Managing Drug Interactions with Oral Oncolytics in the Management of Hematologic Malignancies

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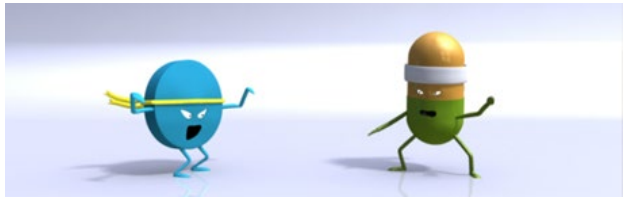
Objectives & Disclosure

- Understand the importance of recognizing and managing drug interactions in patients receiving oral oncolytics for the treatment of hematologic malignancies
- Evaluate a patient's drug regimen for the presence of common drug interactions with oral oncolytics for the treatment of hematologic malignancies
- Develop a plan to mitigate drug interactions in patients receiving oral oncolytics for the treatment of hematologic malignancies



- Disclosure
  - I have no conflicts of interest to disclose
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Clinical Impact of Drug Interactions

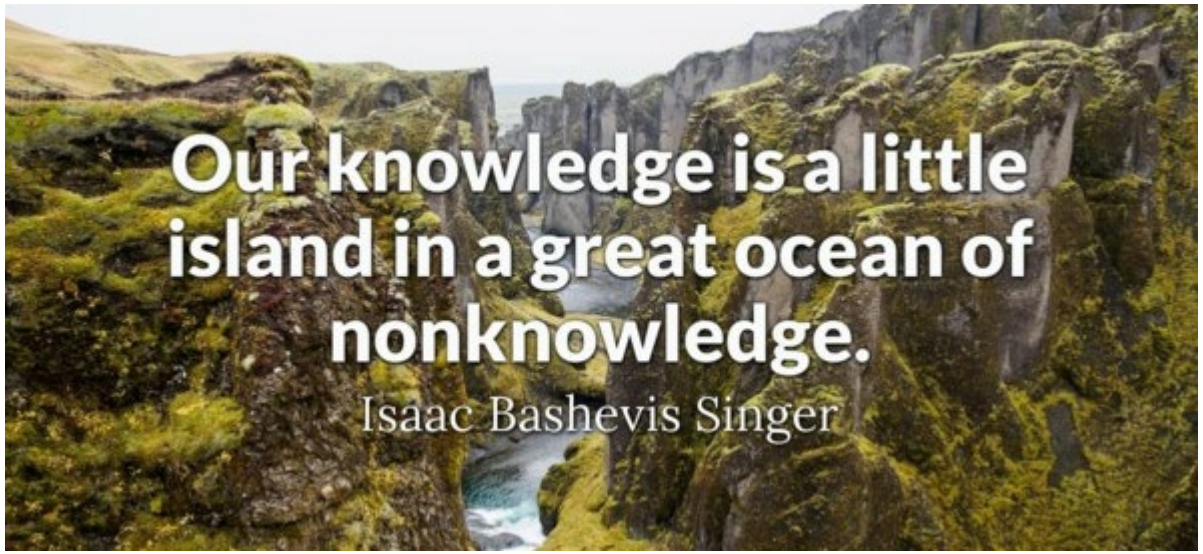
Reference	Interacting Drugs	Mechanism of Interaction	Impact of Interaction	Outcome
J Clin Pharm Pract. 2017;23:470	Idelalisib Diazepam	Idelalisib potent CYP3A4 inhibitor	Altered mental status Progressive weakness Respiratory acidosis Hospital admission Placed on BiPAP	Discharged 3 days later Lorazepam substituted for diazepam
J Clin Pharm Ther. 2016;41:104	Ibrutinib Verapamil	Verapamil moderate CYP3A4 inhibitor	Severe diarrhea Fall/LOC Hospital admission	Discharged 3 days later Olmesartan substituted for verapamil
Isr Med Assoc J. 2016;18:433	Ibrutinib Amiodarone load	Amiodarone moderate CYP3A4 inhibitor	SOB/Volume overload Echo: restrictive LV filling pattern, EF 50-55% BNP 376	Held amiodarone x 2 days and restarted at 200 mg/d Symptoms resolved
Leuk Lymphoma. 2014;55:2213	Bosutinib Warfarin Dilitiazem Lovastatin	Bosutinib inhibition of PgP led to increased levels of diltiazem/lovastatin leading to inhibition of warfarin metabolism (CYP3A4/2C9)	2 weeks after starting bosutinib – hypoxia/hemoptysis INR > 15 Pulmonary hemorrhage	Reversal of anticoagulation and methylprednisolone led to improvement
Am J Hematol. 2012;87:338	Lenalidomide Itraconazole	Itraconazole potent PgP inhibitor	Neutropenia despite dose reductions Elevated lenalidomide concentrations	Not reported
Intern Med J. 2009;39:708	Imatinib Amlodipine	Amlodipine inhibition of ABCG2 and CYP3A4	Nausea, edema Numbness in chin, b/l pain and numbness in feet	Amlodipine stopped Symptoms resolved Mild residual neuropathy resolved over 9 months

Impact of Drug Interactions

- Increased adverse effects
  - Observed in practice
  - Reported in literature
- Decreased efficacy
  - Difficult to pinpoint
  - Not reported in case reports

Reference	Study Design	Results	Hem Meds
Br J Cancer. 2013;108:1071	Retrospective review of oral anti-neoplastic drugs	N=898 patients 1359 Potential drug interactions (426 patients) 16% major or moderate severity	Imatinib – 30 Dasatinib – 9 Nilotinib – 8 Tretinoin - 3
Eur J Cancer Care. 2018;e12994	Prospective study of oral anti-neoplastic drugs	N=219 patients 736 concomitant medications 34 drug-drug interactions (15.5% of patients) 15 considered to be of little relevance (6.8% of patients)	Nilotinib – 4 Thalidomide - 7
J Oncol Pharm Pract. 2018;24:110	Retrospective review of oral TKI	N=356 patients 224 potential interactions 109 (44.7%) considered severe (30.6% of patients) Most common: PPI (decreased absorption), CYP3A4 Potential consequences: QTc prolongation (48.6%), decreased TKI concentration (48.6%), increased TKI concentration (2.8%)	Dasatinib – 16 Nilotinib – 10 Imatinib – 5 Ibrutinib - 3
BMC Cancer. 2018;18:1155	Retrospective review of patients enrolled on NCTN oncology trials	N=128 Moderate/major DDI based on LexiComp: 24.2% 9.4% clinically relevant based on pharmacist evaluation	Dasatinib – 1 Pomalidomide - 10

How/why do interactions reach patients?



