Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

capivasertib (Truqap)

(AstraZeneca Canada Inc.)

Indication: For the treatment of adult females with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Note: Due an administrative error, the patient input submission from Breast Cancer Canada was mistakenly omitted from the review and is not reflected in the review reports or the recommendation document. Canada's Drug Agency appreciates the effort required to compile patient group input. The input from Breast Cancer Canada is included in this summary document to ensure that their contributions to the reimbursement review process are reflected in final documentation and their valuable input is available to our health system partners and other interested parties.

February 26, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CDA-AMC and do not necessarily represent or reflect the views of CDA-AMC. No endorsement by CDA-AMC is intended or should be inferred.

By filing with CDA-AMC, the submitting organization or individual agrees to the full disclosure of the information. CDA-AMC does not edit the content of the submissions received.

CDA-AMC does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the

CADTH

CADTH Reimbursement Review

Patient Input for CADTH Reimbursement Reviews

CADTH Project Number: PC0341-000
Name of Drug: Capivasertib (TRUQAP™)
Indication: TRUQAP™ (capivasertib tablets), in combination with fulvestrant, is indicated for the treatment of adult females with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.
Name of Patient Groups: Breast Cancer Canada and McPeak-Sirois Group for Clinical Research in Breast Cancer
Author of Submission: Kimberly Carson, CEO Breast Cancer Canada

1. About Your Patient Group

Breast Cancer Canada's (BCC) commitment is to save lives through breast cancer research and its outcomes. For the last three decades, you've known us as the Breast Cancer Society of Canada. But with a disease that is ever evolving, we have also evolved. We remain the only national organization in Canada laser focused on precision oncology breast cancer research and education because we believe in building on the outstanding progress in therapeutic outcomes that's been made. Breast Cancer Canada encourages precision oncology research and awareness collaboration among physicians and researchers. Our mission drivers are: Diversity by creating a basis of ethnically diverse breast cancer patients in clinical trials; Acceleration by driving Canadian research from the lab directly to the clinic with precision oncology; Innovation by applying research methodology that utilizes emerging technology; Patient leadership by developing Patient Reported Outcomes (PROs) for breast cancer in Canada, and Connection by rapidly expanding the network of research and sharing of data to support design and running of novel Canadian clinical trials.

About - Breast Cancer Canada (breastcancerprogress.ca)

The McPeak-Sirois Group for Clinical Research in Breast Cancer's vision is to bring together the main players in breast cancer clinical research to make research that cares accessible to as many patients as possible. The organization is a private and unique initiative bringing together public health organizations in Quebec. The McPeak-Sirois Group is a charitable organization supported by Susan McPeak, survivor, and Charles Sirois, a renowned entrepreneur and caregiver to his wife. By joining forces, hospitals that are members of the McPeak-Sirois Group ensure that more people affected by breast cancer can access the best treatments available and that valuable practices based on the latest knowledge are shared within the medical community though Research that cares. All actions taken by the Group are focused on the best interest of the Breast Cancer patient. Whether it be in the selection of Member institutions, research protocol selection or the sharing of best practices, based on the most recent knowledge, within the medical community. In just a few years, the McPeak-Sirois Group has become one of the most important breast cancer clinical research consortia in Canada.

McPeak • Sirois – Recherche clinique en cancer du sein (mcpeaksirois.org)

2. Information Gathering

INFORMATION SOURCE: SURVEY TO RECURRENT METASTATIC BREAST CANCER PATIENTS & CAREGIVERS

An electronic survey was distributed from July 6th – 21st, 2023 to patients living with recurrent metastatic breast cancer (MBC) and their caregivers through our Breast Cancer Canada (BCC) and McPeak-Sirois membership communities. The survey responses included 171 personal experiences with treatment in the recurrent metastatic setting, and their financial impact of living with metastatic breast cancer. An additional survey was conducted from Feb 10th – 18th, 2024 that identified five (5) patients with prior treatment experience using Capivasertib in the indication under review.

DEMOGRAPHICS

TABLE 1: Demographics of Participants with recurrent MBC Experience: (July 2023 Survey)

	Western Canada	Eastern Canada	Quebec	International	Not reported	TOTAL	%
Province	MB, SK, AB & BC	NF, NS and ON	n/a	Nigeria, West Africa	n/a	n/a	
Patient #	51	29	9	0	2	91	53.2%
Caregiver #	29	20	1	1	1	52	30.4%
Not specified	10	15	1	0	2	28	16.4%
Total	90	64	11	1	5	171	100.0%
%	52.6%	37.4%	6.4%	0.6%	2.9%	100.0%	

138 participants shared their receptor subtype: 90% (n=124) of MBC respondents have HR+/HER2- and 10% (n=14) have TNBC receptor sub-type. Of these 138 participants,120 shared their current line of systemic therapy for MBC: ~76% (n=91) of MBC respondents are currently second line (2L), ~11% (n=13) are currently third line (3L) and ~13% (n=15) are fourth line or more (4L+).

3. Disease Experience

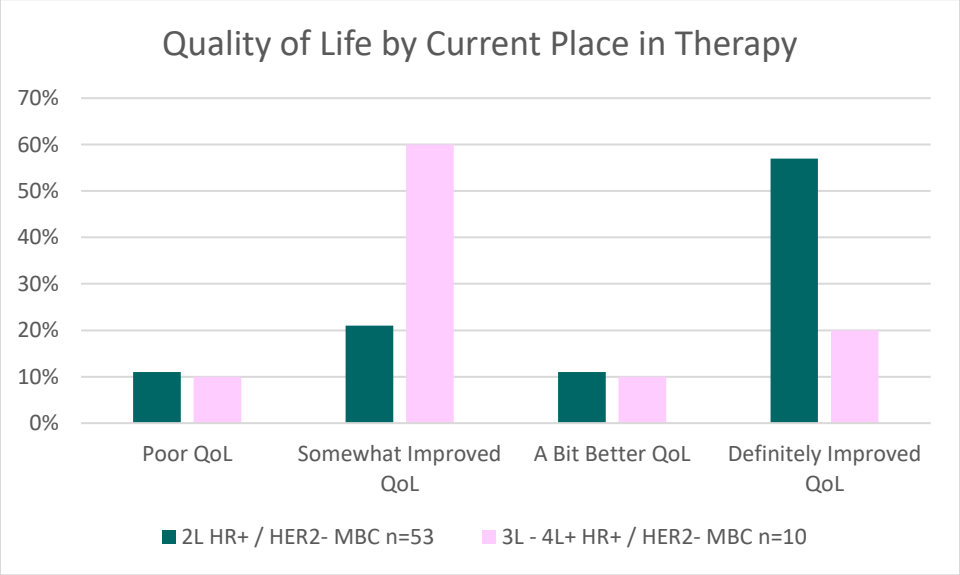
DISEASE / TREATMENT EXPERIENCE AND CURRENT TREATMENT QUALITY OF LIFE AND CANCER CONTROL

With the progress of endocrine therapies and novel CDK4/6 inhibitors in frontline therapy impacting positive overall survival rates[1], patients' disease experience with hormone-receptor positive (HR+), HER-2 negative MBC has significantly evolved. On one hand, new medicine has created HR+ / HER2- MBC as a 'chronic disease' condition and, on the other, has developed new prolonged issues for patients with recurrent, breast cancer following CDK4/6i + endocrine treatment (ET). First, there is a significant unmet need of oral targeted therapy in 2nd and subsequent lines of treatment (2L+) as demonstrated in CADTH Provisional Funding Algorithm (Dec 2023)[2]. Second, MBC patients receiving longer-term therapy are experiencing financial toxicity beyond treatment side effects and cancer symptom burden. We believe our survey explores, for the first time, the HR+/HER2- refractory MBC patient lived experience regarding satisfaction and quality of life with current standard 2L+ systemic therapies, financial burden of long-term advanced breast cancer and the desire for new treatment options that control their chronic disease and extend life.

TABLE 2 HR+/HER2- recurrent MBC respondents' experience with prior hormone and systemic therapy:

# of hormone or chemotherapy lines of therapy (Tx) for MBC	HR+/HER2- MBC		
	# of patients	# of caregivers	Total
Received 2 Lines of Tx	53	16	69
Received 3 Lines of Tx	3	7	10
Received 4 or more Lines of Tx	4	7	11
TOTAL	60	30	90

CHART 3 QOL reported by HR+ / HER2- 2L and 3L/4L+ MBC patient groups:



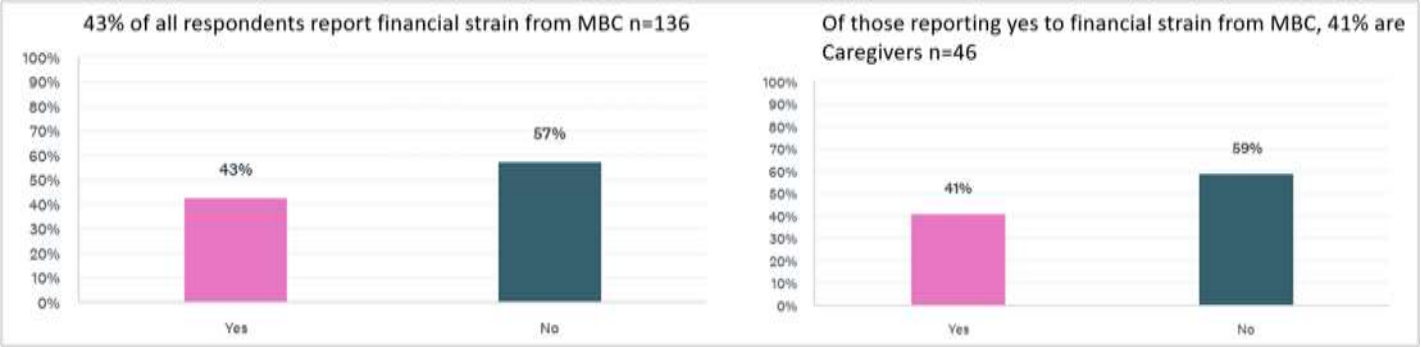
Our July 2023 survey explores Quality of Life (QOL) with two core observations, based on current place in therapy in the HR+ / HER2- MBC patient lived experience (CHART 3). The first showing more completed responses from 2L treated population (n=53 patients compared to 3L / 4L+ treated of n=10 patients), perhaps due to general health well-being for heavily pre-treated MBC patients given the second observation of higher Quality of Life scores between the groups. 57% of 2L treated responders report a 'Definite Improvement' in QOL compared to 60% of 3L/4L+ respondents reporting only 'Somewhat of a QOL Improvement' while on current systemic therapy. Extended QOL in recurrent lines of therapy is of high value to MBC patients. There is an unmet need for improvement in QOL for 3L/4L+ MBC responding patients, and those who have progressive disease after CDK4/6i+ET.

FINANCIAL IMPACT OF LONG-TERM METASTATIC BREAST CANCER

In a recent 2023 systematic review and meta-analysis by Ehsan et al.[3] the "pooled rate of financial toxicity for patients with breast cancer was 78.8% in low- and middle-income countries and 35.3% in high-income countries" "these findings suggest that patients with breast cancer worldwide are at risk for financial toxicity". Living with chronic long-term breast cancer has been an achievement compared to 20 to 25 years ago with 5-year survival rates much higher. However, treatment is constant and ongoing with a majority of MBC patients without private 3rd party insurance making the financial burden of treatment, supportive therapies and compounded

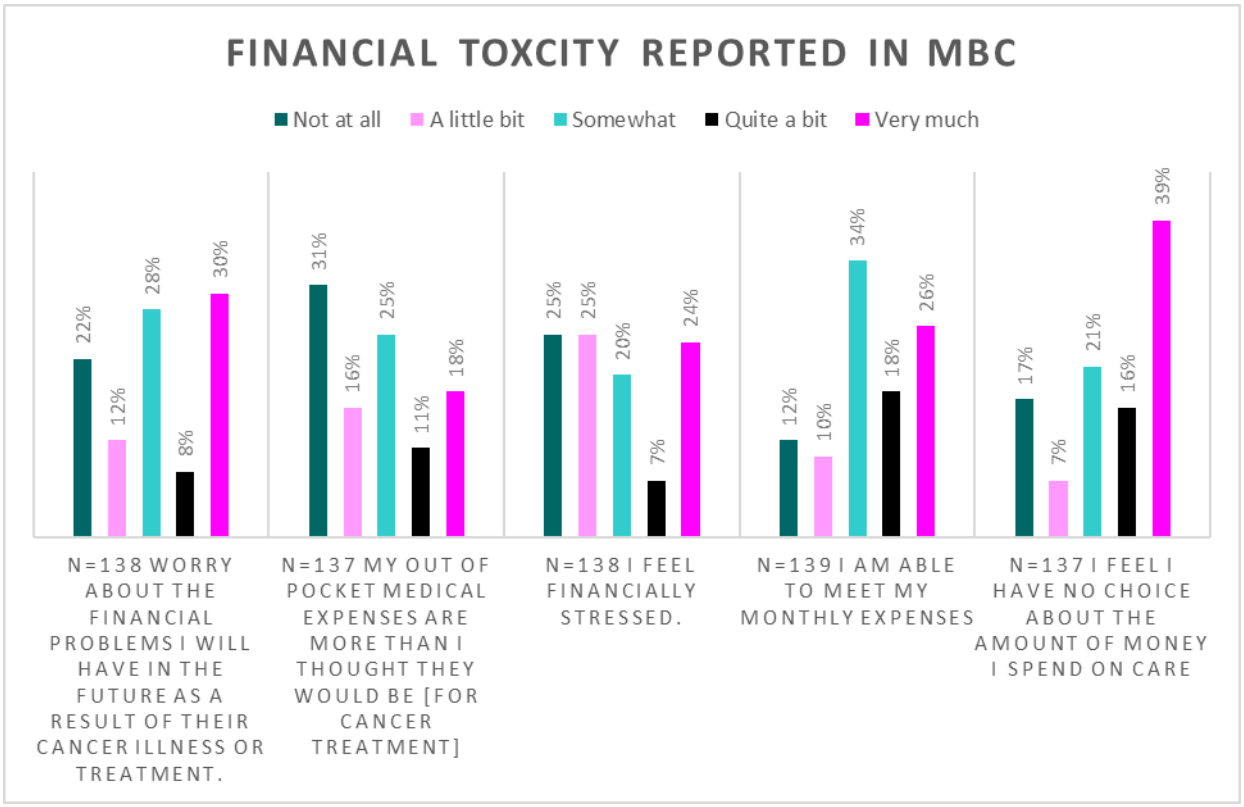
years of reduced income, a particular concern for today's MBC patient in Canada. Our survey included a focus on financial toxicity in the recurrent MBC patient lived experience, with the inclusion of the COST-FACIT PRO[4] questionnaire and other financial-status questions. Within this long-term treated population, and their surviving caregivers left with a financial debt, there is financial vulnerability that should be factored into timely public funding decisions of new treatment access for recurrent MBC.

