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Guidelines

Multidisciplinary Practical Guidance for Implementing Adjuvant CDK4/6 Inhibitors for Patients with HR-Positive, HER2-Negative Early Breast Cancer in Canada

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Section 1 Introduction

This expert opinion review aims to provide practical guidance for implementing adjuvant CDK4/6 inhibitor treatment for patients with HR+, HER2− early-stage breast cancer, incorporating multidisciplinary perspectives from medical and surgical oncologists, a nurse practitioner (NP), an oncology pharmacist, and a patient group representative to maximize successful use of these therapies in Canada

Section 2 - **Patient Identification for Adjuvant CDK4/6 Inhibitor Therapy**

Table 1. Summary of Key Differences Between Abemaciclib and Ribociclib *.

Parameter	Abemaciclib [19,32]	Ribociclib [20,33]	Key Takeaway
Phase III Trial Eligibility Criteria	**monarchE** Cohort 1: • ≥4 positive ALN **OR** • 1–3 positive ALN and at least 1 of: ○ Grade 3 disease ○ Tumour size ≥ 5 cm Cohort 2: • 1–3 positive ALN and Ki-67 ≥ 20% • Tumour grade below 3 • Tumour size < 5 cm *In monarchE, microscopic and macroscopic nodal involvement were allowed*	**NATALEE** • Patients with stage IIB or III disease were eligible irrespective of nodal status. • Patients with stage IIA disease were eligible if: ○ ≥1 lymph node involved ○ No nodal involvement and grade 3 tumours. ○ No nodal involvement and a grade 2 tumour with: ▪ Ki-67 ≥ 20% ▪ High genomic risk score (Oncotype DX Breast RS, MammaPrint®, EndoPredict®)	Abemaciclib may be considered for "higher-risk patients" given the requirement for node-positive disease in monarchE.
ET Partner	AI or tamoxifen †	NSAI	Abemaciclib may be considered with tamoxifen for patients who cannot tolerate AIs. †

Section 2 - **Patient Identification for Adjuvant CDK4/6 Inhibitor Therapy**

Parameter	Abemaciclib [19,32]	Ribociclib [20,33]	Key Takeaway
iDFS in Clinical Trial Overall Population	5-year iDFS [34] Abemaciclib + ET: 83.6% ET alone: 76.0% HR: 0.68 (95% CI: 0.60, 0.77), Nominal $p < 0.001$ **7.6% absolute increase in iDFS with addition of abemaciclib to ET.**	4-year iDFS Ribociclib + NSAI: 88.5% NSAI alone: 83.6% HR: 0.72 (95% CI: 0.61, 0.84), $p < 0.0001$ [21] **4.9% absolute increase in iDFS with addition of ribociclib to NSAI.**	Both abemaciclib and ribociclib demonstrate iDFS benefits in the overall population and across key subgroups [35].
Overall Survival	Not reported	Not reported	Overall survival data remain immature for both abemaciclib and ribociclib.
Data Maturity ‡	5 years	4 years	Abemaciclib has greater data maturity/longer-term follow-up.
Treatment Length	2 years	3 years	A longer treatment duration may extend the burden of toxicity and impact quality of life and/or adherence.
Dosing Regimen	150 mg PO BID	400 mg PO once daily for 21 days, then 7 days off treatment	Scheduling and duration may impact patient preference and adherence.
Recommended Dose Reductions	Reduction 1 to 100 mg PO BID Reduction 2 to 50 mg PO BID	Reduction to 200 mg PO once daily	Both agents can be dose reduced for toxicity.
Most Frequent AEs (All Grades; **Grade ≥ 3**)	• Diarrhea (83.6%; **7.8%**) • Neutropenia (46%; **19.7%**) • Fatigue (40.9%; **2.9%**) • Leukopenia (37.7%; **11.4%**) • Abdominal pain (35.7%; **1.4%**)	• Neutropenia (62.1%; **43.9%**) • Arthralgia (36.5%; **1.0%**) • Liver-related events (25.4%; **8.3%**) • Nausea (23.0%; **0.2%**) • Headache (22.0%; **0.4%**) • Fatigue (21.9%; **0.7%**)	Diarrhea with abemaciclib + ET typically occurred early, was short-lived, and was effectively managed with antidiarrheal medication and dose adjustments [19]. Most ribociclib-related AEs, such as neutropenia and liver-related events, were predominantly asymptomatic laboratory findings requiring additional monitoring [20].
AEs Leading to Treatment Discontinuation (%) [36]	• Diarrhea (5.3%) • Fatigue (**2.0%**) • Neutropenia (**0.9%**)	• Liver-related events (**8.9%**) • Arthralgia (**1.3%**)	