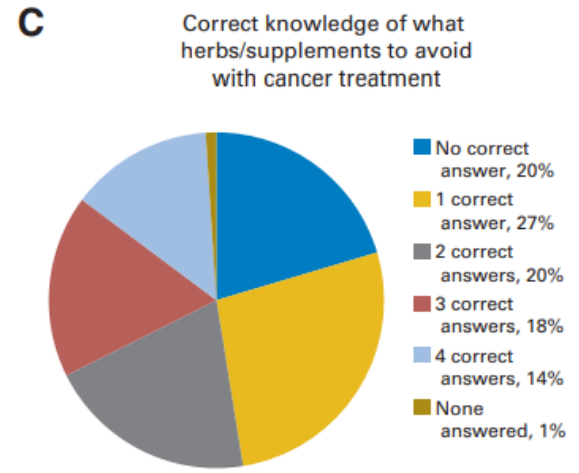
- Lack of assessment
  - Missing alerts in CPOE
  - Fragmented care/multiple providers
  - Specialty pharmacies
  - Prevalence of use of herbal/OTC medications

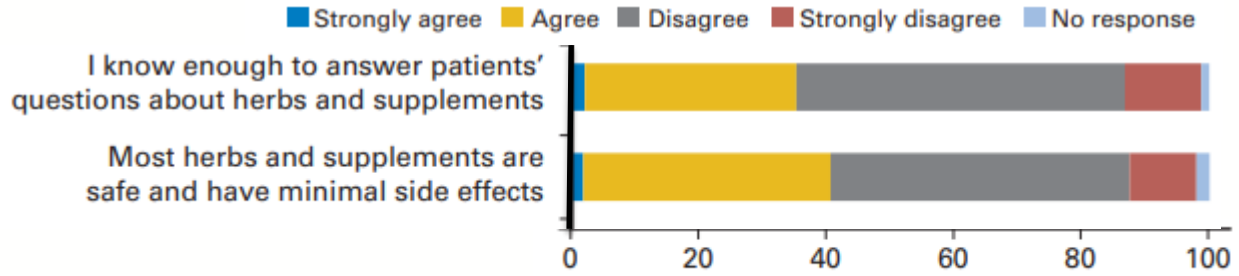
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

National Survey of US Oncologists' Knowledge, Attitudes, and Practice Patterns Regarding Herb and Supplement Use by Patients With Cancer

Table 2. Oncologists' Communication and Practice Patterns With Patients Regarding Herbs and Supplements (N = 392)

Pattern	No.	%
In the past 12 mo, with approximately what percentage of your patients have you discussed the topic of herbs or supplements?		
Mean		41
SD		26.7
Please estimate what percentage of these discussions about herbs or supplements were initiated by you.*		
Mean		26
SD		27.9





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J Clin Oncol. 2014;32:4095

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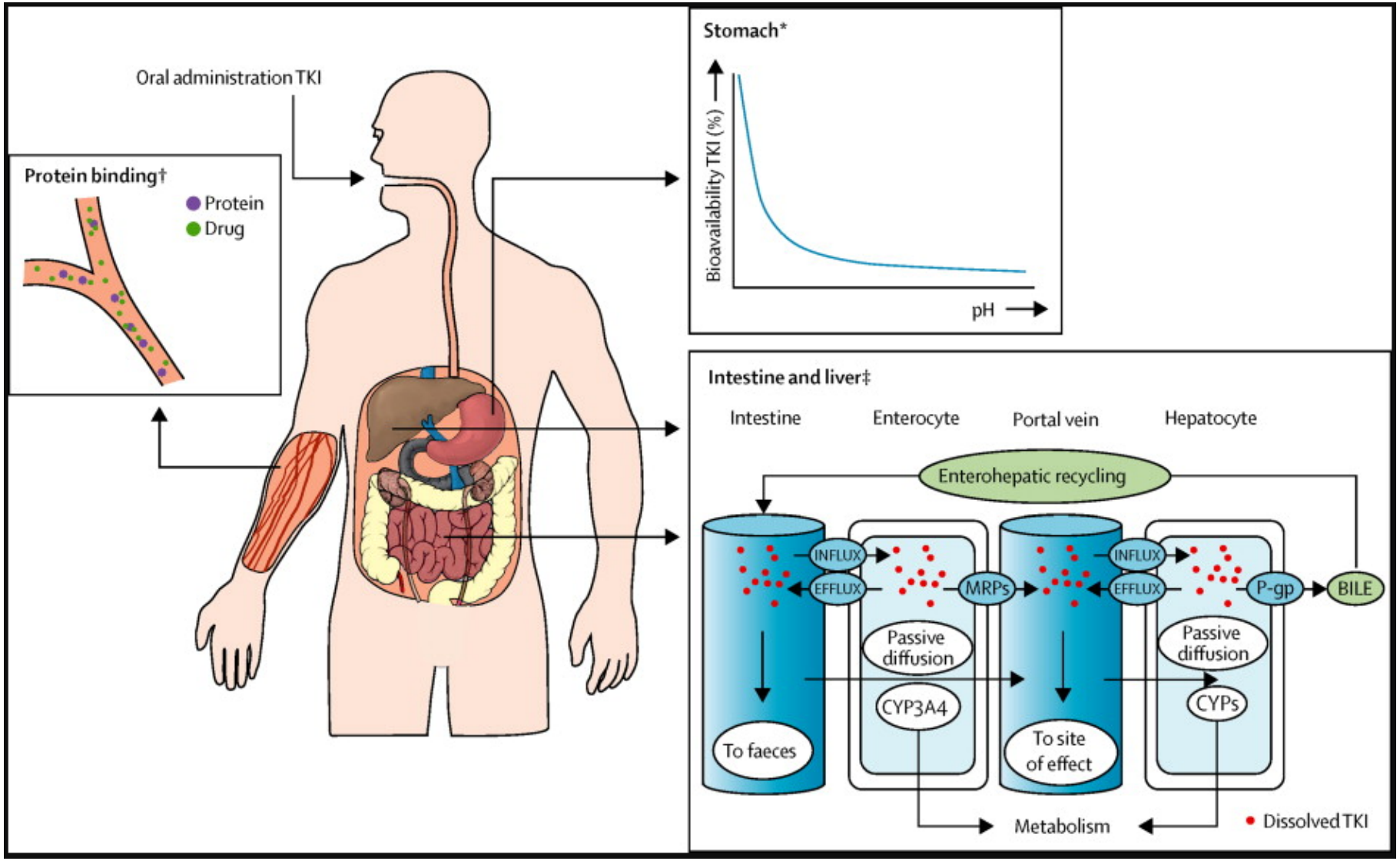
Types of Drug Interactions

