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

Protocol Code	***UBRAVIPBFL***
Tumour Group	*Breast*
Contact Physician	*BR Systemic Therapy*

ELIGIBILITY:
Patients must:
- Have locally advanced or metastatic hormone receptor-positive, HER2-negative breast cancer,
- Have confirmed PIK3CA-mutated tumour,
- Be postmenopausal females (premenopausal females requiring chemically induced menopause and males should be treated with LHRH agonists),
- Have progression of disease during or within 12 months of completing adjuvant endocrine therapy,
- Have BC Cancer “Compassionate Access Program” request approval prior to treatment

Patients should have:
- Good performance status

Notes:
- Patients are eligible to receive one PIK3CA-targeted agent, i.e. either inavolisib (UBRAVIPBFL) or capivasertib (UBRAVCAFLV), but not their sequential use
- Patients are also eligible for any of the following but not their sequential use:
  - Inavolisib plus palbociclib plus fulvestrant (UBRAVIPBFL),
    OR
  - Palbociclib plus fulvestrant (BRAVPBFLV) or ribociclib plus fulvestrant (BRAVRBFLV),
    OR
  - Ribociclib plus letrozole/anastrozole (BRAVRIBAI) or palbociclib plus letrozole/anastrozole (BRAVPALAI)
    OR
  - Everolimus plus exemestane (BRAVEVEX)
- Patients who started treatment with CDK4/6 inhibitor and endocrine therapy for advanced breast cancer may switch to UBRAVIPBFL provided that:
  - all UBRAVIPBFL eligibility criteria are met,
  - they’ve been exposed to the existing therapy for less than 3 months, and
  - no progression has occurred
- Patients that have controlled CNS metastases and patients who receive initial chemotherapy due to visceral crisis are eligible
- Patients requiring management of hyperglycemia should be referred to BCDiabetes. Referrals can be made by email (questions@bcdiabetes.ca) or through the online referral form (https://www.bcdiabetes.ca/gp-referrals/). Referrals related to inavolisib-associated hyperglycemia will be prioritized and expedited as clinically appropriate.

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EXCLUSIONS:
Patients must not have:
- Prior systemic therapy in the metastatic setting,
- Uncontrolled diabetes mellitus

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

TESTS:
- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, GGT, fasting glucose, HbA1C
- Baseline if indicated: LDH, CA15-3, ECG
- Cycle 1 (prescriber responsible for monitoring results and advising patients on management):
    - Days 3, 6, 8: fasting glucose
    - Day 15: CBC & Diff, fasting glucose
    - Day 22: fasting glucose
    - Day 22, if Day 15 ANC 0.5 to less than 1.0 x 10^9/L**:** CBC & Diff
- Cycles 2 to 6:
    - Prior to Day 1 of each cycle: CBC & Diff, creatinine, fasting glucose
    - On Day 15: fasting glucose
    - On Day 15 of Cycle 2 (if clinically indicated; if dose adjustment or delay in Cycle 1): CBC & Diff
    - On Day 22 of Cycle 2, if Day 15 ANC 0.5 to less than 1.0 x 10^9/L: CBC & Diff
    - Prior to Cycle 4 (required, but results do not have to be available to proceed with treatment): HbA1C
- Cycles 7 onwards:
    - Prior to each cycle: fasting glucose, CBC & Diff, creatinine
    - HbA1C every 12 weeks (required, but results do not have to be available to proceed with treatment), i.e., prior to cycles 7, 10, 13, 16, etc.
- If clinically indicated: fasting glucose weekly, ALT, alkaline phosphatase, total bilirubin, GGT, LDH, serum ketones, CA15-3, ECG, serum cholesterol, triglycerides, urea, LH, FSH and serum estradiol levels (see Precautions, below).
- Weekly nursing assessment during Cycle 1 to check fasting glucose levels, then optional in subsequent cycles.

PREMEDICATIONS:
- Antiemetic protocol for low emetogenic treatment (see SCNAUSEA)

SUPPORTIVE CARE MEDICATIONS:
- Stomatitis prophylaxis: alcohol-free dexamethasone 0.1 mg/mL solution. Use 10 mL four times a day. Swish in mouth for 2 minutes then spit out. Do not eat or drink for 1 hour after using mouthwash. Start on Day 1 of inavolisib treatment. Continue for 8 weeks. May continue beyond 8 weeks at the discretion of the treating oncologist.
- Consider metformin for hyperglycemia prophylaxis for patients at high risk of hyperglycemia.

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TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
inavolisib	9 mg* once daily continuously	PO
palbociclib	125 mg once daily on Days 1 to 21 of each 28-day cycle, followed by 7 days off	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)

*For patients with creatinine clearance (CrCl) of 30 to 59 mL/min, the recommended inavolisib starting dose is 6 mg once daily. If CrCl is less than 30 mL/min, the recommended inavolisib starting dose is 3 mg once daily.

- 1 cycle = 28 days
- If palbociclib is resumed after being held due to toxicity:
  - Stop on Day 21 as scheduled
  - Maintain at least 7 days rest before resuming next cycle
- If oral medications are delayed/held/omitted, fulvestrant treatment should continue as planned.
- Treatment is continued until disease progression or unacceptable toxicity.

