Prevalence of Acid-Reducing Agents (ARA) in Cancer Populations and ARA Drug-Drug Interaction Potential for Molecular Targeted Agents in Clinical Development

ARTICLE *in* MOLECULAR PHARMACEUTICS · SEPTEMBER 2013

Impact Factor: 4.38 · DOI: 10.1021/mp400403s · Source: PubMed

molecular pharmaceutics

Article

pubs.acs.org/molecularpharmaceutics

Prevalence of Acid-Reducing Agents (ARA) in Cancer Populations and ARA Drug−Drug Interaction Potential for Molecular Targeted Agents in Clinical Development

Gillian S. Smelick,*[,†] Timothy P. Heffron,[‡] Laura Chu,[§] Brian Dean,[∥] David A. West,[†] Scott L. DuVall,[⊥] Bert L. Lum,[†] Nageshwar Budha,[†] Scott N. Holden,[#] Leslie Z. Benet,[$] Adam Frymoyer,[¶] Mark J. Dresser,[†] and Joseph A. Ware*[,†]

[†]Clinical Pharmacology, Genentech Research and Early Development, 1 DNA Way, South San Francisco, California 94080, United States

[‡]Genentech Medicinal Chemistry, 1 DNA Way, South San Francisco, California 94080, United States

[§]Genentech Epidemiology, 1 DNA Way, South San Francisco, California 94080, United States

[∥]Drug Metabolism and Pharmacokinetics, Genentech Research and Early Development, 1 DNA Way, South San Francisco, California 94080, United States

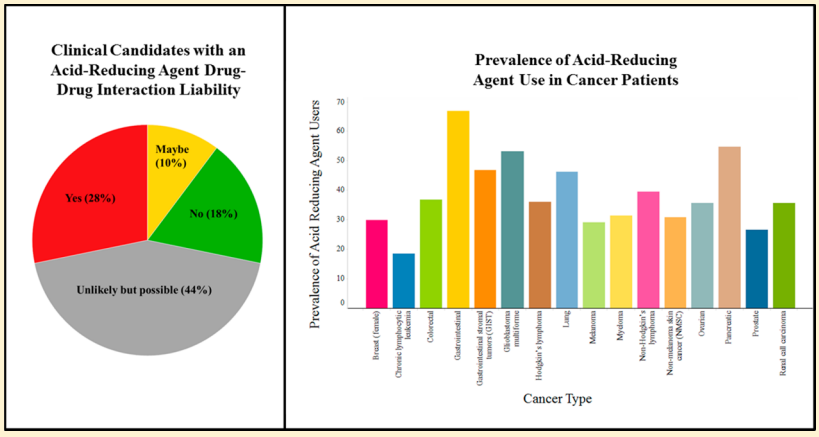
[⊥]VA Salt Lake City Health Care System, Clinical Epidemiology, Internal Medicine, University of Utah, Salt Lake City, Utah 84148, United States

[#]Early Clinical Development, Genentech Research and Early Development, 1 DNA Way, South San Francisco, California 94080, United States

[$]Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, California 94143-0912, United States

[¶]Department of Pediatrics, Stanford University, Palo Alto, California 94304, United States

Supporting Information



ABSTRACT: Acid-reducing agents (ARAs) are the most commonly prescribed medications in North America and Western Europe. There are currently no data describing the prevalence of their use among cancer patients. However, this is a paramount question due to the potential for significant drug−drug interactions (DDIs) between ARAs, most commonly proton pump inhibitors (PPIs), and orally administered cancer therapeutics that display pH-dependent solubility, which may lead to decreased drug absorption and decreased therapeutic benefit. Of recently approved orally administered cancer therapeutics, >50% are characterized as having pH-dependent solubility, but there are currently no data describing the potential for this ARA-DDI liability among targeted agents currently in clinical development. The objectives of this study were to (1) determine the prevalence of ARA use among different cancer populations and (2) investigate the prevalence of orally administered cancer therapeutics currently in development that may be liable for an ARA-DDI.
continued...

Special Issue: Impact of Physical Chemical Drug-Drug Interactions from Drug Discovery to Clinic

Received: July 12, 2013
Revised: September 12, 2013
Accepted: September 17, 2013

To address the question of ARA use among cancer patients, a retrospective cross-sectional analysis was performed using two large healthcare databases: Thomson Reuters MarketScan (N = 1,776,443) and the U.S. Department of Veterans Affairs (VA, N = 1,171,833). Among all cancer patients, the total prevalence proportion of ARA use (no. of cancer patients receiving an ARA/total no. of cancer patients) was 20% and 33% for the MarketScan and VA databases, respectively. PPIs were the most commonly prescribed agent, comprising 79% and 65% of all cancer patients receiving a prescription for an ARA (no. of cancer patients receiving a PPI /no. of cancer patients receiving an ARA) for the MarketScan and VA databases, respectively. To estimate the ARA-DDI liability of orally administered molecular targeted cancer therapeutics currently in development, two publicly available databases, (1) Kinase SARfari and (2) canSAR, were examined. For those orally administered clinical candidates that had available structures, the pK_a's and corresponding relative solubilities were calculated for a normal fasting pH of 1.2 and an "ARA-hypochlorhydric" pH of 4. Taking calculated pK_a's and relative solubilities into consideration, clinical candidates were classified based on their risk for an ARA-DDI. More than one-quarter (28%) of the molecules investigated are at high risk for an ARA-DDI, and of those high risk molecules, nearly three-quarters (73%) are being clinically evaluated for at least one of five cancer types with the highest prevalence of ARA use (gastrointestinal, pancreatic, lung, glioblastoma multiforme, gastrointestinal stromal tumor (GIST)). These data strongly suggest that with the clinical development of ARA-DDI-susceptible cancer therapeutics will come continued challenges for drug-development scientists, oncologists, and regulatory agencies in ensuring that patients achieve safe and efficacious exposures of their cancer therapeutics and thus optimal patient outcomes.

