Canadian Association of Nurses in Oncology
Association canadienne des infirmières en oncologie

This program meets Canadian Association of Nurses in Oncology (CANO) guidelines and is expected to support nurses in their understanding of CDK4/6 Inhibitor Therapy in HR+, HER2– Breast Cancer. Endorsement is provided by CANO for a time period of two years, ending September, 2027.

Canadian Association of Pharmacy in Oncology
Association canadienne de pharmacie en oncologie

This program meets Canadian Association of Pharmacy in Oncology (CAPhO) standards and is expected to support oncology pharmacy practitioners in their understanding of CDK4/6 Inhibitor Therapy in HR+, HER2– Breast Cancer. Endorsement is provided by CAPhO for two years, expiring on October 1, 2027.

Clinical Resource: CDK4/6 Inhibitor Therapy in HR+, HER2– Breast Cancer

LITERATURE REVIEW CONDUCTED: FEBRUARY 2025. PRODUCT MONOGRAPHS CURRENT THROUGH: MAY 2025.*
*Product Monograph updates for abemaciclib, palbociclib, and ribociclib have occurred since May 2025; an update to this resource is anticipated.

RESOURCE FACULTY: Glenn Myers, BScPharm, ACPR, RPh (Dr. Sheldon H Rubin Oncology Clinic, NB), Erica Patocskai, MD, FRCSC (CHUM, QC), Christine Peragine, PhD, PharmD, BScPhm, HBSc, RPh (Odette Cancer Centre, Sunnybrook Health Sciences Centre, ON), Cindy Railton, RN, MN, NP, ACNP (Arthur J. E. Child Comprehensive Cancer Centre, Calgary, AB), Christine Simmons, MD, MSc, FRCPC (BC Cancer - Vancouver, BC)

OBJECTIVE: To support oncology nurses and pharmacists in the routine clinical management of patients beginning or receiving CDK4/6 inhibitors for the treatment of early and advanced HR+, HER2– breast cancer.

1. Introduction

- Breast cancer is the most diagnosed cancer among Canadian women.[1] Hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2–) breast cancer (BC) accounts for 70% of new female breast cancer cases.[2]
- CDK4/6 inhibitors (CDK4/6is) are a class of oral anti-cancer medication that have been found effective in the first- or second-line treatment of advanced or metastatic HR+/HER2– BC and more recently in early higher risk HR+/HER2– BC.[3–5]
- At the time of literature review cut-off, three CDK4/6is (abemaciclib, palbociclib, and ribociclib) have Health Canada authorization for the treatment of advanced/metastatic breast cancer. Abemaciclib also has an early breast cancer indication.[6] See Section 2 for Health Canada indications. *[Due to timing of approval (June 2025), details of the new ribociclib early breast cancer indication do not appear in this resource].*[7]

CDK4/6I MECHANISM OF ACTION

- CDK4/6is induce cell cycle arrest by targeting a novel signalling pathway, distinct from traditional chemotherapy agents.[3]
- CDK4/6is block the activity of cyclin-dependent kinases (CDK) 4 and 6, which are key regulators of cell cycle progression.[8]
- In HR+ BC, estrogen receptor signaling promotes the expression of cyclin D, which activates CDK4/6.[9] The CDK4/6-cyclin D complex phosphorylates the retinoblastoma (Rb) protein, inactivating it and allowing the cell to progress from the G1 to S phase.[8,9]
- CDK4/6is prevent Rb phosphorylation, which maintains Rb in its active, hypo-phosphorylated state. The active Rb protein inhibits E2F-mediated transcription, leading to G1 cell cycle arrest (**Figure 1**).[8]
- Since HR+ BC often relies on this pathway for proliferation, CDK4/6 inhibition is an effective therapeutic strategy, particularly when combined with endocrine therapy.[8,9]

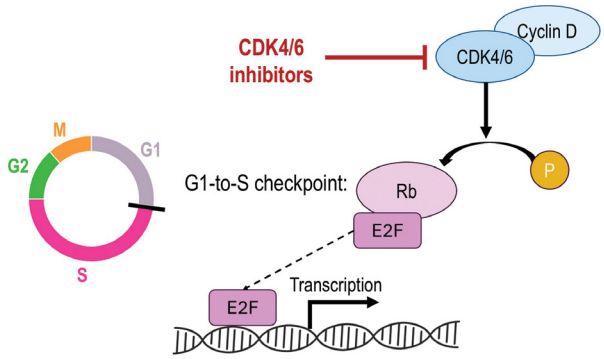

Figure 1: Mechanism of Action of CDK4/6 Inhibitors[10]

This image depicts the role of CDK4/6 and cyclin D in the progression of the cell cycle. CDK4/6/cyclin D phosphorylate the Rb protein, releasing the transcription factor E2F and enabling the cell cycle to progress from the G1 to S phase. CDK4/6 inhibitors block the activity of CDK4/6, preventing downstream Rb phosphorylation and resulting in cell cycle arrest.

- CDK4/6is possess high selectivity but different relative potencies against CDK4 and CDK6 (Table 1.1).[9]
- CDK4/6is have different toxicity profiles despite their common mechanism of action.[11] The unique toxicity profiles may be related to ratios of CDK4 versus CDK6 inhibition and off-target effects.[9]
  - CDK6 is implicated in blood stem cell differentiation, therefore neutropenia and leukopenia are key CDK4/6i-associated toxicities.[12] Abemaciclib, which exhibits high CDK4 selectivity, is associated with lower rates of all-grade neutropenia compared to palbociclib and ribociclib.[12]
  - Gastrointestinal toxicity associated with abemaciclib may occur via CDK9 inhibition.[3]

Table 1.1: Activity of CDK4/6 Inhibitors against Cyclin-dependent Kinases

AGENT	RELATIVE CDK4/6 POTENCY[9]	AFFINITY FOR TARGETED KINASES[13]			
		CDK4	CDK6	CDK9	OTHER KINASES[a]
Abemaciclib	CDK4 >> CDK6	★★★	★	★★	★
Palbociclib	CDK4 ≅ CDK6	★★	★★	–	–
Ribociclib	CDK4 > CDK6	★★★	★★	–	–

Legend: – = absence of affinity; ★= presence of affinity; ★★= high affinity; ★★★= very high affinity.
[a]Abemaciclib inhibits additional kinases involved in cellular proliferation, inflammation, and oncogenesis.[13]

2. Health Canada Indications

- The Health Canada indications in Table 2.1 are accurate at the time of publication.

Table 2.1: Health Canada Indications for Use

CDK4/6i Related trial	HEALTH CANADA INDICATIONS FOR USE	KEY PATIENT AND DISEASE CHARACTERISTICS
Abemaciclib (VERZENIO®)[6] monarchE (NCT03155997)	• Indicated for the treatment of HR+/HER2–, node-positive, early breast cancer at high risk of disease recurrence based on clinicopathological features – in adult patients as adjuvant treatment. – in combination with endocrine therapy (ET).	• HR+/HER2– early BC • Node-positive • High risk of recurrence • Adjuvant treatment
MONARCH 3 (NCT02246621) MONARCH 2 (NCT02107703) MONARCH 1 (NCT02102490)	• Indicated for the treatment of HR+/HER2– advanced (aBC) or metastatic breast cancer (mBC) – in postmenopausal women as initial endocrine-based therapy. – in combination with an aromatase inhibitor.[a] • Indicated for the treatment of HR+/HER2– aBC or mBC – in women with disease progression following ET. – in combination with fulvestrant. – pre- or perimenopausal women must also be treated with a gonadotropin-releasing hormone (GnRH) agonist. • Indicated for the treatment of HR+/HER2– aBC or mBC – in women with disease progression following ET and at least 2 prior chemotherapy regimens with at least one in the metastatic setting, and at least one containing a taxane. – as a single agent.	• HR+/HER2– BC • Advanced or metastatic disease • Combination therapy: as part of initial ET or after progression on ET • Monotherapy: progression following ET and ≥2 prior lines of chemotherapy
Palbociclib (IBRANCE® + generics)[14] PALOMA 2 (NCT01740427) PALOMA 3 (NCT01942135)	• Indicated for the treatment of HR+/HER2– locally advanced or metastatic breast cancer (LA/mBC) – in pre/perimenopausal or postmenopausal women, or men, as initial endocrine-based therapy. – in combination with an aromatase inhibitor.[b] – pre/perimenopausal women and men should also be treated with a GnRH agonist. • Indicated for the treatment of HR+/HER2– LA/mBC – in pre/perimenopausal or postmenopausal women, or men, with disease progression after prior ET. – in combination with fulvestrant. – pre/perimenopausal women and men should also be treated with a GnRH agonist.	• HR+/HER2– BC • Locally advanced or metastatic disease • Combination therapy: as part of initial ET or after progression on ET
INAVO120 (NCT04191499)[15]	• Indicated for the treatment of endocrine-resistant, *PIK3CA*-mutated, HR+/HER2– LA/mBC – in adult patients following recurrence on or after completing adjuvant ET. – in combination with fulvestrant AND inavolisib.[c]	
Ribociclib (KISQALI®)[7] *NATALEE (NCT03701334)*	• *[New indication (June 2025) treatment of HR+/HER2– stage II–III early breast cancer at high risk of recurrence. See Product Monograph for details.]*	
MONALEESA 2 (NCT01958021) MONALEESA 7 (NCT02278120) MONALEESA 3 (NCT02422615)	• Indicated for the treatment of HR+/HER2– aBC or mBC – in pre/perimenopausal or postmenopausal women, or men, as initial endocrine-based therapy. – in combination with an aromatase inhibitor. – pre/perimenopausal women and men on ET should also be treated with a GnRH agonist. • Indicated for the treatment of HR+/HER2– aBC or mBC – in postmenopausal women, as initial endocrine-based therapy *or* following disease progression on ET. – in combination with fulvestrant.	• HR+/HER2– BC • Advanced or metastatic disease • Combination therapy: as part of initial ET or after progression on ET

[a]Clinical effectiveness demonstrated with abemaciclib in combination with letrozole or anastrozole in postmenopausal women. [b]Clinical effectiveness demonstrated with palbociclib in combination with letrozole in postmenopausal women. [c]As of August 2025, inavolisib is under review by Canada's Drug Agency for public reimbursement.[16]

