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

Protocol Code	*UBRAVPBFLV*
Tumour Group	*Breast*
Contact Physician	*Dr. Stephen Chia*

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 may have received up to one prior line of systemic therapy for metastatic disease.
- Patients are eligible for upfront CDK 4/6 inhibitor therapy plus fulvestrant even if < 12 months from prior (neo) adjuvant endocrine therapy
- 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 fulvestrant 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		
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 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.

**In case palbociclib 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
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) *	<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 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. Stephen Chia or tumour group delegate at (604) 930-2098 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Slamon DJ et al. Overall Survival with Ribociclib plus Fulvestrant in Advance Breast Cancer. N Engl J Med. 2020 Feb 6;382(6):514-524.
2. Sledge GW et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2. JAMA Oncol. 2020;6(1):116-124.
3. Turner NC et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2018 Nov 15;379(20):1926-1936.