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Potential cytochrome P-450 drug–drug interactions in adults with metastatic solid tumors and effect on eligibility for Phase I clinical trials

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Abstract

Purpose—Potential cytochrome P-450 (CYP) drug–drug interactions in adults with metastatic solid tumors and their effect on eligibility for Phase I clinical trials were characterized.

Methods—This study included adult patients with metastatic solid tumors seen by a medical oncologist from January 2008 through July 2011. The medications used by these patients were identified. Each medication's potential for interacting with CYP isozymes was also characterized. Medication changes required to meet Phase I trial eligibility criteria were also reviewed.

Results—Data from 1773 patients were analyzed: 1489 were not enrolled in a Phase I trial and 284 were enrolled in a Phase I trial. Polypharmacy was significantly more prevalent in the group enrolled in a Phase I trial compared with those not enrolled (95% versus 80%, $p < 0.001$). The majority of patients not enrolled in a Phase I trial were taking at least one CYP isozyme inhibitor (87%) and at least one CYP isozyme inducer (45%). In a separate analysis, four Phase I trials were evaluated. Of 295 screened patients, 3.2% could not enroll due to concurrent medications. Charts

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from 74 enrolled patients revealed 655 concurrent medications—93 medications required further review for eligibility involving 51 (69%) of patients. Of the 93 medications, 38 (41%) were stopped and 41 (44%) were changed for the study.

Conclusion—Polypharmacy and the use of medications that interact with CYP isozymes were common in adult patients with metastatic solid tumors. Patients enrolling in Phase I studies often require medication changes to meet eligibility requirements.

In recent decades, advances in the management of many chronic diseases have resulted in increased long-term medication use. The use of five or more medications by a patient has become more common in the general population.^{1,2} The taking of multiple medications, or poly-pharmacy, is even more prevalent in patients with cancer because of frequent preexisting comorbidities as well as the use of medications to manage cancer symptoms.^{3,4} Poly-pharmacy is associated with multiple negative clinical outcomes ranging from hospitalization to death.⁵⁻⁸ Over the past decade, multiple new anticancer agents have become available. Many of these are continuously administered oral drugs, thereby increasing the potential for negative outcomes due to pharmacokinetic drug–drug interactions (DDIs) in oncology patients.⁹⁻¹¹

Cytochrome P-450 (CYP) isozymes catalyze the biotransformation of chemicals and play a role in the metabolism of many oral medications.^{12,13} Medications may inhibit or induce the activity of one or more CYP isozymes and thereby interfere with the metabolism of a medication (substrate) by these isozymes.¹⁴ Concurrent use of an inducing medication and a substrate leads to decreased plasma concentrations of the substrate medication. This could lead to a subsequent loss of effectiveness. In contrast, concurrent use of an inhibiting medication with a substrate can lead to increased substrate concentrations and possible toxicity. The therapeutic range of most oncology agents is narrow. Thus, minor alterations in the concentrations of anti-cancer drugs may significantly affect the drugs' activity, toxicity, or both. Many examples of pharmacokinetic DDIs resulting in either decreased effectiveness or increased adverse events with oncological drugs have been reported.^{10,15-17}

Studies regarding the frequency of actual or potential DDIs in oncology patients are limited; however, the existing literature suggests that 30–46% of oncology patients are at risk.¹⁸⁻²⁰ The patient populations in these studies combined solid and hematologic malignancies being treated for palliative or curative intent. This heterogeneity limits the extent to which the results can be applied to patients with metastatic solid tumors. Treatment for this population is heavily dependent on systemic therapies rather than local therapies. Furthermore, medications for symptom management are common in patients with metastatic cancer. The medical literature describes only the concurrent use of medications with known DDIs rather than reporting the use of medications with significant potential for pharmacokinetic interactions. This leaves a gap in the current knowledge regarding the risk of DDIs in patients with metastatic solid tumors for whom a new anticancer agent is being considered.

