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ARTICLE

Intrinsic and Extrinsic Pharmacokinetic Variability of Small Molecule Targeted Cancer Therapy

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Pharmacokinetic (PK) variability in cancer clinical trials may be due to heterogeneous populations and identifying sources of variability is important. Use of healthy subjects in clinical pharmacology studies together with detailed knowledge of the characteristics of patients with cancer can allow for quick identification and quantification of factors affecting PK variability. PK data and sources of variability of 40 marketed molecularly targeted oncology therapeutics were compiled from regulatory approval documents covering an 18-year period (1999–2017). Variability in PK parameters was compared and contributors to variability were identified. The results show that PK variability was ~ 16% higher for peak plasma concentration (C_{max}) and area under the concentration time curve (AUC) in patients with cancer compared with healthy subjects. Several factors were identified as major contributors to variability including hepatic/renal impairment and cytochrome P450 inhibition/induction. Lower PK variability in healthy subjects may represent an opportunity to perform rapid and robust pharmacological and PK assessments to inform subsequent studies in the development of new cancer therapies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ High pharmacokinetic (PK) variability in patients with cancer for cytotoxic and targeted drug therapies has been previously observed. The magnitude and sources of PK variability between patients with cancer and healthy subjects is less clearly defined.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Is PK variability between patients with cancer and healthy subjects different? If so, what is the magnitude of this difference and what intrinsic or extrinsic factors might contribute to PK variability?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This survey confirms that PK variability in patients with cancer is higher than in healthy subjects for molecularly targeted oncology drugs approved between 1999 and 2017.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Safety profile of targeted agents and regulatory guidance(s) have provided a framework for use of healthy subjects in drug development. Finding decreased PK variability in healthy subjects vs. patients with cancer and the identification of factors contributing to PK variability could allow designing studies for more rapid acquisition of critical data to inform optimal dose and schedule decisions.

Drugs must attain efficacious concentrations for sufficient duration to achieve a desired exposure-response relationship. Exposure metrics of interest generally include pharmacokinetic (PK) parameters, such as maximum and minimum plasma concentration (C_{max}, C_{min}), area under the concentration time curve (AUC), and time above threshold concentration. The PKs of orally administered drugs, including targeted oncology therapeutics, are dependent on a variety of extrinsic and intrinsic factors. Extrinsic factors exert their influence from the outside and can be inherent in the drug itself or related to lifestyle or the environment. For oral medications, major PK extrinsic factors include diet, concomitant medication use, smoking habits, and physiochemical properties of the drug.[1-3] Intrinsic factors exert their influence from the inside and are inherent in the physiological characteristics of an individual. Major PK intrinsic factors include sex, age, weight, organ function, and comorbid diseases. Genetic makeup can also be a significant intrinsic factor and can be an important driver in both PK and pharmacodynamic variability.

Compared with traditional cytotoxic agents, targeted therapies have shown greater interindividual variability in PK parameters, such as clearance and oral bioavailability.[1] Some portion of the larger observed variability, in PK exposure for example, will be related to the route of administration because cytotoxic agents are most typically delivered intravenously whereas targeted therapeutics are often administered orally. The consequences of large variability in exposure across

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patient populations are the risk of (i) poor efficacy due to subtherapeutic exposure, (ii) unpredictable toxicity and adverse events associated with higher than optimal concentrations, and (iii) the development of drug resistance caused by inconsistent or inadequate tumor exposure.[4,5] To best understand the disposition of a molecularly targeted therapy, it is important to evaluate the degree of interindividual variability of PK parameters in patients with cancer.

The efficacy and patient benefits (such as reduced toxicity compared with cytotoxic agents) of targeted therapies in oncology has made these drugs a new standard of care, often as single agents.[6,7] Traditionally, oncology clinical drug development has utilized patients in trials, however, more recently, interest has emerged in utilizing healthy subjects in oncology drug development. Iwamoto and colleagues reported the use of healthy subjects in the development of 30 oncology drug candidates.[8] The potential benefits of using healthy subjects include early identification of factors contributing to PK variability, improved early clinical trial design for patient studies using healthy subject findings (ideally speeding phase I development), and improved sample sizes for studies, thus increasing statistical power, which will all contribute to better inform the optimal dose and schedule during clinical development.[8]

The overall objectives of our survey of small molecule cancer therapeutics were to: (i) assess and compare the PK variability of orally delivered targeted oncology drugs between healthy subjects and patients with cancer, and (ii) to identify intrinsic and extrinsic factors contributing to PK variability as reported in Health Authority approval documents (in particular, the US Food and Drug Administration (FDA) Summary Basis of Approval, Clinical Pharmacology sections).

