Table 1: Drug-Drug Interactions of Common Cardiac Drugs and Chemotherapeutic Agents*

Cardiac Drug(s)	Enzyme/ Action	Chemotherapy Drug†	Effect of Drug-Drug Interaction	Suggested Oncologist Management	Suggested Cardiologist Management
Beta-Blockers					
All beta-blockers	Additive clinical effect	Ceritinib	Additive bradycardia	Avoid using the combination of ceritinib with beta-blockers. If concomitant use is necessary and symptomatic bradycardia occurs, hold ceritinib, adjust or discontinue the beta-blocker, and upon recovery resume ceritinib at a reduced dose with frequent monitoring of heart rate.‡	
		Crizotinib		Monitor blood pressure and heart rate regularly. Dose reduction or discontinuation of one of the agents may be necessary if clinically significant bradycardia occurs.‡	
Carvedilol	P-gp inhibition (moderate)	Afatinib	↑ chemotherapy drug concentration	Monitor for adverse effects of afatinib. If not well-tolerated, decrease afatinib daily dose by 10 mg.	Consider alternative agent if possible.
		Doxorubicin Nilotinib Paclitaxel Pazopanib Vincristine Vinblastine		Monitor for adverse effects of chemotherapy drug if concomitant therapy is necessary.	Consider alternative agent if possible. If carvedilol is used for prevention of anthracycline cardiotoxicity, individual risk vs. benefit must be considered. If concomitant therapy is necessary and drug-drug interaction involves QT-prolonging chemotherapy drug, ensure appropriate electrocardiographic (ECG) and electrolyte monitoring.
Carvedilol; metoprolol	CYP2D6 inhibition (moderate)	*Imatinib* *Panobinostat*	↑ beta-blocker concentration	Monitor blood pressure and heart rate. Notify cardiologist if clinically significant bradycardia or hypotension occurs	Monitor blood pressure and heart rate closely if concomitant therapy is necessary. Dose reduction or discontinuation of carvedilol may be necessary if clinically significant bradycardia or hypotension occurs
ACEi/ARBss					
Losartan; Irbesartan	CYP2C9 inhibition (moderate)	Ceritinib	↑ losartan or irbesartan concentration		Monitor for evidence of increased adverse effects or toxicity due to ARB. Dose reduction or alternative agent may be necessary.
Losartan	CYP3A4 inhibition (strong)	*Idelalisib*	↑ losartan concentration	Notify cardiologist/ prescriber to switch to alternative therapy.	Avoid co-administration. Consider alternative agent during idelalisib therapy that does not undergo CYP3A4 metabolism (i.e., irbesartan, valsartan)

Losartan	CYP2C9 induction	*Dabrafenib*	↓ losartan concentration		Seek alternative agent (i.e., valsartan) that is not a CYP2C9 substrate. If concomitant therapy is necessary, monitor for diminished therapeutic effects and/or need for losartan dose increase.
Calcium Channel Blockers					
Verapamil; Diltiazem	Additive clinical effect	Ceritinib	Additive bradycardia	Avoid using the combination of ceritinib with non-dihydropyrimidine calcium channel blockers. If concomitant use is necessary and symptomatic bradycardia occurs, hold ceritinib, adjust or discontinue the calcium channel blocker, and upon recovery resume ceritinib at a reduced dose with frequent monitoring of heart rate.‡	
		Crizotinib		Monitor blood pressure and heart rate regularly. Dose reduction or discontinuation of one of the agents may be necessary if clinically significant bradycardia occurs.‡	
Diltiazem; verapamil	CYP3A4 inhibition (moderate)	Bosutinib	↑ chemotherapy drug concentration	Notify cardiologist/ prescriber to switch to alternative therapy.	Avoid co-administration.‡ Consider alternative agent during bosutinib therapy that does not inhibit CYP3A4.
		Doxorubicin Imatinib Ivosidenib Neratinib Nilotinib		If concomitant therapy is necessary, monitor closely for toxicities.	Concomitant use should be avoided if possible. Consider alternative agent during chemotherapy that does not inhibit CYP3A4. If concomitant therapy is necessary and drug-drug interaction involves QT-prolonging chemotherapy drug, ensure appropriate ECG and electrolyte monitoring.
		Abemaciclib		If concomitant therapy is necessary, consider reducing the dose by 50 mg increments. Monitor closely for toxicities.	
		Acalabrutinib		If concomitant therapy is necessary, dose reduction of acalabrutinib to 100 mg daily is advised. Monitor closely for toxicities.	
		Cobimetinib		If concurrent short-term use (≤14 days) cannot be avoided, reduce cobimetinib to 20 mg daily.	
		Encorafenib		If concomitant therapy is necessary, dose reduction of encorafenib to one-half is advised. Monitor	