Potential DDIs are also very important to consider for patients participating in Phase I studies. Although these studies are necessary for drug development, the drugs often have a narrow therapeutic range and investigators' understanding of the toxicities of the study agents is inherently limited.²¹ This increases the potential risk for harm from a DDI. Our

experience has suggested that polypharmacy and the use of medications that interact with CYP isozymes are very common in patients enrolled in Phase I studies. Medication dosages have frequently been adjusted based on protocol requirements for Phase I study eligibility at our institution, yet the approach to defining concurrent medication eligibility for clinical trials has not been standardized.²² No study to date has described the prevalence of CYP isozyme-interacting medication use in patients with metastatic solid tumors who enroll in Phase I trials. There are also limited data regarding the impact of protocol eligibility language on medication management during the screening process.

The purpose of this study was to characterize the frequency of the use of medications that interact with CYP isozymes among adult patients with metastatic solid tumors who were and were not enrolled in a Phase I study. The secondary objective was to determine the effect of potential DDIs on Phase I clinical trial enrollment.

Methods

Medication use and potential DDIs

Study design and population—This single-institution, cross-sectional retrospective study included adult patients (age 18 years or older) with metastatic solid tumors (Appendix A) seen by a medical oncologist from January 2008 through July 2011. Patients were identified using the hospital's cancer registry (OnCore Database). The OnCore Database was also used to identify patients treated in a Phase I metastatic solid tumor study. Phase II or III studies often enroll patients earlier in the metastatic disease course and have a larger potential medication benefit : risk ratio than Phase I studies; thus, we specifically evaluated only Phase I study participants. Patients treated in a combined Phase I/ II, Phase II, or Phase III trial or those who never began study treatment were excluded. Study patients, all of whom had metastatic solid tumors, were divided into two groups: (1) patients who had never been treated in a Phase I study at the institution and (2) patients enrolled in a Phase I study. This study was approved by the university's health sciences institutional review board.

Data collection—We used the medical record number and date of diagnosis from the cancer registry to search the electronic health records (EHRs) for patients who had an encounter with an oncology provider after January 1, 2008. Data elements were electronically abstracted from the EHR for each patient. Data regarding demographics, prespecified comorbidities (Appendix A), body mass index, and tobacco use were collected for all patients. Medication-use data were recorded from the first oncology encounter after the date of diagnosis of metastatic disease until the last encounter or final date of data collection (May 2012). Due to concerns about cumulative medication use in patients with longer survival times and the expected increase in supportive care medications near the end of life, only the first three months of medication-use data were analyzed. Medication dose, schedule, and start and stop dates also were recorded. Excluded medications included standard cancer therapies (chemotherapy, endocrine therapies, and targeted therapies), minimally systemically absorbed (up to 20% absorption) topical or inhaled medications, drugs no longer available on the U.S. market, and most vitamins and supplements (the use of iron, calcium, vitamin D, magnesium, potassium, phosphorus, pancreatic enzymes, and

multivitamins was recorded). A standard drug reference (Lexicomp, Hudson, OH) was used to classify each medication as a non-interactor with or an inducer (strong, moderate, or weak), inhibitor (strong, moderate, or weak), or substrate (sensitive or nonsensitive) of nine CYP isozymes: 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 1A2.

For the group enrolled in a Phase I trial, the medication list included medications in unexpired (i.e., active) drug orders recorded in the EHR on the study start date or any new drug prescription within the first three months after the study start date that met the previously described inclusion criteria. For patients enrolled in multiple Phase I studies, the corresponding medication list for the first Phase I study from January 2008 through May 2012 was evaluated.

