pertuzumab should be further discussed by the public drug programs and addressed to help facilitate an equitable access to the tucatinib combination.

Background

Tucatinib, in combination with trastuzumab and capecitabine, is approved by Health Canada for the treatment of patients with locally advanced or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and T-DM1, separately or in combination. Tucatinib is a tyrosine kinase inhibitor (TKI) of the HER2 protein. It is available as 50 mg and 150 mg oral tablets and the Health Canada–approved dose is 300 mg orally twice daily, along with trastuzumab (6 mg/kg of body weight IV once every 21 days) and capecitabine (1000 mg/square meter of body surface area orally twice daily on days 1 to 14 of each 21-day cycle).

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of one randomized controlled phase II trial in patients with locally advanced or metastatic HER2-positive breast cancer
- Patients' perspectives gathered by three patient groups: the Canadian Breast Cancer Network (CBCN), Rethink Breast Cancer, and the CanCertainty Coalition
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Three clinical specialists with expertise diagnosing and treating patients with advanced HER2-positive breast cancer
- Input from two clinician groups, including Ottawa Hospital Cancer Centre's (OHCC) Breast Disease Site Group and Ontario Health -Cancer Care Ontario (OH-CCO)'s Breast Disease Site Advisory Committee
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Three patient groups provided input for the review of tucatinib: CBCN, Rethink Breast Cancer, and the CanCertainty Coalition. Information from CBCN was obtained via online surveys. Information from Rethink Breast Cancer was obtained using an online

patient survey and patient interviews. Input from CanCertainty was based on published reports on statistics of breast cancer and patient drug coverage.

Patient groups stated that treatment options vary for patients depending on the line of therapy and patient characteristics. Trastuzumab and pertuzumab were reported to be the most commonly received treatments from patients, followed by T-DM1, capecitabine, paclitaxel, docetaxel, and trastuzumab/pertuzumab/T-DM1. Commonly reported side effects of treatment included fatigue, diarrhea, nausea, and insomnia, all of which had a notable impact on quality of life. The patient groups identified a lack of effective treatment options for patients with brain metastases, who are typically offered local therapies including surgery and radiation.

Eight patients were identified as having experience with tucatinib, including six patients with brain metastases. Commonly reported side effects due to treatment with tucatinib included diarrhea, decreased appetite, fatigue, nausea, hand and foot syndrome and rash. In general, patients reported that side effects from tucatinib were manageable and did not negatively impact their quality of life. The patient groups highlighted the importance of delayed progression, improved quality of life and survival as expectations for new treatments. Additional treatment options that are accessible and affordable were also acknowledged as an important need for patients.

Clinician input

Input from clinical experts consulted by CADTH

The clinicians consulted by CADTH identified unmet treatment needs for patients with advanced or metastatic HER2-positive breast cancer, as patients lack an effective standard of care following progression on second line therapy. In particular, patients with brain metastases lack effective systemic treatment options and are often excluded from clinical trials, resulting in significant unmet need in this patient subgroup. Tucatinib in combination with trastuzumab and capecitabine was suggested to be administered as per the HER2CLIMB trial eligibility criteria and dosing schedule, and mainly in the third line treatment setting. Tucatinib was suggested not to be used for patients with poor Eastern Cooperative Oncology Group performance status (ECOG PS), i.e., ECOG PS of 2 to 4. However, patients with an ECOG PS of 2 may be considered for treatment with tucatinib based on the judgement of the treating physician. As tucatinib is administered along capecitabine and trastuzumab, tucatinib was stated to be administered in an outpatient clinical setting. Discontinuation of tucatinib should occur if there is evidence of disease progression or lack of benefit to patients with continued treatment, a patient has poor performance status, or if a patient experiences severe treatment toxicity.

Clinician group input

Two group clinician inputs were received on behalf of OHCC Breast Disease Site Group and Ontario Health - Cancer Care Ontario (Oh-CCO) Breast Disease Site Advisory Committee. Both groups stated that, after first line treatment with a combination of taxane chemotherapy, trastuzumab, and pertuzumab, and second line treatment with T-DM1, no standard third line options are available for HER2-positive MBC patients. Third line treatment options may differ across jurisdictions and across countries. Both groups also acknowledged that there are limited treatment options for patients with brain metastases, aside from surgery and radiation. Both clinician group inputs suggested that tucatinib would be used in the third line treatment setting. Both groups acknowledged that tucatinib-combination therapy addresses patient needs as it demonstrated improved efficacy in patients with and without brain metastases.

Drug Program Input

Input from the Provincial Advisory Group (PAG) identified factors pertaining to relevant comparators, generalizability, and considerations for initiation, renewal, and discontinuation of therapy. The clinical experts consulted by CADTH weighed evidence from the HER2CLIMB trial and other clinical considerations to provide responses which are presented in Table 3.