METHODS

Source material included data from both patients and healthy subjects from the FDA and the European Medicines Agency (EMA) archives; however, given that the FDA and the EMA documents proved very similar in terms of detail, the clinical pharmacology sections of summary basis of approval documents from the FDA were used (exception: erlotinib also utilized the EMA and literature source material **Table S1**, in supplementary material). The small molecules selected were restricted to molecules with new drug applications approved during the 18-year period 1999–2017 (**Table 1**). The majority of the small molecule orally administered drugs was approved after 2010. A flowchart of the process is provided as **Figure S1**, in supplementary material.

PK parameter data gathered included C_{max} and AUC from noncompartmental analysis for the first dose and at steady-state, biopharmaceutical classification system class (when available), dose regimen, fed or fasted state, and physicochemical characteristics, such as pH-dependency of solubility or dissolution. Variability of PK data (as assessed by source coefficient of variation (%CV) data) were collected for C_{max} and AUC. When available, AUC data were matched for patients with cancer and healthy subjects (e.g., AUC_{024hr}, AUC_{0inf}). Because many of the drugs were administered as a single dose in healthy subject studies, steady-state PK data were not available and steady-state C_{max} and AUC data were available for only six drugs in the data set (erlotinib, exemestane, idelalisib, nilotinib, ruxolitinib, and vismodegib).

For the statistical comparisons (%CV), only first-dose PK data were used. Of the 40 drugs identified, first-dose PK data were available for 38 drugs in patients with cancer and for 33 drugs in healthy subjects for both C_{max} and AUC. Steady-state data in patients were available for 32 and 33 drugs for AUC and C_{max}, respectively. Steady-state PK data in healthy subjects were only available for six drugs. PK data were selected for drugs administered at, or near, the intended therapeutic dose and prioritized for the reporting of data from cohorts with the highest number of subjects.

Information relating to any intrinsic and extrinsic factors contributing to PK variability was collected from sponsors' population PK reports. The identified factors, although seldom provided as quantitative data in the source documents, were considered noteworthy when the source material associated a relevant relationship to the PK parameters in the final population PK model. Statements of "potential" or "likely" effects were not included in this analysis.

In oncology phase I dose escalation clinical trials, PK variability can be quite large due to small dose-cohort sample sizes, especially in broad oncology patient populations. In order to have a base point from which to compare healthy subjects and patients with cancer PKs, a 35% CV cutoff was arbitrarily applied to provide an approximate threshold value to categorize variability as high (> 35%) or low (< 35%) for assessing variability in a typical oncology study and perceived generalized exposure-response relationships. The %CV for healthy subjects was subtracted from %CV for patients with cancer, as reported in the regulatory documents, were used to produce a Δ%CV for an assessment of variability across the PKs in the data set. A paired, two-tailed *t*-test was performed to compare the means of different groups using R version 3.5, and Microsoft Excel was utilized to compute the associated 95% confidence interval (CI).

RESULTS

The survey of the FDA approval documents during the study period 1999–2017 resulted in data for 40 drugs and is summarized in **Table 1**. The most consistent and complete data for PK following the first dose for both patients and healthy human subjects was for C_{max} and AUC. In the majority of cases examined, the C_{max} and AUC values were within two-fold between healthy subjects and patients with cancer allowing reasonable confidence that %CV ranges were representative of differences between these groups (data not presented). Other PK parameters (e.g., terminal half-life, time of maximum plasma concentration (T_{max}), and clearance), although frequently available, were not complete or inconsistently reported across studies and drugs and, thus, did not enable a comprehensive comparison. Steady-state PK data were only available for six drugs for healthy subjects as compared with 33 drugs for patients with cancer. Biopharmaceutical classification system class of the molecules was initially considered as a potential contributor to variability, but lack of robust data as well as an early examination of the available data did not reveal any clear link and was not included in this analysis.

