BC Cancer Protocol Summary for Therapy of Advanced Breast Cancer using Capivasertib and Fulvestrant With or Without LHRH Agonist

Protocol Code	*UBRAVCAFLV*
Tumour Group	*Breast*
Contact Physician	*Dr. Nathalie LeVasseur*

ELIGIBILITY:

Patients must:
- Have locally advanced or metastatic breast cancer, and
- Have hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, and
- Have confirmed PIK3CA, AKT1, or PTEN gene alteration, and
- One of the following:
    - progression on at least one hormone therapy in the metastatic setting, or
    - progression on or within 12 months of completing adjuvant hormone therapy,
- Be post-menopausal women (including women with chemically induced menopause with LHRH agonists) or men, and
- Have BC Cancer "Compassionate Access Program" request approval prior to treatment

Patients should have:
- Good performance status
- Access to a treatment center with expertise in managing capivasertib toxicities

Note:
- Laboratory requisition form for somatic NGS testing available here: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Breast/APL%20Somatic%20NGS%20Testing%20Requisition%20Fillable%20Form.pdf
- Capivasertib monotherapy is not funded

EXCLUSIONS:

Patients must not have:
- Progressed on prior therapy with fulvestrant,
- Received more than 2 lines of hormone therapy,
- Received more than 1 line of chemotherapy in the metastatic setting

CAUTIONS:
- Patients with a medical history of diabetes mellitus (blood glucose should be optimized prior to initiation of treatment), or
- Patients with risk factors for hyperglycemia: obesity (BMI>30), fasting glucose greater than 8.9 mmol/L, HbA1C at or above the upper limit of normal, use of systemic steroids or intercurrent infections.

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, GGT, fasting glucose, HbA1C
- Baseline if indicated: CA15-3, ECG, LDH
- Prior to each cycle: CBC & Diff, fasting glucose
- Cycles 1 and 2:
    - Weekly: fasting glucose (prescriber responsible to monitor results and advise on supportive treatment)
    - If clinically indicated: HbA1C prior to cycle 2
- HbA1C every 12 weeks (prior to cycles 4, 7, 10, 13, 16, etc), required, but results do not have to be available to proceed with treatment
- If clinically indicated: HbA1C, fasting glucose weekly, creatinine, sodium, potassium, calcium, magnesium, lactate, serum ketones, albumin, ALT, alkaline phosphatase, total bilirubin, GGT, LDH, CA15-3, ECG, triglycerides, dermatology consult, endocrinology consult

PREMEDICATIONS:

- Not usually required

SUPPORTIVE MEDICATIONS:

- Consider starting prophylactic non-sedating antihistamine for first 8 weeks of therapy for prevention of cutaneous adverse reactions

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
capivasertib	400 mg twice daily for 4 consecutive days followed by 3 days off. Repeat weekly. (Days 1 to 4 in each week of a 28-day treatment cycle)*	PO
Plus		
fulvestrant Cycle 1	500 mg once on Days 1 and 15	IM (Administer as two 250 mg injections)
**fulvestrant Cycle 2 onwards	500 mg once every 28 days ± 3 days	IM (Administer as two 250 mg injections)

* Repeat capivasertib every 28 days (One cycle = 28 days) until disease progression or unacceptable toxicity.
** In case capivasertib is delayed/held/omitted, fulvestrant treatment should be continued as planned.

For women needing chemically induced menopause and male patients:

Drug	Dose	BC Cancer Administration Guideline
goserelin long acting (ZOLADEX)*	3.6 mg every 4 weeks	subcutaneous
OR		
leuprolide long acting (LUPRON DEPOT)*	7.5 mg every 4 weeks	IM

*Once response has been established, the following long-acting agents may be substituted at the physician's discretion. In women, menstrual function, and if necessary, hormone levels can be monitored to ensure effective dosing.