NOTE: Ribociclib in early breast cancer

- *The early breast cancer indication for ribociclib was evaluated in the NATALEE trial.[7] This indication received Health Canada approval in June 2025 and Canada's Drug Agency has not issued a draft funding recommendation as of August 2025.[7,17]*
- *Due to the timing of approval, this resource does not provide further information regarding the clinical use of ribociclib in early breast cancer.*

3. Dosing and Treatment Duration

- **Dosing instructions for endocrine therapies co-administered with CDK4/6is are beyond the scope of this resource. Refer to the respective Product Monographs for further information.**
- The administration schedules for the CDK4/6is differ, as outlined in the tables that follow.
- Dose reductions may be required due to treatment-related toxicities. Clinical trial analyses support a sustained therapeutic benefit of CDK4/6is at reduced doses.[18–21]

ABEMACICLIB

- Abemaciclib is available in 50 mg (beige), 100 mg (white), 150 mg (yellow), or 200 mg (beige) oval tablets.[6]
- Pre/perimenopausal women and men receiving abemaciclib combined with an aromatase inhibitor should also be treated with a GnRH agonist in line with local clinical practice.[6]

Table 3.1: ABEMACICLIB Dosing and Duration of Treatment

Early breast cancer			
Timing of initiation	• Start treatment within: – 16 months of definitive surgical removal of the primary breast tumour.[22] – 12 weeks of initiating hormone therapy.[5]		
Recommended dose	• In combination with ET: 150 mg tablet PO BID continuously (i.e., no off days in 28-day cycle unless clinically indicated).[6] – In the monarchE trial, standard endocrine therapy included an aromatase inhibitor (AI) or tamoxifen.[6]		
Duration	• Continue until completion of two years of treatment OR until disease recurrence or unacceptable toxicity.[6]		
Advanced or metastatic breast cancer			
Recommended dose	• In combination with ET: 150 mg tablet PO BID continuously.[6] – Administered in combination with an AI or fulvestrant. Refer to Table 2.1 for indications for use. • Single agent: 200 mg tablet PO BID continuously.[6]		
Duration	• Continue until disease progression or unacceptable toxicity.[6]		
Patient instructions			
How to take abemaciclib	• Swallow tablets whole with or without food. Do not ingest tablets that are not intact.[6] • Take doses at approximately the same time every day.[6] • Do NOT take an additional dose if you vomit or miss a dose. Take the next prescribed dose at the usual time.[6] • Store tablets at room temperature (15 to 30°C).[6]		
Precautions and dose adjustments related to organ dysfunction			
Renal impairment	• Mild or moderate renal impairment (CrCl ≥30 mL/min)[a]: no dose adjustment.[6] • Severe renal impairment (CrCl <30 mL/min)[a]; ESRD: no data available.[23]		
Hepatic impairment	• Mild or moderate hepatic impairment (Child-Pugh Class A or B)[b]: no dose adjustment.[23] • Severe hepatic impairment (Child-Pugh Class C): decrease dosing frequency to once daily.[6] • Refer to Table 7.4 for dose modification and management for hepatotoxicity.		
Dose modifications for adverse reactions[6]			
• Dose interruptions, reductions, and/or treatment discontinuation may be necessary to manage some adverse reactions. • Discontinue abemaciclib treatment if the patient cannot tolerate a dose of 50 mg BID.			
	First dose reduction	**Second dose reduction**	**Third dose reduction**
Dose combination with endocrine therapy	• 100 mg BID	• 50 mg BID	• Discontinue abemaciclib
Dose for single agent	• 150 mg BID	• 100 mg BID	• 50 mg BID

[a]In practice, most creatinine clearance values are likely to be estimated. [b]The Child-Pugh score is the sum of values (between 1 and 3) awarded to five domains: hepatic encephalopathy, ascites, bilirubin, albumin, and prothrombin time (INR). Visit https://www.rxcirrhose.ca/child-pugh?hl=en for more information.[24]
AI, aromatase inhibitor; BID, twice daily; CrCl, creatinine clearance; ESRD, end-stage renal disease; ET, endocrine therapy; PO, by mouth.

PALBOCICLIB

- Palbociclib tablets (both generic and brand-name) are available in 75 mg (round, light purple), 100 mg (oval, green), or 125 mg (oval, light purple) tablets.[14,25,26]
- Pre/perimenopausal women treated with palbociclib plus fulvestrant or palbociclib plus an aromatase inhibitor, and men treated with palbociclib plus an aromatase inhibitor, should also be treated with a GnRH agonist in line with local clinical practice.[14]

Table 3.2: PALBOCICLIB Dosing and Duration of Treatment

Advanced or metastatic breast cancer	
Recommended dose	• Palbociclib 125 mg tablet PO once daily, **21 days on, 7 days off** treatment (28-day cycles).[14] • Administered in combination with an AI or fulvestrant.[14] – Consult the corresponding Product Monographs for dosing instructions.
Duration	• Continue treatment as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity.[14]
Patient instructions	
How to take palbociclib	• Swallow tablets whole with or without food. Do not ingest tablets that are broken, cracked, or not intact.[14] • Take dose at approximately the same time every day.[14] • Do NOT take an additional dose if you vomit or miss a dose. Take the next prescribed dose at the usual time.[14] • Store tablets at room temperature (15 to 30°C) in original packaging.[27]
Precautions and dose adjustments related to organ dysfunction	
Renal impairment	• Mild, moderate, or severe renal impairment (CrCl ≥15 mL/min)[a]: no dose adjustment.[14] • Patients requiring hemodialysis: no data available.[14]
Hepatic impairment	• Mild to moderate hepatic impairment (Child-Pugh A or B): no dose adjustment.[14] • Severe hepatic impairment (Child-Pugh C): reduce starting dose to 75 mg once daily. Monitor patients for toxicity.[27]
Dose modifications for adverse reactions[14]	
• Temporary dose interruptions/delays and/or dose reductions, or treatment discontinuation, may be required to manage some adverse reactions.	

First dose reduction	Second dose reduction	Third dose reduction
• 100 mg daily	• 75 mg daily	• Discontinue palbociclib

[a]In practice, most creatinine clearance values are likely to be estimated.
AI, aromatase inhibitor; CrCl, creatinine clearance; PO, by mouth.

RIBOCICLIB

- Ribociclib is available in round, light greyish violet 200 mg film-coated tablets.[28]
- Pre/perimenopausal women, or men, treated with ribociclib combination therapy should also be treated with a GnRH agonist in line with local clinical practice standards.[28]
- Ribociclib should NOT be used in combination with tamoxifen due to safety concerns regarding QT prolongation.[13]

Table 3.3: RIBOCICLIB Dosing and Duration of Treatment

Advanced or metastatic breast cancer[a]	
Recommended dose	• Ribociclib 600 mg (3 x 200 mg film-coated tablets) PO once daily, **21 days on, 7 days off** treatment (28-day cycles).[28] • Administered in combination with an AI or fulvestrant.[28] – Consult the corresponding Product Monograph for dosing instructions.
Duration	• Per the clinical trial protocols, continue until disease progression or unacceptable toxicity.[28]
Patient instructions	
How to take ribociclib	• Swallow tablets whole with or without food. Do not ingest tablets that are broken, cracked, or not intact.[28] • Take dose at approximately the same time every day.[28] – If possible, take ribociclib in the morning.[28,b] • Do NOT take an additional dose if you vomit or miss a dose. Take the next prescribed dose at the usual time.[28] • Store tablets at room temperature (below 30°C) in original packaging to protect from moisture.[29]
Precautions and dose adjustments related to organ dysfunction	
Renal impairment	• Mild or moderate renal impairment: no dose adjustment.[28] • Severe renal impairment (CrCl 15 to <30 mL/min)[c]: recommended starting dose is 200 mg daily.[29] – Exercise caution and monitor patients closely for signs of toxicity.[28] – Initiate ribociclib treatment only when perceived benefit is greater than potential risk.[28] • CrCl <15 mL/min[c]: no data available.[29]
Hepatic impairment[c]	• Mild hepatic impairment (Child-Pugh A): no dose adjustment.[28] • Moderate to severe hepatic impairment (Child-Pugh B or C): recommended starting dose is 400 mg once daily.[28] – Initiate ribociclib treatment only when perceived benefit is greater than potential risk.[28]
Dose modifications for adverse reactions (advanced breast cancer)[28,a]	
• Dose interruption, reduction or treatment discontinuation may be required to manage severe or intolerable adverse drug reactions.	

First dose reduction	Second dose reduction	Third dose reduction
• 400 mg daily (2 x 200 mg tablets)	• 200 mg daily (1 x 200 mg tablet)	• Discontinue ribociclib

[a]Dosing and dose modification instructions for ribociclib in early breast cancer differ from those in advanced disease. Consult the current version of the ribociclib Product Monograph for early breast cancer guidance. [b]Evening dosing may increase the risk of QT prolongation because heart rate naturally slows down during sleep.[30]
[c]In practice, most creatinine clearance values are likely to be estimated.
AI, aromatase inhibitor; CrCl, creatinine clearance; PO, by mouth.

4. Baseline Assessment

- Abemaciclib and ribociclib can cause fetal harm, and palbociclib may cause fetal harm, when administered to pregnant women.[6,14,28]
- Ribociclib is contraindicated in patients[28]:
  - With untreated congenital long QT syndrome
  - With a baseline QTcF interval ≥450 ms
  - Who are at significant risk of developing QTc prolongation
    - For example: patients with congestive heart failure, bradyarrhythmia, unstable angina, and uncontrolled or significant cardiac disease (including recent myocardial infarction).[29]
- Avoid ribociclib treatment in patients with uncorrected hypokalemia, hypomagnesemia, or hypocalcemia.[28]
  - Correct hypokalemia, hypomagnesemia, and hypocalcemia prior to initiating or continuing ribociclib.[28]

BASELINE ASSESSMENTS

- Refer to Tables 3.1, 3.2, and 3.3 for precautions and dose adjustments recommended for hepatic or renal impairment.
- Refer to Table 4.2 and 4.4 for dose adjustments for drug interactions with abemaciclib and ribociclib.