Table 3. Responses to Questions from the Drug Programs

Implementation Issues	Response
Relevant Comparators	
The combination of trastuzumab plus capecitabine (comparator in HER2CLIMB) is not a funded therapy in most Canadian jurisdictions when used after pertuzumab, trastuzumab, and T-DM1. Funded therapies in this setting include capecitabine (monotherapy), and various other chemotherapy options. How does the combination of tucatinib-trastuzumab-capecitabine compare in efficacy/tolerability to chemotherapy alone?	No direct evidence comparing tucatinib plus trastuzumab and capecitabine to chemotherapy alone was identified in this CADTH review; therefore, the clinical experts consulted by CADTH noted that efficacy and safety comparisons to the available chemotherapy regimens cannot be known with certainty. However, based on the limited indirect evidence reviewed, the clinical experts suggested that combination therapy with tucatinib plus trastuzumab and capecitabine would likely be more efficacious than chemotherapy alone. The clinical experts acknowledged that there may be additional toxicities to consider with the tucatinib combination regimen compared to chemotherapy alone, including diarrhea, hand and foot syndrome, fatigue, nausea/emesis, elevated liver enzymes and a small risk of cardiotoxicity.
Some jurisdictions fund the combination of lapatinib plus capecitabine for patients with disease progression after trastuzumab-based therapy. Is lapatinib-capecitabine a relevant comparator to tucatinib-trastuzumab-capecitabine? If so, how do they compare with regards to efficacy/tolerability?	The clinical experts agreed that lapatinib plus capecitabine is a relevant comparator to the combination therapy with tucatinib plus trastuzumab and capecitabine. However, there is no direct evidence comparing tucatinib plus trastuzumab and capecitabine to lapatinib plus capecitabine directly. The clinical experts noted the choice of comparator (trastuzumab plus capecitabine) was made in the HER2CLIMB trial based on the CEREBREL trial which compared combination therapy with lapatinib and capecitabine with trastuzumab plus capecitabine. The indirect comparisons between the HER2CLIMB and CEREBREL trials suggest that tucatinib plus trastuzumab and capecitabine may perform better than lapatinib plus capecitabine, in terms of PFS and OS. The clinical experts expected that there may be fewer or equal rates of diarrhea and nausea with the tucatinib-combination therapy, as lapatinib and capecitabine are associated with more of these toxicities than trastuzumab plus capecitabine. Overall, pERC agreed with the clinical experts consulted by CADTH in that without rigorous direct comparative evidence, the comparative efficacy and tolerability of each regimen remain uncertain.
Considerations for Initiation of Therapy	
All patients in HER2CLIMB were pre-treated with trastuzumab, pertuzumab, and T-DM1. In Canada, pertuzumab (in combination with trastuzumab) is only funded in the metastatic/relapsed setting. Patients with disease relapse during adjuvant trastuzumab or within 6 months of completing adjuvant trastuzumab therapy are eligible to receive TD-M1 at disease relapse but are not eligible for funding for pertuzumab-trastuzumab in some jurisdictions. Therefore, this subset of patients was not addressed in the HER2CLIMB population.	The clinical experts consulted by CADTH agreed that eligibility for treatment with tucatinib plus trastuzumab and capecitabine should be limited to patients with prior exposure to trastuzumab, pertuzumab and T-DM1, as per eligibility criteria of the HER2CLIMB trial. However, despite a lack of evidence to show the efficacy and safety of the tucatinib combination therapy in the subgroup of patients who have not received pertuzumab as part of a previous treatment regimen, pERC recognized that the subgroup of patients who have not received pertuzumab as part of a previous treatment regimen have a specific clinical need for an effective treatment in locally advanced or metastatic setting. Therefore, pERC agreed with the clinical experts in that combination therapy with tucatinib plus trastuzumab and capecitabine would fill a

Implementation Issues	Response
Should eligibility for tucatinib-trastuzumab-capecitabine be limited to patients with prior exposure to T-DM1, trastuzumab **and** pertuzumab?	treatment gap in patients who cannot receive pertuzumab or T-DM1, due to contraindications or toxicity issues, and patients who relapse early on T-DM1 or trastuzumab in the adjuvant setting. pERC noted that the public drug programs may need to consider addressing the variability in funding of pertuzumab across jurisdictions to help facilitate an equitable access to tucatinib plus trastuzumab and capecitabine.
HER2CLIMB excluded patients who received prior capecitabine or a HER2-targeted tyrosine kinase inhibitor (unless completed more than 12 months before trial). Are patients with previous treatment with lapatinib eligible to receive the tucatinib plus trastuzumab and capecitabine combination?	The clinical experts consulted by CADTH agreed that patients previously treated with capecitabine in the metastatic setting should not be treated with the tucatinib combination therapy. Prior treatment with lapatinib was permitted within the HER2CLIMB trial as long as patients had received lapatinib >12 months prior to initiating HER2CLIMB trial regimens. Therefore, the clinical experts agreed that patients may be eligible for treatment with tucatinib in combination with trastuzumab and capecitabine if they were previously treated with lapatinib, as long as they had completed (or stopped) treatment with lapatinib at least 12 months prior to initiating tucatinib-combination therapy.
HER2CLIMB included patients with brain metastases. For patients with brain metastases, how does efficacy and tolerability of the tucatinib-trastuzumab-capecitabine combination compare to currently funded comparators (e.g., chemotherapy)?	The clinical experts consulted by CADTH noted that there were no direct comparisons of the tucatinib combination to lapatinib plus capecitabine or chemotherapy alone. The clinical experts indicated that most chemotherapeutic agents currently used for patients with brain metastases have poor penetration to CNS. Hence, the clinical experts considered treatment with tucatinib plus trastuzumab and capecitabine would be a more a reasonable treatment than chemotherapy alone for patients with brain metastasis. The clinical experts noted that, in the HER2CLIMB trial, tucatinib plus trastuzumab and capecitabine demonstrated a statistically and clinically significant PFS benefit over trastuzumab plus capecitabine in patients with brain metastases; and that in the CEREBREl trial, PFS in patients with brain metastases was not statistically different between the lapatinib plus capecitabine and trastuzumab plus capecitabine combination therapy groups. Given that lapatinib is known to have CNS activity, the clinical experts suggested that it was difficult to assume that the tucatinib combination would be superior to lapatinib plus capecitabine in the subgroup of patients with brain metastases.
The combination of tucatinib-trastuzumab-capecitabine is proposed for use after pertuzumab, trastuzumab, and T-DM1. Is it appropriate to offer the tucatinib plus trastuzumab and capecitabine combination to patients, otherwise eligible for HER2CLIMB criteria, who are currently receiving systemic therapy (e.g., capecitabine) with no evidence of progressive disease/intolerance?	The clinical experts agreed that it would be appropriate to offer tucatinib plus trastuzumab and capecitabine to these patients. pERC agreed that upon the implementation of a funding recommendation for tucatinib plus trastuzumab and capecitabine, jurisdictions may consider addressing the time-limited need for this combination treatment in all, otherwise eligible, patients who are currently receiving systemic therapy (e.g., capecitabine) and who have not experienced disease progression.
Considerations for continuation or renewal of therapy	