- Drugs
- Herbs
- Food

- Pharmacokinetic
  - Absorption/Distribution/Metabolism/Elimination
    - CYP, UGT, PgP, etc.
    - Decreased/increased absorption with food
    - Decreased absorption with drugs

- Pharmacodynamic
  - Active compounds change each others pharmacologic effect – Synergistic, additive, antagonistic
    - Increased QTc
    - Increased bleeding risk - Ibrutinib

Mechanism of Pharmacokinetic Drug Interactions

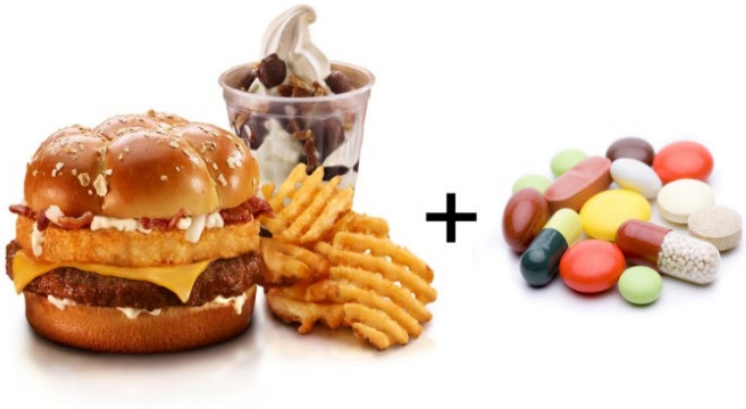


Lancet Oncol. 2014;15:e315-26

Drug – Food Interactions

- Food increases GI secretions – Decreases gastric pH
  - Increased dissolution and absorption of basic drugs
  - Increased degradation of acid-labile drugs
- Large fluid volume intake – increase stomach emptying rates
- Large solid food intake – decrease gastric emptying rates

- High fat meal
  - Decreased gastric empting rates
  - Increased dissolution of fat soluble drugs



- Chelation by polyvalent metal ions

- Grapefruit (pomegranate and star fruit too) – inhibit gut CYP 3A4 and Pgp

Examples of Food Effects on Drug Absorption

	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib	Gilteritinib	Midostaurin	Enasidenib	Ivosidenib	Glasdegib	Venetoclax	Acalabrutinib	Ibrutinib	Duvelisib	Idelalisib	Lenalidomide	Pomalidomide	Thalidomide	Ixazomib	Panobinostat
Take with food	X	X	X*	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X
Take on empty stomach		X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X
High fat meal effects on Cmax	↑ 80%								↑ 98%	↓ 31%		↓ 73%	↑ 200-400%	↓ 37%		↓ 50%	↓ 27%	<10%	↓ 69%	↓ 44%
High fat meal effects on AUC	↑ 70%	↑ 14%					↑ 27%		↑ 25%	↓ 16%	↑ 510%	No effect	↑ 200%	↓ 6%	↓ 40%	↓ 20%	↓ 8%	<10%	↓ 28%	↓ 16%
High fat meal effects on Tmax												↓ 1-2h					↓ 1-2h	↓ 6h		↓ 2.5h

* To decrease gastritis

Interaction potential and recommendations based on information included in Prescribing Information for each medication as of 1/2019

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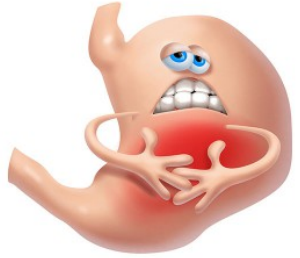
Interactions with Gastric Acid Reducing Medications



	Proton Pump Inhibitors	Histamine 2 Receptor Antagonists	Antacids
Bosutinib	Avoid (AUC ↓ 26%)		
Dasatinib	Avoid (AUC ↓ 43%)	Avoid (AUC ↓ 61%)	Separate by 2 h (AUC ↓ 55% with concomitant use)
Nilotinib	Avoid (AUC ↓ 34%)		Separate by 2 h
Acalabrutinib	Avoid (AUC ↓ 43%)	Take 2 h prior to H2RA	Separate by 2 h (AUC ↓ 53% with concomitant use)
Ponatinib	Not significant (AUC ↓ 6%, Cmax ↓ 25%)		
Glasdegib	Not significant (AUC ↓ 0%, Cmax ↓ 20%)		

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Interaction potential and recommendations based on information included in Prescribing Information for each medication as of 1/2019

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Gastric pH Lowering Drugs – Are we overusing?

- Observational descriptive study in patients with cancer diagnoses
- N=111 patients (40 with hematologic malignancies)
- 56% of patients with solid tumors receiving PPI
- 63% of patients with hematologic malignancies receiving PPI
- No indication: 72% (solid tumors), 12% (hematologic malignancies)

Table 1. *Protocol for the rational use of PPIs: Treatment recommendations for oncohematologic patients*

Coadjuvant treatment for nausea and/or vomiting caused by chemotherapy in patients with dyspepsia

Digestive conditions

- GERD
- Barrett's Oesophagus
- Peptic ulcers
- Eradication of *Helicobacter pylori*
- Non-ulcerous dyspepsia: 4-8 weeks according to response, with subsequent re-assessment.

Gastric protection in chronic treatments with highly gastrolesive drugs

- NSAIDs with prolonged treatment
- Antiaggregants
- Anticoagulants
- Corticosteroids

Only if concomitant treatments, or when there is an associated risk factor*

*Risk factors: Previous history of UGIB, ulcers or perforation
Age ≥ 70 years
Simultaneous drugs with weak gastrolesivity (metamizol, SSRIs)

GERD: gastroesophageal reflux disease; UGIB: upper gastrointestinal bleeding.
Pharmacy Unit, Primary Care, Gastroenterology Unit and Oncology & Hematology Unit. Consensus from December, 2014.

