### Table 1. **Important drug interactions between P450 isoenzyme pathways and targeted therapies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>P450 isoenzyme pathway</th>
<th>Inducer or Substrate</th>
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<tbody>
<tr>
<td>Reproduced with permission from ONCOLOGY Nurse Edition, 2/09, Anne Landry, Editor- full citation to come</td>
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<tr>
<td>Bexarotene (Targretin)</td>
<td>CYP3A4</td>
<td><strong>Inhibitors of CYP3A4</strong> These drugs may increase serum levels of bexarotene-ketoconazole, itraconazole, erythromycin, gemfibrozil, grapefruit, grapefruit juice; also (strong) atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquivaivir, telithromycin, voriconazole; (moderate) amprenavir, aprepitant, diltiazem, fluconazole, verapamil; and (weak) cimitidine. DO NOT give together with gemfibrozil; avoid co-administration with other drug(s) if possible or monitor closely for drug side effects.</td>
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<td><strong>Inducers of CYP3A4</strong> May decrease serum bexarotene concentrations: rifampin, phenytoin, Phenobarbital; also (carbamazepine, dexamethasone, efavirenz, griseofulvin, modafinil, nafcillin, nevirapine, primidone, rifabutin, St. John's Wort. Avoid co-administration if possible. If co-administered, assess need for increased bexarotene dose. Do NOT give together with St. John's Wort.</td>
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<td><strong>Other</strong> Bexarotene decreases tamoxifen plasma concentration by 35%; may also decrease serum levels of systemic hormonal contraceptives; Avoid co-administration if possible, and use 2 types of contraception, including one type of barrier contraceptive</td>
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</table>
**CYP3A4 Inhibitors** May increase serum levels of bortezomib: ketoconazole, also (strong) atazanavir, clarithramycin, indinavir, itraconazole, grapefruit, grapefruit juice, nefazodone, nelfinavir, ritonavir, saquiarv, telithromycin, voriconazole; (moderate) amprenavir, aprepitant, diltiazem, fluconazole, verapamil; and (weak) cimitidine.

Melphalan-prednisone co-administration increased bortezomib serum levels, but this is not thought to be clinically relevant.

**CYP3A4 inducers** can theoretically lower bortezomib levels: rifampin, carbamazepine, phenytoin, St. John's Wort. Assess for efficacy of bortezomib and need for increased drug dose. Do NOT give together with St. John's Wort

**CYP2C9 inhibitor** omeprazole co-administration did not affect bortezomib serum levels.

**CYP3A4 inhibitors** These drugs may decrease metabolism of dasatinib resulting in increased serum concentrations of dasatinib: (strong) atazanavir, clarithramycin, grapefruit juice, grapefruit, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquiarv, telithromycin, voriconazole; (moderate) amprenavir, aprepitant, diltiazem, fluconazole, verapamil; and (weak) cimitidine. Avoid co-administration; if must give together, monitor closely for drug toxicity and consider reducing dasatinib dose.

**CYP3A4 Inducers** may decrease dasatinib
serum levels (eg, rifampin decreased
dasatinib levels by 82%); others:
carbamazepine, phenytoin, St. John's Wort. If
must co-administer, assess efficacy of
dasatinib and need for increased drug dose.
Do NOT give together with St. John's Wort

**Antacids** May decrease dasatinib levels;
avoid co-administration or administer at least
2 hours before or after the dasatinib dose

**H2-Antagonists/Proton Pump
Inhibitors** May decrease dasatinib serum
levels; use antacids instead

**CYP3A4 substrates** drug is a time-
dependent inhibitor of CYP3A and may
decrease metabolism of drugs primarily
metabolized by CYP3A4, such as alfentanil,
stemizole, terfenadine, cisapride,
cyclosporine, fentanyl, pimozide, quinidine,
sirolimus, tacrolimus, or ergot alkaloids so
avoid co-administration or monitor drug
closely for side effects; single dose of
dasatinib with simvastatin increases
simavastatin (AUC) serum level by 37%

**Erlotinib (Tarceva)** CYP3A4; CYP1A2

**CYP3A4 Inhibitors** decreased metabolism
of erlotinib and increase its plasma
concentration when co-administered with
strong inhibitors: atazanavir, clarithromycin,
indinavir, itraconazole, ketoconazole,
nefazodone, nelfinavir, ritonavir, saquiariv,
telithromycin, voriconazole, grapefruit,
grapefruit juice; co-administration with
ketoconazole ↑ erlotinib AUC by 66%; co-
administration with ciprofloxacin ↑ erlotinib
AUC by 39%.
**CYP3A4 Inducers** rifampicin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, St. John’s Wort; coadministration with rifampicin ↓ erlotinib AUC by 66%. DO NOT take with St. John’s Wort

**CYP3A4 Substrates** warfarin- increased INR and bleeding possible, monitor INR and decrease warfarin dose as needed

**CYP1A2 inducers** cigarette smoking: decreases erlotinib serum levels; encourage patients not to smoke but if unable to smoke, consider cautious erlotinib dose increase and closely monitor for side effects