Table 4.1: Recommended Baseline Assessments Prior to CDK4/6i Initiation

	Abemaciclib[6,23]	Palbociclib[14,27]	Ribociclib[28,29]
Complete blood count	✓	✓	✓
Liver function tests (ALT, AST, and bilirubin)[4]	✓	✓	✓
Renal function tests	✓	✓	✓
Electrocardiogram (ECG)			✓
Serum electrolytes[a]	✓[b]		✓
Pregnancy test[c]	✓	✓[d]	✓

[a]Including potassium, calcium, phosphorous and magnesium. [b]Electrolytes are a *suggested* monitoring parameter prior to initiating abemaciclib therapy.[23]
[c]For female patients of reproductive potential. [d]Clinical opinion (March 2025).
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

QT INTERVAL CALCULATION (WITH RIBOCICLIB)

- The QT interval is the time between the beginning of the QRS complex and the end of the T wave on an electrocardiogram.[31]
  - The end of the T wave is defined as the point where the tangent of the downslope of the T wave crosses the baseline.[31]
- The QT interval is routinely transformed to the corrected QT interval (QTc), which corrects the influence of heart rate.[32]
  - Different formulae exist to calculate the QTc interval. Refer to Appendix 1 for further detail.
- **Scan the QR codes to access free online tools for calculating the QTc interval.**
- **At-home ECG monitoring** may be an option with use of a Health Canada-approved personal ECG device (KardiaMobile®) that records cardiac rhythm data on a mobile phone.[33,34]
- Ribociclib is contraindicated in patients with a baseline QTcF interval ≥450 ms.[28]

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DRUG INTERACTION CHECK

- **Consult Pharmacist and/or other comprehensive drug-drug interaction resources. Scan the QR code for access to a resource available on CDK4/6i drug-drug interactions.**
- A detailed patient history of ongoing concomitant medications (including over the counter and prescription medications, supplements, vitamins, and herbal products) is important to minimize adverse outcomes.[35]
- Advise patients to speak to their Oncology Care Team prior to initiating new medications while they are taking CDK4/6is.[35]

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Table 4.2: Drug Interactions and Clinical Considerations for ABEMACICLIB

AGENT	EXAMPLES	CLINICAL CONSIDERATIONS
CYP3A inhibitors/inducers		
Strong CYP3A inducers	• St. John's wort, rifampin, carbamazepine, phenytoin[6]	• Exposure may decrease abemaciclib concentrations.[6] • Avoid concomitant use; consider alternative agents.[6]
Strong CYP3A inhibitors	• Voriconazole, itraconazole, ketoconazole, clarithromycin[6]	• Exposure may increase abemaciclib concentrations.[6] • Avoid concomitant use.[6] • If coadministration with a strong CYP3A inhibitor cannot be avoided, reduce dose of abemaciclib (see below).[6]
Moderate CYP3A inhibitors	• Ciprofloxacin, diltiazem, verapamil[6]	• Exposure may increase abemaciclib concentrations.[6] • Use caution with coadministration of moderate or weak CYP3A inhibitors.[6] • If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce dose of abemaciclib (see below).[6]
Weak CYP3A inhibitors	• Ranitidine[6]	
Transporter substrates		
OCT2, MATE1, MATE2 substrates	• Metformin[6]	• Abemaciclib reduces renal clearance of metformin.[6] • Use caution with coadministration of clinically relevant OCT2, MATE1, MATE2 substrates.[6] • Monitor blood glucose levels and for metformin-related toxicity (e.g., abdominal pain, diarrhea, nausea/vomiting, bloating).[36]
P-glycoprotein and BCRP substrates[a]	• Digoxin[6]	• Interactions between abemaciclib and transporter substrates with a narrow therapeutic index may occur.[6]
Drug-food interactions		
Grapefruit, products containing grapefruit extract, grapefruit juice		• Exposure may increase abemaciclib concentrations.[6] • Patients should avoid these foods during abemaciclib therapy.[6]
Precautions and dose adjustments for drug interactions[b]		
Coadministration with CYP3A inhibitors[6]	• If coadministration with a CYP3A inhibitor cannot be avoided, reduce the abemaciclib dose as follows:	
	Strong CYP3A inhibitor	• Adjust abemaciclib dose to 50 mg BID. • With ketoconazole, reduce abemaciclib dose to 50 mg once daily. • With clarithromycin, reduce abemaciclib dose to 100 mg BID.
	Moderate CYP3A inhibitor	• Adjust abemaciclib dose to 50 mg BID. • With diltiazem or verapamil, reduce abemaciclib dose to 100 mg BID.
	Weak CYP3A inhibitor	• Adjust abemaciclib dose to 100 mg BID.
	• After 3–5 half-lives following discontinuation of the CYP3A inhibitor, increase the abemaciclib dose to that used prior to initiating the strong CYP3A inhibitor. • Avoid grapefruit, grapefruit juice, or grapefruit products.	

[a]Consult the current version of the abemaciclib Product Monograph for guidance on coadministration of abemaciclib with statins. [b]Monitor patients closely for the duration of administration of concomitant medications for which a dose reduction or caution is recommended.[6]

Table 4.3: Drug Interactions and Clinical Considerations for PALBOCICLIB

AGENT	EXAMPLES	CLINICAL CONSIDERATIONS
CYP3A inhibitors/inducers		
Strong CYP3A inducers	• St. John's wort, rifampin, carbamazepine, phenytoin[14]	• Exposure may decrease palbociclib concentrations.[14] • Avoid concomitant use.[14]
Moderate CYP3A inducers	• Efavirenz, etravirine, modafinil, nafcillin, bosentan[14]	• Exposure may decrease palbociclib concentrations.[14] • Dose adjustments are not required if concomitant use of palbociclib with moderate CYP3A inducers is unavoidable.[14]
Strong CYP3A inhibitors	• Voriconazole, itraconazole, ketoconazole, clarithromycin[14]	• Exposure may increase palbociclib concentrations.[14] • Avoid concomitant use.[14]
CYP3A substrates		
Sensitive CYP3A substrates with a narrow therapeutic index	• Everolimus, sirolimus, tacrolimus, midazolam, fentanyl, cyclosporine, pimozide, quinidine, dihydroergotamine, ergotamine[14]	• Exposure to substrate may be increased by palbociclib.[14] • Reduce the dose of the sensitive CYP3A substrate if necessary.[14]
Statins[a]	• Simvastatin, atorvastatin[37]	• Exposure to substrate may be increased by palbociclib.[14] • Cases of severe rhabdomyolysis have been reported with concurrent use of palbociclib and simvastatin (40 or 80 mg/day) or atorvastatin (40 mg/day).[38] • Reduce the dose of the sensitive CYP3A substrate if necessary.[14]
Drug-food interactions		
Grapefruit, products containing grapefruit extract, grapefruit juice		• Exposure may increase palbociclib concentrations.[14] • Patients should avoid these foods during palbociclib therapy.[14]

[a]Consult the current version of the palbociclib Product Monograph for guidance on coadministration of palbociclib with statins.

Table 4.4: Drug Interactions and Clinical Considerations for RIBOCICLIB

AGENT	EXAMPLES	CLINICAL CONSIDERATIONS
CYP3A inhibitors/inducers		
Strong CYP3A inducers	• St. John's wort, rifampin, carbamazepine, phenytoin[28]	• Exposure may decrease ribociclib concentrations.[28] • Avoid concomitant use; consider alternative agents.[28]
Strong CYP3A inhibitors	• Voriconazole, itraconazole, ketoconazole, clarithromycin[28]	• Exposure may increase ribociclib concentrations.[28] • Avoid concomitant use; consider alternative agents.[28] • If coadministration cannot be avoided, reduce the dose of ribociclib (see below). • Monitor patients for adverse drug reactions.[28]
CYP3A4 substrates		
CYP3A4 substrates with a narrow therapeutic index	• Everolimus, sirolimus, tacrolimus, midazolam, fentanyl, cyclosporine, pimozide, quinidine, dihydroergotamine, ergotamine[28]	• Concurrent use of ribociclib with CYP3A4 substrates may increase the concentration of the CYP3A4 substrate.[28] • Avoid concomitant use.[28] • If coadministration cannot be avoided, reduction of the dose of the sensitive CYP3A4 substrate may be required.[29]
Statins	• Simvastatin, atorvastatin[37]	• Concurrent use of ribociclib with CYP3A4 substrates may increase the concentration of the CYP3A4 substrate.[28] • Cases of severe rhabdomyolysis have been reported with concurrent use of ribociclib and simvastatin (40 mg/day).[38,39] • Avoid concomitant use.[28] If coadministration cannot be avoided, reduction of the dose of the sensitive CYP3A4 substrate may be required.[29]
Direct oral anticoagulants (DOACs) *– substrates of CYP3A4 and P-glycoprotein*[40]	• **Apixaban, rivaroxaban**[37]	• Concurrent use of ribociclib with apixaban or rivaroxaban may increase the concentration of the DOAC.[41] • Exercise caution with concomitant use of DOACs and ribociclib; may increase risk of bleeding.[35]

Table continued.