Section 2 - **Patient Identification for Adjuvant CDK4/6 Inhibitor Therapy**

Parameter	Abemaciclib [19,32]	Ribociclib [20,33]	Key Takeaway
Product Monograph Recommended Monitoring	• Prior to initiation, Q2W for first 2 months, QM for next 2 months, as clinically indicated: ○ CBC ○ Liver function • ILD/pneumonitis • Infection/myelosuppress • Thromboembolism (especially in patients receiving concomitant tamoxifen)	• Prior to initiation, Q2W for first 2 cycles, at the beginning of each of the subsequent 4 cycles, as clinically indicated: ○ CBC ○ Liver function • Prior to initiation, during cycle 1 ~D14, beginning of cycle 2, regular intervals thereafter and whenever clinically indicated: ○ ECG • Prior to initiation, then at regular intervals and whenever clinically indicated: ○ Electrolytes • ILD/pneumonitis • Thromboembolism (in those at risk)	Treatment monitoring should follow the Product Monograph for both agents.
DDI Considerations	Metabolic/Transport Effects • CYP3A4 (major), BCRP/ABCG2 (minor), P-glycoprotein/ABCB1 (minor) [37] Avoid Using With • CYP3A inhibitors/inducers	Metabolic/Transport Effects • Substrate of CYP3A4 (major); inhibits CYP3A4 (moderate) [38] • Possible risk of TdP [39] Avoid Using With • CYP3A inhibitors/inducers • Anti-arrhythmic medicines/drugs that prolong the QT interval (e.g., tamoxifen) • Drugs that decrease electrolyte levels • Tamoxifen	Ribociclib requires monitoring for QTc interactions (e.g., with antidepressants, antibiotics), or with drugs affecting electrolyte levels [33].

Section **3. Considerations for Selecting CDK4/6 Inhibitors**

Patient inclusion criteria				monarchE Abemaciclib	NATALEE Ribociclib
Breast cancer stage					
Stage		**T**	**N**		
I	IA	T1	N0		
	IB	T0	N1mi		
	IB	T1	N1mi	Only if Grade 3 or Ki-67 ≥20%	
II	IIA	T0	N1		
	IIA	T1	N1	Only if Grade 3 or Ki-67 ≥20%	
	IIA	T2	N0		Only if Grade 3, or Grade2 with Ki-67 ≥20%, or high genomic risk
	IIB	T2	N1	Only if Grade 3 or Ki-67 ≥20%	
	IIB	T3	N0		
III	IIIA	T0	N2		
	IIIA	T1	N2		
	IIIA	T2	N2		
	IIIA	T3	N1		
	IIIA	T3	N2		
	IIIB	T4	N0		
	IIIB	T4	N1		
	IIIB	T4	N2		
	IIIC	Any T	N3		
Breast involvement					
Unilateral					
Bilateral (diagnosis of invasive tumours in both breasts simultaneously or within 6 months of each other)				Only if all lesions tested on both sides are HR+/HER2− and adequate surgery has been performed in both breasts	Not specified in protocol
ECOG PS					
0					
1					
≥2					
Prior breast cancer therapy					
(Neo)adjuvant chemotherapy					
Adjuvant radiotherapy					
(Neo)adjuvant ET					

Figure 1. Patient Inclusion Criteria for monarchE and NATALEE [31,43,44]. Green indicates patient eligibility and red indicates patient ineligibility. ECOG: Eastern Cooperative Oncology Group; ET:

Section 4. Practical Recommendations for the Clinical Management of CDK4/6 Inhibitors