Farm Hosp. 2016;40:436

Interactions in Drug Metabolism

- Most commonly via hepatic cytochrome P450 enzymes
  - Account for ~75% of drug metabolism[1]

- Impact of many transporters may be under appreciated

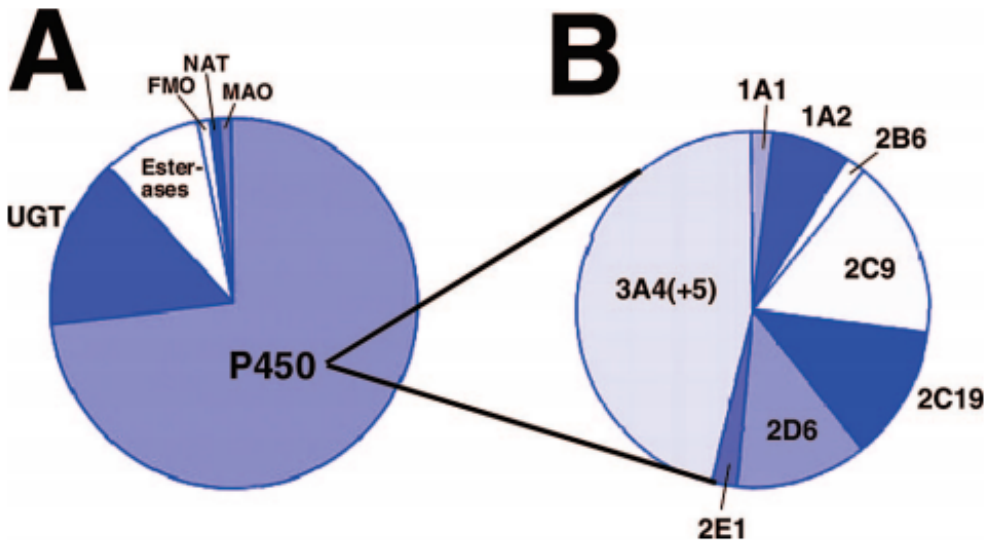

Figure 4. Contributions of enzymes to the metabolism of marketed drugs. The results are from a study of Pfizer drugs (*57*), and similar percentages have been reported by others in other pharmaceutical companies (*58*). (A) Fraction of reactions on drugs catalyzed by various human enzymes. FMO, flavin-containing monoxygenase; NAT, *N*-acetyltransferase; and MAO, monoamine oxidase. (B) Fractions of P450 oxidations on drugs catalyzed by individual P450 enzymes. The segment labeled 3A4 (+3A5) is mainly due to P450 3A4, with some controversy about exactly how much is contributed by other subfamily 3A P450s.

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[1]Chem Res Toxicol. 2008;21:70-83

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Transport-Mediated Drug Interactions

- Intestinal transporters
  - P-gp, breast cancer resistance protein (BCRP), multidrug resistance protein 2 (MRP2)
- Hepatic transporters
  - Organic anion transporting polypeptide (OATP), organic cation transporter (OCT)
- Renal transporters
  - Multidrug and toxin extrusion (MATE), OCT, OAT

- Limited number of drugs whose disposition depends on a single transporter
- Perpetrator drugs are frequently not specific to a single transporter
- No all combinations of drugs tested for transporter-mediated drug interactions

Gessner A, et al. Clin Pharmacol Ther. 2019, Epub ahead of print

Drugs R D (2016) 16:93–107
DOI 10.1007/s40268-015-0120-x

ORIGINAL RESEARCH ARTICLE

Effects of Fostamatinib on the Pharmacokinetics of Oral Contraceptive, Warfarin, and the Statins Rosuvastatin and Simvastatin: Results From Phase I Clinical Studies

P. Martin[1] · M. Gillen[2] · J. Ritter[3] · D. Mathews[4] · C. Brealey[5] · D. Surry[5] · S. Oliver[1] · V. Holmes[6] · P. Severin[7] · R. Elsby[1]

Analyte	Parameter (units)	Treatment	*n*	Geometric LS mean	Statin + fostamatinib/statin alone	
					Ratio (%)	90 % CI
Rosuvastatin	AUC (ng·h/mL)	Rosuvastatin alone	21	93.7		
		Rosuvastatin + fostamatinib	21	183.4	195.6	177.6–215.3
	AUC_t (ng·h/mL)	Rosuvastatin alone	21	92.2		
		Rosuvastatin + fostamatinib	21	181.6	197.1	178.84–217.3
	C_{max} (ng/mL)	Rosuvastatin alone	21	10.6		
		Rosuvastatin + fostamatinib	21	19.9	188.4	169.4–209.6

Mechanism of interaction: Fostamatinib inhibition of intestinal BCRP

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Table of Pharmacokinetic Interactions

Enzyme	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib	Gilteritinib	Midostaurin	Enasidenib	Ivosidenib	Glasdegib	Venetoclax	Acalabrutinib	Ibrutinib	Duvelisib	Idelalisib	Lenalidomide	Pomalidomide	Thalidomide	Ixazomib	Panobinostat
CYP 1A2							I/Ind	I				Ind					S		S	
CYP 2B6				Ind			Ind	I	Ind			Ind							S	
CYP 2C8				Ind/I	S		I/Ind	I	Ind		I	I			I				S	
CYP 2C9							I/Ind	I	Ind		I	I							S	
CYP 2C19							Ind	I				I			I		S		S	I
CYP 2D6			I	I	S		I	I									S		S	I/S
CYP 2E1							I													
CYP 3A	S	S	S/I	S/I	S	S/I	S/I/Ind	I	S/Ind	S	S	S/I/Ind	S	S	S		S		S	S/I
P-gp				I	I	S	I	I	S/I	S/I	S/I	S	I	S	S	S	S		S	S
UGT 1A1				I				I			I				I					S
UGT 1A4															S					
BCRP					I	I	I	I		S/I	S/I	S	I	S	S					
OCT1						I														I
OCT2								I												I
OATP 1B1							I	I			S/I									I
OAT1								I												
OAT3								I	I											I
BSEP					I															
MATE 1						Ind				I										
MATE-2K										I										

S = Substrate
I = Inhibitor
Ind = Inducer

= avoid inducers
= avoid inhibitors
= avoid substrates
= use substrates with caution

P-gp = P-glycoprotein, BCRP = Breast cancer resistance proteins, OCT = organic cation transporter, OATP = Organic anion transporting polypeptide, OAT = Organic anion transporter, BSEP = Bile salt export pump, MATE = Multidrug and toxin extrusion

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Interaction potential and recommendations based on information included in Prescribing Information for each medication as of 1/2019

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Examples of CYP Inhibitors and Inducers