Effect of DDIs on Phase I trial enrollment

Study inclusion—The EHR did not adequately define medications that were discontinued to enable study enrollment or the CYP isozyme-interacting characteristics of Phase I study agents, so a separate enrollment approach was used. National Cancer Institute (NCI)–sponsored Phase I clinical trials opened between January 1, 2007, and December 31, 2009, that involved patients with metastatic solid tumors were selected for evaluation. Studies could include standard-of-care chemotherapy and oral or i.v. investigational agents. Seven trials were opened during this time period; however, one closed after enrolling the first group and was excluded from the analysis. Of the six remaining trials, four involved oral investigational agents that interact with CYP isozymes and two involved investigational agents that did not interact with CYP isozymes. Medication eligibility determinations for study patients are routinely performed by the Pharmaceutical Research Center. For this analysis, an investigator reviewed the medication history and determined the CYP isozyme-interacting potential of each nonstudy medication using the drug monograph in the most recent online version of the *Lexicomp Drug Information Handbook* (UpToDate, Wolters Kluwer Health). This information was then compared with protocol eligibility.

Data collection—Research charts and associated protocols were manually reviewed by one investigator. The metabolic pathway for each of the investigational agents was recorded. Concurrent medication use at baseline, protocol-defined contra-indicated medications, and changes in concurrent medications to meet study eligibility were recorded.

Statistical analyses

The frequencies and percentages of CYP isozyme inducers and inhibitors were calculated and compared between study groups using chi-square analysis. Continuous variables were summarized in terms of medians and ranges. Multivariate logistic regression analysis was conducted to compare the percentages of patients who took at least one weak, moderate, or strong CYP isozyme inducer or inhibitor, and adjustments were made for age, sex, diagnosis, and number of comorbidities. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were reported. All tests were two sided, and the a priori level of significance was set at 0.05. Data compilation and analysis were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC).

Results

Patient characteristics

A total of 1773 patients were included in the data abstraction and analysis (Table 1). Most patients were Caucasian (87%); men and women were about equally represented.

The group not enrolled in a Phase I trial included 1489 patients. The median age at cancer diagnosis was 62 years (range, 18–93 years); sex distribution was nearly equal. As expected, the majority of this group (67%) had common cancers (lung, colorectal, breast, ovarian, pancreatic, or prostate).

A total of 284 patients, 56% of whom were women, were enrolled in a Phase I trial. The median age at cancer diagnosis was 59 years (range, 18–80 years). This group was more likely to have none of the prespecified comorbidities compared with the group not enrolled in a Phase I trial (77% versus 55%, respectively; $p < 0.001$).

Medication use in study groups

Polypharmacy (use of at least five medications) was significantly more prevalent in the group enrolled in a Phase I trial compared with the group not enrolled (95% versus 80%, $p < 0.001$). The majority of patients not enrolled in a Phase I trial were taking at least one CYP isozyme inhibitor (87%) and at least one CYP isozyme inducer (45%) (Table 2). CYP isozyme-sensitive substrates were used in 79% of patients not enrolled in a Phase I trial. A larger proportion of the group enrolled in a Phase I trial (97%) took at least one CYP isozyme inhibitor ($p < 0.0001$); however, once weak inhibitors were removed, this difference was no longer significant ($p = 0.115$). In order to narrow the criteria to those drugs most likely to put the patient at risk for clinically significant DDIs, only moderate or strong CYP isozyme inducers or inhibitors were examined. The use of at least one moderate or strong CYP isozyme inducer was similar between groups (40% in the group not enrolled in a Phase I trial versus 36% in the group enrolled in a Phase I trial). Sixty-one percent of the group not enrolled in a Phase I trial took at least one moderate or strong CYP isozyme inhibitor, compared with 66% in the other study group.

When adjusted for age, sex, diagnosis, and number of comorbidities, patients enrolled in a Phase I study had a significantly higher likelihood of taking at least one inhibitor (OR, 5.25; 95% CI, 2.53–10.91; $p < 0.001$), though the difference was not significant when weak inhibitors were removed (OR, 1.32; 95% CI, 0.99–1.75; $p = 0.057$). Substrate use was also higher in the group enrolled in a Phase I trial compared with the other study group (OR, 17.7; 95% CI, 2.4–128.6; $p = 0.004$). However, the use of a CYP isozyme-sensitive substrate did not differ significantly between groups ($p = 0.16$) (Table 3). The percentage of patients not enrolled in a Phase I trial who were taking strong inducers of CYP isozyme 2A6, 2B6, 2C9, or 3A4 ranged from 35% to 40%. Similarly, the percentage of patients enrolled in a Phase I study who were taking strong inducers of these isozymes ranged from 32% to 35%. Table 4 shows the prevalence of treatment with inhibitors and inducers of CYP isozymes in all study patients.

