BC Cancer Protocol Summary for Treatment of Adjuvant Breast Cancer using Abemaciclib and Aromatase Inhibitor With or Without LHRH Agonist

Protocol Code	*UBRAJABEAI*
Tumour Group	*Breast*
Contact Physician	*Dr. Nathalie LeVasseur*

ELIGIBILITY:

Patients must have:

- Hormone receptor positive, HER-2 negative early breast cancer,
- Fully resected with definitive surgery of primary breast tumour within previous 16 months,
- Ki-67 score of at least 20% confirmed before treatment is initiated,
- Have one of the following:
  - Tumour involvement of 4 or more ipsilateral axillary lymph nodes, or
  - Tumour involvement of 1 to 3 ipsilateral axillary lymph node(s) AND at least one of the following:
    - Grade 3 disease, or
    - Primary tumour size 5 cm or greater, and
- BC Cancer “Compassionate Access Program” request approval prior to treatment

Notes:

- Patients currently stable on adjuvant aromatase inhibitor (BRAJANAS, BRAJLET, BRAJEXE, BRAJLHRHAI) without progression can switch to UBRAJABEAI if all other eligibility are met
- Subsequent treatment with CDK4/6 inhibitor with aromatase inhibitor (BRAVPALAI, BRAVRIBAI) permitted if disease progression 6 months or more after completion of adjuvant abemaciclib, and if 12 months or more from last adjuvant aromatase inhibitor
- Subsequent treatment with CDK4/6 inhibitor with fulvestrant (BRAVPBFLV, BRAVRBFLV) permitted if disease progression 6 months or more after completion of adjuvant abemaciclib
- Patients are eligible to receive one of the following, but not their sequential use: abemaciclib per UBRAJABEAI/UBRAJABET or olaparib per UBRAJOLA
- BC Cancer Compassionate Access Program (CAP) approval is not required to switch between UBRAJABEAI and UBRAJABET
- Abemaciclib (UBRAJABEAI or UBRAJABET) use after capecitabine (BRAJCAP) is funded

EXCLUSIONS:

Patients must not have:

- Metastatic disease,
- Inflammatory breast cancer,
- Prior treatment with a CDK4/6 inhibitor,
- Current pregnancy,
- Abemaciclib monotherapy

CAUTIONS:

- Severe hepatic dysfunction

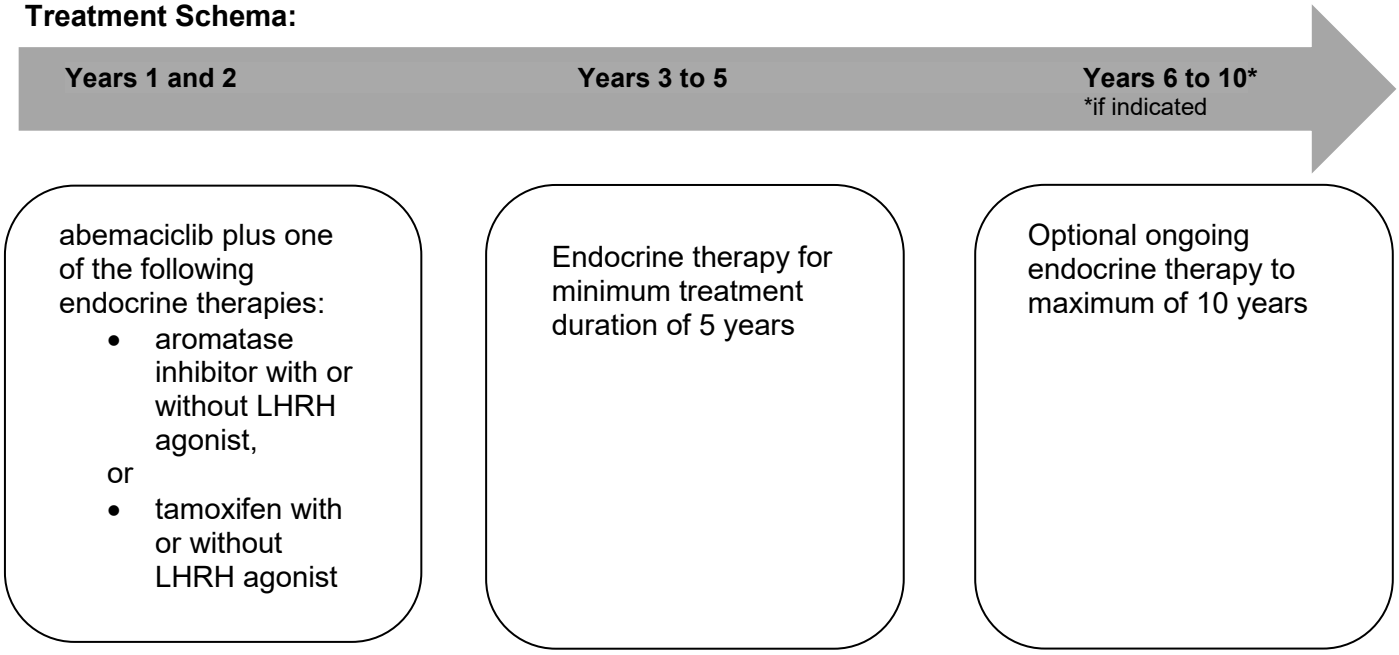
TESTS:

- Baseline: CBC & Diff, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase, GGT, urea
- Baseline if clinically indicated: serum cholesterol, triglycerides
- Day 15 for Cycles 1 and 2 (physician will be responsible to check and advise patient on dose adjustment): CBC & Diff, platelets, total bilirubin, ALT
- Monthly for Cycles 1 to 3, then at each physician visit: CBC & Diff, platelets, creatinine, total bilirubin, ALT, urea
- If clinically indicated: Sodium, potassium, calcium, albumin, magnesium, alkaline phosphatase, GGT, serum cholesterol, triglycerides

PREMEDICATIONS:

- Use antiemetic protocol for low emetogenic chemotherapy protocols (see protocol SCNAUSEA)

Treatment Schema:



TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
abemaciclib One cycle = 28 days	150 mg twice daily	PO
Plus Aromatase Inhibitor:		
letrozole	2.5 mg daily	PO
or		
anastrozole	1 mg daily	PO
or		
exemestane	25 mg daily	PO

Duration of treatment:

- Continuously for a maximum of 26 cycles or 2 years of treatment, unless disease progression or unacceptable toxicity
- Endocrine therapy continues per separate protocol. See BRAJLET, BRAJANAS, BRAJEXE, BRAJLHRHAI, BRAJTAM or BRAJLHRHT

Luteinizing hormone releasing hormone (LHRH) agonist for women needing chemically induced menopause and for male patients:

Drug	Dose	BC Cancer Administration Guideline
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.

Goserelin and leuprolide are preferred LHRH agonist options

Drug	Dose	BC Cancer Administration Guideline
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

Goserelin and leuprolide are preferred LHRH agonist options

Dose modification at initiation for hepatic impairment:

- Severe impairment (Child-Pugh class C): Reduce abemaciclib frequency to once daily
- See BC Cancer Drug Manual for dosing of other drugs in hepatic impairment

DOSE MODIFICATIONS:

Abemaciclib dose levels:

Dose level 0	Dose level -1	Dose level -2
150 mg PO twice daily	100 mg PO twice daily	50 mg PO twice daily

* Discontinue if further dose reduction required below 50 mg twice daily

1. **Hematological: abemaciclib**
   - No hematological dose modifications for aromatase inhibitor or LHRH agonist (if using)

Grade	Neutropenia (ANC x10^9/L)		Thrombocytopenia (Platelets x10^9/L)	Abemaciclib Dose
2 or less	Greater than or equal to 1.0	and	Greater than or equal to 50	100%
3	0.5 to less than 1.0, first occurrence	or	25 to less than 50, first occurrence	Hold until ANC 1.0 and platelets 50, then restart at previous dose
Recurrent Grade 3	0.5 to less than 1.0, recurrent	or	25 to less than 50, recurrent	Hold until ANC 1.0 and platelets 50, then restart at one dose level lower
4	Less than 0.5	or	Less than 25	

2. **Diarrhea:**

- At first sign of loose stools, initiate pharmacological management (e.g., loperamide) and supportive treatment, including increased fluid intake (Refer to Symptom Management Guidelines: Diarrhea)

Grade	Severity	Abemaciclib Dose
1	Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	▪ 100% abemaciclib dose ▪ Pharmacological management of diarrhea with supportive management
2	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	▪ Pharmacological management of diarrhea with supportive management ▪ If no resolution within 24 hours, hold until Grade 1 or less, then restart at same dose of abemaciclib
Persistent or recurrent Grade 2 after restarting the same dose despite maximal supportive treatment	Persistent or recurrent increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	▪ Hold abemaciclib until Grade 1 or less, then restart at next lower dose ▪ Pharmacological management of diarrhea with supportive management
3	Increase of 7 or more stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	
4	Life-threatening consequences; urgent intervention indicated	
Any Grade, requiring hospitalization	-	

