

# Analysis of Drug Interaction Potential of Ribociclib With Commonly Used Medicines and Herbal Supplements in Patients With Advanced Breast Cancer

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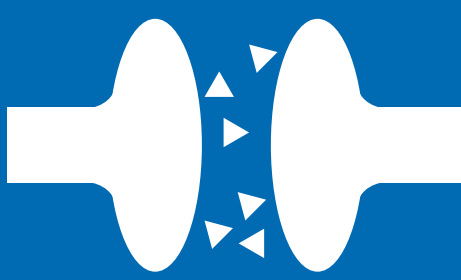








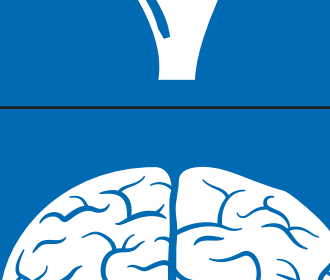
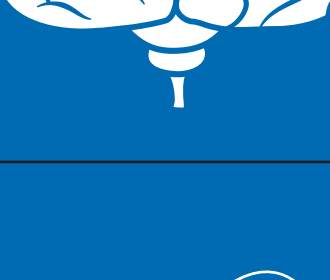
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## Introduction

- Adequate management of comorbidities and adverse events is necessary to maximize drug exposure and treatment benefit in patients with advanced breast cancer
- Ribociclib is an orally bioavailable, selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) approved for use in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced or metastatic breast cancer<sup>1</sup>
  - Results from the second overall survival interim analysis (data cutoff, January 2, 2017) of the Phase 3 trial, MONALEESA-2 (ClinicalTrials.gov number NCT01958021), showed that treatment with ribociclib + letrozole exhibited superior progression-free survival (PFS) versus placebo + letrozole (median duration of PFS, 25.3 vs 16 months, respectively; hazard ratio, 0.568; 95% CI, 0.457–0.704;  $P=9.63 \times 10^{-8}$ ) in postmenopausal patients with advanced breast cancer<sup>2</sup>
- Ribociclib is known to exhibit drug-drug interactions (DDIs) with metabolizers and substrates of cytochrome P450 (CYP) and drugs with known potential to prolong QT interval<sup>1</sup>
  - Ribociclib can exhibit variable exposure with medicines that induce or inhibit CYP3A
- There is inadequate awareness and communication in the literature about safe coadministration of medications and nutritional supplements with ribociclib
- Presented here is an analysis of potential DDIs of common medicines and nutritional supplements with ribociclib based on a single center’s experience

## Methods

- This single-center retrospective chart review of patients (n=42) with advanced breast cancer identified the most commonly used drugs and supplements from 2/1/2016 to 1/31/2017, categorized by comorbidity
- The potential for drug-drug interaction and/or QT interval prolongation was assessed using available clinical pharmacology information listed in the following databases:
  - Lexicomp Online
  - Natural Products
  - Memorial Sloan Kettering Cancer Center Integrative Medicine databases
- A variation of Stockley’s Herbal Medicines Interactions was used to establish severity and recommendation for herbal product interaction with ribociclib<sup>3</sup>
- The pharmacodynamic interactions between medications and supplements were also evaluated for severity and clinical recommendations<sup>4,5</sup>
  - Interactions that involved adverse effects warranting dosing alterations were placed in the “Use with caution” and “Prohibited” categories