As expected, the most common medications used in both groups combined were for supportive care or management of clinically significant comorbidities. The most common moderate or strong CYP isozyme inhibitors and inducers were corticosteroids, antacids, antibiotics, and cardiovascular agents (Table 5).

Assessment of DDIs before Phase I trial enrollment

A total of 426 patients were evaluated for Phase I trial enrollment in the six NCI trials (Appendix B): 295 in the four CYP-interaction trials and 131 in the two trials of agents with no CYP interactions. A total of 113 patients (26.5%) were enrolled in these trials (78 patients [26.4% of screened patients] in the studies involving CYP isozyme interactions and 35 patients [26.7% of screened patients] in the studies of agents not interacting with CYP isozymes).

Study records were reviewed to determine how many patients were excluded from participating in the trials of investigational agents that interact with CYP isozymes due to interacting medications. Across these four trials, 7 patients were excluded because of interacting medications, accounting for 3.2% of screening exclusions (7 of 217). Warfarin was the most frequent cause of screening exclusion (5 patients).

Individual eligibility determinations were then reviewed for patients enrolled in each of these four studies. Of the 78 patients enrolled in one of these CYP isozyme trials, eligibility determinations were not available for 4 patients. The remaining 74 patients were taking 655 concurrent medications (mean, 8.9 per patient); 93 were medications defined by protocol to potentially interact with the study agents. A total of 51 patients (69%) were found to be taking at least 1 interacting medication. To facilitate enrollment in these studies, 38 medications (41%) were stopped, 41 (44%) were changed, and 14 (15%) that did not have absolute contraindications were continued. Ondansetron ($n = 7$), hydroxymethylglutaryl-coenzyme A reductase inhibitors ($n = 6$), and dexamethasone ($n = 5$) were the most frequently discontinued medications. Antihypertensive medications were the most frequently changed ($n = 10$), followed by omeprazole ($n = 9$) and antidiuretics ($n = 8$). The metabolic pathway of the investigational agents and protocol-contraindicated concurrent medications are described in Appendix B.

Discussion

This study identified high rates of polypharmacy among adult patients with metastatic solid tumors. The majority of patients were taking medications with a clinically significant potential for pharmacokinetic CYP isozyme-mediated DDIs. Forty percent of patients not enrolled in a Phase I trial were taking at least one moderate or strong inducer, and 61% were taking at least one moderate or strong inhibitor. Higher rates of polypharmacy were observed in patients enrolled in a Phase I trial (95% versus 80%, $p < 0.001$), perhaps due to the increased use of medications for symptom management during the metastatic disease course. Patients enrolled in a Phase I trial were also more likely to be taking at least one CYP inhibitor or substrate compared with those patients not enrolled in a Phase I study; however, the difference was no longer significant once weak inhibitors and nonsensitive

substrates were removed from the analysis. Thus, the risk for potential serious interactions appears to be similar for both groups.

The CYP pathway is a major route of drug metabolism. This is especially true of oral anticancer therapies.^{10,11} The potential risks of DDIs are important given the narrow therapeutic range associated with anticancer agents. The literature suggests that DDIs are associated with an increased risk of hospitalization.⁸ Suboptimal dosing of anticancer medications due to DDIs is also a concerning possible consequence.¹⁷ It is critical that providers recognize these potential DDIs. We identified specific medications with the potential for DDIs that are commonly used in patients with cancer. Many of these medications (e.g., proton pump inhibitors, ciprofloxacin, amlodipine) have alternatives that could be substituted if the potential for a DDI is identified by the prescribing provider, thus reducing the risk for medical complications or suboptimal anticancer treatment.