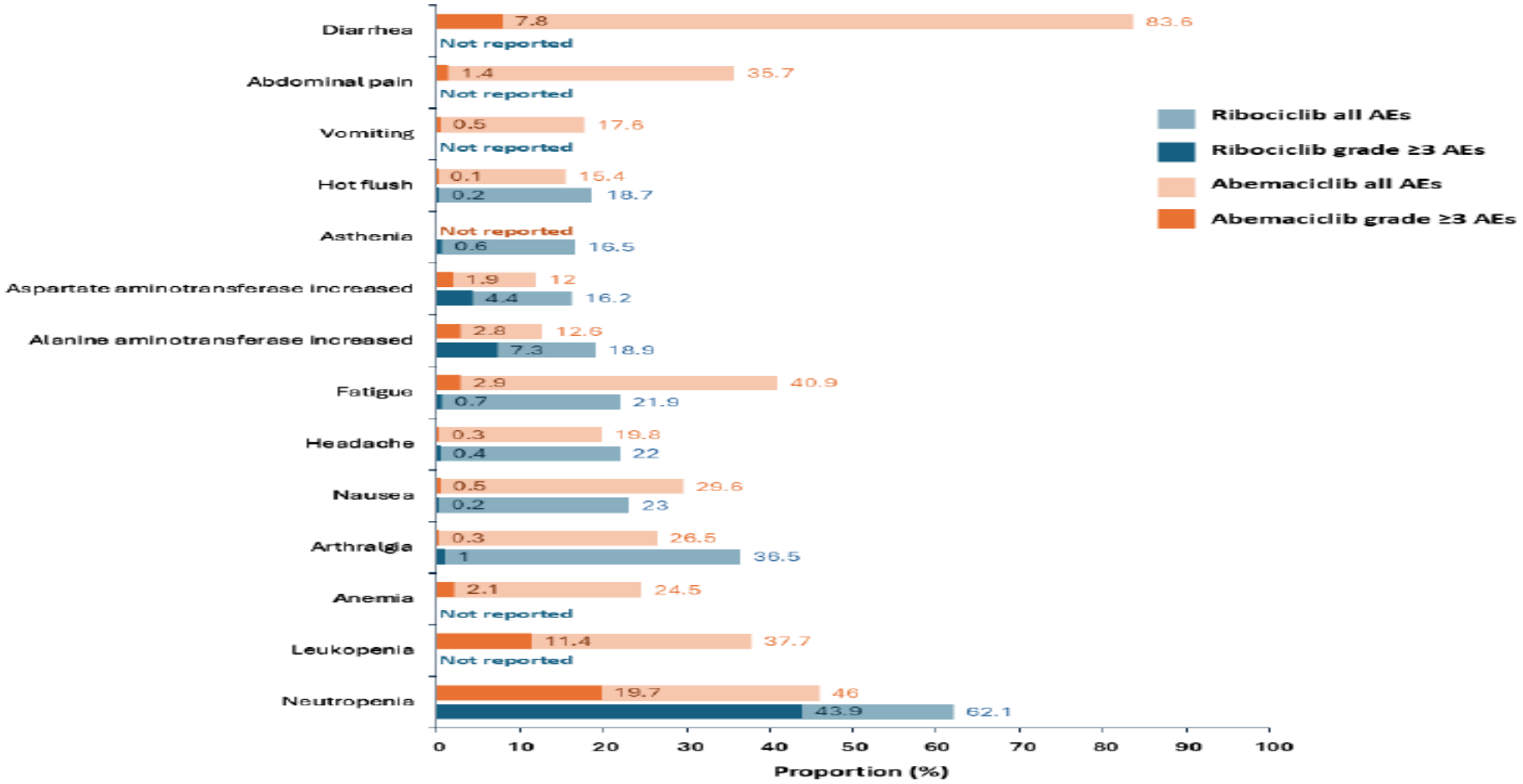

Figure 2. Common Adverse Events (≥15%) from the monarchE and NATALEE Trials [19,20]. AE: adverse event.

Section 4. Practical Recommendations for the Clinical Management of CDK4/6 Inhibitors