Implementation Issues	Response
In HER2CLIMB, CT or MRI occurred every 6 weeks for 24 weeks, and every 9 weeks thereafter, to assess disease status using RECIST v1.1 criteria. Patients with brain metastases were required to be assessed using MRI. In practice, which modality and frequency are most appropriate to assess disease status in patients receiving the tucatinib-trastuzumab-capecitabine combination? Do all patients with brain metastases require assessment by MRI and not CT?	To assess patient's disease status, the clinical experts consulted by CADTH stated that patients can be assessed using CT scans with or without bone scans, in addition to clinical assessments. pERC agreed with the clinical experts that MRI is the preferred modality for brain imaging. However, for patients with brain metastases, CT may be considered where an MRI is not available. The clinical experts indicated that, in clinical practice, imaging assessments are typically performed every 3 to 6 months, based on a clinical judgement. pERC agreed that follow-up intervals may be prolonged at the discretion of the treating physician.
Considerations for discontinuation of therapy	
In HER2CLIMB, patients with only brain disease progression were eligible to continue on study drugs after completion of local treatment (e.g., radiotherapy, surgery). In practice, which patients will be eligible to continue on the tucatinib plus trastuzumab and capecitabine combination despite documented disease progression?	The clinical experts consulted by CADTH agreed that patients with disease progression in an isolated brain lesion which is amenable to local therapies (i.e., radiation therapy or surgery) would be eligible to continue receiving tucatinib plus trastuzumab and capecitabine after the completion of the local treatment.
In HER2CLIMB, patients who discontinued either capecitabine or trastuzumab (but not both) remained on tucatinib treatment. Patients who discontinued tucatinib or both of capecitabine and trastuzumab were not permitted to remain on study. In practice, are treatment discontinuation parameters from HER2CLIMB reasonable?	The clinical experts consulted by CADTH considered the treatment discontinuation parameters in the HER2CLIMB trial to be reasonable, in general. However, in some clinical cases patients may need to discontinue tucatinib due to treatment-related toxicity and clinicians may consider keeping patients on treatment with trastuzumab plus capecitabine. The clinical experts stressed that continuing patients on treatment with trastuzumab plus capecitabine should be made at the treating physician's discretion, considering the risks and benefits of discontinuing each treatment option. The clinical experts agreed that patients who experience disease progression would typically need to be considered for treatment with a different regimen.
The combination of tucatinib plus trastuzumab and capecitabine is proposed for use after pertuzumab, trastuzumab, and T-DM1. Is it appropriate to offer the tucatinib plus trastuzumab and capecitabine combination to patients, otherwise eligible for HER2CLIMB criteria, who are currently receiving systemic therapy (e.g., capecitabine) with no evidence of progressive disease or intolerance?	The clinical experts consulted by CADTH agreed that it would be appropriate to offer tucatinib in combination with trastuzumab and capecitabine to patients who are currently receiving systematic therapy (e.g., capecitabine) with no evidence of disease progression or intolerance, if the patient is otherwise eligible to receive the tucatinib combination.
Considerations for prescribing of therapy	
The combination of tucatinib-trastuzumab-capecitabine will add trastuzumab doses for a patient population that currently does not receive funding for trastuzumab. This will increase health system resource use (chair time, sterile compounding). Self-administration of oral tucatinib and capecitabine is complex due to differing cyclical days of administration, twice daily dosing, and multiple tablets required per drug per dose.	pERC noted that jurisdictions may need to establish a detailed patient and caregiver education to address potential issues around outpatient dosing schedules and pill burden.

Implementation Issues	Response
The combination of tucatinib, trastuzumab, and capecitabine includes oral and IV drugs that would be reimbursed through different drug programs in most jurisdictions. Some jurisdictions may have a co-pay for patients as part of funding for tucatinib and capecitabine.	pERC noted that, upon implementation of the tucatinib reimbursement recommendation, jurisdictions would need to fund trastuzumab for patients who are eligible to receive tucatinib in combination with trastuzumab and capecitabine.
Generalizability	
Patients with ECOG PS >1 were excluded from the HER2CLIMB trial. Which performance status is most appropriate for treatment with the tucatinib plus trastuzumab and capecitabine combination?	Patients with ECOG PS of 0 or 1 were enrolled into the HER2CLIMB trial, and clinical experts agreed that these patients would be most appropriate for treatment with tucatinib in combination with trastuzumab and capecitabine. While patients enrolled in the HER2CLIMB trial were required to have an ECOG PS of 0 or 1, pERC agreed that clinicians may consider using tucatinib plus trastuzumab and capecitabine for patients with an ECOG PS of 2. The decision to use this treatment for patients with an ECOG PS of 2 should be based on the judgement of the treating physician.
Care provision issues	
Tucatinib is supplied as 50 mg and 150 mg strengths in bottles of 60 tablets; the 150 mg tablet size is also available in a bottle of 120 tablets. The product monograph indicates that "A 2g desiccant canister with silica gel is enclosed with the tablets in each bottle. Dispense only in original container. Do not discard desiccant. Replace cap securely each time after opening. Discard any unused tablets 3 months after opening the bottle." As tucatinib must be dispensed in the original container: • Should dose modifications be required, there is the potential for wastage • Patient-specific doses cannot be blister-packed and this is a multi-drug combination, there is potential for confusion regarding intended dose and thus potential for administration errors.	pERC noted that jurisdictions may need to provision adequate pharmacy resources to provide appropriate patient and caregiver education to ensure accurate and safe administration of this regimen.
Determination of HER2 status is part of routine management of breast cancer in all Canadian jurisdictions.	pERC agreed that no companion diagnostic tests are required for the implementation of a funding recommendation for tucatinib plus tucatinib plus trastuzumab and capecitabine.
System and economic issues	
This combination has a high cost per cycle per patient and thus would have budget impact. In addition to new costs for tucatinib, this combination would introduce a new line of therapy for trastuzumab (which is currently not funded in this setting in most jurisdictions) and possible increased use/duration of capecitabine. Using the proposed list price, daily cost of tucatinib would be the same for a dose of 300 mg twice daily or 250 mg twice daily.	pERC noted that the feasibility and equity issues around reimbursing tucatinib combination therapy must be addressed by jurisdictions, upon implementation of a funding recommendation.