KEYWORDS: *acid-reducing agent (ARA), proton pump inhibitor (PPI), drug−drug interaction (DDI), cancer therapeutics, gastroesophageal reflux disease (GERD), MarketScan, U.S. Department of Veterans Affairs (VA)*

INTRODUCTION

Acid-reducing agents (ARAs), most notably proton pump inhibitors (PPIs), are the most commonly prescribed medications in North America and Western Europe, used for the palliative relief of symptoms arising from conditions of gastroesophageal hyperacidity.[1] However, increased gastric pH can have a significant negative impact on the dissolution, absorption, and pharmacokinetics of orally administered therapeutic agents that display pH-dependent solubility. It is estimated that 50% of recently approved molecular targeted oral cancer therapies are weak bases and display solubility-limited dissolution properties that are known to impact drug absorption.[2−4] For example, the aqueous solubility of erlotinib decreases as pH increases, and when administered with a PPI, erlotinib's maximum concentration (C_{max}) decreased by 61% and its plasma exposure (AUC) decreased by 46%.[4] Similarly, the aqueous solubility of dasatinib decreases exponentially as pH increases over the normal physiological range; its C_{max} and AUC decreased by 63% and 61% when administered 10 h after a single H2-receptor antagonist (H2RA) dose and by 42% and 43% when administered 22 h after a steady-state PPI dose.[5] Given the documented clinical significance of drug concentration−response relationships in this family of molecular targeted agents,[6−8] we hypothesize that decreases in exposure of orally administered cancer therapeutics, as a result of concomitant ARA use, may lead to compromised therapeutic benefit and the development of drug resistance pathways due to suboptimal tumor exposure. The prevalence of ARA use in cancer patients and the number of clinical candidates in development with the potential for an ARA-drug−drug interaction (DDI) liability has not been previously examined but is fundamental to understanding the potential and relevance of this DDI. Moreover, this information could impact early lead-optimization strategies regarding drug solubility enhancement and formulation development. The objectives of our study were to (1) describe the prevalence of ARA use (Supporting Information Table 1) in various cancer populations using two large and representative healthcare databases and (2) estimate the likelihood for an ARA-DDI liability of orally administered molecular targeted cancer therapeutics currently in clinical development using two publicly available databases.

METHODS

Prevalence of ARA Use in Cancer Populations: Data Sources. The prevalence of ARA use in different cancer types was determined using two primary data sources: (1) Department of Veterans Affairs (VA) and (2) Thomson Reuters MarketScan.

The VA is the largest healthcare system in the United States, providing care to approximately 6 million veterans at over 1,400 points of care. At the core of virtually all care processes is a broadly scoped and extensively used electronic health record system known as the Veterans Information System Technology Architecture (VistA). VistA provides a longitudinal view for patients receiving care nationwide including diagnosis, procedures, pharmacy orders, laboratories, microbiology, physiologic measurements, and text documents. Clinical and administrative data extracted from VistA for patients nationwide were used to perform this analysis.

Thomson Reuters MarketScan is a nationwide employment-based database that contains information on medical claims as well as outpatient prescription drug claims. The database represents claims from approximately 45 large employers and captures insurance claims data from over 100 payers.[9] It contains all paid claims generated by approximately 29 million commercially ensured lives. We used the MarketScan Commercial Claims and Encounter (CCAE) database and the MarketScan Medicare Supplemental database in this study. The MarketScan CCAE database includes claims for employees and their spouses as well as dependents that are covered under the employer-sponsored insurance. The MarketScan Medicare Supplemental database includes claims for employees who retired from one of these 45 large employers and became Medicare eligible; the database includes claims for services covered by Medicare as well as employer-sponsored supplemental insurance plans.

Prevalence of ARA Use in Cancer Populations: Identification of Cancer Patients and Therapies. Cancer patients were identified by the presence of at least two ICD-9 codes specific to the cancers of interest (Supporting Information Table 2) within 180 days of each other and at least one day apart. Patients could be assigned to multiple cancer types if they met the definition for each cancer type. For the VA, patient records between October 1999 and January 2011 were examined. For MarketScan database, patient records between January 1999 and June 2009 were examined.

An index date was calculated for each patient−cancer combination (i.e., if a patient had breast and lung cancers, an index date for breast cancer and an index date for lung cancer were calculated). The index date was defined as the date of the first qualifying claim of cancer diagnosis within the same cancer type.

Prescriptions and refills of each ARA were identified for all patients in the cancer groups from one month prior to six months

Table 1. Orally-Administered Molecular-Targeted Cancer Therapeutics in Clinical Development and Their Predicted Acid-Reducing Agent Drug−Drug Interaction Liability[a]

molecule	$cpK_{a,b}$	obsd pK_a	rel solubility at pH 1.2	rel solubility at pH 4.0	change in rel solubility	likely to have an ARA-DDI liability?[b]	obsd clinical effect? contraindicated?
abiraterone	NA	NA	1	1	0	no	NA
afatinib	8.7, 4.8		31622778	50120	31572658	unlikely but possible	
bafetinib	8.9, 3.9, 3.2, 2.6		50118724	79434	50039291	unlikely but possible	
BMS-599626	11.3, 6.2		1.259×10^{10}	19952624	1.257×10^{10}	unlikely but possible	
bosutinib	8.6, 6.4, 4.8	NA	25118865	39812	25079054	unlikely but possible	yes[28]
brivanib	5		6311	11	6300	yes	
brivanib alaninate	7.8, 4.1		3981073	6311	3974762	unlikely but possible	
crizotinib	9.8, 5.5	9.4, 5.6	398107172	630958	397476213	unlikely but possible	yes[23]
dasatinib	7.9, 6.7	10.8, 6.8, 3.1	5011873	7944	5003929	unlikely but possible	yes[29]
dovitinib	8.1, 7.0		7943283	12590	7930693	unlikely but possible	
enzastaurin	7.1, 2.5		794329	1260	793069	unlikely but possible	
erlotinib	5.1	5.4	7944	13.6	7931	yes	yes[30]
fostamatinib	5.1, 3.4		7944	13.6	7931	yes	
GDC-0941	4.8, 1.8		3982	7.31	3975	yes	
gefitinib	10.1, 7.4, 3.9	7.2, 5.4	794328236	1258926	793069309	unlikely but possible	yes[24]
imatinib	8.2, 4.1, 3.4, 2.5	7.7	10000001	15850	9984151	unlikely but possible	no[31,32]
lapatinib	5.2, 4.4	NA	10001	16.8	9984	yes	yes[33]
lestaurtinib	NA		1	1	0	no	
midostaurin	NA		1	1	0	no	
MK-2206	5.5		19954	32.6	19921	yes	
motesanib	6.3, 4.2, 3.2		125894	201	125693	maybe	
neratinib	8.7, 6.7, 5.7		31622778	50120	31572658	unlikely but possible	
nilotinib	6.0, 4.0, 2.5	5.4, 2.1	63097	101	62996	maybe	yes[34]
NVP-RAF265	5.4, 3.1		15850	26.1	15824	yes	
olaparib	NA		1	1	0	no	
orantinib	NA		1	1	0	no	
pazopanib	5.1, 2.8	10.2, 6.4, 2.1	7944	13.6	7931	yes	yes[35]
PD-325901	NA		1	1	0	no	
PX-866	7.3		1258926	1996	1256930	unlikely but possible	
saracatinib	8.7, 7.0, 4.0		31622778	50120	31572658	unlikely but possible	
seliciclib	5.6, −0.5		25120	40.8	25079	yes	
selumetinib	5.5		19954	32.6	19921	yes	
sorafenib	4.8	NA	3982	7.31	3975	yes	yes[36,37]
sunitinib	9	9	63095735	100001	62995734	unlikely but possible	no[16,38]
tacrolimus	NA	NA	1	1	0	no	NA
tandutinib	9.2, 6.0		100000001	158490	99841511	unlikely but possible	
vandetanib	7.7, 4.0	9.4, 5.2	3162279	5013	3157266	unlikely but possible	no[16]
vatalanib	6.6, 4.5		251190	399	250791	maybe	
vemurafinib	2.8	NA	40.8	1.06	39.7	maybe	no[39]
tofacitinib[c]	5.1	5.1	7944	13.6	7931	yes	no[26,27]