**Ph Altering Drugs** erlotinib GI absorption is dependent on a low gastric pH; omeprazole ↓ erlotinib AUC by 46%; avoid co-administration with proton-pump inhibitors, or H2-inhibitors; use antacids if needed, and administer 2 hours before or after erlotinib

**Food** ↑ erlotinib absorption to 100% (compared to dosed absorption of 60%); take drug 1 hour before or 2 hours after food intake

**Gefitinib (Iressa) CYP3A4**

**CYP3A4 Inhibitors** decreased metabolism of erlotinib and increase its plasma concentration when co-administered with strong inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit, grapefruit juice; co-administration with itraconazole ↑ gefitinib AUC by 88%; Avoid co-administration if possible; if not, monitor closely for gefitinib side effects
**CYP3A4 Inducers** rifampicin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, St. John's Wort; coadministration with rifampicin ↓ gefitinib AUC by 85%. DO NOT take with St. John’s Wort. If must co-administer with phenytoin or rifampicin, consider gefitinib dose increase to 500 mg PO daily if no adverse side effects, and monitor closely.

**CYP3A4 Substrates** warfarin- increased INR and bleeding possible, monitor INR and decrease warfarin dose as needed.

**Ph Altering Drugs** erlotinib GI absorption is dependent on a low gastric pH; ranitidine and bicarbonate ↓ gefitinib AUC by 44%; avoid co-administration with proton-pump inhibitors, or H2-inhibitors; use antacids if needed, and administer 2 hours before or after gefitinib.

**CYP3A4 Inhibitors** May increase serum levels of imatinib mesylate: (strong) atazanavir, clarithramycin, indinavir, itraconazole, grapefruit, grapefruit juice, ketoconazole, nefazodone, nelfinavir, ritonavir, saquiavir, telithromycin, voriconazole; AVOID co-administration; use cautiously if at all together with (moderate) amprenavir, aprepitant, diltiazem, fluconazole, verapamil; and (weak) cimitidine CYP3A4 inhibitors. If must be co-administered, assess closely for increased imatinib toxicity.

**CYP3A4 inducers** can lower imatinib serum levels. If co-administered with:
rifampin, dexamethasone, phenytoin, carbamazepine, phenobarbital, rifabutin; increase imatinib dose by 50%. Do NOT give together with St. John's Wort

**CYP3A4 Substrates** Imatinib interferes with CYP3A4 metabolism of the following drugs

- ↑ simvastatin levels: monitor LDL and reduce simvastatin dose if needed
- ↑ Cyclosporine, pimozide plasma concentrations; avoid concurrent administration
- Triazolo-benzodiazepines, dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors may have ↑ serum levels; use cautiously and monitor patient closely
- eletriptan (Repax) do not administer within 72 hrs of imatinib; monitor VS closely

**Interference with drugs metabolized by CYP2D6** if drugs metabolized by CYP2D6 are co-administered with imatinib, serum drug levels of these drugs will be elevated; co-administer cautiously and monitor closely;

**Warfarin** do not co-administer; use low molecular weight heparin (LMWH)

**Acetaminophen** ↑ serum acetaminophen serum levels
Lapatinib (Tykerb) CYP3A4; CYP2C8

**CYP3A4 inhibitors** These drugs may decrease metabolism of lapatinib resulting in increased serum concentrations of lapatinib: (strong) atazanavir, clarithramycin, grapefruit juice, grapefruit, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole. Avoid co-administration; if must give together with strong inhibitor, monitor closely for drug toxicity and consider reducing lapatinib dose. Use cautiously if at all, and monitor patient closely if co-administered with (moderate) amprenavir, aprepitant, diltiazem, fluconazole, verapamil; and (weak) cimetidine CYP3A4 inhibitors.

**CYP3A4 Inducers** may decrease lapatinib serum levels: carbamazepine, phenytoin, rifampicin, phenobarbital, dexamethasone, rifabutin, St. John's Wort. If must co-administer, assess efficacy of lapatinib and need for increased drug dose. Do NOT give together with St. John's Wort

**CYP3A4 and CYP2C8 substrates** Lapatinib inhibits both pathways so assess for toxicity in co-administered drugs which are metabolized by either pathway;

**p-glycoprotein (Pgp) metabolism (transport system)** if lapatinib co-administered with Pgp substrates (eg, loperamide, dexamethasone), assess for toxicity from increased substrate concentration. Conversely, lapatinib is also a substrate of Pgp so that if given with an inhibitor of Pgp (eg, quinidine), lapatinib drug levels are likely to be elevated; assess for lapatinib toxicity
**Nilotinib (Tasigna) CYP3A4**

**CYP3A4 Inhibitors** These drugs may increase serum levels of nilotinib—also (strong) atazanavir, ketoconazole, itraconazole, grapefruit, grapefruit juice, indinavir, nefazodone, nelfinavir, ritonavir, saquiarv, telithromycin, voriconazole; AVOID co-administration with strong inhibitors; if must co-administer, consider dose reduction of nilotinib and monitor patient closely for toxicity, including QT intervals on EKG. Co-administer cautiously if at all drugs which are moderate [amprenavir, apreptant, diltiazem, erythromycin, fluconazole, verapamil] or weak [cimitidine] inhibitors of CYP3A4; monitor closely for drug side effects.