CNS= central nervous system; CT = computerized tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; g = gram; mg= milligram; MRI = magnetic resonance imaging

Clinical Evidence

Description of studies

One multicenter, multinational, double-blind, randomized controlled phase II trial met the criteria for the CADTH systematic review protocol. The HER2CLIMB trial evaluated the efficacy and safety of tucatinib in combination with trastuzumab and capecitabine compared to placebo in combination with trastuzumab and capecitabine which, from here on, will be referred to as the tucatinib-combination group and the placebo-combination group, respectively. Eligible patients included adults with histologically confirmed HER2-positive advanced breast cancer, confirmed using IHC, ISH, or FISH testing. Patients must have had prior treatment with pertuzumab, trastuzumab, and T-DM1, measurable disease using RECIST v1.1 criteria and an ECOG PS of 0 or 1. Patients with brain metastases were also eligible for enrollment. Presence of brain metastases was based on medical history and screening contrast brain magnetic resonance imaging (MRI), as assessed by an investigator. This international trial was conducted in 15 countries across 155 sites, including a total of 38 patients from Canada. A total of 410 patients were randomized to the tucatinib-combination group and 202 patients were randomized to the placebo-combination group. Randomization was stratified according to the following: presence of brain metastases (yes versus no), ECOG PS (0 versus 1), and geographic region (US versus Canada versus Rest of the World).

The doses of each treatment in the tucatinib-combination group were as follows:

- Tucatinib (300 mg) administered orally twice daily
- Capecitabine (1000 mg/m2) administered orally twice daily on days 1-14 of each 21-day cycle
- Trastuzumab was administered with an initial loading dose of 8 mg/kg IV, after which trastuzumab was administered at 6 mg/kg once every 21 days, except in specific circumstances where it was given weekly to compensate for modifications to the treatment schedule. Alternatively, trastuzumab could have been administered at a dose of 2 mg/kg IV every week (7 days), but only in circumstances when the trastuzumab infusion has been delayed, and weekly infusions are required to resynchronize the cycle length to 21 days, after discussion with a medical monitor.
    - Subcutaneous use of trastuzumab was permitted; in such instances when subcutaneous trastuzumab was administered, a fixed dose of 600 mg was provided without a loading dose. Subcutaneous trastuzumab was administered once every three weeks as there is no allowance for weekly dosing. Crossover from IV to subcutaneous trastuzumab was permitted within the trial.
    - Where national regulatory authorities approved use of a trastuzumab biosimilar, either IV or subcutaneous, biosimilar trastuzumab could also be administered for patients if considered appropriate by the investigator.

The doses of treatments in the placebo-combination group were the same as the tucatinib-combination group, placebo tablets replacing tucatinib twice daily. Treatment for patients continued until unacceptable toxicity, disease progression, withdrawal of consent, or study closure.

The primary endpoint of the trial was progression free survival (PFS). Key secondary endpoints which were part of a hierarchical testing scheme included PFS among patients with brain metastases (PFS_{BM}) and overall survival (OS). Other secondary and exploratory endpoints included objective response rate (ORR), PFS assessed by investigator (PFS_{INV}), duration of response (DOR) and health related quality of life (HRQoL) assessed using the European Quality of Life Scale – 5 Dimensions – 5 Levels (EQ-5D-5L).

Baseline characteristics of the HER2CLIMB trial were generally well balanced across both treatment groups in both the ITT and ITT-PFS populations; baseline characteristics were also similar across both trial populations. In the ITT population, patients had a mean age of 54 years with most patients (>80%) being less than 65 years of age. Most patients were white (74%) and from the US (54%) or the Rest of the world (40%). Relatively equal proportions of patients had an ECOG PS of 0 (48%) or 1 (51%). The majority of patients had metastatic disease (≥99%), and were positive for at least one hormone receptor (61%) or negative for both (38%). Non-CNS metastases were reported among 98% of patients; with the most frequent metastasis sites being lung (49%), bone (55%), and liver (36%). Brain metastases were reported in 48% of patients. A mean of four lines of prior therapy were reported by all patients in both treatment groups, with a mean of three prior therapies specifically in the metastatic setting. As per eligibility criteria, all patients (100%) had received prior treatment with trastuzumab and T-DM1, and more than 99% of patients had also received prior therapy with pertuzumab.