[a]Observed clinical data as of June 1, 2013. pK_a: acid dissociation constant. NA: not applicable or not available. [b]ARA-DDI liability predicted as outlined in the decision tree presented as Supporting Information Figure 1. [c]Tofacitinib is not currently being developed for an oncologic indication (www.clinicaltrials.gov) and was thus not included in our analysis.

after the index date of cancer. If a patient in a cancer group had at least one ARA medication dispensed during this time period, they were counted in the numerator for that time period. The denominator was the number of cancer patients that were still enrolled in the health plan for at least one day for MarketScan, or that had at least one encounter for the VA data, during the time period of interest.

Prevalence of ARA Use in Cancer Populations: Methods of Analysis. Prevalence proportion was calculated as the ratio of patients that had at least one medication dispensed during a time period to the number of active patients in the cancer group during that time period. Prevalence proportion was reported for all acid-reducing agents and for each drug group separately.

Graphs were generated using Spotfire 3.2.1 (TIBCO, Palo Alto, California).

Clinical Candidates with ARA-DDI Liability: Data Sources. Clinical candidates with a potential ARA-DDI liability were identified using two publicly available databases, which pool and report data from the public domain: (1) Kinase SARfari and (2) canSAR.

dx.doi.org/10.1021/mp400403s | Mol. Pharmaceutics XXXX, XXX, XXX−XXX

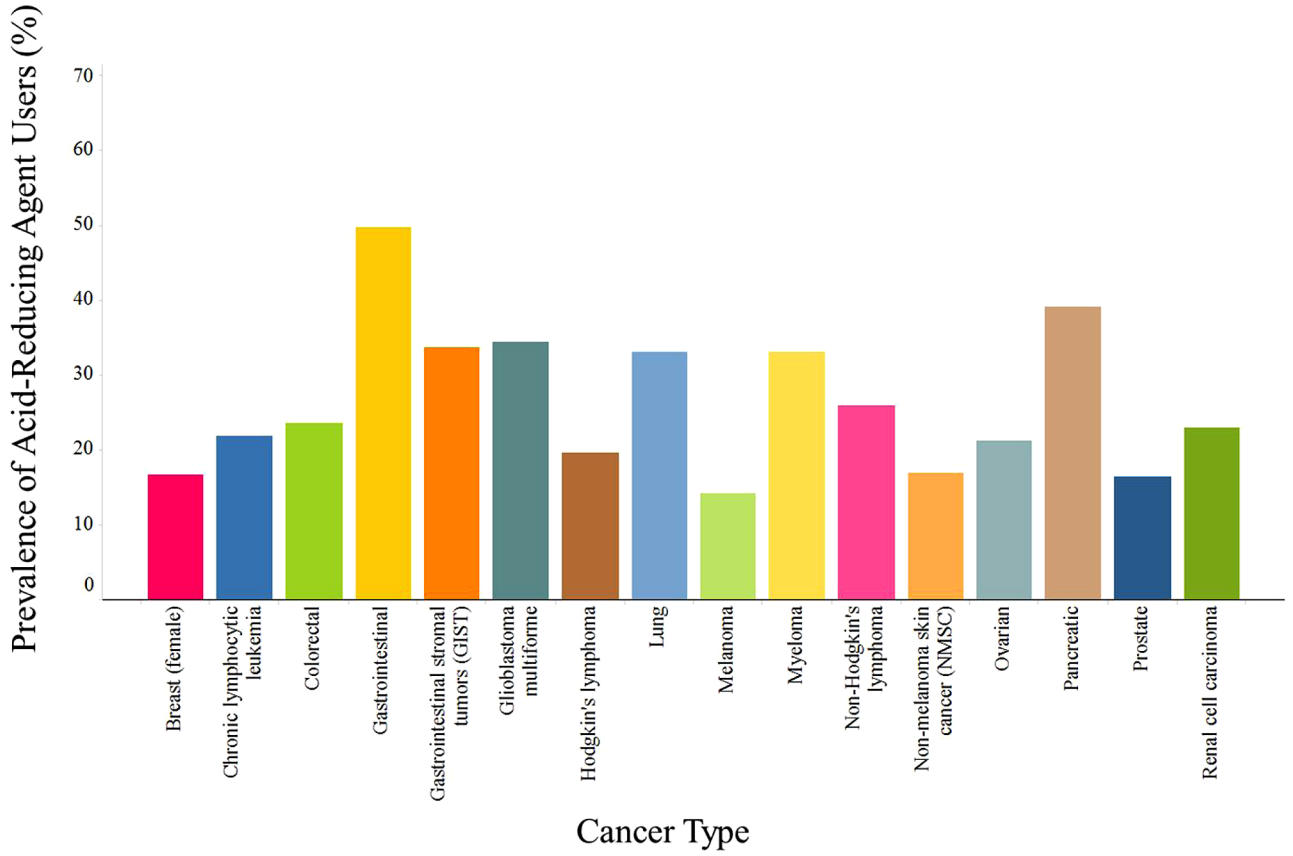


Figure 1. MarketScan database: prevalence of acid-reducing agent use across cancer types.