AGENT	EXAMPLES	CLINICAL CONSIDERATIONS
Transporter substrates		
BCRP, OCT2, MATE1, BSEP	• Metfomin[13]	• Ribocicib may increase the side effects of substrates of these transporters; monitor patients closely during co-administration.[28,37] • Monitor blood glucose levels and for metformin-related toxicity (e.g., abdominal pain, diarrhea, nausea/vomiting, bloating).[36]
QTc prolonging agents ***Avoid concomitant use of ribociclib with other drugs known to prolong the QT interval or induce Torsade de Pointes.[28]***		
QTc prolonging agents	• **Tamoxifen**[28] • Class IA antiarrhythmics (e.g., quinidine)[28] • Class III antiarrhythmics (e.g., sotalol)[28] • Class IC antiarrhythmics (e.g., flecainide)[28] • Opioids (e.g., methadone)[28] • Macrolide antibiotics/analogues (e.g., erythromycin, clarithromycin)[28] • Quinolone antibiotics (e.g., ciprofloxacin)[28] • Domperidone[28] • **5-HT$_3$ receptor antagonists** (e.g., ondansetron)[28] • Beta-2 adrenoceptor agonists (e.g., salmeterol)[28]	• Increased risk of QT interval prolongation.[29] • Avoid concomitant use.[28] • Discontinue other QTc-prolonging drugs during treatment with ribociclib. Choose alternative concomitant medications that do not prolong the QTc interval.[28] • When it is not feasible to avoid concomitant use of QTc-prolonging agents[28]: – Measure electrolytes and ECG prior to treatment and after initiation of any QTc-prolonging drug. – Monitor ECG and electrolytes periodically (as clinically indicated).
Other		
Drugs that reduce heart rate	• **Beta-blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, alpha2-adrenoceptor agonists, sphingosine-1 phosphate receptor modulators, and I_f inhibitors**[28]	• Increased risk of arrythmia.[29] • If not feasible to avoid, exercise caution with concomitant use.[28]
Drugs that affect electrolytes	• **Diuretics, laxatives,** enemas, **high-dose corticosteroids,** amphotericin B**, proton pump inhibitors**[28]	• Serum electrolyte imbalance may occur.[29] • Avoid to the extent possible.[28]
Drug-food interactions		
Grapefruit, grapefruit juice, grapefruit-containing products		• Exposure may increase ribociclib concentrations.[28] • Patients should avoid these foods during ribociclib therapy.[28]
Precautions and dose adjustments for drug interactions (advanced breast cancer)		
Coadministration with CYP3A inhibitors[28,a]	• If coadministration with a strong CYP3A inhibitor cannot be avoided, adjust the ribociclib dose as follows:	
	Strong CYP3A inhibitor	• Reduce ribociclib dose to 400 mg once daily.
	• After at least 5 elimination half-lives following discontinuation of the strong CYP3A inhibitor, adjust the ribociclib dose to that used prior to initiating the strong CYP3A inhibitor.	

[a]Consult the current version of the ribociclib Product Monograph for dose modification instructions in early breast cancer.

5. Monitoring Recommendations

MONITORING PATIENTS ON ABEMACICLIB

- **Serum creatinine elevation:** a stable elevation in serum creatinine is common during abemaciclib treatment.[23]
  - This effect is reversible once treatment is discontinued and is not associated with impaired glomerular function.[23,42]
  - Consider assessing renal function with alternative non-creatinine-based markers, such as blood urea nitrogen.[23]

Table 5.1: Suggested Routine Monitoring During ABEMACICLIB Therapy[4,6]

[28-day cycle]	Baseline	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Thereafter
Day		1	15	1	15	1	15	1	15	
Complete blood count[a]	✓		✓	✓	✓	✓		✓		As clinically indicated at each physician visit.
Liver function tests[b]	✓		✓	✓	✓	✓		✓		As clinically indicated at each physician visit.
Creatinine ± urea[43,44]	✓			✓		✓		As clinically indicated at each physician visit.		
Electrolytes[23,c]	✓	As clinically indicated at each physician visit.								
Serum cholesterol and triglycerides[43,44,d]	✓	As clinically indicated at each physician visit.								
Additional clinical toxicity assessments[23]	Assess signs and symptoms of gastrointestinal, dermatologic effects, and fatigue at each visit. Ask patient about their frequency of loperamide use [CO].									
Infection/myelosuppression	Monitor for signs and symptoms of infection (e.g., chills, fever, shortness of breath).									
Monitoring for less common but serious toxicities										
ILD/pneumonitis	Monitor for pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, hypoxia, cough).									
Venous thromboembolism	Monitor for signs and symptoms of venous thromboembolic events, including pulmonary embolism (e.g., chest pain; shortness of breath; pain, swelling and redness in an arm or leg).									

[a]Monitor CBC prior to start of abemaciclib therapy, Q2W for the first 2 months, monthly for months 3–4, and as clinically indicated at each physician visit.[6] [b]Monitor ALT, AST, and serum bilirubin prior to start of abemaciclib therapy, Q2W for the first 2 months, monthly for months 3–4, and as clinically indicated at each physician visit.[6] [c]Electrolytes (including calcium) are suggested clinical monitoring.[23] [d]Serum cholesterol and triglycerides at baseline if clinically indicated.[43,44]

MONITORING PATIENTS ON PALBOCICLIB

Table 5.2: Suggested Routine Monitoring During PALBOCICLIB Therapy[4,14]

[28-day cycle]	Baseline	Cycle 1		Cycle 2		Cycle 3–6		Thereafter
Day		1	15	1	15	1	15	
Complete blood count[14,45,46,a]	✓		✓	✓	✓	✓		If ANC ≥1.0 x 10^9 /L during cycles 1–6: CBC and creatinine prior to every 3rd cycle.
Creatinine[45,46]	✓			✓		✓		If ANC <1.0 x 10^9 /L during cycles 1–6: CBC and creatinine prior to each cycle.
Liver function tests[27]	✓	As clinically indicated at each physician visit.						
Additional clinical toxicity assessments[27]	Assess bleeding, rash, headache, mucositis, fatigue, and gastrointestinal effects at each visit.							
Infection/myelosuppression	Monitor for signs and symptoms of myelosuppression and infection (e.g., chills, fever, shortness of breath).							
Monitoring for less common but serious toxicities								
ILD/pneumonitis	Monitor for pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, hypoxia, cough).							
Venous thromboembolism	Monitor for signs and symptoms of venous thromboembolic events, including pulmonary embolism (e.g., chest pain; shortness of breath; pain, swelling and redness in an arm or leg).							

[a]Monitor CBC prior to start of palbociclib therapy, at the beginning of each cycle, on Day 15 of the first two cycles, and as clinically indicated at each physician visit. More frequent monitoring is recommended for patients who experience neutropenia. Refer to guidance in Table 6.2.[14]

MONITORING PATIENTS ON RIBOCICLIB

Table 5.3: Suggested Routine Monitoring During RIBOCICLIB Therapy[4,28]

[28-day cycle]	Baseline	Cycle 1		Cycle 2		Cycle 3–6		Thereafter
Day		1	15	1	15	1	15	
Complete blood count[28,47,48,a]	✓		✓	✓	✓	✓		If ANC ≥1.0 x 10^9 /L during cycles 1–6: CBC and creatinine prior to every 3rd cycle. If ANC <1.0 x 10^9 /L during cycles 1–6: CBC and creatinine prior to every 1–2 cycles.
Creatinine[29,47,48]	✓		✓	✓		✓		
Liver function tests[b]	✓		✓	✓	✓			As clinically indicated at each physician visit.
ECG[7,c]	✓		✓	As clinically indicated at each physician visit based on patient's individual risk factors.				
Serum electrolytes[7,c,d]	✓	✓		✓		✓		As clinically indicated at each physician visit based on patient's individual risk factors.
Additional clinical toxicity assessments	Assess bleeding, gastrointestinal and skin effects, and fatigue at each visit.[29] Assess for syncope and palpitations [CO].							
Infection/myelosuppression	Monitor for signs and symptoms of infection (e.g., chills, fever, shortness of breath, painful urination).							
Monitoring for less common but serious toxicities								
ILD/pneumonitis	Monitor for pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, hypoxia, cough).							
Venous thromboembolism	Closely monitor at-risk patients for signs and symptoms of venous thromboembolic events, including pulmonary embolism (e.g., chest pain; shortness of breath; pain, swelling and redness in an arm or leg).							

[a]Monitor CBC prior to start of ribociclib therapy, Q2W for the first two cycles, at the beginning of the following four cycles, and as clinically indicated at each physician visit.[28] [b]Perform LFTs prior to start of ribociclib therapy. Monitor Q2W for the first two cycles, at the beginning of the following four cycles, and as clinically indicated at each physician visit. Increase monitoring frequency if LFT abnormalities are observed. Refer to guidance in Table 7.4.[28] [c]Monitoring frequency based on updated guidance in the June 2025 version of the ribociclib Product Monograph.[7] [d]Serum electrolytes include potassium, phosphorous, magnesium, and calcium.[28]

6. Proactive and Reactive Management of Selected Toxicities

- Please note: CTCAE v4/4.03 grade definitions appear in the tables throughout Section 6, to align with CTCAE versions used in the MONARCH, PALOMA, and MONALEESA trials, and the toxicity management guidance in the Product Monographs.

NEUTROPENIA

Table 6.1: Frequency of Neutropenia During CDK4/6i Therapy

DISEASE SETTING	TRIALS	NEUTROPENIA		FEBRILE NEUTROPENIA
		Any Grade	Grade ≥3[a]	Any Grade
		ABEMACICLIB[6]		
Early breast cancer	**monarchE**	46%	<20%	NR
Metastatic breast cancer	**MONARCH 1,2,3**	37–46%[b]	24–27%[b]	≤1%[c]
		PALBOCICLIB[14]		
Metastatic breast cancer	**PALOMA 2,3**	79–80%[d,e]	62–66%[d,e]	1.8%[c]
		RIBOCICLIB[28]		
Metastatic breast cancer	**MONALEESA 2,3,7**	72–80%[b]	58–69%[b]	1.7%[c]

[a]Grade 3 and 4 adverse reactions or adverse drug reactions. [b]Range represents lowest and highest frequency reported among 3 trials. [c]Frequency across all clinical trials listed. [d]Range represents lowest and highest frequency reported among 2 trials. [e]Neutropenia includes neutropenia and neutrophil count decreased.
NR, not reported in Product Monograph.

CTCAE Grade[49]	1	2	3	4
Neutrophil count decreased	<LLN–1.5 x 10^9 /L	<1.5–1.0 x 10^9 /L	<1.0–0.5 x 10^9 /L	<0.5 x 10^9 /L
Febrile neutropenia	–	–	ANC <1.0 x 10^9 /L[a] with a single temperature of >38.3 °C or a sustained temperature of ≥38 °C for more than one hour	Life-threatening consequences; urgent intervention indicated

[a]Value converted to SI units.