Efficacy Results

Key efficacy results of the HER2CLIMB trial were reported based on a data cut-off date of September 4, 2019 and were considered to be the final analyses. Results of the primary (PFS) (stratified HR=0.54; 95% CI, 0.42 to 0.71; stratified log-rank p-value <0.00001) and key secondary endpoints (PFS_{BM} [stratified HR=0.48; 95% CI, 0.34 to 0.69, stratified log-rank p-value <0.00001] and OS [HR=0.66; 95%CI, 0.50 to 0.88; stratified log-rank p-value 0.00480]) indicated a statistically significant improvement in patients treated with the tucatinib-combination over the placebo-combination. ORR was considered as another secondary endpoint, and also supported the results of the primary and key secondary analyses showing improved efficacy with the tucatinib-combination treatment versus the placebo-combination. A post-hoc analysis was conducted by the sponsor which provided an additional 15.6 months of follow-up time. The post-hoc analysis provided updated data for OS and PFS, assessed among all randomized patients. Results of the post-hoc analyses continued to support trastuzumab-combination therapy over the placebo-combination group. The assessments conducted as post-hoc analyses were not formally tested, therefore they should be considered descriptive. HRQoL data did not indicate any differences in EQ-5D-5L scores between patients in the tucatinib- and placebo-combination groups.

Harms Results

Safety data are reported based on a data cut-off data of September 4, 2019. In general, AEs were more commonly reported among patients in the tucatinib-combination group. The most common AEs of any-grade in both the tucatinib-combination group and the placebo-combination group were diarrhea (80.9% versus 53.3%), hand-foot syndrome (63.4% versus 52.8%), nausea (58.4% versus 43.7%), fatigue (45.0% versus 43.1%), and vomiting (35.9% versus 25.4%); however, the proportion of patients experiencing these AEs was greater in the tucatinib-combination group.[7] A total of 223 patients (55.2%) in the tucatinib-combination group experienced a grade ≥3 AE compared to 96 patients (48.7%) in the placebo-combination group. In both the tucatinib-combination group and placebo-combination group, the most commonly reported grade ≥3 AEs were hand-foot syndrome (13.1% versus 9.1%) and diarrhea (12.9% versus 8.6%). A time-at-risk exposure-adjusted analysis of grade ≥3 AEs of hand-foot syndrome, diarrhea, ALT and AST increased were performed to adjust for the longer exposure to treatment patients in the tucatinib-combination group experienced, as these patients had a longer duration of treatment than patients in the placebo-combination group. After adjustment, the crude incidence of grade ≥3 AEs of hand-foot syndrome (13.1% versus 9.1%), diarrhea (12.9% versus 8.6%), ALT (5.4% versus 0.5%) and AST increase (4.5% versus 0.5%) were all higher in the tucatinib-combination group than the placebo-combination group, respectively; the time-at-risk exposure-adjusted incidence rate per 100 person-years were 21 versus 19, 21 versus 17, eight versus one, and seven versus one, respectively. SAEs of any grade were reported in similar proportion of patients in the tucatinib- and placebo-combination groups (25.7% and 26.9%, respectively). Grade 5 AEs were reported in eight patients (2.0%) in the tucatinib-combination group and six patients (3.0% in the placebo-combination group.

Critical Appraisal

The HER2CLIMB trial was an international, multi-centre, double-blind, placebo-controlled phase II RCT. The baseline demographic and clinical characteristics were balanced across the treatment groups, overall and across important analysis populations (i.e., ITT and ITT-PFS populations). Patients were randomized based on presence of brain metastases (yes versus no), ECOG PS (0 versus 1), and geographic region (US versus Canada versus Rest of the world). This helped to ensure that the comparability between treatment arms in the subgroup analysis results according to each prespecified stratification factor. The sponsor also included specifications for a biased-coin assignment in the randomization scheme to prevent imbalances between treatment groups and any given hierarchical level (i.e., overall treatment group balance, then treatment group balance within each stratification factor).

Results of the HER2CLIMB trial demonstrated statistically significantly improved OS and PFS among patients treated in the tucatinib-combination group compared to the placebo-combination group. In general, subgroup analyses favoured treatment with the tucatinib-combination group versus the placebo-combination group. However, it should be acknowledged that while subgroups for subgroup analyses were prespecified, they were not adjusted for multiplicity, not powered to detect differences, and may be indicative of imprecision due to wide confidence intervals. The lack of adjustment for subgroup analyses may increase the likelihood of type 1 error, resulting in an increased likelihood of detecting a treatment effect when one may not be present. The sponsor conducted a post-hoc analysis which provided 15.6 months longer follow-up time (resulting in a total of 29.7 months of total follow-up time for the tucatinib-combination group and 29.4 months of total follow-up time for the placebo-combination group), and provided additional efficacy (OS, PFS) and safety data. Of note, after the primary analysis, the trial was made unblinded and assessments for

PFS were conducted by the investigator. The results of the post-hoc analysis were consistent with results of the primary analysis which remained blinded, and which used BICR for assessment of PFS.

It is possible that choice of subsequent therapies could have affected efficacy assessments of OS, as analyses for OS included patients who received subsequent therapies. A total of 202 patients (69.2%) in the tucatinib-combination group and 139 patients (79.4%) in the placebo-combination group received subsequent anti-cancer therapies. There were disproportional differences noted between treatment groups in types of subsequent anti-cancer therapies received, as more patients in the placebo-combination group received antibody (57.1% versus 50.0%, respectively) and TKI (24.0% versus 16.8%) anti-HER2 regimens, and trastuzumab (12.2% versus 5.4%), while more patients in the tucatinib-combination group than the placebo-combination group received trastuzumab plus chemotherapy (20.8% versus 15.8%, respectively). The differences in subsequent therapies are expected to introduce bias in the efficacy analyses of OS and other patient outcomes. However, the direction and extent of the biases are difficult to predict.