Kinase SARfari is a chemogenomics workbench provided by the European Bioinformatics Institute (EBI) as part of the European Molecular Biological Laboratory (EMBL) that leverages public and proprietary chemical and biological data for protein kinases in order to provide a centralized resource for protein kinase knowledge.

canSAR is an integrated database provided by the Computational Biology and Chemogenomics Team of the Cancer Research UK Therapeutics Unit at the Institute of Cancer Research. The database incorporates biological, chemical, pharmacological, and clinical data in an effort to support hypothesis generation in translational cancer research.

Clinical Candidates with ARA-DDI Liability: Identification of Candidates with pH-Dependent Solubility. Using Kinase SARfari, 258 kinase inhibitor clinical candidates were identified, 49 of which had reported chemical structures. A search of the canSAR database yielded 162 clinical candidates. After elimination of duplicates from Kinase SARfari and those without structures, an additional 56 compounds were identified from canSAR. The combined list of compounds from both kinase SARfari and canSAR was further trimmed to include only those compounds that are orally administered and have active or enrolling trials with at least one oncologic indication as reported on clinicaltrials.gov. Basic pK_a's were calculated (cp$K_{a,b}$) using MoKa (Molecular Discovery) for the combined list of 39 clinical candidates (Table 1).[10,11] The relative solubility of each compound at a fasting pH of 1.2 and an "ARA-hypochlorhydric" pH of 4.0 were calculated using a derivation of the Henderson–Hasselbalch equation: $S_{total} = S_{int}(1 + 10^{pK_a - pH})$, where S_{total} becomes $S_{relative}$ (relative solubility) when S_{int} (intrinsic solubility) is treated as 1 because it is unknown.[12] The "ARA-hypochlorhydric" pH of 4.0 was selected based on the measured elevation in gastric pH following steady-state administration of a PPI.[13] The most basic cp$K_{a,b}$ was used for pK_a in these calculations. Relative solubility refers to the fold increase in solubility at a particular pH relative to the solubility of the neutral compound.

Clinical Candidates with ARA-DDI Liability: Methods of Analysis. Those clinical candidates with no ionizable functional group (n = 7) and thus no associated cpK_a were categorized as not having an expected ARA-DDI Liability ("no", Table 1). For clinical candidates with a relative solubility >1000 at pH 4 (n = 17), an ARA-DDI liability was deemed to be extremely unlikely but possible as the solubility would likely be very high even with ARA use ("unlikely but possible", Table 1). Along the same line of reasoning, clinical candidates with a relative solubility >1000 at pH 1.2 and a relative solubility ranging 100−1000 at pH 4 (n = 3) were categorized as potentially having an ARA-DDI liability because the solubility at pH 4 may be high even with ARA use ("maybe", Table 1). Those clinical candidates with a relative solubility <100 at both pHs (n = 1) were considered to have a potential for ARA-DDI liability, but the magnitude of difference in relative solubility is not substantial and so these were also categorized as potentially having an ARA-DDI liability ("maybe", Table 1). Clinical candidates with a relative solubility >1000 at pH 1.2 but <100 at pH 4 (n = 11) were deemed most likely to have an ARA-DDI liability ("yes", Table 1). A decision tree which highlights our approach to predicting ARA-DDI liability is provided in Supporting Information Figure 1. The relative solubility cutoff values used to estimate the ARA-DDI liability of these clinical candidates are not exact, and thus those molecules with relative solubility values