Table 6.2: Neutropenia Management During CDK4/6i Therapy

PATIENT EDUCATION		
All CDK4/6is	• CDK4/6is can deplete white blood cell levels and cause severe or life-threatening infections.[6,14,28] • The one week break in ribociclib and palbociclib dosing allows time for blood cell counts to recover.[50] • Advise patients to report signs and symptoms of infection to their HCP immediately: – Fever, chills, infection, flu-like symptoms, fatigue, aches and pains, dizziness, weakness, shortness of breath.[6,14] • Emphasize the importance of avoiding contact with infectious individuals to minimize risk of infection.[12]	
PROACTIVE MEASURES		
	• Myelosuppression at baseline increases the risk of neutropenia.[50] • Monitor CBC at recommended intervals and as clinically indicated (see Section 5).[51]	
TOXICITY MANAGEMENT		
	• Neutropenia usually occurs within the first two treatment cycles and infrequently thereafter (abemaciclib), or 15 days following the first dose (palbociclib and ribociclib). Toxicity does not appear to be cumulative: neutropenia often decreases as treatment cycles progress.[12] • Standard supportive care and dose adjustments can be used to manage hematologic abnormalities.[51] • G-CSF (growth factor) is not generally necessary to manage CDK4/6i-associated neutropenia.[35] – CDK4/6is induce cell cycle arrest without causing DNA damage or apoptosis of neutrophil precursor cells. Therefore neutrophils resume proliferation and counts should recover quickly following CDK4/6i dose interruption and/or reduction.[52] • If the patient exhibits febrile neutropenia, withhold treatment and evaluate signs and symptoms of infection.[4]	
MONITORING AND DOSE MODIFICATIONS		
All CDK4/6is	Grade 1 or 2 (<LLN–1.0 x 10^9 /L)	• No dose adjustment.[6,14,28,53]
Abemaciclib[6]	**Grade**	**Action**
	Grade 3 (<1.0–0.5 x 10^9 /L)	• Withhold until resolution to ≤Grade 2 (<1.5–1.0 x 10^9 /L); dose reduction not required.[6,53]
	At second occurrence, febrile neutropenia, ***or*** Grade 4 (<0.5 x 10^9 /L)	• Withhold until resolution to ≤Grade 2 (<1.5–1.0 x 10^9 /L).[6,53] • Resume at next lower dose level (Table 3.1).[6,53]
Palbociclib[14,a]	**Grade**	**Action**
	Grade 1 or 2 in the first 6 treatment cycles	• Monitor CBC for subsequent cycles, prior to the start of every third cycle, and as clinically indicated at each physician visit.
	Grade 3 (ANC <1.0–0.5 x 10^9 /L)	**Cycle Day 1:** • Withhold treatment and repeat CBC monitoring within 1 week. • Start next cycle at same dose when recovered to ≤Grade 2 (<1.5–1.0 x 10^9 /L). – Treatment duration (number of days per cycle) can be reduced if patient is already on lowest dose (e.g., 75 mg for 2 weeks on, 2 weeks off) [CO]. – A Phase II study found that alternative dosing of palbociclib (5 days on/2 days off) combined with letrozole or fulvestrant reduced the frequency of ≥Grade 3 neutropenia to 40.7% across all treatment cycles.[54] **Day 15 (first 2 cycles):** • If Grade 3 on Day 15: continue treatment at current dose to complete cycle; repeat CBC on Day 22. • If Grade 4 (<0.5 x 10^9 /L) on Day 22 → see row below. Consider dose reduction in the event of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
	Grade 3 neutropenia (ANC <1.0–0.5 x 10^9 /L) with fever ≥38.5°C and/or infection, ***or*** Grade 4 (ANC <0.5 x 10^9 /L)	**At any time:** • Withhold treatment until recovery to ≤Grade 2. • Resume at next lower dose level (Table 3.2).
Ribociclib	**Grade**	**Action**
	Grade 3 (ANC <1.0–0.5 x 10^9 /L)	**Cycle Day 1[28,47,48]:** • Withhold treatment until recovery to ≤Grade 2. Resume at same dose level. • At second occurrence, interrupt dose until recovery to ≤Grade 2, then resume at next lower dose level (Table 3.3).

Table continued.

		Cycle Day 15 (first 2 cycles)[47,48]: • Continue same dose for remainder of cycle. Assess ANC on Day 22. • If ANC ≥0.5 x 10^9 /L on D22: continue at same dose for next cycle, when ANC ≥1.0 x 10^9 /L. • If ANC <0.5 x 10^9 /L on D22: resume at next lower dose level, when ANC ≥1.0 x 10^9 /L.
	Grade 3 febrile neutropenia (ANC <1.0 x 10^9 /L with a single T >38.3 °C or a sustained T ≥38 °C for >1 hour) ***or*** Grade 4 (ANC <0.5 x 10^9 /L)	**Cycle Day 1[28,47,48]:** • Withhold treatment until recovery to ≤Grade 2. • Resume at next lower dose level (Table 3.3). **Cycle Day 15 (first 2 cycles)[47,48]:** • Omit remainder of cycle. • Resume at next lower dose level when ANC ≥1.0 x 10^9 /L.

[a]Grade according to CTCAE v4.0.

DIARRHEA

Table 6.3: Frequency of Diarrhea During CDK4/6i Therapy

DISEASE SETTING	TRIALS	DIARRHEA	
		Any Grade	Grade ≥3[a]
ABEMACICLIB[6]			
Early breast cancer	**monarchE**	84%[b]	8%
Metastatic breast cancer	**MONARCH 1,2,3[c]**	82–90%	10–20%
PALBOCICLIB[14]			
Metastatic breast cancer	**PALOMA 2,3[d]**	19–26%	0–1%
RIBOCICLIB[28]			
Metastatic breast cancer	**MONALEESA 2,3,7[c]**	23–41%	1–2%

[a]Grade 3 and 4 adverse reactions or adverse drug reactions. [b]One Grade 5 event reported in the abemaciclib + ET arm in the monarchE trial. [c]Range represents lowest and highest frequency reported among 3 trials. [d]Range represents lowest and highest frequency reported among 2 trials.

CTCAE Grade[49]	1	2	3	4
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

ADL, activities of daily living.

Table 6.4: General Diarrhea Management

PATIENT EDUCATION	
• Advise patients to[55–57]: – Drink lots of fluids. – Eat and drink often, in small amounts. – Avoid foods with high fibre content.	
• Hydration tips[58]: – Drink 6–8 cups of liquids a day, unless otherwise instructed by healthcare team. – Drink an additional cup of liquid for each watery bowel movement. – Choose drinks with electrolytes that are caffeine-free and non alcoholic. – Sip small volumes of liquid in between meals.	• Dietary modifications: – BRAT diet (bananas, rice, apples, toast) – Eat small meals/snacks.[58] – Eat slowly and chew well.[58] – Limit foods that are high in fat, spicy, or bother the stomach.[58] – Remove peels, seeds, skins and membranes from vegetables and fruits.[58]
TOXICITY MANAGEMENT	
• Carefully monitor patients; patients may experience weakness due to electrolyte alterations and dehydration.[12] • Dose reduction or anti-diarrheal agents can be used to manage CDK4/6i-associated diarrhea (in the absence of signs of infection).[50,51] – Non-pharmacologic therapies include hydration and dietary modification.[51] • For dose modifications and management of palbociclib- and ribociclib-associated diarrhea, follow general dose modification guidance in Table 7.6.	

Table 6.5: Diarrhea Management During ABEMACICLIB Therapy

PATIENT EDUCATION		
• Abemaciclib can cause diarrhea, which may be severe. Diarrhea usually starts in the first month of treatment.[6] • Abemaciclib tablets contain lactose. Lactose in the tablet may cause diarrhea in patients who normally experience diarrhea due to lactose in milk. Advise these patients to take Lactaid® tablets prior to their abemaciclib dose.[55] • Advise patients to have loperamide or other anti-motility agents available.[55] • Advise patient to tell their HCP if they have loose or liquid stools, especially if ongoing after 24hrs of using appropriate anti-motility agent.[6,55]		
PROACTIVE MEASURES		
• Patients with pre-existing gastrointestinal comorbidities may be more likely to experience severe diarrhea during abemaciclib therapy.[50] • Patients should have loperamide or other anti-motility agent on hand.[55] Provide patients with instructions on how to take loperamide (**see below**).		
TOXICITY MANAGEMENT		
• Diarrhea was the most common reason for dose reductions due to an adverse reaction in patients treated with abemaciclib in clinical trials.[6] • Increase oral fluid intake and start antidiarrheal treatment (e.g., loperamide) at the first sign of loose stools.[6,59] • **PATIENT INSTRUCTIONS:** − Take two 2 mg (4 mg) loperamide tablets at the first sign of loose or more frequent stools.[55] − Take one 2 mg loperamide tablet with every loose stool (maximum of 8 tablets/day), until diarrhea has stopped for at least 12 hrs.[55] • Patients should contact their healthcare team if diarrhea does not improve within 24 hours of loperamide initiation or lasts >48 hours.[55] • Dose interruptions and reductions are outlined below.		
Dose modifications and management of diarrhea	**Grade[49]**	**Action[4,6]**
	Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	• No dose adjustment required but may be appropriate if patient cannot tolerate chronic Grade 1 diarrhea.
	Grade 2 Increase of 4–6 stools/day over baseline; moderate increase in ostomy output compared to baseline	• Withhold treatment until resolution if toxicity does not resolve to ≤Grade 1 within 24 hours of appropriate anti-motility agent therapy. • No dose adjustment required.
	Grade 2 (persists/recurs after the same dose with maximal supportive measures)	• Withhold treatment until toxicity resolves to ≤Grade 1. • Resume at next lower dose (Table 3.1).
	Grade 3, Grade 4, or hospitalization required	

NAUSEA

Table 6.6: Frequency of Nausea and Vomiting During CDK4/6i Therapy

DISEASE SETTING	TRIALS	NAUSEA		VOMITING	
		Any Grade	Grade ≥3[a]	Any Grade	Grade ≥3[a]
ABEMACICLIB[6]					
Early breast cancer	**monarchE**	30%	<1%	18%	<1%
Metastatic breast cancer	**MONARCH 1,2,3[b]**	41–64%	1–5%	26–35%	<1–2%
PALBOCICLIB[14]					
Metastatic breast cancer	**PALOMA 2,3[c]**	29–35%	<1%	15–16%	≤1%
RIBOCICLIB[28]					
Metastatic breast cancer	**MONALEESA 2,3,7[d]**	34–55%	0–3%	29–35%	2–4%

[a]Grade 3 and 4 adverse reactions or adverse drug reactions. [b]Range represents lowest and highest frequency reported among 3 trials. [c]Range represents lowest and highest frequency reported among 2 trials. [d]The frequency of vomiting in MONALEESA-7 is not reported in the ribociclib Product Monograph.