Table 1 Characteristics of 40 small molecule targeted therapeutic drugs and difference in %CV between patients with cancer and healthy subjects (a positive Δ%CV value indicates healthy subjects have a lower variability)

Drug	Alias	Approval year	Mechanism of action	Δ%CV C_{max}	Δ%CV AUC
Afatinib	AF	2012	Kinase inhib EGFR	40.2	35.7
Alectinib	AL	2015	Kinase inhib ALK+	–4.3	42.9
Axitinib	AX	2012	VEGF inhib	9	26
Brigatinib	BR	2017	Kinase inhib ALK+	31.8	24.4
Cabozantinib	CA	2012	Receptor TK inhib	2	–2
Ceritinib	CE	2014	Kinase inhib ALK+	7.4	39.9
Cobimetinib	CO	2015	BRAF mutations	48.3	39
Crizotinib	CR	2011	Recep Tyr Kinase inhib ALK	5	24
Dabrafenib	DA	2013	ATP-comp RAF kinase inhib		
Dasatinib	DAS	2005	Multiple kinase inhib	32	29
Erlotinib	ERL	2004	TKI EGFR inhib	13.0	13.3
Everolimus	EV	2008	mTOR inhib	16.1	4.5
Exemestane	EX	1999	Aromatase inhib	29.1	12.4
Gefitinib	GEF	2008	EGFR TKI	–18	–52
Ibrutinib	IB	2014	BTK inhib	–8.6	–3.1
Idelalisib	ID	2014	ATP binding PI3K inhib	3.1	–4.7
Imatinib	IM	2002	TKI PDGF-R inhib	–21.7	–5.5
Ixaxomib	IX	2015	20s proteasome inhib		
Lapatinib	LA	2006	TKI EGFR-ErbB2 inhib	5.0	1.2
Lenalidomide	LE	2005	Immunomodulatory agent	–16.1	49.1
Lenvatinib	LEN	2014	Multitargeted TKI inhib	–0.3	–2.4
Midostaurin	MI	2017	Multiple kinases FLT & KIT		
Nilotinib	NI	2006	BCR-ABL TKI	14.0	16.8
Olaparib	OL	2014	PARP inhib		
Osimertinib	OS	2015	EGFR TKI		
Palbociclib	PAL	2014	Cyclin-dependent KI	9	22
Panobinostat	PAN	2014	HDACi		
Pomalidomide	PO	2012	Immunomodulatory agent	20.2	10.3
Ponatinib	PN	2012	TKI BCR-ABL	37.2	28.3
Regorafenib	RE	2012	Multiple kinases	16	3.6
Rucaparib	RC	2016	PARP inhib		
Ruxolitinib	RU	2011	JAK1, JAK2 inhib	12.3	15.8
Sonidegib	SON	2015	Hedgehog pathway inhib	71.7	41.3
Sorafenib	SOR	2005	Multikinase inhib	27.4	22.8
Sunitinib	SU	2005	Multikinase inhib	15.2	18.2
Trametinib	TR	2012	MEK inhib		
Vandetanib	VA	2010	VEGF, EGF, TK inhib	42.1	36.8
Vemurafenib	VE	2011	BRAF kinase inhib		
Venetoclax	VEN	2016	Bcl-2 inhib		
Vismodegib	VI	2012	Hedgehog pathway inhib	36.9	19.5

Descriptive statistics: Δ%CV C_{max} n = 30; mean (15.8), median (13.5), min/max –21.7/71.7. Δ%CV AUC n = 30; mean (16.8), median (18.9), min/max –52/49.1. The number of subjects across studies ranged from 6–100 for healthy subject (median 19) and 3–88 for patients (median 18). Δ%CV is defined as %CV for patients with cancer minus %CV for healthy subjects for the indicated pharmacokinetic parameter. Where no Δ%CV value is present, there was no matched patient with cancer and healthy subject data available for comparison. For Δ%CV AUC 9 of 29 matches utilized $AUC_{0\text{-}inf}$ for healthy subject data compared against $AUC_{0\text{-}24hr}$ or $AUC_{0\text{-}tau}$ values for patients with cancer data.
%CV, percentage of coefficient of variation; ALK, ALK receptor tyrosine kinase; ATP-comp RAF, adenosine triphosphate competitive RAF; AUC, area under the concentation time curve; Bcl-2, B-cell lymphoma 2; BCR-ABL, Bcr-abl fusion protein oncogene; BRAF, gene encoding B-Raf proto-oncogene; BTK, Bruton's tyrosine kinase; C_{max}, peak plasma concentration; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EGFR-ErbB2, epidermal growth factor receptor-Erb2; FLT & KIT, receptor tyrosine kinases Flt-3 and c-kit; HDACi, histone deacetylase inhibitor; Inhib, inhibitor; JAK1, Janus kinase 1; JAK2, Janus kinase 2; KI, kinase inhibitor; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PARP, Poly (ADP-ribose) polymerase; PDGF-R, platelet-derived growth factor receptor; PI3K, phosphoinositide-3 kinase delta; Recep Tyr Kinase, receptor tyrosine kinase; Recep, receptor; TK, tyrosine kinase; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