CHART 4: Reported financial strain as a result of MBC.



Access to treatment in multi-recurrent MBC should not add to financial toxicity for either MBC patient or surviving caregiver in Canada. As demonstrated in Chart 4, 43% of all responders reported having financial strain because of MBC. 41% of caregiver respondents reported having ongoing financial hardship related to breast cancer either from living on single income, reduced retirement funds and/or medical costs after their loved one has passed. When considering length of curative multi-disciplinary treatment for adjuvant breast cancer management (majority of patients), and then the added toll of recurrent therapies for metastatic disease, this particular MBC population experiences some of the longest-term years of cancer-related costs and financial burden.

CHART 5: The impact of MBC disease on financial burden for patients and their caregivers



As shown in Chart 5, over half of the 137 respondents (54%, n= 74) felt that their out-of-pocket medical expenses are more than expected with ratings of ‘Very much’, ‘Quite a bit’ or ‘Somewhat’.

Of n=138 respondents, 66% (n=91) indicated that they worry about financial problems in the future because of their cancer illness or treatment. 76% (n=105) feel some degree of financial stress related to their MBC.

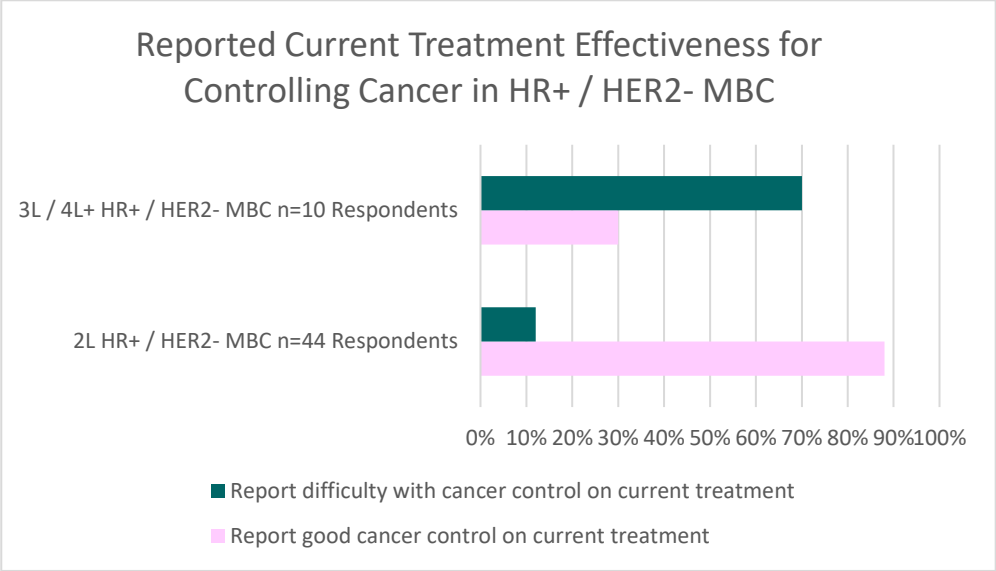
Of n=139 respondents, 56% (n=78) report they are ‘Somewhat’, ‘A little bit’ or ‘Not at all’ able to meet their monthly expenses. Even of those patients and caregivers that had responded to low concerns about financial toxicity, more had indicated that they felt they had no choice about the amount of money spent on care.

These patient-reported financial toxicity outcomes demonstrate a high vulnerability in this chronic population who have felt required to pay out of pocket medical expenses over the long-term. We would put the case forward that compared to other tumor types, MBC patients are more financially vulnerable given that the majority are diagnosed in early stage and then recur, requiring medical expenses over a longer period of their lifetime, and that of the surviving caregiver.

4. Experiences With Currently Available Treatments

Fifty-four (54) patients with HR+/HER2- treated MBC, commented on their satisfaction of treatment on cancer control in their current place in therapy (Chart 6). Patients on 2L treatment report better cancer control compared to the treatment that patients are receiving in 3L or 4L. In addition, 60% of them experienced one (1) to six (6) months of stable disease duration and describe their quality of life with current line of treatment as relatively poor. Drug therapies reported in 3L / 4L+ HR+ / HER2- groups include capecitabine, endocrine-based +/- CDK4/6i, docetaxel and ENHERTU. It is clear that CDK4/6i + ET made a positive impact for patients in earlier lines of treatment for MBC. Patients strongly value oral, targeted therapies that provide extended cancer control and meaningful QOL when facing treatment decisions at 2L and beyond.

CHART 6 Lived experience in cancer control for HR+ / HER2- MBC in 2L compared to 3L / 4L+ MBC patients receiving current standard systemic therapy:



5. Improved Outcomes

HR+ / HER2- MBC has become a chronic disease without any significant oral targeted treatment options for patients after recurrence using CDK4/6 inhibitors + ET, when compared to multi-lines of targeted therapy for HER2+ MBC or other tumour types such as EGFR+ or ALK+ non-small cell lung cancer. Sequential use of endocrine therapy in MBC lacks evidence-based overall survival outcomes. Capivasertib (TRUQAPTM) + Fulvestrant (FL) demonstrated superior progression-free and overall survival in the CAPITELLO-291 study5. This breakthrough, practice-changing regimen is a valued opportunity for HR+/HER-2 MBC patients as a targeted therapy treatment plan to sequence CDK4/6i + ET followed by Capivasertib + FL at disease recurrence. Duration of quality of life, outside of diarrhea, was demonstrated to be longer for Capivasertib + FL than the placebo arm in the patient reported outcomes (PROs) for function and cancer symptom control from CAPITELLO-291 study[6]. These PROs provide an efficacy aspect that is strongly valued and understood by patients in terms of stabilized cancer symptoms, reduced use of pain medication and daily quality living that is not negatively impacted by adding Capivasertib to FL. We note the drug dose reduction, interruption or discontinuation rate for Capivasertib to be <10%, which is a positive finding for the highly treatment-experienced patient and provides overall confidence of QOL when starting a well-tolerated drug.

Our BCC community consistently describes experiencing anxiety when having to return to chemotherapy for recurrent MBC, making oral Capivasertib + FL a meaningful advancement for cancer control, improved function with less clinic interruption in the lives of the HR+/HER2- MBC patients and their caregivers. With a clear unmet need established for the 2L+ HR+/HER2- MBC treatment setting,

clinical outcomes require realistic expectations given the multi-refractory drug experience of patients. Our MBC community is aware of the limitations of treatment in this phase of their cancer journey, and the majority responded in our survey (CHART 7 A-C) that cancer control of 2 or more months longer than current standards is meaningful for extended recurrence time and overall survival while accepting treatment side effects.

CHART 7: Duration of cancer control (A), delay in recurrence (B) and overall life extension (C) of 2 or more months, with treatment side effects taken into consideration.

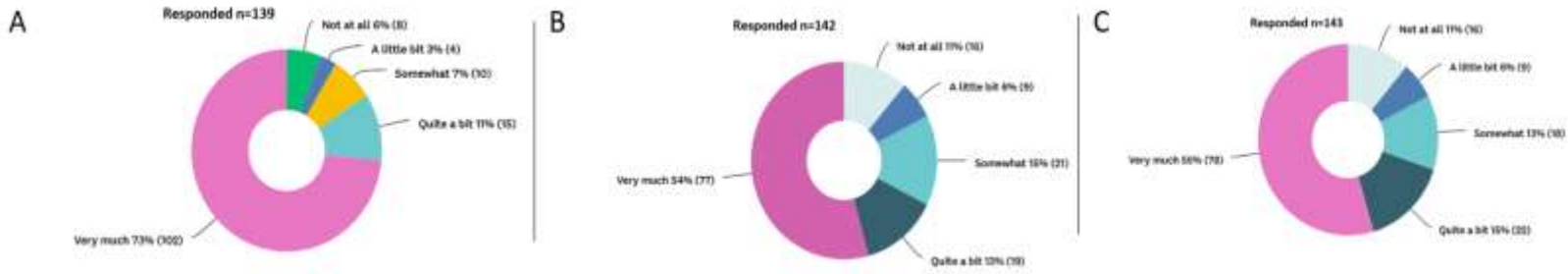
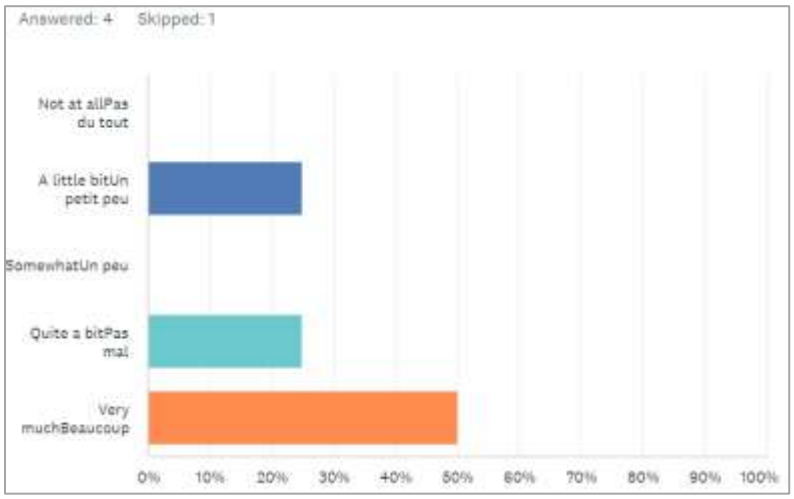


Chart 7A, 7B and 7C show that 2 or more months of additional cancer control is meaningful in 84% (n=117) of respondents, managing treatment side effects is acceptable to live 2 or more months longer than current standard options in 67% (n=96), and living 2 or more months longer than current standard options is important in 70% of respondents (n=100), respectively.

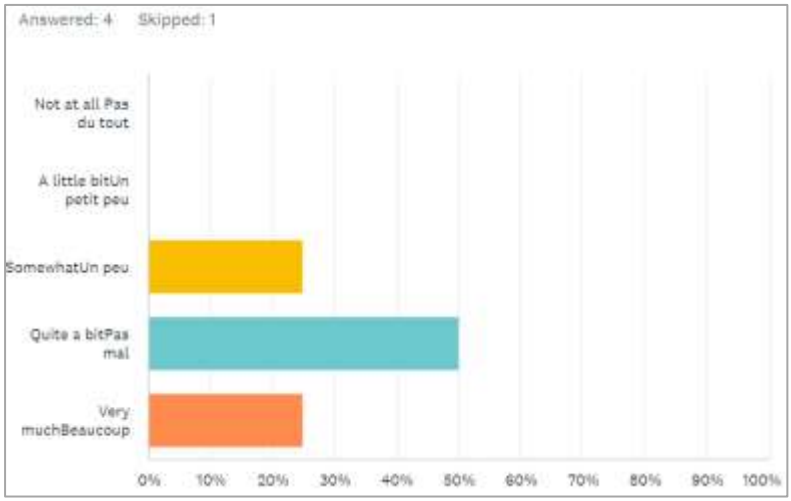
6. Experience With Drug Under Review

Our February 2024 survey identified five (5) patients with Capivasertib lived experience that we presume were part of a clinical trial without the recent Health Canada approval of January 2024[7]. Somatic variants in PIK3CA, APT1 or PTEN were not disclosed by survey responders. In our survey 4 out of the 5 responders describe as very important that the oncologist discusses Capivasertib as a treatment option to consider for their recurrent MBC. Overall, four (4) report satisfaction of cancer control and meaningful (positive) impact on managing the cancer growth or spread, with 3 of 4 Capivasertib-experienced patients describe cancer symptoms were improved to satisfaction for a period of time as “Quite a bit” and “Very much”, with the 4th patient indicating “A little bit” of improvement as seen on Chart 8.