CTCAE Grade[49]	1	2	3	4
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–
Vomiting	1–2 episodes (separated by 5 minutes) in 24 hrs	3–5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated

TPN, total parenteral nutrition.

Table 6.7: Nausea and Vomiting Management During CDK4/6i Therapy

PATIENT EDUCATION
• Advise patients to: − Drink lots of fluids.[55–57] − Eat and drink often, in small amounts.[55–57] − Limit foods that are high in fat, spicy, very sweet/salty, or have a strong odour.[60] • Dosing considerations: − Take medication with food when appropriate.[6,14,28] − Evening or bedtime dosing is an alternative to morning dosing for drugs taken once daily (e.g., palbociclib; with ribociclib, give consideration to QT prolongation with evening dosing).[30] • Provide patients with instructions for how to take antiemetics, and when to contact their HCP if symptoms are worsening or not improving.[60] • Inform patients to tell their HCP if their nausea/vomiting is not controlled with antinausea medication or if nausea is contributing to loss of appetite/anorexia.[55,61]
PROACTIVE MEASURES
• Abemaciclib and ribociclib have high to moderate emetogenic potential. Palbociclib has low to minimal emetogenic potential.[62]
TOXICITY MANAGEMENT
Pharmacologic therapy • Use routine antiemetics as needed to manage nausea and vomiting after evaluating for drug interactions; suggested antiemetics include metoclopramide, prochlorperazine, 5-HT_3 antagonists (e.g., ondansetron)[51,63] and olanzapine (for refractory nausea) [CO].[a] • Some antiemetics may increase the risk of additive QTc prolongation (e.g., ondansetron, olanzapine, domperidone, haloperidol).[37,63] **Non-pharmacologic measures** • Promote good oral hygiene (brushing teeth ≥2 times a day).[64] Oral care should include mouth rinse before/after eating (1/2 tsp each salt and baking soda in 2 cups of water).[60] • If patients are vomiting, they should limit food and drink until vomiting has ceased, then wait 30–60 minutes to start sipping clear fluids.[60] • Suggest patients try adding dry, starchy foods (such as dry toast, crackers, or pretzels) when they can tolerate clear fluids.[60] • Dose interruption or reduction for other/non-hematologic toxicities: refer to Table 7.6.

[a]Olanzapine may be part of a first-line antiemetic strategy at some institutions.

FATIGUE

Table 6.8: Frequency of Fatigue During CDK4/6i Therapy

DISEASE SETTING	TRIALS	FATIGUE	
		Any Grade	Grade ≥3[a]
ABEMACICLIB[6]			
Early breast cancer	**monarchE**	41%	3%
Metastatic breast cancer	**MONARCH 1,2,3[b]**	40–65%	2–3%
PALBOCICLIB[14]			
Metastatic breast cancer	**PALOMA 2,3[c]**	37–38%	2%
RIBOCICLIB[28]			
Metastatic breast cancer	**MONALEESA 2[d]**	43%	<4%

[a]Grade 3 and 4 adverse reactions or adverse drug reactions. [b]Range represents lowest and highest frequency reported among 3 trials. [c]Range represents lowest and highest frequency reported among 2 trials. [d]The frequencies of fatigue in MONALEESA-3 and -7 are not reported in the ribociclib Product Monograph.

CTCAE Grade[49]	1	2	3	4
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest; limiting self care ADL	–

ADL, activities of daily living.

Table 6.9: Fatigue Management During CDK4/6i Therapy

PATIENT EDUCATION
• Inform patients that side effects of CDK4/6is may include fatigue, tiredness, or weakness.[6,14,28] • Patients should not drive or operate machinery if they feel tired.[55–57] • Counsel patients on coping techniques for fatigue and how to modify their physical activity levels.[65] • Educate patients to report signs/symptoms of worsening fatigue (e.g., fatigue not relieved by rest that negatively impacts instrumental ADLs and/or ADLs).[49,65] • Fatigue is multi-factorial and may be related to cancer, medications (for cancer or other conditions), comorbidities (e.g., depression), sleep hygiene, nutritional deficits, lack of exercise, etc.[66–68]
PROACTIVE MEASURES
• Address any symptoms that the patient suggests may contribute to their fatigue, such as sleep, pain, depression, or nutrition.[65] • Establish patient's baseline fatigue levels and discuss severity scale.[68] • Rule out potential contributing factors to fatigue, including but not limited to hypothyroidism, anemia, emotional distress, deconditioning, nutritional deficits, and sleep/wake disturbances.[68] • Encourage patients to engage in relaxing activities, pace themselves, and exercise (e.g., endurance or resistance training if appropriate).[68] • Patients with low ANC and longer sleep duration at baseline [>9 hours weekly average, versus normal (7–9 hours) or short (<7 hours) duration] may be more likely to experience fatigue during CDK4/6i treatment, as demonstrated in a cohort of patients with mBC taking palbociclib.[69]
TOXICITY MANAGEMENT
• Pharmacological interventions are not recommended for the treatment of cancer-related fatigue.[65] • Provide tips to improve nighttime sleep, for example[66]: − Limit naps during the day to 20 minutes. − Avoid screen time before going to bed. − Avoid strenuous activities (e.g., exercise) before going to bed. • Minimize use of other medications contributing to fatigue/somnolence (e.g., olanzapine for nausea).[66,70] • Develop physical activity plans according to the patient's cancer treatment and energy levels.[65] − E.g., moderate level physical activity such as walking, cycling, swimming, resistance training, 30 min/day for 5 days/week as tolerated. • Healthy eating goals include staying hydrated (with caffeine-free liquids e.g., water, juices) and increasing nutrient and protein intake to improve energy levels. Consider Dietician referral.[65] • Encourage patients to rest for short periods if they experience severe fatigue.[65] • Dose interruption or reduction for other/non-hematologic toxicities: refer to Table 7.6.

DERMATOLOGIC TOXICITIES

Table 6.10: Frequency of Select Dermatologic Toxicities During CDK4/6i Therapy

DISEASE SETTING	TRIALS	RASH		DRY SKIN		PRURITUS	
		Any Grade	Grade ≥3[a]	Any Grade	Grade ≥3[a]	Any Grade	Grade ≥3[a]
ABEMACICLIB[6]							
Early breast cancer	**monarchE**	11%	<1%	NR	NR	NR	NR
Metastatic breast cancer	**MONARCH 1,2,3[b]**	8–15%	<1–2%	9–10%	0%	8–14%	<1%
PALBOCICLIB[14]							
Metastatic breast cancer	**PALOMA 2,3[c,d]**	14–18%	≤1%	4.9–12%	0%[e]	NR	NR
RIBOCICLIB[28]							
Metastatic breast cancer	**MONALEESA 2,3,7[b,f]**	20–26%	≤1%	9–10%[g]	0%[h]	12–22%	≤1%

[a]Grade 3 and 4 adverse reactions or adverse drug reactions. [b]Range represents lowest and highest frequency reported among 3 trials. [c]Range represents lowest and highest frequency reported among 2 trials. [d]Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption. [e]Frequency reported in PALOMA-2; Grade ≥3 frequency in PALOMA-3 is not reported in the palbociclib Product Monograph. [f]Rash includes: rash, rash maculopapular, rash pruritic. [g]Range represents lowest and highest frequency reported in MONALEESA-2 and -7; frequency of dry skin in MONALEESA-3 not reported in the ribociclib Product Monograph. [h]Frequency reported in MONALEESA-2 only; the frequency of dry skin in MONALEESA-3 and -7 is not reported in the ribociclib Product Monograph. NR, not reported in Product Monograph.

CTCAE Grade[49]	1	2	3	4
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10–30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	–
Rash maculopapular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	–
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	–

ADL, activities of daily living; BSA, body surface area.

Table 6.11: Dermatologic Toxicity Management During CDK4/6i Therapy

PATIENT EDUCATION		
• Inform patients that skin rashes may occur during treatment.[56,57] − Advise patients to call their oncology team if they experience itching that is very irritating or interrupting sleep quality, resulting in skin changes (e.g., scabbing), etc. Otherwise, mention symptoms at their next visit.[56,57] • Educate patients on red flag symptoms of rash (e.g., skin pain, blistering, skin peeling, fever/malaise with rash, concurrent mucosal involvement).[71] • Symptoms of erythema multiforme[72]: − Target lesions (rounded lesions measuring <3cm with a clear border and 3 concentric circles), which appear on the feet, palms and backs of the hands, extensor surfaces of the limbs; − Mucosal lesions, which start with blisters and most often present in the mouth; − Prodromal symptoms e.g., malaise, fatigue, upper respiratory tract infection; may be mild, nonspecific or absent.		
PROACTIVE MEASURES		
• Dermatologic toxicities appear to be a class effect, but are less common with abemaciclib (compared to palbociclib and ribociclib).[73] − Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) can occur with abemaciclib and palbociclib[6,14]; toxic epidermal necrolysis (TEN) has been reported with ribociclib.[28] − Symptoms of rare but severe immune-mediated drug reactions include fever, Nikolsky's sign, bullae and skin detachment, mucosal lesions, extensive rash.[73] • Assess patients for dermatologic effects at each visit.[23,27,29]		
TOXICITY MANAGEMENT		
• **Immediately and permanently discontinue ribociclib if signs/symptoms of severe cutaneous reactions are observed.**[28] − Signs and symptoms may include progressive widespread skin rash, often with mucosal lesions or blisters. • Dose interruption or reduction for other/non-hematologic toxicities: refer to Table 7.6.		
Pruritus	**Grade**	**Possible symptom management**
	Any grade	• Second-generation anti-H1 antihistamines (e.g., cetirizine, fexofenadine, loratadine) may alleviate itch (any grade).[37,74] • First generation anti-H1 antihistamines may be used at bedtime for nocturnal symptoms (e.g., diphenhydramine, hydroxyzine).[75]
	Grade 1	• Oral antihistamines.[76] • Topical fragrance-free moisturizers.[76]
	Grade ≥2	• Optimize oral antihistamines, emollients, and topical steroid as clinically appropriate [CO]. • Consider potent or high-potency topical steroids (e.g., triamcinolone 0.1% cream BID in pruritic areas).[76] • Consider GABA analogs instead of antihistamines (e.g., gabapentin 100–300 mg TID or pregabalin 50–100 mg TID).[76] • Consider course of systemic corticosteroids (e.g., prednisone 0.5–1 mg/kg body weight/day; taper over 14 days) and GABA analogs.[76]
Maculopapular lesions[76]	**Grade**	**Possible symptom management**
	Grade 1	• Low-potency topical steroid (e.g., hydrocortisone 0.5–1.0% cream) [CO].
	Grade ≥2	• Consider moderate to high-potency topical steroid (e.g., betamethasone dipropionate 0.05%, triamcinolone 0.1% cream, BID) [CO]. • Consider oral corticosteroids (e.g., prednisone 0.5–1 mg/kg/day or equivalent; dose increase up to 2 mg/kg/day if improvement is not observed).