A comparison of C_{max} %CV for the first dose revealed much higher variability in patients with cancer than in healthy subjects (**Figure 1 and Table 1**). For 31 of 38 drugs, the %CV for C_{max} in patients with cancer was > 35% vs. 11 of 33 for healthy subjects (82% vs. 33%). The Δ%CV comparison for C_{max} reveals a mean of 15.8

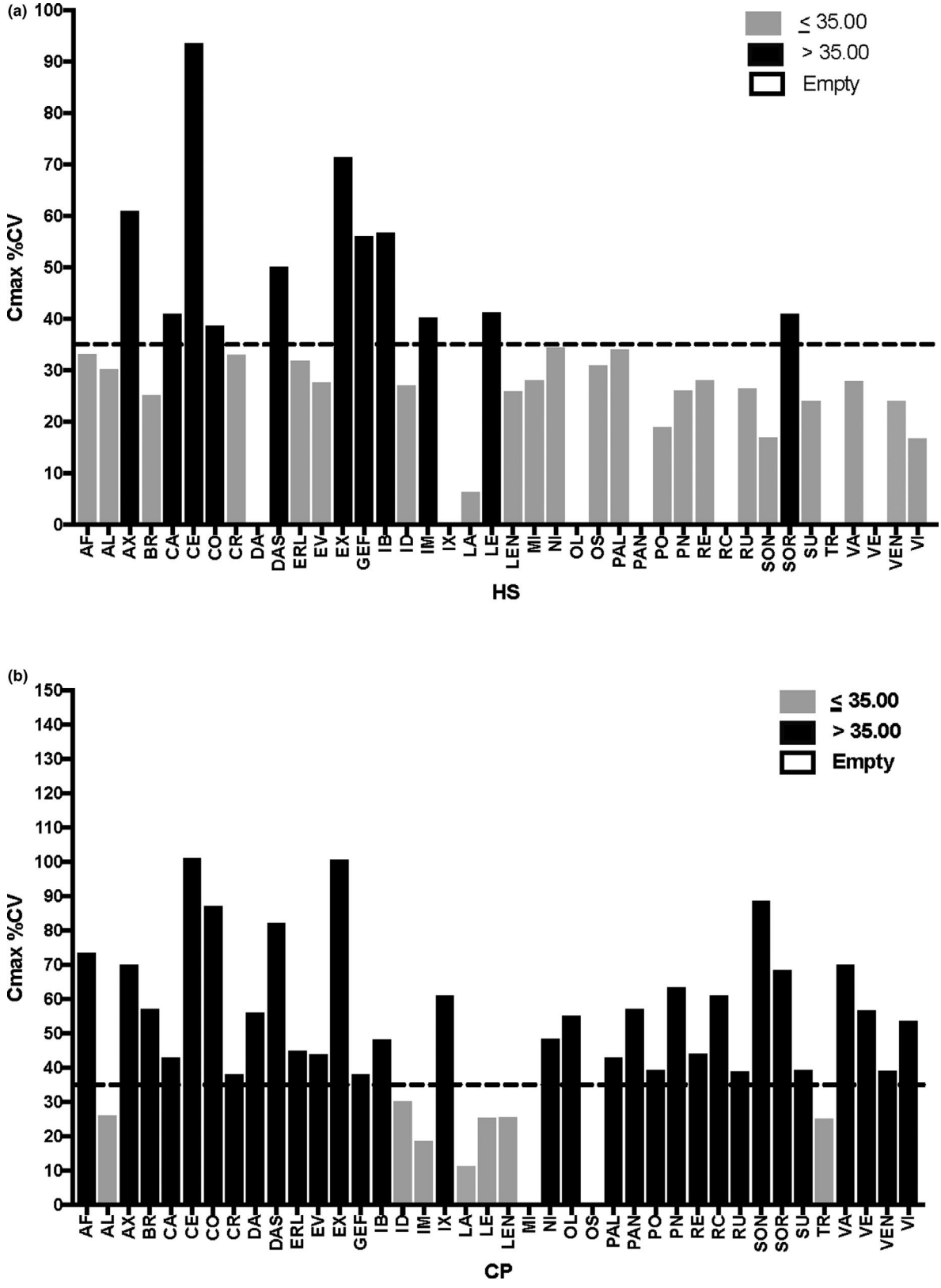

Figure 1 Percentage of coefficient of variation (%CV) for peak plasma concentration (C_{max}) following the first dose for (**a**) healthy subjects (HS) and (**b**) patients with cancer (CP). For the drug abbreviations on the x-axis, aliases are provided in column 2 of **Table 1**. "Empty" indicates no data available for these drugs.