Our results represent the largest study to date evaluating potential DDIs in patients with metastatic solid tumors. Other studies have evaluated patients with early-stage and metastatic cancers. Early-stage cancers are often diagnosed in healthier, younger patients who have fewer cancer symptoms and, for this reason, are less likely to be taking multiple medications. Thus, these studies may have underestimated the true rate of DDIs. For example, Riechelmann et al.¹⁹ reported that nearly 30% (10% major, as defined by Drug Interaction Facts Software, version 4.0) of patients were taking medications with at least one potential interaction. However, 38% of the patients studied had early-stage cancers. These results are similar to the 46% of potential DDIs (16% major) found by van Leeuwen et al.¹⁸ using similar methods and those found in a systematic review indicating that about one third of patients with cancer are at risk for a potential DDI.²⁰ Only one study reported a very low rate of potential DDIs (4.5%) in patients with cancer.²³ However, the sample size in that study was small (200 outpatients). Most of these patients were adult outpatients with breast cancer—a population that is often younger than other cancer populations and that has few comorbidities.

Another unique aspect of our study was the use of pharmacokinetic classifications for medications rather than defined interactions from the clinical resource used (Drug Interaction Facts Software).¹⁹ Our approach strengthens the literature by establishing that the usage rates of medications that interact with CYP isozymes and the resulting potential for DDIs are quite high in patients with metastatic solid tumors. We also identified the most common medications used in this population that can cause potential DDIs.

Moreover, this is the first study to specifically evaluate DDIs and the effect of using these medications on study eligibility in patients enrolling in Phase I clinical trials. This is an important group to study due to the low benefit:risk ratio in these studies. Furthermore, the doses of new anticancer agents are often established in this small patient population. Our study established that significant polypharmacy exists in patients enrolled in Phase I trials and that there are high rates of CYP isozyme-interacting medication use. Potential DDIs affected the eligibility for the majority of the patients participating in Phase I protocols involving investigational agents that interact with CYP isozymes. Nearly 3% of patients were excluded because of interacting medications, and 69% of patients were taking a

medication that required further evaluation to meet trial eligibility requirements. Of the medications evaluated, 85% were discontinued or changed to allow study eligibility. Despite the risk of DDIs being common for patients enrolling in Phase I trials, a consistent approach to protocol definitions for allowed and contraindicated concurrent medications is lacking. You et al.²² demonstrated that the same investigational drug, evaluated using different protocols, had different lists of prohibited medications. Our results support the need to develop a standardized approach to potential DDIs in protocols for early-phase clinical trials.¹⁰

One major limitation of our study is that electronic data were used to capture medication use. Medication lists could have been inaccurate because of limited self-reporting of medications prescribed by outside providers, the potential for not capturing the use of some dietary or herbal supplements or as-needed medications, and the potential for nondocumentation of discontinuation of medication use in the EHR. Medication records indicate only agents that are prescribed or are reported by the patient; however, patients may not take the medications as prescribed.

Another limitation of our study was that the potential for medications to interact with CYP isozymes, which was determined by using Lexicomp, could have been greater than that determined by using other commonly used resources (e.g., Indiana University's Cytochrome P450 Drug Interaction Table [<http://medicine.iupui.edu/clinpharm/ddis>]). However, Lexicomp is a validated, commonly used drug information resource in clinical practice. Interestingly, a study by Anthony et al.²⁴ found that there is little agreement among product labels and commonly used drug compendia in terms of DDIs and of severity classification for interactions involving warfarin, a common drug involved in DDIs.

Our study had several strengths, such as the large sample size, which was representative of a general metastatic cancer population. In addition, our analysis included nonprescription medications and standard vitamin and mineral supplements. We also specifically evaluated the CYP isozyme-interacting effects of each medication rather than only identifying known DDIs; this approach addressed the potential for new DDIs as anticancer agents are changed. This is important, as moderate or strong inhibitors or inducers are the medications most likely to affect the drug levels of concurrent anticancer agents and to result in changes in effectiveness or toxicity.

Conclusion

Polypharmacy and the use of medications that interact with CYP isozymes were common in adult patients with metastatic solid tumors. Patients enrolling in Phase I studies often require medication changes to meet eligibility requirements.