7. Dose Modifications for Other Toxicities

QT INTERVAL PROLONGATION

- A *serious* warning regarding QT interval prolongation is stated in the ribociclib Product Monograph; existing or risk for QT interval prolongation are contraindications.[28]
- Increase ECG monitoring frequency as clinically indicated. For example[28]:
  - In the event of QTc prolongation during treatment with ribociclib.[28]
  - If the patient has underlying risk factors for Torsade de Pointes.[28]
    - E.g., female sex, age ≥68 years, use of loop diuretics, serum potassium ≤3.5 mEq/L.[77]
  - If the patient is receiving concomitant QTc-prolonging medications that cannot be stopped.[28]
    - Additional resource: CredibleMeds®
- Repeat ECGs if electrolyte imbalances or symptoms that may be related to QT prolongation (e.g., palpitations, syncope) are observed.[28]

  [Note: Per the respective Product Monographs, abemaciclib and palbociclib do not have a clinically relevant effect on QTc.[6,14]]

Table 7.1: Dose Modification for QT Prolongation During RIBOCICLIB Treatment[7,a]

ECG READING AND/OR SYMPTOMS	DOSE MODIFICATIONS
QTcF interval >480 ms and ≤500 ms	• Interrupt ribociclib dose. Wait until QTcF resolves to ≤480 ms. • If QTcF interval prolongation resolves to ≤480 ms, resume at next lower dose level (Table 3.3).[b] • If QTcF interval >480 ms recurs: − Interrupt ribociclib dose until QTcF interval resolves to ≤480 ms. − Resume at next lower dose level (Table 3.3).
QTcF interval >500 ms	• Interrupt ribociclib until QTcF interval resolves to ≤480 ms. • Resume at next lower dose level (Table 3.3). • If QTcF interval >500 ms recurs: discontinue ribociclib.
QTcF interval >500 ms OR >60 ms increase from baseline AND Torsade de Pointes, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia	• Permanently discontinue ribociclib.

[a]Based on updated guidance in the June 2025 version of the ribociclib Product Monograph.[7] [b]Consult the current version of the ribociclib Product Monograph for dose modification instructions in early breast cancer.

ILD/PNEUMONITIS

CTCAE Grade[49]	1	2	3	4
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)

ADL, activities of daily living.

Table 7.2: Dose Modification for ILD/Pneumonitis During CDK4/6i Treatment

CTCAE Grade	DOSE MODIFICATION AND MANAGEMENT		
	Abemaciclib[6]	Ribociclib[28]	Palbociclib[14]
Grade 1	• No dose adjustment required.	• No dose adjustment required.[a]	• If patients have new or worsening respiratory symptoms and are suspected to have developed ILD/ pneumonitis, interrupt palbociclib immediately and evaluate the patient. • Permanently discontinue palbociclib in patients with severe drug-related ILD or pneumonitis.
Grade 2	• Persistent/recurrent Grade 2 toxicity that does not resolve with maximal supportive measures ≤7 days to baseline or Grade 1: – Suspend dose until toxicity resolves to baseline or ≤Grade 1. – Resume at next lower dose level (Table 3.1).	• Interrupt ribociclib until recovery to ≤Grade 1. • Resume at next lower dose level (Table 3.3).[b]	
	• If persistent symptoms, consider prednisone 0.5–1 mg/kg daily with a slow taper over 5–6 weeks.[78]		
Grade 3 or 4	• Permanently discontinue abemaciclib.	• Permanently discontinue ribociclib.	• Per above.
	• Meylprednisone 1–2 mg/kg daily with a slow taper over 5–6 weeks.[78] • Consider pulmonary consultation.[78] • Other measures (case by case): supplemental oxygen, antibiotics, infectious disease consult.[78]		

[a]Initiate appropriate medical therapy; monitor patient (as clinically indicated). [b]Perform individualized benefit-risk assessment when considering resuming ribociclib.

VENOUS THROMBOEMBOLIC EVENTS

- A *serious* warning regarding venous thromboembolism is stated in the abemaciclib Product Monograph, and dose modification guidance is provided.[6]
  - Consider the risks/benefits of continuing abemaciclib in patients who experience a severe arterial thromboembolic event.[6]
- Warnings regarding thromboembolic events are also included in the palbociclib and ribociclib Product Monographs; general dose modification guidance is provided[14,28] (see Table 7.6).

CTCAE Grade[49]	1	2	3	4
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated

Table 7.3: Dose Modification for Venous Thromboembolic Events (VTE)

CTCAE Grade	DOSE MODIFICATION AND MANAGEMENT BASED ON ABEMACICLIB	
	Early Breast Cancer	Advanced or Metastatic Breast Cancer
Grade 1 or 2	• Any grade VTE[6]: – Suspend dose; treat as clinically indicated. • Resume treatment when patient is clinically stable.	• No dose adjustment required.[6]
Grade 3 or 4		• Suspend dose; treat as clinically indicated.[6] – In MONARCH 2/3, VTEs were managed with anticoagulant therapy (commonly low-molecular-weight heparin; choice at clinicians' discretion).[20] – Anticoagulant therapy was continued for the duration of study participation.[20] • Resume treatment when patient is clinically stable.[6]

HEPATOTOXICITY

- A *serious* warning regarding hepatoxicity is stated in the ribociclib Product Monograph[28]; a warning is also stated for abemaciclib.[6]
- With ribociclib, increase LFT monitoring frequency (e.g., to twice weekly) if ≥Grade 2 abnormalities are observed. For example, repeat liver enzyme and serum bilirubin twice weekly in the event of liver enzyme or bilirubin increase requiring dose interruption.[28]

Table 7.4: Dose Modification for Hepatotoxicity During ABEMACICLIB or RIBOCICLIB Treatment

CTCAE Grade for Increased AST and ALT	DOSE MODIFICATION AND MANAGEMENT	
	Abemaciclib[6]	**Ribociclib[28,a]**
Grade 1 (AST and/or ALT >ULN–3.0 x ULN without ↑ total bilirubin >2 x ULN)	• No dose adjustment required.	• No dose adjustment required.
Grade 2 (AST and/or ALT >3.0–5.0 x ULN without ↑ total bilirubin >2 x ULN)	• No dose adjustment required. • Persistent/Recurrent Grade 2: − Interrupt abemaciclib until toxicity resolves to baseline or ≤Grade 1. − Resume at next lower dose level (Table 3.1).	• **If baseline was <Grade 2:** − Interrupt ribociclib until recovery to ≤baseline grade. − Resume ribociclib at same dose level (Table 3.3). − If Grade 2 recurs, resume at next lower dose level (Table 3.3). • **If baseline was at Grade 2:** no dose interruption.
Grade 3 (AST and/or ALT >5.0–20.0 x ULN without ↑ total bilirubin >2 x ULN)	• Withhold abemaciclib until toxicity resolves to baseline or ≤Grade 1. • Resume at next lower dose level (Table 3.1).	• Withhold ribociclib until recovery to ≤baseline grade. • Resume at next lower dose level (Table 3.3). • If Grade 3 recurs, discontinue ribociclib.
Grade 4 (AST and/or ALT >20.0 X ULN)	• Discontinue abemaciclib.	• Discontinue ribociclib.
AST and/or ALT >3 x ULN with total bilirubin (>2 x ULN); no cholestasis	• Discontinue abemaciclib.	• Discontinue ribociclib.

[a]Per ribociclib Product Monograph, grading refers to AST and/or ALT elevations from baseline (prior to treatment initiation) without increase in total bilirubin >2 x ULN.

ADVERSE EVENT GRADING AND DOSE MODIFICATION FOR TOXICITIES WITHOUT SPECIFIC GUIDANCE

Table 7.5: General Guidelines for CTCAE Adverse Event Grading[79]

Grade 1	Grade 2	Grade 3	Grade 4
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[b]	Life-threatening consequences; urgent intervention indicated.

A semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a Grade is not available.
[a]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. [b]Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
ADL, activities of daily living.

Table 7.6: Dose Reductions for Non-hematologic or Other Toxicities, by CDK4/6i

CDK4/6i	DOSE MODIFICATION
Abemaciclib[6] *See specific guidance for hepatotoxicity, ILD/pneumonitis, VTEs, diarrhea, hematologic toxicity*	• No dose adjustment required for Grade 1 or 2 toxicities. • For persistent/recurrent Grade 2 toxicity (does not resolve with maximal supportive measures in ≤7 days to baseline or Grade 1); Grade 3, or Grade 4: − Withhold until toxicity resolves to baseline or ≤Grade 1. − Resume at next lower dose level (Table 3.1).
Palbociclib[14] *See specific guidance for hematologic toxicities*	• No dose adjustment required for Grade 1 or 2 toxicities. • If ≥Grade 3 non-hematologic toxicity persists despite medical treatment: − Withhold until symptoms resolve to ≤Grade 1; ≤Grade 2 if not considered a safety risk for the patient. − Resume at next lower dose level (Table 3.2).
Ribociclib[28] *See specific guidance for hepatobiliary toxicity, QT interval prolongation, ILD/ pneumonitis, neutropenia*	• No dose adjustment required for Grade 1 or 2 toxicities. − Initiate appropriate medical therapy; monitor patient (as clinically indicated). • If Grade 3 toxicity occurs: − Withhold ribociclib dose until recovery to ≤Grade 1. − Resume at same dose level (Table 3.3). − If Grade 3 toxicity recurs, resume at next lower dose level (Table 3.3). • If Grade 4 toxicity occurs, discontinue ribociclib.