Chart 8 Lived experience on improved cancer control of 4 HR+ / HER2- MBC patients that received Capivasertib therapy:



Charts 9 Lived experience QOL improvement of cancer symptoms of 4 HR+ / HER2- MBC patients that received Capivasertib therapy:



The PROs data reported in CAPItello-291 study indicates most patients were either “not at all” or “a little bit” bothered by adverse events from therapy in the Patient Global Impression of Treatment Tolerability assessment. In our surveys with 2L+ HR+/HER2- MBC patients lived experience, this would be consistent with the study, with none of the 4 Capivasertib-experienced patients reporting negative impact on QOL. These patients also expressed drug treatment adverse events such as diarrhea, nausea and rash were manageable. Overall, four (4) reported improvements in QOL regarding MBC symptoms such as pain, low energy, lack of appetite while taking Capivasertib drug therapy, as seen in Chart 9. Patients rated their confidence that Capivasertib treatment side effects can be well-managed with their oncologist recommendations. 1 of 4 patients required a dose reduction while the other 3 reported maintaining full dose of therapy. We note from the CAPItello-291 study that treatment side effects mainly impact PROs during the first 2-cycles, and these insights would be reassuring to patients when starting Capivasertib + FL.

7. Companion Diagnostic Test

With the breakthrough survival evidence of novel targeted therapy Capivasertib for HR+/HER2- MBC patients with PIK3CA, APT1 or PTEN variants, BCC and MPSG advocate for public funded, equitable access of upfront routine and timely multigene molecular staging for MBC patients as standard of care in Canada.

With more than 30 molecular subclasses of breast cancer reported[9], comprehensive somatic testing informs precision clinical decisions for commercialized on or off-label gene-target therapeutics and equitable access to clinical trials with novel treatments. Therefore BCC - MPSG strongly align with the Canadian[1] (2023) and International clinical guideline recommendations from ASCO[10] (2022) and ESMO[11] (2021) that genomic somatic testing be adopted in HR+/HER2- MBC as standard of care using next generation sequencing with a multigene panel. Furthermore, we support the recommendations for Canada’s “readiness” to provide optimal comprehensive genomic testing[12] (2023).

8. Anything Else?

We note the exclusion of males in Health Canada’s approved indication for Capivasertib + Fulvestrant (FL). This gender inequity occurs in most breast cancer clinical trials due to the low rate of incidence of male breast cancer. However, incidence of male breast cancer is reported in Canada[8] and routine practice in Canada applies evidence-based therapies across all adult MBC patients regardless of gender. In this CADTH review, we strongly advocate the inclusion of adult males and females with HR+ / HER2- MBC following progression on at least one endocrine-based regimen or recurrence on or within 12 months of completing adjuvant therapy, for funded access eligibility to Capivasertib + FL.

The results of CAPItello-291 using novel Capivasertib + FL is a significant advance in precision medicine with extended and meaningful survival that BCC – MPSG are very eager for HR+ / HER2- MBC patients to have timely access in Canada.

References:

1. Jerzak K, Bouganim N, Brezden-Masley C, et al. HR+/HER2– Advanced Breast Cancer Treatment in the First-Line Setting: Expert Review. *Curr Oncol*. 2023;30(6):5425-5447. doi:10.3390/curroncol30060411

2. CADTH Reimbursement Review: Provisional Funding Algorithm. HR+ HER2- Breast Cancer and Triple Negative Breast Cancer, with inclusion of HER2 Low Breast Cancer. Published December 2023. Accessed February 20, 2024. https://www.cadth.ca/hr-her2-breast-cancer-and-triple-negative-breast-cancer-inclusion-her2-low-breast-cancer

3. . Ehsan AN, Wu CA, Minasian A, Singh T, Bass M, Pace L, Ibbotson GC, Bempong-Ahun N, Pusic A, Scott JW, Mekary RA, Ranganathan K. Financial Toxicity Among Patients With Breast Cancer Worldwide, A Systematic Review and Meta-analysis. JAMA Netw Open. 2023 Feb 1;6(2):e2255388. doi:10.1001/jamanetworkopen.2022.55388

4. de Souza J.A., Yap B.J., Wroblewski K., Blinder V., Araújo F.S., Hlubocky F.J., Nicholas L.H., O'Connor J.M., Brockstein B., Ratain M.J., Daugherty C.K., Cella D. Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the COmprehensive Score for financial Toxicity (COST). Cancer 2017 Feb 1;123(3):476-484. doi: 10.1002/cncr.30369.

5. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2023;388(22):2058-2070. doi:10.1056/NEJMoa2214131

6. Rugo H, Oliveira M, Howell S, et al. Patient-reported outcomes from the Phase 3 CAPItello-291 trial investigating capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR-positive/HER2-negative advanced breast cancer. Presented at: San Antonio Breast Cancer Conference; December 5-9, 2023; San Antonio, TX. Abstract PS02-02.

7. AstraZeneca Canada Inc. TRUQAP Product Monograph. Date of Approval: January 26, 2024. Accessed February 9, 2024. https://health-products.canada.ca/dpd-bdpp/info?lang=eng&code=103334

8. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2023. Canadian Cancer Society. Published 2023. https://cancer.ca/en/research/cancer-statistics

9. Bartlett, JMS., Parelukar, W. Breast cancers are rare diseases—and must be treated as such. NPJ Breast Cancer. 2017; 3: 11. Published online 2017 Apr 11. doi: 10.1038/s41523-017-0013-y

10. Chakravarty,D., Johnson, A., Sklar, J. MD, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. Journal of Clinical Oncology Volume 40, Number 11 Feb 17, 2022. https://doi.org/10.1200/JCO.21.02767

11. A. Gennari, F. André, C.H. Barrios et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. October 19, 2021DOI:https://doi.org/10.1016/j.annonc.2021.09.019

12. Husereau, D., Villalba, E., Muthu, V. et al. Progress toward Health System Readiness for Genome-Based Testing in Canada. Curr. Oncol. 2023, 30(6), 5379-5394; https://doi.org/10.3390/curroncol30060408

Appendix: Patient Group Conflict of Interest Declaration

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No outside help used.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No outside help used.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BCC - Gilead Sciences Canada				x
BCC – AstraZeneca Canada				x
BCC – Novartis Canada				x
BCC – Lilly Canada				x
MPSG – Pfizer Canada				x
MPSG – Lilly Canada				x
MPSG – AstraZeneca Canada				x
MPSG – Gilead Sciences Canada				x
MPSG – Seagen Canada				x
MPSG – Novartis Canada				x
MPSG – Merck Canada				x

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Kimberly Carson
Position: CEO
Patient Group: Breast Cancer Canada
Date: February 23, 2024

CADTH

CADTH Reimbursement Review
Patient Input

Name of the Drug and Indication	Capivasertib for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.
Name of the Patient Group	Canadian Breast Cancer Network
Author of the Submission	JK Harris
Name of the Primary Contact for This Submission	JK Harris
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

The Canadian Breast Cancer Network (CBCN) is a leading, patient-directed, national health charity committed to ensuring the best quality of care for all Canadians affected by breast cancer through the promotion of information, education and advocacy activities. www.cbcn.ca

As a member of the Canadian Cancer Action Network, the Canadian Breast Cancer Network is committed to adhering to the Code of Conduct Governing Corporate Funding.

2. Information Gathering

Information for this submission was collected via:

CBCN's 2022 Triple Negative Breast Cancer Patient Survey: An online survey conducted by the Canadian Breast Cancer Network was distributed to patients living with breast cancer. 981 people completed the English-only survey, of whom 31 had metastatic HR-positive, HER2-negative breast cancer. Survey questions comprised of a combination of scoring options and free form commentary. Patients were contacted through the membership databases of CBCN and other patient organizations.

Patients reported that they lived in the following provinces:

- 26% from Ontario.
- 23% from Alberta.
- 16% from Quebec.
- 16% from British Columbia.

- 19% were from Nova Scotia (1 patient), Newfoundland and Labrador (3 patients), and Saskatchewan (2 patients).

They also reported on their age at the time of the survey, and first language:

- 10% spoke a first language other than English; two patients spoke French as a first language, and one spoke Italian as a first language.
- 23% were between the ages of 40-50.
- 42% were between the ages of 51-60.
- 19% were between the ages of 61-70.
- Only 1 patient (3%) was older than 70, and none were younger than 40.

CBCN's 2017 Metastatic Breast Cancer Patient Survey: An online survey conducted by the Canadian Breast Cancer Network, distributed to patients living with metastatic breast cancer. 180 metastatic patients participated in the survey, of whom 38 had metastatic HR-positive, HER2-negative breast cancer. Survey questions comprised of a combination of scoring options and free form commentary. Patients were contacted through the membership databases of CBCN and other patient organizations.

Patients reported that they lived in the following provinces:

- 47% were from Ontario.
- 24% were from British Columbia, Quebec and Saskatchewan (3 patients from each province).
- 11% were from Alberta and Manitoba (2 patients from each province).
- 5% were from Newfoundland/Labrador and Nova Scotia (1 patient from each province).
- 13% did not report which province they lived in.

They also reported on their age at the time of the survey, and first language:

- 8% spoke a first language other than English; two patients spoke French as a first language, and one spoke German as a first language.
- 15% were between the ages of 30-40.
- 21% were between the ages or 41-50.
- 32% were between the ages of 51-60.
- 13% were between the ages of 61-70.
- Only 1 patient (>3%) was older than 70, and none were younger than 30.

CBCN's 2012 Metastatic Breast Cancer Patient and Caregiver Survey Report: An online survey, conducted in collaboration with ReThink Breast Cancer, was distributed to patients living with metastatic breast cancer and their caregivers. Survey questions comprised of a combination of scoring options and free form commentary. 71 patients and 16 caregivers were contacted through the membership databases of CBCN and other patient organizations. Although older than 10 years, CBCN believes these findings remain relevant because the principal

concerns of metastatic breast cancer patients expressed at that time remains relevant, demonstrating both the historical and persistent needs of this group.

Key informant interviews: CBCN was not able to speak with patients taking capivasertib for the treatment of HR-positive, HER2-negative metastatic breast cancer.

Printed sources: A review was conducted of current studies and grey literature to identify issues and experiences that are commonly shared among many women living with breast cancer.

3. Disease Experience

Metastatic breast cancer is the spread of cancerous cell growth to areas of the body other than where the cancer first formed, and is more severe than cancer that has not spread. It is most commonly spread to the bones, but can also spread to the lungs, liver, brain and skin. In our 2017 Survey, the majority of the HR-positive, HER2-negative metastatic breast cancer patients respondents experienced metastases to their bones, liver and lungs, with 33 respondents reporting metastases to their bones.

Current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Patients with a diagnosis of 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.

HR-positive, HER2-negative is a subtype of breast cancer indicated by the presence of both or either of the progesterone and estrogen hormone, but not the HER2 protein. Overexpression of HER2-proteins can drive cell growth, and HER2-positive breast cancer types have more targeted treatment options. For HR-positive, HER2-negative patients, the level of HER2-protiens is not high enough for HER2 targeted therapies to be effective. Currently, CDK4/6 and kinases inhibitors target HR-positive breast cancers, but are associated with greater side effects than hormone therapies[1]. And for patients who do use hormone therapy, these can lose their effectiveness over time. It's estimated that estrogen therapy resistance and disease progression occurs in 50% of patients[2]. As a result, patients with HR-positive, HER2-negative breast cancer must rely more on systemic treatments (such as chemotherapy) which are less effective, and have greater side effects than many targeted therapies[3].

[1] https://pubmed.ncbi.nlm.nih.gov/31065872/

[2] https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.628690/full

[3] https://www.cbcn.ca/en/subtypes_of_breast_cancer

The Physical Impact of Metastatic Breast Cancer

How the disease presents itself through symptoms, how it progresses, and how it is experienced varies by patient, but many effects of metastatic breast cancer represent a significant or debilitating impact on their quality of life.

In our 2012 Metastatic Breast Cancer Patient and Caregiver Survey (2012 Survey), patients were asked what impact cancer-related symptoms had on their quality of life:

- 54% of patients reported that fatigue resulted in a significant or debilitating impact, and 40% reported some or moderate impact.
- 39% of patients reported that insomnia resulted in a significant or debilitating impact, and 46% reported some or moderate impact.
- 37% of patients reported that pain resulted in a significant or debilitating impact, and 44% reported some or moderate impact.

These results were reinforced by our 2017 Metastatic Breast Cancer Patient Survey (2017 Survey).

The Social Impact of Metastatic Breast Cancer

The impact of this disease spreads across all aspects of a patient's life, restricting an individual's employment and career, ability to care for children and dependents, and their ability to be social and meaningfully participate in their community.

When asked in the 2012 Survey what impact living with metastatic breast cancer has had on quality of life, the following was reported:

- Among those who were employed, 71% of patients identified significant restrictions to their ability to work.
- Among those with children or dependents, 21% identified significant restrictions and 53% reported some or moderate restrictions to their caregiving responsibilities.
- 49% of patients identified significant restrictions and 38% identified some or moderate restrictions to their ability to exercise.
- 42% of patients identified significant restrictions and 42% identified some or moderate restrictions to their ability to pursue hobbies and personal interests.
- 41% of patients identified significant restrictions and 41% identified some or moderate restrictions to their ability to participate in social events and activities.
- 22% of patients identified significant restrictions and 52% identified some or moderate restrictions to their ability to spend time with loved ones.