**Inducers of CYP3A4** May decrease serum nilotinib concentrations: rifampin, phenytoin, phenobarbital, carbamazepine, dexamethasone, rifabutin, rifapentin, St. John's Wort. Avoid co-administration if possible. If co-administered, assess need for increased nilotinib dose by 50%. Do NOT give together with St. John's Wort.

**Substrates:**

- Nilotinib is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6
- Nilotinib may induce CYP2B6, CYP2C8, CYP2C9
  - Warfarin-nilotinib is a competitive substrate so INR needs to be monitored closely and dose adjusted frequently [warfarin is metabolized by CYP2C9 and CYP3A4 so warfarin should be avoided if
Nilotinib is a substrate of the efflux transporter P-glycoprotein (Pgp)- if administered with Pgp inhibitors (e.g., quinidine), serum concentration of nilotinib will be increased; avoid co-administration.

Sorafenib (Nexavar) CYP3A4; UGT1A9; CYP2C9 (warfarin)

**CYP3A4 inhibitors** no interaction

**CYP3A4 inducers** may increase the metabolism of sorafenib and decrease its serum level; rifampin, phenytoin, phenobarbital, carbamazepine, dexamethasone, rifabutin, rifapentin, St. John's Wort. Avoid co-administration if possible. If co-administered, assess need for increased sorafenib dose. Do NOT give together with St. John's Wort.

**Substrates:**

- **CYP2B6** (e.g., bupropion, propofol, ifosfamide) and **CYP2C8** (e.g., rapaglinide, amiodarone, ibuprofen, loperamide): substrate drug serum levels increased; monitor patient closely for drug toxicity
- **UGT1A1** (e.g., irinotecan) and **UGT1A9** (e.g., propofol): sorafenib inhibits glucuronidation by these pathways so substrate serum levels may be increased
- **CYP2C9 substrate** warfarin: potential increased INR; monitor and correct warfarin dose frequently

**Chemotherapy (other) interactions:**
- Docetaxel: ↑36-80% docetaxel AUC; ↑Cmax 16-32%; co-administer with caution, if at all
- Doxorubicin: ↑21% AUC; use together cautiously
- Fluorouracil: ↑21-47% as well as ↓10% in fluorouracil AUC; use caution when co-administering with 5-FU/leucovorin

**CYP3A4 Inhibitors** These drugs may increase serum levels of sunitinib: (strong) atazanavir, clarithromycin, ketoconazole, itraconazole, grapefruit, grapefruit juice, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole; AVOID co-administration with strong inhibitors; if must co-administer, consider dose reduction of sunitinib to 37.5 mg PO daily and monitor patient closely for toxicity and effect. Co-administer cautiously if at all drugs which are moderate [amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, verapamil] or weak [cimetidine] inhibitors of CYP3A4; monitor closely for drug side effects.

**Inducers of CYP3A4** May decrease serum sunitinib concentrations: rifampin, phenytoin, phenobarbital, carbamazepine, dexamethasone, rifabutin, rifapentin, St. John's Wort. Avoid co-administration if possible. If co-administered, assess need for increased sunitinib dose to a maximum of 87.5 mg PO daily. Do NOT give together with St. John's Wort.
**Strong CYP3A4 Inhibitors** May increase serum temsirolimus levels (strong): Clarithromycin, itraconazole, ketoconazole, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, grapefruit, grapefruit juice, and voriconazole. Avoid co-administration; if must be given together, consider temsirolimus dose decrease to 12.5 mg weekly; when interacting drug discontinued, allow 1-week wash-out period, then resume dose taking prior to adding interactive drug.

**Strong Inducers** May decrease serum temsirolimus level: dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, pentobarbital. If must give together, consider temsirolimus dose increase to 50 mg weekly; when interacting drug is discontinued, resume dose given prior to adding interacting drug. Teach patient NOT to take St. John's Wort.

**Strong CYP3A4 Inhibitors** May increase serum tretinoin level (strong): Clarithromycin, itraconazole, ketoconazole, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, grapefruit, grapefruit juice, and voriconazole; also erythromycin, cimetidine, verapamil, diltiazem, and cyclosporine: no data exists to show increased or decreased effect. However, ketoconazole was shown to ↑ tretinoin plasma AUC by 72%. Use together cautiously if at all.

**Strong CYP 3A4 Inducers** May decrease serum tretinoin level: dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, pentobarbital. No data exists to
show increased or decreased effect. Use together cautiously.

**Substrates** antifibriloytic agents (eg, tranexamic acid, aminocaproic acid, aprotinin: may cause fatal thrombotic complications; use together cautiously if at all

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**References**

- Scripture CD, Figg WD. Drug interactions in cancer therapy. *Nat Rev Ca* 2006; 6(7):546-558