3. **Hepatotoxicity: abemaciclib**

- See BC Cancer Drug Manual for dosing of other drugs in hepatic impairment

Grade of ALT or AST Elevation	Severity	Abemaciclib Dose
1	Greater than ULN to 3 x ULN WITHOUT increase in total bilirubin above 2 x ULN	100%
2	Greater than 3 to 5 x ULN WITHOUT increase in total bilirubin above 2 x ULN	
Persistent or recurrent Grade 2	Greater than 3 to 5 x ULN, persistent or recurrent	Hold until baseline or Grade 1, then restart at next lower dose level
3	Greater than 5 to 20 x ULN WITHOUT increase in total bilirubin above 2 x ULN	
Grade 2 or higher, with increased total bilirubin, in the absence of cholestasis	Greater than 3 x ULN WITH total bilirubin greater than 2 x ULN	Discontinue
4	Greater than 20 x ULN	

4. **Interstitial lung disease/pneumonitis: abemaciclib**

Grade	Severity	Abemaciclib Dose
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	100%
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL	
Persistent or recurrent Grade 2 that does not resolve to baseline or Grade 1 with maximal supportive measures within 7 days	Symptomatic; medical intervention indicated; limiting instrumental ADL	Hold until baseline or Grade 1 or less, then restart at next lower dose level
3	Severe symptoms; limiting self care ADL; oxygen indicated	Discontinue
4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	

5. **Drug Interactions:**
    - Abemaciclib is a substrate of CYP3A4, and inhibits OCT2, MATE1 and MATE2-K. Dose adjustment may be required. See BC Cancer Drug Manual.

PRECAUTIONS:

1. **Diarrhea** is reported in up to 90% of patients receiving abemaciclib. Incidence is greatest during the first month of therapy. Median onset of first diarrhea is 7 days. In the majority of events, symptoms resolve with supportive treatment, dose interruptions and/or reductions. Start antidiarrheal therapy at the first sign of loose stools. Treatment interruption and subsequent dose reduction is recommended for persistent Grade 2 diarrhea, Grade 3 or 4 diarrhea, and for diarrhea that requires hospitalization. See Dose Modifications.
2. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Neutropenia occurs in up to 46% of patients on treatment with abemaciclib, with Grade 3 neutropenia in up to 32% of patients. Febrile neutropenia occurs in up to 1% of patients. Dose modifications recommended for neutropenia, see Dose Modifications.
3. **Venous Thromboembolism (VTE)** is reported during abemaciclib treatment in up to 6% of patients, with fatalities reported. Combination with tamoxifen may increase VTE risk. Use with caution. If VTE occurs, hold abemaciclib and treat as clinically indicated. No dose modification is required; restart abemaciclib at previous dose once patient is stable.
4. **Pre-existing hepatic impairment:** Frequency of administration should be reduced to once daily for patients with severe hepatic impairment (Child-Pugh class C).
5. **Hepatotoxicity** with transaminase elevation can occur during treatment with abemaciclib. Dose interruption, reduction, or discontinuation may be required. See Dose Modifications.
6. **Interstitial lung disease (ILD)/pneumonitis** has been reported and can be life-threatening. Monitor patients for pulmonary symptoms which may include cough, dyspnea, hypoxia, or interstitial infiltrates on radiologic exam. Dose interruption and/or reduction is recommended for persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue treatment for Grade 3 or 4 ILD/pneumonitis.
7. **Increased creatinine** during treatment with abemaciclib occurs due to inhibition of renal tubular secretion transporters, without affecting glomerular function. Increases in creatinine usually occur within the first month of treatment and remain elevated but stable during treatment, and are reversible upon treatment discontinuation. Use BUN or other measures of GFR that are not based on creatinine to assess renal function.
8. **Drug interactions** related to CYP3A, OCT2, MATE1, and MATE2 can occur. Some interactions may affect abemaciclib serum level. See BC Cancer Drug Manual.

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

References:

1. Johnston SRD, Harbeck N, Hegg R, et al; monarchE Committee Members and Investigators. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020 Dec 1;38(34):3987-3998.
2. Rugo HS, O'Shaughnessy J, Boyle F, et al; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study. Ann Oncol. 2022 Jun;33(6):616-627.
3. Harbeck N, Rastogi P, Martin M, et al; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581.
4. Abemaciclib (Verzenio) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies October 2022; 2(10): 1-16.
5. CADTH Reimbursement Review. Provisional Funding Algorithm. Hormone-receptor positive human epidermal growth factor receptor 2 negative breast cancer. March 2023.