Other experiences identified by patients included: guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of the impact of cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, as well as marital stress/loss of fidelity and affection from husband.

4. Experiences With Currently Available Treatments

The Goals of Current Therapy

The goals of current treatment options for metastatic breast cancer include controlling the progression of the disease (extending life), and reducing cancer-related symptoms (extending or stabilising quality of life). Treatment options and effectiveness vary by type of cancer, location of cancer, and how symptoms are experienced. People diagnosed with HR-positive, HER2-negative metastatic breast cancer have limited targeted treatment options, poor prognosis, and poor survival outcomes.

In our 2022 Survey, most of the HR-positive, HER2-negative metastatic breast cancer patients had received or were currently receiving hormone therapy (28 patients), surgery (25 patients), and radiation therapy (21 patients). Additional treatments included previous or current treatment with chemotherapy (18 patients), and biologics or targeted therapies (19 patients). None of these patients received immunotherapy, and 11 patients received both chemotherapy and biologics or targeted treatments.

Single-agent chemotherapy is the standard treatment beyond first-line and is associated with low response rates and short progression-free survival. As the disease continues to progress and treatment stops responding, individuals must move to additional lines of treatment after progression to metastatic disease or disease recurrence, making additional treatment options important to patients.

Key Factors for Decision-Making Around Treatment

Respondents in our 2017 Survey indicated that the following key factors influenced their decision-making around treatments:

Effectiveness of the treatment – how well the treatment stabilized their disease and delayed progression of their disease.

Prolonged quality of life – being able to maintain productive, active lives with minimal disruption to daily routines.

Side effect management – minimizing risk while stabilizing their disease.

Cost and accessibility of treatments – affordability and ease of accessing treatments.

Effectiveness of the treatment:

In both the 2022 Survey and the 2017 survey, efficacy of treatment was a high priority for patients. The 2022 Survey found that 92% of HR-positive, HER2-negative metastatic breast cancer patients rated how well a therapy works to treat their cancer as important or very important consideration guiding treatment decisions. In the 2017 Survey, here is what HR-positive, HER2-negative metastatic breast cancer patients said about progression free survival (PFS), overall survival (OS), and treatment effectiveness:

- 68% rated treatment effectiveness as the most important factor when making decisions about their treatment.
- 55% indicated that progression-free survival of less than 3 months was important or very important.
- 68% indicated that progression-free survival of 3-5 months was important or very important.
- 89% indicated that progression-free survival of 6 months or longer was important or very important.
- 92 % indicated that overall survival was important or very important.

Anecdotally, metastatic patients in our 2017 Survey spoke on the importance of treatment effectiveness in their decision-making:

> *"The most important factors for me are progression free survival and quality of life."*
>
> *"Anything to prolong my survival and maintain quality of life."*
>
> *"Survival is of upmost importance to me."*

Prolonged quality of life:

In addition to efficacy, quality of life was routinely cited by patients as a key factor in making treatment decisions. In our 2017 Survey, 89% of HR-positive, HER2-negative metastatic breast cancer patients revealed that quality of life was important or very important to them when considering treatment options. More specifically, 87%, 66% and 63% of HR-positive, HER2-negative metastatic breast cancer patients indicated that minimal side effects, productivity, and mobility, respectively, were important or very important considerations when making decisions regarding treatment options.

This concern was reiterated anecdotally:

> *"Making sure I have some quality of life so I can [spend] as much time with my kids and family I don't want them to watch me suffer"*
>
> *"Trying to balance the most effective treatment regime with the least impact on my day to day living/quality of life. Maintaining a certain level of independence is important to me."*
>
> *"Definitely the balance of quality of life vs side effects with the [effectiveness]."*

Side effect management:

In our 2012 Metastatic Patient and Caregiver Survey, participants were asked about the balance between treatment risk and treatment benefit. We asked them to consider the level of side effect and its associated impact on their quality of life that would be worth extending progression-free disease by six months. These were their responses:

- Almost two-thirds of patients indicated that when it comes to 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 when it comes to pain, some or a moderate impact on one's quality of life would be considered acceptable, and 27% of patients indicated that a strong or debilitating impact would be considered acceptable.

In our 2017 Survey, HR-positive, HER2-negative metastatic breast cancer respondents indicated that:

- In exchange for 6 months or less of benefits, pain, fatigue, nausea, insomnia, lack of concentration, memory loss, diarrhea, and hair loss were very acceptable or somewhat acceptable.
- 15 individuals indicated that depression as a symptom in exchange of 6 months or less of benefits from breast cancer treatment was not acceptable while 16 individuals indicated that it would be somewhat acceptable.
- 15 individuals indicated that vomiting not be acceptable.
- 13 individuals indicated that vomiting would be somewhat acceptable.

Cost and accessibility of treatments:

The financial burden associated with advanced 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, metastatic breast cancer patients can incur substantial costs associated with treatment and disease management.

Research on the financial impact of breast cancer on patients identified the following:

- 58% of Black and 34% of while patients reported an adverse financial impact from their cancer.[4]
- 80% of breast cancer patients report a financial impact due to their illness. [5]
- 44% of patients have used their savings, and 27% have taken on debt to cover costs. [6]

[4] https://ascopubs.org/doi/10.1200/JCO.2017.77.6310

[5] Janet Dunbrack, Breast Cancer: Economic Impact and Labour Force Re-entry. Canadian Breast Cancer Network, 2010

[6] Janet Dunbrack, Breast Cancer: Economic Impact and Labour Force Re-entry. Canadian Breast Cancer Network, 2010

These findings were consistent with the responses in our 2012 Survey:

- 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.

In our 2017 Survey, the majority of HR-positive, HER2-negative metastatic patients reported that their diagnosis had some (32%) or a very large (45%) impact on their finances. In addition to this, 42% of HR-positive, HER2-negative metastatic patients indicated that the time required to travel to treatment had some or a significant impact of their quality of life. 63% reported the same in regard to the cost of other treatments (i.e. massage, physiotherapy, etc.) and 53% reported the same in regard to costs associated with travel.

Our 2022 Survey indicated that among HR-positive, HER2-negative metastatic patients:

- 45% were prescribed treatments not covered publicly.
- 61% were prescribed support medication not covered publicly.
- 3% reported that the cost of support medication or treatment medication prevented them from taking the drug.

Other financial barriers that metastatic breast cancer patients mentioned include prescribed cancer treatments not qualifying for insurance through 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."*

> *"Always a concern as you never know if the next drug will be covered or how long it takes to get approval from private coverage. Many times it delays treatment and this weighs on one's mind."*

> *"I wanted to try [immunotherapy], but it is [$]7500.00 every 3 weeks not covered by private insurance, now will probably have to go on chemo again, and the last ones were very hard on me causing toxicity and having to get blood transfusions."*

> *"Just because I am not in the lowest income bracket does not mean I don't need assistance. I am excluded from all programs I have tried to access."*

Patient Access to Local Resources and Supports During Treatment:

When living with cancer, many patients experience significant barriers and challenges around availability of health care services and quality childcare in their community. In response to the 2012 Survey questions about the availability of supports such as childcare, transportation and alternative treatments in their community:

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

Our 2017 Survey found that among HR-positive, HER2-negative metastatic patients with children at the time of their diagnosis:

- 21% indicated that finding appropriate care for their children/dependents when experiencing side effects of cancer treatments was not accessible.
- 23% indicated that finding appropriate care for their children/dependents during cancer treatment was not accessible.
- 13% indicated that finding symptom management options in or around their community was not accessible.

Patient Willingness to Tolerate Risk

All cancer therapies come with some level of risk and side effects. It's important that patients are at the forefront of deciding which side effects are worth the benefits of the given treatment.

When asked in the 2012 Survey about their willingness to tolerate risk with a new treatment:

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

Need for Personal Choice

Open ended question responses demonstrated the imperative for metastatic breast cancer patients to have access to and options regarding what drugs they take. In our 2022 survey, 35% percent of HR-positive, HER2-negative metastatic breast cancer patients expressed being very comfortable in treatment decisions. Most patients are well aware of the adverse effects of treatment up front and they want to make a personal choice that works for them.

Metastatic breast cancer patients expressed the need for personal choice and autonomy in our 2012 Survey, as well as in the 2017 Survey:

"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." – 2012 Survey

"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." – 2012 Survey

"It would be nice to have more choices and more information about them. I was lucky to get on a clinical trial perhaps because my oncologist was a research oncologist and involved in many. While I knew friend and acquaintances that had Stage IV BC and never informed of clinical trials, and sadly several did not survive the disease." – 2017 Survey

"I am frustrated that ALL the treatment choices aren't given to me... I am told what I am taking next with no option or discussion on other options. My oncologist has assured me there are many treatments available, but have never shared which, so I have to turn to Facebook groups for guidance." – 2017 Survey

5. Improved Outcomes

For metastatic patients, extension of progression-free survival (PFS) is of critical concern. Like any other treatment for metastatic breast cancer, patients have an expectation that capivasertib (Truqap) will extend their progression-free survival with good quality of life when recurrence or progression to metastatic disease occurs within 12 months of competing adjuvant therapy.

Among HR-positive, HER2-negative breast cancer patients, it's estimated that between 40-50% of patients have a PIK3CA mutation, which is associated with a greater likelihood of treatment resistance leading to disease progression.[7] Mounting research shows that PI3K/AKT1/MTOR inhibitors can help to overcome drug resistance leading to improved PFS.[8]

The phase 3 CAPItello-291 randomized, double-blind trial compared capivasertib in combination with fulvestrant to placebo with fulvestrant in pre-, peri-, and postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer who had had a relapse or disease progression during or after treatment with an aromatase inhibitor, with or without previous cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy[9].

The results showed that the overall population in the treatment arm had a median of 7.2 month PFS compared with 3.6 months in the placebo–fulvestrant arm. Those with an AKT pathway

[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9633529/

[8] https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.628690/full

[9] https://www.nejm.org/doi/full/10.1056/NEJMoa2214131

alteration experienced a median of 7.3 months of PFS in the treatment arm compared with 3.1 months in the placebo–fulvestrant arm. This means that capivasertib had 3.6 and 4.2 months improved PFS over the placebo–fulvestrant arm in the whole population and AKT pathway altered population respectively. As noted above in the effectiveness of treatment section, 68% of respondents to CBCN's 2017 Survey indicated that progression-free survival of 3-5 months was important or very important, which makes these results a reflection of patient stated values.

Adverse Effects

The phase 3 data from CAPItello-291 showed that the safety profile was manageable. Commonly reported side effects from the capivasertib–fulvestrant arm of any grade were: diarrhea (72.4%), rash (38%), and nausea (34.6%) compared to 20%, 7.1% and 15.4% respectively in the placebo–fulvestrant arm. Commonly reported side effects from capivasertib–fulvestrant verses placebo–fulvestrant of grade 3 or higher were: rash (12.1% vs 0.3%), diarrhea (9.3% vs. 0.3%), hyperglycemia (2.3% vs. 0.3%), stomatitis (2% vs. 0%), and anemia (2% vs. 1.1%). Death due to adverse events occurred in 4 patients (1.1%) receiving capivasertib–fulvestrant and in 1 patient receiving placebo–fulvestrant. None of the deaths were considered by the local investigators to be related to capivasertib or fulvestrant.[10]

Impact of Treatment Options to Patients

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

Value to Patients

The value to patients of extending the time that their cancer is progression-free cannot be overestimated. Patients living with metastatic breast cancer are aware that their advanced disease will progress with worsening symptoms until death, and embrace opportunities to try new treatments, even if benefits may be as little as a six month extension of progression-free disease. It is also very important for patients to have good quality of life when receiving treatment for metastatic disease. Patients that we speak to on a regular basis acknowledge the importance of having the energy to attend their children's activities and to spend time with family and friends.

[10] https://www.nejm.org/doi/full/10.1056/NEJMoa2214131

Companion Diagnostic Test

In order for patients to enjoy equitable access to this treatment, there must be equitable access to PIK3CA/AKT/PTEN alteration testing. Currently, testing standards are varied across Canada and access issues are exacerbated when private rather than public funding and resources are relied on to fill the gaps.[11] CBCN recognises that fully addressing this equity gap is outside the scope of both this submission, and CADTH's mandate, however a recommendation which takes into account how these implementation issues can be addressed is warranted. Having equitable access and reimbursement to companion tests in order to access capivasertib go hand in hand.

6. Anything Else?

Not applicable

[11] https://www.mdpi.com/1718-7729/30/6/408

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   CBCN did connect with the manufacturer, AstraZeneca, to learn about the results of CAPItello-291 clinical trial.

   All other research, interviews and outreach to patients was conducted independently by the Canadian Breast Cancer Network, as was the compilation of information and data for the writing of this submission.

   As a member of the Canadian Cancer Action Network, the Canadian Breast Cancer Network is committed to adhering to the Code of Conduct Governing Corporate Funding.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No. The Canadian Breast Cancer Network compiled and wrote this submission independently.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Gilead				X
Eli Lilly				X
Novartis				X
Roche				X
Pfizer				X
AstraZeneca				X
Janssen			X	
Merck				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: JK Harris

Position: Health Policy and Advocacy Lead

Patient Group: Canadian Breast Cancer Network (CBCN)

Date: October 4, 2024

CADTH

Patient Input for CADTH Reimbursement Review

Name of Drug: capivasertib (Truqap)
Indication: HR+, HER2- negative locally advanced or metastatic breast cancer
Name of Patient Group: Rethink Breast Cancer
Author of Submission: Jenn Gordon

1. About Your Patient Group

Rethink Breast Cancer (Rethink) is a Canadian charity known for making positive change. Rethink educates, empowers, and advocates for system changes to improve the experience and outcomes of those with breast cancer, focusing on historically underserved groups: people diagnosed at a younger age, those with metastatic breast cancer and people systemically marginalized due to race, income, or other factors. Rethink's strategic priorities and organizational direction are guided by the unique, unmet needs identified by breast cancer patients and their families. We foster spaces to connect, listen, empower, and rethink breast cancer, together.