Standard first line therapies for patients with MBC may include treatment with pertuzumab in combination with trastuzumab and taxane followed by pertuzumab plus trastuzumab. Second line therapies for these patients may then include T-DM1. Eligibility criteria in the HER2CLIMB trial specified that all patients must have had prior treatment with trastuzumab, pertuzumab, and T-DM1. Therefore, the patient population of patients in the HER2CLIMB trial is likely reflective of patients in the Canadian population and treatment algorithms standard in Canadian clinical practice. Prior treatment with trastuzumab, T-DM1 and pertuzumab were not required to have specifically been in the metastatic setting; although, most patients did receive each agent in the metastatic setting, with some patients receiving it in both the neoadjuvant/adjuvant and metastatic setting, and few patients receiving prior therapy in the neoadjuvant/adjuvant setting only. The sponsor noted that the treatment landscape for HER2-positive breast cancer patient has changed drastically since completion of patient enrollment for the HER2CLIMB trial. During patient enrollment, T-DM1 was approved for and used only in the metastatic setting; however, since completion of patient enrollment, T-DM1 has been approved for use in the adjuvant setting. Almost all patients in the HER2CLIMB trial (>98%) reported having received prior therapy with T-DM1 in the metastatic setting only. It is expected that a greater proportion of patients in clinical practice will have received prior therapy with T-DM1 in other treatment settings as well.

In the Health Canada approved product monograph, tucatinib in combination with trastuzumab and capecitabine is indicated for patients who have received at least one prior HER2-directed therapy in the metastatic setting. The treatment landscape for patients with MBC is complex and has changed to include new HER2-directed treatments, such as pertuzumab and T-DM1. Patients in the HER2CLIMB trial reported having received a mean of three prior therapies in the metastatic setting, and the sponsor confirmed that every patient in the HER2CLIMB trial received at least one prior therapy in the metastatic setting. Therefore, it was considered appropriate that, given the changes to the treatment landscape for this setting and the characteristics of patients in the HER2CLIMB trial, treatment with tucatinib in combination with trastuzumab and capecitabine be used for patients who received at least one HER2-targeted therapy in the metastatic setting.

The HER2CLIMB trial eligibility criteria required patients to have prior treatment with trastuzumab, pertuzumab, and T-DM1, alone or in combination, and most patients (>90%) reported having received each treatment. The median and mean number of therapies used among patients in the HER2CLIMB trial was four, with most patients having received trastuzumab, pertuzumab, and T-DM1 in either the metastatic setting or in the metastatic and neoadjuvant/adjuvant setting. Therefore, patients would have received tucatinib-combination therapy in the second- or later-line setting. It may be unreasonable to suggest using tucatinib-combination therapy as a first line treatment option for patients with MBC as there is no evidence to support the use of this treatment in this context. Input received from the clinical expert consulted by CADTH and the Canadian clinician groups providing input on this submission suggest that tucatinib-combination therapy would most likely be used as a third-line therapy.

Indirect Comparisons

Description of studies

The sponsor-submitted indirect treatment comparison (ITC) compared the efficacy of tucatinib in combination with trastuzumab and capecitabine to relevant comparators, including lapatinib plus capecitabine, margetuximab plus capecitabine, neratinib, neratinib plus capecitabine, pertuzumab plus trastuzumab and capecitabine, trastuzumab plus capecitabine, capecitabine, T-DM1, and T-DM1

plus capecitabine, among patients with HER2-positive MBC who had received at least one prior therapy. The ITC was conducted using a network metanalysis (NMA) that included 14 phase II and III trials identified by a systematic literature search.

Efficacy Results

Regarding PFS, the NMA results suggested that tucatinib-combination treatment was favoured compared to capecitabine monotherapy (HR = 0.33, 95% credible interval [CrI]: 0.23 to 0.47; p<0.0001), neratinib (HR = 0.47, 95% CrI: 0.30 to 0.71; p = 0.0007), lapatinib plus capecitabine (HR = 0.55, 95% CrI, 0.40 to 0.76; p = 0.0003), trastuzumab plus capecitabine (HR = 0.53, 95% CrI: 0.42 to 0.68; p<0.0001), and pertuzumab plus trastuzumab plus capecitabine (HR = 0.65, 95% CrI: 0.47 to 0.90; p= 0.0110). No differences were shown between the tucatinib combination and margetuxumab plus capecitabine, neratinib plus capecitabine, T-DM1, and T-DM1 plus capecitabine.

Regarding OS, the NMA results suggested that the tucatinib-combination treatment was favoured compared to capecitabine monotherapy (HR = 0.45, 95% CrI: 0.27 to 0.77; p<0.0017), neratinib (HR = 0.47, 95% CrI: 0.27 to 0.80; p = 0.0073), lapatinib plus capecitabine (HR = 0.59, 95% CrI, 0.41 to 0.83; p = 0.0030), and trastuzumab plus capecitabine (HR = 0.66, 95% CrI: 0.50 to 0.88; p=0.0040). No differences were shown between the tucatinib combination and margetuxumab plus capecitabine, neratinib plus capecitabine, pertuzumab plus trastuzumab plus capecitabine, and T-DM1.

Regarding ORR, the tucatinib-combination therapy was favoured over capecitabine (HR = 0.90, 95% CrI: 0.48 to 1.31; p<0.0001), neratinib (HR = 0.82, 95% CrI: 0.29 to 1.33; p=0.0010), and trastuzumab plus capecitabine (HR = 0.39, 95% CrI: 0.18 to 0.60; p=0.003). There were no differences between tucatinib-combination therapy and lapatinib plus capecitabine, neratinib plus capecitabine, pertuzumab plus trastuzumab plus capecitabine, T-DM1, and T-DM1 plus capecitabine.

Harms Results

No comparisons for harms or safety were incorporated in the sponsor's ITC.