dx.doi.org/10.1021/mp400403s | Mol. Pharmaceutics XXXX, XXX, XXX−XXX

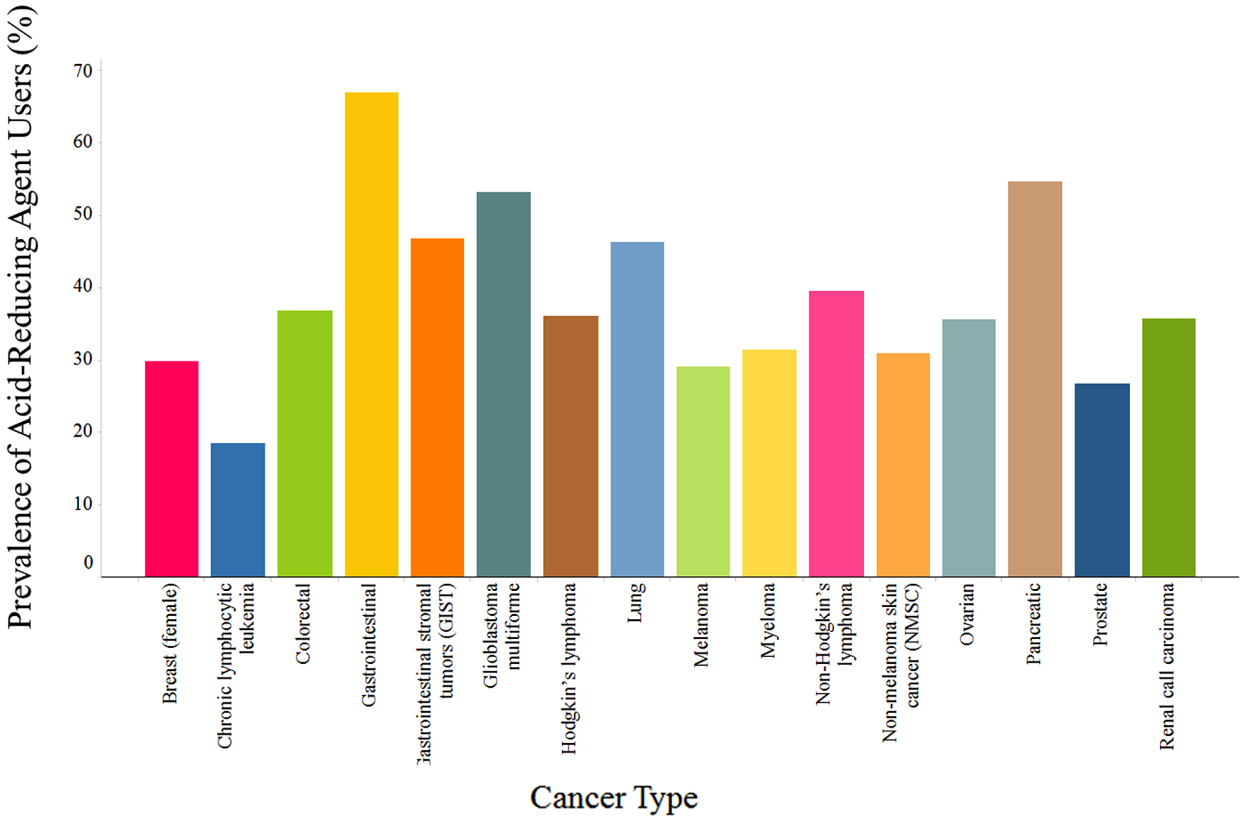


Figure 2. U.S. Department of Veterans Affairs: prevalence of acid-reducing agent use across cancer types.

approaching the outlined cutoff values should be interpreted accordingly.

RESULTS

Prevalence of ARA Use in Cancer Patients. Among all cancer patients, the total prevalence proportion of ARAs (no. of cancer patients receiving an ARA/total no. of cancer patients) was 20% and 33% for the MarketScan and VA databases, respectively (Figures 1 and 2, Tables 2 and 3). In both database populations, the cancer populations with the greatest prevalence of acid-reducing agent use were gastrointestinal (MarketScan, 50%; VA, 67%), pancreatic (MarketScan, 39%; VA, 55%), glioblastoma multiforme (MarketScan, 35%; VA, 53%), lung (MarketScan, 33%; VA, 46%), and gastrointestinal stromal tumors (GIST) (MarketScan, 34%; VA, 47%).

Prevalence of Specific ARA Use in Cancer Patients. Of cancer patients receiving an ARA prescription, PPIs were the most commonly prescribed agent, comprising 79% and 65% for the MarketScan and VA databases, respectively (no. of cancer patients prescribed PPI/no. of cancer patients receiving ARA prescription). The overall prevalence of PPI use across all cancer types was 17% for the MarketScan database and 23% for the VA database (no. of cancer patients prescribed PPI/total no. of cancer patients). H2RA prescriptions were the second most prevalent agent, representing 19% and 34% of all cancer patients receiving an ARA prescription for the MarketScan and VA databases, respectively. Prescriptions for Carafate were low in both databases, and it was not possible to estimate the prevalence of Magic Mouthwash, as this is a compounded prescription that contains various proportions of sodium bicarbonate ($NaHCO_3$), lidocaine, and antacids, which may be used in the treatment of drug-induced mucositis.[14]

Table 2. MarketScan Database: Prevalence of Acid-Reducing Agent Use Across Cancer Types

	N		
cancer	total	acid-reducing agent	prevalence proportion
lung	126849	42097	33.2
breast (female)	321676	53724	16.7
ovarian	30850	6574	21.3
colorectal	120787	28512	23.6
pancreatic	27625	10836	39.2
gastrointestinal	15148	7537	49.8
gastrointestinal stromal tumors (GIST)	3116	1053	33.8
prostate	235865	38907	16.5
melanoma	72299	10291	14.2
nonmelanoma skin cancer (NMSC)	601461	102173	17.0
glioblastoma multiforme	30310	10456	34.5
renal cell carcinoma	42705	9805	23.0
non-Hodgkin's lymphoma	85208	22106	25.9
Hodgkin's lymphoma	17082	3371	19.7
chronic lymphocytic leukemia	23196	5072	21.9
myeloma	22266	7376	33.1
total	1776443	359890	20.3

Prevalence of Clinical Candidates with ARA-DDI Liability. Of the 39 identified orally administered clinical candidates with available molecular structures, seven have no ionizable functional group and thus no associated cpK_a or expected ARA-DDI liability. Of the remaining 32 molecular targeted agents currently under clinical evaluation, 11−15 (Table 1, 11 "yes" and 4 "maybe") are expected to have an

dx.doi.org/10.1021/mp400403s | *Mol. Pharmaceutics* XXXX, XXX, XXX−XXX

Table 3. U.S. Department of Veterans Affairs: Prevalence of Acid-Reducing Agent Use Across Cancer Types

	N		
cancer	total	acid-reducing agent	prevalence proportion
lung	146404	67812	46.3
breast (female)	14351	4298	29.9
ovarian	1059	378	35.7
colorectal	101147	37317	36.9
pancreatic	14618	8017	54.8
gastrointestinal	9492	6364	67.0
gastrointestinal stromal tumors (GIST)	1625	760	46.8
prostate	434494	116205	26.7
melanoma	36549	10676	29.2
nonmelanoma skin cancer (NMSC)	279936	86889	31.0
glioblastoma multiforme	9882	5261	53.2
renal call carcinoma	36191	12967	35.8
non-Hodgkin's lymphoma	42789	16913	39.5
Hodgkin's lymphoma	6052	2184	36.1
chronic lymphocytic leukemia	21104	3895	18.5
myeloma	16140	5083	31.5
total	1171833	385019	32.9

ARA-DDI liability based on their pK_a's and relative solubilities at pH 1.2 and pH 4. Despite a substantial decrease in calculated relative solubilities at pH 4 relative to pH 1.2, the remaining 17 clinical candidates with reported cpK_a's are not expected to have an ARA-DDI liability based on a high (>1000) calculated relative solubility at pH 4. Last, of the 11 clinical candidates that are expected to have an ARA-DDI liability, eight (73%) are being pursued in one of the five cancer types with the highest prevalence of ARA use (gastrointestinal, pancreatic, glioblastoma multiforme, lung, and GIST).

