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

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

ELIGIBILITY:

Patients:

- Must have ER-positive, HER2-negative advanced or metastatic breast cancer,
- Must be post-menopausal women (including women with chemically induced menopause with LHRH agonists) or men,
- May have received any lines of prior endocrine therapy (except fulvestrant) and up to one prior line of chemotherapy for advanced or metastatic disease. This includes patients whose disease progressed:
    - On (neo) adjuvant endocrine therapy,
    - Within 12 months of completing adjuvant endocrine therapy, or
    - On or after endocrine therapy for advanced or metastatic disease.
- Must not be resistant to prior adjuvant abemaciclib (patients must be a minimum of 6 months from completion of adjuvant abemaciclib)

Patients should have:

- Good performance status

Notes:

- Patients are eligible to receive any of the following, but not their sequential use:
    - 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)
- For patients recently diagnosed with metastatic breast cancer, and who have initiated fulvestrant monotherapy within the past 6 months, ribociclib can be added if the rest of the above criteria are met.

EXCLUSIONS:

Patients must not have:

- Active or uncontrolled metastases to the central nervous system,
- Advanced symptomatic and life-threatening visceral metastases,
- Untreated congenital long QT syndrome, a QTc interval of greater than or equal to 450 ms at baseline, and those who are at significant risk of developing QTc prolongation,
- Pregnant women, or
- Ribociclib monotherapy

CAUTIONS:

- Severe hepatic dysfunction
- Severe renal impairment

TESTS:

- Baseline: CBC and differential, 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:
    - Day 15: CBC and differential, platelets, creatinine, albumin, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, calcium, magnesium, phosphorus, ECG
    - Day 22 if ANC on Day 15 is 0.5 to less than 1.0, or if platelets on Day 15 are 50 to less than 74: CBC and differential, platelets
- Cycle 2 of ribociclib
    - Prior to Day 1: CBC and differential, platelets, creatinine, albumin, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, calcium, magnesium, phosphorus, ECG
    - Day 15 (if clinically indicated; for dose adjustment or delay in cycle 1): CBC and differential, platelets
    - Day 22 if ANC on Day 15 is 0.5 to less than 1.0, or if platelets on Day 15 are 50 to less than 74: CBC and differential, platelets
- Cycles 3 to 6 of ribociclib:
    - Prior to each cycle: CBC and differential, 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 and differential, platelets, creatinine
    - If ANC less than 1.0 $x10^9$/L during first 6 cycles:
        - Prior to every 1 to 2 cycles: CBC and differential, 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:

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		
fulvestrant Cycle 1	500 mg once daily on Days 1 and 15	IM (Administer as two 250 mg injections)
**fulvestrant Cycle 2 onwards	500 mg once daily on Day 1 of cycle 2 then repeat every 28 days ± 3 days	IM (Administer as two 250 mg injections)

*Repeat ribociclib every 28 days until disease progression or unacceptable toxicity

- One cycle = 28 days
- If a dose is missed, take the **next** dose at the same usual time.
- If ribociclib is resumed after being held due to toxicity:
    - Stop on Day 21 as scheduled
    - Maintain at least 7 days rest before resuming next cycle.

**In case ribociclib 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 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

* buserelin 6.3 mg every 8 weeks is an option for post Cycle 1 if there is toxicity or break through on other LHRH agents.

**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:

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 per day.

1. Hematological- for Ribociclib

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

Neutropenia (ANC x10^9/L)	Ribociclib 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 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 greater than or equal to 1.0 x 10^9/L, resume at next lower dose.
	<u>Day 15 of cycle 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)	Ribociclib 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 and 2</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 and 2</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 and 2</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	Ribociclib 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	Ribociclib Dose
Less than or equal to 2 x ULN	And	Greater than 3 to 5 x ULN	If baseline ALT or AST greater than 3 to 5 x ULN, continue at same dose. If baseline ALT or AST less than 3 x ULN, delay until less than or equal to baseline, then resume at same dose. If recurs, then resume at next lower dose
		Greater than 5 to 20 x ULN	Delay until less than or equal to baseline, then resume at next lower dose. If recurs, then discontinue
		Greater than 20 x ULN	Discontinue
Greater than 2 x ULN (in absence of cholestasis)	And	Greater than 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** greater than 500 ms **or** greater than 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. 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.