Critical Appraisal

The sponsor's ITC included both phase II and III trials. Some phase II trials were not powered to detect differences between treatment groups which may have affected the precision of treatment estimates obtained from those studies. Inclusion of such studies into the sponsor's ITC may have introduced uncertainty into the comparisons within made within the network. Treatment crossover reported in trials is likely to have introduced bias into the comparisons of the ITC, as crossover is likely to have diluted treatment estimates of investigational therapies. In addition, differences in patient characteristics across the studies introduces uncertainty regarding the comparability of patients across trials. For example, patients receiving treatment in later lines of therapy are likely to have worse clinical outcomes as they have already progressed on more therapies than patients in earlier lines. Further, there were differences in patients ECOG PS, hormone receptor status, and presence of brain metastases. The sponsor's ITC included trials published between 2008 and 2020. Due to changes in treatment paradigms for HER2-positive MBC, it is highly likely that patients across studies are not comparable due to the changing treatment landscapes which would have affected overall patient outcomes over time. There were some methodological limitations, as some trials reported violation of the proportional hazard assumption and there was a lack of available data to incorporate relevant effect modifiers.

Other Relevant Evidence

Results of exploratory analyses of intracranial efficacy were reported in a subgroup of patients with brain metastases from the pivotal HER2CLIMB study. Patients with brain metastases, were classified as follows:

- Treated and stable (prior local treatment and no evidence of progression at baseline brain MRI, including patients treated during the screening period)
- Treated and progressing (prior local treatment but evidence of progression of existing lesions, new lesions, or untreated lesions remaining after prior treatment at baseline brain MRI)
- Untreated (no prior local treatment)

A total of 198 patients randomized to the tucatinib-combination group and 93 patients randomized to the placebo-combination group had brain metastases. The interventions have been previously described for the HER2CLIMB study. Treatment with dexamethasone

(up to 2 mg per day) was permitted to control symptoms of brain metastases. The majority of patients were older than 65 years (83.5%), 60.8% resided in North America, and 93.9% had non-CNS metastatic disease. Regarding ECOG PS, 44.7% of patients had a score of 0 and 55.3% had a score of 1, and 57.0% of patients were hormone receptor positive. The brain metastasis treatment status at baseline was treated and stable, treated and progressing, or untreated for 40.2%, 37.1%, and 22.7% of patients, respectively. Most patients (70.1%) had prior radiation therapy for brain metastases, 41.9% had WBRT, 42.6% had targeted radiation therapy, and 15.8% had surgery.

The treatment groups were well balanced by baseline characteristics with the exception of the proportion of patients that were hormone receptor positive (54.0% tucatinib-combination group vs. 63.4% placebo-combination group), patients with an ECOG PS score of 1 (53.5% tucatinib-combination group vs. 59.1% placebo-combination group), history of prior targeted radiation therapy (46.5% tucatinib-combination group vs. 34.4% placebo-combination group).

Efficacy Results

For patients treated in the tucatinib-combination group, 40.2% (95% CI: 29.5 to 50.6) of patients with brain metastases, 35.0% (95% CI: 23.2 to 47.0) of patients with active brain metastases, and 53.3% (95% CI: 31.4 to 71.0) of patients with stable brain metastases had CNS-PFS at one year. None of the patients receiving the placebo-combination had CNS-PFS at one year. A hazard ratio of 0.32 (95% CI: 0.22 to 0.48) was reported for the tucatinib-combination group compared to the placebo-combination group in all patients with brain metastases. Similar results were reported for patients with active brain metastases (hazard ratio of 0.36, 95% CI: 0.22 to 0.57) and patients with stable brain metastases (hazard ratio of 0.31, 95% CI: 0.14 to 0.67).

Among all patients with brain metastases, 1-year OS was reported for 70.1% (95% CI: 62.1 to 76.7) of patients in the tucatinib-combination treatment group and 46.7% (95% CI: 33.9 to 58.4) of patients in the placebo-combination treatment group. For patients with active brain metastases, 1-year OS was reported for 71.7% (95% CI: 61.4 to 79.7) and 41.1% (95% CI: 25.5 to 56.1) of patients randomized to the tucatinib- and placebo-combination groups, respectively. For patients with stable brain metastases, 1-year OS was reported for 67.6% (95% CI: 53.8 to 78.0) and 55.6% (95% CI: 34.1 to 72.6) of patients randomized to the tucatinib- and placebo-combination groups, respectively. This data for 1-year OS corresponded to a hazard ratio of 0.58 (95% CI: 0.40 to 0.85) for all patients with brain metastases, 0.49 (95% CI: 0.30 to 0.80) for patients with active brain metastases, and 0.88 (95% CI: 0.45 to 1.70) for patients with stable brain metastases.

Intracranial response was also reported for patients with active brain metastases and measurable intracranial lesions at baseline.

Harms Results

Safety outcomes were not reported for the subgroup of patients with brain metastases.