Programs and Activities

- Rethink Breast Cancer builds community, bringing patients with various stages of breast cancer together through our private and public social spaces and in-person events.
- Rethink runs patient retreats and provides professional psychosocial support.
- Rethink creates and runs education forums and conferences.
- Rethink creates support and education tools, resources, and content.
- Rethink funds and brings the patient voice to breast cancer research.
- Rethink advocates for system changes to cancer care to improve outcomes.

You can find out more at: Rethink Breast Cancer Instagram and Rethink Breast Cancer Website

2. Information Gathering

For over 20 years, Rethink has been working closely with breast cancer patients in Canada. We learn from and listen to the community to understand their values, priorities and pain points to help drive change and system improvements. Each year, we learn from the patients we serve, survey and collaborate with. We learn from the 40 individuals that we work extremely closely with as key patient advisors; the 100 patients that share their stories on our blog; the 500 patients that participate in our virtual support groups; the 2,000 members of our private peer-support network; the 40,000 people that have joined our Instagram community; and the 150,000 individuals reached each month through the reach of that channel. We listen, learn, engage and have conversations in all these spaces.

Rethink also benefits from regular knowledge exchange with our Scientific Advisory Committee, which includes some of the leading clinical scientists in Canada who treat breast cancer.

For this submission, we have drawn on our general observations and insights gathered through programming and meetings with breast cancer patients as described above. We have also drawn on the results from an online survey with 78 patients living with metastatic breast cancer (MBC) conducted by Rethink Breast Cancer to document the lived experience of patients and caregivers. Patients completed the survey between September 2018 and April 2019.

In addition, we drew on insights from interviews in February 2024 with two people living with MBC who are currently taking capevasertib. **Tina, Kathleen, Caroline and Rebecca** are American patients with HR+/HR-negative metastatic breast cancer. We also interviewed **Vesna** who a Canadian living with HR+/HER2-negative metastatic breast cancer

and is currently taking a CDK4/6 inhibitor and has a PIK3CA mutation; capevasertib would be her next line of therapy and she shares the significance of having another therapy available to her, and funded, if/when needed.

Please read an additional short testimonial from Vesna in Appendix B.

3. Disease Experience

Most people in the Rethink community are diagnosed at a younger age. When young people get breast cancer it may be more aggressive, which can lead to tougher treatments. In addition, those diagnosed in their 20s, 30s and early 40s face age-specific issues such as fertility or family-planning challenges, diagnosis during pregnancy, childcare, impact on relationships, body image, dating and sexuality, feeling isolated from peers who don't have cancer, career hiatuses, and financial insecurity. The physical and emotional toll that a breast cancer diagnosis and treatment take on a young person's life is devastating and traumatic.

Fear of recurrence is a reality for our community and for good reason. Despite improvements made with early detection and treatment for early-stage breast cancer, there's approximately a 20-30% chance that early breast cancer will metastasize. Moreover, 5-10% of newly diagnosed breast cancers are metastatic. There is currently no cure for metastatic breast cancer and patients' goal with treatment is to live as well as they can for as long as they can. Patients with metastatic HR+/HER2- cancers survive 4 to 5 years on average.

Processing this reality of a life-limiting diagnosis is extremely difficult, especially for the young patients in our community and the emotional impacts on quality of life cannot be understated. The physical and psychosocial challenges of metastatic breast cancer negatively impact both the patients and their loved ones who are often their caregivers. Most people with metastatic breast cancer have widespread disease, with metastasis to bone being the most common. Lung, liver, lymph nodes and skin are also commonly involved; while mets to the brain is less common for hormone positive MBC patients, it can happen too. Symptoms of hormone positive MBC depend on the sites of the metastasis and include fatigue, shortness of breath for lung metastasis, pain, and bone fractures for bone mets as well as nausea, headache and of course challenges doing normal daily activity. The challenges and uncertainty of living with MBC affects both the patients and their loved ones who support and help care for them.

4. Experiences With Currently Available Treatments

For people with HR+/HER2-negative MBC with one or more PIK3CA/AKT1/PTEN-alterations whose disease progresses after one endocrine-based regimen in the metastatic setting current treatment options are mostly limited to standard IV chemotherapy and not a targeted therapy. These chemotherapies are given sequentially usually with diminishing responses with each line of chemotherapy. Although initial lines of chemotherapy may provide a few months of progression free survival, this decreases substantially with later lines.

Metastatic breast cancer patients in our community go to great lengths to avoid standard chemotherapy and they are hit hard both emotionally and physically when it does come to that. In our community, we see a rapid decline once patients progress to having only standard chemotherapies as remaining options.

"While your tumour is responding to endocrine therapy, you tend to be able to remain longer on the treatment and stable. Then when it starts to progress, and you need to go into chemo because you don't have anything else, it's just faster, you know, and things go down so quickly."
-**Rosilene**, MBC patient

Patients on standard chemo have a lot of difficulty managing their illnesses. Hospital appointments increase and they become mostly housebound managing side-effects of treatment.

"On weekly IV chemo, your normal life pretty much ends. It requires two visits per week for either blood work or for the chemo. The rest of the week is managing side effects of nausea, fatigue, pain, worsening neuropathy. And that's with me being in the cohort of people who 'tolerates well.'"
-**Heather**, MBC patient

"My year on chemotherapy was a full-time job dealing with suppressed neutrophil counts that caused countless treatment delays and quality of life compromising side effects. When I was offered the chance to rely entirely on a newer therapy, the results were game changing and allowed me to get back to my active and scheduled lifestyle as it once had been. Knowing that a cutting-edge treatment option like Trodelvy may be available to me when/if I need it outside of standard of care shelf-life chemotherapies, in the precious time to come, is what helps me stay present and positive as I navigate life with this incurable diagnosis. Everyone deserves a shot at what works best for them and the more therapies available to us are key. Stage 4 needs so much more."
-**Jen**, MBC patient, diagnosed de novo

"My biggest concern with fear of progression, is that my subtype changes from triple positive to any other subtype. So of course, the more treatments that are available that are effective and not chemo are important to me. I already did loads of chemo because my targeted therapy had to go on pause because of the damage to my heart. It was not fun knowing that I could be left on chemo if the cardiotoxicity didn't improve."
-Margaret, MBC patient, diagnosed de novo while pregnant

5. Improved Outcomes

Each individual patient brings their own personal values and goals to their discussions with their oncology team. Communication and trust in their team is essential. It's important that patients have a clear understanding of trade-offs and are well prepared for common side-effects of a given treatment.

When it comes to metastatic breast cancer therapies, in general, the primary improvement MBC patients seek is to extend their life beyond what is expected with the current publicly funded therapies available and with a better quality of life. They also know a later-line therapy is likely not as easy to tolerate at their first-line MBC treatment was but are anticipating better quality of life than on a weekly IV standard chemotherapy.

As **Jessica,** a hormone positive, MBC patient from our community explains, when the stakes are so high, even a few extra months of survival matter. She explains:

"…those months could be the difference that lets me see my son start kindergarten; they could be the ones that give me time to get him off diapers before it all falls on dad; Or they could be the first time he says I Love You. While a few months are short on time they are bursting with possibility. Life happens in moments after all. Every scan matters.

Only, it's not simply a matter of days, it's also a matter of quality days. It's hard to make memories suffering the side effects of chemo on the couch. It's impossible to keep up with a toddler while managing the debilitating fatigue. An additional line of treatment that allows me quality time with my family is welcomed with open grateful arms…It's not easy for anyone to estimate the value of an extra day of life, but in my case, it could also mean my two-year old has one more day with mom. I'll give him every day I can."

Patients are also looking for improvement in quality of life and ability to manage daily life over standard IV chemotherapy.

In our 2018-2019 MBC survey, patients rated controlling disease and extending life expectancy as the most important outcomes for treatment. This suggests that patients value long-term health outcomes over immediate concerns like reducing

symptoms or managing side effects. (See the full survey results, along with methodology in Appendix C.) Comments from MBC patients surveyed included:

- Symptoms and shrinking the cancer is the most important thing. Living well is the next most important thing.
- Keep me alive for my kids.
- I want to live, LIVE, and enjoy my life for many more years and not be so afraid.

6. Experience With Drug Under Review

We connected with four patients, **Tina, Kathleen, Caroline** and **Rebecca** who had experience taking capivasertib for HR+/HER2-negative metastatic breast cancer.

Tina is living with ER+ HER2-low metastatic breast cancer and shares her treatment regime leading to capevasertib (Truqap) and what her experience has been taking this therapy, including the good quality of life she is experiencing:
"I have been on 5 different lines of treatment in the last 7 years with Truqap being my 5th line of treatment.

I was placed on Truqap 2.5 months ago when I had progression from bones to liver. My tumour markers, which have always been an accurate indicator of when progression occurs, have dropped 20 points. My oncologist sees this as an early indication that the drug is working for me. I will be evaluated with scans after 3 months on the drug.

One of the things I value about this drug is the high quality of life I have had on this drug. The only side effect I have had is some diarrhea that may occur after some meals. I have even taken the drug on an empty stomach without any difficulty. I have not had any concerns with my lab either, although my oncologist watches me closely for any blood sugar issues that might occur.

Every day is precious to me and to have a treatment that does not slow down my enjoyment of the world and people around me is a blessing."

We also connected with **Kathleen**, who spoke about being able to continue working a busy and demanding job while being on this treatment:
"I work 40-hour weeks for an autobody shop and haven't had any ill effects from the medication that prevented me from working. The biggest concern is sugar levels and in the eight weeks that I've been on it, I have had no significant issues with that. I do have nausea, but that is controlled by medication."

We asked her about recommending this medication to other patients and she shared:

"Absolutely, I would recommend this as a line of treatment. Just be ready for nausea (that's only my experience) and a little restlessness, but if you're active you can burn the energy quite easily."

Caroline just started taking capevasertib the day that we spoke to her but shared:
" I have the PIK3CA mutation and think that this is an important treatment option to have since it's specific to that mutation."

Rebecca was the fourth person we connected with who started taking capevasertib on December 8th, 2023 for HR+/HER2-negative MBC with a PIK3CA mutation. This is Rebecca's 8th line of therapy, and she expressed several times how thankful she was that this treatment had been approved (in the US) as she had just run out of treatment options prior to the approval. She spoke candidly about the improvement in her quality of life since taking capevasertib:

"The side effects are tolerable, I am currently on the lowest dose as my blood sugars are elevated, but I do not need insulin on this dose. My quality of life before taking this (capevasertib) was so bad; I was sleeping 16 hours a day and was still exhausted, and now I am back to sleeping a regular 8 hours per day and can have a much more normal routine. I also don't need as much help as I did before, even with tasks such as laundry." She did also mention experiencing a rash at the 12-week mark but that it resolved on its own and was tolerable.

She shared the importance of having access to new treatment options, what it means to her, and highlighted why it's so important for patients to get to try treatments:
"It's difficult knowing you are running out of treatment options, I am lucky that this drug got approved when it did. I am following what other drugs may be approved in the near future. How can you put a value on time, I don't want to leave my family. I was on a CDK4/6 inhibitor for 4.5 years, which is well above the average amount of time that people respond to it, but if I had not had the opportunity to access that therapy, I wouldn't have had that extra time."

When asked about how well the treatment was working she shared, *"I just had my first scan today, so I do not yet have the results, but my markers have always been a good indication of when treatment is working or not and my markers have dropped since taking capevasertib".*

Lastly, we spoke with **Vesna**, a member of Rethink's MBC Advisory Board, who is not currently receiving Truqap, but is currently being treated with a CDK4/6 inhibitor and has a PIK3CA mutation, making Truqap her next line of therapy should her current treatment stop working. Vesna is a veteran in the MBC space, having been treated with a CDK4/6 inhibitor for the past 7 years. Her original life expectancy was 2-3 years, and having access to innovative therapies has allowed her to surpass that expectancy and continue to live an active lifestyle with an excellent quality of life. She is also someone who is part of the "long tail" of this therapy, referring to patients who are super responders that see a benefit to treatment long after the average PFS and OS projections. Vesna's experience highlights the need for patients to be able to try new therapies, given that there are patients who remain stable for several years and are able to continue living with an excellent quality of life.

When asked about the impact of having a new treatment option, specific to her cancer type and mutation available and reimbursed she shared:

"There is a peace of mind, knowing that if/when this treatment fails (because we know the other shoe is going to drop eventually) that there will be another treatment option available to extend my life. The worry is that you won't have more treatment options. When treatments aren't covered, you're seeing friends having to fight and fight and fight for a chance to try these treatments. There is a whole other stress that you're putting on the patient."