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Appendix A—Solid tumor and comorbid diagnoses and International Classification of Diseases, Ninth Edition (ICD-9), codes analyzed

Solid tumor diagnosis (ICD-9 code)

Adenocarcinoma, unknown primary (195.8, 199)

Bladder cancer (188)Breast cancer (174, 175)

Cervical cancer (180)

Colorectal cancer (153, 154)

Esophageal cancer (150)

Gallbladder cancer (156)

Gastric cancer (151)

Head and neck cancer (141, 145, 149, 161, 171, 195)

Hepatocellular cancer/cholangiocarcinoma (155)

Lung cancer (162, 165)

Melanoma (172)

Neuroendocrine carcinoma (238.9, 259.2)

Ovarian cancer (183)

Pancreatic cancer (157)

Prostate cancer (185)

Renal cell carcinoma/kidney cancer (189, 236.99)

Sarcoma (159.1, 170, 171)

Secondary neoplasm (196, 197, 198)

Uterine cancer (179, 182)

Comorbid condition (ICD-9 code)

Cardiomyopathy, heart failure (425, 428) Cerebrovascular disease, nonhemorrhagic (434, 435, 436, 437, 438)

Chronic bronchitis and emphysema (491, 492)

Depression (296.2, 296.3, 311)

Diabetes mellitus (249, 250)

Disorders of lipid metabolism (272)

Hypertension (401, 402, 405)

Ischemic heart disease (410, 411, 412, 413, 414)

Seizure disorder (345)

Appendix B—Involvement of cytochrome P-450 (CYP) isozymes in metabolic pathways of agents studied in National Cancer Institute (NCI)–sponsored Phase I clinical trials^a

NCI Study No.	Relationship Between Trial Agent and CYP Isozymes	Medications Contraindicated Because of CYP Involvement
8062	None	None
8604	None	None
8515	Inducer and substrate of 3A4	Inducers, inhibitors, and substrates of 3A4
	Moderate inhibitor of 2C9, 2C19, and 2D6	CYP-metabolized medications with narrow therapeutic window
8516	Inducer and substrate of 3A4	Inducers, inhibitors, and substrates of 3A4
	Moderate inhibitor of 2C9, 2C19, and 2D6	CYP-metabolized medications with narrow therapeutic range
8627	Substrate of 3A4, 1A2, and 2C9	Strong inducers and inhibitors of 1A2 and 3A4
8709	Agent 1: substrate of 3A4 and inhibitor of 2C8 Agent	Strong or moderate inducers and inhibitors of 3A4
	2: substrate of 3A4	

^aIncludes only those trials in which current study patients were enrolled.

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Table 1
Characteristics of Patients in Study Groups^a

Characteristic	Not Enrolled in Phase I Trial (<i>n</i> = 1489)	Enrolled in Phase I Trial (<i>n</i> = 284)
Median (range) age at diagnosis, yr	62 (18–93)	59 (18–80)
Median (range) BMI, kg/m ²	26.7 (14.8–63.2)	27.8 (16.4–53.5)
BSA, m ²	1.9 (0.9–3.1)	2.0 (1.4–2.9)
Sex, no. (%)		
Male	719 (48)	122 (43)
Female	769 (52)	159 (56)
Unknown	1 (0)	3 (1)
Primary tumor type, no. (%) ^b		
Breast	124 (8)	12 (4)
Colorectal	182 (12)	45 (16)
Lung	382 (26)	48 (17)
Ovarian	113 (8)	20 (7)
Pancreatic	122 (8)	18 (6)
Prostate	73 (5)	42 (15)
Unknown	11 (1)	5 (2)
Other	482 (32)	94 (33)
No. comorbidities, no. (%) ^b		
None	812 (55)	220 (77)
1 or 2	455 (31)	45 (16)
3 or 4	153 (11)	17 (6)
5 or more	69 (4)	2 (1)

^aBMI = body mass index, BSA = body surface area.

