Data Supplement
Fradley et al
Recognition, Prevention, and Management of Arrhythmias and Autonomic Disorders in Cardio-Oncology: A Scientific Statement From the American Heart Association

Table I: Relevant Arrhythmia and Cancer Therapeutic Drug-Drug Interactions

Cancer Therapy	Malignancies Treated	Arrhythmia Therapy	Mechanism	Effect
Abiraterone	Metastatic prostate cancer	Rate Control • Carvedilol Metoprolol Propranolol Rhythm Control • Flecainide Propafenone	• Unknown • CYP 2D6 inhibition	• [↑] beta blocker/bradycardic effect • [↑] antiarrhythmic drugs
Afatinib	NSCLC	Rate Control • Carvedilol Verapamil Rhythm Control • Quinidine Propafenone Amiodarone Dronedarone	• Pgp inhibition • Pgp inhibition	• [↑] afatinib • [↑] afatinib
Axitinib	Advanced Renal Cell Carcinoma	Rate Control • Non-dihydropyridine CCB Rhythm Control • Dronedarone	• CYP 3A4 inhibition	• [↑] axitinib • [↑] axitinib

			• CYP 3A4 inhibition	
Bosutinib	CML	Rate Control • Non-dihydropyridine CCB Rhythm Control • Dronedarone	• CYP 3A4 inhibition • CYP 3A4 inhibition	• [↑] bosutinib • [↑] bosutinib
Brentuximab vendotin	Hodgkin's and other lymphomas	Rate Control • Carvedilol Verapamil Rhythm Control • Quinidine Propafenone Amiodarone	• Pgp inhibition • Pgp inhibition	• [↑] brentuximab • [↑] brentuximab
BTK Inhibitors (ibrutinib and acalbrutinib)	CLL and other B cell malignancies	Rate Control • Non-dihydropyridine CCB • Digoxin Rhythm Control • Dronedarone	• CYP 3A4 inhibition • Pgp inhibition	• [↑] BTK inhibitors • [↑] ibrutinib • [↑] BTK inhibitors

		Anticoagulants • Factor Xa Inhibitors • Direct Thrombin Inhibitor • Warfarin	• CYP 3A4 inhibition • Inhibition of multiple clotting pathways • Pgp inhibition • Inhibition of multiple clotting pathways	• ↑ anticoagulant effect • ↑ anticoagulant effect • ↑ anticoagulant effect
CDK 4/6 Inhibitors (abemaciclib, palbociclib and ribociclib)	Hormone receptor positive, HER2 negative breast cancer)	Rate Control • Non-dihydropyridine CCB Rhythm Control • Disopyramide Quinidine Amiodarone	• CYP 3A4 inhibition • CYP 3A4 inhibition	• [↑] abemaciclib • [↑]rhythm controlling medications; [↑] abemaciclib
Ceritinib	NSCLC	Rate Control	• Unknown	• ↑ bradycardic effect

		• Beta blockers Non-dihydropyridine CCB Digoxin Rhythm Control • Amiodarone; Sotalol Anticoagulant • Warfarin	• Unknown • CYP 2C9 inhibition	• ↑ bradycardic effect • ↑ anticoagulant effect
Cobimetinib	Advanced melanoma	Rate Control • Non-dihydropyridine CCB Rhythm Control • Dronedarone	• CYP 3A4 inhibition • CYP 3A4 inhibition	• [↑] cobimetinib • [↑] cobimetinib
Crizotinib	NSCLC	Rate Control • Beta blockers Digoxin • Non-dihydropyridine CCB	• Unknown • CYP 3A4 Inhibition	• ↑ bradycardic effect • [↑] crizotinib

		Rhythm Control • Amiodarone Sotalol	• Unknown	• ↑ bradycardic effect
Dabrafenib (BRAF inhibitor for advanced melanoma)		Rate Control • Bisoprolol; non-dihydropyridine CCB	• CYP 3A4 induction	• [↓] rate controlling medications
		Rhythm Control • Disopyramide Quinidine • Amiodarone Dronedarone	• CYP 3A4 induction	• [↓] rhythm controlling medications
		Anticoagulants • Factor Xa inhibitors	• CYP 3A4 induction	• [↓] anticoagulants
		• Warfarin	• CYP 2C9 inhibition	• ↑ anticoagulant effect
Dasatinib	CML	Anticoagulants • Factor Xa inhibitors	• Inhibition of multiple clotting pathways	• ↑ anticoagulant effect
			• Inhibition of multiple	• ↑ anticoagulant effect