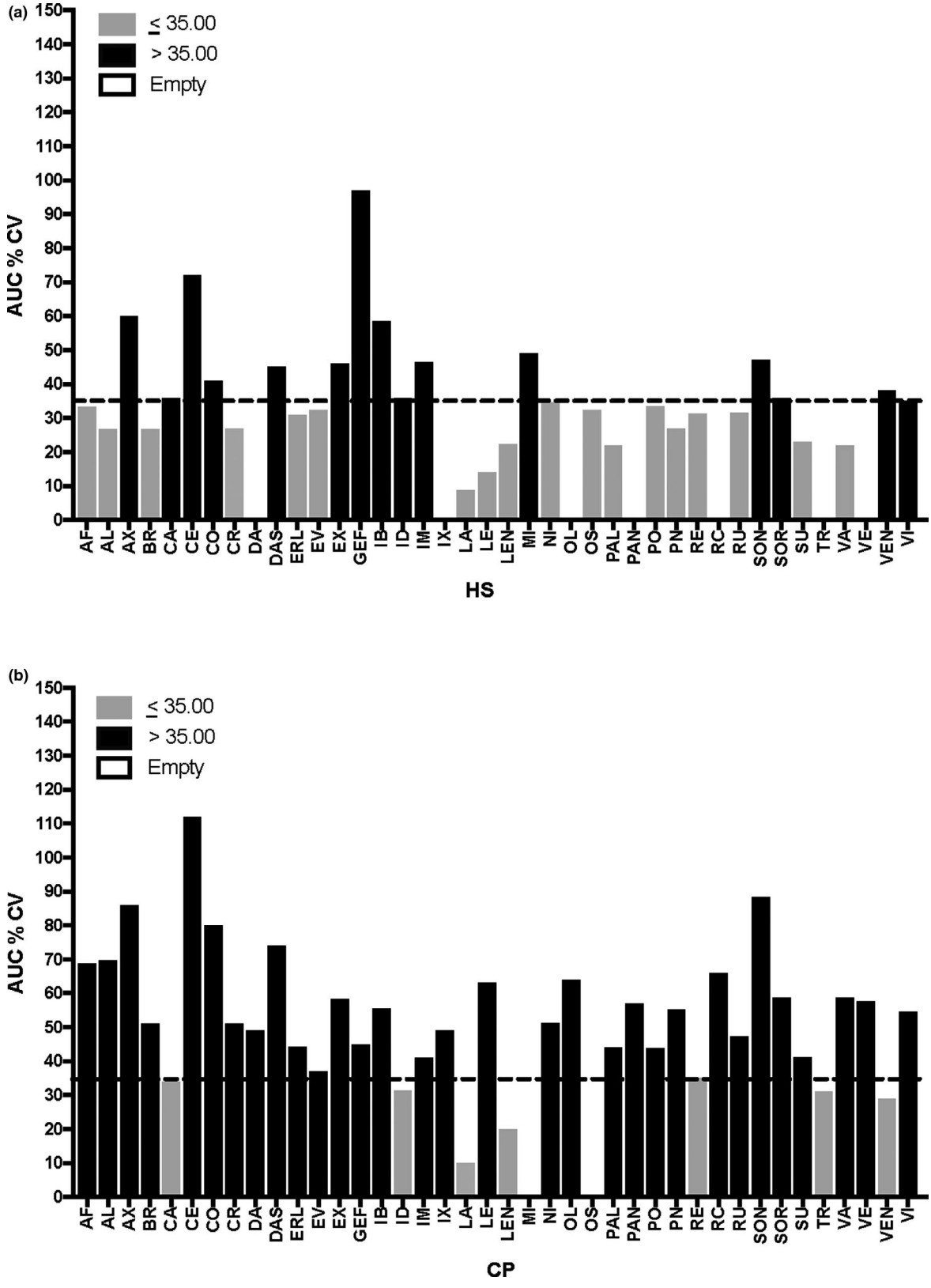

Figure 2 Percentage of coefficient of variation (%CV) for area under the concentration time curve (AUC) for following the first dose for (**a**) healthy subjects (HS) and (**b**) patients with cancer (CP). For the drug abbreviations on the x-axis, aliases are provided in column 2 of **Table 1**. "Empty" indicates no data available for these drugs.