DISCUSSION

The frequent use of ARAs among cancer patients described in this analysis is of particular importance when considering the direct physicochemical impact of ARAs on the dissolution and subsequent absorption of orally administered molecular targeted anticancer agents with pH-dependent solubility.[2,3] Proton pump inhibitors, the most commonly prescribed ARAs, have recently been the subject of particular scientific scrutiny in light of growing evidence of adverse events associated with their long-term use and potential for clinically significant DDIs.[15−18] Because of their unique and potent mechanism of action (covalent binding to the cysteine residues of the H^+/K^+-ATPase pump), the resulting suppression of gastric acid secretion can be sustained for several days after stopping treatment.[19] Therefore, if a patient receives an orally administered cancer therapeutic with pH-dependent solubility on a daily regimen, they may experience prolonged acid suppression or hyper-acid (rebound) secretion several days after they stop taking their PPI concomitantly, which may in turn lead to erratic and variable drug absorption. Use of an ARA with a shorter pharmacodynamic duration, which mirrors its pharmacokinetic half-life, such as an H2RA or antacid, may allow the patient to strategically time their cancer therapeutic-ARA treatment to avoid or limit a DDI. Such time-staggering mitigation strategies are sometimes recommended in the prescribing information of molecular targeted agents with pH-dependent solubility where clinical data has shown a pronounced effect on drug concentrations, as is the case with dasatinib and erlotinib.[4,5] Specifically, the AUC of erlotinib decreased by 33% when coadministered with an H2RA but decreased by only 15% when administered 10 h after an H2RA dose, further suggesting the potential efficacy of staggering treatments in an effort to lessen or avoid clinically significant interactions.[4] However, in the case of dasatinib, its C_{max} and AUC decreased by 63% and 61% when administered 10 h after a single H2RA dose, suggesting that a time staggering mitigation strategy may not be effective for every molecule.[5] Furthermore, the time staggering strategy assumes patient compliance, and it is important to keep in mind that gastric acidity can be symptomatically severe and the most common and effective ARAs (PPIs and H2RAs) are readily available over-the-counter.

The prevalence of ARA use was higher in the VA database (33% overall) relative to the MarketScan database (20% overall) for nearly all cancer types, which is consistent with the demographics of each database, as the VA population is generally older than the MarketScan population (66% of VA population was 65 years of age or over compared with 44% of the MarketScan population) and ARA users tend to be older.[1] The estimated prevalence of ARA use in both databases likely underrepresents the true prevalence due to the wide availability and common use of over-the-counter ARAs, which were not included in this analysis.[20] The high prevalence of ARA use among patients with gastrointestinal and pancreatic cancers is not surprising considering the etiology and location of their disease. There has also been evidence for chemotherapy-induced GERD in pancreatic cancer patients, which further explains the high prevalence of ARA use in this population.[21] One limitation of the prevalence proportion calculation for acid-reducing agent users across all cancer types is that patients included in this analysis could be assigned to multiple cancer types if they met the definition for each cancer type. However, because the included ICD-9 cancer codes are specific to primary tumors, we estimate that the number of patients with more than one primary tumor (two separate ICD-9 codes) with overlapping index dates, as defined by the outlined Methods, is small.

Our analysis of orally administered molecular targeted cancer therapeutics currently in clinical development and their potential for an ARA-DDI foreshadows the continued challenges that drug development scientists, oncologists, and regulatory agencies will face as these molecules are clinically evaluated and may provide further insight into mechanisms of drug candidate attrition or the failure of approved drugs to work in cancers where a high prevalence of patients take ARAs. Given that so many of the clinical candidates with available structures (28%) are characterized by a markedly reduced relative solubility at the "ARA-hypochlorhydric" pH of 4 and that a majority of the liable molecules are indicated for cancer types with high ARA use, it is imperative that practical mitigation strategies are developed and implemented so as to avoid the potential for decreased therapeutic benefit of the targeted cancer therapies. For example, temporary gastric reacidifcation with betaine-hydrochloride at the time of dosing of a weak base oral cancer therapeutic with pH-dependent solubility may allow for the dissolution, solubilization, and absorption of the cancer therapeutic over the critical absorption window, after which the gastric pH would rebound to an "ARA-hypochlorhydric" pH. This mitigation strategy would allow for maximum absorption of the cancer therapeutic, thereby circumventing potentially subefficacious drug exposures and simultaneously allowing patients to continue taking their ARA therapies for symptomatically severe GERD.[13]

dx.doi.org/10.1021/mp400403s | Mol. Pharmaceutics XXXX, XXX, XXX−XXX

For molecular targeted cancer therapeutics, achieving and maintaining a threshold drug concentration is important not only to achieve desired efficacy but also to mitigate the potential development of acquired resistance due to underexposure of the tumor.[6−8,22]

Some of the molecules that were included in this analysis have already received FDA approval and are currently under clinical evaluation for additional indications. Thus, the ARA-DDI potential of a number of the approved molecules has already been clinically evaluated and suggests that the methods used in this analysis to estimate their ARA-DDI liability can be predictive (sorafenib, erlotinib, sunitinib, etc.). However, not all of the pK_a's were accurately predicted, which, for some of the molecules, resulted in false negative results (dasatinib, crizotinib, gefitinib), suggesting that purely in silico means of evaluating this ARA-DDI will not suffice in predicting the observed clinical interaction and that additional preclinical studies should be pursued to better quantify the in vivo significance of the DDI prior to conducting a clinical DDI study.[5,16,23−25] It is also important to consider that molecule-specific factors such as dose, dynamic solubility, permeability, and dissolution can impact the absorption and extent of this ARA-DDI. While tofacitinib was excluded from our final analysis because it is not currently being developed for an oncologic indication, it nonetheless provides a valuable example of how the in silico methods used in this analysis can generate false-positive results. In the case of tofacitinib, the pK_a was accurately predicted by MOKA and tofacitinib does in fact have pH-dependent solubility but, contrary to our predictions, there is no evidence of a clinically significant DDI (false positive). The solubility of tofacitinib is 0.20−0.59 mg/mL in aqueous solution of pH 4.53 to >8, but its highest marketed dose strength is 5 mg, suggesting it would be soluble in 250 mL of water at elevated pH and thus not be impacted by concomitant ARA therapy. This lends further explanation to tofacitinib being "freely soluble" in water as indicated in the drug label.[26,27] Last, it is valuable to consider the potential DDI between ARAs and orally administered molecular targeted therapeutics that display increased solubility at elevated hypochlorhydric pH values. Such an interaction could result in increased exposure of the molecular targeted agent and thus pose potential safety concerns, depending on the candidate's therapeutic window.