8. Patient Education Checklist

- Note: lack of adherence to self-administered oral anti-cancer medications is a concern.[80] Patient adherence is critical to optimize treatment outcomes for breast cancer patients.[4]

☐ How to take CDK4/6is
- Instruct patients to swallow tablets whole with or without food. Patients should not ingest tablets that are broken, cracked, or not intact.[6,14,28]
- Instruct patients to take their dose at approximately the same time every day.[6,14,28]
  — Ribociclib combined with an aromatase inhibitor or fulvestrant should preferably be taken in the morning.[28]
- If a patient vomits or misses a dose, they should NOT take an additional dose. Instruct the patient to take the next prescribed dose at the usual time.[6,14,28]

☐ Drug interactions
- Review interactions with common foods and precautions regarding starting and stopping other medications and alternative/complementary medicines (refer to Tables 4.2, 4.3, and 4.4).

☐ Pregnancy/sexual health, fetal harm
- Abemaciclib and ribociclib can cause fetal harm, and palbociclib may cause fetal harm, when administered to pregnant women.[6,14,28]
- CDK4/6i therapy may affect male fertility.[23,27,29]
- Duration of contraception during/after treatment with CDK4/6is and other reproductive health warnings are outlined below.

REPRODUCTIVE HEALTH WARNINGS		
CDK4/6i	**Female patients**	**Male patients**
Abemaciclib	• Pregnancy test prior to treatment[6] • Patients and their partners should use adequate contraception[23]: − During treatment − For ≥3 weeks after the last dose	
Palbociclib	• Use adequate contraception[27]: − During treatment − For ≥3 weeks after the last dose	• Consider sperm preservation (prior to therapy)[14] • Male patients with female partners with reproductive potential should use adequate contraception[14]: − During treatment −For ≥97 days after the last dose
Ribociclib	• Pregnancy test prior to treatment[28] • Use effective contraception[28]: − During treatment − For ≥3 weeks after the last dose	• Use adequate contraception[29]: − During treatment − For ≥6 months after the last dose

☐ Breastfeeding
- Breastfeeding is not recommended during CDK4/6i treatment, and for ≥3 weeks following the last dose of abemaciclib or ribociclib.[6,23,27–29]

☐ Vaccinations
- Discuss vaccinations per local guidance

☐ Proactive approach to minimize common side effects (see Section 6)
- Educate patients at baseline and throughout treatment that the therapeutic benefit of CDK4/6is is sustained at reduced doses, including in the adjuvant setting.[18–21] Dose reductions to manage toxicities can be made without concern for lessening effectiveness.

SIDE EFFECT	KEY POINTS
Low blood counts	• Stress importance of regular lab tests and monitoring for signs and symptoms of low blood counts (e.g., fever, chills, infection, flu like symptoms, aches and pains, shortness of breath, fatigue, weakness).[6,14,28]
Diarrhea	• Advise patients to report episodes of loose stools.[6] • Importance of hydration, dietary modifications.[55–57] • Have loperamide on hand (especially with abemaciclib), and ensure comprehension of appropriate dosing.[55]
Nausea	• Provide advice on dietary strategies and good oral hygiene.[55–57,60] • Advise on how to take antiemetics and when to contact their HCP.[60]
Fatigue	• Counsel patients on coping techniques for fatigue and how to modify their physical activity levels.[65] • Establish patient's baseline fatigue level and discuss severity scale.[68]
Rash, dry skin, itching	• Advise patient to report skin changes and itchiness.[56,57] • Suggest use of emollients and regular hydrating cream for mild conditions.[74]

☐ Instruct patients to notify the oncology team immediately if they experience side effects or symptoms which may be serious, troublesome, or severe enough to interfere with daily activities, including symptoms or side effects not listed here.

SIDE EFFECT	KEY POINTS	Abemaciclib[6]	Palbociclib[14]	Ribociclib[28]
Liver problems (hepatotoxicity)	• Importance of regular lab tests and monitoring for loss of appetite, pain in right side of abdomen	✓		✓*
Infections	• Report chills, cough, fever, sore throat, shortness of breath • Report painful, frequent urination, cloudy urine	✓	✓	✓*
Lung problems (pneumonitis)	• Trouble breathing, shortness of breath, cough, chest pain	✓	✓	✓*
Blood clots (venous thromboembolism)	• Report chest pain, shortness of breath, rapid breathing, and heart rate; pain, swelling, and redness of leg or arm	✓	✓*	✓*
Heart problems	• Report chest pain, irregular heartbeat, dizziness, fainting, swelling in legs	✓		✓*

*Per Product Monograph guidance, stop taking drug and seek immediate medical help.

PATIENT EDUCATION RESOURCES

- Links:
  - Cancer Care Ontario (CCO): https://www.cancercareontario.ca/en/drugformulary/drugs
  - BC Cancer (Systemic Therapy): http://www.bccancer.bc.ca/our-services/patient-guide/systemic-therapy-teaching
  - Groupe d'étude en oncologie du Québec (GEOQ): https://www.geoq.info/fr/pub/essais-cliniques-institution-0-site-19-page-1
  - Canadian Cancer Society: Life after Cancer Treatment: https://cdn.cancer.ca/-/media/files/cancer-information/resources/publications/life-after-cancer/32060-life-after-cancer-treatment-en.pdf?rev=ad4b66e5184e460ead7d78e8e6875116&hash=8DC741A1D8B6F08AC362B524BAC96367
  - The Ottawa Hospital: How to Manage Nausea and Vomiting During Cancer Treatment
  - The Ottawa Hospital: Diarrhea
  - Ottawa Cancer Foundation: https://www.ottawacancer.ca/calendar/
  - Princess Margaret Cancer Answers: https://www.uhn.ca/PrincessMargaret/search/Pages/cancer_answers.aspx
  - eviQ Patient Information Sheets: https://www.eviq.org.au/patients-and-carers/patient-information-sheets
  - Oral Chemotherapy Education: https://oralchemoedsheets.com/
- Breast Cancer-specific Links:
  - Cancer Care Ontario: Breast Cancer
  - Canadian Breast Cancer Network (CBCN):
    - — Patient Education Videos: https://cbcn.ca/en/webinars
    - — Community and Support: https://cbcn.ca/en/mbc_community
    - — Side Effect Management: https://cbcn.ca/en/side-effects
  - CDK4/6is in Breast Cancer (2-minute video): https://youtu.be/UNxSJN7Twh4

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[AB/CP/SB, membership on advisory boards, consultant panels, or speakers' bureaus; FP/H, financial payment/honoraria; G/CT, funded grants or clinical trials].

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10. Acronyms and Abbreviations

5-HT_3, 5-hydroxytryptamine 3
AB, Alberta
aBC, advanced breast cancer
ADL, activities of daily living
AI, aromatase inhibitor
ALT, alanine aminotransferase
ANC, absolute neutrophil count
AST, aspartate aminotransferase
BC, British Columbia
BC, breast cancer
BCRP, breast cancer resistance protein
BID, twice daily
BPM, beats per minute
BSA, body surface area
BSEP, bile salt export pump
CBC, complete blood count
CDK, cyclin-dependent kinase
CDK4/6is, cyclin-dependent kinase 4/6 inhibitors
CO, clinical opinion
CrCl, creatinine clearance
CTCAE, common terminology criteria for adverse events
DNA, deoxyribonucleic acid
DOAC, direct oral anticoagulant
ECG, electrocardiogram
ESRD, end-stage renal disease
ET, endocrine therapy
G-CSF, granulocyte-colony stimulating factor
GABA, gamma-aminobutyric acid
GnRH, gonadotropin-releasing hormone
HCP, healthcare professional
HER2−, human epidermal growth factor receptor 2-negative
HR+, hormone receptor-positive
ILD, interstitial lung disease
LA, locally advanced
LFT, liver function test
LLN, lower limit of normal
MATE-1/2, multidrug and toxic compound extrusion protein-1/2
mBC, metastatic breast cancer
mEq, milliequivalent
mg, milligram
mo, month
ms, millisecond
NB, New Brunswick
NR, not reported
OCT2, organic cation transporter 2
ON, Ontario
PO, by mouth
Q*W, every * weeks
QC, Quebec
QTa, absolute QT interval measurement
QTc, QT interval corrected for heart rate
QTcF, QT interval corrected for heart rate by Fridericia's formula
Rb protein, retinoblastoma tumour suppressor protein
RR, R-R interval on electrocardiogram
TID, three times a day
TPN, total parenteral nutrition
ULN, upper limit of normal
VTE, venous thromboembolic event

11. Appendix

- Healthcare Provider Resources: OnTarget: https://ontargetonco.com/
- How to measure QTc manually[31]:
  1. Determine the baseline (TP-line).
  2. Draw two lines perpendicular to the TP line: one at the Q-wave and one at the peak of the T-wave.
  3. Draw a tangent at the maximum slope of the T-wave crossing the peak of the T-wave and the TP-line. This is the absolute QT interval measurement (QTa).
  4. Calculate the QTc interval (in milliseconds) using a correction formula.

Table 11.1: Correction Formulae for Calculating the QTc interval[81]

Bazett	Fridericia	Framingham	Hodges
$QT/RR^{1/2}$	$QT/RR^{1/3}$	QT+0.154 (1−RR)	QT+1.75 ([60/RR]–60)

- Bazett's formula is most used in Canadian clinical practice. Bazett's formula is most accurate when heart rate is 60–100 BPM.[31]
  - Bazett's formula overestimates QTc when heart rate is high, and underestimates QTc when heart rate is low.[81]
- The Fridericia formula has improved accuracy for high heart rates.[31]
  - This formula is commonly used in cancer clinical trials.[37]
- At high heart rates, the Framingham formula slightly overcorrects the QTc in males and under corrects the QTc in females.[81]

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