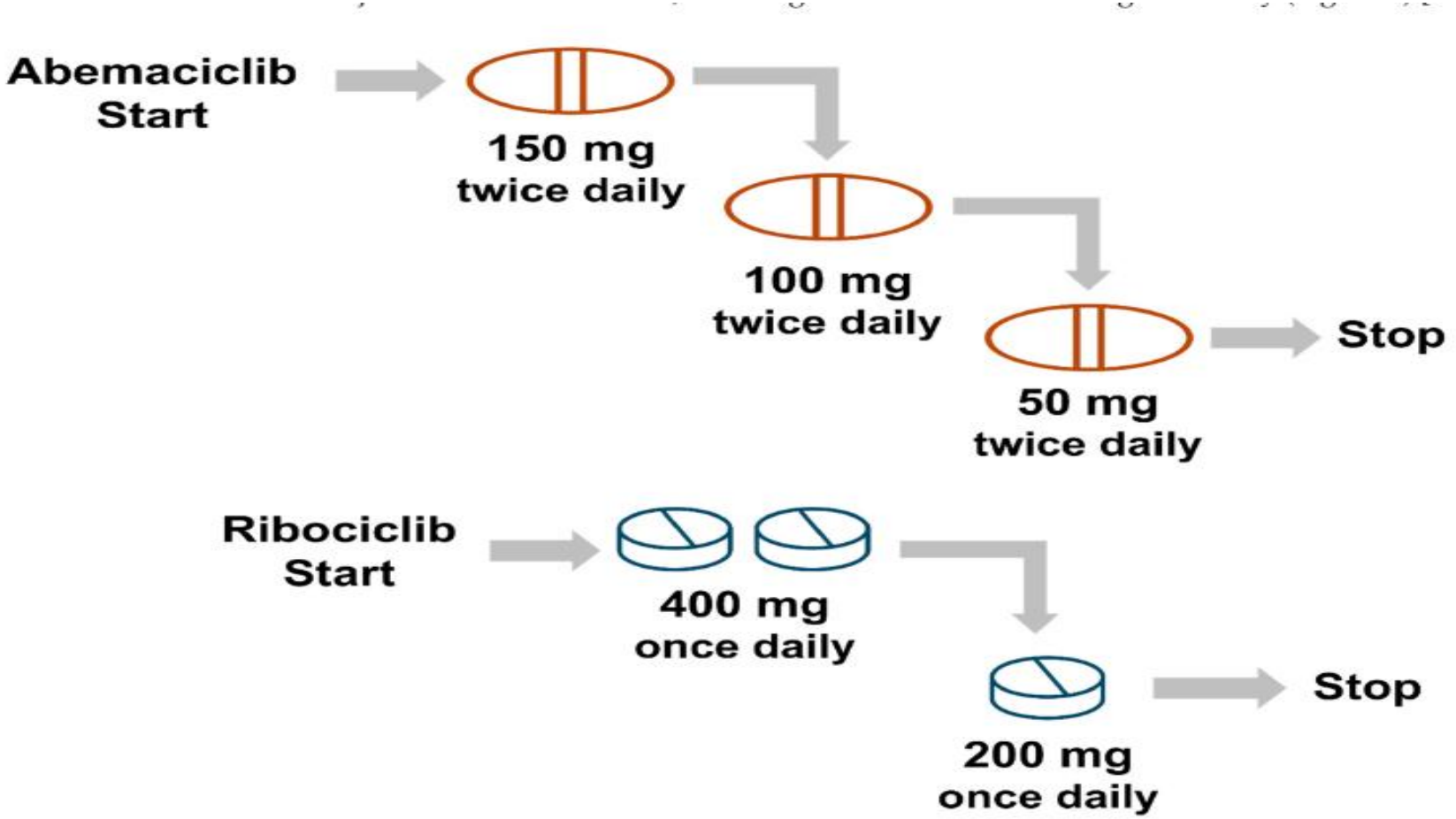

Figure 3. Recommended Dose Holds for Abemaciclib and Ribociclib [32,33].

Section 4. Practical Recommendations for the Clinical Management of CDK4/6 Inhibitors

	Abemaciclib	Ribociclib
CBC	Prior to start Q2W for months 1, 2 QM for months 3, 4 *As clinically indicated*	Prior to start Q2W for cycles 1, 2 At the start of cycles 3–6 *As clinically indicated*
Liver function		
ILD/pneumonitis	Monitor for pulmonary symptoms indicative of ILD/pneumonitis	
ECG	-	Prior to start ~Day 14 of cycle 1 *As clinically indicated*
Electrolytes	-	Prior to start *At regular intervals during steady state in later cycles & as clinically indicated*
Infection or myelosuppression	Monitor for signs and symptoms	
Thromboembolism	Monitor for signs and symptoms	Monitor for signs and symptoms in patients at risk

Figure 4. Monitoring Recommendations for Abemaciclib and Ribociclib [32,33]. CBC: complete blood count; ECG: electrocardiogram; ILD: interstitial lung disease; Q2W: every two weeks; QM: every month.

4.8. Optimizing Multidisciplinary Collaboration During Monitoring and Follow-Up

NPs and pharmacists can oversee routine follow-ups, identify early signs of toxicity, and provide timely interventions. Alternative models of care can also be implemented to help alleviate resource and time burden faced by many clinics. A nurse-led supportive care program for women with newly diagnosed breast cancer demonstrated significant improvement of quality of life and symptom management during adjuvant chemotherapy [23]. In this randomized controlled pilot study, patients in the intervention group showed significantly higher global health and functional status scores, and lower symptom burden compared to controls [23]. Furthermore, a pharmacist-led virtual clinic for patients with breast cancer on CDK4/6 inhibitors improved adherence to laboratory testing and the patient-reported adherence to the prescribed medication was more than 99% [24]. In this model, patients received structured follow-ups every 2 weeks initially, then monthly, focusing on lab review, adherence, AE monitoring, and drug interactions [24]. The clinic identified 38 potential drug therapy issues, leading to targeted interventions such as patient education, symptom management, and QT monitoring [24].