(95% CI 8.2, 23.4), indicating patients with cancer exhibit greater variability in C_{max} than healthy subjects. PK data for AUC revealed a similarly higher variability in patients with cancer than in healthy subjects (**Figure 2, Table 1**). The AUC %CV was greater than the 35% cutoff value for 31 of 38 drugs in patients with cancer in contrast to 15 of 33 for healthy subjects (82% vs. 45%). Similar to the findings for C_{max}, the Δ%CV for AUC revealed a mean of 16.1 (95% CI 8.5, 23.6) indicating that patients with cancer have variability in AUC that is typically larger than in healthy subjects.

A graphical examination of mean values for AUC %CV following first-dose and at steady-state was produced (**Figure S2**, in supplementary material) where healthy subjects' and patients' with cancer data for first-dose and steady-state were both available. This figure illustrates a larger variability in patients with cancer than in healthy subjects for both first-dose and at steady-state. However, no

Table 2 Distribution of intrinsic factors noted in regulatory documents as having impact on PK (note that more than one factor may be indicated for an individual drug)

	Intrinsic factors affecting PK								
	Age	**Bilirubin/AAG**	**Body weight**	**Sex**	**Genetic variance**	**Race**	**Hepatic impair**	**Renal impair**	**Total intrinsic factors**
Afatinib			x						1
Alectinib									
Axitinib						x	x		2
Brigatinib									
Cabozantinib									
Ceritinib			x			x			2
Cobimetinib									
Crizotinib			x			x			2
Dabrafinib									
Dasatinib			x						1
Erlotinib		x							1
Everolimus		x				x	x		3
Exemestane							x	x	2
Gefitinib				x					1
Ibrutinib					x		x		2
Idelalisib									
Imatinib									
Ixazomib									
Lapatinib							x		1
Lenalidomide	x							x	2
Lenvatinib			x				x	x	3
Midostaurin									
Nilotinib				x					1
Olaparib								x	1
Osimertinib			x						1
Palbociclib									
Panobinostat	x						x	x	3
Pomalidomide							x	x	2
Ponatinib							x pmr		1
Regorafenib									
Rucaparib									
Ruxolitinib									
Sonidegib									
Sorafenib						x			1
Sunitinib				x					1
Trametinib				x					1
Vandetanib						x		x	2
Vemurafenib									
Venetoclax									
Vismodegib		x							1

PK, pharmacokinetic; pmr, post-marketing requirement to examine this factor.

substantial difference in variability was observed between the first dose and steady-state in either healthy subjects ($P = 0.85$) or in patients with cancer ($P = 0.039$). Mean %CV for AUC was 37.0% and 34.7% in healthy subjects for first-dose and steady-state, respectively, where only sparse steady-state data were available, whereas the mean for AUC in patients with cancer was 53.0% and 48.8% for first-dose and steady-state, respectively.

Intrinsic factors influencing PK behavior are presented in **Table 2** and **Figure 3**. For 40% of the molecules (16/40), no intrinsic factors affecting either C_{max} or AUC were reported. Body weight, race, and hepatic and renal impairment were the most common intrinsic factors identified to influence PK.

Extrinsic factors noted in the data as having influence on PK are presented in **Table 3** and **Figure 4**. No extrinsic factors were reported for 30% of the molecules (12/40) in this survey. However, cytochrome P450 (CYP) inhibition or induction was identified as an extrinsic factor in 62.5% of cases. Drug transporters, acid reducing agents, and food effects were also identified as factors affecting PK for a limited number of drugs (7.5%, 10%, and 12.5%, respectively; **Table 3**).

DISCUSSION

The development of noncytotoxic oncology therapeutics has increased the opportunity for clinical investigations beyond patients with cancer using healthy subjects. Historically, oncology drugs did not have properties amenable for administration in healthy subjects primarily due to drug-associated genotoxicity. The safety profile of molecularly targeted agents and regulatory guidance(s) have provided a framework for the safe use of healthy subjects in drug development. Healthy subject studies, in contrast to patients with cancer studies, are generally faster to recruit and may provide key PK, pharmacodynamic, and mechanistic information in a timelier manner and with fewer subjects.[8] Early translational studies in healthy subjects can also support assessment of a number of intrinsic and extrinsic factors in terms of formulation development, food-effect, and the potential for drug-drug or drug-gene interactions on drug exposure. Evaluation of formulation