CYP Enzyme	Strong Inhibitor	Moderate Inhibitor	Strong/ Moderate Inducers
1A2	Ciprofloxacin, fluvoxamine	Mexiletine, oral contraceptives	Phenytoin, rifampin, ritonavir, smoking, teriflunomide
2B6			Carbamazepine, efavirenz, rifampin, ritonavir
2C8	Clopidogrel, gemfibrozil	Defarasirox, teriflunomide	Rifampin
2C9		Amiodarone, felbamate, fluconazole, miconazole	Aprepitant, carbamazepine, rifampin, ritonavir
2C19	Fluconazole, fluoxetine, fluvoxamine, ticlopidine		Rifampin, ritonavir, efavirenz, phenytoin
2D6	Bupropion, fluoxetine, paroxetine, quinidine, terbinafine	Cimetidine, cinacalcet, duloxetine, fluvoxamine, mirabegron	
3A4	Boceprevir, cobicistat, conivaptan, ritonavir, itraconazole, ketoconazole, posaconazole, telaprevir, voriconazole	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, tofisopam, verapamil	Carbamazepine, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, modafinil

Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

Examples of CYP Substrates

CYP Enzyme	Sensitive Substrate	Moderate Sensitive Substrate
1A2	Caffeine, duloxetine, melatonin, ramelteon, theophylline, tizanidine	Clozapine
2B6	Bupropion	Efavirenz
2C8	Repaglinide	Montelukast, pioglitazone, rosiglitazone
2C9	Celecoxib	Glimepiride, phenytoin, warfarin
2C19	Omeprazole	Diazepam, lansoprazole, rabeprazole, voriconazole
2D6	Atomoxetine, desipramine, dextromethorphan, nebivolol, nortriptyline, venlafaxine	Amitriptyline, imipramine, metoprolol, propafenone, propranolol, tramadol
3A4	Buspirone, conivaptan, darifenacin, dronedarone, darunavir, felodipine, indinavir, lovastatin, midazolam, maraviroc, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil	Alprazolam, aprepitant, atorvastatin, colchicine, rivaroxaban, tadalafil

Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

Journal of Oncology Practice®
An American Society of Clinical Oncology Journal

Potential Drug-Drug and Herb-Drug Interactions in Patients With Cancer: A Prospective Study of Medication Surveillance

- N=149
- 56.4% reported using concurrent herbal supplements
- 122 possible interactions detected

Table 3. Potential HDIs Found in Data Set

Herbal Supplement	Mechanism of Interaction	Anticancer Agent Involved (No. of patients)
Allium sativum	Inhibits CYP3A4 and 2C9 Induces P-glycoprotein synthesis	Paclitaxel (8), irinotecan (4), abiraterone acetate (2), cyclophosphamide (2)
Aloe barbadensis/capensis	Decreases intestinal absorption Inhibits CYP3A4	Tamoxifen (8), capecitabine (6), cyclophosphamide (6), paclitaxel (6), abiraterone acetate (2), irinotecan (2) anastrozole (2), imatinib (2), vincristine (1), vinorelbine (1), erlotinib (1)
Annona muricata	Inhibits P-glycoprotein	Paclitaxel (3)
Camelia sinesis	Inhibits P-glycoprotein and CYP3A4 Increases bioavailability of tamoxifen	Paclitaxel (4), abiraterone acetate (2), cyclophosphamide (2), tamoxifen (1), irinotecan (1)
Ecchinacea angustfolia	Inhibits CYP3A4	Sorafenib (1), erlotinib (1)
Gingo biloba	Inhibits CYP2C9 and 1A2 Induces CYP1A2	Anastrozole (4)
Matricata recutita	Inhibits CYP2D6, 3A4, and 2C9	Tamoxifen (1)
Moringa oleifera	Inhibits CYP3A4	Cyclophosphamide (3), docetaxel (1)
Panax ginseng	Induces CYP3A4	Abiraterone acetate (1), sorafenib (1), cyclophosphamide (1), docetaxel (1)
Spirulina sp.	Inhibits CYP1A2	Anastrozole (1)
Uncaria tomentosa	Inhibits CYP3A4	Abiraterone acetate (2), paclitaxel (1)
Valeriana officinalis	Inhibits CYP2D6 Induces CYP3A4	Tamoxifen (4), paclitaxel (4)
Vitis vinifera	Inhibits CYP3A4 and 2C9	Paclitaxel (9), cyclophosphamide (8), vincristine (1), tamoxifen (3), anastrozole (3), abiraterone acetate (2), exemestane (1), irinotecan (1), imatinib (1)

Abbreviations: HDI, herb-drug interaction; P-glycoprotein, phosphoglycoprotein.

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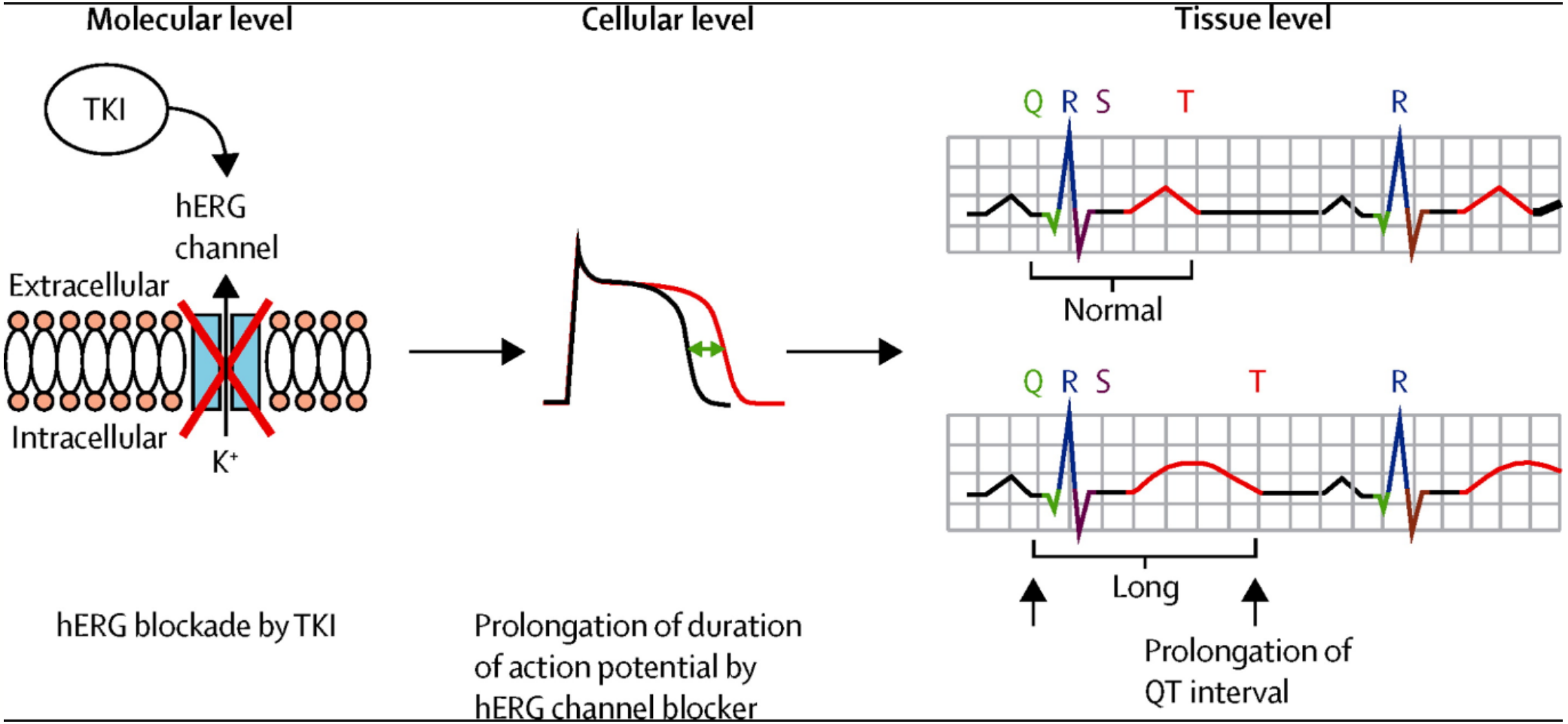
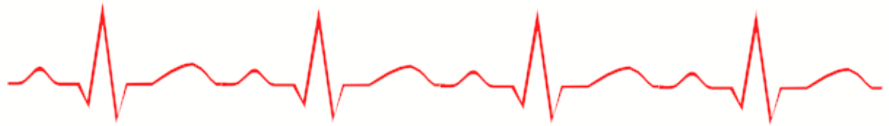
J Oncol Pract. 2017;13:443