For female patients 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

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DOSE MODIFICATIONS:

Dose Levels:

Dose Level	Inavolisib*	Palbociclib
Starting dose	9 mg	125 mg
First dose reduction	6mg	100 mg (should not re-escalate to 125 mg)
Second dose reduction	3 mg	75 mg (may re-escalate to 100 mg at physician's discretion)
Further dose reduction	Discontinue	Discontinue

*Inavolisib dose may be re-escalated to a maximum daily dose of 9 mg based on clinical evaluation of the patient by the treating healthcare provider.

1. Hyperglycemia:

Fasting Glucose (mmol/L)	Inavolisib Management
Less than or equal to ULN	Continue with current dose
Greater than ULN to 8.9	• No inavolisib dose adjustment required • Consider dietary modification and ensure adequate hydration • Consider initiating or intensifying anti-hyperglycemic medications if patient has risk factors for hyperglycemia
Greater than 8.9 to 13.9	• Withhold inavolisib • Initiate/optimize antihyperglycemic therapy and adequate hydration • Once fasting glucose level decreases to 8.9 mmol/L or lower, resume inavolisib at the same dose level. • If elevated fasting glucose levels of 11.1 to 13.9 mmol/L persists for more than 7 days despite appropriate antihyperglycemic management, consider endocrinology consult
Greater than 13.9 to 27.8	• Withhold inavolisib • Initiate/optimize antihyperglycemic therapy and adequate hydration • If fasting glucose level decreases to 8.9 mmol/L or lower within 7 days, resume inavolisib at same dose level • If fasting glucose level decreases to 8.9 mmol/L or lower takes longer than 7 days, resume inavolisib at the next lower dose level • If fasting glucose level greater than 13.9 – 27.8 mmol/L recurs within 30 days, withhold inavolisib until fasting glucose level decreases to 8.9 mmol/L or lower, then resume inavolisib at next lower dose level
Greater than 27.8	• Withhold inavolisib • Initiate/optimize antihyperglycemic therapy • If fasting glucose level decreases to less than 8.9, resume inavolisib at next lower dose level

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	• If fasting glucose level greater than 27.8 recurs within 30 days, permanently discontinue inavolisib

2. Hematological:

No hematological dose modifications for fulvestrant or LHRH agonist (if using).

Neutropenia:

Neutropenia (ANC x10^9/L)	Inavolisib Management	Palbociclib Management*
Greater than or equal to 1.0	Continue both drugs at same dose.	

0.5 to less than 1.0	Continue at same dose.	<u>Day 1:</u>
		• Delay.
		• If ANC greater than or equal to 1.0 x 10^9/L within 1 week*, resume at same dose.
		
		<u>Day 15 of Cycles 1 and 2:</u>
		• Continue same dose for remainder of cycle. Check ANC on Day 22;
		• If ANC on Day 22 is:
		  • greater than or equal to 0.5 x 10^9/L: continue at same dose for next cycle, when ANC greater than or equal to 1.0 x 10^9/L
		  • less than 0.5 x 10^9/L: resume at next lower dose level, when ANC greater than or equal to 1.0 x 10^9/L
		
		Consider palbociclib dose reduction if hematologic recovery takes more than 1 week, or if toxicity recurs on Day 1 of subsequent cycles.

Less than 0.5 OR Less than 1.0 plus fever and/or infection	• Withhold. • When ANC recovers to greater than or equal to 1.0 x 10^9/L, may resume at same dose level or reduce to next lower dose level as clinically indicated.	<u>Day 1:</u> • Delay. • When ANC greater than or equal to 1.0 x 10^9/L, resume at next lower dose. <u>Day 15 of Cycles 1 and 2:</u> • Omit for the remainder of cycle. • When ANC recovers to greater than or equal to 1.0 x 10^9/L, resume at next lower dose.

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Thrombocytopenia:

Platelets ($x10^9$/L)	**Inavolisib Management**	**Palbociclib Management***
Greater than or equal to 50	Continue at same dose	
25 to 49	Continue at same dose	<u>Day 1:</u> • Delay. • When greater than or equal to 50 x 10^9/L, resume at next lower dose. <u>Day 15 of Cycles 1 and 2:</u> • Omit for the remainder of cycle. • When platelets are greater than or equal to 50 x 10^9/L, resume at next lower dose.
Less than 25	• Withhold inavolisib. • Once platelets recover to greater than or equal to 50, may resume at same dose level or reduce to next lower dose level as clinically indicated.	<u>Day 1:</u> • Delay. • When greater than or equal to 50 x 10^9/L, resume at next lower dose. <u>Day 15 of Cycles 1 and 2:</u> • Omit remainder of cycle. • When platelets are greater than or equal to 50 x 10^9/L, resume at next lower dose.

***Consider palbociclib dose reduction hematologic recovery takes more than 1 week, or if toxicity recurs on Day 1 of subsequent cycles.