When further asked about why there is a need for a variety of treatment options **Vesna** noted:

"The tag line that you hear a lot is metastatic breast cancer is not curable, but it's treatable. <u>But this is only true if oncologists are given the tools to treat the disease</u>. It may seem that there are always new breast cancer drugs, but when you look further into it, that's because they are specifically for certain sub-types, mutations, etc. Patients are not being treated with ALL drugs, they need the RIGHT drug, and it's important that oncologists have all of the options available to them to help provide their patients with the RIGHT treatment."

When asked about having access to the right treatment means to her, **Vesna** replied. *"It means I can be a good mom. My kids can have an active, healthy, present mom."*

Summary:

All of the patients we spoke with highlighted the importance of having access to new therapies that have the possibility of extending their life. **Kathleen, Tina** and **Rebecca** also shared that they are experiencing a good quality of life while taking capivasertib, allowing them to continue to work, enjoy time with loved once, and live their lives.

Vesna highlighted the that in order for metastatic breast cancer to be treatable, patients need access to a variety of treatment options. All patients thought that others should have the opportunity to try this therapy given the favorable results and good quality of life. In our experience, MBC patients value a treatment that offers more time, more disease stability and improvements in day-to-day functioning – capivasertib does all three.

7. Companion Diagnostic Test

Companion diagnostic testing will need to be provided to determine if the patient has PIK3CA/AKT1/PTEN alterations; this testing is completed through a biopsy. Patients currently have a biopsy taken as part of the initial diagnostic process; providing that full NGS testing is conducted at the diagnostic work-up there would not be an additional testing burden on patients. Given that many of the therapies under development for breast cancer, and other cancers, are targeting specific mutations, proactively adding NGS testing to the diagnostic process for breast cancer patients would ensure that they are receiving treatments that are going to offer them the best outcomes. Having this testing completed as part of the diagnostic process would also ensure that additional delays are not incurred by sequencing testing. Furthermore, access to this testing can also provide information to prevent treating patients with therapies that are not of benefit.

We were unable to speak with any patients in Canada who accessed this therapy; however, the Canadian patient we spoke with, **Vesna**, accessed testing when she was initially diagnosed with metastatic breast cancer by participating in a study. Patients shouldn't need to rely on whether or not a study is open to be able to access testing that will provide them with critical information on making treatment decisions.

When asked about her general thoughts around companion diagnostic testing **Rebecca** shared *"I'm happy to do whatever tests are needed to find out what treatment options there may be".*

8. Anything Else?

We are grateful there are now targeted therapies for all breast cancer subtypes. Prior to the introduction of CDK 4/6 inhibitors into the treatment landscape, it was common for the young hormone positive breast cancer patients in our community to die within two years of their metastatic diagnosis. While things are better than 10 years ago, for the metastatic community, the uncertainty does not go away. Later line therapies that work better than palliative chemotherapy is vital.

When it comes to "anything else," we give our last patient quote to **Vesna**, as she raises another "why" on behalf of the community:

"Consider the MBC patient facing yet another setback. Someone who's cancer has progressed on their current treatment and must now once again grapple with the uncertainty and fear with what lies ahead. ***This patient will have a harder time being accepted into a clinical trial with each subsequent line due to restrictive inclusion criteria that often excludes patients who've been heavily treated from participating.*** *An ever-diminishing list of treatments is reduced yet again, with chemotherapy being one of the few options still available.*

Many of us remember the experience of chemotherapy with an earlier stage diagnosis; the memories linger. While the cancer that resides in my body is stable at this time, I am told with fair certainty that one day, this treatment will fail, and the cancer will grow again. It will bring me back to square one, requiring my oncologist to choose whatever treatment would give me the best chance of staving off debilitating illness again. An additional line of treatment offers hope and compassion to those carrying the burden of experience."

Rethink is grateful to the people living with metastatic breast cancer who are quoted directly in this input submission for sharing their insights and experiences with us. And we are grateful for the opportunity to bring forward these important voices from the metastatic breast cancer community to the CADTH decision making process.

Appendix A: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   Astra Zeneca provided us with information about the general characteristics of the drug and its benefits and side-effects.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range with an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca 2022 Funding				X
Astra Zeneca 2023 funding				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Jenn Gordon
Position: Lead Strategic Operations and Engagement
Patient Group: Rethink Breast Cancer
Date: February 26, 2024

APPENDIX B: Patient Profile

Vesna's Why:
"Consider the MBC patient facing yet another setback. Someone who's cancer has progressed on their current treatment and must now once again grapple with the uncertainty and fear with what lies ahead. This patient will have a harder time being accepted into a clinical trial with each subsequent line due to restrictive inclusion criteria that often excludes patients who've been heavily treated from participating. An ever- diminishing list of treatments is reduced yet again, with chemotherapy being one of the few options still available.

Many of us remember the experience of chemotherapy with an earlier stage diagnosis; the memories linger. While the cancer that resides in my body is stable at this time, I am told with fair certainty that one day, this treatment will fail and the cancer will grow again. It will bring me back to square one, requiring my oncologist to choose whatever treatment would give me the best chance of staving off debilitating illness again. An additional line of treatment offers hope and compassion to those carrying the burden of experience." **— Vesna, living with HR+HER2-MBC**

APPENDIX C: MBC Patient Survey Results

Information for this report was gathered through an online survey published in English and circulated through communications from Rethink Breast Cancer as well as the Rethink Network and other partner organizations. Messages were also posted on Facebook and Twitter as well as the Breastcancer.org, Cancer Connection and Cancer Survivors Network online discussion forums. 78 metastatic breast patients completed the survey between September 2018 and April 2019.

An independent contractor was hired to develop this survey and present the results. Survey questions were all reviewed by Rethink staff and Metastatic Patient Advisory Board prior to being posted online.

Rethink Breast Cancer asked respondents to evaluate the importance of different outcomes for their breast cancer treatment on a scale of 1 (not important) to 5 (very important). All the listed outcomes were considered important with no average scores lower than 4.4. However, controlling disease and extending life expectancy were rated as the most important results suggesting that patient values prioritize long-term health outcomes over immediate concerns like reducing symptoms or managing side effects.

Importance of outcome	1 - not important	2	3	4	5 — very important	Average
Controlling disease progression	0.00% 0	0.00% 0	0.00% 0	2.60% 2	97.40% 75	4.97 77
Reducing symptoms	1.30% 1	0.00% 0	12.99% 10	19.48% 15	66.23% 51	4.49 77
Maintaining quality of life	0.00% 0	0.00% 0	1.30% 1	12.99% 10	85.71% 66	4.84 77
Managing side effects	1.30% 1	1.30% 1	12.99% 10	19.48% 15	64.94% 50	4.45 77
Achieving NED (no evidence of disease)	1.32% 1	1.32% 1	1.32% 1	6.58% 5	89.47% 68	4.82 76
Extending life expectancy	0.00% 0	0.00% 0	0.00% 0	2.63% 2	97.37% 74	4.97 76

Comments included:

- Symptoms and shrinking the cancer is the most important thing. Living well is the next most important thing.
- Keep me alive for my kids.
- I want to live, LIVE and enjoy my life for many more years and not be so afraid.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0341
Generic Drug Name (Brand Name): Capiversatib
Indication: For the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.
Name of Clinician Group: Ontario Health Cancer Care Ontario Breast Cancer Drug Advisory Committee
Author of Submission: Dr. Andrea Eisen, Dr. Orit Freedman, Dr. Ronita Lee, Alaina Charlton, Dr. Olexiy Aseyev

1. About Your Clinician Group

OH-CCO's Cancer Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

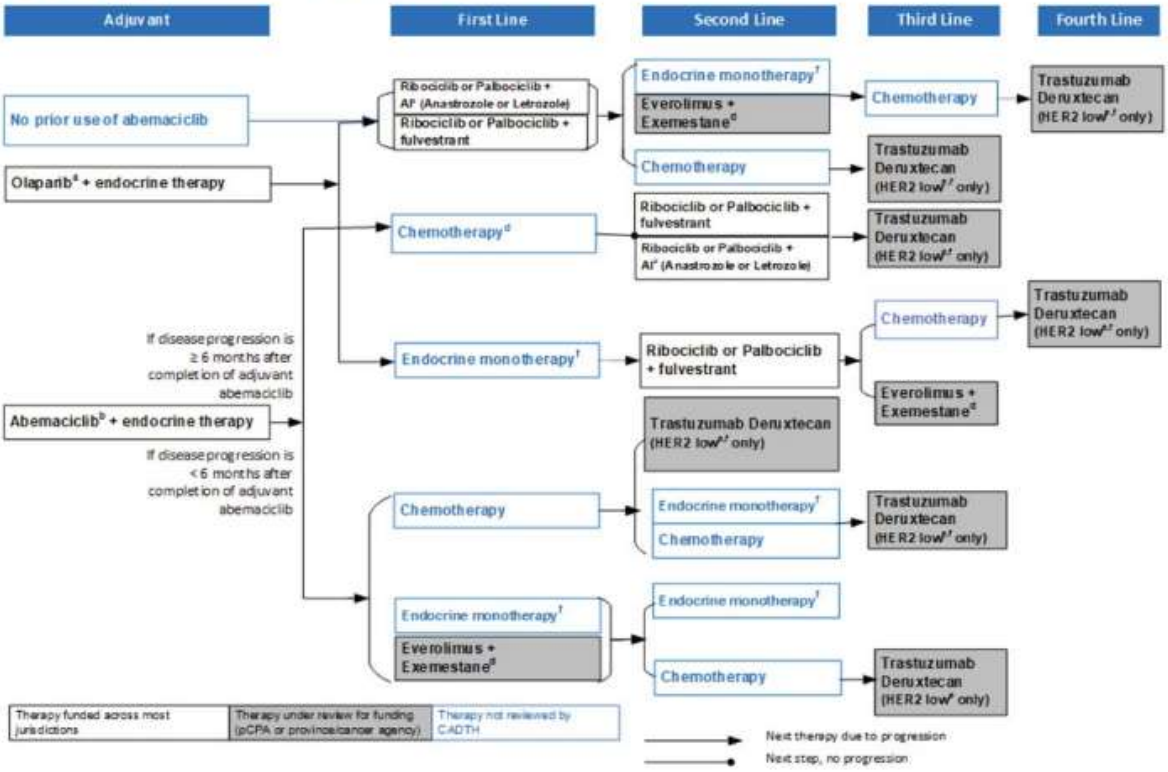
Information was gathered via videoconferencing.

3. Current Treatments and Treatment Goals

Refer to algorithm below. In Ontario, for patients who did not receive adjuvant CDK 4/6 inhibitors, first line therapy would typically be given ribociclib or palbociclib with an aromatase inhibitor. Depending on the clinical status of the patient, second line treatment would be endocrine monotherapy, everolimus plus exemestane, or chemotherapy.

The treatment is palliative in intent. The goal is to improve survival and maintain/improve quality of life, with acceptable toxicity.

Figure 1: Provisional Funding Algorithm Diagram For HR-Positive HER2-Negative Breast Cancer, With Inclusion of HER2 Low



AI = aromatase inhibitor; HR = hormone receptor; HER2 = human epidermal growth factor 2; pCPA = pan-Canadian Pharmaceutical Alliance.

Notes: Single chemotherapy options could include capecitabine, docetaxel, paclitaxel, nab-paclitaxel, doxorubicin, epirubicin, vinorelbine, gemcitabine, eribulin, or combinations therapies.

Endocrine monotherapy options include anastrozole or letrozole, exemestane, tamoxifen, fulvestrant (re-treatment not funded if disease progression occurred during any prior fulvestrant therapy).

For individuals who are premenopausal, treatments might include luteinizing hormone-release hormone agonists such as goserelin, leuprolide, or buserelin.

Breast cancer therapies are available for patients of all genders.

[a] Olaparib adjuvant therapy is for patients with deleterious or suspected deleterious germline *BRCA* mutation who have been treated with neoadjuvant or adjuvant chemotherapy. Patients must have confirmation of germline *BRCA* mutation before olaparib treatment is initiated.

[b] Abemaciclib should be reimbursed for a maximum of 2 years (150 mg orally twice daily).

[c] In some jurisdictions, aromatase inhibitors may also include exemestane. Everolimus plus exemestane is under review for funding by the provinces or cancer agencies.

[d] Chemotherapy might be the first choice if visceral crisis is suspected; after adequate response, consider other choices.

[e] Patients with HER2-low breast cancer must have the following pathology results: IHC 1+ or IHC2+ with in situ hybridization negative.

[f] Patients with HR-positive breast cancer should have received at least 1 endocrine therapy and be no longer considered for endocrine therapy.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Advanced breast cancer is a common and incurable disease, and improved treatments are needed.

Given that there are many lines of treatment, it is useful to have oral therapies available.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The proposed indication would be in line with the trial criteria, and it would complement other available treatments. The proposed indication restricts usage of this drug to those with AKT pathway alterations even though the trial included those with and without such alterations. The analysis showed the effect was greater in patients with pathway alterations.

If approved, this drug would add an additional line of endocrine based therapy.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

In general, the DAC would support the use of this drug in patients who met the clinical trial criteria. However, the DAC notes that the published Capitello 291 trial included both patients with and without AKT pathway alterations. 41% of the total study population had AKT pathway alterations. The published study outcomes were similar for the whole population and those with AKT pathway alterations. However, the DAC notes that the FDA approval was based on a presented subgroup analysis that showed that study subjects without AKT pathway alterations did not significantly benefit.