Drug	Dose	BC Cancer Administration Guideline
goserelin long acting (ZOLADEX LA)	10.8 mg every 12 weeks	subcutaneous
OR		
leuprolide long acting (LUPRON DEPOT)	22.5 mg every 12 weeks	IM

DOSE MODIFICATIONS:

capivasertib dose levels

Dose level	Dose and schedule
Starting dose	400 mg twice daily for 4 consecutive days followed by 3 days off
First dose reduction	320 mg twice daily for 4 consecutive days followed by 3 days off
Second dose reduction*	200 mg twice daily for 4 consecutive days followed by 3 days off

*A maximum of 2 dosing reductions are recommended, after which treatment should be discontinued

1. Diarrhea:

Grade*	Severity	Management
1	Increase of up to 3 stools per day over baseline	Continue current capivasertib dose Start anti-diarrheal treatment at the first sign of diarrhea and increase oral fluids
2	Increase of 4 to 6 stools per day over baseline, limiting instrumental ADL	**Hold capivasertib** Start or intensify appropriate anti-diarrheal treatment and monitor as clinically indicated: • If improvement to grade 1 or less within 28 days, resume capivasertib at the same or at one lower dose level as clinically indicated • If persistent or recurring: maintain anti-diarrheal treatment and restart capivasertib at one lower dose level as clinically indicated
3	Increase of equal to or greater than 7 stools per day over baseline; hospitalization indicated; limiting self care ADL	**Hold capivasertib** • If improvement to grade 1 or less within 28 days, resume capivasertib at one lower dose level • If no improvement within 28 days, permanently discontinue capivasertib
4	Life-threatening consequences; urgent intervention indicated	Permanently discontinue capivasertib

*CTCAE Version 5.0

2. Cutaneous adverse reactions:

Grade*	Management**
1	Continue current capivasertib dose Start emollients, topical steroid treatment (or intensify) and consider adding an oral non-sedating antihistamine treatment as clinically indicated to manage symptoms
2	Continue current capivasertib dose Start or intensify topical steroid treatment and consider non-sedating oral antihistamines. • If no improvement, **hold** capivasertib • Resume at the same dose level once symptoms improve to grade 1 or baseline
3	**Hold capivasertib** Start topical steroids of moderate or high strength, non-sedating oral antihistamines and/or systemic steroids. • If symptoms improve within 28 days to grade 1 or less, restart capivasertib at one lower dose level • If symptoms do not improve to grade 1 or less within 28 days, permanently discontinue capivasertib • Recurrent grade 3 rash, permanently discontinue capivasertib
4	Permanently discontinue capivasertib

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**Consider consultation with a Dermatologist as indicated.

3. **Hyperglycemia:** If hyperglycemia develops after initiating treatment, monitor fasting glucose at least twice weekly (on days on and off treatment) until fasting glucose decreases to baseline levels.

Grade*	Fasting glucose level (mmol/L)	Management**
1	Greater than ULN to 8.9 (or HbA1C >7%)	Continue current capivasertib dose Consider starting or adjusting oral anti-diabetic† treatment
2	9 to 13.9	**Hold capivasertib** Start or adjust oral anti-diabetic† treatment. Hold capivasertib for up to 7 days: • If improvement to grade 1 or less occurs within 7 days, restart capivasertib at the same dose level and maintain anti-diabetic treatment • If hyperglycemia persists for more than 7 days, restart capivasertib at one lower dose level and maintain anti-diabetic treatment
3	14 to 27.8	**Hold capivasertib** Start or adjust oral anti-diabetic† treatment. Consider additional anti-diabetic medications such as insulin, as clinically indicated: • If improvement to grade 1 or less within 7 days, restart capivasertib at one lower dose level and maintain anti-diabetic treatment • If no improvement to grade 1 or less within 7 days, permanently discontinue capivasertib • If symptoms of diabetic ketoacidosis are observed, hold capivasertib immediately. If confirmed, permanently discontinue capivasertib
4	Greater than 27.8 or life-threatening sequelae	**Hold capivasertib** Start or adjust oral anti-diabetic† treatment. Consider insulin, intravenous hydration and provide appropriate clinical management: • If fasting glucose decreases to less than or equal to 27.8 within 24 hours, follow the management in the table for the relevant grade • If fasting glucose is confirmed greater than 27.8 after 24 hours, permanently discontinue capivasertib • For life-threatening sequelae of hyperglycemia permanently discontinue capivasertib • If symptoms of diabetic ketoacidosis are observed, hold capivasertib immediately. If confirmed, permanently discontinue capivasertib

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** Consult a healthcare practitioner with expertise in hyperglycemia management as indicated. Counsel patients on lifestyle modifications.
†Treat as per current hyperglycemia management guidelines.