		• Direct Thrombin Inhibitor • Warfarin	clotting pathways • Inhibition of multiple clotting pathways	• ↑ anticoagulant effect
Docetaxel	Various cancers including breast and gastric	Rhythm Control • Dronedarone	• CYP 3A4 and Pgp inhibition	• [↑] decetaxel
Doxorubicin	Various cancers including breast and leukemia/lymphoma	Rate Control • Carvedilol Verapamil • Digoxin Rhythm Control • Quinidine Propafenone Amiodarone Dronedarone	• Pgp inhibition • Decreased oral bioavailability of digoxin; mechanism uncertain • Pgp inhibition	• [↑] doxorubicin • [↓] digoxin • [↑] doxorubicin
Erdafitinib	Advanced urothelial cancer	Rate Control • Bisoprolol Non-dihydropyridine CCB	• CYP 3A4 induction	• [↓] rate controlling medications

		• Digoxin Rhythm Control • Disopyramide Quinidine Amiodarone Dronedarone Anticoagulants • Factor Xa inhibitors • Direct Thrombin Inhibitor	• Pgp inhibition • CYP 3A4 induction • Inhibition of multiple clotting pathways • Inhibition of multiple clotting pathways	• [↑] digoxin • [↓] rhythm controlling medications • ↑ anticoagulant effect • ↑ anticoagulant effect
Erlotinib	Metastatic NSCLC and pancreatic cancer	Anticoagulants • Warfarin	• Unknown	• ↑ anticoagulant effect
Etoposide	Small cell lung cancer and testicular cancer	Anticoagulants • Warfarin	• CYP 2C8 and CYP 3A4 inhibition	• ↑ anticoagulant effect
5-Fluorouracil	Various GI malignancies	Anticoagulants • Warfarin	• CYP 2C9 inhibition	• ↑ anticoagulant effect
Gemcitabine	Pancreatic, NSCLC and ovarian cancer	Anticoagulant • Warfarin	• Unknown	• ↑ anticoagulant effect

Gilteritinib	AML	Rate Control • Non-dihydropyridine CCB	• CYP 3A4 inhibition	• [↑] gilteritinib
Idelalisib	CLL and follicular lymphoma	Rate Control • Non-dihydropyridine CCB Rhythm Control • Disopyramide Quinidine Dronedarone	• CYP 3A4 inhibition • CYP 3A4 inhibition	• [↑] CCB concentration/enhanced bradycardia • [↑] rhythm controlling medications
Ifosfamide	Testicular and ovarian cancer	Rate Control • Verapamil Anticoagulants • Warfarin	• CYP 3A4 inhibition • Unknown	• ↓ metabolism of ifosfamide • ↑ anticoagulant effect
Imatinib	CML	Rate Control • Carvedilol Metoprolol Propranolol • Non-dihydropyridine CCB Rhythm Control	• CYP 2D6 inhibition • CYP 3A4 inhibition	• [↑] beta blocker/enhanced bradycardia • [↑] imatinib • [↑] antiarrhythmics

		• Class 1C Agents Anticoagulant • Warfarin	• CYP 2D6 inhibition • CYP 3A4 and CYP 2C9 inhibition	• ↑ anticoagulant effect
Lenalidomide	Multiple myeloma and various B cell malignancies	Rate Control • Digoxin	• Pgp interactions	• [↑] digoxin
Mitotane	Adrenocortical carcinoma	Rate Control • Bisoprolol Non-dihydropyridine CCB Rhythm Control • Disopyramide Quinidine Amiodarone Anticoagulants • Factor Xa inhibitors	• CYP 3A4 induction • CYP 3A4 induction • CYP 3A4 induction	• [↓] rate controlling medications • [↓] rhythm controlling medications • [↓] anticoagulants
Neratinib	HER2+ breast cancer	Rate Control		• [↑] neratinib