FDA approves capivasertib with fulvestrant for breast cancer | FDA

“An exploratory analysis of PFS in the 313 (44%) patients whose tumors did not have a PIK3CA/AKT1/PTEN-alteration showed a HR of 0.79 (95% CI: 0.61, 1.02), indicating that the difference in the overall population was primarily attributed to the results seen in the population of patients whose tumors have PIK3CA/AKT1/PTEN-alteration.”

In Ontario, patients with metastatic breast cancer have access to funded testing for PIK3CA mutations however testing for PTEN and AKT1 mutations is not currently funded.

The least suitable patients would be those not eligible for the study.

In this study patients were not required to have a CDK 4/6 inhibitor in the first line setting, however in Ontario, it is anticipated that most patients would receive CDK 4/6 inhibitor in the first line setting.

For access to this drug, patients would require testing for AKT pathway alterations. In the trial, this could be done on archival or newly obtained tissue. The DAC wishes to flag that access to timely results may be an issue for patients with metastatic disease, who need to start a new therapy as soon as possible.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Patients would be assessed clinically and radiologically as per routine clinical practice. Patients may require close monitoring due to toxicities related to capivasertib.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Treatment is generally discontinued upon disease progression or if there is unacceptable toxicity.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Treatment should be given in centers with expertise in the management of metastatic breast cancer and toxicity related to oral drugs. These drugs are typically prescribed by medical oncologists.

6. Additional Information

This drug has a significant toxicity profile (i.e., 72% of patients had diarrhea). There are other choices of treatment for this line of therapy that are better tolerated. Diarrhea management protocol is needed for this drug.

The Breast DAC believes the toxicity of this drug may outweigh the benefits.

The Breast DAC notes that currently only testing for PIK3CA is funded in ON and there may be delays in access to this. Testing for AKT and PTEN mutations is not standard at this time.

Premenopausal women require ovarian suppression for this regimen.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided a secretariat function to this group.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Andrea Eisen
Position: Lead, OH (CCO) Breast Cancer Drug Advisory Committee
Date: 22-02-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Orit Freedman
Position: Member, OH (CCO) Breast Cancer Drug Advisory Committee
Date: 16-02-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Ronita Lee
Position: Member, OH (CCO) Breast Cancer Drug Advisory Committee
Date: 16-02-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Alaina Charlton

Position: Member, OH (CCO) Breast Cancer Drug Advisory Committee
Date: 16-02-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Olexiy Aseyev
Position: Member, OH (CCO) Breast Cancer Drug Advisory Committee
Date: 16-02-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AstraZeneca (talk for lung)	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

CADTH

Clinician Group Input Template
CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: <PC0341-000>
Generic Drug Name (TRUQAP™): Capivasertib
Indication: TRUQAPTM (capivasertib tablets), in combination with fulvestrant, is indicated for the treatment of adult females with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.
Name of Clinician Group: REAL Canadian Breast Cancer Alliance
Author of Submission: Dr. Mita Manna, Medical Oncologist, Saskatoon Cancer Center and Provincial Disease Site Lead for Breast Oncology in Saskatchewan, Assistant Professor at the University of Saskatchewan, MD, FRCPC.

1. About Your Clinician Group

REAL (Research Excellence Active Leadership) Canadian Breast Cancer Alliance is a newly formed organization with the goal of providing an ecosystem of academic leadership with the most impactful voice of breast cancer therapeutic recommendations for timely health policy, funding, and **consistent clinical adoption** based on medical evidence to ensure optimal outcomes for breast cancer patients across all provinces and territories in Canada.

REAL Alliance consists of a multidisciplinary breast oncology expert membership (nucleus committee) who have established a partnership with Breast Cancer Canada with the vision to improve breast cancer outcomes in Canada. REAL members aim to work alongside health policy makers, clinicians, and patients, to ensure evidence-based, equitable breast cancer management is delivered.

Mission statement: **“When research meets the real world, we save lives.”**

2. Information Gathering

Our members met virtually and exchanged views via email to discuss our **clinical recommendations for capivasertib**. We recommend that capivasertib be accessible to all adult patients **with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2–) metastatic breast cancer with one or more *PIK3/AKT1/PTEN* alterations** in the **second-line setting and in the first-line setting for patients who relapse on or within 12 months of completing adjuvant endocrine therapy**. Using this CADTH template, our recommendations were compiled to reflect our clinical opinion on what we believe is best for our patients. Our opinion is based on literature review, data from clinical trials and recent international congresses, as well as our collective clinical experience. We urge CADTH to consider our clinical recommendation in this document along with the submissions put forward by patient advocacy groups to make an informed decision regarding the place in therapy for capivasertib in patients with HR+/HER2–or metastatic breast cancer.

3. Current Treatments and Treatment Goals

Breast Cancer in Canada

Breast cancer is the leading cause of cancer among Canadian women. In 2023, the Canadian Cancer Society estimated that 29,400 Canadian women would be diagnosed with breast cancer, representing 26% of all new cancer cases in women. It was also estimated that 5,400 Canadian women would die from breast cancer in 2023, accounting for 13% of all cancer deaths in women for that year.[1] Additionally, 260 Canadian men were estimated to be diagnosed in 2023, with 55 anticipated deaths.[1] Although most women are diagnosed with early stage disease (>90%), many women who undergo several years of adjuvant therapy for early breast cancer still have a persistent risk of distant recurrence and death from the disease.[2] Further, between 5-10% of women are initially diagnosed with metastatic breast cancer.[3] Approximately 70-80% of metastatic breast cancers express the hormone receptor (HR) estrogen or progesterone (or both) and do not overexpress the human epidermal growth factor receptor 2 (HER2); this subtype is classified as HR+/HER2–.[4–7]

Therapeutic Goals

The selection of a therapeutic strategy depends on clinical factors and tumour biology, with the goal being a personalized approach. Although a minority of patients with oligometastatic disease may benefit from an intensified locoregional approach, most patients with advanced breast cancer receive systemic therapy consisting of chemotherapy, endocrine therapy (ET), targeted and/or biologic therapies, and supportive care measures. The primary goals of systemic treatment for advanced breast cancer are: a) **prolongation of survival** (progression-free survival [PFS] and overall survival [OS]); b) **alleviation of symptoms**, and maintenance or improvement in **quality of life**; c) **managing/minimizing toxicities** associated with treatment; d) and **delaying the initiation of chemotherapy including the use of antibody drug conjugates (ADCs)**, which is a recognized clinical trial endpoint and a priority for patients in this setting.[8,9]

First-line and Adjuvant Treatment

Prior to 2016, the mainstay of treatment for HR+/HER2– metastatic breast cancer in postmenopausal women was ET either with tamoxifen, aromatase inhibitors (AIs; anastrozole, exemestane, or letrozole), or fulvestrant, combined with ovarian suppression in premenopausal women.[7] In the last decade, the focus has been on developing targeted therapies, including cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors. ET combined with a CDK4/6 inhibitor is now the standard-of-care (SOC) for HR+/HER2– metastatic breast cancer, with improved PFS and OS and a favorable toxicity profile seen in several trials.[8,9] ET alone in the first-line setting should be reserved for the small group of patients with comorbidities or a performance status (PS) that prevents the use of combinations with a CDK4/6 inhibitor. Historically, chemotherapy has been favored in patients with visceral metastases, however, evidence indicates that ET plus CDK4/6 inhibitors is also beneficial in this setting.[10]

In the adjuvant setting, use of ET has proven beneficial to reduce breast cancer recurrence.[11] Similar to the metastatic setting, there is growing evidence that the addition of CDK4/6 inhibitors in adjuvant therapy increases benefits for patients with HR+/HER2– early breast cancer at higher risk of relapse.[12,13] Currently abemaciclib is indicated in combination with ET for select high risk patients in Canada.[14]

Second-line Treatment

Selection of therapy (chemotherapy versus continuation of ET-based therapy) is based on disease aggressiveness, extent and function of affected organs, and consideration of the associated toxicity profile. Although the optimal sequence after progression on first-line treatment is not well defined, several strategies are possible and are primarily guided by tumour genomics, including *PIK3CA* mutations, estrogen receptor 1 (*ESR1*) mutations, and germline *BRCA1*/2 mutations. Evidence-based options for second-line therapy include exemestane-everolimus, tamoxifen-everolimus, fulvestrant-everolimus, or chemotherapy.[8,9] Notably, none of these treatment options have demonstrated an OS benefit and all are associated with tolerability issues. Furthermore, BOLERO-2 (everolimus plus exemestane) was conducted before the availability of CDK4/6 inhibitors. More recently, new targeted therapies have been investigated, including alpelisib plus fulvestrant (for *PIK3CA*-mutated tumours), or poly-(ADP-ribose)-polymerase (PARP) inhibitors for tumours harbouring germline *BRCA1*/2 mutations.[8,9] In Canada, alpelisib plus fulvestrant has received Health Canada

approval, though there is no public funding and thus limited access for patients. This implies that a significant number of patients with *PIK3CA*-mutated breast cancer will not have access to this combination.

Later-line Treatment

For women who progress after two lines of ET, treatment must be individualized based on their prior treatment response, tumour burden, and preferences. Options include chemotherapy and ADCs (sacituzumab govitecan and trastuzumab deruxtecan). For patients who are asymptomatic with slowly progressive disease, continuation of ET is reasonable, and tamoxifen may be an appropriate later-line option.[8,9]

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The focus of this submission is **patients in the second-line setting (**i.e., those who have relapsed on first-line therapy in the metastatic setting) **and patients who relapse on or within 12 months of completing adjuvant ET**. While the combination of ET and CDK4/6 inhibitor has significantly improved PFS and OS as compared to ET alone in the first-line setting most patients will experience disease progression, and **treatment options with survival benefit and good tolerability are limited.**[9,15] Thus, the treatment goals that are not being met by currently available treatments in this population are **OS**, **maintenance of quality of life, minimizing toxicities,** and **delaying the onset of chemotherapy.**

Patients who **relapse on or within 12 months of completion of adjuvant endocrine therapy** are a particularly difficult patient population as they likely have more **aggressive disease** and/or a certain degree of **endocrine resistance** where estrogen receptor dysregulation may be more effective.[10,16] **Not all patients respond** to available treatments and patients may **become refractory to current treatment options**; thus, additional treatment options are needed for these patients.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

AKT is the key signaling node of the phosphatidylinositol 3-kinase (PI3K)–AKT–PTEN pathway.[17] This pathway is of particular interest in the second-line setting as it is overactivated in approximately 50% of HR+/HER2- breast cancers by means of activating mutations in *PIK3CA* and *AKT1* and inactivating mutations of the tumour suppressor *PTEN*.[18–20] While some alterations may be present at the time of diagnosis of metastatic disease, they can also develop in response to selection pressure during first-line treatment (e.g., with CDK4/6 inhibitors).[21,22] AKT signaling may also be activated in the absence of genetic alterations in patients with endocrine resistance.[23–25] The inhibition of this pathway has led to the regulatory approval of the PI3K α-selective inhibitor alpelisib, combined with fulvestrant, in *PIK3CA*-mutant tumours.[26–28] However, there is limited data about efficacy after CDK 4/6 inhibition and there is currently no public access to alpelisib in Canada.

More recently, **capivasertib**, an oral small molecule inhibitor of all 3 AKT isoforms (AKT1/2/3), has received Health Canada approval based on the results of the **CAPItello-291** clinical trial (NCT04305496) for tumours harbouring alterations in the AKT pathway (PI3K/AKT/PTEN), and in tumours reliant on signaling via this pathway for survival.[29,30]

Recommendation

We recommend that capivasertib (in combination with fulvestrant) be made available as a treatment option for all patients (men and pre, peri, and postmenopausal women) who have HR+/HER2– metastatic breast cancer and have progressed on first-line SOC treatment in the metastatic setting or have progressed on or within 12 months after completing adjuvant ET and have one or more *PIK3/AKT/PTEN* alterations. Capivasertib is a first-in-class medication that works to block all 3 isoforms of the cancer-driving protein, AKT (AKT1/2/3).[31]

The **median PFS**, **OS, and quality of life** results of **CAPItello-291 are the basis for our recommendation**.[17] Capivasertib (in combination with fulvestrant) would be preferred to alpelisib and would replace everolimus in the CADTH algorithm in the second-line setting for patients with one or more *PIK3/AKT/PTEN* alterations. This would allow us to offer our patients a treatment with **demonstrated OS** and **improved tolerability**.

Even though the mechanism of action of capivasertib is at a different place in the PI3K–AKT–PTEN pathway than alpelisib (i.e., inhibiting AKT isoforms versus inhibiting PIK3 kinase) they do share some common toxicities. The ESMO guidelines note that "toxicity was increased substantially in the alpelisib arm, especially hyperglycemia, rash, gastrointestinal (GI) toxicity (nausea, vomiting, loss of appetite, mucositis, diarrhea) and fatigue, which led to dose reductions/interruptions in ~70% and discontinuations in 25% of patients."[26]

The ASCO Rapid Update addresses this issue as follows: "There are no comparative efficacy data for choosing a PIK3CA targeted option for those who are potential candidates for capivasertib or alpelisib treatment. For such patients, the Panel recommends selecting the targeted agent based on perceived risk-benefit considerations such as hyperglycemia, diarrhea, or treatment discontinuation for adverse events (AEs) (Evidence quality: Low; Strength of recommendation: Weak)." The ASCO Rapid Update noted the rates of Grade 3 or greater AEs as follows: diarrhea (9.3% capivasertib vs 6.7% alpelisib), rash (12.1% capivasertib vs 9.9% alpelisib), and **hyperglycemia (2.3% capivasertib vs 36.6% alpelisib).**

The clinical trial efficacy evidence for capivasertib is superior to that of alpelisib. And it is our opinion that capivasertib is better tolerated than alpelisib and that the monitoring to mitigate AEs is clear.