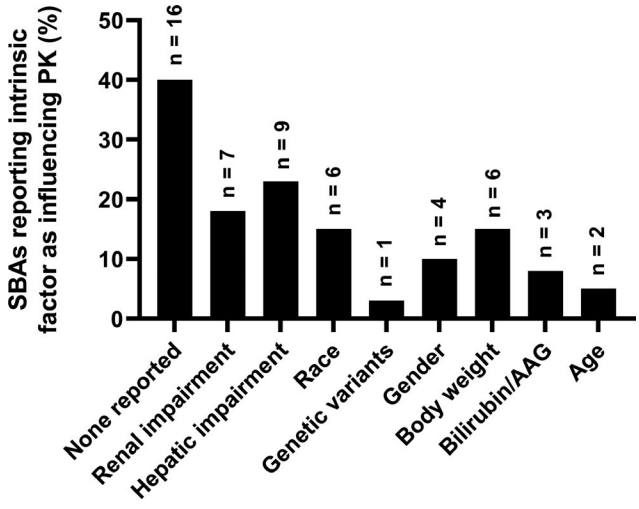

Figure 3 Bar graph showing the percentage of summary basis of approvals (SBAs) that report a specific intrinsic factor influencing pharmacokinetics (PKs). Data were obtained as described in the Methods section. Values above the bars indicate the actual number of SBAs.

Table 3 Distribution of extrinsic factors noted in regulatory documents as having impact on PK (note that more than one factor may be indicated for an individual drug)

	Extrinsic factors affecting PK					
	ARA	CYP	Food	P-gp	Smoking	Total extrinsic factors
Afatinib				x		1
Alectinib				x		1
Axitinib		x		x		2
Brigatinib		x				1
Cabozantinib						
Ceritinib						
Cobimetinib						
Crizotinib	x	x				2
Dabrafinib		x				1
Dasatinib	x	x				2
Erlotinib		x			x	2
Everolimus		x				1
Exemestane			x			1
Gefitinib		x				1
Ibrutinib		x				1
Idelalisib		x				1
Imatinib		x				1
Ixazomib		x	x			2
Lapatinib		x				1
Lenalidomide						
Lenvatinib						
Midostaurin		x	x			2
Nilotinib						
Olaparib		x				1
Osimertinib						
Palbociclib		x	x			2
Panobinostat		x				1
Pomalidomide		x				1
Ponatinib	x	x				2
Regorafenib		x	x			2
Rucaparib						
Ruxolitinib		x				1
Sonidegib	x	x				2
Sorafenib						
Sunitinib		x				1
Trametinib						
Vandetanib						
Vemurafenib		x				1
Venetoclax		x				1
Vismodegib						

ARA, acid reducing agent; CYP, cytochrome P450 (substrate/inhibitor/inducer risk); P-gp, P-glycoprotein (substrate/inhibitor risk); PK, pharmacokinetic.

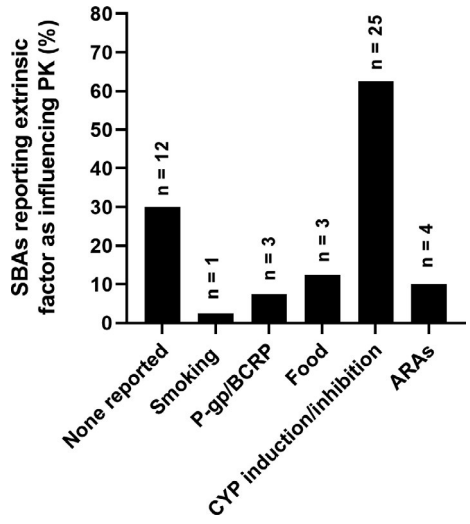

Figure 4 Bar graph showing the percentage of summary basis of approvals (SBAs) that report a specific extrinsic factor influencing pharmacokinetics (PKs). Data were obtained as described in the Methods section. Values above the bars indicate the actual number of SBAs reporting the data. ARAs, acid reducing agents.

as an influencing factor of variability of overall PK would be ideal. Because more complete PK is common in early development phases, a general assumption was made that similar formulations were used for healthy subjects and patients with cancer. Formulation differences could not be confirmed for all drugs and, thus, may be a contributor to the "none reported" extrinsic factor category. Due to the inconsistency of reporting, we were unable to analyze and report formulation-related differences.