		• Non-dihydropyridine CCB • Carvedilol Verapamil • Digoxin Rhythm Control • Dronedarone	• CYP 3A4 inhibition • Pgp inhibition • Pgp interaction • CYP 3A4 and Pgp inhibition	• [↑] neratinib • [↑] digoxin • [↑] neratinib
Obinutuzumab	CLL and follicular lymphoma	Rate Control • Beta blockers Non-dihydropyridine CCB Anticoagulants • Factor Xa inhibitors • Direct Thrombin Inhibitor • Warfarin	• Unknown • Inhibition of multiple clotting pathways • Inhibition of multiple clotting pathways	• ↑ bradycardia • ↑ anticoagulant effect • ↑ anticoagulant effect • ↑ anticoagulant effect

			• Inhibition of multiple clotting pathways	
Olaparib	Metastatic BRCA+ breast cancer	Rate Control • Non-dihydropyridine CCB Rhythm Control • Dronedarone	• CYP 3A4 inhibition • CYP 3A4 inhibition	• [↑] olaparib • [↑] olaparib
Panobinostat	Multiple myeloma	Rate Control • Carvedilol Metoprolol Propranolol Rhythm Control • Class 1C Agents	• CYP 2D6 inhibition • CYP 2D6 inhibition	• [↑] beta blocker/enhanced bradycardia • [↑] antiarrhythmic drugs
Pazopanib	Advanced renal cell carcinoma and soft tissue sarcomas	Rate Control • Carvedilol Verapamil Rhythm Control • Quinidine Propafenone Dronedarone	• Pgp inhibition • Pgp inhibition	• [↑] pazopanib • [↑] pazopanib
Regorafenib	Metastatic colorectal cancer, hepatocellular	Rate Control • Beta blockers Non-	• Unknown	• ↑ bradycardia

	carcinoma and GIST tumors	dihydropyridine CCB Digoxin Rhythm Control • Sotalol	• Unknown	• ↑ bradycardia
Romidepsin	T-cell lymphoma	Anticoagulant • Warfarin	• Unknown	• ↑ anticoagulant effect
Ruxolitinib	Myelofibrosis	Rate Control • Beta blockers; non-dihydropyridine CCB Digoxin Rhythm Control • Propafenone Amiodarone Dronedarone	• Unknown • Unknown	• ↑ bradycardia • ↑ bradycardia
Sorafenib	Renal cell and hepatocellular carcinoma	Anticoagulant • Warfarin	• CYP 2C9 inhibition	• ↑ anticoagulant effect
Talazoparib	BRCA+ breast cancer	Rate Control • Beta blockers Non-dihydropyridine CCB Rhythm Control	• Unknown, possibly Pgp related • Pgp inhibition	• [↑] talazoparib • [↑] talazoparib

		• Quinidine Propafenone Amiodarone		
Tamoxifen	Breast cancer	Anticoagulant • Warfarin	• CYP 2C9 inhibition	• ↑ anticoagulant effect
Topotecan	Various cancers including cervical and ovarian	Rate Control • Carvedilol Verapamil Rhythm Control • Quinidine Propafenone Amiodarone	• Pgp inhibition • Pgp inhibition	• [↑] topotecan • [↑] topotecan
Vandetanib	Medullary thyroid cancer	Rate Control • Digoxin	• Pgp interaction	• [↑] digoxin
Vemurafenib	Advanced melanoma and NSCLC	Rate Control • Digoxin Anticoagulant • Warfarin	• Pgp interaction • CYP 2C9 inhibition	• [↑] digoxin • ↑ anticoagulant effect
Venetoclax	CLL and mantle cell lymphoma	Rate Control • Carvedilol Verapmail • Digoxin	• Pgp inhibition • Pgp inhibition	• [↑] venetoclax • [↑] digoxin

		Rhythm Control • Quinidine; Propafenone Amiodarone • Dronedarone Anticoagulant • Warfarin	• Pgp inhibition • CYP 3A4 inhibition • Unknown	• [↑] venetoclax • [↑] venetoclax • ↑ anticoagulant effect
Vincristine	Various cancers including leukemias and lymphomas	Rate Control • Carvedilol Verapamil Rhythm Control • Quinidine Propafenone	• Pgp inhibition • Pgp inhibition	• [↑] vincristine • [↑] vincristine

AML = acute myeloid leukemia; BTK = Bruton's Tyrosine Kinase; CCB = calcium channel blocker; CDK = cyclin dependent kinase; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; GI = gastrointestinal; GIST = gastrointestinal stromal tumor; NSCLC = non-small cell lung cancer; Pgp = P-glycoprotein/ ABCB1 Inhibition; [↑] = increased concentration; [↓] = decreased concentration; ↑ = increased; ↓ = decreased