QTc Prolongation



QTc Monitoring Recommendations



Drug	Baseline QTc Monitoring	QTc Monitoring During Treatment
HDAC Inhibitor		
Panobinostat	ECG	ECG q 3 weeks x 8
Romidepsin	In patient at risk or receiving QT prolonging medications: ECG	In patient at risk or receiving QT prolonging medications: ECG 1 week after initiation*
Vorinostat	ECG	If patient at risk or receiving QT prolonging medications: ECG 2 weeks after drug initiation and at 1 and 3 months*
BTK Inhibitor		
Acalabrutinib		ECG in patients who develop palpitations, lightheadedness, syncope, or chest pain
Ibrutinib		ECG in patients who develop palpitations, lightheadedness, syncope, or chest pain
BCR-ABL Inhibitor		
Bositinib	ECG	ECG q 4 weeks x 3
Dasatinib	ECG	ECG at week 4
Imatinib		
Nilotinib	ECG	ECG on day 8 then every 3 cycles x 3
Ponatinib	ECG	ECG week 4
FLT 3 Inhibitor		
Midostaurin	ECG	In patient at risk or receiving QT prolonging medications: ECG on day 3 and 14 of midostaurin during induction and consolidation cycles then every other cycle during continuation therapy
Gilteritinib	ECG	ECG on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles
IDH1 Inhibitor		
Enasidenib		
Ivosidenib	ECG	ECG weekly x 3 then monthly

Recommendations based on QT prolongation risk and recommended monitoring included in Prescribing Information for each medication as of 1/2019

QTc Prolonging Medications

Drug Class	Known Risk	Possible Risk
Alpha-blocker		Alfuzosin
Antiarrhythmic	Amiodarone, dofetilide, flecainide, procainamide, quinidine, sotolol	
Anticonvulsant		Felbamate
Antidepressant	Citalopram, escitalopram	Clomipramine, desipramine, imipramine, lithium, mirtazapine, nortriptyline, venlafaxine
Antiemetic	Ondansetron, droperidol	Dolasetron, granisetron, promethazine
Antifungal	Fluconazole, pentamidine	
Antihypertensive		Isradipine, nicardipine
Antipsychotics	Chlorpromazine, haloperidol, thioridizine	Aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone
Antibiotic	Azithromycin, clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin	Norfloxacin, ofloxacin, telavancin
Antispasmodic		Mirabegron
H2 receptor antagonist		Famotidine
Illicit drugs	Cocaine	
Opiates	Methadone	
Phosphodiesterase 5 inhibitors		Vardenafil

Adapted from: Can Pharm J. 2016;149:139

Management Strategies – Identifying Drug Interactions

- Many databases available to assist in detecting the presence of drug-drug interactions
  - Lexicomp/LexiInteract, MicroMedex, ClinPharm, Epocrates, Drugs.com

- Sensitivities of detecting known interactions with oncologic medications[1]
  - Micromedex: 70%
  - Facts & Comparisons: 70%
  - Epocrates: 90%
  - Lexi-Interact: 95%
  - Drugs.com: 95%
- Only 3 of 20 interactions were classified at the same level of severity in all databases

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[1]J Oncol Pract. 2017;13:e217-e222