^bSee Appendix A for solid tumor and comorbidity diagnoses included in the analysis.

Table 2
Frequency of Treatment With Inducers, Inhibitors, or Substrates of Cytochrome P-450
(CYP) Isozymes^a

Relationship to CYP Isozymes	Not Enrolled in Phase I Trial (<i>n</i> = 1489)	Enrolled in Phase I Trial (<i>n</i> = 284)	<i>p</i>
Inducer			
Weak, moderate, or strong	671 (45)	118 (42)	0.275
Moderate or strong	602 (40)	101 (36)	0.124
Strong	600 (40)	100 (35)	0.108
Inhibitor			
Weak, moderate, or strong	1299 (87)	276 (97)	<0.001
Moderate or strong	912 (61)	188 (66)	0.115
Strong	266 (18)	49 (17)	0.805
Substrate			
Sensitive or nonsensitive	1295 (87)	278 (98)	<0.001
Sensitive	1049 (79)	209 (74)	0.285
Nonsensitive	1281 (86)	276 (97)	<0.0001

^aIncludes patients taking at least one medication of the indicated type.

Table 3
ORs and 95% CIs for Being Treated With CYP Isozyme Inducers, Inhibitors, or
Substrates Among All Study Patients^a

Relationship to CYP Isozymes	OR (95% CI) ^b	<i>p</i>
Inducer		
Weak, moderate, or strong	0.88 (0.66–1.16)	0.354
Moderate or strong	0.80 (0.07–0.62)	0.138
Strong	0.80 (0.11–0.88)	0.119
Inhibitor		
Weak, moderate, or strong	5.25 (2.53–10.91)	<0.001
Moderate or strong	1.32 (0.99–1.75)	0.057
Strong	0.82 (0.58–1.18)	0.2912
Substrate		
Sensitive or nonsensitive	17.7 (2.4–128.6)	0.004
Sensitive	1.4 (0.9–2.2)	0.16
Nonsensitive	9.4 (2.3–38.7)	0.002

^a Includes patients taking at least one medication of the indicated type. OR = odds ratio, CI = confidence interval, CYP = cytochrome P-450.

^b Indicates risk in patients enrolled in Phase I trials compared with risk in patients not enrolled in Phase I trials. Adjusted for age, sex, diagnosis, and number of comorbidities.

Table 4
Prevalence of Treatment With Inducers or Inhibitors of CYP Isozymes Among All Study Patients (*n* = 1773)^a

CYP Isozyme	% Treated With CYP Inducer			% Treated With CYP Inhibitor		
	Weak	Moderate	Strong	Weak	Moderate	Strong
1A2	22	1	11	54	12	9
2A6	0	0	36	12	1	0
2B6	0	1	37	17	7	0
2C1	7	1	1	39	38	5
2C8	0	1	1	29	10	2
2C9	0	1	38	68	27	5
2D6	0	0	0	70	15	6
2E1	0	0	1	7	0	0
3A4	16	0	39	74	21	1

^a CYP = cytochrome P-450.

Table 5
Top 10 Moderate or Strong CYP Isozyme Inhibitors and Inducers in Patients Not Enrolled in Phase I Trial ($n = 1489$)^a

Relationship to CYP Isozymes	No. (%) Patients
Inhibitor	
Omeprazole	321 (22)
Pantoprazole	142 (10)
Ciprofloxacin	132 (9)
Aprepitant	125 (8)
Amlodipine	103 (7)
Diphenhydramine	70 (5)
Esomeprazole	56 (4)
Fluconazole	52 (3)
Metronidazole	50 (3)
Sulfamethoxazole–trimethoprim	47 (3)
Inducer	
Dexamethasone	539 (36)
Pantoprazole	142 (10)
Aprepitant	125 (8)
Lansoprazole	24 (2)
Montelukast	13 (1)
Colchicine	10 (1)
Phenytoin	10 (1)
Dicloxacillin	9 (1)
Carbamazepine	8 (1)
Estradiol acetate	8 (1)

^aCYP = cytochrome P-450.