4. Other adverse reactions:

Grade*	Management
1	No dose adjustment required. Initiate appropriate medical treatment and monitor if clinically indicated.
2	**Hold capivasertib** until symptoms improve to grade 1 or less
3	**Hold capivasertib** until symptoms improve to grade 1 or less. If symptoms improve, restart capivasertib at same dose or one lower dose level as clinically appropriate.
4	Permanently discontinue capivasertib

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PRECAUTIONS:

1. **Hyperglycemia:** Hyperglycemia including diabetic ketoacidosis and diabetic metabolic decompensation has been reported in patients receiving capivasertib. Diabetic patients should self-monitor fasting glucose daily at home for the first 2 weeks after treatment initiation, then continue to monitor fasting glucose as frequently as needed to manage hyperglycemia according to the instructions from the healthcare team. Additional HbA1c testing is recommended on week 4, and then at least every 3 months, in patients with diabetes, pre-diabetes, or hyperglycemia at baseline. More frequent fasting glucose and HbA1C monitoring is required in patients with a medical history of diabetes mellitus, pre-diabetes, or those subjects with risk factors for hyperglycemia such as obesity (BMI>30), elevated fasting glucose of >ULN 8.9 mmol/L, HbA1C at or above the upper limit of normal, use of concomitant systemic steroids, intercurrent infections, sepsis or other conditions that may require intensified glycemic management. Management of hyperglycemia may include initiation or intensification of oral anti-diabetic agents (such as metformin), insulin as clinically indicated (if severe), or treatment interruption and/or dose reduction. Endocrinology consult may be required. Permanently discontinue capivasertib in the event of life-threatening hyperglycemia. See dose modifications.
2. **Diarrhea:** Diarrhea is common with capivasertib and can be severe. Serious complications of diarrhea such as dehydration, hypokalemia, acute kidney injury, and arrhythmia have been reported. Increased frequency of diarrhea is reported when metformin is initiated during capivasertib treatment. Patients are advised to start anti-diarrheal treatment (e.g., loperamide) at the first sign of diarrhea and increase oral fluids. Depending on the severity, capivasertib treatment interruption, dose reduction, or permanent discontinuation may be required to manage diarrhea. See dose modifications.
3. **Cutaneous adverse reactions:** Frequently occur with capivasertib and may include maculopapular rash, pruritis, erythema, blisters, drug eruption, dermatitis, eczema, exfoliative dermatitis, purpura, and hyperpigmentation. Erythema multiforme (EM), palmar-plantar erythrodysesthesia (PPE), and drug reaction with eosinophilia and systemic symptoms (DRESS) have also been reported. Management may include emollients, antihistamines, and/or

topical or systemic corticosteroids. Early consultation with dermatologist is recommended. Depending on the severity and duration of reactions, treatment interruption, dose reduction, or permanent discontinuation may be required. See dose modifications.

4. **Drug Interactions:** capivasertib is predominantly metabolized by cytochrome P450 3A4. Potential drug interactions with cytochrome P450 3A4 interacting agents must be considered if combination cannot be avoided and capivasertib dose modifications may be necessary. Avoid concurrent use with moderate or strong CYP3A4 inducers. See BC Cancer Drug Manual.

Call Dr. Nathalie LeVasseur or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Turner NC, Oliveira M, Howell SJ, et al; CAPItello-291 Study Group. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2023 Jun 1;388(22):2058-2070.
2. Capivasertib (Truqap) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies. Sep 2024; 4(9):1-35.
3. Canada's Drug Agency (CDA-AMC) Provisional Funding Algorithm: Breast cancer that is hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, with inclusion of HER2 low. Dec 2024.