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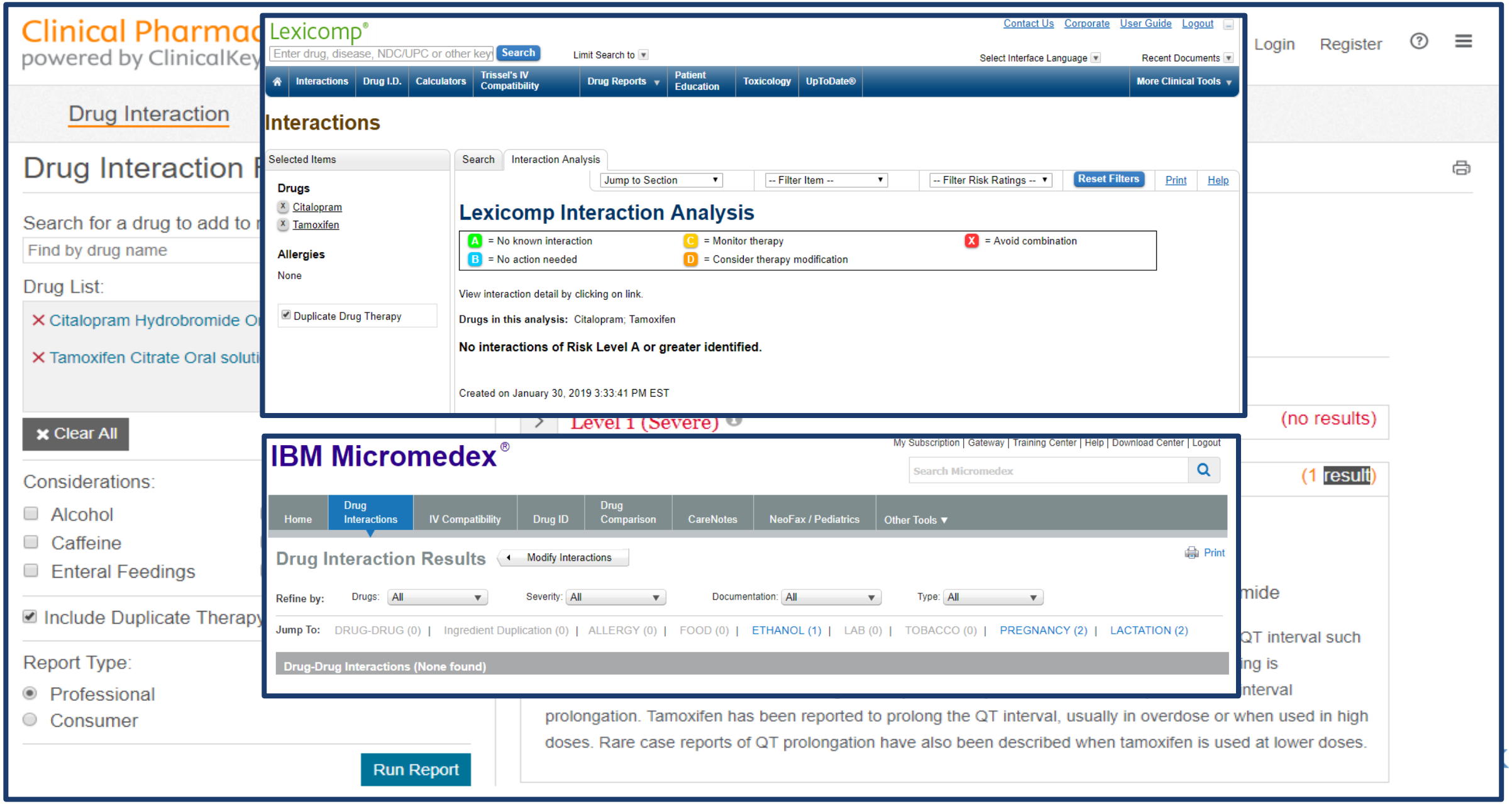
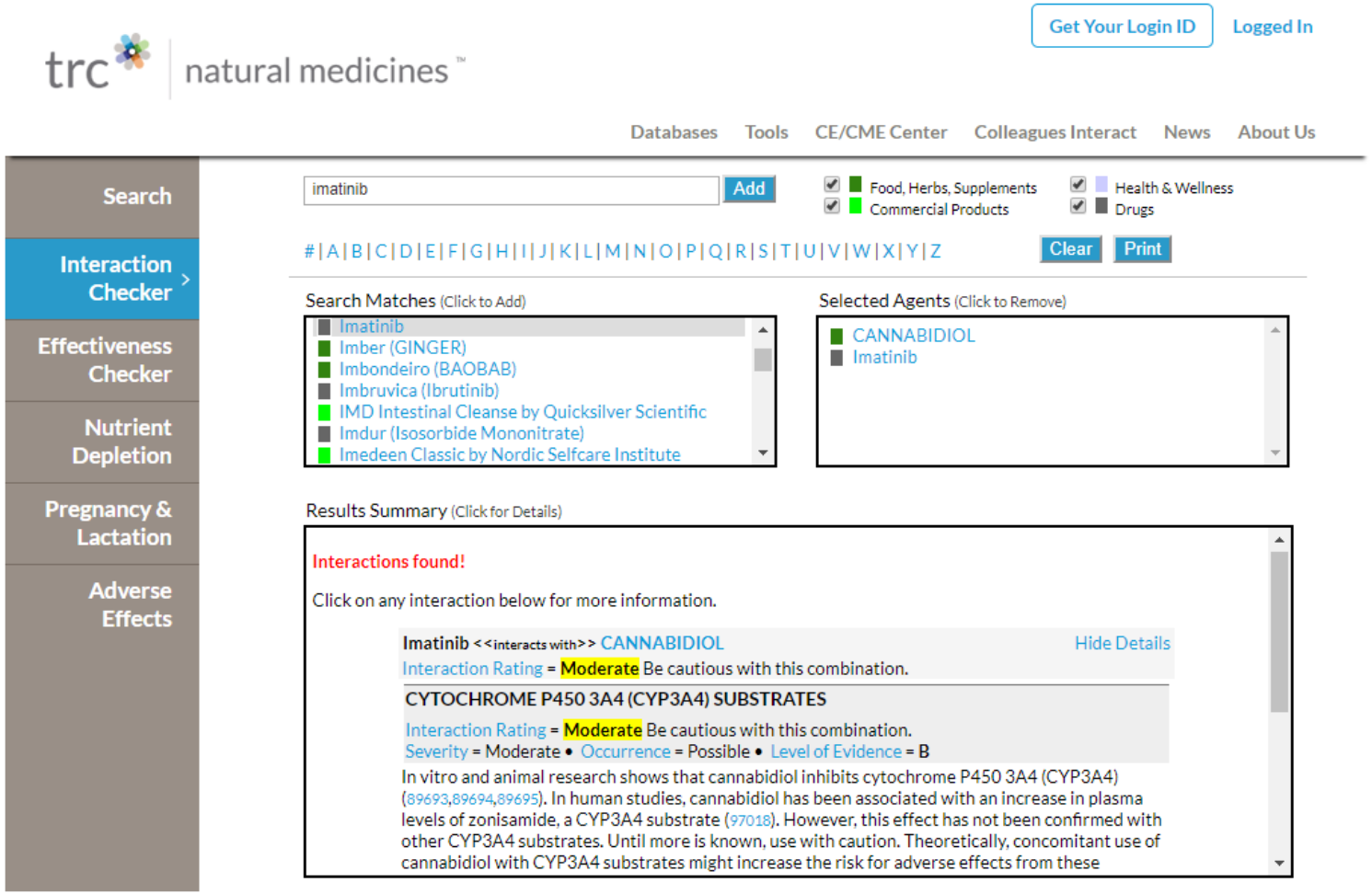
Interpreting Drug Interaction Report Significance



Drug – Herb Interaction Databases

Natural Medicines Comprehensive Database

https://naturalmedicines.therapeuticresearch.com/



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Drug – Herb Interaction Databases