Critical Appraisal

Information about reasons for or timing of discontinuation from treatment was not available in the intracranial efficacy subgroup analyses report. The proportion of patients that were hormone receptor positive and that had a history of prior targeted radiation therapy was greater in the tucatinib treatment group, which may bias the results for PFS and OS against tucatinib. Additionally, a greater proportion of patients had received prior targeted radiation therapy in the tucatinib treatment group, which may also indicate bias against tucatinib. The analyses were exploratory, and the statistical tests could not be interpreted as statistically significant. Lastly, CNS target lesions were assessed by the investigator and not externally validated. Issues of generalizability for the overall HER2CLIMB study also apply to the exploratory analyses described here. This study or exploratory analysis was specific to patients with brain lesions, which were identified using MRI and is consistent with Canadian clinical practice. Trastuzumab was available for administration intravenously or subcutaneously; however, the available evidence (published article) did not provide this level of detail for patients in the post-hoc analyses.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adults with locally advanced unresectable or metastatic HER2+ breast cancer who have received prior treatment with trastuzumab, pertuzumab, and T-DM1, separately or in combination.
Treatment	Tucatinib in combination with trastuzumab + capecitabine (Tucatinib combination therapy)
Submitted price	Tucatinib, 50 mg: $60.17 per tablet Tucatinib, 150 mg: $119.50 per tablet
Treatment price	First 21-day cycle: $10,038 for tucatinib, $12,216 in combination Subsequent 21-day cycles: $10,038 for tucatinib, $11,710 in combination
Comparators	• trastuzumab + capecitabine • lapatinib + capecitabine • capecitabine monotherapy • trastuzumab emtansine (T-DM1)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (10 years)
Key data source	HER2CLIMB trial and network meta-analysis
Submitted results	• Based on the sequential analysis, the four optimal treatments (i.e., on the frontier) are capecitabine monotherapy, trastuzumab + capecitabine, T-DM1, and tucatinib + trastuzumab + capecitabine. • The sequential ICER for tucatinib + trastuzumab + capecitabine was $245,096 per QALY compared to T-DM1 (incremental costs: $42,960, incremental QALYs: 0.18).
Key limitations	• The magnitude of benefit of tucatinib-combination therapy compared to included comparators is uncertain owing to the limitations of the sponsor-submitted ITC including the limited number of studies informing the comparisons within the network, considerable heterogeneity between trials, and limitations in the methods of analyses. • The sponsor's selected overall survival (OS) curve for trastuzumab with capecitabine, and consequently, the OS curves for comparator agents (including tucatinib-combination therapy) were an overestimation of the underlying survival estimates for the indicated patient population according to the clinical experts consulted by CADTH. This likely resulted in an overestimation of the incremental OS benefit associated with tucatinib-combination therapy relative to the included comparators. • The sponsor's model did not include relevant comparators in the third-line setting (e.g., neratinib with capecitabine, trastuzumab with endocrine therapy, and endocrine therapy alone) owing to the lack of comparative clinical efficacy and safety. • The comparators included in the sponsor's model were not differentiated based on the line of therapy which has implications on the interpretation on the cost-effectiveness of tucatinib-combination therapy. • According to feedback from the clinical experts consulted by CADTH, the relative dose intensity (RDI) used to calculate drug costs for trastuzumab was thought to be an underestimate. Additionally, the sponsor inappropriately applied an RDI for drugs administered orally. These assumptions led to an underestimate of the incremental costs associated with tucatinib-combination therapy when compared to other agents. • The sponsor's model included progressively higher progression-free health state utility values depending on the treatment cycle received by patients (i.e., separate utility values for cycles 1-2, 3-4, 5-6, 7+). Consequently, patients remaining in the progression-free health state would accrue a greater number of QALYs, which led to an overestimate of the incremental QALYs associated with tucatinib-combination therapy relative to comparator agents.

Component	Description
	• The CADTH reanalysis could not be run fully probabilistically with an alternate OS curve selection (i.e., CADTH could not retain the variability in the OS curve parameters) due to calculation errors included in the sponsor's model which produced invalid results. CADTH was unable to determine the source of the error due to limited transparency with the sponsor's model programming.
CADTH reanalysis results	• CADTH undertook a reanalysis to address the limitations in the sponsor's submission, including: the use of an alternative overall survival curve for trastuzumab and capecitabine; efficacy data from the HER2CLIMB trial for tucatinib-combination therapy; 100% RDI for trastuzumab in cycles ≥2 and drugs administered orally; the same progression-free health state utility value regardless of treatment cycle number; and, presenting the results for tucatinib-combination therapy according to its use in the second- and third-line setting. ○ In the second line setting, tucatinib-combination therapy was associated with an ICER of $512,403 per QALY compared to T-DM1 (incr. costs, $59,163; incr. QALYs, 0.12). ○ In the third line setting, tucatinib-combination therapy was associated with an ICER of $381,429 per QALY compared to trastuzumab with capecitabine (incr. costs, $119,950; incr. QALYs, 0.31) • At a WTP threshold of $50,000 per QALY, tucatinib-combination therapy has a 0% chance of being cost-effective in both the second line and third line settings. A price reduction of at least 48% for the second and 94% for third-line setting is required for tucatinib-combination therapy to be cost-effective at $50,000 per QALY. • The cost-effectiveness of tucatinib-combination therapy relative to other relevant comparators and according to the presence of brain metastasis is unknown.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: uncertainty associated with the exclusion of relevant comparators, the inclusion of comparators that may not be funded in most jurisdictions, uncertain estimates for the derivation of the eligible patient population and an underestimate of market share estimates for tucatinib in the third line treatment setting.

CADTH revised the mean treatment durations assumed for tucatinib-combination therapy and trastuzumab with capecitabine to align with the pharmacoeconomic evaluation, increased the percentage of patients assumed to have HER2+ breast cancer, and increased the market share assumptions for tucatinib for Years 1 to 3. In the CADTH reanalysis, the estimated budget impact for tucatinib-combination therapy was $64,395,873 in Year 1, $80,786,751 in Year 2, and $99,110,926 in Year 3, for a three-year expected total budget impact of $244,293,549.

The majority of the budget impact (98% to 99%) in the CADTH base case and across all scenario analyses is driven by the use of tucatinib in the third line setting. The price of tucatinib, market share estimates, and percentage of patients eligible for tucatinib are key drivers of the results. Changes to the eligible population size, including assumptions related to public coverage may make the budget impact even larger.

pCODR Expert Review Committee (pERC) Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting Date: September 8, 2021

Regrets

None

Conflicts of Interest

None