Everolimus (in combination with exemestane) is currently a second-line treatment option in the CADTH algorithm. The final analysis of BOLERO-2 failed to demonstrate an OS advantage with everolimus.[28] Of the patients in the everolimus treatment arm, 40% experienced a treatment-related Grade 3/4 AE (compared to 8% in the placebo group) and 30% of patients discontinued treatment due to an AE (compared to 5% in the placebo arm). Furthermore, BOLERO-2 was conducted prior to the CDK4/6 inhibitor era and thus the patient population is completely different than the patients we treat every day. Thus, capivasertib is a preferred treatment option over everolimus.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

We recommend that the patients most likely to benefit from treatment with capivasertib are those who meet the CAPItello-291 study criteria, including patients progressing on or within 12 months of adjuvant endocrine therapy. These patients can be identified by the primary treating physician based on diagnosis, clinical examination, physician judgment, and appropriate genomic testing for alterations. Patients most likely to respond would be those with relevant pathway alterations (PIK3, AKT, PTEN). Patients with contraindications (uncontrolled medical conditions) or other diseases severely limiting their expected survival, or with ECOG PS 3-4 would not be appropriate for treatment. Companion diagnostic tests would need to be accessible to assess for alterations in the above pathway. Treatment would be continued if demonstrating clinical benefit (response or stable disease) and tolerability until disease progression.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Assessing Treatment Response

The outcomes used in the CAPItello-291 study were aligned with clinical practice.

In practice, we monitor treatment response by considering changes in symptoms, physical findings, or tumour markers, as well as evidence of disease progression based on serial imaging, with scans usually performed at least every 3 months initially. Treatment is continued if the disease is either stable or responding radiographically according to Response Evaluation Criteria for Solid Tumours (RECIST) 1.1.

We consider the following outcomes as clinically meaningful responses:

- Stabilization or reduction in the frequency or severity of symptoms (e.g., pain, dyspnea)
- Maintenance or improvement of performance status
- Ability to maintain or increase activities of daily living
- Tumour radiographic response with either stabilization of disease or response by RECIST 1.1 criteria.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Capivasertib would be discontinued upon evidence of disease progression by RECIST 1.1 criteria or the occurrence of severe toxicity not amenable to treatment. The CAPItello-291 trial criteria for discontinuation would serve as guidance.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

As for any breast cancer, many clinicians may be involved in the diagnosis of metastatic disease. However, capivasertib should only be prescribed by physicians with expertise in the management of systemic cancer therapies and monitoring conducted by oncologists or their teams, which may include advance practice nurses, oncology pharmacists and general practitioners in oncology.

6. Additional Information

Nothing to include.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   liV Medical Education Inc. provided our physician group with writing support.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   All data and experience was collected and analyzed within our physician group.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician Dr. Karen Gelmon

Name: Dr. Karen Gelmon
Position: Medical Oncologist, Department of Medical Oncology, British Columbia Cancer Agency, Professor of Medicine, University of British Columbia
Date: February 14, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AstraZeneca		X		
Eli Lilly	X			
Gilead Sciences	X			
Novartis	X			
Pfizer	X			
Seagan	X			
McGill University	X			
CIHR	X			
Merck	X			
City of Hope Hospital	X			
Celuity	X			

Declaration for Clinician Dr. Jan-Willem Henning

Name: Dr. Jan-Willem Henning
Position: Medical Oncologist, Clinical Associate Professor, Tom Baker Cancer Centre, University of Calgary, Canada.
Date: 2/13/2024 | 2:03:36 PM EST

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AstraZeneca		X		
Eli Lilly	X			
Gilead Sciences	X			
Novartis		X		
Pfizer		X		
Seagan		X		
University of Toronto	X			
Rethink Breast Cancer (Research Grant)	X			

Declaration for Clinician Dr. Mita Manna

Name: Dr. Mita Manna
Position: Medical Oncologist, Saskatoon Cancer Center and Provincial Disease Site Lead for Breast Oncology in Saskatchewan, Assistant Professor at the University of Saskatchewan, MD, FRCPC.
Date: 2/13/2024 | 9:54:14 AM PST

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca		X		
Ipsen	X			
Advanced Accelerator Applications	X			
Knights Therapeutics	X			
Eli Lilly		X		
Gilead Sciences		X		
Novartis		X		
Pfizer	X			
Bristol Myers Squibb	X			
Merck		X		
McGill University	X			

Declaration for Clinician Dr. Sandeep Sehdev

Name: Dr. Sandeep Sehdev
Position: Medical Oncologist, lead of breast cancer disease site group at The Ottawa Hospital Cancer Centre. Assistant Professor, U of Ottawa.
Date: 10-FEB-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AstraZeneca			X	
Novartis			X	

Declaration for Clinician Dr. Nathaniel Bouganim

Name: Dr. Nathaniel Bouganim
Position: Assistant Professor, Gerald Bronfman Department of Oncology, Faculty of Medicine and Health Sciences, McGill University
Date: 2024-02-20

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AstraZeneca	X			
Novartis		X		
Knight	X			
Gilead	X			
McGill University	X			
Pfizer	X			

Declaration for Clinician Dr. Stephen Chia

Name: Dr. Stephen Chia
Position: Medical Oncologist, BC Cancer Breast Tumour Group Chair
Date: Feb 20, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis		X		
Eli Lilly	X			
AstraZeneca		X		
Daiichi Sankyo	X			
Merck	X			
Gilead	X			
Hoffmann LaRoche	X			

Declaration for Clinician Dr. Christine Brezden-Masley

Name: Dr. Christine Brezden-Masley
Position: Medical Oncologist and Associate Professor of Medicine, University of Toronto
Date: February 21, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 7

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astellas	☐	☐	☒	☐
Eli Lilly	☐	☐	☒	☐
Astra Zeneca	☐	☐	☒	☐
Pfizer	☐	☐	☒	☐
Merck	☒	☐	☐	☐
BMS	☐	☒	☐	☐
Amgen	☐	☐	☐	☐
Beigene	☒	☐	☐	☐
Gilead Sciences	☐	☒	☐	☐
Novartis	☐	☐	☒	☐
Seagen	☐	☒	☐	☐
Hoffman La Roche	☒	☐	☐	☐

Declaration for Clinician Dr. Jeffrey Cao

Name: Dr. Jeffrey Cao
Position: Radiation Oncologist, Tom Baker Cancer Centre, Clinical Associate Professor, University of Calgary Provincial Breast Tumour Team Lead, Alberta Health Services Cancer Care Alberta Chair, Canadian Radiation Oncology Foundation
Date: Feb 21, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
CIHR				X
Roche	X			
Pfizer		X		
Novartis	X			
AstraZeneca		X		
Well Doc Alberta	X			
Merck	X			
La Roche-Posay		X		
Knight	X			
Seagen	X			
Oncology Education	X			
Gilead	X			

References

1. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2023. Canadian Cancer Society. Published 2023. https://cancer.ca/en/research/cancer-statistics

2. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med*. 2017;377(19):1836-1846. doi:10.1056/NEJMoa1701830

3. Courtney D, Davey MG, Moloney BM, et al. Breast cancer recurrence: factors impacting occurrence and survival. *Ir J Med Sci*. 2022;191(6):2501-2510. doi:10.1007/s11845-022-02926-x

4. Setiawan VW, Monroe KR, Wilkens LR, Kolonel LN, Pike MC, Henderson BE. Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. *Am J Epidemiol*. 2009;169(10):1251-1259. doi:10.1093/aje/kwp036

5. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*. 2014;106(5):dju055. doi:10.1093/jnci/dju055

6. Seung SJ, Traore AN, Pourmirza B, Fathers KE, Coombes M, Jerzak KJ. A population-based analysis of breast cancer incidence and survival by subtype in Ontario women. *Curr Oncol*. 2020;27(2):e191-e198. doi:10.3747/co.27.5769

7. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. *Nat Rev Dis Primer*. 2019;5(1):66. doi:10.1038/s41572-019-0111-2

8. NCCN Guidelines. NCCN Guidelines - Breast Cancer (Version 1.2024). NCCN Clinical Practice Guidelines in Oncology. Published 2024. Accessed February 7, 2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

9. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32(12):1475-1495. doi:10.1016/j.annonc.2021.09.019

10. Jerzak K, Bouganim N, Brezden-Masley C, et al. HR+/HER2– Advanced Breast Cancer Treatment in the First-Line Setting: Expert Review. *Curr Oncol*. 2023;30(6):5425-5447. doi:10.3390/curroncol30060411

11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *The Lancet*. 2015;386(10001):1341-1352. doi:10.1016/S0140-6736(15)61074-1

12. Rastogi P, O'Shaughnessy J, Martin M, et al. Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. *J Clin Oncol*. Published online January 9, 2024:JCO.23.01994. doi:10.1200/JCO.23.01994

13. Slamon DJ, Stroyakovskiy D, Yardley DA, et al. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: Primary results from the phase III NATALEE trial. *J Clin Oncol*. 2023;41(17_suppl):LBA500-LBA500. doi:10.1200/JCO.2023.41.17_suppl.LBA500

14. Eli Lilly Canada Inc. Verzenio Product Monograph. Date of Revision: December 1, 2023. Accessed February 20, 2024. https://pi.lilly.com/ca/verzenio-ca-pm.pdf

15. Huang J, Zheng L, Sun Z, Li J. CDK4/6 inhibitor resistance mechanisms and treatment strategies (Review). *Int J Mol Med*. 2022;50(4):1-13. doi:10.3892/ijmm.2022.5184

16. Turner NC, Swift C, Kilburn L, et al. ESR1 Mutations and Overall Survival on Fulvestrant versus Exemestane in Advanced Hormone Receptor-Positive Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT Trials. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2020;26(19):5172-5177. doi:10.1158/1078-0432.CCR-20-0224

17. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. *N Engl J Med*. 2023;388(22):2058-2070. doi:10.1056/NEJMoa2214131

18. Millis SZ, Ikeda S, Reddy S, Gatalica Z, Kurzrock R. Landscape of Phosphatidylinositol-3-Kinase Pathway Alterations Across 19 784 Diverse Solid Tumors. *JAMA Oncol*. 2016;2(12):1565-1573. doi:10.1001/jamaoncol.2016.0891

19. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490(7418):61-70. doi:10.1038/nature11412

20. Pereira B, Chin SF, Rueda OM, et al. The somatic mutation profiles of 2,433 breast cancers refines their genomic and transcriptomic landscapes. *Nat Commun*. 2016;7:11479. doi:10.1038/ncomms11479

21. Wander SA, Cohen O, Gong X, et al. The Genomic Landscape of Intrinsic and Acquired Resistance to Cyclin-Dependent Kinase 4/6 Inhibitors in Patients with Hormone Receptor-Positive Metastatic Breast Cancer. *Cancer Discov*. 2020;10(8):1174-1193. doi:10.1158/2159-8290.CD-19-1390

22. O'Leary B, Cutts RJ, Liu Y, et al. The Genetic Landscape and Clonal Evolution of Breast Cancer Resistance to Palbociclib plus Fulvestrant in the PALOMA-3 Trial. *Cancer Discov*. 2018;8(11):1390-1403. doi:10.1158/2159-8290.CD-18-0264

23. Frogne T, Jepsen JS, Larsen SS, Fog CK, Brockdorff BL, Lykkesfeldt AE. Antiestrogen-resistant human breast cancer cells require activated protein kinase B/Akt for growth. *Endocr Relat Cancer*. 2005;12(3):599-614. doi:10.1677/erc.1.00946

24. Miller TW, Hennessy BT, González-Angulo AM, et al. Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. *J Clin Invest*. 2010;120(7):2406-2413. doi:10.1172/JCI41680

25. Ma CX, Reinert T, Chmielewska I, Ellis MJ. Mechanisms of aromatase inhibitor resistance. *Nat Rev Cancer*. 2015;15(5):261-275. doi:10.1038/nrc3920

26. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. *N Engl J Med*. 2019;380(20):1929-1940. doi:10.1056/NEJMoa1813904

27. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520-529. doi:10.1056/NEJMoa1109653

28. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. *Ann Oncol Off J Eur Soc Med Oncol*. 2014;25(12):2357-2362. doi:10.1093/annonc/mdu456

29. ClinicalTrials.gov. *ClinicalTrials.Gov Identifier: NCT04305496*. clinicaltrials.gov; 2023. Accessed December 31, 2023. https://clinicaltrials.gov/study/NCT04305496

30. AstraZeneca Canada Inc. TRUQAP Product Monograph. Date of Approval: January 26, 2024. Accessed February 9, 2024. https://health-products.canada.ca/dpd-bdpp/info?lang=eng&code=103334

31. The Institute of Cancer Research. ICR welcomes FDA approval of first-in-class breast cancer drug. Published November 17, 2023. Accessed February 20, 2024. https://www.icr.ac.uk/news-archive/icr-welcomes-fda-approval-of-first-in-class-breast-cancer-drug