This is the first paper to describe the prevalence of ARA use among cancer patients by cancer type and estimate the ARA-DDI liability of orally administered molecular targeted cancer therapeutics currently under clinical evaluation. ARAs can reduce the solubility and subsequent absorption of orally administered therapeutics with pH-dependent solubility, and many such cancer therapeutics currently in the clinical pipeline not only are at risk for this ARA-DDI but are also indicated for a cancer type with high ARA use. Additional studies are warranted to determine the impact of this DDI on patient outcomes and to identify potential mitigation strategies that will ensure safe and efficacious molecular targeted therapies for the many cancer patients who also suffer from conditions of gastric hyperacidity and concomitantly take an ARA.

■ ASSOCIATED CONTENT

Supporting Information

Figure S1 depicting decision tree used for predicting ARA-DDI liability of clinical candidates, Table S1 of acid-reducing agents, and Table S2 of ICD-9-CM codes for defining cancer types. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: (650) 467-8781. E-mail: smelick.gillian@gene.com.
*Phone: (650) 467-3123. Fax: (650) 742-5234. E-mail: ware.joseph@gene.com.

Notes

The authors declare the following competing financial interest(s): This study was funded by a grant from Genentech. Authors GS, TH, BD, DW, LC, BL, NB, SH, MD and JAW are and/or were employees of Genentech, Inc. when this study was conducted. Authors LB, AF, and SD have no financial relationships to report. We attest that we have herein disclosed any and all financial or other relationships and that all sources of financial support for this study are indicated in the acknowledgments.

■ ACKNOWLEDGMENTS

This manuscript is dedicated to the patients and families who are affected by cancer and to the health-care practitioners and scientists who devote their lives to improving cancer therapeutics. In addition, Dr. Amita Joshi, Dr. Ru-Fang Yeh, and Dr. Sandra Horning are acknowledged for their helpful suggestions and support during the preparation of this work, and Alan Nevitt for his programming support. This work was supported using resources and facilities at the VA Salt Lake City Health Care System with funding support from the VA Informatics and Computing Infrastructure (VINCI), VA HSR HIR 08-204; and the Consortium for Healthcare Informatics Research (CHIR), VA HSR HIR 08-374. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

■ ABBREVIATIONS USED

pK_a, acid dissociation constant; ARA, acid-reducing agent; $cpK_{a,b}$, calculated basic acid dissociation constant; DDI, drug−drug interaction; GERD, gastroesophageal reflux disease; GIST, gastrointestinal stromal tumor; H2RA, H2-receptor antagonist; PPI, proton pump inhibitor; VA, Veterans Affairs

■ REFERENCES

(1) Targownik, L. E.; Metge, C.; Roos, L.; Leung, S. The prevalence of and the clinical and demographic characteristics associated with high-intensity proton pump inhibitor use. *Am. J. Gastroenterol.* **2007**, *102* (5), 942−50.

(2) Duong, S.; Leung, M. Should the concomitant use of erlotinib and acid-reducing agents be avoided? The drug interaction between erlotinib and acid-reducing agents. *J. Oncol. Pharm. Pract.* **2011**, *17* (4), 448−52.

(3) Eley, T.; Luo, F. R.; Agrawal, S.; Sanil, A.; Manning, J.; Li, T.; Blackwood-Chirchir, A.; Bertz, R. Phase I study of the effect of gastric acid pH modulators on the bioavailability of oral dasatinib in healthy subjects. *J. Clin. Pharmacol.* **2009**, *49* (6), 700−9.

(4) The US Food and Drug Administration. *Erlotinib (Tarceva) Prescribing Information*. 2010.

(5) The US Food and Drug Administration. *Dasatinib (Sprycel) Prescribing Information*. 2011.

(6) Guilhot, F.; Hughes, T. P.; Cortes, J.; Druker, B. J.; Baccarani, M.; Gathmann, I.; Hayes, M.; Granvil, C.; Wang, Y. Plasma exposure of imatinib and its correlation with clinical response in the Tyrosine Kinase Inhibitor Optimization and Selectivity Trial. *Haematologica* **2012**, *97* (5), 731−8.

(7) Koren-Michowitz, M.; Volchek, Y.; Naparstek, E.; Gavish, I.; Levi, I.; Rowe, J. M.; Shimoni, A.; Nagler, A. Imatinib plasma trough levels in