Memorial Sloan Kettering Cancer Center – About Herbs, Botanicals & Other Products

https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs

Herb-Drug Interactions

Anticoagulants / Antiplatelets: Turmeric may increase risk of bleeding, as it also has antiplatelet properties [54] [55] [66].
Camptothecin: Turmeric inhibits camptothecin-induced apoptosis of breast cancer cell lines in vitro [28].
Mechlorethamine: Turmeric inhibits mechlorethamine-induced apoptosis of breast cancer cell lines in vitro [28].
Paclitaxel: In a recent case report, a lung cancer patient suffered liver toxicity while undergoing active treatment with paclitaxel. Although he was taking multiple supplements, one of which was tainted, turmeric was thought to be among the likely causes [73].
Doxorubicin: Turmeric inhibits doxorubicin-induced apoptosis of breast cancer cell lines in vitro [28].
Cyclophosphamide: Dietary turmeric inhibits cyclophosphamide-induced tumor regression in animal studies [28].
Norfloxacin: Pretreatment with curcumin resulted in increased plasma elimination half-life, thereby reducing the dosage of norfloxacin [56].
Amphotericin B: Curcumin may enhance the effect and decrease the toxicity of amphotericin B [57].
Drugs metabolized by the CYP3A4 enzyme: Curcumin inhibits cytochrome 3A4 enzyme, altering the metabolism of some prescription drugs [26]. But according to conflicting data, short-term use of curcumin may not result in a clinically relevant interaction [67].
Drugs metabolized by the CYP1A2 enzyme: Curcumin inhibits cytochrome 1A2 enzyme, affecting the metabolism of certain prescription medicines [27].
Drugs metabolized by the CYP2A6 enzyme: Curcumin enhances cytochrome 2A6 enzyme, and can affect the metabolism of certain prescription drugs [27].
Drugs metabolized by the CYP2D6 enzyme: Curcumin inhibits cytochrome 2D6 activity and has the potential to interact with CYP2D6 substrates [74].
Celiprolol and Midazolam: Curcumin was shown to downregulate intestinal P-gp levels, thereby increasing the concentrations of celiprolol and midazolam [48].
Verapamil: Curcumin inhibited intestinal P-gp expression and function, thereby increasing concentrations of verapamil [47].
Tacrolimus: Pretreatment with turmeric increases the plasma levels of tacrolimus [59].
Acetaminophen: The cytotoxic effects of curcumin increased significantly in the presence of acetaminophen [60].
Ibuprofen: The cytotoxic effects of curcumin increased significantly in the presence of ibuprofen [60].
Aspirin: The cytotoxic effects of curcumin increased significantly in the presence of aspirin [60].

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Management Strategies - Reacting

- Determination of need to continue interacting medications
- Alternative therapy
- Dose adjustments
- Increased monitoring
  - Adverse effects
  - ECG monitoring

Ibrutinib-induced Atrial Fibrillation

- Ibrutinib: 16% incidence of atrial fibrillation
- Commonly used treatments have significant interactions
  - CYP3A4, PgP

- Recommendations:
  - Rate control: Metoprolol
  - Stroke prevention: none recommended due to increased bleeding risk
  - Warfarin: Not recommended
  - Direct oral anticoagulants:
    - Least potential for interaction: dabigatran and edoxaban
    - Apixaban may be considered in elderly with renal dysfunction
    - Consider dose reductions – limited data

Agents	CYP 3A4	P-glycoprotein	Potential Impact on Ibrutinib Conc.	Potential Impact on Cardiac Medication Conc.	Pharmacodynamic* Interaction	Co-Administer	Comment
Ibrutinib	**S**	**INH**					
Rate Control Agents							
Metoprolol						Y	
Verapamil	S, INH	INH	↑			N	
Diltiazem	S, INH		↑[†]			N	
Digoxin	S	S		±/↑		N	
Rhythm Control Agents							
Flecainide						Y	
Propafenone	S	INH				?	
Sotalol						Y	
Dofetilide	S					?	
Dronedarone	S, INH	INH	↑			N	
Amiodarone	S, INH	S, INH	↑	↑		N	
Stroke Prevention Agents							
Dabigatran		S		↑	X	?	Consider dose reduction
Rivaroxaban	S	S		±/↑	X	?	
Apixaban	S	S		±/↑	X	?	
Edoxaban		S		↑	X	?	
Betrixaban		S		↑	X	?	
Warfarin	S			±	X	?	
Antiplatelet Agents							
Clopidogrel					X	N	Discontinue unless critical due to ibrutinib inherent bleeding risk
Prasugrel					X	N	
Ticagrelor	S	INH			X	N	
Aspirin						N	

*Footnotes: Conc: Concentrations; **INH:** Inhibitor; **S**: substrate; ↑: Increase; ↓: Decrease;*
±: Effect unknown of potential impact of competition for metabolism by CYP 3A4 among drugs with a narrow therapeutic index.
**Additive bleeding risk*
[†]Combination of diltiazem and ibrutinib contraindicated

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Rao VU, Buck M, Reeves D, Skurka K, Rubenstein S. Clinical Challenges Associated with Management of Ibrutinib-induced Atrial Fibrillation. Global Cardio Oncology Summit 2018. Sept 2018

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Recommended Dose Adjustments - Examples

Ibrutinib Dose Adjustment Recommendations

Co-administered Drug	Recommended Ibrutinib Dose – B-Cell Malignancies	Recommended Ibrutinib Dose – Chronic Graft versus Hose Disease
Moderate CYP3A inhibitor	280 mg daily	420 mg daily
Voriconazole 200 mg BID	140 mg daily	280 mg daily
Posaconazole suspension 100 mg daily, 100 mg BID, or 200 mg BID	140 mg daily	280 mg daily
Posaconazole suspension 200 mg TID or 400 mg BID	70 mg daily	140 mg daily
Posaconazole IV 300 mg daily	70 mg daily	140 mg daily
Posaconazole delayed-release 300 mg daily	70 mg daily	140 mg daily
Other strong CYP3A inhibitors	Avoid concomitant use	Avoid concomitant use

Imbruvica (ibrutinib) Prescribing Information. Jansen Biotech, Inc. Horsham PA. 8/2018

Venetoclax Dose Adjustment Recommendations

Co-administered Drug	Venetoclax Initiation and Ramp-Up Phase	Stead Daily Dose (After Ramp-Up Phase)
Posaconazole	CLL/SLL Contraindicated AML Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	AML 70 mg
Other strong CYP3A inhibitor	CLL/SLL Contraindicated AML Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	AML 100 mg
Moderate CYP3A inhibitor or P-gp inhibitor	Reduce dose by 50%	Reduce dose by 50%

Venclexta (venetoclax) Prescribing Information. AbbVie, Inc. North Chicago, Il. 11/2018

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Managing Drug Interactions with Oral Oncolytics in the Management of Hematologic Malignancies

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