				closely for toxicities.	
		Ibrutinib		If concomitant therapy is necessary, dose reduction of ibrutinib to 280 mg daily is advised for B cell malignancies. Monitor closely for toxicities.	
		Olaparib		If concomitant therapy is necessary, dose reduction of olaparib tablet to 150 mg twice daily or olaparib capsule to 200 mg twice daily is advised. Monitor closely for toxicities.	
		Sonidegib		If concomitant therapy is necessary, limit concurrent use to less than 14 day and monitor closely for toxicities, especially musculoskeletal.	
Amlodipine	CYP3A4 inhibition (moderate)	*Ceritinib* *Crizotinib* *Imatinib* *Palbociclib*	↑ amlodipine concentration		Monitor for evidence of increased adverse effects or toxicity due to amlodipine. Amlodipine dose reduction may be necessary.
	CYP3A4 inhibition (strong)	*Idelalisib*		Notify cardiologist/ prescriber to switch to alternative therapy.	Avoid co-administration. Consider alternative agent during idelalisib therapy. If concomitant use is necessary, closely monitor for adverse effects due to amlodipine (i.e., hypotension, peripheral edema)
Statins					
All statins	Unknown (atorvastatin- also P-gp-inhibitor)	Pazopanib	Increased incidence of alanine transaminase (ALT) elevations; statins may enhance hepatotoxicity of pazopanib	Monitor aspartate aminotransferase (AST)/ALT levels if used concurrently. Consider adjusting pazopanib if concomitant statin use is absolutely necessary.	Exercise caution. Monitor AST/ALT levels if used concurrently. Dose reduction, interruption, or discontinuation of therapy may be necessary. Documented interaction is with simvastatin. Insufficient data are available to assess the risk of concomitant pazopanib with alternative statins.‡ Atorvastatin should be avoided because it is also a P-gp inhibitor.

Atorvastatin Simvastatin Lovastatin	CYP3A4 inhibition (moderate)	*Ceritinib* *Crizotinib* *Imatinib* *Palbociclib*	↑ statin exposure		Monitor AST/ALT and creatine kinase. Dose reduction of statin may be necessary. May consider alternative statin that does not undergo CYP3A4 metabolism (i.e., pravastatin) during chemotherapy.
	CYP3A4 inhibition (strong)	*Idelalisib*	↑ statin exposure; increased risk of myopathy and rhabdomyolysis	Notify cardiologist/ prescriber to switch to alternative statin therapy.	Avoid co-administration. Consider alternative statin that does not undergo CYP3A4 metabolism (i.e., pravastatin) during idelalisib therapy.
Antiarrhythmics					
Amiodarone *Dronedarone*	P-gp inhibition (moderate)	Brentuximab	↑ chemotherapy drug concentration	If concomitant therapy is necessary, monitor for adverse effects of brentuximab.	Consider alternative antiarrhythmic agent if possible.
		Afatinib		Monitor for adverse effects of afatinib. If not well-tolerated, decrease afatinib daily dose by 10 mg.	
		Doxorubicin Nilotinib Paclitaxel Pazopanib Vincristine Vinblastine		Monitor for adverse effects of chemotherapy drug if concomitant therapy necessary.	Avoid co-administration if possible. Consider alternative antiarrhythmic agent during chemotherapy that does not inhibit P-gp. If concomitant therapy is necessary and drug-drug interaction involves QT-prolonging chemotherapy drug, ensure appropriate ECG and electrolyte monitoring.
Amiodarone Dronedarone	CYP3A4 inhibition (moderate)	*Ceritinib* *Crizotinib* *Imatinib* *Palbociclib*	↑ antiarrhythmic drug concentration		Monitor for increased adverse effects or toxicity due to amiodarone or dronedarone. Dose reduction may be necessary.
Dronedarone	CYP3A4 inhibition (moderate)	Bosutinib Cobimetinib Ibrutinib	↑ chemotherapy drug concentration	See above recommended action under "Diltiazem; verapamil" and individual chemotherapy drug.	Avoid co-administration if possible. Consider alternative agent during chemotherapy that does not inhibit CYP3A4.
Digoxin	Additive clinical effect	Ceritinib	Additive bradycardia	Avoid using the combination of ceritinib with digoxin. If concomitant use is necessary and symptomatic bradycardia occurs, hold ceritinib, adjust or discontinue digoxin, and upon recovery resume ceritinib at a reduced	

				dose with frequent monitoring of heart rate.‡	
		Crizotinib		Monitor blood pressure and heart rate regularly. Dose reduction or discontinuation of one of the agents may be necessary if clinically significant bradycardia occurs.‡	
	P-gp inhibition	*Ibrutinib* *Neratinib* *Vandetanib*	↑ digoxin drug concentration		Monitor levels and signs/symptoms of digoxin toxicity closely. Decreased digoxin doses may be required.
		Vemurafenib			Avoid co-administration if possible. If concomitant use cannot be avoided, consider digoxin dose reduction and monitor levels and signs/symptoms of digoxin toxicity closely.
Flecainide	CYP2D6 inhibition	*Imatinib* *Panobinostat*	↑ flecainide concentration		Monitor for increased adverse effects or toxicity due to flecainide.
Amiodarone Dofetilide Dronedarone Flecainide Sotalol	Additive clinical effect	*Moderate risk QTc prolongers (see Table 4)*	Additive QTc prolongation	Recommend ECG and electrolyte monitoring. Frequency to be determined by patient-specific factors and QT-prolonging drug risk. Avoid combination of high-risk QT-prolonging chemotherapy and cardiac drugs (i.e., arsenic and dofetilide).	
		High risk QTc prolongers (see Table 4)			

* Drug in *italics* represents enzyme inhibitor in proposed interaction.

† Color denotes severity of interaction as follows:

- *Red.* Major interaction; Black Box warning and/or strong clinical effects; avoid combination.
- *Orange.* Moderate interaction; known, reliable mechanism of interaction such as enzyme effects, protein binding, etc. Data demonstrate that there is a clinically significant drug interaction. Individual risk-benefit assessment for each patient should be considered with concomitant therapy. Actions such as aggressive monitoring or empiric dose changes should be taken to minimize toxicity. Alternative agents should be chosen if risks outweigh benefits.
- *Yellow.* Minor interaction; potential interaction between the agents; however, benefits usually outweigh risks. Evidence may be limited to only case reports. Appropriate monitoring plan should be implemented; a small number of patients may need dose adjustments or consideration of alternative agent.

‡ Package insert recommendation.