	Safe to use			Use with caution	Prohibited
 Acid-reducing agents <sup>a</sup>	Esomeprazole Famotidine	Omeprazole Pantoprazole		Ranitidine (MATE1/OCT2)	
 Analgesics	Celecoxib Codeine Ibuprofen	Meloxicam Morphine Naproxen	Oxycodone Sumatriptan Tramadol	Hydrocodone and acetaminophen (CYP3A4)	Fentanyl (CYP3A4)
 Antiarrhythmic agents		Digoxin			Amiodarone (QT prolongation)
 Anticholinergic/ Antihistamine agents	Cetirizine	Oxybutynin	Tolterodine		
 Anticoagulation agents <sup>b</sup>	Aspirin Clopidogrel		Dabigatran Warfarin	Apixaban (CYP3A4)	Enoxaparin
 Antiemetics				Ondansetron, oral/sublingual 4–8 mg/dose maximum (CYP3A4, possible QT prolongation)	Ondansetron, intravenous (CYP3A4, QT prolongation)
 Antihyperglycemic agents <sup>d</sup>	Glimepiride Glipizide Glyburide	Liraglutide Pioglitazone	Saxagliptin Sitagliptin	Metformin (GI effects)	
 Antihyperlipidemia agents <sup>e</sup>	Ezetimibe	Fenofibrate	Gemfibrozil	Atorvastatin (CYP3A4)	Rosuvastatin <sup>f</sup>
 Antihypertensive agents <sup>g</sup>	Atenolol Carvedilol Clonidine Enalapril	Irbesartan Labetalol Lisinopril Losartan	Olmesartan Propranolol Ramipril Spironolactone	Amlodipine (CYP3A4) Diltiazem (CYP3A4) Furosemide (possible QT prolongation)	Hydrochlorothiazide (possible QT prolongation) Losartan (MATE1/OCT2) Verapamil (CYP3A4)
 Antimicrobial agents		Valacyclovir		Amoxicillin	Metronidazole (QT prolongation)
 Miscellaneous	Allopurinol Carisoprodol Cyclobenzaprine Dexamethasone Donepezil	Fluticasone Gabapentin Levothyroxine Magnesium sulfate Potassium chloride	Prednisone Pregabalin Rivastigmine Topiramate	Albuterol (QT prolongation)	Budesonide (CYP3A4) Lidocaine (CYP3A4)
 Osteoporosis treatments	Alendronate	Ibandronate	Risedronate		
 Psychotropic agents	Alprazolam Bupropion Butalbital Clonazepam	Duloxetine Levetiracetam Lorazepam Memantine	Modafinil Oxcarbazepine Trazodone Varenicline	Zaleplon Zolpidem	Amitriptyline (possible QT prolongation) Bupirone (CYP3A4) Desvenlafaxine (CYP3A4)
 Nutritional supplements	Chlorella Cranberry Echinacea	Lycopene Modified citrus pectin Probiotics	Resveratrol Selenium Vitamin C	Coenzyme Q10 Curcumin Flaxseed Frankincense essential oil	Grape seed extract Green tea <sup>h</sup> Indole-3-carbinol Lugol's solution Melatonin
				Soy Turmeric Vitamin B complex Vitamin D	Phenobarbital (CYP3A4) Phenytoin sodium (CYP3A4) Sertraline (possible QT prolongation)
				Black cohosh (hepatotoxicity, hormonal effects) Fish oil Gingko (palpitations, QT prolongation)	Carbamazepine (QT prolongation) Citalopram (QT prolongation) Escitalopram (QT prolongation) Fluoxetine (QT prolongation) Venlafaxine (QT prolongation) Quetiapine (QT prolongation) Venlafaxine (QT prolongation)
					Ginseng (CYP3A4, QT prolongation) Garlic Ginger
					Milk thistle Saw palmetto St John's wort (CYP3A4)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GI, gastrointestinal; MATE1, multidrug and toxin extrusion protein 1; OCT2, organic cation transporter 2. <sup>a</sup>No obvious pharmacokinetic/pharmacodynamic interactions with proton pump inhibitors and H2-receptor antagonists. <sup>b</sup>There is increased risk of bleeding with all the anticoagulants listed above because of ribociclib’s myelosuppressive effects. <sup>c</sup>Depends on additional drug/group, international labeling, and renal function. <sup>d</sup>The listed antihyperglycemic agents do not have any pharmacokinetic interactions but may cause nausea. <sup>e</sup>Statins have a higher potential for myopathy complications than the other medications listed. <sup>f</sup>Rosuvastatin is a better alternative to simvastatin and atorvastatin because its pharmacokinetic interactions are limited. <sup>g</sup>Ribociclib has a peripheral edema adverse effect profile similar to calcium channel blockers (CCBs). The interaction between ribociclib and CCBs is further compounded by pharmacokinetic interactions (CYP3A4). The other drug classes (ACE inhibitors, ARBs, thiazides, loop diuretics [with the exception of indapamide], beta blockers, alpha-2 adrenergic receptor agonists) may be better alternatives. <sup>h</sup>Avoid prior to surgery; may cause bleeding.

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## Results

- The most common 120 prescription medicines and 32 nutritional supplements (eg, herbal supplements, vitamins, natural foods and extracts) to treat acute symptoms (eg, nausea, pain, infections) and chronic comorbidities (eg, diabetes, hypertension, cardiovascular disease) were identified
  - Commonly used supplements had varied potential effects on ribociclib metabolism

## Conclusions

- Therapies considered to be standard of care for commonly reported side effects and comorbidities in patients with advanced breast cancer can likely be safely administered with ribociclib
- Nutritional supplements can exhibit variable physiological effects when used concomitantly with ribociclib
- Patients should be advised to inform their healthcare professionals about any new medications, herbal drugs, or supplements they take or plan to take during treatment with ribociclib
- Physicians should monitor patients carefully for adverse effects from concomitant medications and supplements
- Pharmacists and physicians are advised to use individualized clinical judgment when determining the best treatment option for patients


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