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 no prior systemic treatment (including chemotherapy) for metastatic disease (including women with chemically induced menopause with LHRH agonists).
- 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), nor have active or uncontrolled metastases to the central nervous system.
- Good performance status
- BC Cancer CAP approval

** Note: Patients are eligible to receive palbociclib plus letrozole/anastrozole (UBRAVPALAI) or everolimus plus exemestane (BRAVEVEX), but not sequential use of these combination regimens.*
*** 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:

- 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 each cycle and on day 15: CBC & diff, platelets
- Cycles 3 to 6 of palbociclib
  - Prior to each cycle: CBC & diff, platelets
- 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
  - If ANC less than 1.0 $x10^9$/L during first 6 cycles:
    - Prior to each cycle: CBC & diff, platelets

- If clinically indicated: creatinine, 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 with food
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:

Drug	Dose	BC Cancer Administration Guideline
buserelin (base) depot (SUPREFACT DEPOT®)*	6.3 mg every 6 weeks x 2 treatments then every 8 weeks	SC
OR		
goserelin (ZOLADEX®)*	3.6 mg every 4 weeks	SC
OR		
leuprolide (LUPRON®)*	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. Menstrual function, and if necessary, hormone levels can be monitored to ensure effective dosing.

Drug	Dose	BC Cancer Administration Guideline
buserelin (base) depot (SUPREFACT DEPOT®)*	9.45 mg every 12 weeks	SC
OR		
goserelin (ZOLADEX®)*	10.8 mg every 12 weeks	SC
OR		
leuprolide (LUPRON®)*	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 same dose.
Grade 3* (0.5 to less than 1.0)	<u>Day 1 lab</u> Hold. If ANC 1.0 x 10^9/L or higher within 1 week, resume at same dose.
	<u>Day 15 of cycles 1 and 2</u> Continue same dose. If ANC on day 22 is: • 1.0 x 10^9/L or higher: resume at same dose. • 0.5 to less than 1.0 x 10^9/L: resume at same dose. • less than 0.5 x 10^9/L: resume at next lower dose
Grade 4 (less than 0.5) OR Grade 3 plus fever and/or infection	Hold. When ANC 1.0 x 10^9/L or higher, resume at next lower dose.

** Consider dose reduction if more than 1 week to recover, 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 30 mL/min.
3. **Hepatic dysfunction:** palbociclib has not been studied in patients with moderate or severe hepatic impairment (total bilirubin greater than 1.5 × ULN).
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.