The large PK variability of targeted anticancer drugs in patients with cancer has been previously recognized and discussed.[2,3,7] Our survey of the new drug application summary basis of approval documents confirmed that PK variability in patients with cancer is higher than for healthy subjects by ~ 16% for both AUC and C_{max}. Factors related to the complex disease state are likely to make significant contributions to PK variability.[2,3,9] A review by Undevia *et al*. nicely outlines potential sources of absorption, distribution, metabolism, and excretion-based PK variability in patients with cancer, which could help explain the differences observed between patients with cancer and healthy subjects.[3] For instance, nausea and/or vomiting, which can be common in patients with cancer, could affect drug absorption, whereas hypoalbuminemia could potentially affect drug distribution. We direct the readers to this comprehensive review (particularly box 3, p. 451 of Undevia reference[3]) for more information.

The effects of cancer on drug metabolizing enzymes have been previously investigated, although the effects on drug transporters are not well understood.[3,10,11] One study by Rivory *et al*. showed that hepatic cytochrome P450, family 3, subfamily A (CYP3A) was significantly reduced in patients with cancer but only in those who were experiencing an acute phase response as measured by C-reactive protein.[10] This reduction in CYP3A activity was irrespective of tumor type and suggests that not only the disease itself but also the severity could be an important factor contributing to PK variability. Thus, one potential limitation to our study is the inability to stratify patients with cancer based on the severity of their disease. Kacevska *et al*. investigated the molecular signaling by which extrahepatic tumors could exert changes on hepatic drug clearance using an Engelbreth-Holm-Swarm sarcoma mouse model.[13] Their findings suggest that extrahepatic malignancies cause major changes in the levels and localization of key nuclear receptors, including pregnane X receptor, constitutive androstane receptor, and retinoid X receptor alpha, which are involved in the expression of drug metabolizing enzymes and transporters. Their results also indicate that dysregulation of several nuclear receptors involved in energy balance may contribute to cachexia, a common occurrence in patients with advanced cancer. Cachexia may also lead to PK variability due to altered absorption and reduced volume of distribution.[14] These data illustrate the complexity by which cancer could alter PK and lead to increased PK variability.

Our study also identified intrinsic and extrinsic factors associated with PK variability in patients with cancer, and these are consistent with previous publications.[2,3,7,12] Although regulatory approval documents can provide useful information on intrinsic and extrinsic factors important for PK variability, the analyses and subsequent documentation may be incomplete as it may be unfeasible or impractical to look beyond a limited "typical" set of factors. A case in point is the documentation of intrinsic factors associated with PK variability in the current study where 40% of the molecules surveyed report no intrinsic factors associated with PK (**Figure 4**). Of note, the top three intrinsic or extrinsic factors associated with PK variability were CYP inhibition/induction (62.5%), renal impairment (18%), and hepatic impairment (23%), which likely reflects our advanced understanding of these factors as contributors to PK variability and guidance documents from health authorities that recommend the study of these factors. The ability to identify factors associated with PK variability has improved greatly over the years and will hopefully continue with the advent of advanced data curation, sharing, and analytics.

Our review of regulatory documents for 40 approved small molecule oral oncology drugs, spanning the 18-year period from 1999–2017, verified higher PK variability in patients with cancer vs. healthy subjects. In addition, the quantification of the magnitude of this effect and identifying factors contributing to the PK variability should be of use to investigators when designing clinical studies for patients with cancer and healthy subjects. Finally, the differences in PK variability between the two groups must be considered when predicting PK and selecting the dose for patients based upon early clinical data collected in healthy subjects.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Flowchart diagram outlining the methods process from data gathering to final document.

Figure S2. Mean estimated AUC %CV +/- SD for healthy subjects (HS) and cancer patients (CP) following the first-dose and at steady-state. Mean %CV for AUC in healthy subjects was 37.0% and 34.7% following first-dose

and steady-state, respectively. Mean %CV for AUC in cancer patients was 53.0% and 48.9% for first-dose and steady-state, respectively.

Table S1. List of drugs, their assigned aliases and actual first dose and steady-state coefficient of variance (%CV) for Cmax and AUC, Cancer Patients and Healthy Subjects collected from the source material.

Reference S1. Source links to the Summary Basis of Approval (SBA), Clinical Pharmacology sections from US Food and Drug Administration, European Medicines Agency and literature source material. These sources provided the pharmacokinetic parameters (C_{max} and AUC) and available intrinsic and extrinsic data used in this review document.

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Conflict of Interest. E.R., B.L, J.J., and M.K. are employees of Genentech, Inc. (a member of the Roche Group) and stockholders in Roche Holding AG. No competing interests for this work exist for J.A.W. or L.J.D.

Author Contributions. E.R., B.L., J.J., J.A.W., and L.J.D. wrote the article. E.R. and J.A.W. designed the research. E.R. performed the research. E.R., J.A.W., M.K., and L.J.D. analyzed the data.

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