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3. Stomatitis:

Severity	Inavolisib Management
Grade 1 Asymptomatic or mild symptoms	• No inavolisib adjustment required • Initiate/optimize appropriate supportive care therapy (e.g. corticosteroid-containing mouthwash) as indicated
Grade 2 Moderate pain or ulcer that does not interfere with oral intake; modified diet as indicated	• Withhold inavolisib • Initiate/optimize appropriate supportive care therapy • Once symptoms recover to Grade 1 or less, resume inavolisib at same dose level • For recurrent Grade 2 stomatitis, withhold inavolisib until recovery to Grade 1 or less, then resume at next lower dose level
Grade 3 Severe pain; interfering with oral intake	• Withhold inavolisib • Initiate/optimize appropriate supportive care therapy • Once symptoms recover to Grade 1 or less, resume inavolisib at next lower dose level
Grade 4 Life-threatening consequences; urgent intervention indicated	Permanently discontinue inavolisib

4. Diarrhea:

Severity	Inavolisib Management
Grade 1 Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	• No inavolisib adjustment required • Initiate/optimize appropriate supportive care therapy and monitor as clinically indicated
Grade 2 Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living	• Withhold inavolisib • Initiate/optimize appropriate supportive care therapy • Once symptoms recover to Grade 1 or less, resume inavolisib at same dose level • For recurrent Grade 2 diarrhea, withhold inavolisib until recovery to Grade 1 or less, then resume at next lower dose level
Grade 3 Increase of greater than or equal to 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Withhold inavolisib • Initiate/optimize appropriate supportive care therapy • Once symptoms recover to Grade 1 or less, resume inavolisib at next lower dose level
Grade 4	Permanently discontinue inavolisib

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Life-threatening consequences; urgent intervention indicated	

5. Other Adverse Reactions:

Severity	Inavolisib Management	Palbociclib Management
Grade 1	No dose adjustment required	
Grade 2	Consider withholding inavolisib, until recovery to Grade 1 or less, then resume at same dose level	No dose adjustment required
Grade 3	• Withhold inavolisib • If first occurrence: Upon recovery to Grade 1 or less, resume inavolisib at same dose level • If second or subsequent recurrence: Upon recovery to Grade 1 or less, resume inavolisib at next lower dose level	• Withhold palbociclib • Initiate/optimize appropriate supportive care therapy • Upon recovery to less than or equal to Grade 2, resume at next lower dose level
Grade 4	Permanently discontinue inavolisib	

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Hepatic dysfunction:** No dose adjustment is required for mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), use 75 mg PO once daily for 21 consecutive days in a 28-day cycle.
3. **Drug-drug interactions:** palbociclib is metabolized via CYP3A enzymes. Concurrent use of CYP3A inhibitors, substrates or inducers may affect palbociclib serum level.
4. **Ovarian suppression** with LHRH agonists can be less effective in women with BMI above 26. Consider intermittently testing LH, FSH, and serum estradiol levels in this population.
5. **Hyperglycemia:** Severe cases of hyperglycemia, including ketoacidosis have been reported with inavolisib use. Fasting blood glucose and HbA1C testing should be completed at baseline, and monitored at regular intervals throughout treatment. Lab monitoring of fasting blood glucose levels is preferred, but home self-monitoring may be considered in selected cases. Patients should contact their healthcare team as soon as possible for guidance for any fasting blood glucose reading of 9 mmol/L or greater. Particularly close monitoring is indicated for patients with hyperglycemia risk factors which include HbA1C greater than or equal to 5.7%, BMI greater than or equal to 30, age greater than or equal to 45 years, history of gestational diabetes, or family history of diabetes mellitus. Blood glucose levels should be optimized before inavolisib treatment initiation, and inavolisib should be avoided in patients with uncontrolled diabetes mellitus. Management of hyperglycemia may include initiation or intensification of antihyperglycemic therapy, lifestyle changes, inavolisib treatment interruption, dose reduction or permanent discontinuation.
6. **Diarrhea** is a frequently reported adverse effect of inavolisib. Patients are advised to start anti-diarrheal treatment at the first sign of diarrhea and to increase oral fluids. Depending on the

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severity, inavolisib treatment interruption, dose reduction or permanent discontinuation may be required.

7. **Stomatitis** has been reported with inavolisib treatment. Prophylactic corticosteroid mouthwash may be considered. Patients should avoid alcohol- and peroxide-containing mouthwashes as they may worsen symptoms. Treatment of stomatitis may include corticosteroid mouthwashes, lifestyle changes, inavolisib treatment interruption, dose reduction or permanent discontinuation.
8. **Skin reactions** such as dry skin, rash, dermatitis and folliculitis have been reported with inavolisib. All events were Grade 1 or 2 in severity. Routine rash prophylaxis with a non-sedating antihistamine or topical agents is not required but may be considered on a case-by-case basis.

Contact the BR Systemic Therapy physician at your regional cancer centre or the BR Tumour Group Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Turner NC, Im SA, Saura C et al. Inavolisib-Based Therapy in PIK3CA-Mutated Advanced Breast Cancer. N Engl J Med 2024;391:1584-96.
2. Inavolisib (Itovebi) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. Canadian Journal of Health Technologies. December 2025; 5(12): 1-37.

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