BC Cancer Protocol Summary for Therapy of Advanced Breast Cancer using Palbociclib and Aromatase Inhibitor With or Without LHRH Agonist

Protocol Code	*UBRAVPALAI*
Tumour Group	*Breast*
Contact Physician	*Dr. Sophie Sun*

ELIGIBILITY:

- Post-menopausal women and men with ER-positive, HER2-negative advanced breast cancer with metastatic disease (including women with chemically induced menopause with LHRH agonists).
- Patients should have no prior endocrine treatment for metastatic disease, but may have up to one prior line of chemotherapy
- Patients should not be resistant to prior (neo) adjuvant aromatase inhibitor therapy (patients must be a minimum of 12 months from last adjuvant aromatase inhibitor)
- Good performance status
- A Compassionate Access Program (CAP) approval is required prior to the initiation of treatment (please refer to https://cap.phsa.ca/).

** Note: Patients are eligible to receive any of the following, but not their sequential use:*

- *Palbociclib plus fulvestrant (UBRAVPBFLV) or Ribociclib plus fulvestrant (UBRAVRBFLV), OR*
- *Ribociclib plus letrozole/anastrozole (UBRAVRIBAI) or Palbociclib plus letrozole/anastrozole (UBRAVPALAI).*

Patients who have received the above regimens are NOT eligible for subsequent use of everolimus plus exemestane (BRAVEVEX).

*** Note: For patients recently diagnosed with metastatic breast cancer, and who have initiated anastrozole or letrozole monotherapy within the past 6 months, palbociclib can be added if the rest of the above criteria are met.*

EXCLUSIONS:

- Patients should not have active or uncontrolled metastases to the central nervous system.
- Advanced symptomatic and life-threatening visceral metastases
- Pregnant women
- Palbociclib monotherapy

CAUTIONS:

- Severe hepatic dysfunction (total bilirubin greater than 50 micromol/L)
- Severe renal impairment (calculated creatinine clearance less than 30 mL/min)

TESTS:

- Baseline: CBC & diff, platelets, creatinine, ALT, alkaline phosphatase, total bilirubin, GGT, LDH
- Baseline if indicated: CA15-3, ECG
- Cycles 1 and 2 of palbociclib
  - Prior to day 1 of each cycle: CBC & diff, platelets, creatinine
  - On day 15: CBC & diff, platelets
- Cycles 3 to 6 of palbociclib
  - Prior to each cycle: CBC & diff, platelets, creatinine
- Cycles 7 onwards of palbociclib
  - If ANC 1.0 $x10^9$/L or higher during first 6 cycles:
    - Prior to every third cycle: CBC & diff, platelets, creatinine
  - If ANC less than 1.0 $x10^9$/L during first 6 cycles:
    - Prior to each cycle: CBC & diff, platelets, creatinine
- If clinically indicated: ALT, alkaline phosphatase, total bilirubin, GGT, LDH, CA15-3, ECG, serum cholesterol, triglycerides

PREMEDICATIONS:

- Not usually required

TREATMENT:

Until disease progression or unacceptable toxicity

Drug	Dose	BC Cancer Administration Guideline
palbociclib	125 mg once daily for 21 days on, 7 days off (one cycle = 28 days)*	PO
Plus Aromatase Inhibitor		
letrozole	2.5 mg once daily continuously	PO
OR		
anastrozole	1 mg once daily continuously	PO

* Repeat palbociclib every 28 days. If a dose is missed, take the **next** dose at the same usual time. If a dose is held due to toxicity, patient should stop on day 21 of the original schedule when resuming dose to maintain the 1-week rest.

For women needing chemically induced menopause and male patients:

Drug	Dose	BC Cancer Administration Guideline
buserelin long acting (SUPREFACT DEPOT)*	6.3 mg every 6 weeks x 2 treatments then every 8 weeks	subcutaneous
OR		
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
buserelin long acting (SUPREFACT DEPOT)*	9.45 mg every 12 weeks	subcutaneous
OR		
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:

Palbociclib dose level

Dose level	Daily dose
Starting dose	125 mg/d
First dose reduction	100 mg/d (should not re-escalate to 125 mg/d)
Second dose reduction	75 mg/d* (may re-escalate to 100 mg/d at physician's discretion

* Discontinue if further dose reduction required below 75 mg/d

1. Hematological

Neutropenia (ANC x10^9/L)	Dose Modifications
Grade 1 and 2 (greater than or equal to 1.0)	Continue at same dose.
Grade 3 (0.5 to less than 1.0)*	<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, when ANC greater than or equal to 1.0 x 10^9/L
Grade 4 (less than 0.5) OR Grade 3 plus fever and/or infection	<u>Day 1</u> Delay. When ANC ≥ 1.0 x 10^9/L, resume at next lower dose.
	<u>Day 15 of cycles 1 and 2</u> Omit remainder of cycle. When ANC greater than or equal to 1.0 x 10^9/L, resume at next lower dose.

Thrombocytopenia (Platelets x10^9/L)	Dose Modifications
Grade 1 and 2 (greater than or equal to 50)	Continue at same dose.
Grade 3 (25 to 49) and Grade 4 (less than 25) *	Day 1 Delay. When greater than or equal to 50 x 10^9/L, resume at next lower dose.
	Day 15 of cycles 1 and 2 Omit remainder of cycle. When platelets greater than or equal to 50 x 10^9/L, resume at next lower dose.

*Consider dose reduction if more than 1 week to recover, or recurrent on day 1 of subsequent cycles.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Renal dysfunction:** palbociclib has not been studied in patients with creatinine clearance less than 15 mL/min.
3. **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.
4. **Drug-drug interactions:** palbociclib is metabolized via CYP3A enzymes. Concurrent use of CYP3A inhibitors, substrates or inducers may affect palbociclib serum level.

Call Dr. Sophie Sun or tumour group delegate at (604) 930-2098 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Finn RS, et al. Palbociclib and letrozle in advanced breast cancer. N Engl J Med 2016;375:1925-36.
2. Finn RS, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25-35.
3. Pfizer Canada Inc. IBRANCE® product monograph. Kirkland, Quebec; 24 January 2020.