Table II. Frequency of ECG Monitoring

Drug Type	Risk Level*	Indications for ECG Evaluation**
Antimetabolites		
Fluorouracil	Rare	Pre-treatment Dose Adjustments As Clinically Indicated
Capecitabine	Frequent	Pre-treatment Dose Adjustments As Clinically Indicated
Purine analogs		
Fludarabine	Rare	Pre-treatment Dose Adjustments As Clinically Indicated
Antimicrotubule agents		
Paclitaxel	Rare	Conduction Abnormalities During Infusion As Clinically Indicated
Tyrosine kinase inhibitors		
Afatinib	Rare	Pre-treatment Dose Adjustments As Clinically Indicated
Aflibercept	Rare	Pre-treatment Dose Adjustments As Clinically Indicated

Bosutinib	Frequent	Pre-treatment Dose Adjustments As Clinically Indicated
Ceritinib	Rare	Known CHF Bradyarrhythmias Electrolyte abnormalities Concomitant QT prolonging medications As Clinically Indicated
Crizotinib	Rare	Known CHF Bradyarrhythmias Electrolyte abnormalities Concomitant QT prolonging medications As Clinically Indicated
Dasatinib	Common	Pre-treatment Dose Adjustments As Clinically Indicated
Dovitinib	Common	Pre-treatment Dose Adjustments As Clinically Indicated
Imatinib	Rare	Pre-treatment Dose Adjustments As Clinically Indicated
Lapatinib	Rare	Monitor for QTc prolongation during treatment
Lenvatinib	Common	Known CHF Bradyarrhythmias Congenital Long QT syndrome As Clinically Indicated
Nilotinib	Rare	Pre-treatment 7-days post initiation

		Dose Adjustments As Clinically Indicated
Nintedanib	Rare	Pre-treatment Dose Adjustments As Clinically Indicated
Pazopanib	Rare	Pre-treatment As Clinically Indicated
Ponatinib	Rare	Pre-treatment Dose Adjustments As Clinically Indicated
Sorafenib/ sunitinib	Common	Known CHF Bradyarrhythmias As Clinically Indicated
Vandetanib	Common	Pre-treatment Dose Adjustments As Clinically Indicated
Histone deacetylase inhibitors		
Belinostat	Common	Pre-treatment Dose Adjustments As Clinically Indicated
Panobinostat	Rare	Pre-treatment Dose Adjustments As Clinically Indicated
Romidepsin	Rare	Pre-treatment Dose Adjustments As Clinically Indicated

Vorinostat	Frequent	Pre-treatment Dose Adjustments As Clinically Indicated
Proteasome inhibitor		
Bortezomib	Rare	CV Risk Factors CV Disease As Clinically Indicated
Vascular endothelial growth factor inhibitors		
Cediranib	Frequent	Pre-treatment Dose Adjustments As Clinically Indicated
Antiangiogenic		
Combretastatin (CA4P)	Frequent	Pre-treatment Dose Adjustments As Clinically Indicated
Vadimezan (ASA404)	Frequent	Pre-treatment Dose Adjustments As Clinically Indicated
Protein kinase C inhibitor		
Enzastaurin	Frequent	Pre-treatment Dose Adjustments As Clinically Indicated
Monoclonal antibodies		
Trastuzumab and Pertuzumab	Rare	Pre-treatment Dose Adjustments As Clinically Indicated

B-Raf inhibitor		
Vemurafenib	Rare	Pre-treatment Monthly for first 3 months Every 3 months thereafter As Clinically Indicated
Cyclin Dependent Kinase (CDK) 4/6 Inhibitor		
Ribociclib	Frequent	Pre-treatment Day 14 of cycle 1 Start of cycle 2 As Clinically Indicated
Other		
Arsenic trioxide	Frequent	Pre-treatment Dose Adjustments As Clinically Indicated

*Frequent (>10% incidence); Common (5%-10% incidence); and Rare (<1%-5% incidence).
**From drug labels catalogued by the National Library of Medicine, https://dailymed.nlm.nih.gov/dailymed/index.cfm, as well as https://www.rxlist.com. For drugs without specific label recommendations, general recommendations have been provided.
CHF = congestive heart failure; CV = cardiovascular; ECG = electrocardiogram