chronic myeloid leukaemia: results of a multicentre study CSTI571AIL11TGLIVEC. *Hematol. Oncol.* **2012**, *30* (4), 200−5.
(8) The US Food and Drug Administration. *Nilotinib (Tasigna) Clinical Pharmacology and Biopharaceutics Review*. 2007.
(9) *Medstat. MarketScan Research Database user guide and database dictionary*. 2007.
(10) Milletti, F.; Storchi, L.; Goracci, L.; Bendels, S.; Wagner, B.; Kansy, M.; Cruciani, G. Extending pKa prediction accuracy: high-throughput pKa measurements to understand pKa modulation of new chemical series. *Eur. J. Med. Chem.* **2010**, *45* (9), 4270−9.
(11) Milletti, F.; Storchi, L.; Sforna, G.; Cruciani, G. New and original pKa prediction method using grid molecular interaction fields. *J. Chem. Inf. Model.* **2007**, *47* (6), 2172−81.
(12) Kerns, E. H.; Di, L. *Drug-like Properties: Concepts, Structure Design and Methods from ADME to Toxicity Optimization*; Elsevier Inc.: Oxford, 2008.
(13) Yago, M. R.; Frymoyer, A. R.; Smelick, G. S.; Frassetto, L. A.; Budha, N. R.; Dresser, M. J.; Ware, J. A.; Benet, L. Z. Gastric Reacidification with Betaine HCl in Healthy Volunteers with Rabeprazole-Induced Hypochlorhydria. *Mol. Pharmaceutics* **2013**, DOI: 10.1021/mp4003738.
(14) Ferte, C.; Paci, A.; Zizi, M.; Gonzales, D. B.; Goubar, A.; Gomez-Roca, C.; Massard, C.; Sahmoud, T.; Andre, F.; Soria, J. C. Natural history, management and pharmacokinetics of Everolimus-induced-oral ulcers: Insights into compliance issues. *Eur. J. Cancer* **2011**, *47* (15), 2249−55.
(15) Bezabeh, S.; Mackey, A. C.; Kluetz, P.; Jappar, D.; Korvick, J. Accumulating evidence for a drug-drug interaction between methotrexate and proton pump inhibitors. *Oncologist* **2012**, *17* (4), 550−4.
(16) Budha, N. R.; Frymoyer, A.; Smelick, G. S.; Jin, J. Y.; Yago, M. R.; Dresser, M. J.; Holden, S. N.; Benet, L. Z.; Ware, J. A. Drug absorption interactions between oral targeted anticancer agents and PPIs: is pH-dependent solubility the Achilles heel of targeted therapy? *Clin. Pharmacol. Ther.* **2012**, *92* (2), 203−13.
(17) Cote, G. A.; Howden, C. W. Potential adverse effects of proton pump inhibitors. *Curr. Gastroenterol. Rep.* **2008**, *10* (3), 208−14.
(18) Yang, Y. X.; Hennessy, S.; Propert, K.; Hwang, W. T.; Sedarat, A.; Lewis, J. D. Chronic proton pump inhibitor therapy and the risk of colorectal cancer. *Gastroenterology* **2007**, *133* (3), 748−54.
(19) Sachs, G.; Shin, J. M.; Pratha, V.; Hogan, D. Synthesis or rupture: duration of acid inhibition by proton pump inhibitors. *Drugs Today (Barcelona, Spain)* **2003**, *39* (Suppl. A), 11−4.
(20) Haag, S.; Andrews, J. M.; Katelaris, P. H.; Gapasin, J.; Galmiche, J. P.; Hunt, R.; Layer, P.; Malfertheiner, P.; Holtmann, G. Management of reflux symptoms with over-the-counter proton pump inhibitors: issues and proposed guidelines. *Digestion* **2009**, *80* (4), 226−34.
(21) Uwagawa, T.; Misawa, T.; Iida, T.; Sakamoto, T.; Gocho, T.; Wakiyama, S.; Hirohara, S.; Yanaga, K. Proton-pump inhibitor as palliative care for chemotherapy-induced gastroesophageal reflux disease in pancreatic cancer patients. *J. Palliative Med.* **2010**, *13* (7), 815−8.
(22) Eechoute, K.; Sparreboom, A.; Burger, H.; Franke, R. M.; Schiavon, G.; Verweij, J.; Loos, W. J.; Wiemer, E. A.; Mathijssen, R. H. Drug transporters and imatinib treatment: implications for clinical practice. *Clin. Cancer Res.* **2011**, *17* (3), 406−15.
(23) The US Food and Drug Administration. *Crizotinib (Xalkori) - Prescribing Information*. 2011.
(24) The US Food and Drug Administration. *Gefitinib (Iressa) - Prescribing information*. 2004.
(25) Pang, J.; Dalziel, G.; Dean, B.; Ware, J. A.; Salphati, L. Pharmacokinetics and Absorption of the Anticancer Agents Dasatinib and GDC-0941 under Various Gastric Conditions in Dogs - Reversing the Effect of Elevated Gastric pH with Betaine HCl. *Mol. Pharmaceutics* **2013**, DOI: 10.1021/mp400356m.
(26) The US Food and Drug Administration. *Tofacitinib (Xeljanz) - Prescribing Information*. 2012.
(27) The US Food and Drug Administration. *Tofacitinib (Xeljanz) - Clinical Pharmacology and Biopharmaceutics Review*. 2012.
(28) The US Food and Drug Administration. *Bosutinib (Bosulif) - Prescribing Information*. 2012.
(29) The US Food and Drug Administration. *Dasatinib (Sprycel) - Prescribing information*. 2010.
(30) The US Food and Drug Administration. *Erloitinib (Tarceva) - Prescribing information*. 2010.
(31) Egorin, M. J.; Shah, D. D.; Christner, S. M.; Yerk, M. A.; Komazec, K. A.; Appleman, L. R.; Redner, R. L.; Miller, B. M.; Beumer, J. H. Effect of a proton pump inhibitor on the pharmacokinetics of imatinib. *Br. J. Clin. Pharmacol.* **2009**, *68* (3), 370−4.
(32) Sparano, B. A.; Egorin, M. J.; Parise, R. A.; Walters, J.; Komazec, K. A.; Redner, R. L.; Beumer, J. H. Effect of antacid on imatinib absorption. *Cancer Chemother. Pharmacol.* **2009**, *63* (3), 525−8.
(33) EMEA. *Lapatinib (Tykerb) - Summary of product characteristics*. 2010.
(34) The US Food and Drug Administration. *Nilotinib (Tasigna) - Clinical Pharmacology and Biopharmaceutics Review*. 2007.
(35) Tan, A. R.; Gibbon, D. G.; Stein, M. N.; Lindquist, D.; Edenfield, J. W.; Martin, J. C.; Gregory, C.; Suttle, A. B.; Tada, H.; Botbyl, J.; Stephenson, J. J. Effects of ketoconazole and esomeprazole on the pharmacokinetics of pazopanib in patients with solid tumors. *Cancer Chemother. Pharmacol.* **2013**, *71* (6), 1635−43.
(36) Lind, J. S.; Dingemans, A. M.; Groen, H. J.; Thunnissen, F. B.; Bekers, O.; Heideman, D. A.; Honeywell, R. J.; Giovannetti, E.; Peters, G. J.; Postmus, P. E.; van Suylen, R. J.; Smit, E. F. A multicenter phase II study of erlotinib and sorafenib in chemotherapy-naive patients with advanced non-small cell lung cancer. *Clin. Cancer Res.* **2010**, *16* (11), 3078−87.
(37) The US Food and Drug Administration. *Sorafenib (Nexavar) - Prescribing information*. 2010.
(38) The US Food and Drug Administration. *Sunitinib (Sutent) - Prescribing information*. 2010.
(39) The US Food and Drug Administration. *Vemurafenib (Zelboraf) - Prescribing Information*. 2011.