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

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

ELIGIBILITY:

Patients must be:

- Post-menopausal women (including women with chemically induced menopause with LHRH agonists) and men with ER-positive, HER2-negative advanced or metastatic breast cancer,
- should have no prior endocrine treatment for advanced or metastatic disease, but may have up to one prior line of chemotherapy for advanced or metastatic disease, and
- should not be resistant to prior (neo) adjuvant aromatase inhibitor therapy (i.e., a minimum of 12 months from last adjuvant aromatase inhibitor)

Notes:

- Patients should have 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 ribociclib plus letrozole/anastrozole (UBRAVRIBAI) or palbociclib plus letrozole/anastrozole (UBRAVPALAI) or everolimus plus exemestane (BRAVEVEX), but not sequential use of these combination regimens.*

** 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, ribociclib 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
- Patients with untreated congenital long QT syndrome, a QTc interval of ≥ 450 ms at baseline, and those who are at significant risk of developing QTc prolongation
- Pregnant women
- Ribociclib monotherapy

CAUTIONS:

- Severe hepatic dysfunction
- Severe renal impairment

TESTS:

- Baseline: CBC & diff, platelets, creatinine, albumin, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, calcium, magnesium, phosphorus, GGT, LDH, ECG
- Baseline if indicated: CA15-3
- Cycle 1 of ribociclib
  - Prior to days 1 and 15: CBC & diff, platelets, creatinine, albumin, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, calcium, magnesium, phosphorus, ECG
- Cycle 2 of ribociclib
  - Prior to day 1 only: CBC & diff, platelets, creatinine, albumin, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, calcium, magnesium, phosphorus, ECG
- Cycles 3 to 6 of ribociclib
  - Prior to each cycle: CBC & diff, platelets, creatinine, ALT, alkaline phosphatase, total bilirubin
- Cycles 7 onwards of ribociclib
  - 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 every 1-2 cycles: CBC & diff, platelets, creatinine
- If clinically indicated: albumin, ALT, alkaline phosphatase, total bilirubin, GGT, LDH, sodium, potassium, calcium, magnesium, phosphorus, CA15-3, ECG, serum cholesterol, triglycerides, CEA, CA125

PREMEDICATIONS:

- Not usually required

TREATMENT:

Until disease progression or unacceptable toxicity

Drug	**Dose**	**BC Cancer Administration Guideline**
ribociclib	600 mg once daily in the morning 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 ribociclib every 28 days. If a dose is missed, take the **next** dose at the same usual time.

For women needing chemically induced menopause:

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)*	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 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:

Ribociclib dose level

Dose level	Daily dose
Starting dose	600 mg
First dose reduction	400 mg
Second dose reduction	200 mg*

* Discontinue if further dose reduction required below 200 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. When ANC greater than or equal to 1.0 x 10^9/L, resume at same dose (If grade 3 neutropenia recurs, delay until recovery to 1.0 x 10^9/L, and reduce to next lower dose)
	<u>Day 15 of cycle 1</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 cycle 1</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 (greater than or equal to 75)	Continue at same dose.
Grade 2 (50 to 74)	<u>Day 1</u> Delay. When platelets greater than or equal to 75 x 10^9/L, resume at same dose.
	<u>Day 15 of cycle 1</u> Continue same dose for remainder of cycle. Check platelets on day 22; If platelets on day 22 are: • greater than or equal to 50 x 10^9/L: continue at same dose for next cycle, when platelets greater than or equal to 75 x 10^9/L • less than 50 x 10^9/L: resume at next lower dose, when platelets greater than or equal to 75 x 10^9/L
Grade 3 (25 to 49)	<u>Day 1</u> Delay. When platelets greater than or equal to 75 x 10^9/L, resume at same dose. (If grade 3 thrombocytopenia recurs, delay until recovery to 75 x 10^9/L, and reduce to next lower dose)
	<u>Day 15 of cycle 1</u> Omit remainder of cycle. • When platelets greater than or equal to 75 x 10^9/L, resume at next lower dose.
Grade 4 (less than 25) *	<u>Day 1</u> Delay. When greater than or equal to 75 x 10^9/L, resume at next lower dose.
	<u>Day 15 of cycle 1</u> Omit remainder of cycle. When platelets greater than or equal to 75 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.

2. Hepatic dysfunction:

Hepatic Impairment	Starting Dose at Baseline
Mild (Child-Pugh class A)	600 mg
Moderate (Child-Pugh class B)	400 mg
Severe (Child-Pugh class C)	400 mg

Bilirubin		ALT or AST	Dose
≤ 2 x ULN	And	> 3 to 5 x ULN	If baseline ALT or AST > 3 to 5 x ULN, continue at same dose. If baseline ALT or AST < 3 x ULN, delay until ≤ baseline, then resume at same dose. If recurs, then resume at next lower dose
		> 5 to 20 x ULN	Delay until ≤ baseline, then resume at next lower dose. If recurs, then discontinue
		> 20 x ULN	Discontinue
> 2 x ULN (in absence of cholestasis)	And	> 3 x ULN	Discontinue

ULN = upper limit of normal

3. Renal dysfunction:

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Starting Dose at Baseline
greater than or equal to 30	600 mg
15 to 29	200 mg

*as reported in patient's laboratory report

4. QT interval prolongation:

QTc Interval (ms)	Dose
> 480	Delay. If QTc resolves to < 481 ms, restart at same dose level. If recurs, delay until QTc resolves to < 481 ms, then resume at next lower dose.
> 500	Delay, if QTc > 500 ms. If QTc resolves to < 481 ms, resume at next lower dose.
If QTc interval prolongation is **either** > 500 ms **or** > 60 ms increase from baseline **AND** associated with torsades de pointes or polymorphic ventricular tachycardia, unexplained syncope or signs/symptoms of serious arrhythmia, permanently discontinue ribociclib.	

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **QT interval prolongation:** has been reported; caution in patients with known risk factors (concurrent therapy with drugs associated with QTc prolongation, torsades de pointes, bradycardia, and/or drugs that disrupt electrolyte levels). Correct preexisting electrolyte disturbances and monitor ECG and electrolytes. Administer ribociclib in the morning as QT prolongation risk may be increased when it is taken in the evening due to bradycardia which naturally occurs during sleep.
3. **Hepatic dysfunction:** Hepatotoxicity has been reported, including hepatocellular injury and drug-induced liver injury.
4. **Renal dysfunction:** ribociclib has not been studied in patients with creatinine clearance less than 15 mL/min.
5. **Drug-drug interactions:** ribociclib is metabolized via CYP3A enzymes. Concurrent use of CYP3A inhibitors, substrates or inducers may affect ribociclib 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. Hortobagyi G, et al. Ribociclib and First line Therapy for HR Positive Advanced Breast Cancer. N Engl J Med 2016;375:1738-48..
2. Im SA, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med Published Online June 4, 2019.